

Reducing the lipophilicity of perfluoroalkyl groups by CF₂-F/CF₂-Me or CF₃/CH₃ exchange

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Abstract.

Fluorination is commonly employed to optimize bioactivity and pharmaco-kinetic properties of drug candidates. Aliphatic fluorination often reduces the lipophilicity ($\log P$), but polyfluoroalkylation typically increases lipophilicity. Hence, identification of polyfluorinated motifs that nonetheless lead to similar or even reduced lipophilicities is of interest to expand the arsenal of medicinal chemistry tools in tackling properties such as compound metabolic stability or off target selectivity. We show that changing a CF₃-group of a perfluoroalkyl chain to a methyl group leads to a drastic reduction in lipophilicity. We also show that changing a C-F bond of a trifluoromethyl group, including when incorporated as part of a perfluoroalkyl group, to a C-Me group, leads to a reduction in $\log P$ despite the resulting chain elongation.

The observed lipophilicity trends were identified in perfluorinated alkanol models and reproduced when incorporated in analogues of a drug candidate, and the metabolic stability of these motifs was demonstrated.

Introduction.

The introduction of fluorine is a frequently used medicinal chemistry strategy to optimize the properties of bioactive compounds, including stability against oxidation and acid-mediated degradation processes, pK_a , conformations, hydrogen bonding capacity, lipophilicity and off target selectivity.¹⁻⁴ In addition, many synthetic bioisosteric groups have been designed based on the unique electronic and steric properties of fluorine.⁵⁻⁷ The vast majority of cases involve the introduction of fluorine, CF_2 - and CF_3 groups, as well as a range of heteroatom containing fluoroalkyl groups,⁸⁻⁹ with other types of groups such as pentafluorosulfanyl (SF_5) rapidly becoming more popular.^{7, 10}

There are very few polyfluoroalkyl containing drugs on the market (Chart 1).¹¹ Examples include the herbicide flupoxam¹² and the potent estrogen receptor antagonist fulvestrant.¹³⁻¹⁴ Analogues of fulvestrant with a 1,4-perfluorobutylidene group as part of a C11-sulfoxide containing side chain have been reported.¹⁵ Vilaprisan is a highly potent selective progesterone receptor modulator that was found to markedly reduce the growth of human leiomyoma tissue in a preclinical model of uterine fibroids, and is currently in phase II clinical trials for this indication.¹⁶⁻¹⁷ The Vitamin D₃ analogue pefcalcitol is currently being investigated as a more potent and more selective anti-psoriatic drug candidate.¹⁸

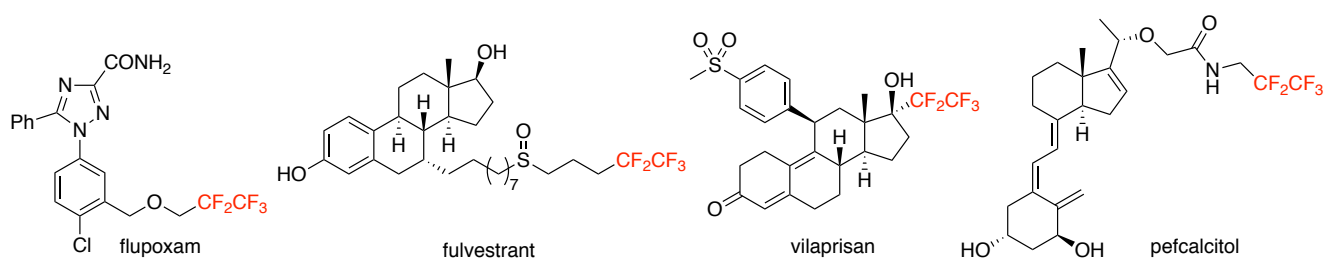


Chart 1. Perfluoroalkyl containing herbicide and anticancer drug, and drug candidates in clinical trials.

Incorporation of perfluorinated alkyl fragments typically increases the $\log P$ value. Incidentally, while by definition this represents an increase in lipophilicity, this may have less to do with an increased solubility into the octanol phase, than with a decrease in solubility for both phases, with a larger decrease in the water phase compared to that in the octanol phase.¹⁹ It has been estimated that a CF_2 group as part of a perfluoroalkyl chain is about 1.5 times more hydrophobic than a CH_2 group in an alkyl chain.²⁰ Interestingly, with respect to hydrophobic interactions with protein residues, alkyl and perfluoroalkyl groups were found to have the same mechanism of hydrophobicity, and any difference would be due to differences in hydrophobic surface area (and not to differences in dispersion interactions).²¹

Introduction of a perfluoroalkyl group to aromatic substrates generally leads to a larger $\log P$ increase compared to introduction of the equivalent alkyl group (Hansch hydrophobicity parameters for Me and CF_3 are 0.56 and 0.88; for Et and C_2F_5 1.02 and 1.23),²²⁻²³ although it is worth mentioning that this is not always the case, especially with partial fluorination of aromatic substituents.²⁴⁻²⁶ In contrast, the effect on the lipophilicity upon introducing a perfluoroalkyl group on an aliphatic chain is less clear-cut:² examples with CH_3/CF_3 exchange that lead to either $\log P$ reduction or $\log P$ increase have been reported.²⁷⁻²⁹ This is further illustrated by a systematic study of fluorinated alkanols (Figure 1), where it was shown that CH_3/CF_3 exchange next to an alcohol group leads to a large $\log P$ increase (eg **A1**→**A2**).³⁰⁻³¹ However, as the distance between the trifluorination site and the alcohol group increases, the $\Delta\log P$ becomes smaller, and quickly leads to a significant $\log P$ decrease (cf **E1**→**E2**). The same observation can be made for Et/ C_2F_5 exchange (cf **B1**→**B3**), although pentafluoropentan-1-ol **E3** is still more lipophilic than pentanol **E1**. The effect of fluorination on lipophilicity modulation has been attributed to the balance of competing effects, principally an increase in hydrophobic surface ($\log P$ increasing) and the introduction of a dipole moment ($\log P$ decreasing).^{29, 32} Hence, as already noted by Muller,²⁹ this clearly illustrates the context-dependency of the effect of fluorination on lipophilicity: the dipole effect of the trifluoromethyl or pentafluoroethyl groups are more prominent with increasing lipophilicity of the parent compound. This

context-dependence is also valid for higher polyfluorination: while heptafluorination of 1-butanol leads to a significant lipophilicity increase (cf **D1**→**D4**), a $\log P$ decrease for a butyl to heptafluorobutyl ester modification has been reported.³³

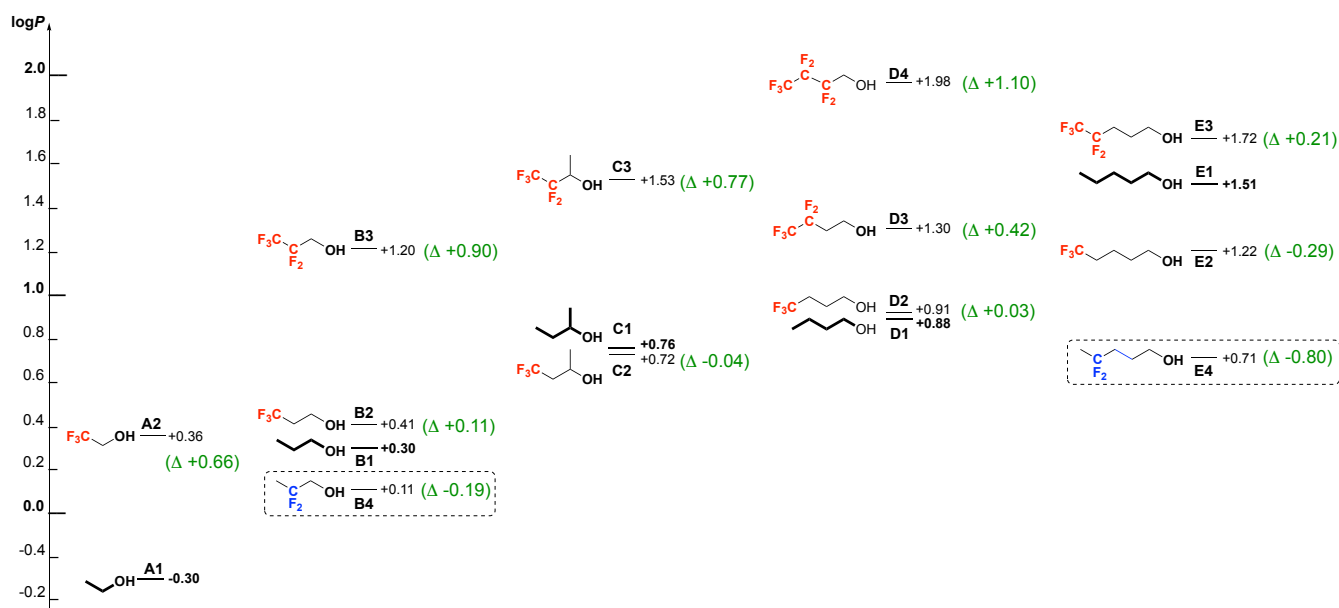


Figure 1. Lipophilicity change upon tri-, penta- and heptafluorination of alkanols. The $\Delta\log P$ values refer to the difference in lipophilicity with the nonfluorinated ‘parent’ alcohol.

A detailed structural understanding of how fluorination affects molecular lipophilicity is of great importance. It is now well-recognized that efficient drug development consists of simultaneous potency and physical property optimization, with lipophilicity being one of the important properties, as opposed to a dominating focus on the former.³⁴ Lipophilicity affects solubility and ADME properties, which determine to a large degree dosing, and thus toxicity effects. New ligand efficiency measures which take both elements into account, such as LLE (lipophilic ligand efficiency), have been proposed as a superior way to guide compounds through a drug development process.³⁵⁻³⁷ In this context, the development of lipophilicity-reducing motifs is of great relevance.

Our group has an interest in investigating the influence of fluorination on lipophilicity of aliphatic substrates, and we have developed a ¹⁹F NMR based protocol for a convenient and accurate measurement of the octanol-water partition coefficients of such non-UV active compounds.³¹ As part of this work, it

was noticed that alkanols with a terminal $-\text{CF}_2\text{CH}_3$ group (eg **B4**, **E4**, Figure 1), have lower $\log P$ values compared to the nonfluorinated alcohols **B1** and **E1**. Muller had described the same observation for propyl- and 2,2-difluoropropyl ethers.²⁸ As shown in Figure 1, $-\text{CF}_2\text{CH}_3$ containing alcohols have lower $\log P$ values than their trifluoroethyl ($-\text{CH}_2\text{CF}_3$) equivalents (eg **B2**, **E2**), and considerably lower values than the pentafluoroethyl ($-\text{CF}_2\text{CF}_3$) equivalents (eg **B3**, **E3**). In the latter case, the opposing C–F dipoles of the pentafluoroethyl CF_2 and CF_3 moieties, combined with the larger hydrophobic surface, contribute to this difference. It was also noted that these $-\text{CF}_2\text{CH}_3$ alkanols even have a lower $\log P$ value than the next lower homologue trifluorinated alcohols (compare **B4** with **A2**, and **E4** with **D2**). A similar observation has been made by O’Hagan within the aryl fluoroalkyl sulfide structure: lipophilicities of $\text{ArSCF}_2\text{CH}_3$ are lower than these of the corresponding ArSCF_3 analogues.²⁵

Using alkanol structures as models for alkyl chains, we wished to explore whether significant attenuation of the lipophilicity of longer perfluoroalkyl chains was possible by CF_3/CH_3 exchange, and whether that change would also be significant enough for its $\log P$ to drop below that of the next lower perfluoroalkanol homologue. Hence, compounds **D5** and **E6** were targeted (Figure 2). Their $\text{clog} P$ values, obtained by three different calculation methods (see Supporting Information) were all lower than the values of **D4/E5**, but only one method, which underestimated the value of the perfluoroalkyl derivatives **D4/E5**, predicted similar or lower values compared to the nonfluorinated alcohols. Hence, experimental determination of the $\log P$ values of **D5/E6** was justified. In addition, two more difluorinated examples **C4** and **D6** were synthesized to investigate a wider scope of the lipophilicity change observations as discussed above. Finally, these motifs were also evaluated when incorporated in a drug-like scaffold, via $\log D_{7.4}$ determination of a panel of analogues of evenamide **1a**, a schizophrenia drug currently in phase II clinical trials.³⁸ We report a number of surprising outcomes regarding the magnitude of the measured $\log P$ (and $\log D$) changes, which will render these motifs of interest in medicinal chemistry.

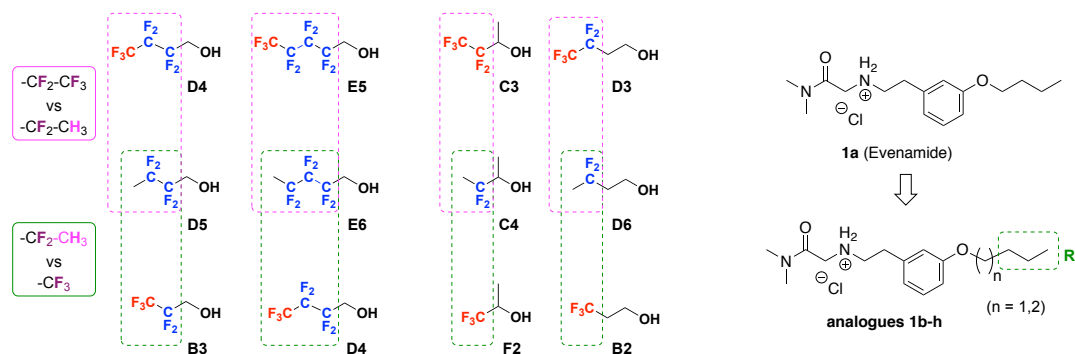
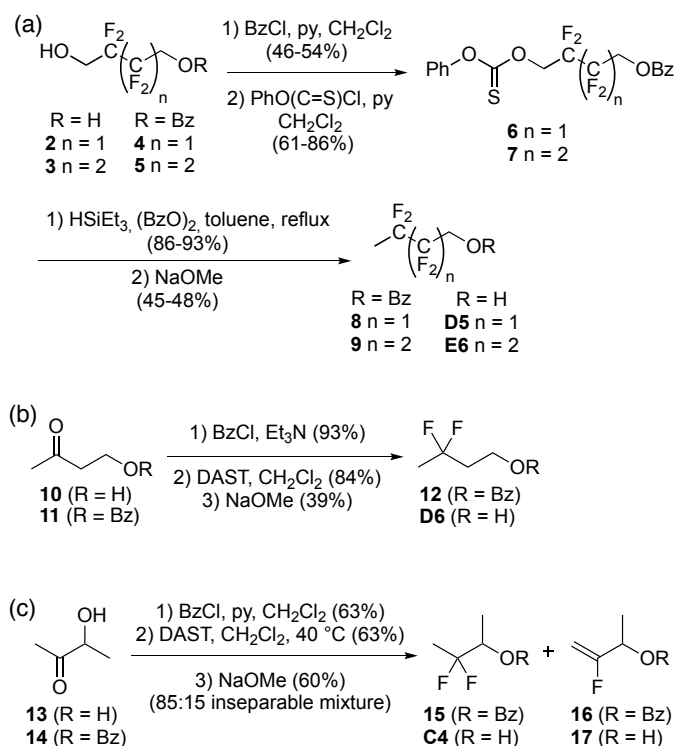


Figure 2. Motif changes under investigation using model alkanols and as evenamide side chain.

Results.

