Synthesis and Physicochemical Properties of Functionalized *cis*-2-((Fluoro)alkyl)cyclobutanes

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Dedicated to the people of Ukraine

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Abstract: Efficient decagram-scale synthesis of (fluoro)alkyl-containing *cis*-1,2-disubstited cyclobutane-derived building blocks is described. Starting from commercially available chemicals, target cyclobutylamines, carboxylic acids, and other valuable derivatives were obtained in 3–8 steps on up to 39 g scale. Physicochemical characterization of the prepared compounds and their model derivatives revealed the distinct features of *cis*-1,2-disubstituted cyclobutanes (namely, significantly lowered lipophilicity) as compared to their previously reported *trans*-isomeric counterparts. Computational analysis along with experimentally obtained structural properties suggested the decisive influence of the compounds' conformation on the discussed properties.

Introduction

An outstanding contribution of the fluorine in contemporary drug development and production is widely recognized.[1] Every year, dozens of new fluorine-containing new chemical entities are approved, now representing more than 20% of the marketed drugs.[2–7] Fluorine and fluorine-containing fragments are typically incorporated into drug substances *via* direct fluorination methodologies[8–10] or by application of the fluorinated building blocks (BBs) (Figure 1, *A*).[11] Contrary to the fluorination, the latter approach benefits from versatility, expedience, and low susceptibility to the substrate variation.[12–14]

Cyclobutane, the second smallest and one of the most strained rings among cycloalkanes, has also received increased attention from medicinal chemistry community over the last decade. While it is widely represented among natural products,[15] its presence in bioactive small molecules remains limited.[16,17] Among many useful features offered by the cyclobutane ring,[16] one could mention the ability to lock the conformation of the molecule upon replacement of flexible fragments.[18] rigid structure of the cyclobutane ring also serves as a structure-defining element, tuning and stabilizing the relative direction of the substituents (Figure 1, *B*).

The importance of relative spatial orientation of fluorinated and non-fluorinated substituents mounted onto the same scaffold was

discussed previously, giving birth to valuable concepts in physical chemistry of organofluorine compounds.[19–22] In particular, evaluation of fluoroalkyl-substituted cyclopropylamines and carboxylic acids revealed distinctive properties of *cis* orientation patterns within these series.[23] Herein, we propose a further study of this effect by preparation of (fluoro)alkyl-containing *cis*-1,2-disubstituted functionalized cyclobutanes (including those with CH_2F_2, CHF_2, CF_3, C_2F_5, and CH_3 groups) and their comparison with the previously reported *trans*-isomeric counterparts (Figure 1, *C*).

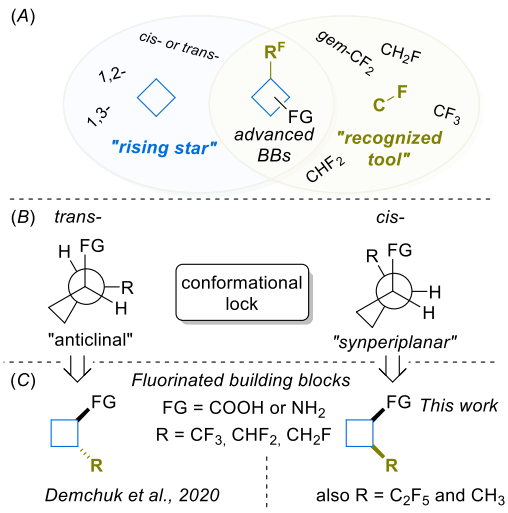


Figure 1. (*A*) Fluorine and cyclobutane in design of advanced building blocks (BBs) for medicinal chemistry; (*B*) Newman' projections of *trans*- (*left*) and *cis*-1,2-disubstituted (*right*) cyclobutanes; (*C*) Compounds discussed in this work.

Results and Discussion

Synthesis. Initially, modification of CH_2OH or other related functional groups in properly functionalized *cis*-1,2-disubstituted cyclobutanes (used previously for the preparation of *trans* isomers[24]) was suggested as a main route towards target building blocks *cis*-**1** and *cis*-**2**, thus leading to commercially available anhydride **3** as the key starting material (Figure 2). As shown below, this strategy performed well only in case of methyl-substituted cyclobutanes (*cis*-**1a**/*cis*-**2a**); intermediates of the corresponding reaction sequence also were useful for the synthesis of CH_2F-substituted compounds *cis*-**1b**/*cis*-**2b**. For the remaining derivatives, an alternative approach was necessary.

Following the selected strategy, lactone **3** was treated with *i*PrOH or *t*BuOH, which produced monoesters *cis*-**4** and **5** in nearly quantitative yields (Scheme 1).[25,26] Since we also aimed at the preparation of hereto unreported isomers *trans*-**1a** and *trans*-**2a**, base-promoted isomerization of isopropyl ester *cis*-**4** was performed, cleanly giving *trans*-disubstituted cyclobutane *trans*-**4** in high yield.[27]

With significant amounts of esters **4** in hands, target *cis*- and *trans*-isomeric Me-substituted cyclobutanes **1a**/**2a** were prepared using a series of simple chemical transformations (Scheme 2). Thus, reduction of either *cis*-**4** or *trans*-**4** with $BH_3{\cdot}Me_2S$ gave corresponding alcohols, which were immediately transformed into mesylates **6** in high yields. Further nucleophilic substitution of the mesylate moiety with NaI produced iodides *cis*-**7** and *trans*-**7** in 72% and 75% yield, respectively. Reductive dehalogenation[28] with subsequent hydrolysis of the ester moiety gave target carboxylic acids *cis*-**2a** and *trans*-**2a** as pure diasteromers in up to 97% yield over 2 steps on up to 145-g scale in a single run. Next, a modified Curtius rearrangement[29,30] with further *N*-deprotection gave amine hydrochlorides *cis*-**1a** and *trans*-**1a** in 65 and 69% yield over 2 steps on up to 33 g scale.

