The effects on lipophilicity of replacing oxygenated functionality with fluorine

Richard J. Glyn and Graham Pattison*

Chemistry Research and Enterprise Group, School of Pharmacy and Biomolecular Sciences, University of Brighton, Lewes Road, Brighton, UK. BN2 4GJ.

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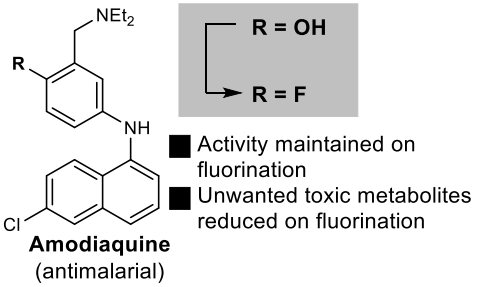
ABSTRACT: The replacement of oxygenated functionality (hydroxy, alkoxy) with a fluorine atom is a commonly used bioisosteric replacement in medicinal chemistry. In this paper we use Molecular Matched Pair Analysis to better understand the effects of this replacement on lipophilicity. It seems that the reduced log P of the oxygenated compound is normally dominant in determining the size of this difference. We observe that the presence of additional electron-donating groups on an aromatic ring generally increase the difference in lipophilicity between an oxygenated compound and its fluorinated analogue, whilst electron-withdrawing groups lead to smaller differences. *Ortho*-substituted compounds generally display a reduced difference in log P compared to *para*- and *meta*- substituted compounds, particularly if an *ortho*-substituent can form an intramolecular hydrogen bond. Hydrogen-bond acceptors remote to an aromatic ring containing fluorine / oxygen can also reduce the difference in log P between oxygen and fluorine-substituted compounds.

Introduction

During a lead optimization process, medicinal chemists routinely switch simple functional groups for alternatives to establish what effect these substitutions have on drug activity and properties. Some of these changes are known to have relatively little effect on biological activity on many occasions, and are known as bioisosteric replacements.[1]

One of the most important bioisosteric replacements that medicinal chemists make during a lead optimization program is the replacement of oxygenated functionality (often a hydroxy or methoxy group on an aromatic ring) with a fluorine atom.[1, 2] Fluorine is one of the most important elements in drug design; its high electronegativity can be used to modulate parameters ranging from the binding of a drug to its target, to acidity, and the charge state of a drug under physiological conditions.[3-7] Fluorine and oxygen are similar in size, and both are highly electronegative, giving them similar properties in many ways. However, transformation of a hydroxyl group to a fluorine atom leads to the loss of a hydrogen-bond donor, and fluorine's extreme electronegativity means that it has very low polarizability compared to oxygen.

A key reason that chemists may choose to replace oxygenated functionality with a fluorine atom is in blocking unwanted metabolic processes.[8] Electron-rich aromatic rings such as phenols and anisoles are particularly susceptible to oxidative metabolism. Replacement of these groups with a fluorine atom can block these processes. One example of this was seen during a study on the optimization of the antimalarial amodiaquine (Scheme 1).[9]



Scheme 1: Comparing the pharmaceutical behavior of hydroxy- and fluoro-substituted compounds

The parent hydroxy compound (amodiaquine) was highly susceptible to metabolic oxidation, often forming toxic quinone byproducts. Replacement of hydroxy with fluorine prevented these metabolic processes, whilst maintaining similar activity (IC_{50} (OH) = 20 nM, IC_{50} (F) = 40 nM).

However, the replacement of oxygenated functionality with a fluorine atom may lead to a change in the physicochemical properties of a molecule, in particular its lipophilicity. Lipophilicity plays a key role in drug design; not only does it play a key role in biodistribution of a drug, but is also of great importance to factors such as potency, metabolic clearance and toxicology.[10-13]

The effect of fluorination on lipophilicity is fairly complex and not always well-understood. In general, fluorination of an aromatic ring with either a single fluorine atom or a perfluoroalkyl group (e.g. CF_3 group) leads to an increase in lipophilicity relative to hydrogen at the same position. However, evidence is also

beginning to emerge that partial fluorination of alkyl groups can be used to successfully reduce lipophilicity.[14-24]

Alcohol- and ether-based functionality generally reduce the lipophilicity of a compound relative to a hydrogen at the same position. Therefore, the bioisosteric replacement of an aromatic hydroxy or methoxy group with a fluorine atom would therefore be expected to lead to an increase in lipophilicity. However, the magnitude of this increase is poorly understood, as is how other functional groups that are present in a molecule may affect this magnitude. Medicinal chemists who are making oxygen to fluorine bioisosteric replacements need to understand the effects this replacement will have on the physicochemical properties of a molecule, particularly lipophilicity because of the key role it plays in biodistribution, metabolism and binding. As part of an interest in the chemistry of fluorinated aromatic compounds,[25-31] in this paper we will describe how structural features in a drug-like molecule may affect the change in lipophilicity on transformation of an aromatic hydroxy or methoxy group to a fluorine atom.

Results and Discussion

We chose to take a Molecular Matched Pairs Analysis (MMPA) approach to understanding this problem.[32-35] Several databases (including the Reaxys, OCHEM and PhysProp databases) were searched for pairs of molecules where lipophilicity values were known for either both an OH-containing and F-containing aromatic ring, or an OCH_3-containing and F-containing aromatic ring, and the lipophilicity values and structures recorded. This data relied heavily on previous work by Hansch and Sangster among others, who determined accurate log P values (normally using a shake-flask method) for a broad range of compounds.[36-38] In addition, we ourselves determined, using an HPLC method,[19, 39, 40] log P values for a range of simple substituted aromatic systems where these were not available in the literature.

The OCHEM database showed 1287 examples of replacement of OH to F, as well as 6574 examples of an OCH_3 to F matched pair, showing that this is a common bioisosteric replacement. However, the majority of these pairs did not have lipophilicity data and our continuing analysis only includes those where log P data was available for both O and F compounds within a matched pair.

Figure 1 shows histograms representing the difference in log P between a fluorinated aromatic compound and its hydroxylated or methoxylated matched pair. They show that for the sample of 127 matched pairs studied, 114 showed an increase in lipophilicity on conversion of a hydroxy group to a fluorine atom, with the mean and median increases both being +0.57 log P units (Figure 1a). However, the change in log P on conversion of a hydroxy group to a fluorine atom ranged from -0.74 to +1.64, demonstrating the wide variability on the effect on lipophilicity upon this bioisosteric replacement, and indeed, 13 of the studied compounds in fact showed a decrease in log P on conversion from a hydroxyl group to a fluorine atom.

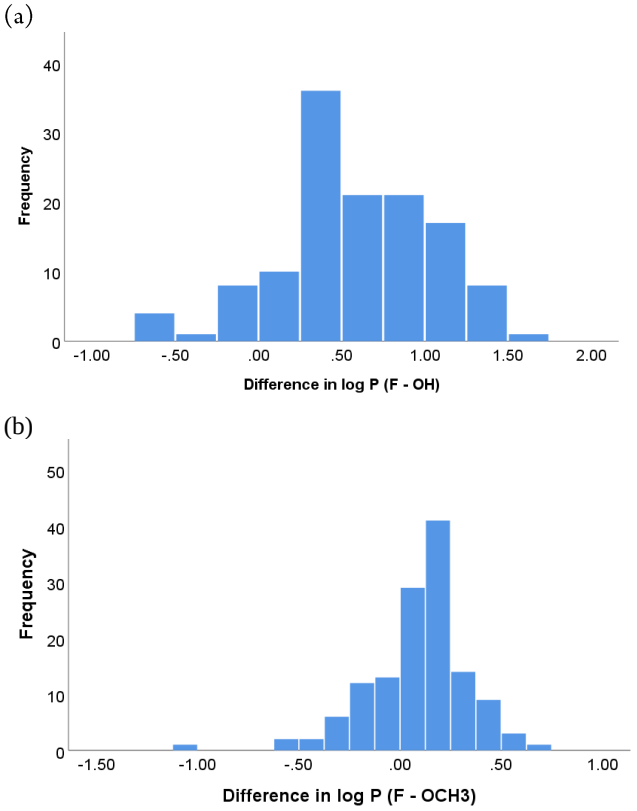
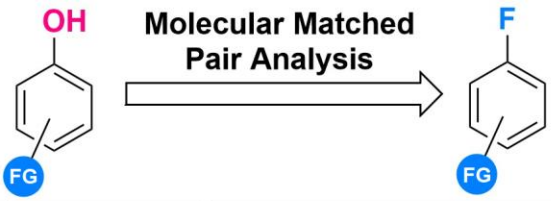


Figure 1: Histograms showing the difference in log P between (a) F – OH matched pairs; (b) F – OCH_3 matched pairs

The situation was further nuanced when comparing a methoxy compound to its fluorinated matched pair (Figure 1b). Of the 133 matched pairs studied, 97 showed an increase in log P on fluorination, with a mean increase of +0.09 log P units, and median increase of +0.13 log P units. The change in log P on conversion of a methoxy group to a fluorine atom ranged from -1.08 to +0.63. The smaller increase in log P of methoxy compounds relative to hydroxy compounds is likely to be reflective of the increased lipophilicity of a methoxy group compared to a hydroxy group. 36 of our compounds showed a decrease in log P on transformation of a methoxy group to a fluorine atom, around 25% of the sample.