Chemistry. The heptafluorinated **D4** and nonafluorinated **E5** were commercially available. The synthesis of the other polyfluorinated targets was achieved using a fluorinated building block strategy. Hence, commercially available 1, ω -diols **2** and **3** (Scheme 1a) were monobenzoyleated to give **4** and **5**, and the remaining alcohol group was removed via a radical deoxygenation reaction. Deprotection of the resulting **8** and **9** led to the targets **D5** and **E6**.

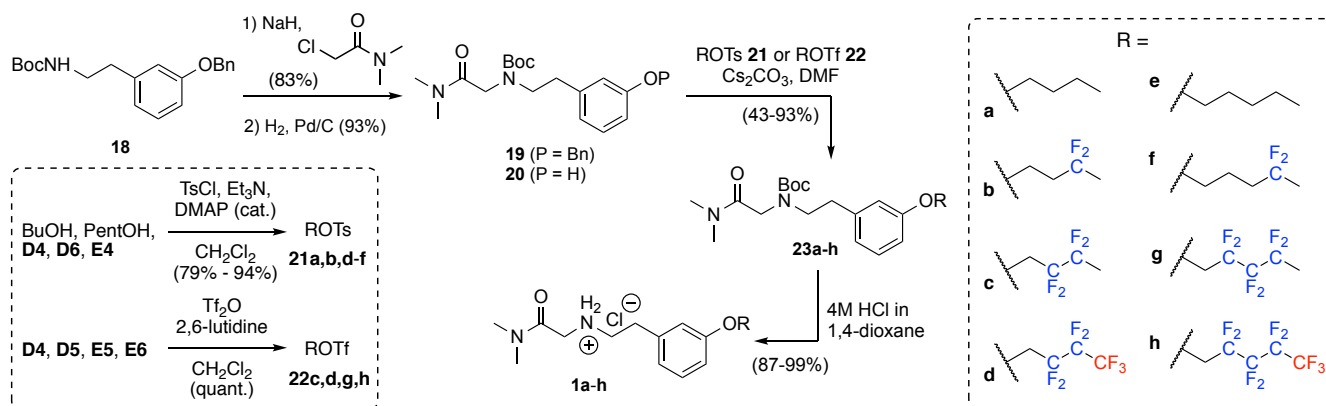


Scheme 1. Synthesis of the model compounds.

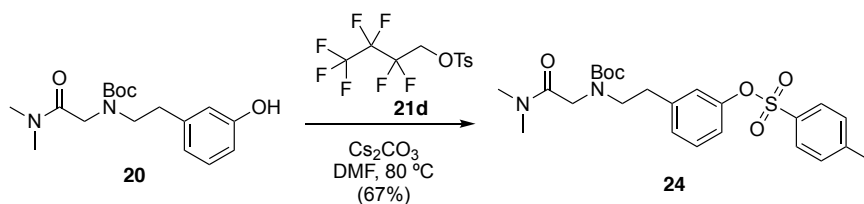
Targets **D6** and **C4** (Scheme 1b,c) were obtained from commercially available **10** and **13** by an alcohol protection, carbonyl deoxofluorination, and deprotection sequence. In the latter case, the deoxofluorination was accompanied by an elimination side reaction, leading to an 85:15 mixture of **15** and **16**. Even after deprotection, the alkene and difluoro compound could not be separated. However, this was of no consequence for the lipophilicity determination (see below).

All the synthesized fluorinated alcohols proved to be rather volatile, hampering isolation. Hence, Et₂O, CH₂Cl₂ or *n*-pentane were used as solvents for the final deprotection reaction, or as part of the eluent mixture used for the final chromatographic purification. Removal of these solvents was typically performed using a controlled pressure pump which was set to 700-750 mbar with a ~30 °C water bath until the volatile alcohols had reached ~80wt% (¹H NMR analysis). We found that compound losses were minimized by allowing the final amounts of solvent to be removed by slow evaporation in the open atmosphere.

The evenamide analogues syntheses started from known **18** (Scheme 2).³⁹ Deprotonation of the BocNH group followed by nucleophilic substitution with *N,N*-dimethyl chloroacetamide led to **19**. Protecting group hydrogenolysis to give **20** then allowed introduction of the alkyl chains **a–h**. Ether synthesis via conversion of the various alcohol derivatives to the corresponding tosylates **21** followed by reaction of the deprotonated phenolate only worked well when there was no α -CF₂ group present. For example, reaction of **20** with base and the tosylate **21d**, derived from **C8**, did not lead to the expected S_N2 reaction, but to tosyl exchange, leading to **24** (Scheme 3).



Scheme 2. Synthesis of evenamide analogues.



Scheme 3. Side reaction with perfluoroalkylmethyl tosylates.

It is well-known that leaving groups adjacent to perfluoroalkyl groups are very unreactive towards S_N2 reactions, even when present on a primary CH₂-group, due to an electronic deactivation effect and, certainly with anionic nucleophiles, a destabilizing repulsion with the fluorine atoms.⁴⁰⁻⁴² This results in slow reactions and, as observed here, S–O instead of C–O cleavage.⁴³ This can be mitigated by the use of a more reactive triflate leaving group.⁴⁴⁻⁴⁵ Interestingly, an electrophile with a heptafluoropropyl substituent has a significantly reduced reaction rate compared to when a trifluoromethyl substituent is present.⁴⁴ Hence, the process was optimized starting from alcohol **D4**, and the best conditions were found when the reaction mixture obtained after addition of Tf₂O and 2,6-lutidine in dichloromethane had Cs₂CO₃ added after 1 h, directly followed by a solution of **20** in DMF. Following this protocol, **D5**, **E5**, and **E6** were also introduced leading to the collection of evenamide **1a** and seven analogues **1b-h** in good yields.

Lipophilicity.

The direct determination of $\log P$ values by measuring the octanol/water partition coefficients P is typically efficiently accomplished by concentration measurements through UV-spectroscopy, which is a standard procedure and often high-throughput in most companies. However, for compounds that do not contain a chromophore, this is unsuitable, and a number of NMR-based methodologies can be used for such cases.⁴⁶⁻⁴⁸ Our group has developed a ^{19}F NMR based method for shake-flask $\log P$ measurement of fluorinated derivatives.³¹ The use of an internal standard as a mixture with the compound of interest conveniently obviates the need for accurate weight/partition volume/sample volume measurements. The NMR sensitivity limitation translates into a $\log P$ window of $\sim \pm 2$ – 2.5 before NMR-experiment times become impractically long, although the use of a cryoprobe extends the $\log P$ window to $\sim \pm 3$ – 3.5 . A very useful practical advantage is that the $\log P$ of impure compounds (eg **C4** and **17**, see Scheme 1) can be easily measured provided the fluorine chemical shift values of the desired compound and that of any impurities are different. This method was used to measure the $\log P$ of all compounds below, unless indicated.

The results for the polyfluoroalkyl CH_3/CF_3 exchange are shown in Figure 3. As expected the measured $\log P$ of **E5** was significantly higher than that of 1-pentanol **E1**. For both the nonafluorobutyl and heptafluoropropyl group containing compounds **E5** and **D4**, changing the CF_3 -group into a CH_3 group resulted in a dramatic decrease in $\log P$. Both perfluoroalkyl groups have the same distance to the alcohol group, hence the alcohol functional group is not expected to play a part in this $\log P$ modulation. Very unexpectedly, the $\log P$ of the internally tetrafluorinated butanol **D5** is almost identical to that of the parent butanol. Strikingly, this is also the case for the internally hexafluorinated pentanol **E6** vs pentanol **E1**. It is also interesting to contrast these observations with a $\text{CF}_3 \rightarrow \text{CH}_3$ exchange applied to the trifluorinated **D2** and **E2**: this has either no effect (eg **D2** \rightarrow **D1**) or even shows a $\log P$ increase (eg **E2** \rightarrow **E1**). Hence, these results suggest that polyfluorination of alkyl groups need not lead to a punishing increase in lipophilicity, if the terminus remains nonfluorinated.

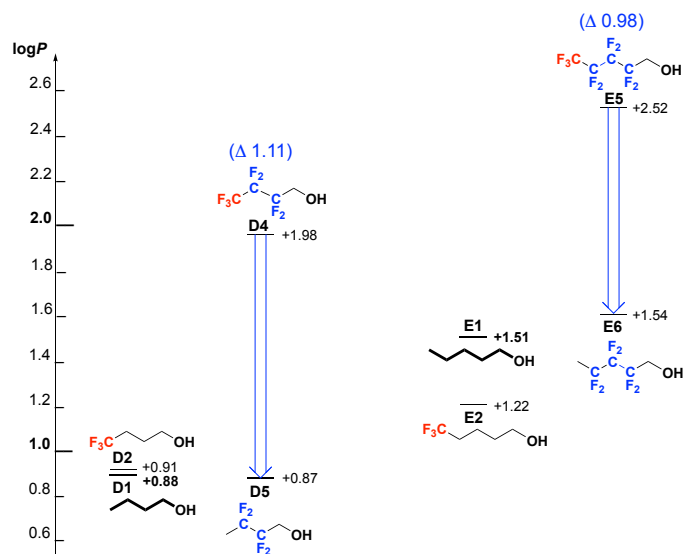


Figure 3. CF₃/CH₃ exchange as part of a perfluoroalkyl group.

Next, the lipophilicity of the two novel difluorinated alkanols **C4** and **D6** was determined (Figure 4). For comparison purposes the known data for **B4** and **E4** are also included. Clearly the same large lipophilicity decrease is observed upon changing a pentafluoroethyl group for a CH₃CF₂- group.

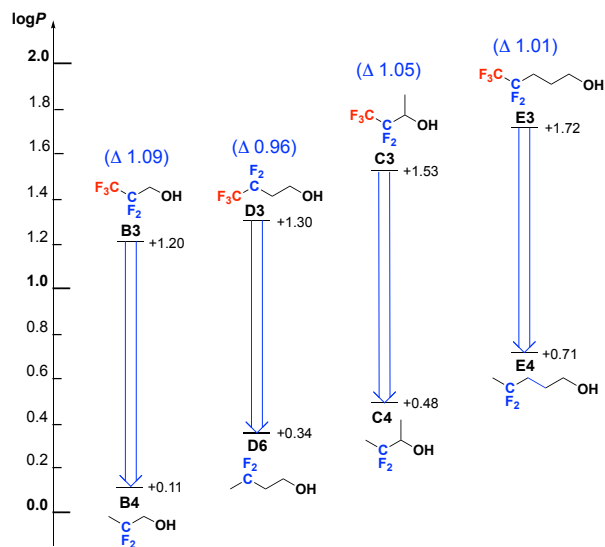


Figure 4. CF₂CF₃ to CF₂CH₃ exchange.

Finally, the lipophilicities of Me-CF₂-R with the lower homologues CF₃-R were compared (Figure 5). As can be seen from the log*P* values of the nonfluorinated alcohols, extending the alkyl chain leads to an increase in log*P*. However, in all cases investigated, regardless of the length of the perfluoroalkyl chain, extending a CF₃-terminated alkyl chain by one carbon through replacing a single fluorine by a methyl group, leading to a terminal Me-CF₂- group, results in a lipophilicity reduction. Hence, these results are consistent with the work of O'Hagan regarding the lower lipophilicities of ArSCF₂CH₃ compared to the corresponding ArSCF₃ analogues.²⁵

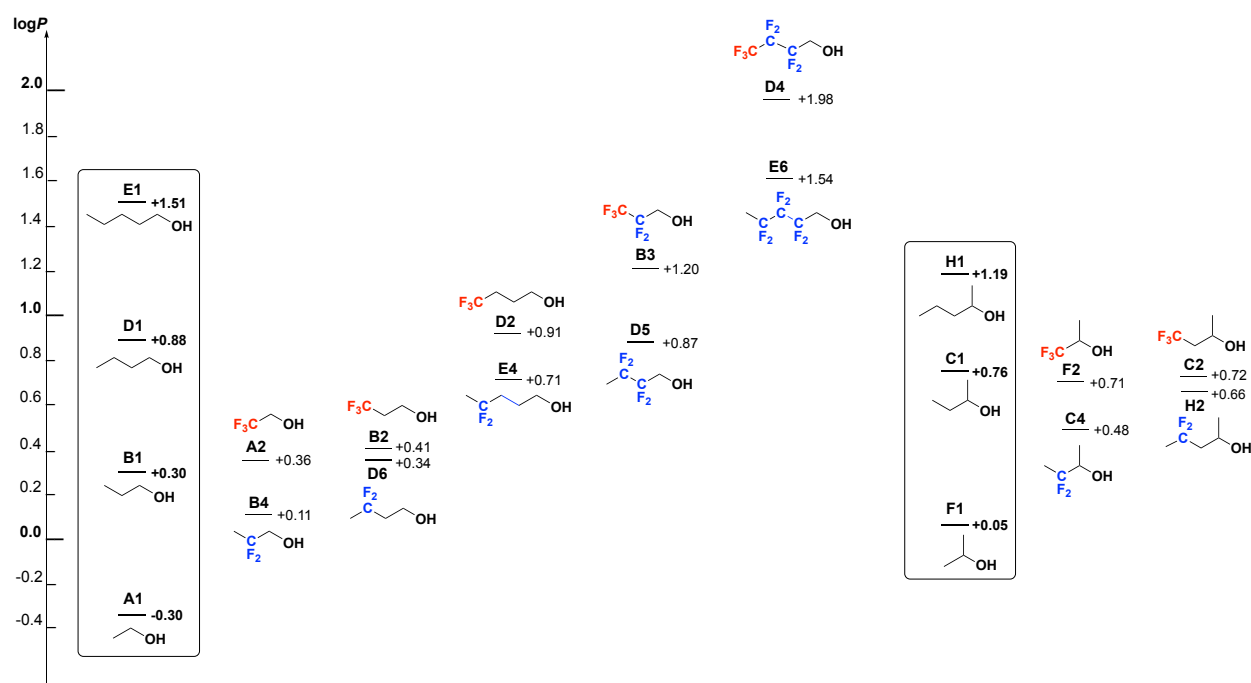


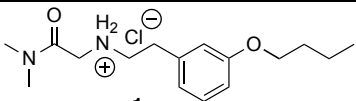
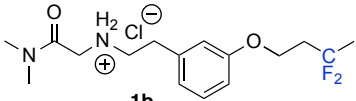
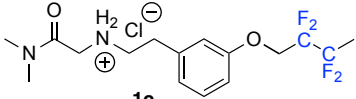
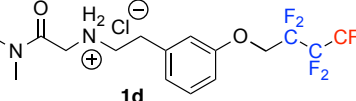
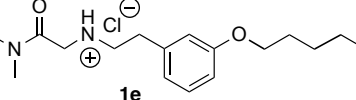
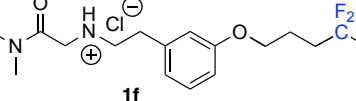
Figure 5. CF₃-R to Me-CF₂-R replacement.

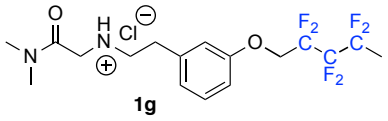
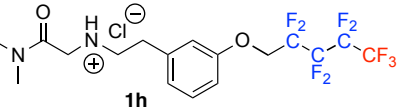
This type of motif change was further investigated by the synthesis of analogues of evenamide, an antipsychotic drug candidate now in Phase IIa clinical trials, not only to establish whether the log*P* differences will be maintained when incorporated in a different structural context, but also to evaluate metabolic stabilities of these fluorinated moieties. In the event, the linear butyl chain of evenamide was replaced by fluorinated butyl chains **b–d** and pentyl chains **e–g** (cf Scheme 2), leading to the evenamide analogues **1a–g** (Table 1).