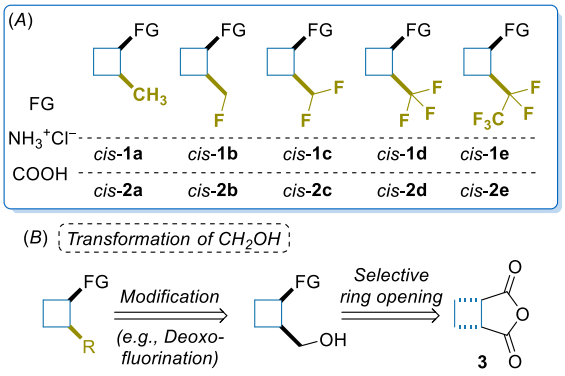
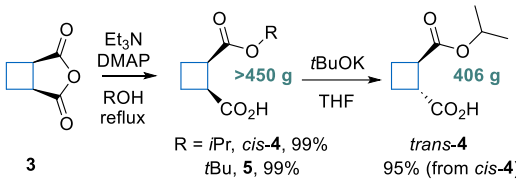


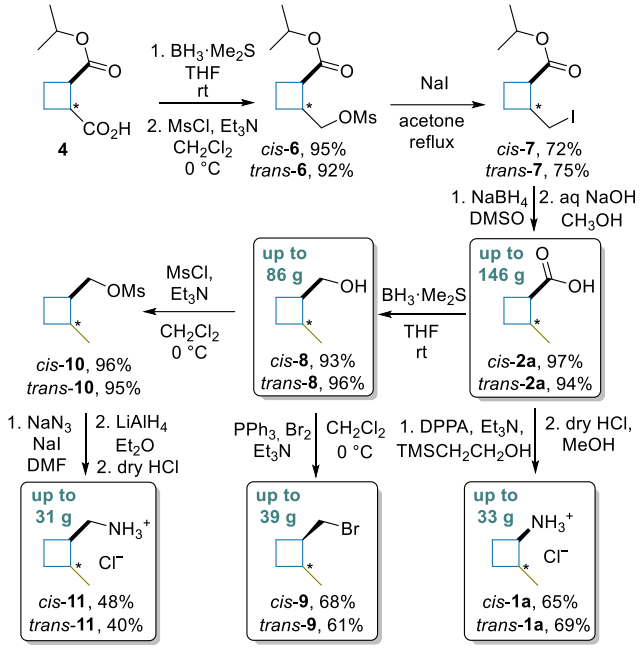
Figure 2. (*A*) Building blocks studied in this work. (*B*) Initial retrosynthetic approach to the target compounds.



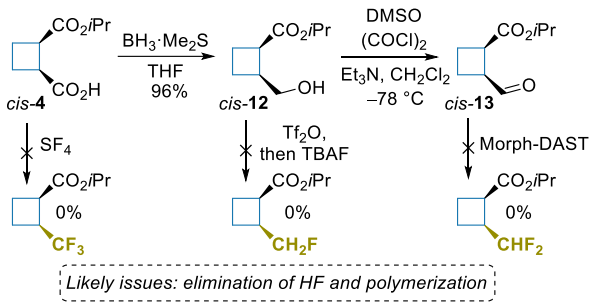
Scheme 1. Multigram synthesis of precursors **4** and **5**.

Several other 2-methylcyclobutyl-containing building blocks were also prepared from carboxylic acids *cis*-/*trans*-**2a**. In particular, reduction of *cis*-/*trans*-**2a** with $BH_3{\cdot}Me_2S$ gave in alcohols *cis*-**8** and *trans*-**9** (93 and 96% yield) that were transformed to corresponding bromides *cis*-**9** and *trans*-**9** by the Appel reaction. Reaction of *cis*-/*trans*-**8** with MsCl gave corresponding mesylates **10** that produced hydrochlorides *cis*-**11** and *trans*-**11** upon reaction with NaN_3 and subsequent reduction of the intermediate azides with $LiAlH_4$ in satisfactory 48 and 40% yield (over 2 steps).

Following the strategy developed previously for the *trans*-1,2-disubstituted cyclobutane derivatives, we tested the deoxofluorination protocols for carboxylic acid *cis*-**4**, alcohol *cis*-**12** (prepared from *cis*-**4** by reduction with $BH_3{\cdot}Me_2S$ complex), and aldehyde *cis*-**13** (prepared by Swern oxidation of *cis*-**12**) (Scheme 3). Unfortunately, none of the standard nucleophilic fluorination protocols were successful with these substrates. Instead, rapid decomposition of the starting compounds was observed, likely due to the close proximity of the ester functionality, resulting in complex mixtures of products with traces of HF elimination products detected by ^{1}H NMR spectra. Therefore, alternative strategies were necessary to prepare the target fluoroalkyl-substituted cyclobutanes.