We then sought to better understand these observations, in particular why sometimes increases or decreases in log P occurred within a matched pair, and why this magnitude differed. We first chose to analyze a series of simple disubstituted aromatic systems; matched pairs containing a fluorine atom and either a hydroxy or methoxy group, with another functional group at the *ortho*, *meta* or *para* position. The functional groups were chosen to cover a broad range of electron-withdrawing / donating, polar / non-polar, and hydrophobic / hydrophilic functionality. Where lipophilicity data for a compound in our series was not available reliably in the literature, we determined log P values experimentally using an HPLC method. Information on which values were obtained from literature sources and which were experimentally determined is given in the Supporting Information.[19, 39, 40]



Entry	Substituent	Difference in log P (F - OH)		
		Para	Meta	Ortho
1	NO_2	-0.11	-0.1	-0.1
2	CF_3	0.06	0.00	0.03
3	C(=O)-H	0.19	0.64	0.11
4	I	0.29	0.35	0.42
5	$C(=O)-OCH_3$	0.32	0.45	-0.73
6	CN	0.30	-0.23	0.32
7	F	0.36	0.28	0.66
8	$C(=O)-CH_3$	0.37	0.38	0.11
9	Cl	0.39	0.26	0.63
10	Ph	0.48	0.46	0.47
11	C(=O)-OH	0.49	0.65	-0.49
12	Br	0.49	0.29	0.54
13	$C(=O)-NH_2$	0.58	0.52	-0.69
14	OAc	0.59	0.51	0.31
15	CH_3	0.64	0.79	0.87
16	H	0.8	0.8	0.8
17	$O-CH_3$	0.85	1.02	0.82
18	NHAc	1.01	0.92	0.31
19	NH_2	1.11	1.09	0.64
20	OH	1.18	1.13	0.83

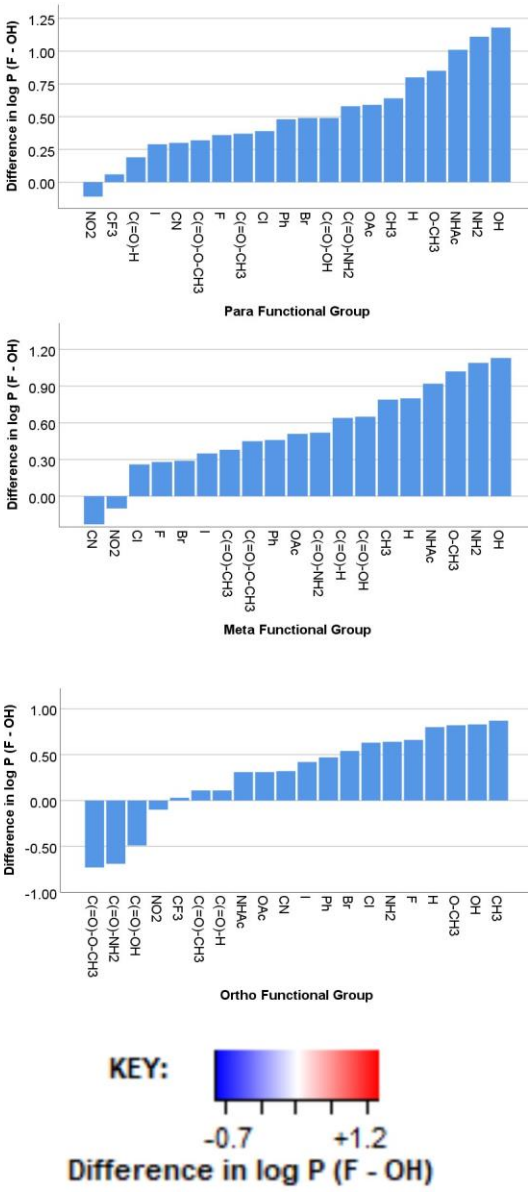
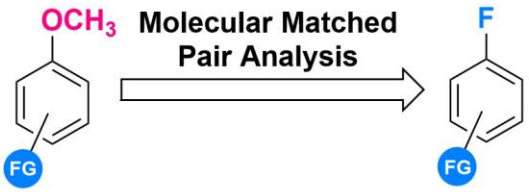


Figure 2: Differences in log P for monosubstituted fluoro and hydroxy compounds

To validate our experimentally-determined results we obtained a log P value for 8 compounds of known log P using our HPLC method, and compared this to the known literature value. This allowed us to estimate a mean error of ±0.08 log P units on our experimentally determined values (see Supporting Information for more details).

The results of this analysis are shown in Figures 2 and 3. Figure 2 shows the difference in log P between an aromatic ring containing a fluorine atom or hydroxyl group, and a single other substituent at either the *ortho*, *meta* or *para* positions (see Supporting Information for details of which values we determined experimentally, and which were available in the literature). These showed that, as expected, within a F/OH matched pair fluorination led to an increase in lipophilicity for the majority of functional groups. Interestingly however, a trend was observed in the kinds of functional group which lead to the largest increase in log P. Electron-donating groups such as OH, NH_2, OMe and NHCOR lead to the largest increases in Δlog P on replacement of a phenol with a fluorine atom, often around +0.75 to +1.2 log P units. Acetylation of these nitrogen or oxygen substituents attenuated this



Entry	Substituent	Difference in log P (F – OCH_3)		
		Para	Meta	Ortho
21	NO_2	-0.23	-0.26	-0.04
22	C(=O)-H	-0.22	0.22	0.20
23	F	-0.13	-0.15	0.23
24	CH_3	-0.08	0.09	0.08
25	CF_3	-0.06	0.16	0.05
26	C(=O)-CH_3	-0.02	-0.07	0.20
27	Cl	0.00	-0.22	0.10
28	C(=O)-OCH_3	0.01	0.03	-0.22
29	Br	0.03	-0.11	0.03
30	I	0.04	0.10	0.17
31	C(=O)-NH_2	0.05	0.06	-0.27
32	C(=O)-OH	0.11	0.13	0.18
33	Ph	0.15	0.21	0.18
34	H	0.16	0.16	0.16
35	NH_2	0.2	0.37	0.08
36	CN	0.2	-0.56	0.06
37	O-CH_3	0.22	0.15	0.54
38	OH	0.36	0.59	0.39
39	NHAc	0.44	0.35	0.36
40	OAc	0.44	0.13	0.38

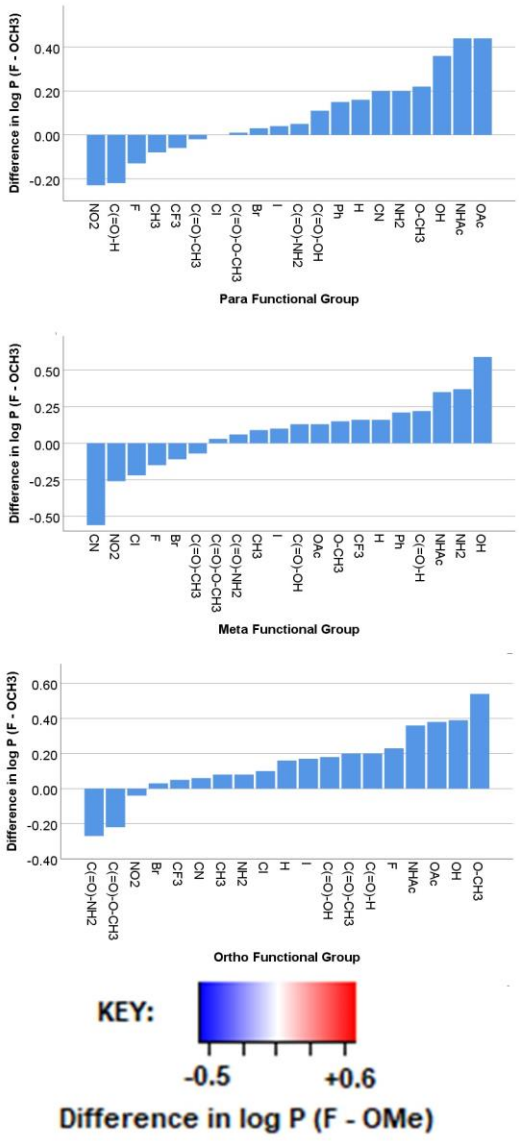
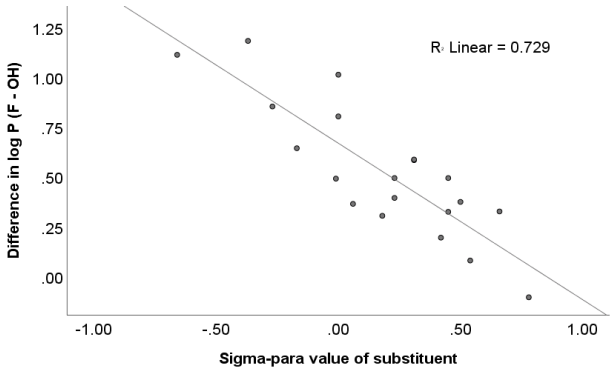


Figure 3: Differences in log P for monosubstituted fluoro and methoxy compounds

a)



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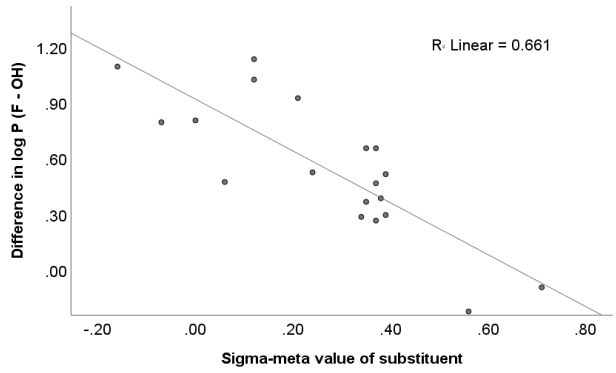


Figure 4: Plots of log P difference against substituent σ-values for a) *para*- and b) *meta*- substituents

effect slightly (compare e.g. *p*-OH **20-*para*** Δlog P = +1.18 to *p*-OAc **14-*para*** Δlog P = 0.59), with the effect being smaller for nitrogen than oxygen (e.g compare *p*-NH_2 **19-*para*** Δlog P = +1.11 to *p*-NHAc **18-*para*** Δlog P = +1.01).

At the other end of the scale, electron-withdrawing groups such as carbonyl groups, and halogen atoms, lead to moderate increases in log P (+0.2 – +0.6 log P units), whilst stronger electron withdrawing groups including nitro, trifluoromethyl and cyano groups led to the smallest increases or even decreases in log P on fluorination (Δlog P -0.1 – +0.3).

Whilst *meta*- and *para*-substituted compounds generally showed similar results, some interesting differences were observed amongst the *ortho*-substituted compounds. In general, for *ortho*-substituted compounds, the difference in log P between a fluorinated compound and its hydroxylated analogue was smaller for the large majority of substituents, compared to a *meta*- or *para*-substituted compound. The range in Δlog P for *ortho* compounds was -0.7 to +0.8 log P units, compared to -0.1 to +1.2 log P units for *meta*- and *para*-substituted compounds. Compounds substituted with an ester, amide or carboxylic acid at the *ortho* position actually showed significant decreases in log P on fluorination, of generally around -0.7 to -0.5 log P units.

We then repeated this analysis to compare fluorine- and methoxy-substituted molecular matched pairs (Figure 3). Whilst overall magnitudes of log P changes were generally smaller within a matched pair for methoxy systems, a similar order of substituent effects was observed. Amine, alcohol and ether-based functionality showed the largest increases in log P (Δlog P approximately +0.25 to +0.5), and carbonyl, nitro and halogen-based functional groups showed either a decrease or a very small increase in log P on fluorination (Δlog P approx. -0.25 to + 0.2 in general).

This order of functional groups clearly suggested that electron-donating / withdrawing character of a distant functional group on an aromatic ring was playing a key role in the difference in log P between fluorinated and oxygenated bioisosteres. To confirm this, we plotted the difference in log P against the Hammett σ-value of the substituent (Figure 4). This gave a moderate linear negative correlation showing that as σ-values became more negative, the difference in log P increased. However, r^2 values of only approximately 0.7 showed that these two variables were only moderately correlated, and that the situation was likely to be more complicated than a simple analysis of electronic character of functional groups, with other parameters likely to be in play.

