3,3-Difluorooxetane – a Versatile Functional Group for Bioisosteric Replacements in Drug Discovery

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Dedicated to the people of Ukraine

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Abstract: Functional group (FG) is one of the cornerstone concepts in organic chemistry and related areas. Wide spread of bioisosterism ideas in medicinal chemistry and beyond caused a striking rise in demand for novel FGs with defined impact on the developed compound properties. In this work, evaluation of 3,3-difluorooxetane unit (3,3-*di*Fox) as a functional group for bioisosteric replacements is disclosed. Comprehensive experimental study (including multigram building block synthesis, quantification of steric and electronic properties, measurements of pK_a, Log*P*, chemical stability, and biological evaluation of the 3,3-*di*Fox-derived bioisostere of a drug candidate) revealed a prominent behavior of the 3,3-*di*Fox fragment as a versatile substituent for early drug discovery programs.

Introduction

Functional group (FG), an atom or a group of atoms that has similar chemical properties whenever it occurs in different compounds, is a cornerstone concept in fundamental organic chemistry.[1,2] In medicinal chemistry and related areas, FGs usually play several important roles, being responsible not only for the chemical transformations of organic molecules, but also for establishing specific ligand-target interactions and improving physicochemical parameters – key desirable features in drug design.[3] Examples of the classical FGs most often occurring in medicinal chemistry include the derivatives of carboxylic acids (*i.e.*, amides and esters), ethers, amines, or halogens.[4] For the last decade, increased attention to fluorinated moieties[5] was observed due to the unique properties of the Fluorine atom. Among them, one should mention enhanced resistance to metabolic degradation,[6] a striking effect on pK_a and Log*P*,[7] or amenability for establishing weak interactions with N–H, C–H, and C=O fragments.[8] The type of fluorination pattern has a profound impact on the overall effect of the Fluorine-containing substituent,[9] therefore design and implementation of novel fluorinated moieties is of special significance to modern drug discovery.

Recently, an overwhelmingly increased interest to potential drug substances enriched in sp^3-hydbrid carbon atoms the led to increased exploitation of small cycloalkyl groups and their heterocyclic analogs in medicinal chemistry.[10–13] Oxetane, an oxa-analog of the cyclobutane ring, was unfairly omitted from the drug discovery campaigns until early 2000s, when its application as hydrophilic *gem*-dimethyl[14] or metabolically stable carbonyl[15] surrogate was demonstrated.[16] Since then, a large (and still growing) number of oxetane-centered studies have been reported in the literature, revealing a special place of this ring as a promising core for bioisosteric replacements.[17–19]

A major bias that suspended the application of oxetanes in drug discovery is connected with its potential liability under certain conditions.[15,18] Refuting this statement, recent studies demonstrated the enhanced tolerance of 3,3-disubstituted oxetanes to the external conditions[20,21] despite several reported exclusions related to the specific structural environment.[22]

With increased interest in 2-substituted oxetanes,[16,18,19,23] application of the Fluorine-containing substituents aimed at modulation of the stability and/or other molecular properties could be regarded as a promising approach to the development of novel oxetane-based functional groups (Figure 1, *bottom*). In this work, we have turned our attention to 3,3-difluorooxetane (3,3-*di*Fox) that potentially resembles many common FGs (e.g., ester or amide, acetal, small (cyclo)alkyl, etc.) and hence has a great potential for bioisosteric replacements. In view of that, we developed an approach to the multigram synthesis of 3,3-*di*Fox-containing building blocks and studied numerous physicochemical (i.e. acidity/basicity, lipophilicity, Hammett constant), structural, and electronic properties, as well as chemical stability of model derivatives. Finally, we demonstrated feasibility of bioisosteric replacement of *tert*-butyl group with 3,3-

difluorooxetane fragment by preparation and evaluation of 3,3-*di*Fox-substituted Tenovin-6 analog.