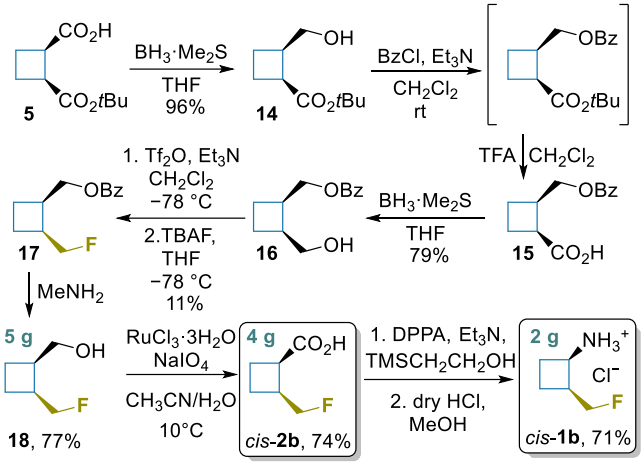


Scheme 2. Synthesis of building blocks *cis*-/*trans*-**1a**, *cis*-/*trans*-**2a**, *cis*-/*trans*-**8**, *cis*-/*trans*-**9**, and *cis*-/*trans*-**11** (DPPA – diphenyl phosphoroyl azide).



Scheme 3. Attempted synthesis of fluoroalkyl-substituted cis-1,2-disubstituted cyclobutanes via deoxo(y)fluorination reactions.

In the case of fluoromethyl derivatives *cis*-**1b** and *cis*-**2b**, the alternative synthetic scheme started with selective reduction of monoester **5** to alcohol **14** using the method mentioned above in 96% yield (Scheme 4). As expected, direct deoxofluorination of **14** was also unsuccessful, likely due to the competing elimination process. To overcome this issue, we temporarily masked the ester functionality in the molecule of **14**. Thus, benzoylation of the hydroxyl moiety followed by selective cleavage of *tert*-butyl ester (that's why we could not use *cis*-**4** as the starting material) gave carboxylic acid **15**. A key precursor for the monofluorination – alcohol **16** was obtained after reduction of the COOH moiety with $BH_3{\cdot}Me_2S$ in 79% yield. Activation of the hydroxyl group with Tf_2O and subsequent substitution with fluorine anion under mild conditions produced desired CH_2F-substituted cyclobutane **17** in relatively low 11% yield. Unfortunately, elimination and other side processes remained a significant problem in this case. Nevertheless, cleavage of the ester moiety in the molecule of **17** with aqueous methylamine produced target alcohol **18** in 77% yield. Catalytic oxidation of the latter compound with $RuCl_3$ – $NaIO_4$ produced carboxylic acid *cis*-**2b** in 74% yield. Finally, modified Curtius rearrangement gave amine hydrochloride *cis*-**1b** in 71% yield. Despite the modest efficiency of the deoxyfluorination step, both building blocks were successfully obtained on a gram scale.

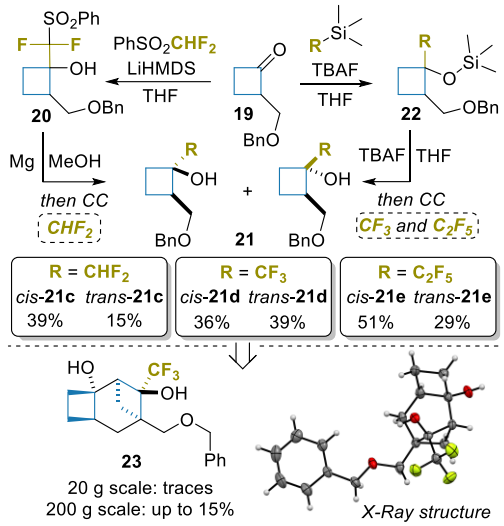


Scheme 4. Synthesis of CH_2F-substituted building blocks *cis*-**1b** and *cis*-**2b**.

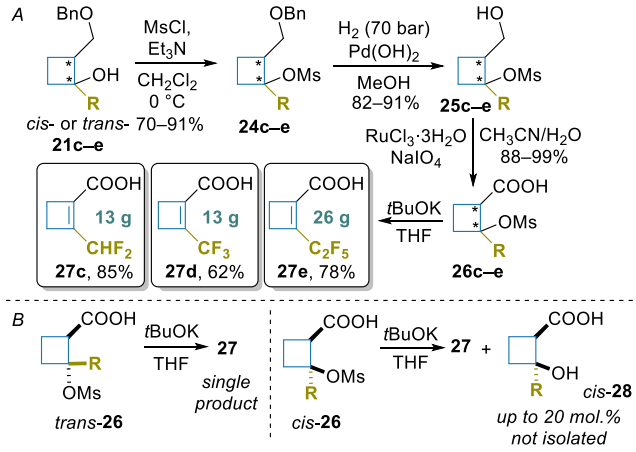
Synthesis of other fluoroalkyl-substituted cyclobutanes commenced from known cyclobutanone **19**[31] (Scheme 5, *A*). The CHF_2 group was introduced via a two-step protocol, involving base-promoted addition of $PhSO_2CHF_2$ to the carbonyl moiety and subsequent desulfonylation with Mg in MeOH.[32] After column chromatography, diastereomers *cis*-**20** and *trans*-**20** were isolated separately in 39% and 15% yield, respectively. Perfluorinated groups (i.e. CF_3 and C_2F_5) were introduced by F^--catalyzed reaction of cyclobutanone **19** with $TMSCF_3$ or $TMSC_2F_5$. Obtained intermediate O-TMS protected products **22** were immediately treated with equivalent amounts of anhydrous TBAF, giving desired products **21d** and **21e** in 78% and 80% overall yield after stereoisomer separation by column chromatography. Notably, the reaction of ketone **19** with the Ruppert-Prakash reagent ($TMSCF_3$) was accompanied by formation of byproduct **23** (up to 15%) upon scale-up (Scheme 5, *B*). We believe that this compound might be obtained by elimination of BnOH from **19**[33] and further reaction of the *α*,*β*-unsaturated intermediate with another molecule of **19** and $TMSCF_3$.[34]