We then decided that to gain further understanding of these results we should try to separate out the effects of fluorination and hydroxylation on lipophilicity. It is known that, in general, fluorination increases log P relative to a hydrogen substituent, and hydroxylation decreases log P relative to hydrogen, but less is known about the subtle substituent effects of these transformations. We therefore performed an additional Molecular Matched Pair Analysis, comparing our disubstituted fluoro- / hydroxy- compounds to their parent monosubstituted benzene (i.e. replacing OH / F with H).

In comparing aryl fluorides and phenols to their parent unsubstituted benzene (Figure 5) the obvious expected trend was initially observed, in that fluorination generally leads to

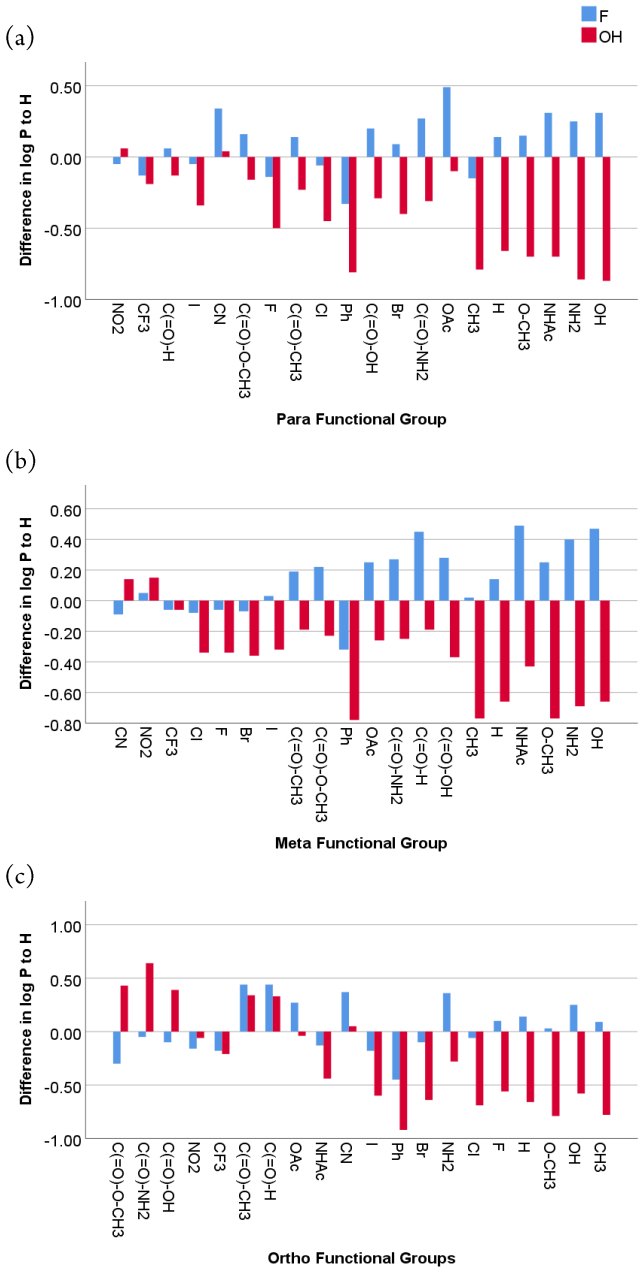


Figure 5: Matched Pair Analysis comparing fluoro / hydroxy compounds to parent benzenes for (a) *para*-; (b) *meta*-; (c) *ortho*-substituted systems

an increase in log P relative to hydrogen at the same position, and hydroxylation leads to a decrease in log P relative to hydrogen. Interestingly, the decrease due to hydroxylation is normally larger than the increase due to fluorination.

We shall now discuss substituent effects on these log P changes in more detail, starting with substituent effects on log P decreases due to hydroxylation (Figure 5, red bars). Electron-donating groups such as OH, NH_2, OCH_3, CH_3 and Ph show the largest log P

decreases on transformation of H to OH. Moderate electron-withdrawing substituents such as carbonyl and halogen substituents generally show a moderate decrease in log P on hydroxylation Finally, stronger electron-withdrawing groups such as NO_2, CN and CF_3 groups show the smallest changes on hydroxylation and sometimes even show a small increase in log P.

We believe that the key driver behind these observed trends is the hydrogen bond acceptor ability of the phenol. Electron-donating substituents will make a phenol a stronger hydrogen bond acceptor and decrease a phenol's relative lipophilicity compared to its hydrogen-substituted matched pair.

Of course, an electron-donating group would be expected to make a phenol a worse hydrogen bond donor. However, it would seem that this has little impact on its octanol-water log P value. This result has been previously supported by work by Abraham who showed that log P_{oct} was mainly influenced by hydrogen bond basicity as well as solute polarity and polarizability.[41] Hydrogen bond acidity was only a factor in log P values determined in alkane-water mixtures.

Our next focus was on how substitution affects the log P of fluorinated compounds, which we will again analyze by comparing substituted aryl fluorides to their hydrodefluorinated matched pair (Figure 5, blue bars). Aryl fluorides containing a substituent that is capable of acting as a hydrogen-bond acceptor (e.g. OR, NR_2, carbonyl) tend to show the largest increase in log P on fluorination. Non-hydrogen-bond donor substituents (e.g. CH_3, Ph, halogen) tend to give much smaller increases, or even decreases in log P on fluorination.

This would suggest that the highly electron-withdrawing nature of fluorine plays a key role in reducing the hydrogen-bond donor capability of other substituents, therefore increasing lipophilicity relative to if fluorine were absent. Aromatic fluorine is always a very weak hydrogen bond acceptor,[42-49] so its effects on log P are mainly confined to the way its high electronegativity can alter the electronic distribution of other functional groups.

However, in cases where substituents are not hydrogen-bond acceptors the change in log P between a fluorinated and hydrogen-substituted compound is often very small (<0.1 log P units). This again confirms the critical role that hydrogen bond acceptors play in reducing log P – if hydrogen bond acceptor groups are absent completely then log P is little changed. In some of these cases log P decreases slightly on fluorination. This is likely due to an increase in polarity slightly increasing water solubility on fluorination.

Polarizability also plays a key role in the lipophilicity of fluorine-substituted systems. Fluorine has very low polarizability (related to its very high electronegativity).[50] This increases the log P of fluorine-substituted systems. However, our matched pair analysis suggests that the presence of a highly polarizable substituent elsewhere in the molecule (particularly Ph) can overcome fluorine's non-polarizability and that in these cases fluorination leads to an increase in dipole moment and a more significant decrease in log P. Note the large decreases in log P comparing Ph-substituted aryl fluorides to non-fluorinated biaryls (Figure 5).

We can then combine these individual effects on hydroxylated and fluorinated systems to consider the overall log P change between F / OH bioisosteres. This allows us to categorize functional groups into those which should have similar effects:

i) Electron-donating groups which can also act as hydrogen-bond acceptors (e.g. OR, NR_2) show the largest difference in log P (~+0.8 to +1.3 log P units) on transformation from OH to F. These functional groups increase the hydrogen-bond acceptor strength of a phenol, but their own hydrogen acceptor strength is reduced by fluorination.

ii) Electron-donating groups which are not hydrogen-bond acceptors (e.g. Ph, CH_3) show moderate to large increases in log P (~+0.5 to +0.8 log P units). Their electron-donating nature increases the hydrogen-bond accepting ability of a phenol, decreasing log P. However, fluorination can also lead to log P decreases when these functional groups are present due to their high polarizability overcoming the low polarizability of fluorine, as well as fluorination increasing the polarity of these molecules.

iii) Carbonyl substituents show a moderate increase in log P (+0.2 to +0.6 log P units) between phenol and aryl fluoride matched pairs. As they are electron-withdrawing, they reduce a phenol's hydrogen-bond acceptor strength, but the hydrogen-bond acceptor strength of a carbonyl group is reduced by fluorination.

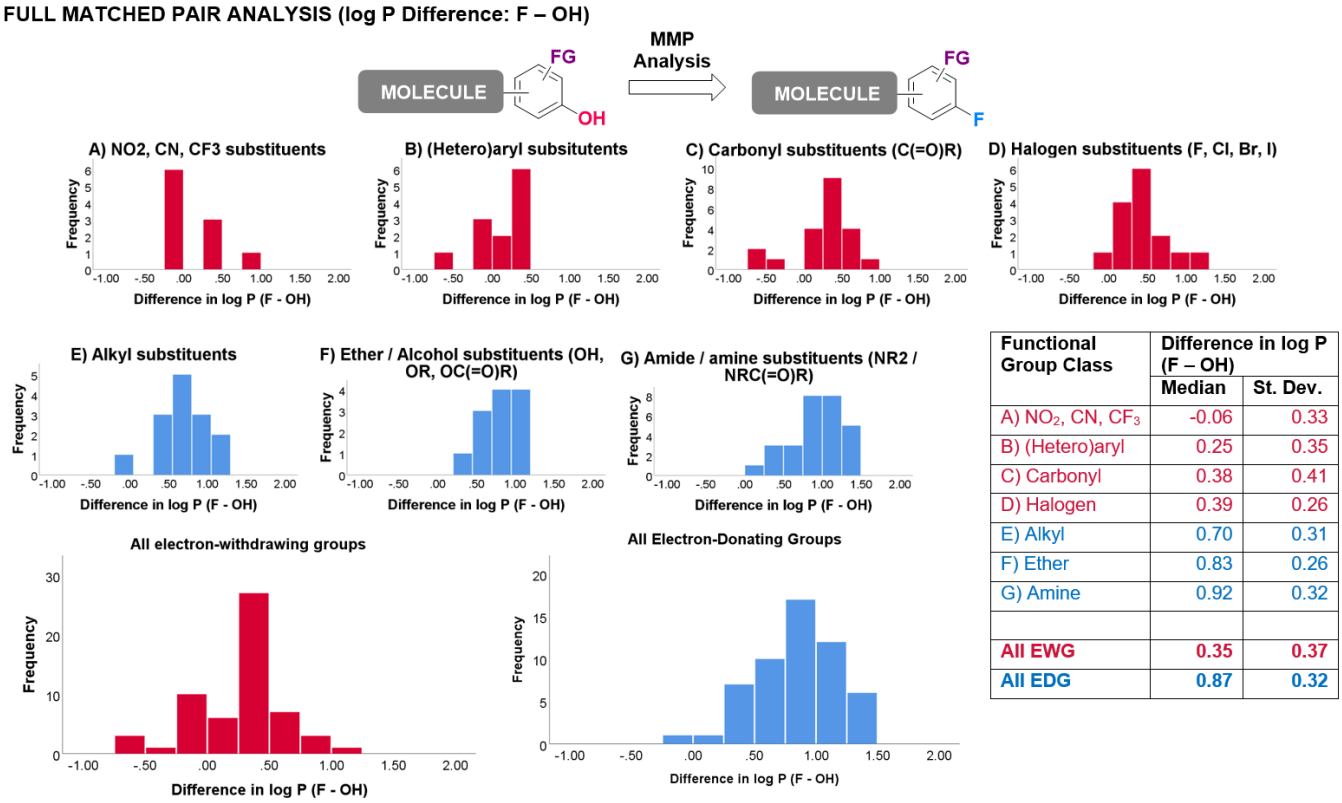
iv) Halogen substituents show a small to moderate increase in log P (+0.3 to +0.5 log P units) on transformation of a hydroxy group to fluorine. They are electron-withdrawing, so reduce hydrogen-bond acceptor ability of a phenol group, but fluorination only has a small effect on these compounds due to competing decreases in polarizability but increases in local polarity.

v) Stronger electron-withdrawing groups (e.g. NO_2, CN, CF_3) show small increases or small decreases in log P (-0.2 to +0.3) on transformation of OH to F. This is due to their strong reduction in the hydrogen-bond acceptor capability of the phenol, alongside increases in local polarity in the fluorinated matched pair.