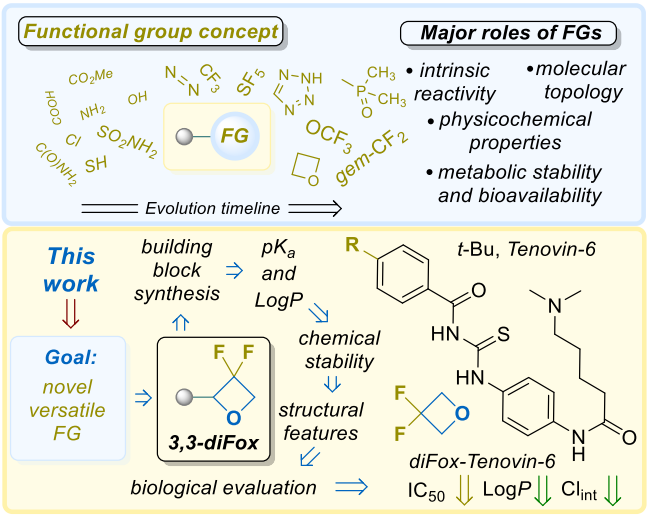
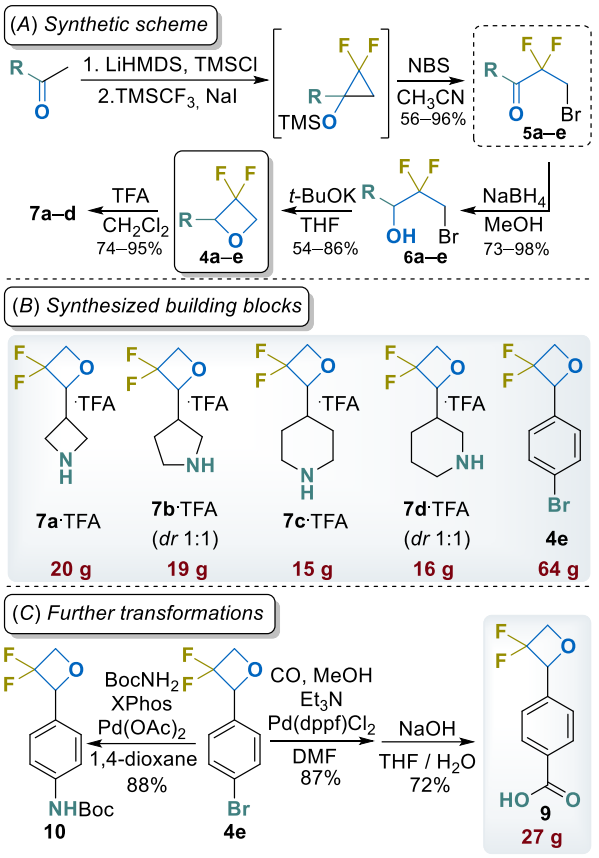


Figure 1. Functional group concept (*top*) and 3,3-difluoroxetane (3,3-*di*Fox) as studied in this work (*bottom*).

Results and Discussion

Synthesis. Previously, preparation of polyfluorinated oxetanes has been performed *via* formal [2+2] cycloaddition,[24–26] intramolecular radical cyclization,[27,28] or base-promoted reaction of fluorinated enolates and carbonyl compounds;[29,30] all these methods are hardly extendable to the synthesis of 3,3-difluorooxetanes. Construction of the target 3,3-difluoroxetane core could be achieved by the intramolecular nucleophilic substitution in 2,2-difluoro-3-haloalcohols of type **6** (Scheme 1); a few precedents of this transformation has been mentioned in the literature for the non-functionalized substrates.[31–33] This retrosynthetic disconnection is easily telescoped to ketones **5** that can be obtained *via* the difluorocyclopropanation of silyl enolates according to the reported method.[34] Aiming at the multigram preparation of building blocks suitable for further functionalization by common chemical transformations, we synthesized α-bromo-ketones **5a**–**e** bearing an *N*-Boc-protected amine or aryl bromide moieties. Reduction of compounds **5a–e** with $NaBH_4$ cleanly produced alcohols **6a**–**e** in good to excellent yields (73–98%). After evaluating several reaction conditions for the key cyclization step, we have found that *t*-BuOK in THF[35] gave the best results (Table 1). In this way, *N*-Boc protected derivatives **4a**–**d** and aryl bromide **4e** were synthesized in 40–72% yield over two steps. Compounds **4a**–**d** were treated with TFA in CH_2Cl_2 giving target amine building blocks **7a**–**d** as trifluoroacetates in 74–95% yield. Expectedly, both compounds **4b** and **4d** were synthesized as *ca.* 1:1 mixtures of diastereomers. While their bulk separation appeared to be difficult, we were able to isolate individual (*R**,*S**) and (*S**,*S**) isomers on a subgram scale after the column chromatography. The relative configuration of each product was established by 2D NMR spectroscopy and, in the case of (*S**,*S**)-**4d**, by X-Ray diffraction studies.



