

# Turning the Other Cheek: Influence of the *cis*-Tetrafluorocyclohexyl Motif on Physicochemical and Metabolic Properties

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Cite This: *ACS Med. Chem. Lett.* 2022, 13, 1517–1523



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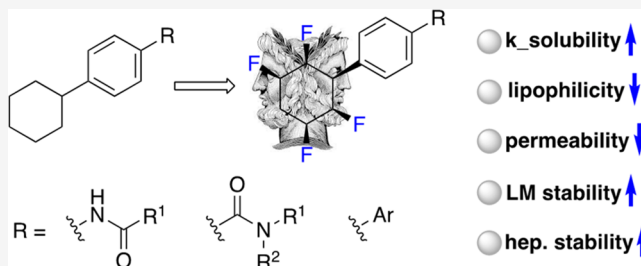
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**ABSTRACT:** The targeted introduction of substituents in order to tailor a molecule's pharmacologic, physicochemical, and metabolic properties has long been of interest to medicinal chemists. The all-*cis* tetrafluorocyclohexyl motif—dubbed Janus face, due to its electrostatically polarized cyclohexyl ring—represents one such example where chemists might incorporate a metabolically stable, polar, lipocompatible motif. To better understand its potential utility, we have synthesized three series of matched molecular pairs (MMPs) where each MMP differs only in the cyclohexane unit, i.e., with a tetrafluorocyclohexyl or a standard cyclohexyl motif. With the introduction of the facially polarized all-*cis* tetrafluorocyclohexyl ring, the resulting compounds have significantly modified physicochemical properties (e.g., kinetic solubility, lipophilicity and permeability) and metabolic stabilities. These results further speak to the promise of this substituent as a tactic to improve the drug-like properties of molecules.

**KEYWORDS:** *Janus face*, tetrafluorocyclohexane, matched molecular pairs, kinetic solubility, log *D*, permeability, metabolic stability



- k<sub>s</sub> solubility** ↑
- lipophilicity** ↓
- permeability** ↓
- LM stability** ↑
- hep. stability** ↑

Drug discovery could be seen as being akin to juggling, with medicinal chemists striving to keep multiple balls in the air when balancing physicochemical, biochemical, and absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties. Despite the advances in screening technologies and predictive science in drug discovery, rational strategies to modulate molecules' drug-like properties are still of high value in the hit-to-lead and lead optimization process. In addition to the classic optimization tactics such as Topliss decision tree approach<sup>1–3</sup> and bioisostere replacement,<sup>4</sup> there is continued interest in structurally editing small molecules by incorporating atoms, such as fluorine, or functional groups to tailor the aforementioned properties.<sup>5–12</sup>

As the most electronegative element ( $\chi = 3.98$  by the Pauling electronegativity scale), fluorine incorporation into molecules can uniquely influence its properties in the context of a drug development program. It presents both a strong dipole moment ( $\mu \text{ C-F} = 1.41 \text{ D}$ ) and a low-lying C–F  $\sigma^*$  orbital available for hyperconjugative donation (*gauche* effect).<sup>13</sup> Indeed, fluorine incorporation has long represented a strategy to modulate the physicochemical and pharmacological properties of small molecular drug candidates, generally resulting in increased lipophilicity and metabolic stability, among other drug-like properties.<sup>10</sup> In the context of alkyl chains and carbocycles, the conformationally controlled inclusion of several C–F bonds can also allow for the polarization of fluorinated alkanes and cycloalkanes. Since 2011, O'Hagan and co-workers have reported on the

properties of multifluorinated cyclohexane rings,<sup>14–22</sup> in particular where no more than one fluorine resides on each carbon and at least two C–F bonds lie 1,3-diaxial to each other. Such a diaxial arrangement should, in principle, generate two parallel C–F bonds and thus polarize the two faces of the cyclohexyl rings. Among other interesting findings, they noted that the introduction of these polarized “Janus face” rings into small molecules could significantly impact the intrinsic physicochemical properties of their parent compounds, based upon individual data points. This encouraged us to explore the utility of this facially fluorinated cyclohexane in terms of both physicochemical and metabolic properties, relative to its nonfluorinated counterpart, in the context of more drug-like molecules. Since few such examples had been reported, we now present data from three subclasses of cyclohexyl- and Janus face cyclohexyl-containing molecular matched pairs (MMPs), and the summarized contributions of this “Janus face” ring on various properties through MMP analysis (Scheme 1).