Whilst these trends hold well for *para*- and *meta*-substituted benzenes, some additional trends were observed for *ortho*-substituted compounds. In general, the difference in log P for a phenol / fluorinated matched pair is smaller for *ortho*-substituted systems. Figure 5c would seem to suggest that this is mainly being driven by a smaller increase in log P on fluorination, as decreases in log P on hydroxylation are often similar. This may be due in general due to an increase in the dipole moment of the *ortho*-fluorinated system increasing their water solubility. Indeed, the log P of *ortho*-substituted aryl fluorides are generally lower than their *meta*- and *para*-substituted isomers.

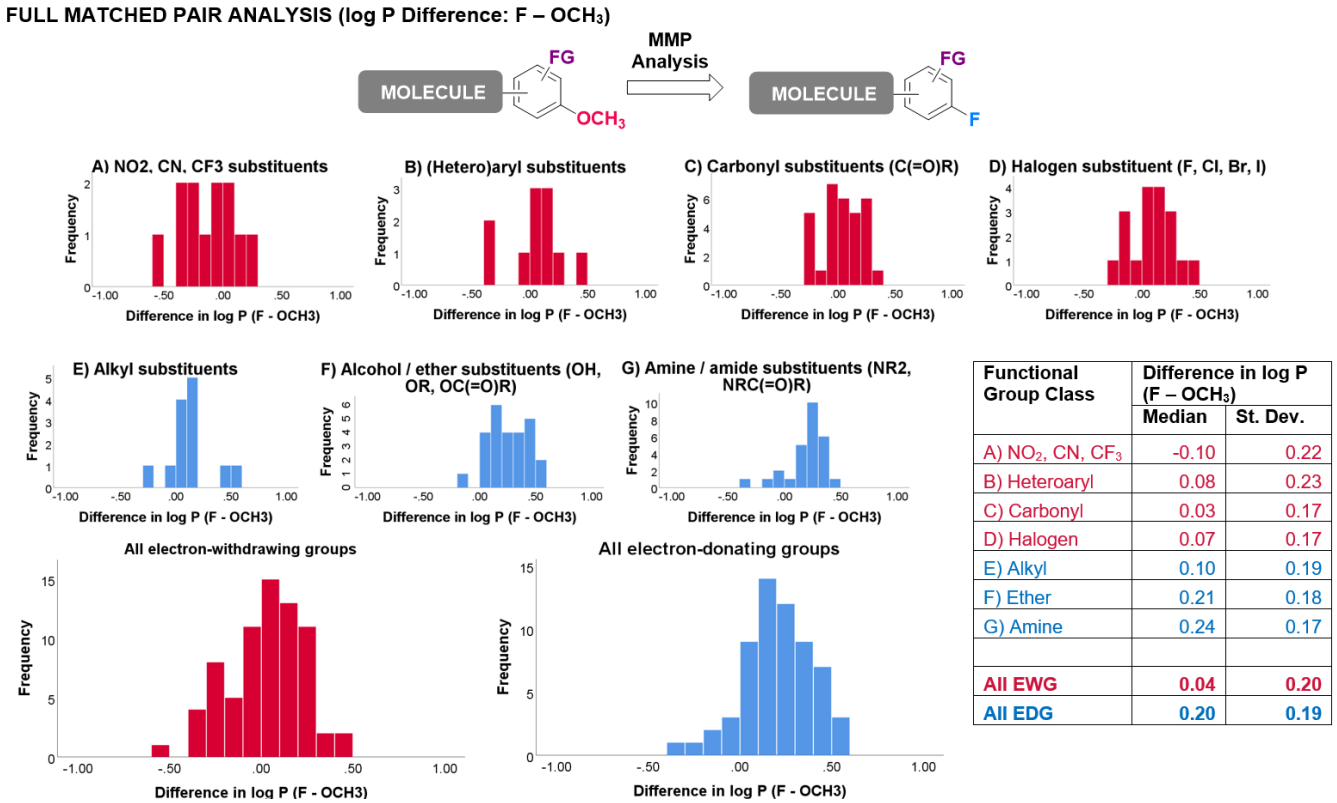
Ortho-substituted carbonyl compounds show the largest decreases in log P on transformation of a phenol to its aryl fluoride matched pair (up to -0.7 log P units). This is made up from a moderate to large increase in log P on hydroxylation, which is compounded by a small decrease in log P on fluorination for esters, amides and carboxylic acids to give an overall large decrease in log P on transformation of OH to F. For aldehydes and ketones, fluorination leads to an increase in log P making the overall change from transforming OH to F much smaller.

The log P increase behavior of *ortho*-substituted carbonyl compounds is due to the formation of a particularly strong



Functional Group Class	Difference in log P (F – OH)	
	Median	St. Dev.
A) NO_2, CN, CF_3	-0.06	0.33
B) (Hetero)aryl	0.25	0.35
C) Carbonyl	0.38	0.41
D) Halogen	0.39	0.26
E) Alkyl	0.70	0.31
F) Ether	0.83	0.26
G) Amine	0.92	0.32
All EWG	**0.35**	**0.37**
All EDG	**0.87**	**0.32**

Figure 6: Histograms representing matched pair analysis for functional group classes showing difference in log P (F – OH)



Functional Group Class	Difference in log P (F – OCH_3)	
	Median	St. Dev.
A) NO_2, CN, CF_3	-0.10	0.22
B) Heteroaryl	0.08	0.23
C) Carbonyl	0.03	0.17
D) Halogen	0.07	0.17
E) Alkyl	0.10	0.19
F) Ether	0.21	0.18
G) Amine	0.24	0.17
All EWG	**0.04**	**0.20**
All EDG	**0.20**	**0.19**

Figure 7: Histograms representing matched pair analysis for functional group classes showing difference in log P (F – OCH_3)

intramolecular hydrogen bond between the phenolic O-H (donor) and carbonyl oxygen (acceptor). This increases the log P of the phenol considerably as the six-membered hydrogen-bonded complex is stabilized by resonance, which reduces its polarizability.[51, 52]

We then wished to investigate how the rules and effects we had established and observed applied to a broader series of more complex drug-like molecules, so performed an analysis on our full series of F / OH matched pair compounds. These were grouped into classes based on the functional groups present, and for each class of compounds a histogram was produced based on the frequency of compounds in that class, showing different log P changes on transformation of O to F. This analysis was performed on our OH – F (Figure 6) and OCH_3 – F (Figure 7) datasets.

This showed results that were aligned with the trends we observed with the disubstituted systems. Looking first at the hydroxylated comparison (Figure 6) we see that the median increase of log P on fluorination is much lower for compounds bearing an electron-withdrawing group (+0.35 log P units) than those bearing an electron-donating group (+0.87 log P units). This pattern is repeated for the methoxylated compounds (median Δlog P +0.04 EWG vs. + 0.20 EDG), although the effect is less pronounced (Fig. 7).

Classifying the functional groups further into categories similar to those described above (i.e strong EWG (NO_2, CN, CF_3); hetero(aryl); carbonyl; halogen; alkyl; ether / alcohol; amine / amide) gave data series that were spread by a similar standard deviation in each case, demonstrating their similar effects. The order of these categories was similar to that of categories i)-v) above (i.e hydrogen-bond accepting EDG (i.e. OR, NR_2 > non-hydrogen-bond accepting EDG (i.e alkyl) > carbonyl ~ halogen > stronger EWG (i.e. NO_2, CN, CF_3).

Our final goal was then to begin to understand better how multiple substitution on an aromatic ring would affect log P differences in more complex systems. To achieve this we performed a similar matched-pair analysis on a series of phenols / aryl fluorides with *two* additional substituents to examine how the effects of multiple functional groups would compete against each other (Figure 8). This data was again obtained from the literature and original values were measured using the shake-flask method.

Multiple electron-withdrawing groups showed an enhanced log P decrease effect. Di-nitro substituted system **41** showed a greater decrease in log P on fluorination than the mono-nitrated system (Δlog P -0.17 **41** vs. -0.11 **1-*para***), perhaps due to a further increased dipole moment. Similarly, nitration decreases the log P difference between a *para*-fluoro substituted system **42** (Δlog P -0.02 **42** vs. +0.36 **7-*para***), although it had little effect on an *ortho*-hydroxy system **43** (Δlog P +0.86 **43** vs. 0.83 **20-*ortho***).