These analogues were subjected to $\log D_{7.4}$, solubility determination, metabolic stability studies and hERG activity. hERG (human ether-a-go-go-related gene) potassium channels are essential for normal electrical activity and function of the heart. Arrhythmia can be induced by a blockage of hERG channels by a diverse set of drugs, with this side effect being a common reason for drug failure in preclinical safety trials. Therefore minimization of hERG channel blocking activity is an important aspect of drug discovery.

Pleasingly, the lipophilicity trends for the fluorinated motifs identified in Figures 3–5 were confirmed after incorporation in evenamide, showing they were not specific for alkanols. Because of the presence of the ammonium group, $\log D$ values were measured at pH 7.4, this time using AstraZeneca's routine shake-flask method involving UV-detection for concentration determination. The change in $pK_{a(H)}$ of the amine due to the fluorination of the remote alkoxy group is expected to be very minimal. Hence, this factor was assumed to have a negligible influence on the $\log D_{7.4}$ of the evenamide analogues.

Table 1. Analysis of evenamide 1a and analogues 1b-h

Structure	$\log D_{7.4}^a$	Solubility ^b (μM)	PPB ^c (%free)	Hu Mics CLint ^d	Rat Heps CLint ^e	hERG ^f (% inhib)
 1a	+1.8	782	45	13	82	31
 1b	+1.1	960	62	7	34	35
 1c	+1.6	929	51	10	32	41
 1d	+2.5	952	20	8	20	57
 1e	+2.3	779	23	29	91	70
 1f	+1.7	1000	49	7	38	45

 1g	+2.2	946	25	9	64	63
 1h	+3.3	955	7.6	7	21	81

^alog $D_{7.4}$ determined by shake flask method; ^bSolubility of compounds in aqueous phosphate buffer at pH 7.4 after 24 h at 25 °C; ^cDetermined from DMSO stock solution by equilibrium dialysis in 10% human plasma supplied by Quintiles; ^dRate of metabolism ($\mu\text{L}/\text{min}/\text{mg}$) determined from DMSO stock solution in human microsomes; ^eRate of metabolism ($\mu\text{L}/\text{min}/10^6$ cells) determined from DMSO stock solution in isolated rat hepatocytes diluted to 1×10^6 cells/mL; ^f% inhibition of hERG ion channel at a concentration of 10 μM .

The log D values of the nonfluorinated evenamide **1a** is +1.8. As expected, its homologue **1e** shows an increased value +2.3 owing to the longer alkyl chain. Difluorination at the penultimate position led to a significant log D decrease (0.6-0.7 log D units, **1b**, **1f**), and perfluorination to a significant log D increase (**1d**, **1h**). Pleasingly, changing the CF₃ group of the perfluoroalkylmethyl groups in **1d** and **1h** to the corresponding methyl groups (**1c** and **1g** respectively) leads to a reduction in log D to a value that is similar and even slightly lower than that of the nonfluorinated chains (compare **1c** with **1a**, and **1g** with **1e**). In addition, the evenamide analogue with the hexafluoropentyl chain has a lower log D compared to that with a heptafluorinated butyl chain (compare **1g** with **1d**). Hence, the log P trends that were obtained upon introducing these fluorinated motifs in the butanol and pentanol models are fully replicated in the log $D_{7.4}$ trends of a pharmaceutically relevant drug candidate when they are introduced as part of an aromatic butoxy/pentoxy chain.

Importantly, the introduction of the fluorine atoms did not lead to a decrease in aqueous solubility; on the contrary, in all cases the solubility increased, even for the analogues with increased log D values. Human plasma protein binding correlates with the lipophilicity. For example, **1e** and its hexafluorinated analogue **1g** are isolipophilic and have the same levels of human plasma binding. Metabolic stability studies (human

microsomes and rat hepatocytes) showed the increased stability of the fluorinated derivatives towards oxidative degradation. Hence, a terminal methyl group adjacent to a perfluoroalkylidene moiety is not metabolically labile, which was presumed to be due to the electronegativity of the adjacent fluorine atoms. With respect to percentage inhibition of the hERG receptor at a concentration of 10 μ M, this correlated broadly with lipophilicity in that only the most lipophilic heptafluorinated **1d** and nonafluorinated **1h** analogues showed increased inhibition relative to the parent compounds (compare **1d** with **1a**, and **1h** with **1e**). All of the internally fluorinated compounds (**1b**, **1c**, **1f**, **1g**) showed similar or lower levels of inhibition relative to the parent compounds.

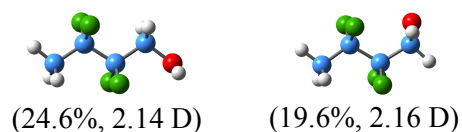
Discussion

Having observed a significant $\log P$ decrease for a perfluoroalkyl CF_3/CH_3 exchange, leading to internally polyfluorinated butoxy and pentoxy groups having similar lipophilicities as their nonfluorinated counterparts, we were keen to understand the underlying factors in terms of conformation and polarity contributing to this.

Polarity effects can be gauged by estimation of the overall molecular dipole moments, which require knowledge of the conformational profiles, more precisely of the individual energetic minima dipole moments. Hence, conformational analysis of a number of fluorinated butanol and pentanols was carried out in water and octanol medium, and showed that these compounds are very flexible, with in all but one of the examples studied, no clear major conformer with a population of greater than 20% being identified (full data in the Supporting Information). For the non-fluorinated and perfluoroalkylated alcohols, the flexibility appears mainly due to the presence of the alcohol head group (see Supporting Information for the structures of the main minimum-energy conformers), while the internally polyfluorinated chains possess more flexibility along the carbon chain. The only substrate with a conformer having a population of >20% was the tetrafluorinated **D5**. In all cases, there was a clear difference in conformational profile between the octanol and water phases, as exemplified by the different computed weighted dipole moments

(Table 2). These were always lower in the octanol phase. This trend is expected as it illustrates that a polar medium stabilizes polar conformations. While this difference was typically <0.2 D, the exception was **D5**, for which the dipole moment was much larger (about 1.0 D) in the water phase compared to that in the octanol phase. This was also the compound with the most biased conformational profile, its two most abundant conformers in octanol having a much lower dipole moment than those in water (Figure 6). Hence, **D5** adopts a very different conformational profile in water compared to octanol, with significantly populated but close in energy conformers possessing very different dipole moments, a behavior which has been referred to by Muller as a “lipophilicity chameleon”.²⁸

Octanol phase



Water phase :

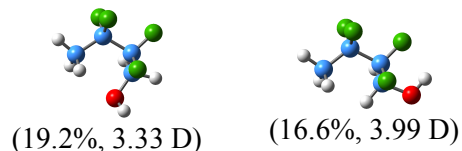


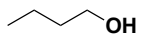
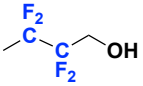
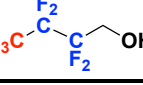
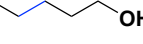
Figure 6. The two most abundant conformations of 2,2,3,3-tetrafluorobutanol **D5** in the octanol phase (top) and water phase (bottom), with Boltzmann population and conformer dipole moment.

A qualitative comparison of the calculated dipole moments is instructive (Table 2). All fluorinated derivatives have a higher dipole moment compared to the parent nonfluorinated alkanols. The hexafluorinated **E6** has a larger weighted dipole moment than the nonfluorinated **E5**, both in the water and octanol phases. When comparing tetrafluorinated **D5** with heptafluorinated **D4**, this is only true in the water phase, but not in the octanol phase, which originates, as explained before, by its ability to adopt very apolar conformers (Figure 6). Indeed, while the C–F dipoles in these conformers are opposed and

hence cancel each other out, this is not possible for the hexafluorinated derivative, explaining its higher averaged dipole moment. Nevertheless, the low-polarity conformers of **E6** in the octanol phase do not lead to a high $\log P$, as may be expected. Hence, the stabilization of the polar conformations in water must dominate the partitioning equilibrium.

In addition, the C–H bonds of the resulting CH₃ group are also strongly polarized by the electron withdrawing effect of the perfluoroalkylidene group. This was apparent from their experimental chemical shift, showing a deshielding, as well as by the partial atomic charges calculated at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory using the Natural Population Analysis methodology (Table 3). Owing to the fluorine inductive effect, an increase of the hydrogen positive charge is found as more internal fluorines are introduced. The values, which are the mean values over the three hydrogen atoms weighted upon the conformation relative populations, are just slightly lower in octanol than in water. They are very similar between conformations. Hence, a CF₃/CH₃ exchange introduces a more polar moiety than perhaps expected, further leading to a downwards effect on lipophilicity. Interestingly, The Polar Surface Area was calculated to be very similar for all compounds, both in the water and in the octanol phase.

Table 2. Calculated dipole moments^a and polar surface areas^b in the octanol and water phase and measured^c lipophilicities.

Compound		phase	μ (D) ^a (weighted)	$\Delta\mu$ ^a (D)	PSA ^b (Å ²)	$\log P$ ^c
	D1	oct	2.21	0.19	22.69	0.88
		H ₂ O	2.40		22.75	
	D5	oct	2.87	0.95	21.69	0.87
		H ₂ O	3.82		21.83	
	D4	oct	3.34	0.04	21.31	1.98
		H ₂ O	3.38		21.42	
	E1	oct	2.20	0.20	22.60	1.51
		H ₂ O	2.40		22.65	
	E6	oct	3.37	0.20	21.60	1.54

		H ₂ O	3.57		21.58
	E5	oct	3.12	0.19	21.29
		H ₂ O	3.31		21.58

^a Calculated at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory in water and octanol medium, and weighted by the relative populations of each conformer. ^b Calculated using the QikProp module of the Schrödinger suite, and weighted by the relative populations of each conformer. ^c Measured $\log P$.

Table 3. Chemical shift values,^a and weighted partial atomic charges per hydrogen atom,^b of the methyl group in compounds **D1**, **D6** and **D5**.

Compound ^a	δ_{Me} (ppm) ^a	Water q_{H}	Octanol q_{H}
D1	0.93	0.2017	0.2012
D6	1.67	0.2336	0.2322
D5	1.78	0.2444	0.2426
E6	1.83	0.2476	0.2458

^a In CDCl₃. ^b Calculated at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory in water and octanol medium.

The other main contributing factor involves the reduction in hydrophobic surface which results from replacing a CF₃-group with a CH₃-group. Comparing **E5** with **E6** (Table 2), the observed $\log P$ change of ~ 1 unit is consistent with Muller's predictive model, which assigns a 0.3 $\log P$ unit per H/F exchange, together with a contribution for polarity change (in this case ~ 0.1 - $0.2 \mu_{\text{C-F}}$).

The similarity in lipophilicity between the nonfluorinated and internally polyfluorinated alkanols could therefore be rationalized by a compensation of the increased dipole of the latter with the increase in hydrophobic surface due to fluorine introduction.

Conclusions

This work concerns an investigation on lipophilicity modulation upon changing the CF_3 -group of a perfluoroalkyl moiety into a Me-group. We have confirmed an observation that changing a CF_3CF_2 - group for a MeCF_2 - group leads to a drastic reduction in lipophilicity. A key finding was that this is also the case when a $\text{CF}_3(\text{CF}_2)_n$ - group ($n>1$) is converted to a $\text{Me}(\text{CF}_2)_n$ - group. Remarkably, tetrafluorinated $\text{MeCF}_2\text{CF}_2\text{CH}_2\text{OH}$ and hexafluorinated $\text{MeCF}_2\text{CF}_2\text{CF}_2\text{CH}_2\text{OH}$ have the same or very similar lipophilicities compared with the nonfluorinated BuOH and PentOH. In addition, we have shown that extending a CF_3 - group into a MeCF_2 -group, or a $\text{CF}_3(\text{CF}_2)_n$ -group into a $\text{MeCF}_2(\text{CF}_2)_n$ -group, despite resulting in a longer alkyl chain, still leads to a reduction in lipophilicity (in contrast to nonfluorinated *n*-alkanols). These lipophilicity changes were also investigated when various fluorinated butyl and pentyl ethers were incorporated into evenamide, a schizophrenia drug candidate currently in Phase II clinical trials. Pleasingly, all the lipophilicity trends observed for the alkanol model compounds were confirmed. In addition, these evenamide analogues have slightly improved aqueous solubilities, and enhanced metabolic stabilities compared to the nonfluorinated analogues, showing that a $\text{MeCF}_2(\text{CF}_2)_n$ -group is not metabolically labile. Conformational analysis shows that in general, the conformational profile in the water and octanol phases is different, with a higher weighted dipole moment in the more polar water phase. This was especially pronounced for the internally tetrafluorinated butanol, making this a new example of a 'lipophilicity chameleon'. The internally fluorinated compounds have an increased dipole moment compared to the perfluorinated alkanols, which in turn was much increased compared to the nonfluorinated species.

With lipophilicity control typically being a standard concern throughout the drug optimization process, the results described herein will be of great interest to medicinal chemists as it demonstrates the ability to introduce polyfluoroalkylation without $\log P$ penalization.

Experimental Section.

General Methods. All chemical reagents were obtained from commercial sources and used without further purification. Anhydrous solvents were purchased from commercial sources. All glassware was flame-dried under vacuum and cooled under Ar prior to use. Water or air sensitive reactions were performed under inert atmosphere, using dry solvents. Reactions were monitored by TLC (Merck Kieselgel 60 F₂₅₄, aluminium sheet) and spots were visualized by UV and/or by exposure to a basic solution of KMnO₄, followed by brief heating. Flash column chromatography was performed on silica gel (Merck silica gel 60, particle size 40–63 μm). All reported solvent mixtures are volume measures. Nuclear magnetic resonance spectra were recorded using either a Bruker Ultrashield 400 MHz or 500 MHz spectrometer. The chemical shift (δ) is given in ppm using the residual solvent peak as an internal standard. The coupling constants (J) are given in Hertz (Hz). IR spectra were recorded on a Thermo Scientific™ Nicolet iS5 as films and absorption peaks are given in cm^{-1} . Low resolution electrospray mass spectra were recorded with a Waters Acquity TQD mass tandem quadrupole mass spectrometer. HRMS were measured on a Bruker Daltonics MaXis time of flight (TOF) mass spectrometer or, for volatile compounds, a Thermo MAT900 XP double focusing sector mass spectrometer. All compounds subjected to biological assays were of >95% purity (LC-MS).

Determination of $\log P$

Lipophilicities of the fluorinated alkanols were determined using a previously published protocol:³¹ to a 10 mL pear-shaped flask was added the compound (1.0 - 10 mg) for $\log P$ determination, the reference compound (1.0 - 10 mg, with known $\log P$ value, e.g., 2,2,2-trifluoroethanol, $\log P$: +0.36), water (2 mL) and *n*-octanol (2 mL). The resulting biphasic mixture was stirred (at 600 rpm) for 2 h at 25 °C, and then

left without stirring for 16 h at 25 °C to allow phase separation. An aliquot of 0.5 mL was taken from each phase using 1 mL syringes with long needles, and added to two separate NMR tubes. A deuterated NMR solvent (0.1 mL, e.g., acetone- d_6), or a capillary tube containing deuterated NMR solvent, was added to the NMR tubes to enable signal locking. Because of the volatility of the used compounds, the NMR tubes were sealed using a blowtorch. For NMR samples with directly added deuterated solvent, the tubes were inverted 20 times for mixing. For $^{19}\text{F}\{^1\text{H}\}$ NMR experiments, NMR parameters were set as follows: D1 30 sec for the octanol sample, D1 60 sec for the water sample; and O1P centered between two diagnostic fluorine peaks. If needed, an increased number of transients (NS) and/or narrower spectral window (SW) for a good S/N ratio (typically >300) was applied. After NMR data processing, integration ratios ρ_{oct} and ρ_{aq} (ρ_{oct} is defined as the integration ratio between the compound and the reference compound in the octanol sample; likewise for ρ_{aq}) were obtained, and used in the equation ($\log P^X = \log P^{\text{ref}} + \log[\rho_{\text{oct}}/\rho_{\text{aq}}]$) to obtain the $\log P$ value of the compound. The $\log P$ measurement of each compound was run in triplicate. $\log P$ values of non-fluorinated compounds were taken from the literature.