As a first step, we designed and synthesized three classes of molecular matched pairs that differed only by the inclusion of a

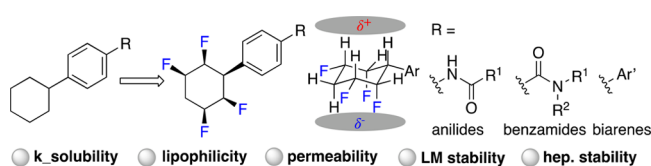
**Received:** July 7, 2022

**Accepted:** August 4, 2022

**Published:** August 14, 2022



### Scheme 1. Scope of Current Study on the Influence of the Facially Polarized “Janus Face” Cyclohexyl Motif on Physicochemical and Metabolic Stabilities<sup>a</sup>



<sup>a</sup>LM, liver microsomes; hep., hepatocytes.

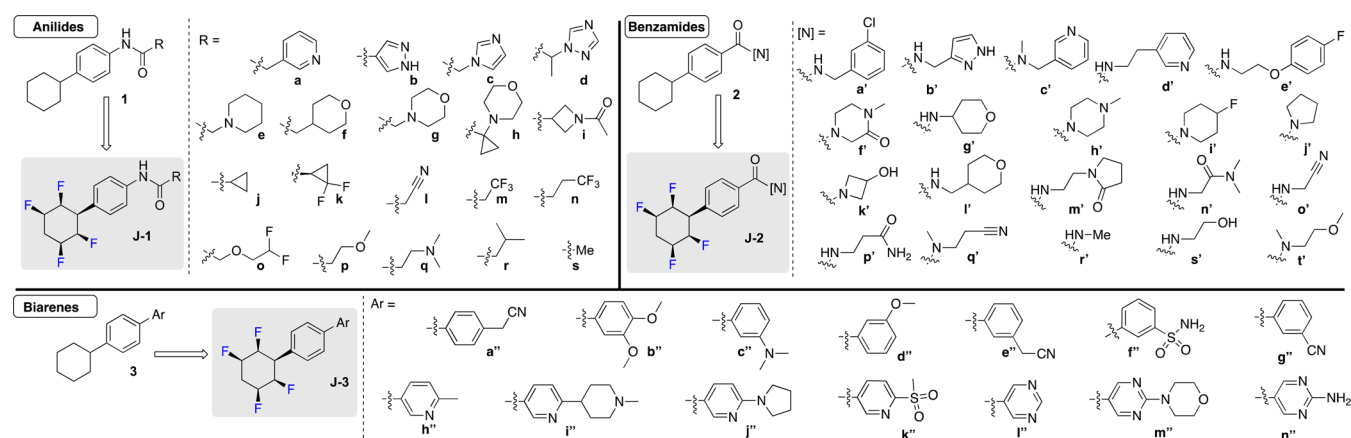
cyclohexyl (Cy) or its corresponding all-*cis* tetrafluorocyclohexyl (Janus-Cy, J-Cy) rings. As displayed in Scheme 2, these MMPs contain functionalities that feature prominently in drugs and drug-like molecules, anilides (1 vs J-1), benzamides (2 vs J-2), and biarenes (3 vs J-3), and incorporate either saturated or unsaturated heterocycles, linear ethers, and amines. For the parent cyclohexyl compounds chosen, they span a range of properties, including molecular weight, topological polar surface area (TPSA), and lipophilicity (see detailed pie charts in Figure S1, Supporting Information). The resulting MMPs were then assessed in a series of high-throughput assays to evaluate their kinetic solubility, lipophilicity, permeability, and metabolic stability.