Comparison of compounds **44** and **45** demonstrates further the effects of an *ortho*-carbonyl group. Compound **44**, with an *ortho*-carboxylic acid, shows a much smaller difference in log P than compound **45** in which the carbonyl group is not *ortho* to the phenol / fluoro substituent (Δlog P +0.40 **44** vs. +0.91 **45**), again likely due to intramolecular hydrogen bonding. Compound **46**

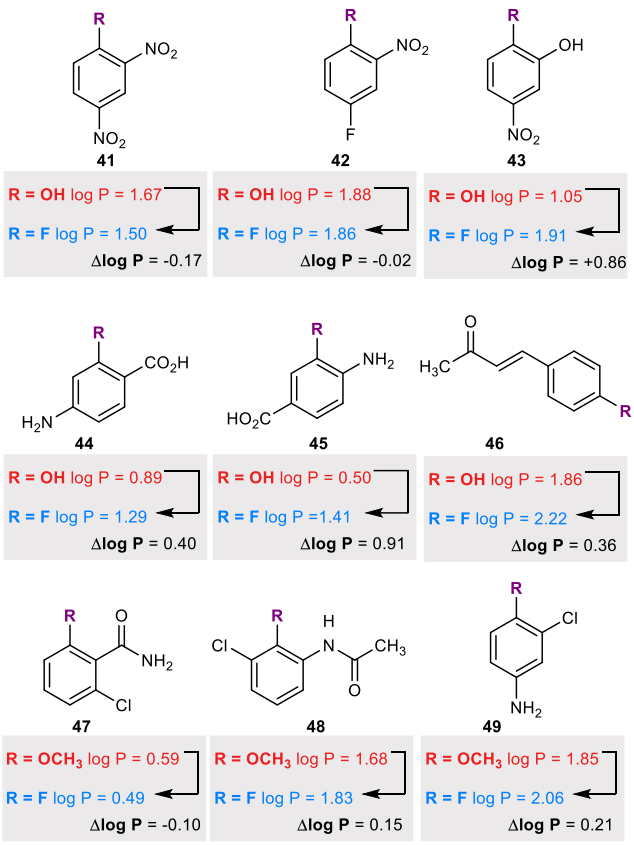


Figure 8: Multi-substituted systems

demonstrates that conjugation of a carbonyl group to an aromatic ring through an alkene leads to a similar effect as a non-π-extended ketone substituent (Δlog P +0.36 **46** vs +0.37 **8-*para***), further supporting the assertion that this log P difference effect is mainly electronic in nature.

Compounds **47-49** show how an electron-withdrawing chlorine substituent can modulate the effect of amide and amine substituents. Chlorination decreases the effect of an *ortho*-amide substituent through reducing the strength of an intramolecular hydrogen bond (Δlog P -0.10 **47** vs -0.27 **31-*ortho***). It also modulates the effect of an electron-donating nitrogen substituent (Δlog P +0.15 **48** vs +0.36 **39-*ortho***), although showed much less effect on a *para*-amino substituent (Δlog P +0.21 **49** vs +0.20 **35-*para***)

We then wanted to see whether these rules applied to a broader series of more complex drug-like molecules (Figure 9). We found in the patent literature a series of thiazolyl-pyrimidine compounds bearing OH / F matched pairs on an aromatic ring, which had been developed during the lead optimization of a fungicide.[53] These compounds all had an experimentally measured log P value (determined by the shake-flask method). All of these compounds had an amine substituent *para* to the OH / F group. For the 9 compounds **50-58** the difference in log P between the OH and F analogues ranged from +0.60 to +1.40 log P units. The mean increase (+1.05 log P units) was in line with what we observed for the *para*-amino system **19-*para***, however the range we observed

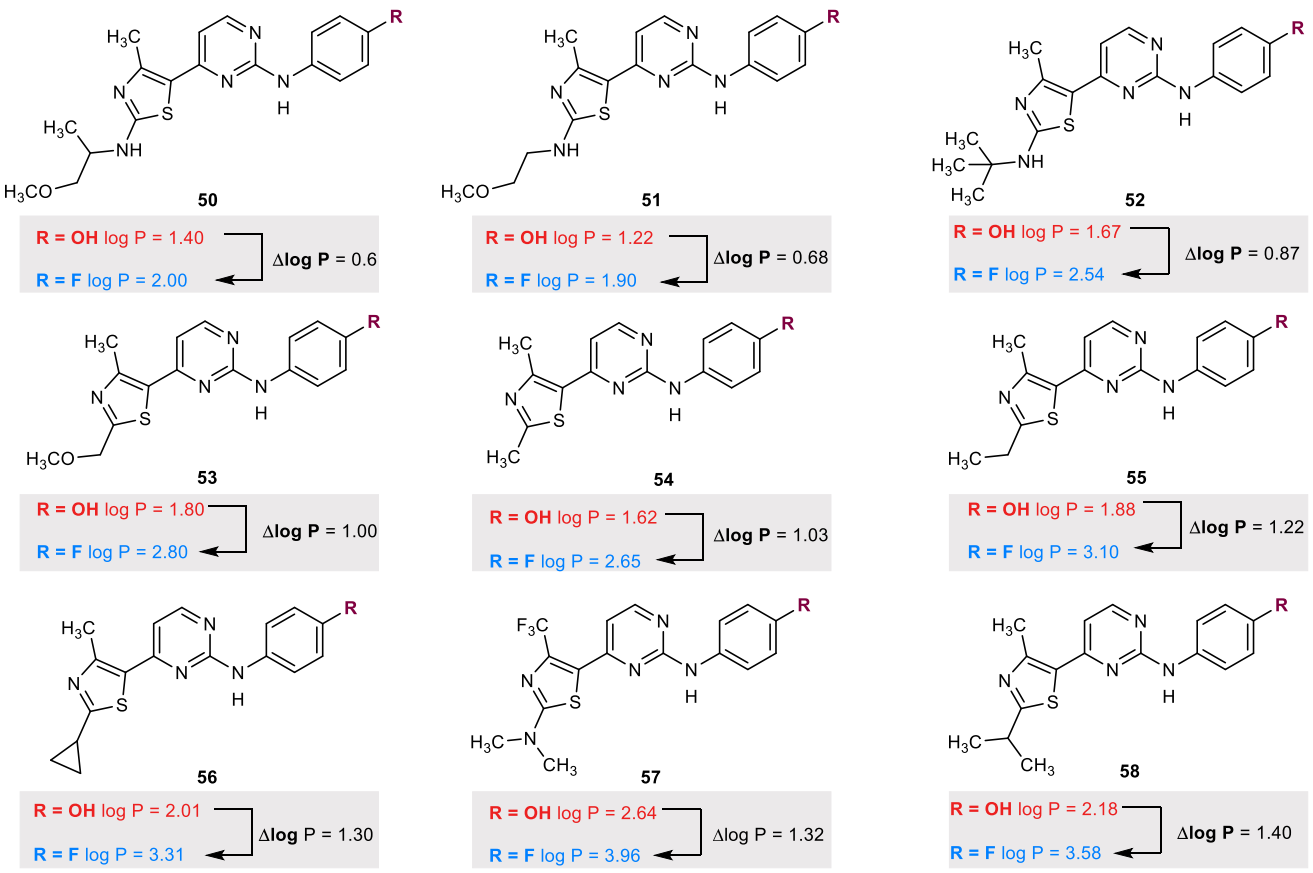


Figure 9: log P data for matched F / OH pairs in thiazolyl-pyrimidine fungicide molecules

was relatively large given that all the phenols would be expected to be electronically very similar.

We looked to hydrogen-bonding characteristics to explain these differences in results. Compounds **50-52** have a much smaller difference in log P (+0.60 to +0.87 log P units) than others in the series. Compounds **50-52** have an additional contribution to hydrogen bonding from a pendent side-chain containing an amine functional group, which will be a strong hydrogen-bond acceptor. This makes the overall contribution of the phenol to hydrogen bonding in **50-52** less important than in compounds **54-56** and **58** which have no functionality capable of hydrogen-bonding in their side chains. This both makes the phenol in **50-52** less important to overall solubility, and also makes their fluorinated matched pair more water soluble than might otherwise be predicted as fluorine's non-polarizability can be compensated for by a hydrogen bonding substituent elsewhere in the molecule. Overall, these additional hydrogen-bond acceptor groups decrease the difference between the log P of the phenol and aryl fluoride matched pair. Compounds **53** with an ether-containing side-chain shows a larger OH-F matched pair difference in log P (+1.00 log P units) relative to the amine-containing side chains **50-52**. This may be because the ether will be a weaker additional hydrogen-bond acceptor than the amine substituents, so make a smaller relative contribution to decreasing the log P of the aryl fluoride compound.

Compounds **57** shows a large difference in log P (+1.32 log P units) between the phenol and aryl fluoride, despite the presence of a hydrogen-bond acceptor amine in the side chain. There could be two potential reasons for this. Firstly, the trifluoromethyl substituent present in the aromatic ring may act as a powerful electron-withdrawing group to diminish the hydrogen-bond acceptor capability of the amine substituent, meaning there are effectively no other hydrogen-bond acceptor groups to compensate for the low polarizability of the fluorine atom. Alternatively, the trifluoromethyl substituent in **57** may be acting as a second region of low polarizability which disproportionately reduces the aqueous solubility of the already non-polarizable aryl fluoride relative to the more polarizable phenol.

We then examined how well the Δlog P rules we had established applied to other complex drug-like molecules for which lipophilicity data of matched OH / F pairs was available in the literature (Figure 10). Aryl-thiazolones **59** showed a relatively small log P difference of +0.33 log P units, to be expected as the phenol is conjugated to an electron-withdrawing carbonyl-containing thiazolone unit.[54] Similarly, potential anticonvulsant **60** bearing an electron-withdrawing imine unit had a moderate log P difference of +0.44.[55] On the other hand, dual D_2-receptor/β_2-adrenoceptor agonists for the treatment of chronic obstructive pulmonary disease **61** gave a larger log P difference of +0.76 log P units between the phenol and aryl fluoride as these substituents are on an aromatic ring bearing an electron-donating alkyl substituent.[56]