Determination of $\log D_{7.4}$

$\log D_{7.4}$ measurements were made using a shake-flask method where the extent of partitioning between pH 7.4 buffer and octanol was measured. Compounds were dissolved in a known volume buffer, and following the addition of a known amount of octanol, the solutions were shaken for 30 min. Following centrifugation, analysis of the aqueous layer was performed by LC-UV to quantify the amount of compound in solution and then compared to analysis of the compound in solution before the addition of octanol to calculate the partitioning coefficient, $D_{7.4}$. Experiments were run as pools with 10 compounds including three QC compounds per experiment. Cyclobenzaprine with moderate $\log D$, nicardipine, with high $\log D$ and caffeine, with low $\log D$, are used and randomly placed in all runs. The method has been thoroughly validated against the previous shake flask methodologies.

Determination of solubility

Assessments of aqueous solubility were made using a shake-flask approach that uses 10 mM DMSO solutions which are supplied from AstraZeneca Compound Managements Liquid Store and is a high throughput method. The dried compounds were equilibrated in an aqueous phosphate buffer (pH 7.4) for 24 hours at 25 °C, the portion with the dissolved compound was then separated from the remains. The solutions were analyzed and quantified using UPLC/MS/MS, QC-samples were incorporated in each assay-run to ensure the quality of the assay.

Determination of human plasma protein binding

The automated equilibrium dialysis assay in human plasma used a RED (Rapid Equilibrium Dialysis) Device and sample handling. After dialysis for 18 h, plasma and buffer samples were prepared for analysis by liquid chromatography and mass spectrometry. Samples were generally tested in singlicates and quantified by LC/MSMS by using a 7-point calibration curve in plasma. The compounds were pooled together in plasma pools up to 10 compounds. Three reference compounds (propranolol, metoprolol and warfarin) were used in each run. Warfarin was used as a control in each pool and propranolol and metoprolol were placed randomly in each run.

Determination of human Microsome Metabolism Cl_{int}

Test compounds were incubated with human liver microsomes and NADPH in up to three 96-well plates at 37 °C for 30 min. An aliquot of the incubation mixture was taken at six determined time points (0.7, 5.8, 11.6, 17.2, 22.7 and 30 min), after the incubation had been initialized. The reaction was stopped with cold acetonitrile containing volume marker. The samples were centrifuged at 4 °C and the supernatant was transferred and diluted with water in 96 well plates. LC-MS/MS technique was used to determine substrate disappearance. To ensure microsomes activities during incubation time, 6 marker compounds metabolized by specific human P450 isoforms were included in each run: Diclofenac (2C9), Imipramine (2C19), Metoprolol (2D6), Benzydamine (FMO's), Phenacetin (1A2) and Verapamil (3A4).

Determination of rat Hepatocyte Metabolism Cl_{int}

Test compounds were incubated with rat han wistar cryopreserved hepatocytes in up to three 96-well plates at 37 °C for 30 min. An aliquot of the incubation mixture was taken at determined time points (0.5, 5, 15, 20, 30, 45, 60, 80, 100 and 120 min), after the incubation had been initialized. The reaction was stopped with cold acetonitrile containing volume marker. The samples were centrifuged at 4 °C and the supernatant was transferred and diluted with water in 96 well plates. LC-MS/MS technique was used to determine substrate disappearance.

The hERG Binding Assay

The hERG single shot assay was run on an IonWorks Quattro device. Each compound was tested at 33 μM . During a single experiment, the effect of each compound concentration was independently determined from up to 4 individual wells (in the Quattro format the recording from each well was the sum of up to 64 cells). For each compound test concentration, the % inhibition was determined as a ratio of the pre- and post-compound hERG current metric, and was taken as an average from the 1 to 4 wells. The effects of the test compound on the hERG current are normalized relative to current amplitudes in the presence of vehicle (0.33% DMSO) and those in the presence of a 100% blocking concentration of cisapride (10 μM).

Calculations

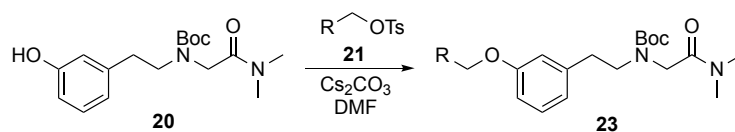
The theoretical calculations were carried out with the Gaussian16 program.⁴⁹ The conformational analysis of the various compounds investigated was performed with the MN15 functional⁵⁰ in combination with the triple-zeta quality aug-cc-pVTZ basis set.⁵¹⁻⁵³ Scans along the various rotatable bonds: C-C, C-O, and O-H bonds of the compounds have systematically been conducted. The solvent effects (octanol and water) were taken into account using the SMD solvation continuum model.⁵⁴ The vibrational spectrum of each optimized conformer was computed to confirm its nature of true minimum and to obtain free energies. The relative populations, p_i , of the various conformers were evaluated at 298K from the computed free energies through a Boltzmann distribution (Eq. (1)).

$$P_i = \frac{e^{-\Delta G_i / RT}}{\sum_{i=1}^n e^{-\Delta G_i / RT}} \quad (1)$$

The various theoretical descriptors (molecular dipole moments, partial atomic charges) computed for each conformer were weighted according to these populations.

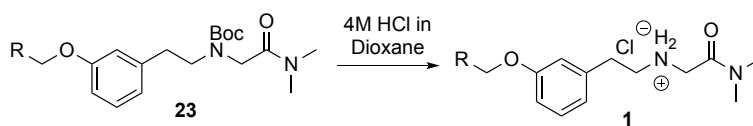
The Polar Surface Area of each compound was computed using the QikProp module of the 2018 Schrödinger suite (Schrödinger release 2018-2, QikProp; LLC, New York, 2018). It was calculated for each conformer found at the SMD/MN15/aug-cc-pVTZ//MN15/cc-pVTZ level of theory, and weighted according to the conformer relative populations.

General procedure A for aryl ether formation via the tosylate



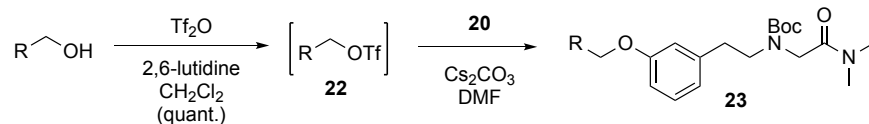
To a solution of **20** (1 equiv) and the tosylate **21** (1.1 equiv) in DMF was added Cs_2CO_3 (2 equiv). After 16 h the solvent was removed *in vacuo*. The residue was dissolved in water (30% v/v of DMF volume) and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude was purified by column chromatography (1:1, EtOAc/heptane) to afford the ether **23**.

General procedure B for Boc-deprotection



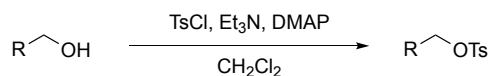
To the Boc protected amine **23** was added 4M HCl in dioxane (0.5 mL). The reaction was concentrated after complete consumption of starting material as confirmed by mass-spec analysis (roughly 4 h). The residue is then dissolved in CH_2Cl_2 (5 mL) and concentrated 3 times. The salt is then stirred in Et_2O (10 mL), filtered and further rinsed with Et_2O (10 mL). The resultant solid is then dissolved in CH_2Cl_2 and washed through the filter and concentrated to afford the evenamide analogues **1** as the pure HCl salt.

General procedure C for aryl ether formation via the triflate



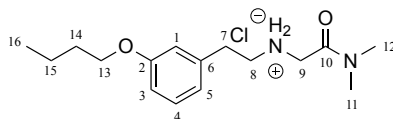
To a solution of the alcohol (1 equiv) in CH_2Cl_2 was added triflic anhydride (1.05 equiv) and 2,6-lutidine (1.1 equiv). Once complete consumption of the alcohol was shown by ^{19}F NMR analysis (roughly 1 h), Cs_2CO_3 (3 equiv) was added to the reaction mixture followed by a solution of **20** (1.2 equiv) in DMF. After 16 h the solvent was removed *in vacuo*. The residue was dissolved in water (similar volume as DMF) and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude mixture was purified by column chromatography (1:1 EtOAc/heptane) to afford the ether **23**.

General procedure D for tosylate formation



To a solution of alcohol (1 equiv) in CH_2Cl_2 was added Et_3N (1.1 equiv), DMAP (0.05-0.1 equiv) and tosyl chloride (1.1 equiv). After 1 h the reaction was quenched with 2M aq. HCl and the layers were separated. The organic layer was washed with aq. sat. NaHCO_3 , dried over Na_2SO_4 and concentrated to afford the tosylate **21**, which was used immediately without further purification.

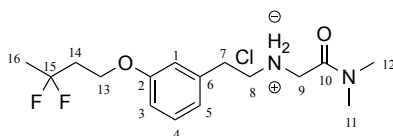
2-((3-Butoxyphenethyl)amino)-*N,N*-dimethylacetamide•HCl (**1a**)



Using general procedure A with **20** (61 mg) and **21a**⁵⁷ (48 mg) in DMF (1 mL), **23a** was obtained as a colorless gum (53 mg, 74%). According to general procedure B, *N*-Boc cleavage of **23a** (97 mg, 1 equiv) yielded **1a** as an off white solid (75 mg, 93%). ^1H NMR (400 MHz, CDCl_3) δ 9.54 (br s, 2H, NH_2^+), 7.20 (t, $J=7.8$ Hz, 1H, H4), 6.86 (d, $J=7.6$ Hz, 1H, H5), 6.83 (s, 1H, H1), 6.77 (d, $J=8.2$ Hz, 1H, H3), 4.00 (s, 2H, H9), 3.93 (t, $J=6.4$ Hz, 2H, H13), 3.44–3.33 (m, 2H, H8), 3.31–3.21 (m, H7), 2.96 (s, 3H, H11 or H12), 2.94 (s, 3 H, H11 or H12), 1.74 (tt, $J=7.5, 6.4$, 2H, H14), 1.48 (qt, $J=7.5, 7.4$ Hz, 2H, H15), 0.97

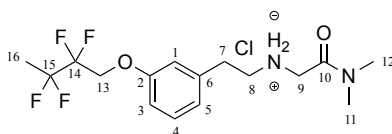
(t, $J=7.4$ Hz, 3H, H16) ppm; ^{13}C NMR (101 MHz, CDCl_3) δ 164.5 (C10), 159.6 (C2), 137.8 (C6), 129.8 (C4), 120.8 (C5), 114.9 (C1), 113.4 (C3), 67.7 (C13), 49.7 (C8), 48.0 (C9), 36.3 (C11 or C12), 35.8 (C11 or C12), 32.5 (C7), 31.3 (C14), 19.2 (C15), 13.8 (C16) ppm; IR (neat) 2930 (br., m), 2745 (br., m), 1665 (s), 1253 (s), 1161 (s) cm^{-1} ; MS (ESI+) m/z 279.3 $[\text{M}+\text{H}]^+$, 301.3 $[\text{M}+\text{Na}]^+$; HRMS (ESI+) for $\text{C}_{16}\text{H}_{27}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$, calculated 279.2067, found 279.2073 (-2.3 ppm error), for $\text{C}_{16}\text{H}_{26}\text{N}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$, calculated 301.1886, found 301.1887 (-0.3 ppm error).

2-((3-(3,3-Difluorobutoxy)phenethyl)amino)-*N,N*-dimethylacetamide•HCl (1b)



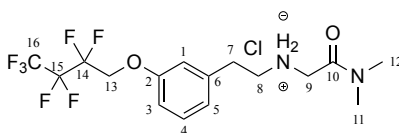
Using general procedure A with **20** (1 equiv) and **21b** (80 mg) in DMF (2 mL), **23b** was obtained as a colorless gum (54 mg, 43%). According to general procedure B, *N*-Boc cleavage of **23b** (51 mg, 1 equiv) yielded **1b** as an off white solid (40 mg, 93%). ^1H NMR (400 MHz, CDCl_3) δ 9.57 (br. s, 2H, NH_2^+), 7.22 (t, $J=7.8$ Hz, 1H, H4), 6.90 (br. d, $J=7.5$ Hz, 1H, H5), 6.86 (s, 1H, H1), 6.78 (dd, $J=8.1, 1.5$ Hz, 1H, H3), 4.13 (t, $J=6.4$ Hz, 2H, H13), 4.01 (br s, 2H, H9), 3.44–3.32 (m, 2H, H8), 3.32–3.23 (m, 2H, H7), 2.96 (s, 3H, H11 or H12), 2.93 (s, 3H, H11 or H12), 2.35 (tt, $J=15.1, 6.4$, 2H, H14), 1.70 (t, $J=18.8$ Hz, 3H, H16) ppm; ^{13}C NMR (101 MHz, CDCl_3) δ 164.5 (C10), 158.8 (C2), 138.0 (C6), 130.0 (C4), 121.5 (C5), 123.3 (t, $J=238.1$ Hz, C15), 115.0 (C1), 113.3 (C3), 62.2 (t, $J=6.2$ Hz, C13), 49.6 (C8), 48.0 (C9), 37.6 (t, $J=26.0$ Hz, C14), 36.3 (C11 or C12), 35.8 (C11 or C12), 32.4 (C7), 23.9 (t, $J=27.1$ Hz, C16) ppm; ^{19}F NMR (376 MHz, CDCl_3) δ -89.3 (qt, $J=18.8, 15.1$ Hz, 2F) ppm; $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3) δ -89.3 (s, 2F) ppm; IR (neat) 2921 (br., m), 2746 (br., m), 1667 (s), 1255 (w), 1160 (m) cm^{-1} ; MS (ESI+) m/z 315.3 $[\text{M}+\text{H}]^+$, 337.3 $[\text{M}+\text{Na}]^+$; HRMS (ESI+) for $\text{C}_{16}\text{H}_{25}\text{F}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$, calculated 315.1879, found 315.1882 (-1.2 ppm error), for $\text{C}_{16}\text{H}_{24}\text{F}_2\text{N}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$, calculated 337.1698, found 337.1701 (-0.8 ppm error).