To obtain the target building blocks **1** and **2**, compounds *cis*- and *trans*-**21c**–**e** were separately converted to corresponding mesylates *cis*- and *trans*-**24c**–**e** in high yields (Scheme 6, *A*). Subsequent hydrogenolysis of the benzyl protection group and Ru-catalyzed oxidation of resulting alcohols *cis*- and *trans*-**25c–e** gave carboxylic acids *cis*- and *trans*-**26c–e** in 88–99% yield. Elimination of the mesylate moiety promoted with *t*BuOK as a base allowed preparation corresponding cyclobutenecarboxylic acid derivatives **27c**–**e** in 62–78% yields on up to 26 g scale. Worth noting a significant impact of the relative stereochemistry of mesylates *cis*- and *trans*-**26c–e** on the outcome of the elimination process. Typically, *trans*-substituted mesylates **26** cleanly produced target products **27**, whereas *cis*-isomers underwent partial cleavage of the methanesulfonic fragment (likely through the neighbouring COOH group participation), giving up to 20 mol. % of corresponding hydroxycarboxylic acids *cis*-**28** (detected by LCMS of the crude mixture; Scheme 6, *B*). Unfortunately, all attempts to separate alkenes **27** from byproducts **28** failed;

therefore, these mixtures were used in the next step without purification.



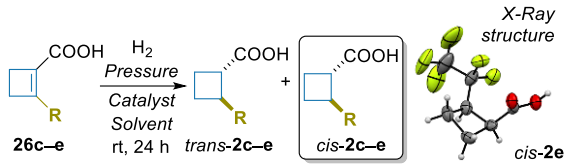
Scheme 5. (*A*) Preparation of precursors for the synthesis of CHF_2-, CF_3-, and C_2F_5-substituted cyclobutanes. (*B*) Side product **23** obtained in the reaction of **19** with $TMSCF_3$.



Scheme 6. Synthesis of cyclobutenecarboxylic acids **27c–e**.

Catalytic *syn*-hydrogenation of the double bond, a typical and well-renowned method for the preparation of *cis*-disubstituted saturated cyclic fragments,[35] faced an unexpected issue in our case (Table 1). While the reduction of the CHF_2-substutited cyclobutene **27c** resulted in acceptable 2 mol. % admixture of undesired isomer *trans*-**2c**, the same conditions applied to CF_3- and C_2F_5-substituted substrates **27d** and **27e** resulted in 12% and 20 mol. % of *trans*-isomers, respectively. An optimisation of the reaction conditions improved the ratio of *cis*- and *trans*-substituted products **2**; however, we have found that these compounds could be enriched to 98% *de* by column chromatography (for the CF_3-substituted cyclobutane) or by recrystallization from apolar solvent (for the C_2F_5-substituted derivative), giving products *cis*-**2d** and *cis*-**2e** in up to 72% overall yield on up to 17 g scale. To complete the series of *cis*- and *trans*-1,2-disubstituted cyclobutane building blocks containing the fluoroalkyl group (already including the *trans* isomers described previously and the *cis* isomers prepared in this work), a diastereomerically impure fraction of carboxylic acid *cis*-**2e** was isomerised to *trans*-**2e** by treatment with *t*BuOK in THF in 83% yield.

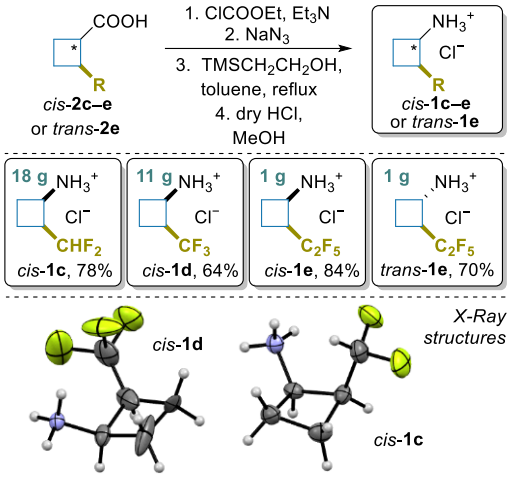
Table 1. Optimization of the double bond reduction conditions in the molecules of **27c–e**



#	R	Catalyst	Solvent	Pressure	*c*, M	*cis* : *trans*
1	CHF_2					98:2
2	CF_3	Pd/C (10 % w/w)	THF	40		88:12
3						60:40[a]
4				60	0.5	57:43
5	C_2F_5	Raney nickel	THF	20		80:20[a]
6		Crabtree's catalyst[b]	CH_2Cl_2	40		61:39[c]
7		Pd/C (30 % w/w)	AcOH	120	0.67	82:18

[a] 30% conversion of **27e**; [b] (SP-4)-(η_2,η_2-Cycloocta-1,5-diene)(pyridine)(tricyclohexylphosphine)iridium hexafluoridophosphate; [c] 10% conversion of **27e**.