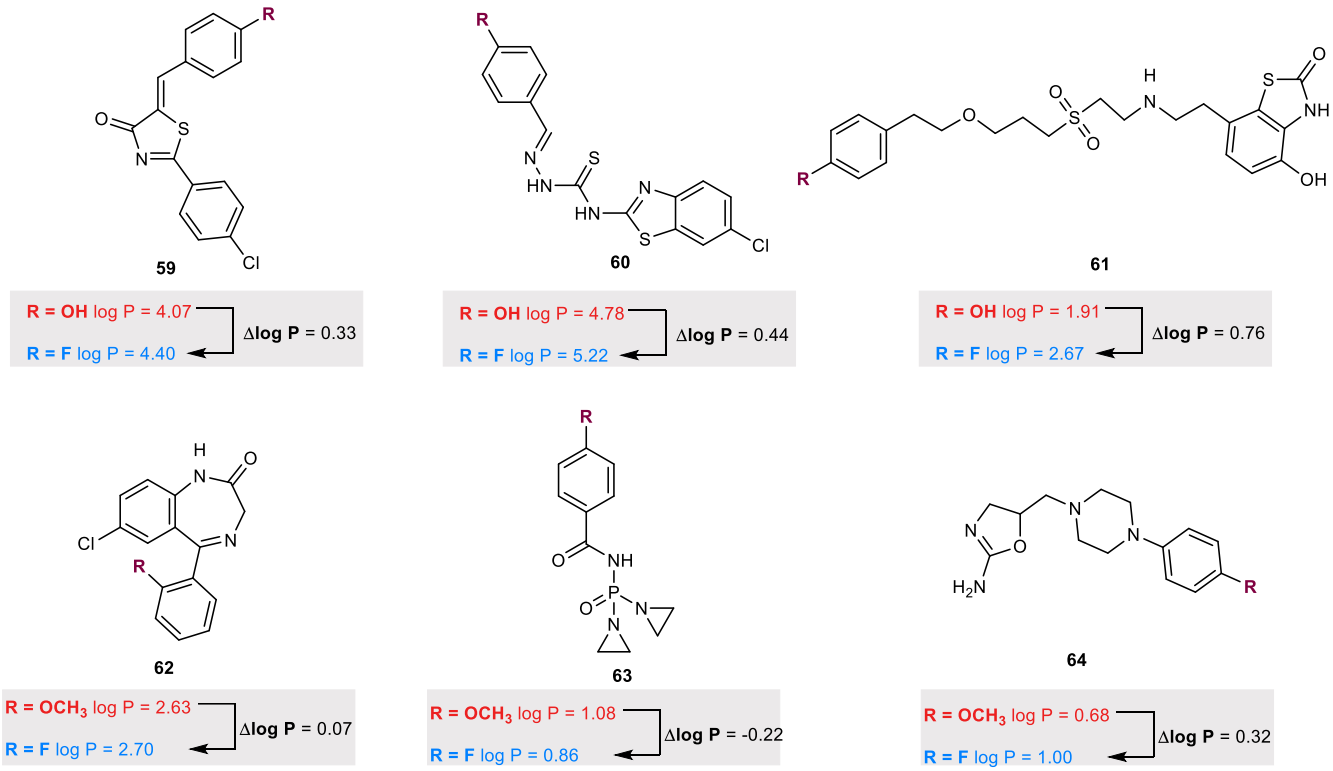


Figure 10: log P data for matched F / OH and F / OCH_3 pairs in assorted drug-like molecules

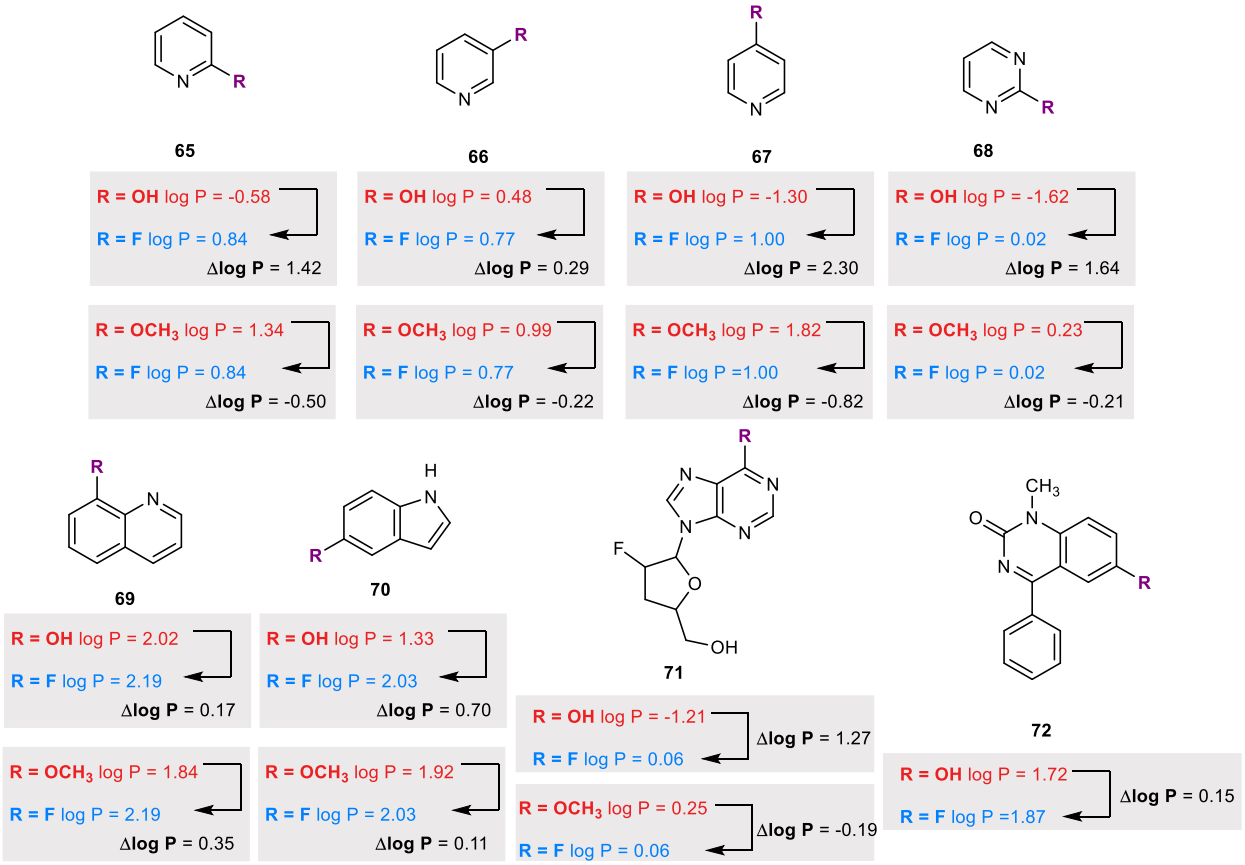


Figure 11: log P data for matched F / OH and F / OCH_3 pairs in heterocyclic molecules

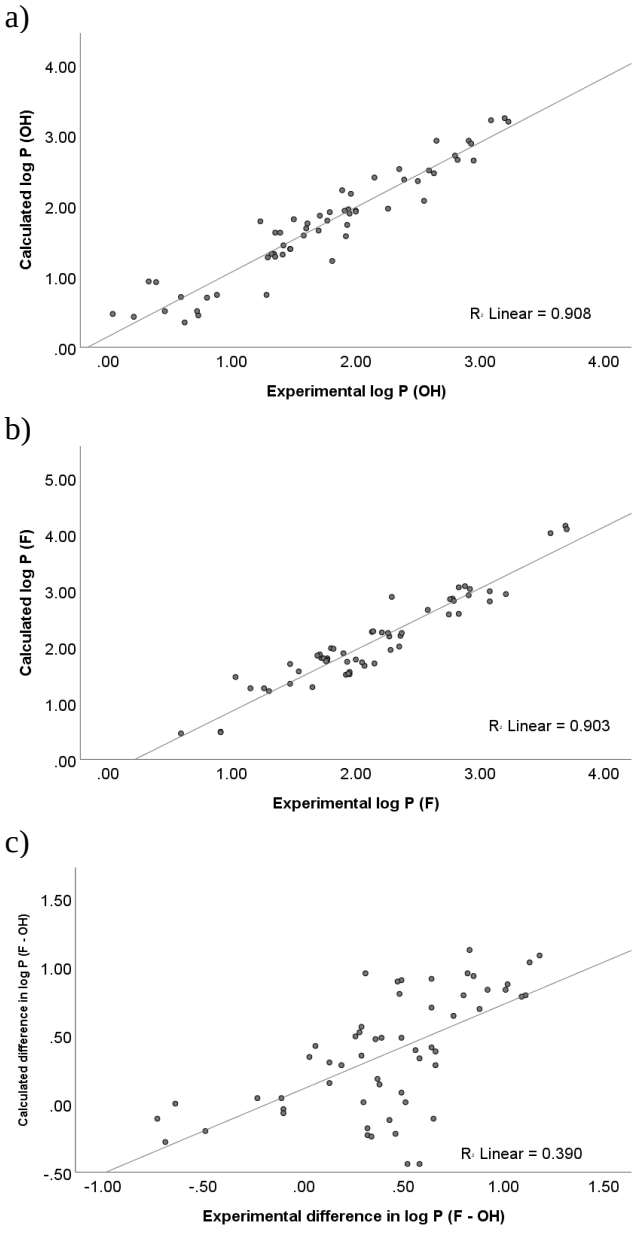


Figure 12: Comparing experimental and calculated log P values for a) phenols; b) aryl fluorides; c) difference between F - OH

When comparing methoxy substituents to fluoro in more complex systems, benzodiazepine **62** showed a log P difference of +0.07 log P units, relatively small due to conjugation to a C=N unit in the benzodiazepine ring.[57] Derivative **63** bearing a more strongly electron-withdrawing amide substituent showed a negative change in log P on transformation from OCH_3 to F of -0.22 log P units.[58] Oxazolyl-piperidine compounds **64** gave a much larger log P difference of +0.32 log P units due to the presence of a *para*-amine substituent on the aromatic ring.[59]

Finally, we chose to examine log P differences of some heterocyclic derivatives (Figure 11). Pyridine derivatives showed some very interesting trends. For 2-substituted pyridines **65** the fluoro-compound was significantly more lipophilic than the hydroxy-compound (Δlog P +1.42), yet this was reversed between 2-methoxy and 2-fluoropyridine with the methoxy compound being more lipophilic (Δlog P -0.50). This trend was further exacerbated in the 4-substituted pyridine derivatives **67**, which showed an even larger increase on transformation of the hydroxy-compound to the fluoro-compound (Δlog P +2.30), but a decrease on fluorination of the methoxy compound (Δlog P -0.82). However, these differences were nowhere near as pronounced for the 3-substituted pyridines **66**, (F – OH Δlog P = +0.29 log P units, F – OCH_3 Δlog P = -0.22).

It seems likely that these differences are being controlled by the ability of 2- and 4-hydroxypyridines to exist as a pyridone tautomer, which have significantly lower log P values (compare 2-hydroxypyridine **65-OH** Δlog P = -0.58 to 3-hydroxypyridine **66-OH** Δlog P = +0.48). The formation of a pyridone tautomer is not possible for methoxy- or 3-substituted systems. This reduced lipophilicity of pyridone tautomers was previously observed in work by Altomare.[60]

Pyrimidine **68** showed a large increase in log P on fluorination of the hydroxy compound, but a small decrease on fluorination of the methoxy compound. Similarly to **65** and **67**, this compound can form a pyrimidone tautomer. On the other hand, 8-substituted quinoline **69**, which is fluorinated / oxygenated on the benzenoid ring and cannot form pyridone-like tautomers shows only a small increase in lipophilicity on fluorination. Indole **70**, which is a more electron-rich ring system than quinoline **69** shows a larger increase in log P on fluorination, perhaps reflecting a larger hydrogen-bond acceptor capability of the phenol than in the less-electron-rich quinoline **69**.

These rules are again transferable to more complex molecules. Purine-based system **71** shows a large increase in log P on transformation from OH to F (Δlog P +1.27), reflective of an ability to form a pyridone-like tautomer. On the other hand, this compound shows a small decrease in log P on transformation from OCH_3 to F, perhaps due to the electron-deficient nature of this ring system. Pyrimidine **72**, which is fluorinated / hydroxylated on the benzenoid ring, shows a much smaller difference in log P between its OH and F analogues (Δlog P +0.15).