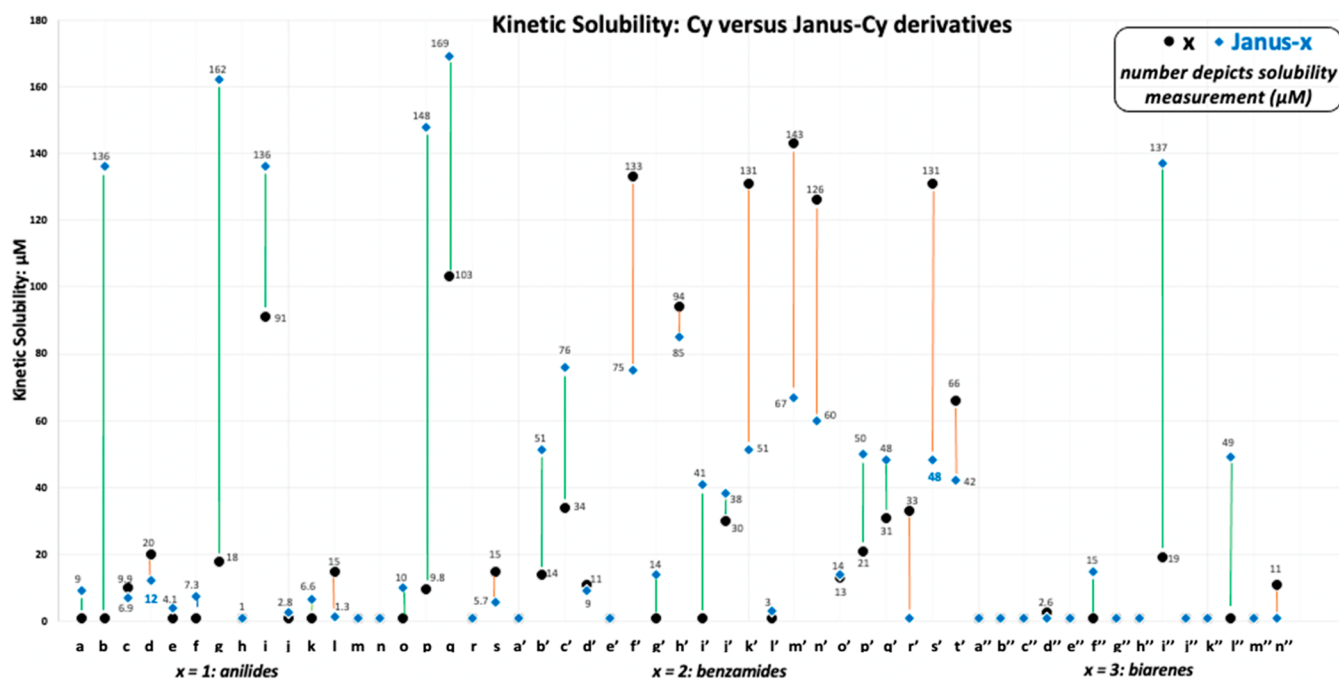
Solubility is a critical parameter in drug design, influencing not only our ability to accurately measure compound properties in *in vitro* assays but also bioavailability and formulation approaches for *in vivo* studies. It is commonplace to measure and attempt to modulate the aqueous solubility of lead compounds during drug discovery, and we were intrigued to explore whether the introduction of a polarized F-substituted cyclohexyl group could influence the kinetic solubility. As shown in Figure 1, the fluorinated Janus face compounds are generally more soluble than corresponding cyclohexane analogues, which is mainly attributed to the large dipole moment (5.2 D) of the tetrafluorocyclohexyl group.<sup>21</sup> For example, in the anilide series, 11 out of 19 MMPs proved more soluble with Janus-Cy compounds. In particular, for those cyclohexyl compounds with very low solubility (e.g., 1a, 1b, 1f, 1k, 1o, all <1 μM), their Janus-Cy matched pairs had significantly increased solubility. For example, for imidazole-containing 1b, replacing with the tetrafluorocyclohexyl group (J-1b) significantly improved its solubility from <1 to 136 μM.

In contrast, for MMPs in the benzamide category, there was no clear trend; some cyclohexyl derivatives, such as 2f, 2h', and 2k', had slightly improved solubility, albeit within a similar range as the Janus-Cy derivatives. In the biarene series, we anticipated that increased levels of *sp*<sup>2</sup>-hybridization in relatively small molecules would result in poor solubility. In general terms, measured solubility was poor across this series, as shown by the number of points on the baseline. Nevertheless, the strategy of introducing facial polarity proved fruitful in a handful of cases. For instance, the corresponding fluorinated compounds of sulfonamide 3f', piperidine 3i'', and pyrimidine 3l'' had significantly improved solubility (greater than 7-fold).