Scheme 1. Synthesis of 3,3-difluorooxetane building blocks **4e**, **7a**–**d**, and **9**.

Table 1. Optimization of the heterocyclization step (**6c** → **4c**).[a]

Entry	Base	Temperature, °C	Yield of **4c**, %
1	K_2CO_3	60	0
2	LiHMDS	–78	31
3	NaH	0	25
4	*t*-BuOK	25	79

[a] Conditions: **6c** (1 mmol), base (1.5 mmol), THF

Pd-catalyzed carbonylation of aryl bromide **4e** followed by alkaline saponification of the ester formed produced carboxylic acid **9** in 63% overall yield (Scheme 1, *C*). Buchwald-Hartwig amination[36] of compound **4e** with $BocNH_2$ cleanly afforded *N*-Boc-protected aniline **10** in 88% yield**.** Unfortunately, all attempts to cleave the carbamate moiety in the molecule of **10** were accompanied by oxetane ring opening, so the corresponding aniline derivative could not be obtained.

Acidity/basicity. The pK_a values of synthesized amine **7c** (trifluoroacetate) and carboxylic acid **9**, as well as their analogs **11a**–**n** and **12a**–**n**, respectively, were measured by standard acid-base titration (Figure 5, Table S1 in the Supporting Information). For the piperidine series, the effect of 3,3-*di*FOx substituent (**7c**) was somewhat more pronounced (ΔpK_a = 1.1), thus illustrating weak electron-acceptor properties of this group. The pK_a value (10.0) was similar to that of oxetane (**11b**, 10.2), 1,3-dioxolane

(**11m**, 10.0), *gem*-difluorocyclopropane (**11k**, 10.1), and $CHF_2CH(OMe)$-substituted (**11l**, 9.9) derivatives. It was by 0.7–0.8 units lower than those of (cyclo)alkyl derivatives **11e–h**, and by 0.2–0.4 units higher than those for CF_3-, $C(O)NH_2$, or CO_2Me-substituted counterparts (**11i**, **11n**, and **11o**, respectively).

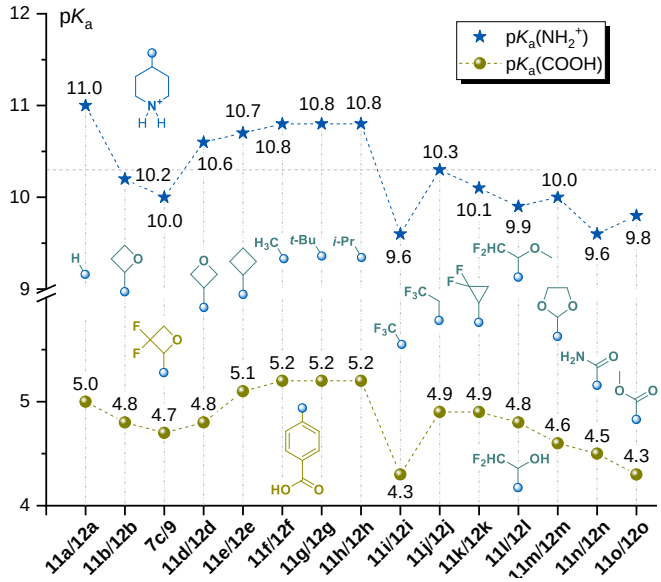


Figure 5. pK_a values for protonated 4-substituted piperidines **7c**, **11a**–**k** and benzoic acids **9**, **12a**–**k**.