We finally looked to determine the accuracy of various log P calculators in assessing log P differences between oxygen and fluorinated bioisosteres. Several calculators, including ChemDraw, clog P, milog P and xlog P did not take any account of functionality when calculating the difference in log P between a phenol and an aryl fluoride, and gave a constant result for the difference. The Alog P calculator however,[61-63] did give different results for the Δlog P between an oxygen and fluorinated matched pair depending on functionality elsewhere in the molecule, so became our focus for further analysis (Figure 12). To determine whether this calculator is likely to be useful for estimating the effect of an oxygen / fluorine replacement on log P we compared the results for our disubstituted systems highlighted in figure 2 to calculated values. However, whilst a plot of experimental log P against calculated Alog P gave a reasonably good correlation for both phenols and aryl fluorides independently (Figure 12a/b), a plot of experimental and

calculated Δlog P values gave almost no correlation (Figure 12c). This would suggest that the majority of commonly-used log P calculators cannot be relied upon to accurately predict the difference between oxygen and fluorinated bioisosteres.

Conclusion

We have compared the lipophilicities of substituted phenols and anisoles with their corresponding aryl fluorides, using a Molecular Matched Pair Analysis. This is a common bioisosteric replacement used during drug design. Our analysis has revealed several factors which appear to be important in the difference in log P between an oxygen and fluorinated bioisostere.

Perhaps most important is the electronic character of any other substituents present on the ring. Electron-donating substituents increase the hydrogen bond acceptor capability of a phenol, whilst having a much smaller effect on intermolecular forces in aryl fluorides. This leads to a large increase in log P on fluorination of electron-rich systems.

On the other hand, electron-withdrawing substituents weaken phenols as hydrogen bond acceptors, whilst simultaneously increasing water solubility of aryl fluorides through increasing polarity. This gives a much smaller increase in log P on fluorination of electron-poor systems, or even a decrease in some cases.

The ability to participate in intramolecular hydrogen bonding is also a key factor in determining log P differences between oxygen and fluorine bioisosteres. Phenols which can act as an intramolecular hydrogen bond donor, particularly where a carbonyl group acts as acceptor, show anomalously high lipophilicity, making these compounds often more lipophilic than their fluorinated matched pair.

In more complex molecules, the presence of additional hydrogen bond acceptor sites reduce the net importance of the phenol / fluoro substituent to overall solubility of the molecule and reduce the difference in log P between oxygen and fluorine bioisosteres. On the other hand, the inclusion of groups of low polarizability disproportionately decrease the water solubility of a fluorinated compound in a O / F matched pair and increase the log P difference between them.

Of course, the majority of drug discovery programmes involve making acidic or basic molecules in which protonation state will affect a partition coefficient. It may be expected that fluorination would increase the acidity of an acidic compound, lowering its log D relative to a hydroxy-substituted compound. On the other hand, fluorination could decrease the basicity of a basic compound, making the difference in log D between the hydroxy- and fluorinated compounds larger at physiological pH. These effects are likely to be compound dependent, and more work is needed to understand the effects of fluorination on log D of ionizable drug-like compounds.

This work has set out a series of empirical rules which affect the difference in lipophilicity between oxygen and fluorinated bioisosteres. We hope that it will be useful in rational drug design when this common bioisosteric replacement is made during a drug discovery program.

Experimental section

Log P determination: log P values that were not available in the literature were determined using an HPLC method.

The HPLC data was obtained on a Agilent 1100 series, fitted with a reverse-phase Sphereclone 5μm ODS(2) 80Å column (Length 150mm, diameter 4.6 mm; Flow rate 1 ml / min, temperature 20°C). The eluent used was MeCN : H_2O (60:40).

A calibration plot was produced for each run using compounds of known log P and of a similar (aromatic) structure: (Phenol, 2-Fluorophenol, Toluene, o-Xylene, Naphthalene, Cumene, t-Butylbenzene, Anthracene, Pyrene). Their retention times were measured using the HPLC conditions stated above, and then log (retention time) was plotted against log P to obtain a linear plot. This linear plot was then used to determine the unknown log P values of the compounds of interest after their HPLC retention times were measured.

See Supporting Information for full details on HPLC retention times and log P data.

ASSOCIATED CONTENT

Supporting Information. Details on log P determination using HPLC. Molecular formula strings in SMILES format. This material is available free of charge via the Internet at http://pubs.acs.org.

Abbreviations Used. HPLC, High pressure liquid chromatography; IC_{50}, Half-maximal inhibitory concentration; log P, Partition coefficient; Δlog P, Difference in partition coefficients; MMPA, Molecular matched pair analysis; r^2, Correlation coefficient.

AUTHOR INFORMATION

Corresponding Author

* Graham Pattison - Chemistry Research and Enterprise Group, School of Pharmacy and Biomolecular Sciences, University of Brighton, Lewes Road, Brighton, UK. BN2 4GJ.
Email: g.pattison@brighton.ac.uk

Author Contributions

The manuscript was written through contributions of all authors.

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REFERENCES

1. Meanwell, N. A., Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design. *J. Med. Chem* **2011,** *54,* 2529-2591.

2. Meanwell, N. A., Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem* **2018,** *61,* 5822-5880.

3. Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A., Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem* **2015,** *58,* 8315-8359.

4. Müller, K.; Faeh, C.; Diederich, F., Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science* **2007,** *317,* 1881.

5. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V., Fluorine in Medicinal Chemistry. *Chem. Soc. Rev.* **2008,** *37*, 320-330.

6. Inoue, M.; Sumii, Y.; Shibata, N., Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020,** *5*, 10633-10640.

7. Han, J.; Remete, A. M.; Dobson, L. S.; Kiss, L.; Izawa, K.; Moriwaki, H.; Soloshonok, V. A.; O'Hagan, D., Next Generation Organofluorine Containing Blockbuster Drugs. *J. Fluorine Chem.* **2020,** *239*, 109639.

8. Park, B. K.; Kitteringham, N. R.; O'Neill, P. M., Metabolism of Fluorine-Containing Drugs. *Annu. Rev. Pharmacool. Toxicol.* **2001,** *41*, 443-470.

9. O'Neill, P. M.; Harrison, A. C.; Storr, R. C.; Hawley, S. R.; Ward, S. A.; Park, B. K., The Effect of Fluorine Substitution on the Metabolism and Antimalarial Activity of Amodiaquine. *J. Med. Chem* **1994,** *37*, 1362-1370.

10. Arnott, J. A.; Planey, S. L., The Influence of Lipophilicity in Drug Discovery and Design. *Expert Opin. Drug Discov.* **2012,** *7*, 863-875.

11. Gleeson, M. P.; Hersey, A.; Montanari, D.; Overington, J., Probing the Links between in vitro Potency, ADMET and Physicochemical parameters. *Nat. Rev. Drug Discov.* **2011,** *10*, 197-208.

12. Johnson, T. W.; Gallego, R. A.; Edwards, M. P., Lipophilic Efficiency as an Important Metric in Drug Design. *J. Med. Chem* **2018,** *61*, 6401-6420.

13. Waring, M. J., Lipophilicity in drug discovery. *Expert Opin. Drug Discov.* **2010,** *5*, 235-248.

14. Linclau, B.; Wang, Z.; Compain, G.; Paumelle, V.; Fontenelle, C. Q.; Wells, N.; Weymouth-Wilson, A., Investigating the Influence of (Deoxy)fluorination on the Lipophilicity of Non-UV-Active Fluorinated Alkanols and Carbohydrates by a New log P Determination Method. *Angew. Chem. Int. Ed.* **2016,** *55*, 674-678.

15. Jeffries, B.; Wang, Z.; Graton, J.; Holland, S. D.; Brind, T.; Greenwood, R. D. R.; Le Questel, J.-Y.; Scott, J. S.; Chiarparin, E.; Linclau, B., Reducing the Lipophilicity of Perfluoroalkyl Groups by CF2–F/CF2–Me or CF3/CH3 Exchange. *J. Med. Chem* **2018,** *61*, 10602-10618.

16. Jeffries, B.; Wang, Z.; Felstead, H. R.; Le Questel, J.-Y.; Scott, J. S.; Chiarparin, E.; Graton, J.; Linclau, B., Systematic Investigation of Lipophilicity Modulation by Aliphatic Fluorination Motifs. *J. Med. Chem* **2020,** *63*, 1002-1031.

17. Troup, R. I.; Jeffries, B.; Saudain, R. E.-B.; Georgiou, E.; Fish, J.; Scott, J. S.; Chiarparin, E.; Fallan, C.; Linclau, B., Skipped Fluorination Motifs: Synthesis of Building Blocks and Comparison of Lipophilicity Trends with Vicinal and Isolated Fluorination Motifs. *J. Org. Chem.* **2021,** *86*, 1882-1900.

18. Rodil, A.; Bosisio, S.; Ayoup, M. S.; Quinn, L.; Cordes, D. B.; Slawin, A. M. Z.; Murphy, C. D.; Michel, J.; O'Hagan, D., Metabolism and Hydrophilicity of the Polarised 'Janus face' all-cis Tetrafluorocyclohexyl Ring, a Candidate Motif for Drug Discovery. *Chem, Sci.* **2018,** *9*, 3023-3028.

19. Tomita, R.; Al-Maharik, N.; Rodil, A.; Bühl, M.; O'Hagan, D., Synthesis of Aryl α,α-Difluoroethyl Thioethers: a Novel Structure Motif in Organic Chemistry, and Extending to Aryl α,α-Difluoro Oxyethers. *Org. Biomol. Chem.* **2018,** *16*, 1113-1117.

20. Fang, Z.; Cordes, D. B.; Slawin, A. M. Z.; O'Hagan, D., Fluorine Containing Cyclopropanes: Synthesis of Aryl Substituted all-cis 1,2,3-Trifluorocyclopropanes, a Facially Polar Motif. *Chem. Commun.* **2019,** *55*, 10539-10542.

21. Huchet, Q. A.; Kuhn, B.; Wagner, B.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Müller, K., On the Polarity of Partially Fluorinated Methyl Groups. *J. Fluorine Chem.* **2013,** *152*, 119-128.

22. Huchet, Q. A.; Kuhn, B.; Wagner, B.; Kratochwil, N. A.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Müller, K., Fluorination Patterning: A Study of Structural Motifs That Impact Physicochemical Properties of Relevance to Drug Discovery. *J. Med. Chem* **2015,** *58*, 9041-9060.

23. Vorberg, R.; Trapp, N.; Zimmerli, D.; Wagner, B.; Fischer, H.; Kratochwil, N. A.; Kansy, M.; Carreira, E. M.; Müller, K., Effect of Partially Fluorinated N-Alkyl-Substituted Piperidine-2-carboxamides on Pharmacologically Relevant Properties. *ChemMedChem* **2016,** *11*, 2216-2239.