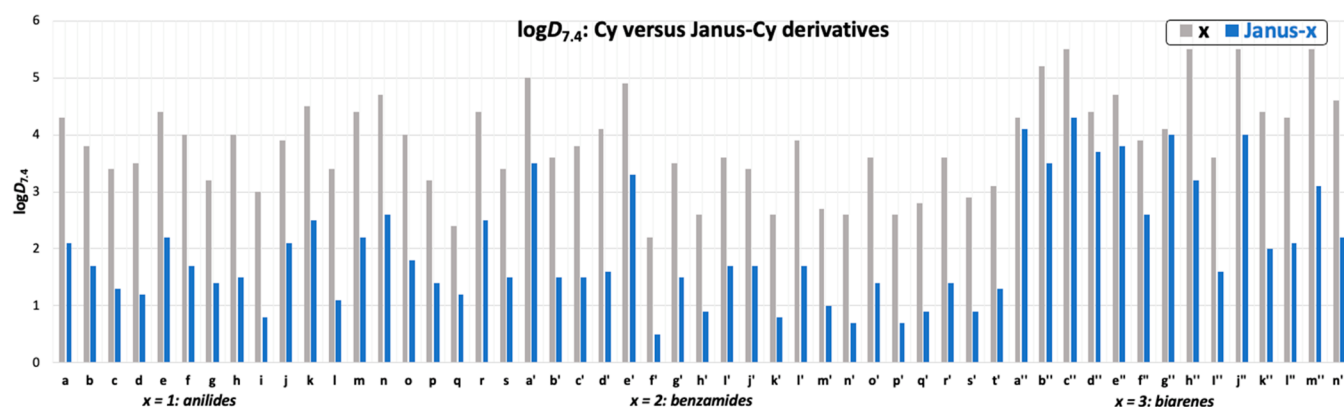
Recognized as a useful bellwether for a range of properties related—but not limited—to the ADMET of orally administered bioactive compounds, lipophilicity has long been a focus of the compound optimization process.<sup>23</sup> Since this is often tracked or calculated as distribution coefficient (log *D*<sub>7.4</sub>) of a compound in octanol versus in water at pH 7.4, we next examined this property, with the trends visualized in Figure 2. It is striking to observe that these “Janus face” analogues had reduced lipophilicity among all the molecules synthesized. While the trend is less pronounced in the biarene series, in both the anilide and benzamide families, the log *D*<sub>7.4</sub> values dropped by around 2 log units. Most of the cyclohexyl-containing anilide compounds shown in Figure 2 have log *D*<sub>7.4</sub> values around 3–4. Upon replacement of cyclohexyl with the fluorinated cyclohexyl group, log *D*<sub>7.4</sub> values dropped to around 2 or lower. A similar trend was observed in the benzamide family. In the biarene series, the same overall trend was observed, albeit without the same level of consistency. In this case, the aforementioned issues with solubility—with increased aromatic character contributing to both high log *D*<sub>7.4</sub> value and property forecast indices<sup>24</sup>—can often confound these measurements.<sup>23</sup> On average, replacement of a Cy group with Janus-Cy lowered measured log *D*<sub>7.4</sub> values by ~1.8, based upon the listed 53 MMPs. Such effective modulation of compound lipophilicity could result in a number of commonly perceived advantages in drug discovery, including improved metabolic stability. Of course, the impact of the polarized cyclohexyl group and resultant electrostatic interactions, such as within protein binding pockets, would be expected to be highly variable, and thus beyond the scope of this work.

### Scheme 2. Three Classes of Matched Molecular Pairs: Cyclohexyl- versus all *cis*-1,2,4,5-Tetrafluorocyclohexyl-Containing Anilides (1 and J-1), Benzamides (2 and J-2), and Biarenes (3 and J-3)





**Figure 1.** MMP analysis of kinetic solubility between cyclohexyl (Cy, black circle) and all *cis*-1,2,4,5-tetrafluorocyclohexyl (Janus-Cy, blue diamond) derivatives. Green lines indicate examples with greater solubility for Janus-Cy; orange lines, greater solubility for Cy. For MMPs with solubility < 1  $\mu\text{M}$ , the black circle and blue diamond overlap in the figure.