In the benzoic acid series, similar trends were observed, albeit with lower ΔpK_a magnitude. In particular, difluorooxetanyl-substituted benzoic acid **9** had the pK_a value (4.7) comparable to those of oxetane (**12b** and **12d**, 4.8) 1,3-dioxolane- (**12m**, 4.6) and $CHF_2CH(OMe)$-substituted (**12l**, 4.8) analogs. The pK_a value of compound **9** was by 0.3 and 0.5 units lower than that of parent benzoic acid **12a** (5.0) and alkyl-substituted counterparts **12f–h** (5.2), respectively, and by 0.4 units higher than CF_3- or CO_2Me-substituted analogs **12i** and **12o** (4.3).

These data show that the 3,3-*di*FOx substituent is intermediate in terms of its effect on the pK_a value, and it can be used as a replacement for both (cyclo)alkyl groups and relatively strong acceptors to fine-tune the acidity/basicity of the compounds in the necessary direction.

Lipophilicity. Log*P* values were measured for benzamides **13a–o** (prepared by benzoylation of amines **7c** and **11a–o** under the standard reaction conditions) using the classical shake-flask method combined with HPLC quantitative analysis as reported previously (Figure 6).[7] The 3,3-*di*Fox substituent slightly increased the lipophilicity upon introduction into parent piperidine derivative **13a** (Log*P* = 1.6 vs 1.1, respectively); this effect was similar to those of methyl or $CHF_2CH(OMe)$ groups. Notably, *gem*-difluorination of the oxetane ring resulted in nearly the same Log*P* increase (1.6 vs 1.1 for **13c** and **13c**, respectively), which is contrary to the case cycloalkane derivatives where *gem*-difluorination typically led to increased hydrophilicity.[7] Analysis of the remaining data presented in Figure 6 revealed that the 3,3-*di*Fox substituent had intermediate position between lipophilic (cyclo)alkyl or CF_3-substituted compounds and hydrophilic derivatives bearing polar groups (*e.g.*, ester, amide, or 1,3-dioxolane). Therefore, according to these results, the 3,3-diFOx moiety can be considered as a possible replacement for both substituent types to fine-tune the compound's lipophilicity in the desired direction.

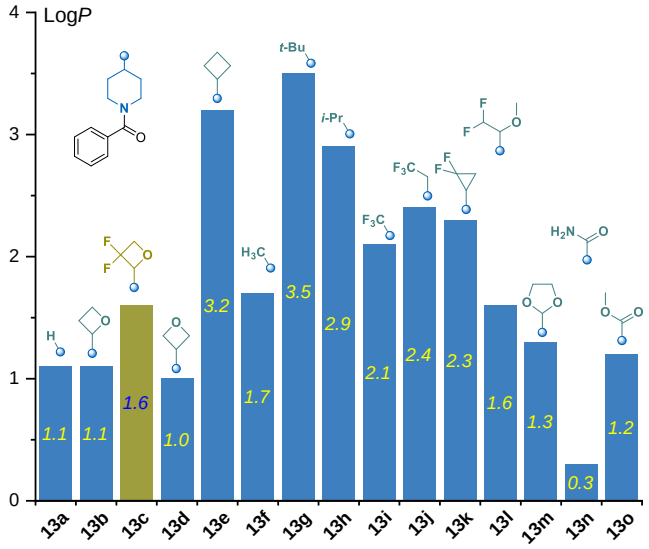


Figure 6. Log*P* values measured for benzamides **13a**–**k**.

Linear free energy relationships. A quantitative relationships between the structure and reactivity of benzene derivatives was formulated by L.P. Hammett in 1937[37] and is still actively used in QSAR studies.[38,39] In its essence, the Hammett equation states that there is a linear relation between the reaction rates and equilibrium constants for a similar series of compounds (e.g., benzoic acid derivatives):

$$\mathrm{Log}(k/k_H) = \rho\mathrm{Log}(K_a/K_{aH}) = \rho\sigma,$$

where k and k_H – rate constants for a model reaction of the studied compound and parent benzoic acid (**12a**) derivatives, K_a and K_{aH} – dissociation constants of the studied molecule and parent benzoic acid **12a**, ρ – reaction rate constant, $\sigma = \mathrm{Log}(K_a/K_{aH})$ – substituent constant (Hammett constant).