Finally, carboxylic acids *cis*-**2c–e** and *trans*-**2e** were converted to corresponding amine hydrochlorides **1** by Curtius rearrangement via mixed anhydride strategy (64–84% yield after recrystallization, Scheme 7).



Scheme 7. Preparation of amine hydrochlorides *cis*-**1c-e** and *trans*-**1e**.

Physicochemical evaluation: acidity. After achieving our synthetic goals, we turned our attention to the physicochemical properties of the prepared compounds. At first, we established the effects of the fluoroalkyl groups on the acidity of the

corresponding functional groups in *cis*-1,2-disubstituted cyclobutanes and compared them with the reported data for *trans*-isomers, as well as parent compounds **1f**/**2f**[24] (Figure 3). For both amine hydrochlorides **1a–e** and carboxylic acids **2a–e**, substitution at β-position led to an increase in acidity (from $\Delta pK_a = -0.1$ for *trans*-**2b**/**2f** up to $\Delta pK_a = -2.1$ for *cis*-**1d**/**1f**). Expectedly, the observed effect was significantly higher for hydrochlorides **1** (average $\Delta pK_a = -1.1$) as compared to carboxylic acids **2** (average $\Delta pK_a = -0.4$), confirming the prevalence of the inductive effect (fading with increasing the through-bond distance) on the acid-base properties. Notably, introduction of the methyl group (commonly classified as a σ-electron donor substituent) led to decreased pK_a values similar to the case of electron-withdrawing CH_2F group (compare the **1a**/**1b** and **2a**/**2b** pairs). This observation correlates with results of recent studies on the electronic properties of alkyl groups.[36,37] In the series of hydrochlorides **1a**–**d**, the acidity correlated with the number of fluorine atoms for both *cis* and *trans* isomers. Counterintuitively, for C_2F_5-substituted derivatives **1e**, the pK_a effects were close or even less pronounced than for CF_3-substituted counterparts **1d**. For the carboxylic acids **2a–e**, the pK_a trends were similar to those described above for hydrochlorides **1a–e** albeit less pronounced. Worth noting higher acidity of *cis* derivatives as compared to the corresponding *trans* isomers; moreover, the *cis* vs *trans* difference increased in the series $CH_2F<CHF_2\leq CF_3$. This trend could be explained by the through-space field effects of fluorine-containing groups, also observed in the previous works.[38,39]

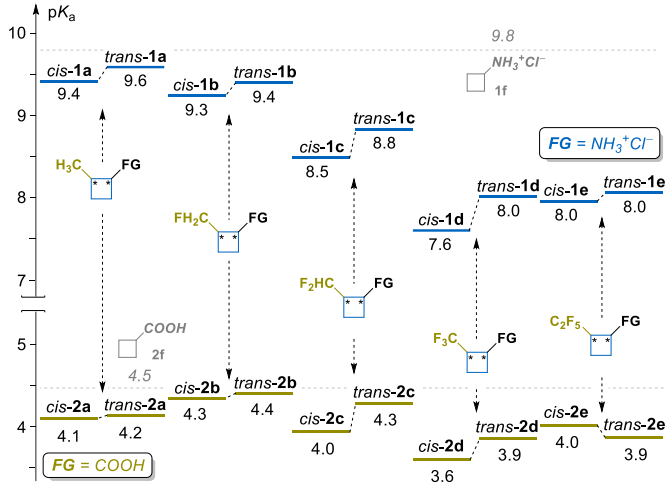


Figure 3. Acidity of amine hydrochlorides **1a–f** and carboxylic acids **2a–f** (H_2O, 21 °C).

Lipophilicity. Log*P* values were measured for anilides **29a–e** and benzamides **30a–e** (prepared by the reaction of carboxylic acids **2** with aniline and *N*-benzoylation of hydrochlorides **1**, respectively, under the standard reaction conditions, see the Supporting Information) using the classical shake-flask method combined with HPLC quantitative analysis as reported previously (Figure 4).[40] In general, the lipophilicity trend in the series of compounds **29** and **30** with various fluorination patterns correlated with the literature data;[38,39] thus, the Log*P* values typically increased in the following series: $CH_2F\leq CHF_2<CH_3\leq CF_3<C_2F_5$. At the same time, the relative configuration appeared to be crucial in certain cases. Indeed, while the lipophilicities of the compounds with CH_3, CH_2F and CHF_2 substituents were very close for the *cis* and *trans* isomer pairs (ΔLog*P* = –0.07…0.15, 0.04 on average), the derivatives with CF_3 and C_2F_5 groups demonstrated significant differences (ΔLog*P* = 0.29…0.61, 0.47 on average). This effect was especially prominent for anilides *cis*-/*trans*-**29d** and *cis*-/*trans*-**29e**. With anticipated increase in lipophilicity of ca. 0.4–0.6 Log*P* units upon transition from the CHF_2- to CF_3-substituted derivatives,[38,39,41] *cis*-**29d** was significantly less lipophilic than expected (Log*P* = 2.31 vs 2.29 for **29c**). In turn, this effect resulted in the large Log*P* difference between *cis*-**29d** and *trans*-**29d** (ΔLog*P* = 0.69). Similar effect was also observed for C_2F_5-substituted cyclobutanes *cis*-**26e** and *trans*-**29e** (ΔLog*P* = 0.61).