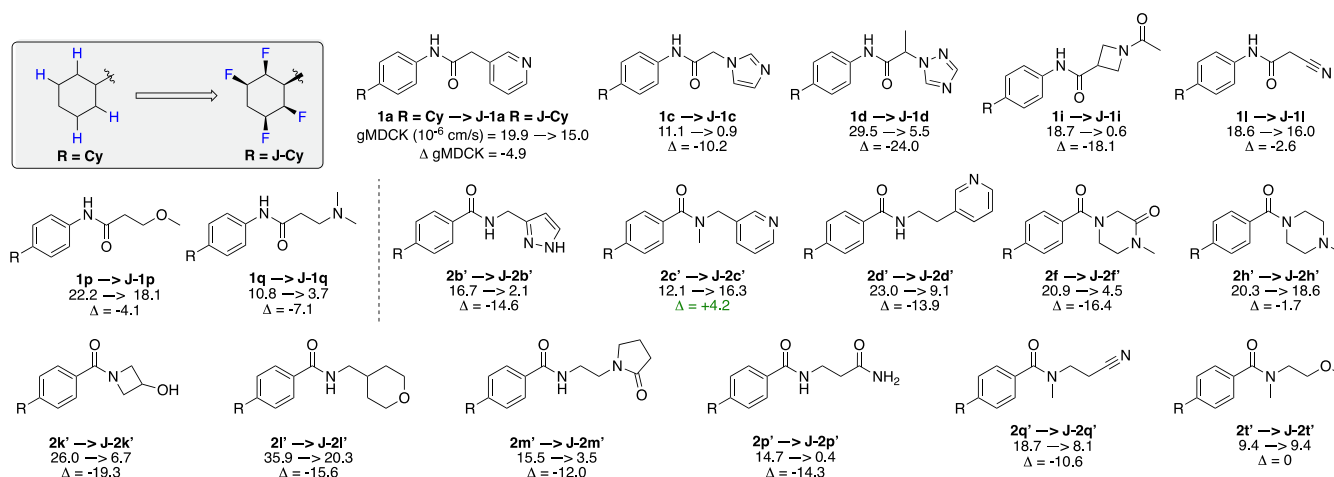


**Figure 2.** MMP analysis of measured lipophilicity ( $\log D_{7.4}$ ) with cyclohexyl (Cy, gray) and all *cis*-1,2,4,5-tetrafluorocyclohexyl (Janus-Cy, blue) derivatives.

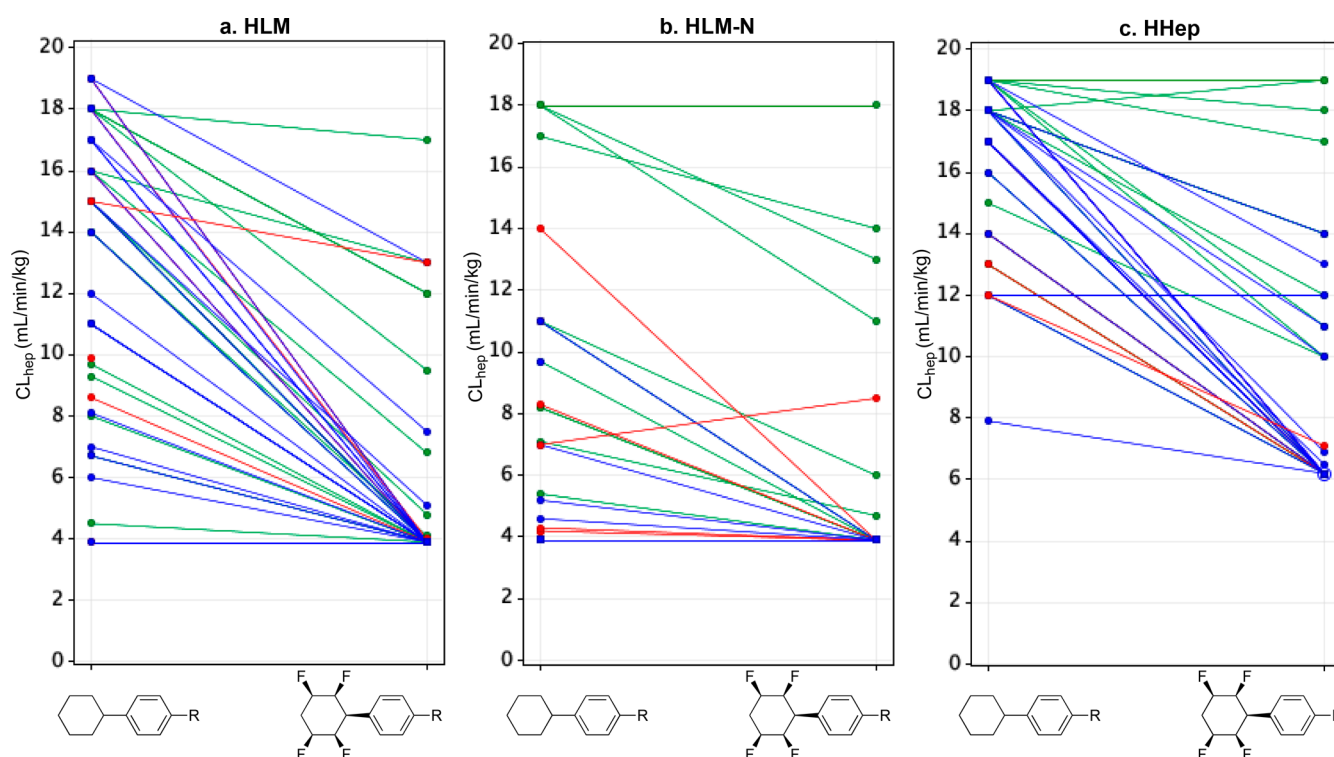
Due to the limited number of examples of Janus face compounds in the literature, we anticipated a divergence between calculated and measured  $\log D$  values (see Figure S2 in the Supporting Information, blue circles). Indeed, and as expected, the  $\log D_{7.4}$  values of these facially polarized compounds were typically overpredicted by  $\sim 1$  unit, which could result from an inability to account for the induced dipole in this Janus-Cy motif.