2-((3-(2,2,3,3-Tetrafluorobutoxy)phenethyl)amino)-*N,N*-dimethylacetamide•HCl (1c)



Using general procedure C with **D5** (30 mg) in CH₂Cl₂ (0.5 mL), and **20** (79 mg) in DMF (0.6 mL), **23c** was obtained as a colorless gum (69 mg, 75%). According to general procedure B, *N*-Boc cleavage of **23c** (69 mg, 1 equiv) yielded **1c** as an off white solid (53 mg, 89%). ¹H NMR (400 MHz, CDCl₃) δ 9.59 (br s, 2 H, NH₂⁺), 7.24 (t, *J*=7.9 Hz, 1H, H4), 6.97 (d, *J*=7.5 Hz, 1H, H5), 6.93 (s, 1H, H1), 6.83 (dd, *J*=8.3, 1.9 Hz, 1H, H3), 4.39 (t, *J*=13.4 Hz, 2H, H13), 4.02 (s, 2H, H9), 3.46–3.34 (m, 2H, H8), 3.34–3.25 (m, 2H, H7), 2.96 (s, 3H, H11 or H12), 2.92 (s, 3H, H11 or H12), 1.82 (tt, *J*=19.3, 1.5 Hz, 3H, H16) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 164.5 (C10), 158.1 (C2), 138.3 (C6), 130.1 (C4), 122.6 (C5), 115.4 (C1), 113.5 (C3), 64.7 (t, *J*=26.8 Hz, C13), 49.4 (C8), 48.0 (C9), 36.3 (C11 or C12), 35.7 (C11 or C12), 32.3 (C7), 17.8 (t, *J*=24.2 Hz, C16) ppm. C14 and C15 were not observed due to multiple fluorine-fluorine couplings; ¹⁹F NMR (376 MHz, CDCl₃) δ -107.7– -107.2 (m, 2F, F15), -122.1– -121.7 (m, 2F, F14) ppm; ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -107.5– -107.4 (m, 2F, F15), -122.0– -121.8 (m, 2F, F14) ppm; IR (neat) 2943 (br., m), 2784 (br., m), 1663 (s), 1269 (w), 1161 (s), 1141 (s) cm⁻¹; MS (ESI⁺) *m/z* 351.3 [M+H]⁺, 373.3 [M+Na]⁺; HRMS (ESI⁺) for C₁₆H₂₃F₄N₂O₂ [M+H]⁺, calculated 351.1690, found 351.1693 (-0.9 ppm error), for C₁₆H₂₂ F₄N₂NaO₂ [M+Na]⁺, calculated 373.1510, found 373.1512 (-0.5 ppm error).

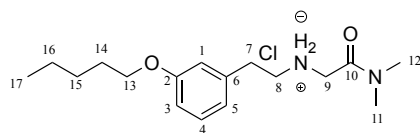
2-((3-(2,2,3,3,4,4,4-Heptafluorobutoxy)phenethyl)amino)-*N,N*-dimethylacetamide•HCl (**1d**)



Using general procedure C with **D4** (20 mg) in CH₂Cl₂ (0.3 mL), **20** (32 mg) in DMF (0.2 mL), but only 2 equiv of Cs₂CO₃, **23d** was obtained as a colorless gum (33 mg, 66%). According to general procedure B, *N*-Boc cleavage of **23d** (57 mg, 1 equiv) yielded **1d** as an off white solid (49 mg, 99%). ¹H NMR (400 MHz, CDCl₃) δ 9.53 (br s, 2 H, NH₂⁺), 7.26 (t, *J*=7.8 Hz, 1H, H4), 6.99 (d, *J*=7.2 Hz, 1H, H5), 6.95 (s,

1H, H1), 6.83 (d, $J=7.9$ Hz, 1H, H3), 4.47 (t, $J=12.7$ Hz, 2H, H13), 4.03 (s, 2H, H9), 3.38 (s, 2H, H8), 3.31 (br s, 2H, H7), 2.97 (s, 2H, H11 or H12), 2.93 (s, 3H, H11 or H12) ppm; ^{13}C NMR (101 MHz, CDCl_3) δ 164.5 (C10), 157.7 (C2), 138.5 (C6), 130.2 (C4), 123.0 (C5), 115.4 (C1), 113.7 (C3), 65.0 (t, $J=27.1$ Hz, C13), 49.5 (C8), 48.1 (C9), 36.3 (C11 or C12), 35.7 (C11 or C12), 32.3 (C7) ppm. C14, C15, and C16 were undetected due to multiple fluorine-fluorine couplings; ^{19}F NMR (376 MHz, CDCl_3) δ -81.0 (t, $J=9.5$ Hz, 3F, F16), -120.3– -120.9 (m, 2F, F14), -127.1– -127.8 (m, 2F, F13) ppm; $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3) δ -81.0 (br t, $J=9.5$ Hz, 3F, F16), -120.5– -120.7 (m, 2F, F14), -127.4– -127.5 (m, 2F, F13) ppm; IR (neat) 2892 (br., w), 2744 (br., w), 1666 (s), 1227 (s), 1185 (s), 1162 (s) cm^{-1} ; MS (ESI+) m/z 405.2 $[\text{M}+\text{H}]^+$, 427.2 $[\text{M}+\text{Na}]^+$; HRMS (ESI+) for $\text{C}_{16}\text{H}_{20}\text{F}_7\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$, calculated 405.1408, found 405.1413 (-1.5 ppm error), for $\text{C}_{16}\text{H}_{19}\text{F}_7\text{N}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$, calculated 427.1227 found 427.1231 (-1.0 ppm error).

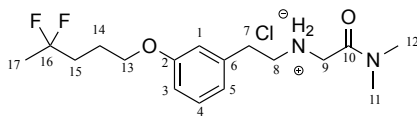
2-((3-Pentoxyphenethyl)amino)-*N,N*-dimethylacetamide•HCl (**1e**)



Using general procedure A with **20** (114 mg) and **21e**⁵⁸ (90 mg) in DMF (2 mL), **23e** was obtained as a colorless gum (126 mg, 91%). According to general procedure B, *N*-Boc cleavage of **23e** (90 mg, 1 equiv) yielded **1e** as an off white solid (67 mg, 89%). ^1H NMR (400 MHz, CDCl_3) δ 9.55 (br s, 2 H, NH_2^+), 7.20 (t, $J=7.8$ Hz, 1H, H4), 6.86 (d, $J=7.5$ Hz, 1H, H5), 6.83 (s, 1H, H1), 6.77 (dd, $J=8.2, 1.8$ Hz, 1H, H3), 4.00 (s, 2H, H9), 3.93 (t, $J=6.5$ Hz, 2H, H13), 3.44–3.31 (m, 2H, H8), 3.31–3.21 (m, 2H, H7), 2.96 (s, 3H, H11 or H12), 2.94 (s, 3H, H11 or H12), 1.76 (tt, $J=7.3, 6.5$ Hz, 2H, H14), 1.51–1.30 (m, 4H, H15 + H16), 0.93 (t, $J=7.1$ Hz, 3H, H17); ^{13}C NMR (101 MHz, CDCl_3) δ 164.5 (C10), 159.6 (C2), 137.8 (C6), 129.9 (C4), 120.8 (C5), 114.9 (C1), 113.4 (C3), 68.0 (C13), 49.7 (C8), 48.0 (C9), 36.2 (C11 or C12), 35.8 (C11 or C12), 32.5 (C7), 28.9 (C14), 28.2 (C15), 22.4 (C16), 14.0 (C17); IR (neat) 2929 (br., s), 2744 (br., m), 1668 (s), 1252 (s), 1162 (s) cm^{-1} ; MS (ESI+) m/z 293.3 $[\text{M}+\text{H}]^+$, 315.3 $[\text{M}+\text{Na}]^+$; HRMS (ESI+)

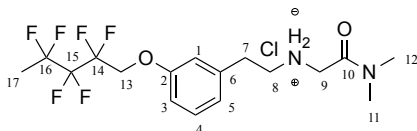
for C₁₇H₂₉N₂O₂ [M+H]⁺, calculated 293.2224, found 293.2226 (-0.7 ppm error), for C₁₇H₂₈N₂NaO₂ [M+Na]⁺, calculated 315.2043, found 315.2043 (+0.1 ppm error).

2-((3-(4,4-Difluoropentoxy)phenethyl)amino)-N,N-dimethylacetamide•HCl (**1f**)



Using general procedure A with **20** (74 mg) and **21f** (53 mg) in DMF (2 mL), **23f** was obtained as a colorless gum (74 mg, 91%). According to general procedure B, *N*-Boc cleavage of **23f** (74 mg, 1 equiv) yielded **1f** as an off white solid (56 mg, 89%). ¹H NMR (400 MHz, CDCl₃) δ 9.58 (br. s, 2H, NH₂⁺), 7.20 (t, *J*=7.6 Hz, 1H, H4), 6.88 (d, *J*=7.3 Hz, 1H, H5), 6.85 (s, 1H, H1), 6.77 (d, *J*=8.1 Hz, 1H, H3), 4.02 (br s, 2H, H9), 3.97 (t, *J*=5.5 Hz, 2H, H13), 3.38 (br s, 2H, H8), 3.28 (br s, 2H, H7), 2.96 (s, 3H, H11 or H12), 2.94 (s, 3H, H11 or H12), 2.14–1.86 (m, 4H, H14 + H15), 1.63 (t, *J*=18.3 Hz, 3H, H17); ¹³C NMR (101 MHz, CDCl₃) δ 164.5 (C10), 159.2 (C2), 138.0 (C6), 129.9 (C4), 124.1 (t, *J*=238.1 Hz, C16), 121.2 (C5), 115.0 (C1), 113.3 (C3), 67.0 (C13), 49.7 (C8), 48.1 (C9), 36.4 (C11 or C12), 35.8 (C11 or C12), 34.6 (t, *J*=25.7 Hz, C15), 32.5 (C7), 23.5 (t, *J*=27.9 Hz, C15), 22.7 (t, *J*=4.4 Hz, C14) ppm; ¹⁹F NMR (376 MHz, CDCl₃) δ -91.4 (apt. sxt, *J*=17.3 Hz, 2F) ppm; ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -91.4 (s, 2F) ppm; IR (neat) 2914 (br., m), 2743 (br., m), 1669 (s), 1251 (m), 1163 (m) cm⁻¹; MS (ESI+) *m/z* 329.3 [M+H]⁺, 351.3 [M+Na]⁺; HRMS (ESI+) for C₁₇H₂₇F₂N₂O₂ [M+H]⁺, calculated 329.2035, found 329.2033 (+0.7 ppm error), for C₁₇H₂₆F₂N₂NaO₂ [M+Na]⁺, calculated 351.1855, found 351.1847 (+2.0 ppm error).

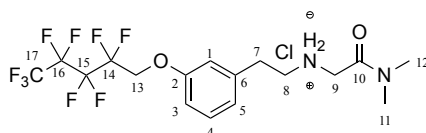
2-((3-(2,2,3,3,4,4-Hexafluoropentoxy)phenethyl)amino)-N,N-dimethylacetamide•HCl (**1g**)



Using general procedure C with **E6** (30 mg) in CH₂Cl₂ (0.5 mL), and **20** (79 mg) dissolved in DMF (0.5 mL), **23g** was obtained as a colorless gum (58 mg, 74%). According to general procedure B, *N*-Boc cleavage of **23g** (58 mg, 1 equiv) yielded **1g** as an off white solid (44 mg, 87%). ¹H NMR (400 MHz,

CDCl₃) δ 9.61 (br s, 2 H, NH₂⁺), 7.25 (t, *J*=7.9 Hz, 2H, H4), 6.98 (br. d, *J*=7.5 Hz, 1H, H5), 6.93 (s, 1H, H1), 6.83 (dd, *J*=8.0, 1.8 Hz, 1H, H3), 4.44 (t, *J*=13.6 Hz, 2H, H13), 4.01 (s, 2H, H9), 3.49–3.33 (m, 2H, H8), 3.33–3.25 (m, 2H, H7), 2.96 (s, 3H, H11 or H12), 2.92 (s, 3H, H11 or H12), 1.85 (t, *J*=19.3 Hz, 3H, H17); ¹³C NMR (101 MHz, CDCl₃) δ 164.5 (C10), 158.0 (C2), 138.3 (C6), 130.1 (C4), 122.8 (C5), 115.5 (C1), 113.7 (C3), 65.4 (t, *J*=25.7 Hz, C13), 49.5 (C8), 48.0 (C9), 36.2 (C11 or C12), 35.7 (C11 or C12), 32.3 (C7), 18.6 (br. t, *J*=24.2 Hz, C17) ppm. C14, C15 and C16 were undetected due to multiple fluorine-fluorine couplings; ¹⁹F NMR (376 MHz, CDCl₃) δ -106.3 (qt, *J*=19.6, 9.5 Hz, 2F, F16), -119.6 (tt, *J*=13.6, 9.5 Hz, 2F, F14), -126.4 (s, 2F, F15) ppm; ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -106.3 (t, *J*=9.5 Hz, 2F, F16), -119.9 (t, *J*=9.5 Hz, 2F, F14), -126.4 (s, 2F, F15) ppm; IR (neat) 2915 (br., m), 2745 (br., m), 1666 (s), 1160 (s), 1123 (m) cm⁻¹; MS (ESI+) *m/z* 401.3 [M+H]⁺, 423.3 [M+Na]⁺; HRMS (ESI+) for C₁₇H₂₃F₆N₂O₂ [M+H]⁺, calculated 401.1658, found 401.1660 (-0.5 ppm error), for C₁₇H₂₂F₆N₂NaO₂ [M+Na]⁺, calculated 423.1478, found 423.1476 (+0.5 ppm error).

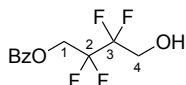
2-((3-(2,2,3,3,4,4,5,5-Heptafluorobutoxy)phenethyl)amino)-*N,N*-dimethylacetamide•HCl (**1h**)



Using general procedure C with **E5** (20 mg) in CH₂Cl₂ (0.3 mL) and **20** (31 mg) dissolved in DMF (0.2 mL), **23h** was obtained as a colorless gum (31 mg, 70%). According to general procedure B, *N*-Boc cleavage of **23h** (57 mg, 1 equiv) yielded **1h** as an off white solid (46 mg, 91%). ¹H NMR (500 MHz, CDCl₃) δ 9.58 (br s, 2 H, NH₂⁺), 7.23 (t, *J*=7.9 Hz, 2H, H4), 6.98 (d, *J*=7.4 Hz, 1H, H5), 6.94 (s, 1H, H1), 6.81 (dd, *J*=9.2, 2.1 Hz, 1H, H3), 4.46 (t, *J*=12.9 Hz, 2H, H13), 4.05 (s, 2H, H9), 3.46–3.35 (m, 2H, H8), 3.35–3.25 (m, 2H, H7), 2.96 (s, 3H, H11 or H12), 2.91 (s, 3H, H11 or H12); ¹³C NMR (101 MHz, CDCl₃) δ 164.6 (C10), 157.7 (C2), 138.6 (C6), 130.1 (C4), 123.0 (C5), 115.4 (C1), 113.6 (C3), 65.2 (t, *J*=27.1 Hz, C13), 49.3 (C8), 48.1 (C9) 36.3 (C11 or C12), 35.7 (C11 or C12), 32.2 (C7), C14, C15, C16 and C17 undetected due to multiple fluorine-fluorine couplings; ¹⁹F NMR (471 MHz, CDCl₃) δ -80.9 (tt, *J*=9.7, 2.5 Hz, 3F, F17), -119.8– -119.6 (m, 2F, F14), -124.1– -124.0 (m, 2F, F16), -126.4– -126.2 (m, 2F, F15)

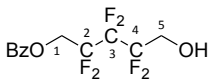
ppm; $^{19}\text{F}\{^1\text{H}\}$ NMR (471 MHz, CDCl_3) δ -80.9 (tt, $J=9.7, 2.5$ Hz, 3F, F17), -119.8– -119.6 (m, 2F, F14), -124.1– -124.0 (m, 2F, F16), -126.5– -126.2 (m, 2F, F15) ppm; IR (neat) 2942 (br., w), 1664 (m), 1231 (s), 1163 (s), 1134 (s) cm^{-1} ; MS (ESI+) m/z 455.3 $[\text{M}+\text{H}]^+$, 477.3 $[\text{M}+\text{Na}]^+$; HRMS (ESI+) for $\text{C}_{17}\text{H}_{20}\text{F}_9\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$, calculated 455.1376, found 455.1387 (-2.6 ppm error), for $\text{C}_{17}\text{H}_{19}\text{F}_9\text{N}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$, calculated 477.1195, found 477.1206 (-2.3 ppm error).