Hammett constants σ measure the magnitude of the substituent electronic effects, thus allowing positioning new functional groups among the known ones in terms of their electronic properties. To achieve this for the 3,3-*di*Fox moiety, we have studied 14 *p*-substituted benzoic acids **9**, **12a–p** (9 – with known σ values of the para substituent, and 5 – with yet unreported ones, Table S1 in the Supporting Information). Based on the previously established acidity data shown in Figure 5, the σ values were calculated. The obtained results for the compounds with known σ values was in good agreement with previously reported.[40] In addition to that, kinetic experiments were performed following the methodology reported by Keenan and colleagues.[41] For this purpose, *p*-nitrophenolate esters **14a–p** were synthesized from benzoic acids **12a–p** via acyl chloride activation, and the kinetics data of the ester hydrolysis upon action of aq NaOH were studied by UV-Vis spectrophotometry. The obtained logarithmic relative rate constants $\mathrm{Log}(k/k_H)$ were plotted against calculated Hammett constant values σ and linearized using the least square method (Figure 7). A good linear correlation was found (R^2=0.953); the obtained ρ value was slightly lower than the previously reported (1.7 *vs.* 2.1–2.4[41]), which can be related to differences in the experiment conditions.

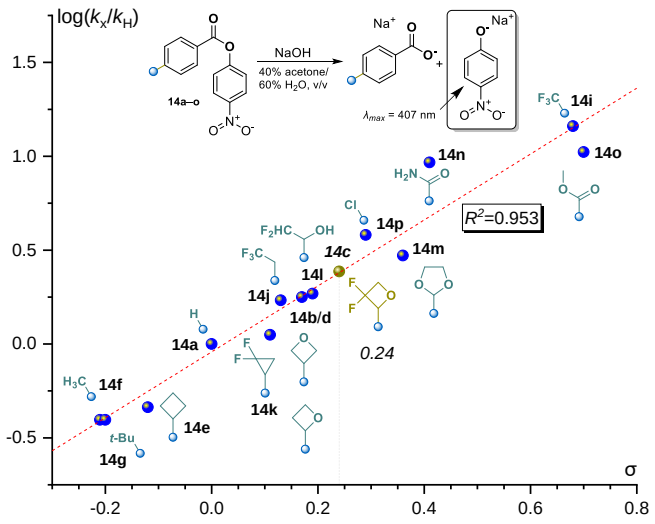


Figure 7. Linear free energy relationship graph.

According to the obtained Hammett constant value (σ = 0.24), the 3,3-*di*Fox functional group can be considered a weak electron acceptor, comparable to chlorine (**14p**, 0.29) and significantly less pronounced than CF_3 (**14i**, 0.68) or CO_2Me (**14o**, 0.70) groups. As might be expected, *gem*-difluorination results in slight increase of electron-acceptor properties relatively to the parent oxetan-2-yl and oxetan-3-yl substituents (**14b**/**14d,** σ = 0.17). When the 3,3-*di*Fox is compared to the donor (cyclo)alkyl groups such as cyclobutyl (**14e**, σ = –0.12), a considerable increase of electron-withdrawing properties is observed. Therefore, it is the oxygen atom which is mainly responsible for the electron-acceptor properties of the 3,3-*di*FOx functional group.

Stability of the 3,3-difluorooxetane moiety. Full profiling of a novel drug candidate necessarily requires metabolic stability assaying as one of the key parameters.[42,43] At the same time, the chemical stability of the studied molecule often stays out of attention.[44,45] Considering the known oxetane reactivity,[16,18,46–48] as well as our unsuccessful experience with *N*-Boc cleavage from compound **10**, one could question the 3,3-diFox moiety stability. To overcome these biases, we evaluated compound **4e** as a model substrate under common organic transformation conditions.[49] We included highly acidic (TFA and anhydrous HCl), basic (LiOH), oxidative (Dess-Martin periodinane and 30% aq H_2O_2), and reductive agents (H_2 – Pd/C and $LiAlH_4$), irradiation (at 365 and 450 nm), and air.[50] The experiment included mixing the compound **4e** and indicated reagents at low (0 °C), ambient (24 °C), and elevated (60 °C) temperatures (or irradiation at the corresponding wavelengths) for 2 h, work-up of the reaction mixture. Then, the recovery yields were measured by quantitative ^{1}H NMR spectroscopy against a control sample of **4e**. The results have been depicted as a radar diagram (Figure 8). It is apparent that the 3,3-diFox moiety is compatible with most common reaction conditions at 0 °C and 24 °C. As expected, elevated temperature was detrimental for the relative recovery ratio (42–88%); in this case, significant decomposition was observed in the presence of HCl and $LiAlH_4$ (but not LiOH). Notably, dehalogenation was the main decomposition pathway in the presence of reductants: while the oxetane fragment remained virtually intact, significant amounts of defluorinated products were detected (up to 11% for catalytic hydrogenation and 80% for $LiAlH_4$). Finally, the stability of the 3,3-*di*Fox fragment was illustrated by a five-year on-shelf storage with no detected loss of the sample quality (see the Supporting Information). The observed results correlate with previously reported data on other 3,3-substituted oxetanes.[15] This effect was typically referred to reduced ring strain[51] and/or sterically hindered access to C–O σ* antibonding orbital;[18] these explanations are less pertinent for the 3,3-*di*Fox fragment.