Membrane permeability of small molecules is another important property to take into consideration during the drug design process. It is of particular importance when oral drug candidates are sought, and in the case of intracellular targets. The permeability of these analogues was evaluated using Madin-Darby canine kidney (MDCK) cells that have endogenously expressed canine MDR1 knocked out using a method that was previously described.<sup>25</sup> Unfortunately, in part due to the intrinsically poor solubility of the parental cyclohexyl molecules or both MMPs—as presented earlier—

we found it difficult to obtain reliable and analyzable data for all the compounds synthesized, i.e., in this case defined as where an acceptable recovery rate (70%–130%) of a tested compound could not be obtained in the apical to basolateral direction. Nevertheless, from the qualifying data collected, we were able to observe that the more polar Janus face compounds generally have lower permeability in the MDCK assay compared to their cyclohexyl analogues, as summarized in Scheme 3. Among a set of 7 MMPs in the anilide case, all the parental cyclohexyl compounds became less permeable upon the incorporation of the polarized Janus face cyclohexane. The effect was even more pronounced with compounds containing pyrazole (**1c** vs **J-1c**) and azetidine (**1i** vs **J-1i**) functionality, where the presence of the Janus-Cy group significantly decreased passive diffusion rate from high to low levels. As discussed earlier, the benzamide subgroup generally had a better solubility profile in contrast to the other two series, which allowed us to collect permeability data with

Scheme 3. MMP Analysis of Permeability between Selected Cyclohexyl (Cy) and all *cis*-1,2,4,5-Tetrafluorocyclohexyl (J-Cy) Derivatives<sup>a</sup>