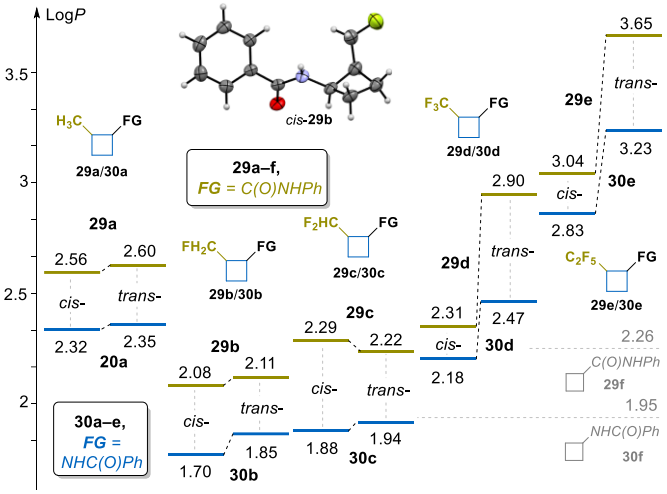


Figure 4. Lipophilicity of anilides **29a–f** and benzamides **30a–f** (H_2O – 1-octanol, 21 °C).

Molecular electrostatic potential (MEP) and conformational analysis. Previously, a number of solute parameters connected to its lipophilicity were established empirically using a linear solvation energy relationships (LSER) methodology.[42] Among others, molecular size (V_x) and hydrogen bond basicity (β) were referred as the major contributors to the compound's lipophilicity; however, solute dipolarity/polarizability (π_2^H) often had a decisive impact on the Log*P* value.[41,43] Whereas the effects of the fluorination pattern on the β[44,45] and V_x[46] are more or less predictable, these parameters could not be used for rationalizing the lipophilicity discrepancies observed for CF_3- and C_2F_5-substituted *cis*- and *trans*-isomeric cyclobutanes **29d** and **29e**.

To get better insight into the observed phenomenon, we decided to compare molecular electrostatic potential surfaces (MEPS)[47] for amides **29** (Figure 5, *A*). Previously, Hunter demonstrated that maxima and minima distributions on the calculated gas-phase MEPS correlated with free energies of interphase transfer, in turn directly related to Log*P* *via* specific solute-solvent interactions.[48,49]