24. Huchet, Q. A.; Trapp, N.; Kuhn, B.; Wagner, B.; Fischer, H.; Kratochwil, N. A.; Carreira, E. M.; Müller, K., Partially Fluorinated Alkoxy Groups – Conformational Adaptors to Changing Environments. *J. Fluorine Chem.* **2017,** *198*, 34-46.

25. Fox, M. A.; Pattison, G.; Sandford, G.; Batsanov, A. S., 19F and 13C GIAO-NMR Chemical Shifts for the Identification of Perfluoro-quinoline and -isoquinoline Derivatives. *J. Fluorine Chem.* **2013,** *155*, 62-71.

26. Pattison, G., Fluorination of Organoboron Compounds. *Org. Biomol. Chem.* **2019,** *17*, 5651-5660.

27. Pattison, G.; Sandford, G.; Wilson, I.; Yufit, D. S.; Howard, J. A. K.; Christopher, J. A.; Miller, D. D., Polysubstituted and Ring-fused Pyridazine Systems from Tetrafluoropyridazine. *Tetrahedron* **2017,** *73*, 437-454.

28. Pattison, G.; Sandford, G.; Yufit, D. S.; Howard, J. A. K.; Christopher, J. A.; Miller, D. D., N-Functionalised Polyfluoropyridazin-3(2H)-one Derivatives. *Tetrahedron* **2009,** *65*, 8844-8850.

29. Pattison, G.; Sandford, G.; Yufit, D. S.; Howard, J. A. K.; Christopher, J. A.; Miller, D. D., 9,10-Dioxa-1,2-diaza-anthracene Derivatives from Tetrafluoropyridazine. *Beilstein J. Org. Chem.* **2010,** *6*, 45.

30. Pinfold, H.; Greenland, C.; Pattison, G.; Costantini, G., Fluorinated Carboxylic Acids as Powerful Building Blocks for the Formation of Bimolecular Monolayers. *Chem. Commun.* **2020,** *56*, 125-128.

31. Pinfold, H.; Pattison, G.; Costantini, G., Fluorination as a Route Towards Unlocking the Hydrogen Bond Donor Ability of Phenolic Compounds in Self-Assembled Monolayers. *CrystEngComm* **2020,** *22*, 2425-2428.

32. Dossetter, A. G.; Griffen, E. J.; Leach, A. G., Matched Molecular Pair Analysis in Drug Discovery. *Drug Discov. Today* **2013,** *18*, 724-731.

33. Wassermann, A. M.; Bajorath, J., Large-scale Exploration of Bioisosteric Replacements on the Basis of Matched Molecular pairs. *Future Med. Chem.* **2011,** *3*, 425-436.

34. Griffen, E.; Leach, A. G.; Robb, G. R.; Warner, D. J., Matched Molecular Pairs as a Medicinal Chemistry Tool. *J. Med. Chem* **2011,** *54*, 7739-7750.

35. Papadatos, G.; Alkarouri, M.; Gillet, V. J.; Willett, P.; Kadirkamanathan, V.; Luscombe, C. N.; Bravi, G.; Richmond, N. J.; Pickett, S. D.; Hussain, J.; Pritchard, J. M.; Cooper, A. W. J.; Macdonald, S. J. F., Lead Optimization Using Matched Molecular Pairs: Inclusion of Contextual Information for Enhanced Prediction of hERG Inhibition, Solubility, and Lipophilicity. *J. Chem. Inf. Model.* **2010,** *50*, 1872-1886.

36. Sangster, J., Octanol-Water Partition Coefficients of Simple Organic Compounds. *J. Phys. Chem. Ref. Data* **1989,** *18*, 1111-1229.

37. C. Hansch; A. Leo; Hoekman, D., In *Exploring QSAR – Hydrophobic, Electronic, and Steric Constants*, American Chemical Society,: Washington, DC, 1995.

38. von der Ohe, P. C.; Kühne, R.; Ebert, R.-U.; Altenburger, R.; Liess, M.; Schüürmann, G., Structural Alerts - A New Classification Model to Discriminate Excess Toxicity from Narcotic Effect Levels of Organic Compounds in the Acute Daphnid Assay. *Chem. Res. Toxicol.* **2005,** *18*, 536-555.

39. Du, C. M.; Valko, K.; Bevan, C.; Reynolds, D.; Abraham, M. H., Rapid Gradient RP-HPLC Method for Lipophilicity Determination: A Solvation Equation Based Comparison with Isocratic Methods. *Anal. Chem.* **1998,** *70*, 4228-4234.

40. Terada, H., Determination of Log Poct by High-Performance Liquid Chromatography, and its Application in the Study of Quantitative Structure-Activity Relationships. *Quant. Struct.-Act. Relat.* **1986,** *5*, 81-88.

41. Abraham, M. H.; Chadha, H. S.; Whiting, G. S.; Mitchell, R. C., Hydrogen Bonding. 32. An Analysis of Water-Octanol and Water-Alkane Partitioning and the Δlog P Parameter of Seiler. *J. Pharm. Sci.* **1994,** *83*, 1085-1100.

42. Howard, J. A. K.; Hoy, V. J.; O'Hagan, D.; Smith, G. T., How Good is Fluorine as a Hydrogen Bond Acceptor? *Tetrahedron* **1996,** *52,* 12613-12622.

43. Dunitz, J. D.; Taylor, R., Organic Fluorine Hardly Ever Accepts Hydrogen Bonds. *Chem. Eur. J.* **1997,** *3,* 89-98.

44. O'Hagan, D., Understanding Organofluorine Chemistry. An Introduction to the C–F Bond. *Chem. Soc. Rev.* **2008,** *37,* 308-319.

45. Schneider, H.-J., Hydrogen Bonds with Fluorine. Studies in Solution, in Gas Phase and by Computations, Conflicting Conclusions from Crystallographic Analyses. *Chem, Sci.* **2012,** *3,* 1381-1394.

46. Panini, P.; Chopra, D., Experimental and Theoretical Characterization of Short H-Bonds with Organic Fluorine in Molecular Crystals. *Cryst. Growth Des.* **2014,** *14,* 3155-3168.

47. Struble, M. D.; Kelly, C.; Siegler, M. A.; Lectka, T., Search for a Strong, Virtually "No-Shift" Hydrogen Bond: A Cage Molecule with an Exceptional OH···F Interaction. *Angew. Chem. Int. Ed.* **2014,** *53,* 8924-8928.

48. Champagne, P. A.; Desroches, J.; Paquin, J.-F., Organic Fluorine as a Hydrogen-Bond Acceptor: Recent Examples and Applications. *Synthesis* **2015,** *47,* 306-322.

49. Taylor, R., The Hydrogen Bond between N-H or O-H and Organic Fluorine: Favourable Yes, Competitive No. *Acta Crystallogr. B Struct. Sci. Cryst.* **2017,** *73,* 474-488.

50. Chopra, D., Is Organic Fluorine Really "Not" Polarizable? *Cryst. Growth Des.* **2012,** *12,* 541-546.

51. Kuhn, B.; Mohr, P.; Stahl, M., Intramolecular Hydrogen Bonding in Medicinal Chemistry. *J. Med. Chem* **2010,** *53,* 2601-2611.

52. Chen, D.; Zhao, M.; Tan, W.; Li, Y.; Li, X.; Li, Y.; Fan, X., Effects of Intramolecular Hydrogen Bonds on Lipophilicity. *Eur. J. Pharm. Sci.* **2019,** *130,* 100-106.

53. THIAZOLES AS FUNGICIDES. US2009/30024, 2009.

54. Shrivastava, S. K.; Patel, B. K.; Tripathi, P. N.; Srivastava, P.; Sharma, P.; Tripathi, A.; Seth, A.; Tripathi, M. K., Synthesis, Evaluation and Docking Studies of some 4-Thiazolone Derivatives as Effective Lipoxygenase Inhibitors. *Chem. Pap.* **2018,** *72,* 2769-2783.

55. Amir, M.; Asif, S.; Ali, I.; Hassan, M. Z., Synthesis of Benzothiazole Derivatives having Acetamido and Carbothioamido Pharmacophore as Anticonvulsant Agents. *Med. Chem. Res.* **2012,** *21,* 2661-2670.

56. Austin, R. P.; Barton, P.; Bonnert, R. V.; Brown, R. C.; Cage, P. A.; Cheshire, D. R.; Davis, A. M.; Dougall, I. G.; Ince, F.; Pairaudeau, G.; Young, A., QSAR and the Rational Design of Long-Acting Dual D2-Receptor/β2-Adrenoceptor Agonists. *J. Med. Chem* **2003,** *46,* 3210-3220.

57. Seiler; Zimmermann, 5-Phenyl-1,3-dihydro-1,4-benzodiazepin-2-ones. Experimental Verification of Substituent Constants. *Arzneim.-Forsch.* **1983,** *33,* 1519 - 1522.

58. Kabankin, A. S.; Boldeskul, I. E.; Trinus, F. P.; Protsenko, L. D.; Landau, M. A., Physicochemical Characteristics, Antineoplastic Activity, and Quantitative Aspects of the Relationship of Structure and Biological Activity for Benzoyldiethylenetriamides of Phosphoric Acid. *Pharm. Chem. J.* **1982,** *16,* 626 - 632.

59. Jarry; Dubost; Pehourcq, Comparison of Lipophilic Parameters in a Series of 5-(1-Aryl-4-piperanzinyl)methyl-2-amino-2-oxazolines. *Pharm. Sci.* **1997,** *3,* 213 - 216.

60. de Candia, M.; Fossa, P.; Cellamare, S.; Mosti, L.; Carotti, A.; Altomare, C., Insights into Structure–Ativity Relationships from Lipophilicity Profiles of Pyridin-2(1H)-one Analogs of the Cardiotonic Agent Milrinone. *Eur. J. Pharm. Sci.* **2005,** *26,* 78-86.

61. Tetko, I. V.; Tanchuk, V. Y.; Villa, A. E. P., Prediction of n-Octanol/Water Partition Coefficients from PHYSPROP Database Using Artificial Neural Networks and E-State Indices. *J. Chem. Inform. Comput. Sci.* **2001,** *41,* 1407-1421.

62. Tetko, I. V.; Tanchuk, V. Y., Application of Associative Neural Networks for Prediction of Lipophilicity in ALOGPS 2.1 Program. *J. Chem. Inform. Comput. Sci.* **2002,** *42,* 1136-1145.

63. Tetko, I. V.; Poda, G. I., Application of ALOGPS 2.1 to Predict log D Distribution Coefficient for Pfizer Proprietary Compounds. *J. Med. Chem* **2004,** *47,* 5601-5604.

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