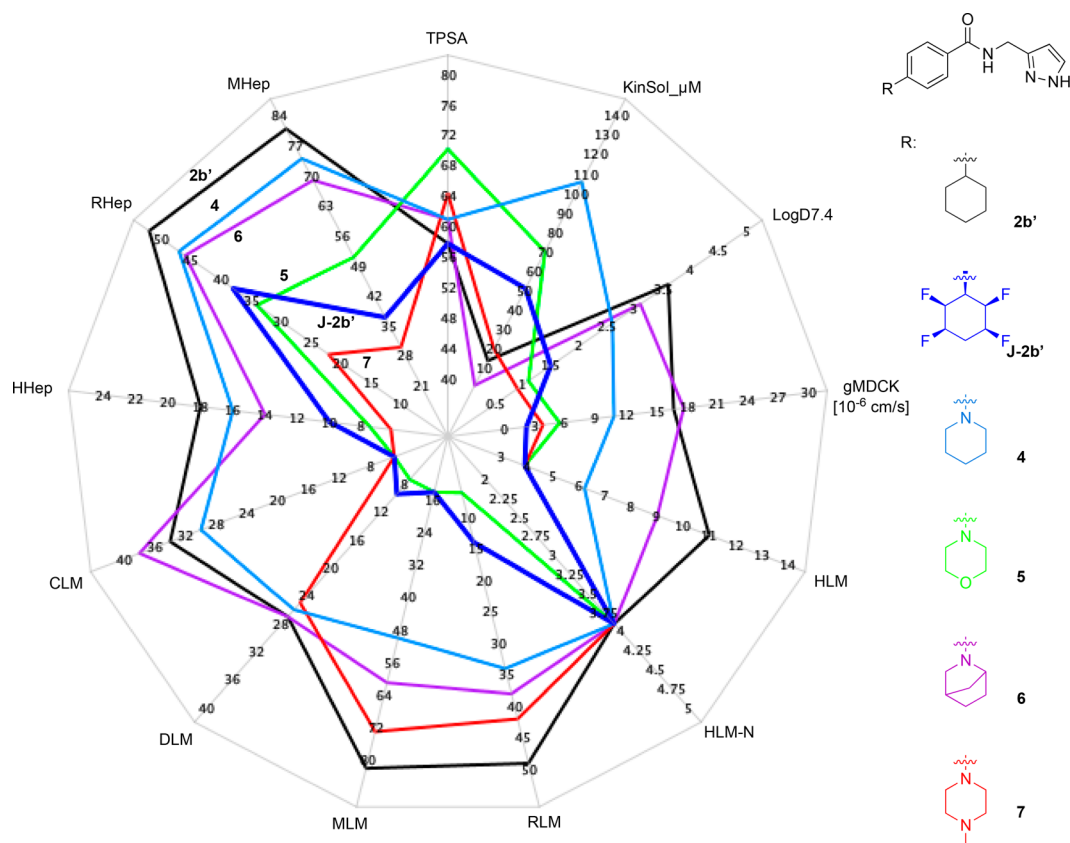
<sup>a</sup>The permeability data ( $10^{-6}$  cm/s) was measured in Madin-Darby canine kidney (MDCK) cells in the apical to basolateral direction.



**Figure 3.** MMP analysis of human liver microsomal (HLM, with and without NADPH) and human hepatocyte (HHep) stability between cyclohexyl (Cy) and all *cis*-1,2,4,5-tetrafluorocyclohexyl (Janus-Cy) derivatized anilides (green), benzamides (blue), and biarenes (red).

more MMPs. Among the 11 MMPs with data, only one pair (2c' vs J-2c') showed a reversed effect, where the parent compound is less permeable, and both in the highly permeable range. Notably, 8 out of the 11 MMPs had a significant ( $>10$ ) difference in this MDCK cell assay. The decreased permeability observed with Janus face compounds might be attributed to lowered lipophilicity. While an issue in relatively small compounds such as these, it is conceivable that, in a more complex drug molecule, the Janus face fragment may induce a reduction of lipophilicity that results in a more balanced set of properties.

Finally, and following this exploration of primarily physicochemical properties, we turned to an examination of *in vitro* metabolic stability. To this end, the microsomal stability of different animal species (mouse, rat, dog, cynomolgus monkey, and human) was measured and the data is summarized in Figures 3a,b and S3. As might be expected from the relatively high  $\log D_{7.4}$  of cyclohexyl compounds, these parent cycloalkyl compounds have predominantly moderate to labile liver microsomal stability profiles. Notably, the corresponding MMPs bearing the Janus-faced ring had significantly improved metabolic stabilities. For the bulk of the examples, the metabolic clearance rates are within



**Figure 4.** Radar plot MMP analysis of Janus face **2b'** (**J-2b'**) versus analogues bearing different saturated (hetero)cycles.