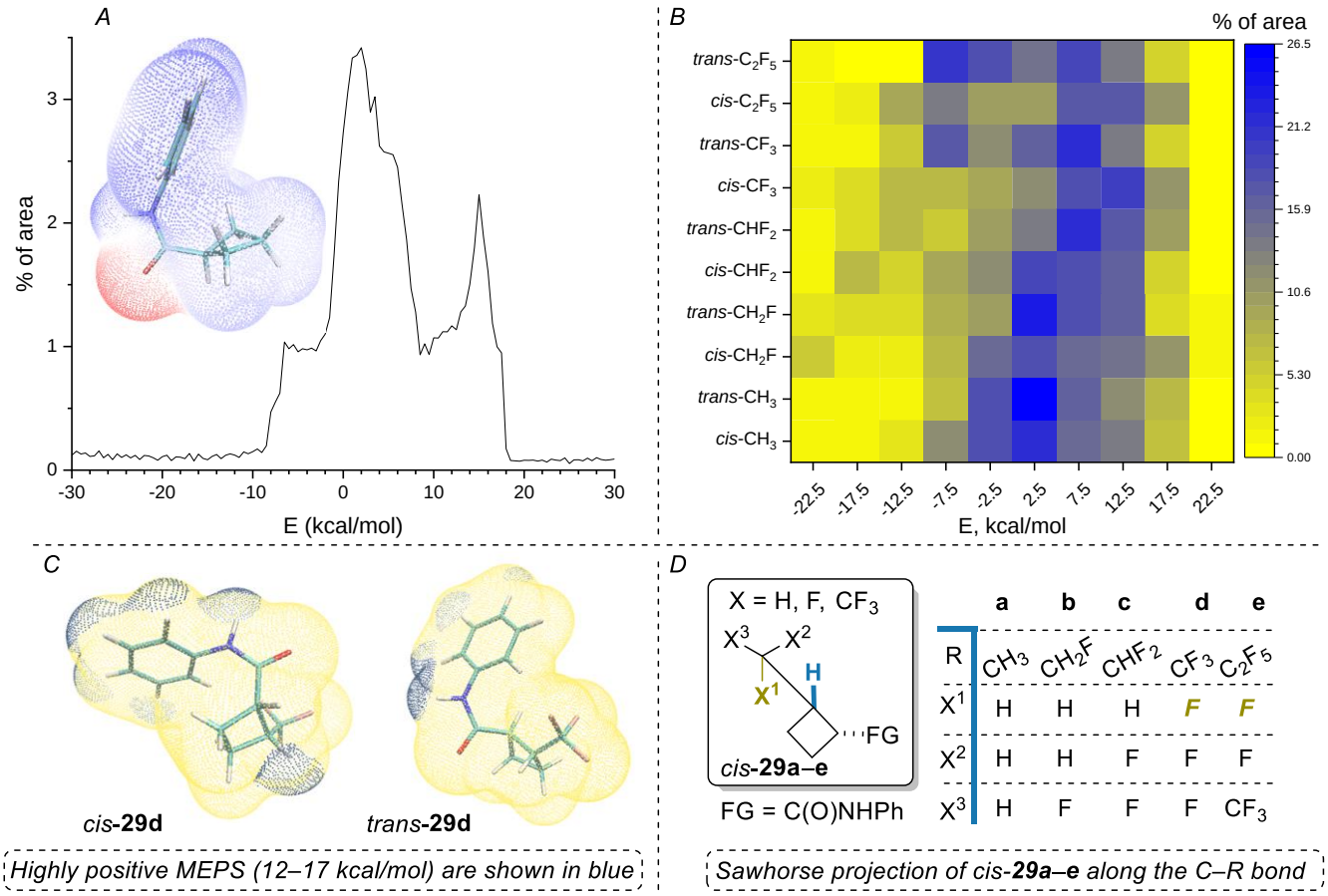


Figure 4. (*A*) Molecular electrostatic potential (MEP) of compound **29f** mapped on an 0.01 au electron density surface and distribution of the potential over the molecular surface. Red regions indicate electron-rich negative MEPS, while the blue regions correspond to electron-deficient positive MEPS. (*B*) Heatmap of the MEP distribution for compounds **29a**–**f**. (*C*) Localized positive fragments of MEPS of compounds *cis*-**29d** and *trans*-**29d.** Blue regions correspond to areas with electrostatic potential of 12–17 kcal/mol. (*D*) Preferential conformations of compounds *cis*-**29a–e** shown as a sawhorse projection along the *C–R* bond.

In our approach, we calculated the MEPS for all amides *cis*-**29** and *trans*-**29** and analysed the distribution of the potential over surface by plotting the corresponding relative surface area versus the potential values (Figure 4, *A*/*B* and Figures S12–17 in the Supporting Information). Visualisation of the obtained data for amides **29a–e** in the form of heatmap revealed few interesting features of these structures. For most compounds (except *trans*-**29c**, *cis*-**29d**, and *cis*-**29e**) over 50% of the molecule's surface had molecular electrostatic potential values within a range –5…10 kcal/mol, and over 2/3 – within a range of –5…15 kcal/mol. For compounds *cis*-**29d** and *cis*-**29e,** less than 40% and 60% of the molecular surface occupied the same intervals, respectively. Meanwhile, ca. 30% of their molecular surface had electrostatic potential between 10 and 20 kcal/mol (compare with ca. 18–25% for other compounds). Visualization of the numerical data and localization of the "highly positive region" of the MEPS (12–17 kcal/mol) clearly demonstrated the main difference between *cis*-**29d**/*cis*-**29e** and other compounds from the studies series. For *cis*-**29d** and *cis*-**29e**, significant positive MEPS was observed around the hydrogen atom adjacent to the fluoroalkyl substituent (CF_3 or C_2F_5). For the remaining series, positive MEPS was localised only at the N–*H* and aromatic C–*H* fragments for the remaining compounds (Figure 4, *C*).

Detailed analysis of the optimized structures of *cis*-**29a–e** revealed a possible reason for such observations. When moving from the CH_3 to CHF_2 group in *cis*-disubstituted cyclobutanes, each fluorine atom had *gauche* (synclinal) orientation to the *α*-C–H bond, potentially due to energetically favourable $\sigma_{C-C} \rightarrow \sigma^*_{C-F}$ delocalization.[41,50] Introduction of the last Fluorine atom (for CF_3) or trifluoromethyl fragment (for C_2F_5) allowed for antiperiplanar positioning of one of the C–F and C–H bonds, enabling efficient C–H/C–F hyperconjugation and resulting in the observed polarization effect.

In case of *trans*-**29c**, additional positive MEPS is localized at the H-atom of the CHF_2 fragment and (to a lesser extent) at the nearby H-atoms. In this case, the inductive effect of the fluorine atoms might govern the formation of the positive MEPS, simultaneously leading to a slight decrease of lipophilicity.

Worth noting that X-ray diffraction studies supported the computational results, clearly indicating synclinal orientation of the *α*-C–H bond to the fluorine atom(s) of the CH_2F and CHF_2 substituents in the solid state (see Table 1, Scheme 7, and Figure 3). In addition to that, the observed spin-spin coupling $^3J_{HH}$ constants (6.6…9.5 Hz, relatively large) and $^3J_{HF}$ (10.0…17.7 Hz, relatively low) for amides *cis*-**29b–d** also suggested preferential adoption of the synclinal orientation by the C–H and C–F bonds.[51–53] Furthermore, the previously

obtained data for *cis*-/*trans*-isomeric fluoroalkyl-substituted cyclopropanes[23] and 2-/3-fluorinated cyclobutanes[25] also support these conclusions: compounds where *anti*-orientation of the corresponding C–F and C–H bonds was inevitable (i.e., CF_3-substituted cyclopropanes or *cis*-isomeric monofluorinated cyclobutanes) typically demonstrated lowered lipophilicity as compared to other compounds in the series.