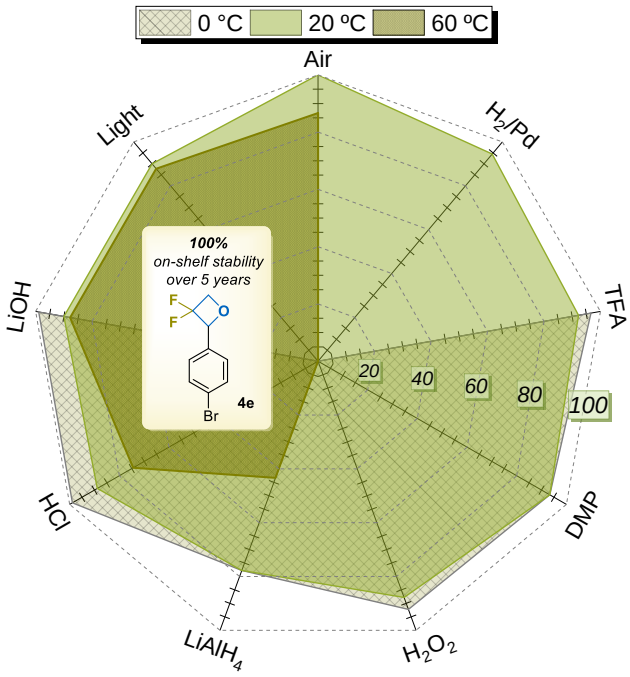


Figure 8. Stability assessment of compound **4e** (the recovery yields measured by quantitative ^{1}H NMR spectroscopy against a control sample are shown as a radar diagram).

Structural and electronic properties. An X-Ray diffraction study of (*S**,*S**)-**4d** and comparison of the obtained results with the CCDC data for oxetane,[52] cyclobutane,[53] and 3,3-difluoro-cyclobutane[54] derivatives revealed several structural features of the 3,3-*di*Fox moiety (Figure 9, *A*). While the *gem*-CF_2 or O fragments had minor effects on the valent angles φ_1 and φ_2 as compared to the parent cyclobutane scaffold (1–2° difference), ring puckering angle θ was affected significantly. Thus, introducing oxygen atom to the cyclobutane ring led to its significant flattening (θ = 26.9° and 6.9° for cyclobutane and oxetane, respectively), while *gem*-difluorination slightly increased puckering (26.9° and 29.7°, respectively). For the oxetane core, the latter effect of *gem*-difluorination was even more pronounced: the θ value was increased by 10°.