2,2,3,3-Tetrafluoro-4-hydroxybutyl benzoate (4)



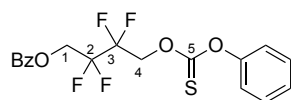
To a solution of benzoyl chloride (1.46 mL, 1.05 equiv) and pyridine (1.94 mL, 2 equiv) in CH_2Cl_2 was added 2,2,3,3-tetrafluoro-1,4-butandiol **2** (1.95 g, 1 equiv) portion wise at 0 °C. After 20 h the reaction was quenched with aq. HCl (2M, 15 mL) and the aqueous phase was extracted with CH_2Cl_2 (2×15 mL). The combined organic phases were washed with sat. aq. NaHCO_3 (2×40 mL) and water (40 mL), dried over MgSO_4 , and concentrated *in vacuo*. The crude oil was purified by column chromatography (CH_2Cl_2) to afford **4** as a colorless oil (1.26 g, 46%). ^1H NMR (500 MHz, CDCl_3) δ 8.12–8.03 (m, 2H, H_{Ar}), 7.68–7.57 (m, 1H, H_{Ar}), 7.52–7.42 (m, 2H, H_{Ar}), 4.82 (tt, $J=14.0, 1.1$ Hz, 2H, H1), 4.10 (t, $J=13.9$ Hz, 2H, H4) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 165.4 (C=O), 133.7 (C_{Ar}), 123.0 ($\text{C}_{\text{Ar}}\times 2$), 128.7 (C_{Ar}), 128.6 ($\text{C}_{\text{Ar}}\times 2$), 116.0 (tt, $J=252.3, 32.2$ Hz, C2 or C3), 115.4 (tt, $J=252.8, 32.9$ Hz, C2 or C3), 60.3 (t, $J=26.3$ Hz, C1 and C4, overlapped) ppm; ^{19}F NMR (376 MHz, CDCl_3) δ -121.4 (t, $J=13.9$ Hz, 2F, F2), -123.9 (t, $J=13.9$ Hz, 2F, F3) ppm; $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3) δ -121.4 (s, 2F, F2), -123.9 (t, $J=5.2$ Hz, 2F, F3) ppm; IR (neat) 3454 (br. w), 3082 (w), 2967 (w), 1730 (s), 1272 (s), 1111 (s), 1072 (s) cm^{-1} ; HRMS (ESI+) for $\text{C}_{11}\text{H}_{10}\text{F}_4\text{NaO}_3$ $[\text{M}+\text{Na}]^+$, calculated 289.0458, found 289.0465 (-2.3 ppm error).

2,2,3,3,4,4-Hexafluoro-5-hydroxypentyl benzoate (5)



To a solution of 2,2,3,3,4,4-hexafluoropentane-1,5-diol **3** (5.00 g, 1 equiv) and pyridine (3.81 mL, 2 equiv) in CH₂Cl₂ (50 mL) was added a solution of benzoyl chloride (3.29 mL, 1.2 equiv) in CH₂Cl₂ (100 mL) dropwise over 30 min at 0 °C. The reaction was allowed to warm to rt and was quenched after 24 h with water (75 mL). The aqueous phase was washed with CH₂Cl₂ (2×30 mL), and the combined organic phases were washed with aq. HCl (1M, 50 mL) and sat. aq. NaHCO₃ (100 mL). The organic phase was dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by column chromatography (CH₂Cl₂) to afford **5** as a colorless oil (4.02 g, 54%). ¹H NMR (500 MHz, CDCl₃) δ 8.12–8.05 (m, 2H, H_{Ar}), 7.66–7.59 (m, 1H, H_{Ar}), 7.51–7.45 (m, 2H, H_{Ar}), 4.82 (t, *J*=13.9 Hz, 2H, H1), 4.11 (t, *J*=13.8 Hz, 2H, H5), 2.34 (br. s, 1H, OH) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 165.2 (C=O), 133.8 (C_{Ar}), 130.0 (C_{Ar}×2), 128.6 (C_{Ar}×2), 128.5 (C_{Ar}), 115.6 (tt, *J*=255.6, 29.8 Hz, C4), 114.8 (tt, *J*=256.4, 31.0 Hz, C2), 111.5 (tquin, *J*=263.5, 33.1 Hz, C3), 60.6 (t, *J*=25.5 Hz, C5), 60.3 (t, *J*=26.7 Hz, C1) ppm; ¹⁹F NMR (471 MHz, CDCl₃) δ -119.7 (tt, *J*=13.9, 10.3 Hz, F2), -122.5 (tt, *J*=14.7, 9.9 Hz, F4), -125.7 (s, F3) ppm; ¹⁹F{¹H} NMR (471 MHz, CDCl₃) δ -119.7 (t, *J*=10.0 Hz, F2), -122.5 (t, *J*=10.0 Hz, F4), -125.7 (s, F3) ppm; IR (neat) 3459 (br. w), 2997 (w), 1733 (s), 1268 (s), 1147 (s) cm⁻¹; HRMS (ESI+) for C₁₂H₁₀F₆NaO₃ [M+Na]⁺, calculated 339.0426, found 339.0425 (+0.3 ppm error).

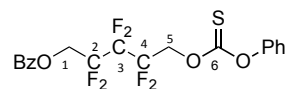
2,2,3,3-Tetrafluoro-4-(phenoxythiocarbonyloxy)butyl benzoate (**6**)



To a solution of **4** (1.26 g, 1 equiv) and pyridine (0.90 mL, 2 equiv) in CH₂Cl₂ (25 mL) was added *O*-phenyl chlorothionoformate 0.93 mL, 1.2 equiv) dropwise. After 1.5 h the reaction mixture was diluted with CH₂Cl₂ (25 mL), washed with sat. aq. NaHCO₃ (50 mL) and the organic phase was dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by column chromatography (3:97, Et₂O/pentane) to afford **6** as a colorless oil (1.37 g, 61%). ¹H NMR (500 MHz, CDCl₃) δ 8.14–8.07 (m, 2H, H_{Ar}), 7.67–7.60 (m, 1H, H_{Ar}), 7.52–7.47 (m, 2H, H_{Ar}), 7.47–7.42 (m, 2H, H_{Ar}), 7.35–7.30 (m, 1H, H_{Ar}), 7.15–7.08 (m, 2H, H_{Ar}), 5.03 (tt, *J*=31.4, 1.3 Hz, 2H, H4), 4.85 (tt, *J*=13.5, 1.2 Hz, 2H, H1) ppm;

¹³C NMR (126 MHz, CDCl₃) δ 194.0 (C5), 165.1 (C=O), 153.4 (C_{Ar}), 133.8 (C_{Ar}), 130.0 (C_{Ar}×2), 129.7 (C_{Ar}×2), 128.6 (C_{Ar}×2), 128.6 (C_{Ar}), 126.9 (C_{Ar}), 121.6 (C_{Ar}×2), 115.1 (tt, *J*=254.9, 31.7 Hz, C2), 114.6 (tt, *J*=255.0, 33.0 Hz, C3), 67.7 (t, *J*=26.7 Hz, C4), 59.9 (t, *J*=27.4 Hz, C1) ppm; **¹⁹F NMR** (471 MHz, CDCl₃) δ -120.4– -120.5 (m, 2F, F3), -120.5– -120.6 (m, 2F, F2) ppm; **¹⁹F{¹H} NMR** (471 MHz, CDCl₃) δ -120.3– -120.5 (m, 2F, F3), -120.5– -120.7 (m, 2F, F2) ppm; **IR** (neat) 3064 (w), 2963 (w), 1734 (s), 1266 (s), 1244 (s), 1228 (s), 1196 (s) cm⁻¹; **HRMS** (ESI+) for C₁₈H₁₄F₄NaO₄S [M+Na]⁺, calculated 425.0441, found 425.0447 (-1.5 ppm error).

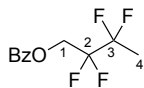
2,2,3,3,4,4-Hexafluoro-5-((phenoxythiocarbonyl)oxy)pentyl benzoate (7)



To a solution of **5** (3.10 g, 1 equiv) in CH₂Cl₂ (110 mL) was added pyridine (3.37 mL, 4.25 equiv) then *O*-phenyl chlorothioformate (1.62 mL, 1.2 equiv) at 0 °C. The reaction was allowed to warm to rt and after 1.5 h the reaction mixture was diluted with CH₂Cl₂ (50 mL) and quenched with sat. aq. NaHCO₃ (50 mL). The aqueous phase was extracted with CH₂Cl₂ (3×50 mL) and the combined organic phases were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by column chromatography (3:97, Et₂O/petroleum ether 40-60 °C) to afford **7** as a pale-yellow oil (3.81 g, 86%). **¹H NMR** (500 MHz, CDCl₃) δ 8.14–8.06 (m, 2H, H_{Ar}), 7.64 (tt, *J*=7.5, 1.3 Hz, 1H, H_{Ar}), 7.53–7.47 (m, 2H, H_{Ar}), 7.48–7.42 (m, 2H, H_{Ar}), 7.37–7.30 (m, 1H, H_{Ar}), 7.17–7.12 (m, 2H, H_{Ar}), 5.03 (t, *J*=13.4 Hz, 2H, H5), 4.87 (t, *J*=13.6 Hz, 2H, H1) ppm; **¹³C NMR** (126 MHz, CDCl₃) δ 193.9 (C6), 165.0 (C=O), 153.4 (C_{Ar}), 133.8 (C_{Ar}), 130.0 (C_{Ar}×2), 129.7 (C_{Ar}×2), 128.6 (C_{Ar}×2), 128.5 (C_{Ar}), 126.9 (C_{Ar}), 121.6 (C_{Ar}×2), 114.8 (tt, *J*=256.8, 31.3 Hz, C2), 114.3 (tt, *J*=259.1, 31.3 Hz, C4), 111.1 (tquin, *J*=263.7, 32.4 Hz, C3), 67.8 (t, *J*=26.2 Hz, C5), 60.2 (t, *J*=26.9 Hz, C1) ppm; **¹⁹F NMR** (471 MHz, CDCl₃) δ -119.0– -119.2 (m, 2F, F4), -119.2– -119.4 (m, 2F, F2), -125.2 (s, 2F, F3) ppm; **¹⁹F{¹H} NMR** (471 MHz, CDCl₃) δ -119.1 (t, *J*=10.7 Hz, 2F, F4), -119.3 (t, *J*=10.4 Hz, 2F, F2), -125.2 (s, 2F, F3) ppm; **IR** (neat) 3065 (w), 2964 (w), 1735 (s), 1490

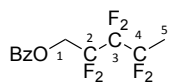
(m), 1265 (s), 1196 (s), 1150 (s) cm^{-1} ; **HRMS** (ESI+) for $\text{C}_{19}\text{H}_{14}\text{F}_6\text{NaO}_4\text{S}$ $[\text{M}+\text{Na}]^+$ calculated 475.0709, found 475.0420 (-2.3 ppm error).

2,2,3,3-Tetrafluorobutyl benzoate (8)



To a solution of **6** (1.36 g, 1 equiv) in toluene (20 mL, degassed) was added triethylsilane (2.70 mL, 5 equiv) and benzoyl peroxide (0.17 g, 0.2 equiv). The reaction was then brought to reflux. After 90 min, more triethylsilane (2.70 mL, 5 equiv) and benzoyl peroxide (0.17 g, 0.2 equiv) was added, and the reaction was brought back to reflux. After 2 h the reaction mixture was concentrated *in vacuo* and purified by column chromatography (1:99, Et_2O /pentane) to afford **8** as a colorless oil (0.79 g, 93%). **^1H NMR** (500 MHz, CDCl_3) δ 8.15–8.03 (m, 2H, H_{Ar}), 7.64–7.58 (m, 1H, H_{Ar}), 7.51–7.46 (m, 2H, H_{Ar}), 4.78 (tt, $J=13.9, 1.2$ Hz, 2H, H1), 1.82 (tt, $J=19.1, 1.8$ Hz, 3H, H4) ppm; **^{13}C NMR** (126 MHz, CDCl_3) δ 165.4 (C=O), 133.6 (C_{Ar}), 130.0 ($\text{C}_{\text{Ar}}\times 2$), 128.9 (C_{Ar}), 128.5 ($\text{C}_{\text{Ar}}\times 2$), 118.5 (tt, $J=247.2, 34.6$ Hz, C-2), 115.0 (tt, $J=251.7, 35.6$ Hz, C3), 59.8 (t, $J=26.8$ Hz, C1), 17.4 (t, $J=24.6$ Hz, C4) ppm; **^{19}F NMR** (471 MHz, CDCl_3) δ -107.1– -107.3 (m, 2F, F3) -120.9– -121.1 (m, 2F, F2) ppm; **$^{19}\text{F}\{^1\text{H}\}$ NMR** (471 MHz, CDCl_3) δ -107.2– -107.3 (m, 2F, F3) -120.9– -121.1 (m, 2F, F2) ppm; **IR** (neat) 3070 (w), 2968 (w), 1733 (s), 1452 (m), 1273 (s), 1108 (s), 1066 (s) cm^{-1} ; **HRMS** (ESI+) for $\text{C}_{11}\text{H}_{10}\text{F}_4\text{NaO}_2$ $[\text{M}+\text{Na}]^+$, calculated 273.0509, found 273.0515 (-2.1 ppm error).

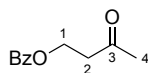
2,2,3,3,4,4-Hexafluoropentyl benzoate (9)



A solution of **7** (3.60 g, 1 equiv) in toluene (40 mL, degassed) and triethylsilane (6.36 mL, 5 equiv) was heated to reflux and benzoyl peroxide (387.0 mg, 0.2 equiv) was added. Benzoyl peroxide (387.0 mg, 0.2 equiv) and triethylsilane (6.36 mL, 5 equiv) were then added every 30 min to the refluxing reaction mixture until all the starting material had been consumed (3 additions). The reaction mixture was then

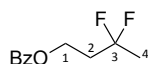
concentrated *in vacuo* and the crude oil was purified by column chromatography (2:98, Et₂O/petroleum ether 40-60 °C) to afford **9** as a pale-yellow oil (2.17 g, 91%). **¹H NMR** (400 MHz, CDCl₃) δ 8.13–8.06 (m, 2H, H_{Ar}), 7.66–7.58 (m, 1H, H_{Ar}), 7.52–7.43 (m, 2H, H_{Ar}), 4.81 (t, *J*=13.9 Hz, 2H, H1), 1.94–1.77 (m, 3H, H5) ppm; **¹³C NMR** (126 MHz, CDCl₃) δ 165.1 (C=O), 133.7 (C_{Ar}), 130.0 (C_{Ar}×2), 128.6 (C_{Ar}), 128.6 (C_{Ar}×2), 117.9 (tt, *J*=250.2, 31.9 Hz, C4), 114.9 (tt, *J*=256.3, 30.9 Hz, C2), 111.2 (ttt, *J*=261.5, 34.3, 31.5 Hz, C3), 60.5 (t, *J*=26.5 Hz, C1), 18.5 (t, *J*=24.2 Hz, C5) ppm; **¹⁹F NMR** (376 MHz, CDCl₃) δ -106.4 (qt, *J*=19.1, 9.5 Hz, 2F, F4), -119.5 (tt, *J*=13.9, 10.4 Hz, 2F, F2), -126.4 (s, 2F, F3) ppm; **¹⁹F{¹H} NMR** (376 MHz, CDCl₃) δ -106.4 (t, *J*=9.5 Hz, 2F, F4), -119.5 (t, *J*=10.4 Hz, 2F, F2), -126.4 (s, 2F, F3) ppm; **IR** (neat) 3065 (w), 2964 (w), 1735 (s), 1267 (s), 1151 (s), 1107 (s) cm⁻¹; **HRMS** (ESI+) for C₁₂H₁₀F₆NaO₂ [M+Na]⁺, calculated 323.0477, found 323.0483 (-1.7 ppm error).