what are typically regarded as the moderate (30–70%) to stable (<30%) range, showing a clear impact of the incorporation of the fluorine atoms and resultant ring polarization. Based upon the data from 48 MMPs, the replacement of Cy by Janus face Cy enabled the reduction of  $\Delta\text{CL}_{\text{hep}}$  (mL/min/kg) by an average of 7 (HLM), 35 (MLM), 27 (RLM), 12 (DLM), and 22 (CLM), across five species. There are a handful of exceptions to the trend in the biarene family, but again this data may be confounded due to low solubility (*vide supra*). It is also worth noting that this trend aligns with the decreased lipophilicity of these compounds. Interestingly, the introduction of Janus-Cy also improves the HLM-N (i.e., in the absence of NADPH) stability of the parent compounds, despite the absence of CYP-mediated metabolism. Previous analyses have indicated that HLM-N is typically only capable of metabolizing specific functional groups (such as esters, amides, aldehydes, oxetanes).<sup>26</sup> In turn, it could be inferred that a remote/simple change from Cy-to-Janus-Cy may be affecting the metabolism of these groups on the molecule—perhaps as a result of lower nonspecific affinity to hydrolase enzymes and hence lower likelihood of hydrolysis.

The compounds were subsequently tested in hepatocyte stability assays, using species-specific cryopreserved hepatocytes. Again, a global trend of improved metabolic stability was observed across human, mouse, and rat systems (Figures 3c and S4).

With an improved appreciation of the assay trends one might expect upon adding this motif into molecules, we set out to make a further comparison of this to commonly used 6-membered aliphatic ring motifs, with a focus on N-linked rings. We synthesized a series of additional MMPs of **2b'**, where the

cyclohexyl unit was replaced with commonly used saturated heterocycles (e.g., piperidine, morpholine, and piperazine), and compared their corresponding properties in the aforementioned assays. Using a radar plot, the resultant measured (or calculated, for TPSA) properties can be compared at a glance (Figure 4). It is notable that a morpholine analogue **5**, oft-regarded as a privileged—and certainly frequently encountered—motif in drug discovery projects, exhibits a very similar physicochemical and metabolic stability profile to that of **J-2b'**. In contrast to other matched pairs, morpholine **5** and the facially polarized **J-2b'** offer balanced profiles in terms of solubility, lipophilicity, and metabolic stability (with the anticipated larger TPSA through adding a morpholine). These results (for **5** and **J-2b'**) illustrate the potential of the Janus face cyclohexyl unit as an effective surrogate for morpholine, without increasing TPSA or incorporation of N/O atoms.

In summary, based upon the intriguing reports from O'Hagan and co-workers regarding this electrostatically polarized all-*cis* tetrafluorocyclohexyl motif, we have systematically investigated its impact on both physicochemical and metabolic properties by synthesizing and analyzing series of matched pair compounds. The introduction of this “Janus face” cyclohexyl ring seems to lead to improved solubility, lowered lipophilicity by almost 2 log units, and enhanced metabolic stability (e.g., in HLM,  $\Delta\text{CL}_{\text{hep}}$  on average reduced by 7 mL/min/kg) but might come at the cost of lower permeability. Given the relative scarcity of reported Janus face examples to date, we hope this data set will enable chemists to better anticipate its potential applicability in their research efforts. As drug discovery is an iterative process where different properties (e.g., physicochemical, biochemical, and ADMET character-

istics) of lead molecules need to be balanced and optimized, groups like this represent useful additions to the medicinal chemist's toolbox, and might just allow them to keep one more ball in the air.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsmmedchemlett.2c00312>.

Additional information about synthetic procedures and small-molecule characterization (PDF)

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<https://pubs.acs.org/doi/10.1021/acsmmedchemlett.2c00312>

### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Funding

This work was funded by Genentech (part of the Roche Group).

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

The authors acknowledge Matthew Landry and Christian Gampe for input on the manuscript, Fabio Broccatelli, Paul Beroza, Mike Siu, and Steve Magnuson for assistance and helpful discussions, as well as Mengling Wong, Crystal Ye, Kewei Xu, Newton Wu, and Eric Low for their assistance with compound purification, analysis, and registration.

## ■ ABBREVIATIONS

MMP, molecular matched pair; ADMET, absorption, distribution, metabolism, excretion, and toxicity; Cy, cyclohexyl; J-Cy, Janus face all-*cis* tetrafluorocyclohexyl; TPSA, topological polar surface area, MDCK, Madin-Darby canine kidney; LM, liver microsomes; HLM, human liver microsomes; HLM-N, human liver microsomes without NADPH; MLM, mouse liver microsomes; RLM, rat liver microsomes; DLM, dog liver

microsomes; CLM, cyno liver microsomes; HHep, human hepatocytes; MHep, mouse hepatocytes; RHep, rat hepatocytes; MDRI, multidrug resistance mutation 1

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