These results demonstrate that our previous hypothesis[54] about importance of the neighbouring C–H bond polarization caused by the fluorine atoms is consistent (also including C–H bonds at the vicinal position), albeit additional factors should be also taken into account.

Conclusion

In this work, an expedient approach to the preparation of *cis*-1,2-disubstituted (fluoro)alkyl cyclobutanes is developed. The proposed synthetic methodologies are based on simple transformations of commercially available starting materials, enabling access to a variety of valuable (fluoro)alkyl-substituted cyclobutane building blocks (amines, carboxylic acids, and alcohols). In particular, reductive dehalogenation strategy granted access to *cis*- (and *trans*-) CH_3-substituted building blocks in 3 to 6 steps with preparative yields on up to 39 g scale. CH_2F-substituted cyclobutanes were accessed via the nucleophilic substitution in the corresponding activated bis(hydroxymethyl) derivatives; further functional group transformations produced target building blocks in reasonable yields on up to 5 g scale. Other fluorinated substituents (*i.e.*, CHF_2, CF_3, and C_2F_5) were introduced through addition of the corresponding fluorine-containing reagents ($PhSO_2CHF_2$, $TMSCF_3$, or $TMSC_2F_5$) to the carbonyl group in a properly 2-functionalized cyclobutanone; the subsequent 6-step synthetic scheme (including deprotection, alcohol oxidation, elimination of the activated alcohol species, and *cis*-selective catalytic hydrogenation) gave the desired *cis*-fluroalkyl-substituted cyclobutane building blocks.

Physicochemical characterization of the prepared compounds revealed a crucial role of the relative configuration of the substituents, especially in the case of CF_3 and C_2F_5 groups. The pK_a values in the discussed series of *cis*- and *trans*-substituted cyclobutanes varied in an expected manner (with more fluorine atoms typically leading to increased acidity). For most derivatives studied, the Log*P* values followed the trends established in the previous works and increased in the series: $CH_2F \leq CHF_2 < CH_3 \leq CF_3 < C_2F_5$. Nevertheless, the lipophilicity of *cis*-isomeric CF_3- and C_2F_5-substituted model amides was lower than might be anticipated. Analysis of the molecular electrostatic potential surfaces (MEPS) of the discussed compounds revealed increased polarization of the α-C–H bond, which could be a possible reason of the observed decrease in the lipophilicity. Conformational analysis (either by computational studies or using X-ray diffraction and NMR experimental data) revealed the prevalent synclinal orientation of the C–F and α-C–H bond in the case of CH_2F- and CHF_2-substituted derivatives. On the contrary, antiperiplanar orientation of one of the C–F and α-C–H bonds for the *cis*-isomeric CF_3- and C_2F_5-substituted cyclobutanes enabled H–H/C–F hyperconjugation, possibly being the reason behind the observed positive polarisation of the molecular surface and hence lowered lipophilicity.

Considering prominent physicochemical properties and accessibility via the proposed gram- to decagram-scale synthetic protocols, we believe that *cis*-1,2-disubstituted (fluoro)alkyl cyclobutane building blocks introduced in this work will receive special attention of medicinal chemists and find their applications in drug discovery programs in the nearest future.

Experimental Section

The solvents were purified according to the standard procedures.[55] All starting materials were obtained from Enamine Ltd. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase ^{1}H, ^{13}C{^{1}H}, ^{19}F{^{1}H} NMR, and 2D NMR spectra were recorded on an Agilent ProPulse 600 spectrometer (at 600 MHz for ^{1}H NMR and 151 MHz for ^{13}C{^{1}H} NMR), a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H, 126 MHz for ^{13}C, and 470 MHz for ^{19}F), or a Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H, 101 MHz for ^{13}C, and 376 MHz for ^{19}F). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. Coupling constants (J) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 MS instrument (electron impact ionization (EI)). High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

Supporting Information

The authors cited have cited additional references within the Supporting Information.[40,56,65,66,57–64]

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Conflict of Interest

The authors are / have been employees, trainees, or consulting scientists of Enamine Ltd. that offers all the building blocks described in this paper in the company's catalog.

Keywords: Cyclobutane • Fluorine • Building blocks • Acidity • Lipophilicity

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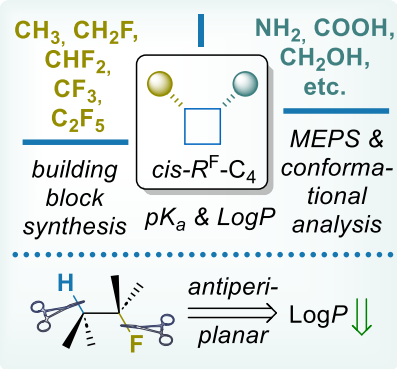
Fluorinated Cyclobutanes



Expedient gram- to decagram-scale synthesis of *cis*-1,2-disubstited (fluoro)alkyl cyclobutanes – valuable small building blocks for medicinal chemistry – was developed. Physicochemical evaluation of the title compounds through the pK_a and Log*P* measurements revealed interesting trends affected by the compound's fluorination pattern and stereochemistry, which was rationalized through molecular electrostatic potential surface (MEPS) and conformational analysis.

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