3-Oxobutyl benzoate (11)



A stirred solution of benzoyl chloride (8.6 mL, 1.3 equiv), CH₂Cl₂ (30 mL) and pyridine (9.2 mL, 2 equiv) was prepared at 0 °C. After 1 h 4-hydroxy butan-2-one **10** (4.9 mL, 1 equiv) was added dropwise, and the reaction mixture was allowed to warm to rt. After 19 h, further benzoyl chloride (3 mL, 0.45 equiv) was added. After 21 h, the reaction mixture was washed with aq. HCl (2 M, 50 mL), aq. sat. NaHCO₃ (2×50 mL) and water (50 mL). The organic phase was dried over MgSO₄ and concentrated to afford **11** as a colorless oil (10.10 g, 93%). **¹H NMR** (CDCl₃, 400 MHz) δ 7.99 (dd, *J*=8.2, 1.0 Hz, 2H, H_{Ar}), 7.51–7.61 (m, 1H, H_{Ar}), 7.36–7.47 (m, 2H, H_{Ar}), 4.58 (t, *J*=6.3, 2H, H1), 2.90 (t, *J*=6.3 Hz, 2H, H2), 2.22 (s, 3H, H4) ppm; **¹³C NMR** (CDCl₃, 101 MHz) δ 205.5 (C3), 166.3 (PhC=O), 133.0 (C_{Ar}), 129.9 (C_{Ar}), 129.5 (C_{Ar}×2), 128.3 (C_{Ar}×2), 59.8 (C1), 42.3 (C2), 30.2 (C4) ppm. Data consistent with literature.⁵⁵

3,3-Difluorobutyl benzoate (12)



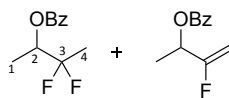
To a solution of **11** (9.50 g, 1 equiv) in CH₂Cl₂ (40 mL), DAST (13.06 mL, 2 equiv) was added dropwise at 0 °C. The reaction mixture was then heated to 40 °C. After 41 h the reaction was cooled to 0 °C, diluted with CH₂Cl₂ (50 mL) and neutralized with aq. sat. NaHCO₃ until pH 7. The aqueous phase was washed with CH₂Cl₂ (3×100 mL) and the combined organic phases were dried over MgSO₄ and concentrated *in vacuo*. The crude oil was purified by column chromatography (1:9, Et₂O/pentane) to afford **12** as a pale-yellow oil (8.90 g, 84%). ¹H NMR (CDCl₃, 400 MHz) δ 8.05 (dd, *J*=8.1, 1.0 Hz, 2H, H_{Ar}), 7.66–7.53 (m, 1H, H_{Ar}), 7.50–7.42 (m, 2H, H_{Ar}), 4.53 (t, *J*=6.5 Hz, 2H, H1), 2.38 (tt, *J*=15.4, 6.6 Hz, 2H, H2), 1.71 (t, *J*=18.6 Hz, 3H, H4) ppm; ¹³C NMR (CDCl₃, 101 MHz) δ 166.3 (C=O), 133.1 (C_{Ar}), 129.9 (C_{Ar}), 129.6 (C_{Ar}×2), 128.4 (C_{Ar}×2), 123.0 (t, *J*=237.7 Hz, C3), 59.2 (t, *J*=6.2 Hz, C1), 37.1 (t, *J*=26.0 Hz, C2), 23.8 (t, *J*=27.5 Hz, C4) ppm; ¹⁹F NMR (CDCl₃, 376 MHz) δ -89.7– -90.0 (m, 2F) ppm; ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -89.8 (s, 2F) ppm; IR (neat) 2980 (w), 1710 (s), 1270 (s), 700 (s) cm⁻¹; HRMS (ESI+) for C₁₁H₁₂F₂NaO₂ [M+Na]⁺, calculated 237.0698, found 237.0698 (-0.1 ppm error).

3-Oxobutan-2-yl benzoate (**14**)



To a solution of acetoin **13** (7.30 g, 1 equiv), pyridine (12.8 mL, 2 equiv) and DMAP (1.07 g, 0.1 equiv) in CH₂Cl₂ (100 mL) was added benzoic anhydride (19.68 g, 1.1 equiv). After 10 h the reaction mixture was quenched with water (250 mL) under vigorous stirring. The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3×200 mL). The combined organic extracts were washed with aq. HCl (2 M, 50 mL) followed by aq. sat. NaHCO₃ (200 mL), dried over MgSO₄ and concentrated. The crude was purified by column chromatography (2:1, petroleum ether 40-60 °C/Et₂O) to afford **14** as a colorless oil (10.37 g, 63 %). ¹H NMR (400 MHz, CDCl₃) δ 8.08–8.12 (m, 2H, H_{Ar}), 7.61 (tt, *J*=7.5, 1.34 Hz, 1H, H_{Ar}), 7.45–7.51 (m, 2H, H_{Ar}), 5.34 (q, *J*=7.1 Hz, 1H, H2), 2.26 (s, 3H, H4), 1.55 (d, *J*=7.1 Hz, 3H, H1) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 205.8 (C3), 165.9 (C=O), 133.4 (C_{Ar}), 129.8 (C_{Ar}×2), 129.4 (C_{Ar}), 128.5 (C_{Ar}×2), 75.5 (C2), 25.7 (C4), 16.2 (C1) ppm. Data consistent with literature.⁵⁶

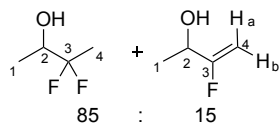
3,3-Difluorobutan-2-yl benzoate (15)



To a solution of **14** (2.99 g, 1 equiv) in dry CH_2Cl_2 (50 mL) was added DAST (4.1 mL, 2 equiv) at 0 °C. The reaction mixture was allowed to warm to rt and then heated at 40 °C. After 48 h the reaction mixture was cooled to 0 °C and quenched with sat. aq. NaHCO_3 till pH 7. The layers were then separated and the aqueous phase was extracted with CH_2Cl_2 (2×150 mL), dried over MgSO_4 and concentrated. The crude was purified by column chromatography (9:1, petroleum ether 40-60 °C/ Et_2O) to afford a mixture of **15** and **16** as a pale-yellow oil (2.02 g, 61 % ~9:1 mix). **^1H NMR** (400 MHz, CDCl_3) δ 8.10–8.05 (m, 2H, H_{Ar}), 7.64–7.57 (m, 1H, H_{Ar}), 7.51–7.44 (m, 2H, H_{Ar}), 5.33 (ddq, $J=12.9, 7.6, 6.5$ Hz, 1H, H2), 1.70 (t, $J=18.7$ Hz, 3H, H4), 1.45 (d, $J=6.6$ Hz, 3H, H1) ppm; **^{13}C NMR** (101 MHz, CDCl_3) δ 165.3 (C=O), 133.4 (C_{Ar}), 129.8 ($\text{C}_{\text{Ar}}\times 2$), 129.6 (C_{Ar}), 128.5 ($\text{C}_{\text{Ar}}\times 2$), 121.9 (dd, $J=243.2, 241.0$ Hz, C3), 71.0 (dd, $J=33.0, 30.1$ Hz, C2), 20.0 (t, $J=26.4$ Hz, C4), 13.7 (t, $J=3.3$ Hz, C1) ppm; **^{19}F NMR** (376 MHz, CDCl_3) δ -100.4 (dq, $J=251.4, 19.1, 6.9$ Hz, 1F, FF'), -104.8 (dq, $J=251.4, 18.5, 12.1$ Hz, 1F, FF') ppm; **$^{19}\text{F}\{^1\text{H}\}$ NMR** (376 MHz, CDCl_3) δ -100.4 (d, $J=251.4$ Hz, 1F, FF'), -104.8 (d, $J=251.4$ Hz, 1F, FF') ppm; **IR** (neat) 3076 (w), 2999 (w), 2961 (w), 1723 (s), 1268 (s), 1246 (s), 1105, 1071 (s) cm^{-1} ; **HRMS** (CI) for $\text{C}_{11}\text{H}_{12}\text{F}_2\text{O}_2$ [M^+], calculated 214.07999, found 214.07960 (-0.39 ppm error).

Data for **16**: **^1H NMR** (400 MHz, CDCl_3) δ 8.10–8.05 (m, 2H, H_{Ar}), 7.64–7.57 (m, 1H, H_{Ar}), 7.51–7.44 (m, 2H, H_{Ar}), 5.66 (dq, $J=13.4, 6.6$ Hz, 1H, CH), 4.72 (m, 2H, CH_2), 1.55 (d, $J=6.6$, 2H, CH_3) ppm; **^{13}C NMR** (101 MHz, CDCl_3) δ (C_{Ar} , C=O, C-F not observed likely due to overlap with **15** and low concentration) 91.86 (d, $J=17.6$ Hz, CH_2), 68.10 (d, $J=32.3$ Hz, CH), 17.45 (d, $J=2.2$ Hz, CH_3) ppm; **^{19}F NMR** (376 MHz, CDCl_3) δ -110.5 ppm (ddd, $J=48.6, 16.5, 13.0$ Hz) ppm; **$^{19}\text{F}\{^1\text{H}\}$ NMR** (376MHz, CDCl_3) δ -110.5 ppm (s) ppm; **HRMS** (CI) for $\text{C}_{11}\text{H}_{12}\text{FO}_2$ [$\text{M}+\text{H}$] $^+$, calculated 195.08158, found 195.08000 (-1.59 ppm error).

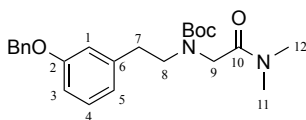
3,3-Difluorobutan-2-ol (C4) and 3-fluorobut-3-en-2-ol (17)



To the mixture of **15** and **16** (800 mg, 1 equiv) in Et₂O (20 mL) was added NaOMe in MeOH (25 %, 16 mL, 2 equiv). After 24 h the reaction mixture was neutralized with aq. HCl (2 M) until pH 7. The aqueous phase was extracted with Et₂O (3×30 mL) and the combined organic layers were dried over MgSO₄ and carefully concentrated (30 °C, 750 mbar). The crude mixture was purified by column chromatography (9:1 to 1:1, pentane/Et₂O) to yield C4 and **17** as a mixture (247 mg, 60%, ~85:15 mix). **Data for C4:** ¹H NMR (400 MHz, CDCl₃) δ 3.90 (tqd, *J*=9.5, 6.5, 5.6 Hz, 1H, H2), 1.92 (d, *J*=5.6 Hz, 1H, OH), 1.62 (t, *J*=18.9 Hz, 3H, H4), 1.28 (d, *J*=6.5 Hz, 3H, H1) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 123.9 (dd, *J*=241.4, 239.9 Hz, C3), 69.8 (dd, *J*=30.1, 28.6 Hz, C2), 18.6 (t, *J*=26.8 Hz, C4), 16.3 (dd, *J*=4.4, 2.2 Hz, C1) ppm; ¹⁹F NMR (376 MHz, CDCl₃) δ -102.5 (dq, *J*=248.0, 19.1, 8.7 Hz, 1F, FF'), -105.7 (dq, *J*=248.0, 19.1, 10.0 Hz, 1F, FF') ppm; ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -102.6 (d, *J*=275.7 Hz, 1F, FF'), -105.7 (d, *J*=248.0 Hz, 1F, FF') ppm; IR (neat) 3390 (br. w), 2988 (w), 2924 (w), 1111 (s), 1081 (s), 918 (m) cm⁻¹; HRMS (CI) for C₄H₇OF₂ [M-H]⁻, calculated 109.0460, found 109.0473 (+1.34 ppm error).

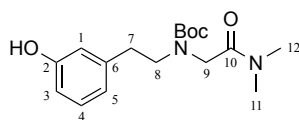
Data for 17: ¹H NMR (400 MHz, CDCl₃) δ 4.62 (d, *J*=3.2 Hz, 1H, H4b), 4.58 (dd, *J*=67.0, 3.2 Hz, 1H, H4a), 4.33 (dq, *J*=17.2, 6.0, 0.6 Hz, 1H, H2), 1.84 (d, *J*=1.84 Hz, 1H, OH), 1.39 (dd, *J*=6.6, 0.5 Hz, 3H, H1) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 167.7 (d, *J*=259.69, C3), 89.2 (d, *J*=18.4 Hz, C4), 66.1 (d, *J*=32.3 Hz, C2), 20.3 (d, *J*=1.5 Hz, C1) ppm; ¹⁹F NMR (376 MHz, CDCl₃) δ -110.8 (ddd, *J*=49.0, 17.8, 9.5 Hz) ppm; ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -110.8 (s) ppm; HRMS (CI) for C₄H₈FO [M+H]⁺, calculated 91.0554, found: 91.0560 (+0.6 ppm error).

2-((3-(Benzyloxy)phenethyl)-N-Boc-amino)-N,N-dimethylacetamide (**19**)



To a suspension of sodium hydride 60% in mineral oil (0.57 g, 2 equiv) in DMF (35 mL) at 0 °C was added a solution of **18** (2.35 g, 1 equiv) in DMF (35 mL) dropwise. The reaction mixture was allowed to warm to rt and after 1 h, 2-chloroacetamide (1.47 mL, 2 equiv) was added. After 24 h, the reaction was quenched with water (5 mL) and the solvent was removed *in vacuo*. The residue was dissolved in water (40 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated. The crude was purified by column chromatography (1:1, EtOAc/heptane) to afford **19** as a colorless gum (2.46 g, 83%). ¹H NMR (400 MHz, CDCl₃, mixture of rotamers) δ 7.46–7.41 (m, 2H, H_{Ar}), 7.40–7.35 (m, 2H, H_{Ar}), 7.35–7.29 (m, 1H, H_{Ar}), 7.19 (t, *J*=7.7 Hz, 1H, H₄), 6.93–6.71 (m, 3H, H₁ + H₃ + H₅), 5.04 (s, 2H, PhCH₂), 3.94 (s, 2H, H₉ major), 3.82 (s, 2H, H₉ minor), 3.51 (m, 2H (*J*=7.4 observed br t, H₈ major and minor), 2.97–2.88 (m, 6H, H₁₁ + H₁₂), 2.82 (m, 2H (*J*=7.4 observed br t, H₇ major and minor), 1.52–1.39 (m, 9H, CH₃×3, Boc) ppm; ¹³C NMR (101 MHz, CDCl₃) δ (only major rotamer reported) 168.6 (C₁₀), 158.9 (C₂), 155.9 (C=O, Boc), 141.2 (C₆), 137.1 (C_{Ar}), 129.4 (C₄), 128.6 (C_{Ar}×2), 127.9 (C_{Ar}), 127.5 (C_{Ar}×2), 121.6 (C₅), 115.6 (C₁), 112.4 (C₃), 80.0 (C-(Me)₃), 69.9 (C₁₃), 50.0 (C₈), 48.7 (C₉), 36.2 (C₁₁ or C₁₂), 35.7 (C₁₁ or C₁₂), 35.0 (C₇), 28.4 (CH₃×3, Boc) ppm; IR (neat) 2974 (m), 1691 (s), 1663 (s), 1252 (s), 1156 (s) cm⁻¹; MS (ESI+) *m/z* 413.4 [M+H]⁺, 435.4 [M+Na]⁺; HRMS (ESI+) for C₂₄H₃₃N₂O₄ [M+H]⁺, calculated 413.2435, found 413.2435 (+0.1 ppm error), for C₂₄H₃₂N₂NaO₄ [M+Na]⁺, calculated 435.2254, found 435.2256 (-0.4 ppm error).

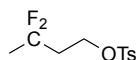
2-((3-Hydroxyphenethyl)-*N*-Boc-amino)-*N,N*-dimethylacetamide (**20**)



To a solution of **19** (2.37 g, 1 equiv) in EtOH (18 mL) was added a slurry of 10% Pd/C (0.50 g) in EtOH (2 mL). The reaction was degassed and placed under a H₂ environment. After 2.5 h the reaction mixture was filtered through celite and concentrated. The crude was purified by column chromatography (3:7, acetone/heptane) to afford **20** as a colorless gum (1.73 g, 93%). ¹H NMR (400 MHz, CDCl₃) δ 7.13 (t, *J*=7.5 Hz, 1H, H₄), 6.75–6.64 (m, 3H, H₁ + H₃ + H₅), 6.40 (s, 1H, OH minor), 6.21 (s, 1H, OH major),

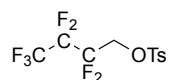
3.95 (s, 2H, H9, major), 3.86 (s, 2H, H9 minor), 3.49 (br t, $J=7.3$ Hz, 2H, H8), 3.01–2.87 (m, 6H, H11 + H12), 2.78 (t, $J=7.3$ Hz, 2H, H7), 1.51–1.40 (m, 9H, $\text{CH}_3 \times 3$, Boc) ppm; ^{13}C NMR (101 MHz, CDCl_3) δ (only major rotamer reported) 168.9 (C10), 156.5 (C2), 156.0 (C=O, Boc), 141.0 (C6), 129.5 (C4), 120.6 (C5), 115.9 (C1), 113.4 (C3), 80.2 (C-(Me)₃), 50.1 (C8), 48.7 (C9), 36.3 (C11 or C12), 35.8 (C11 or C12), 34.8 (C7), 28.3 ($\text{CH}_3 \times 3$, Boc) ppm; IR (neat) 3274 (br. w), 2975 (m), 1646 (s), 1249 (m), 1156 (s) cm^{-1} ; MS (ESI+) m/z 323.4 $[\text{M}+\text{H}]^+$, 345.3 $[\text{M}+\text{Na}]^+$; HRMS (ESI+) for $\text{C}_{17}\text{H}_{27}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$, calculated 323.1965, found 323.1961 (+1.4 ppm error), for $\text{C}_{17}\text{H}_{26}\text{N}_2\text{NaO}_4$ $[\text{M}+\text{Na}]^+$, calculated 345.1785, found 345.1782 (+0.5 ppm error).

3,3-Difluorobutyl tosylate (21b)



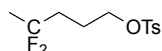
Using general procedure D with 3,3-difluorobutan-1-ol (45 mg) in CH_2Cl_2 (5 mL), **21b** was obtained as a colorless oil (86 mg, 80%). ^1H NMR (500 MHz, CDCl_3) δ 7.84–7.76 (m, 2H), 7.36 (d, $J=8.6$ Hz, 2H), 4.20 (t, $J=6.7$ Hz, 2H), 2.46 (s, 3H), 2.26 (tt, $J=15.2, 6.7$ Hz, 2H), 1.60 (t, $J=18.7$ Hz, 3H) ppm; ^{19}F NMR (471 MHz, CDCl_3) δ -90.2 (tq, $J=18.7, 15.2, 2\text{F}$) ppm; $^{19}\text{F}\{^1\text{H}\}$ NMR (471 MHz, CDCl_3) δ -90.2 (s, 2F) ppm.

2,2,3,3,4,4,4-Heptafluorobutyl tosylate (21d)



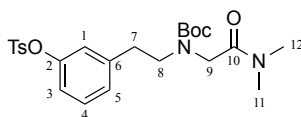
Using general procedure D with 2,2,3,3,4,4,4-heptafluorobutan-1-ol (0.11 g) in CH_2Cl_2 (5 mL), **21d** was obtained as a colorless oil (0.181 g, 93%). ^1H NMR (500 MHz, CDCl_3) δ 7.85–7.78 (m, 2H), 7.39 (d, $J=8.6$ Hz, 2H), 4.45 (tt, $J=12.9, 1.2$ Hz, 2H), 2.48 (s, 3H) ppm; ^{19}F NMR (471 MHz, CDCl_3) δ -80.80 (t, $J=9.1$ Hz, 3F), -120.32– -120.43 (m, 2F), -127.24– -127.38 (m, 2F) ppm; $^{19}\text{F}\{^1\text{H}\}$ NMR (471 MHz, CDCl_3) δ -80.79 (t, $J=9.1$ Hz, 3F), -120.29– -120.46 (m, 2F), -127.21– -127.38 (m, 2F) ppm.

4,4-Difluoropentyl tosylate (21f)



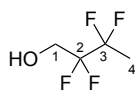
Using general procedure D with 4,4-difluoropentan-1-ol **E4**³¹ (30 mg) in CH₂Cl₂ (2 mL), **21f** was obtained as a colorless oil (53 mg, 79%). ¹H NMR (400 MHz, CDCl₃) δ 7.84–7.75 (m, 2H), 7.36 (dd, *J*=8.6, 0.6 Hz, 2H), 4.08 (t, *J*=5.9 Hz, 2H), 2.47 (s, 3H), 2.00–1.80 (m, 4H), 1.58 (t, *J*=18.3 Hz, 3H) ppm; ¹⁹F NMR (376 MHz, CDCl₃) δ -92.1 (tq, *J*=18.3, 15.6 Hz, 2F) ppm; ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -92.1 (s, 2F) ppm.

2-((3-(Tosyloxy)phenethyl)-*N*,*N*-dimethylacetamide (**24**)



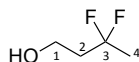
Using general procedure A with **20** (0.150 g) and **21d** (0.181 g) in DMF (2 mL), **24** was obtained as a colorless oil (0.15 g, 68%). ¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, *J*=8.1 Hz, 2H, H_{Ar(o)}), 7.32 (d, *J*=7.9 Hz, 2H, H_{Ar(m)}), 7.19 (t, *J*=7.9 Hz, 1H, H₄), 7.14–7.01 (m, 1H, H₅), 6.86 (br. s, 1H, H₁), 6.80 (br. d, *J*=8.1 Hz, 1H, H₃), 3.91 (s, 2H, H₉, major), 3.79 (s, 2H, H₉ minor), 3.42 (t, *J*=7.3 Hz, 2H, H₈), 2.94 (s, 6H, H₁₁ + H₁₂), 2.86–2.74 (m, 2H, H₇), 2.46 (s, 3H, PhCH₃), 1.55–1.37 (m, 9H, CH₃×3, Boc) ppm; ¹³C NMR (101 MHz, CDCl₃) δ (only major rotamer reported) 168.4 (C₁₀), 155.7 (C=O, Boc), 149.6 (C₂), 145.3 (C_{Ar(i)}), 141.6 (C₆), 132.5 (C_{Ar(p)}), 129.7 (C_{Ar(m)}×2), 129.5 (C₄), 128.4 (C_{Ar(o)}×2), 127.7 (C₅), 122.8 (C₁), 120.1 (C₃), 80.1 (C-(CH₃)₃), 49.9 (C₈), 48.9 (C₉), 36.2 (C₁₁ or C₁₂), 35.7 (C₁₁ or C₁₂), 34.7 (C₇), 28.4 (CH₃×3, Boc), 21.7 (PhCH₃) ppm; IR (neat) 2930 (m), 1695 (s), 1663 (s), 1367 (s), 1178 (s) cm⁻¹; MS (ESI+) *m/z* 477.4 [M+H]⁺, 499.4 [M+Na]⁺; HRMS (ESI+) for C₂₄H₃₃N₂O₆S [M+H]⁺, calculated 477.2054, found 477.2058 (-1.0 ppm error), for C₂₄H₃₂N₂NaO₆S [M+Na]⁺, calculated 499.1873, found 499.1880 (-1.3 ppm error).

2,2,3,3-Tetrafluorobutanol (**D5**)



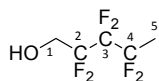
To a solution of **8** (0.67 g, 1 equiv) in Et₂O (50 mL), NaOMe (25% w/w in MeOH, 1.20 mL, 2 equiv) was added dropwise. After 23 h, the reaction was neutralized with aq. HCl (2M, 15 mL) and the aqueous phase was washed with Et₂O (3×90 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated (750 mbar, 30 °C). The crude mixture was purified by column chromatography (CH₂Cl₂) to afford **D5** as a pale-yellow oil (186 mg, 48%). **¹H NMR** (400 MHz, CDCl₃) δ 4.04 (tdt, *J*=14.2, 7.1, 1.3 Hz, 2H, H1), 1.83 (t, *J*=7.3 Hz, 1H, OH), 1.78 (tt, *J*=19.3, 1.7 Hz, 3H, H4) ppm; **¹³C NMR** (126 MHz, CDCl₃) δ 118.8 (tt, *J*=246.3, 34.8 Hz, C2), 115.8 (tt, *J*=250.5, 35.0 Hz, C3), 60.0 (t, *J*=26.3 Hz, C1), 17.6 (t, *J*=24.6 Hz, C4) ppm; **¹⁹F NMR** (376 MHz, CDCl₃) δ -107.3– -107.5 (m, F3), -124.0– -124.1 (m, F2) ppm; **¹⁹F{¹H} NMR** (376 MHz, CDCl₃) δ -107.4– -107.4 (m, F3), -124.0– -124.1 (m, F2) ppm; **IR** (thin film) 3367 (br. w), 2929 (w), 1174 (s), 1118 (s), 1084 (s), 1064 (s) cm⁻¹; **HRMS** (CI) for C₄H₆F₄O [M⁺], calculated 147.04275, found 147.04344 (+0.69 ppm error).

3,3-Difluorobutan-1-ol (D6)



To a solution of **12** (8.90 g, 1 equiv) in Et₂O (90 mL), NaOMe (25% w/w in MeOH, 21.52 mL, 2 equiv) was added dropwise. After 22 h, the reaction mixture was neutralized with aq. HCl (2 M) and the aqueous phase was washed with Et₂O (3x50 mL). The combined organic phases were washed with water (2×100 mL), dried over MgSO₄, and carefully concentrated (30 °C, 750 mbar). The crude mixture was purified by column chromatography (2:8, Et₂O/CH₂Cl₂) to afford **D6** as a pale-yellow oil (1.78 g, 39%). **¹H NMR** (CDCl₃, 400 MHz) δ 3.87 (q, *J*=6.0 Hz, 2H, H1), 2.16 (tt, *J*=16.3, 6.2 Hz, 2H, H2), 1.65 (br s, 1 H, OH), 1.67 (t, *J*=18.8 Hz, 3H, H4) ppm; **¹³C NMR** (CDCl₃, 101 MHz) δ 124.1 (t, *J*=236.2 Hz, C3) 57.3 (t, *J*=5.5 Hz, C1) 40.4 (t, *J*=24.6 Hz, C2) 23.9 (t, *J*=26.4 Hz, C4) ppm; **¹⁹F NMR** (CDCl₃, 376 MHz) δ -89.8 (app. dtd, *J*=34.7, 19.1, 15.6 Hz, 2F) ppm; **¹⁹F{¹H} NMR** (376 MHz, CDCl₃) δ -89.8 (s, 2F) ppm; **IR** (neat) 3387 (br. w), 2972 (w), 2947 (w), 2899 (w), 1124 (s) cm⁻¹; **HRMS** (CI) for C₄H₈F₂O [M⁺], calculated 110.05377, found 110.05312 (-0.65 ppm error).

2,2,3,3,4,4-Hexafluoropentanol (E6).



To a solution of **9** (0.91 g, 1 equiv) in Et₂O (6.6 mL), NaOMe (25% w/w in MeOH, 1.33 mL, 2 equiv) was added dropwise. After 23 h, the reaction was neutralized with aq. HCl (2M, 15 mL) and the aqueous phase was washed with CH₂Cl₂ (3×30 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated (750 mbar, 30 °C). The crude mixture was purified by column chromatography (CH₂Cl₂) to afford **E6** as a pale-yellow oil (256 mg, 45%). **¹H NMR** (400 MHz, CDCl₃) δ 4.08 (tdt, *J*=14.5, 7.5, 1.3 Hz, 2H, H1), 1.89 (tt, *J*=7.1, 0.9 Hz, 1H, OH), 1.83 (ttt, *J*=19.3, 1.9, 0.9 Hz, 3H, H5) ppm; **¹³C NMR** (126 MHz, CDCl₃) δ 118.0 (tt, *J*=249.6, 32.2 Hz, C4), 115.7 (ttt, *J*=254.6, 30.3, 1.2 Hz, C2), 111.4 (ttt, *J*=261.1, 34.3, 31.5 Hz, C3), 60.8 (ttt, *J*=25.4, 2.5, 1.5 Hz, C1), 18.4 (t, *J*=24.3 Hz, C5) ppm; **¹⁹F NMR** (376 MHz, CDCl₃) δ -106.5 (tq, *J*=19.4, 9.1 Hz, 2F, F4), -122.6 (tt, *J*=14.3, 10.0 Hz, 2F, F2), -126.8 (s, 2F, F3) ppm; **¹⁹F{¹H} NMR** (376 MHz, CDCl₃) δ -106.5 (t, *J*=9.5 Hz, 2F, F4), -122.6 (t, *J*=9.5 Hz, 2F, F2), -126.8 (s, 2F, F3) ppm; **IR** (thin film) 3354 (br. w), 2962 (w), 2888 (w), 1397 (m), 1149 (s), 1119 (s), 955 (s) cm⁻¹; **HRMS** (CI) for C₅H₇F₆O [M+H]⁺, calculated 197.03956, found 197.04020 (+0.64 ppm error).

Supporting Information Available. The supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of ¹H, ¹³C, and ¹⁹F NMR spectra of all novel compounds, ¹⁹F NMR spectra of the H₂O and octanol phases of all new fluorohydrin log*P* measurements, tables with the relative Gibbs energy and populations of the energetic minima of **D1**, **D4-6**, **E1**, **E5**, **E6** (PDF). Molecular formula strings (CSV). The raw data are stored in (to be completed in case of acceptance).

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Abbreviations used.

ADME, absorption, distribution, metabolism, excretion; Ar, aromatic; Boc, *t*-butoxycarbonyl; Bz, benzoyl; Cat, catalytic; CI, chemical ionisation; Clint, intrinsic clearance; DAST, diethylaminosulfur trifluoride; DMAP, 4-dimethylamino pyridine; DMF, dimethyl formamide; ESI, electrospray ionisation; Et, ethyl; hERG, human ether-a-go-go related gene; Hu Mics, human microsomes; LC-MS, liquid chromatography-mass spectroscopy; LLE, lipophilic ligand efficiency; $\log P$, lipophilicity; $\log D_{7.4}$, distribution coefficient at pH 7.4; mbar, millibar; Me, methyl; MHz, megahertz; NMR, nuclear magnetic

resonance; pK_a , logarithm of the acid dissociation constant; PPB, plasma protein binding; Rat Heps, rat hepatocytes; ppm, parts per million; PSA, polar surface area; rt, room temperature; SMD, solvation model based on density; Tf, trifluoromethylsulfonyl; TLC, thin layer chromatography; TOF, time of flight; Ts, tosyl; UV, ultraviolet.

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