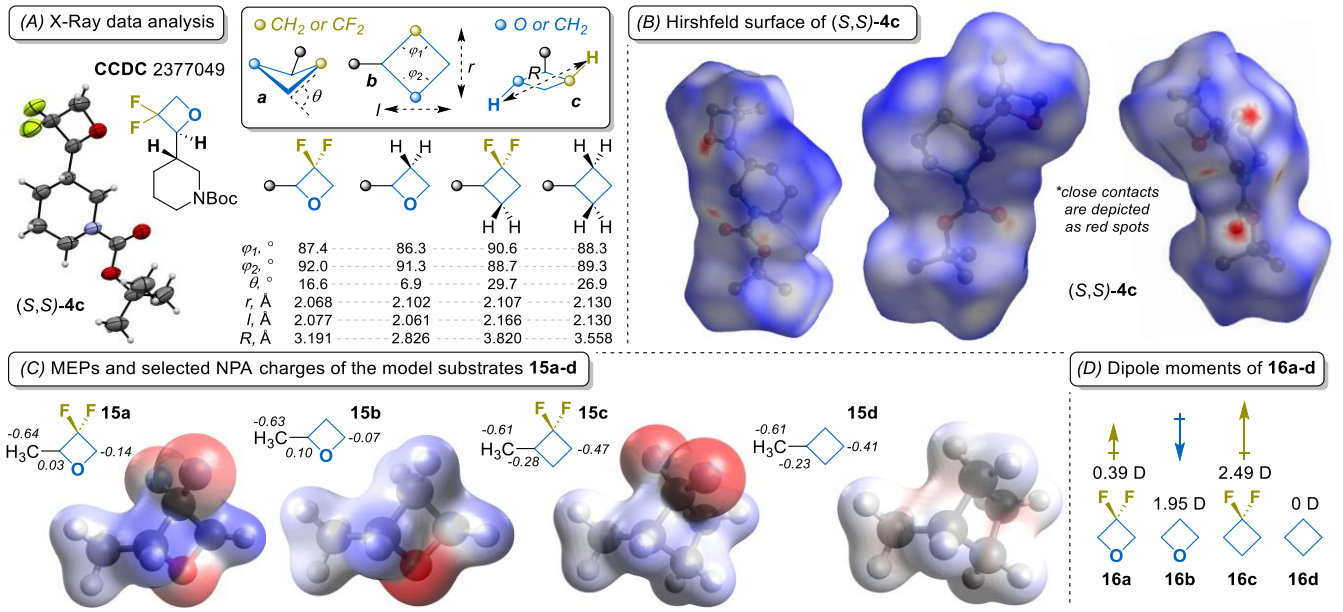


Figure 9. (*A*) X-Ray structure of (*S**,*S**)-**4c** and comparison of the geometric parameters of 3,3-*di*Fox fragment with its closest analogs. (*B*) The Hirshfield surface of (*S**,*S**)-**4c**. (*C*) The molecular electrostatic potential (MEP) surfaces for the optimized geometry of **15a**–**d** and calculated NPA-derived partial atomic charges (DFT/PBE0/ma-def2-TZVP).[55] (*D*) Dipole moments calculated for parent cyclic compounds **16a–d**.

As for the relative size of the discussed moieties, introducing oxygen atom decreased both C1–C3 (*l*) and C2–C4/O (*r*) interatomic distances (numeration of the parent cyclobutane ring was preserved). For the CF_2 moiety, the corresponding effects were opposite, i.e., decrease for *r* and increase for *l*. Also, the 3,3-*di*FOx moiety had the second lowest value of maximum fragment diameter (*R*) withing the series studied.

Analysis of the Hirshfeld surface[56] of (*S**,*S**)-**4c** (Figure 9, *B*) demonstrated high involvement of the Oxygen and Nitrogen atoms into the formation of intermolecular contacts in the solid state (red spots), whereas the Fluorine atoms did not participate in these interactions (blue areas).

To get a deeper insight into the structural and electronic features of the studied fragments, DFT study of 2-methyl-3,3-difluoro-oxetane (**15a**), 2-methyloxetane (**15b**), 1,1-difluoro-2-methyl-cyclobutane (**15c**), and methylcyclobutane (**15d**) was performed. Molecular electrostatic potential (MEP) analysis was used to identify reactive sites of the corresponding fragments (Figure 9, *C*). Negative (red) and positive (blue) regions of the electrostatic potential contour maps denote the sites of possible electrophilic and nucleophilic attack, respectively. Thus, introduction of a single electron-withdrawing moiety (either O or CF_2) mainly affected α-Carbon atoms, inverting their electrostatic potentials from slightly negative to neutral or positive values (compare **15d** and **15b**/**15c**). At the same time, the combination of both CF_2 and O fragments in the molecule **15a** had a synergistic effect, significantly decreasing the electrostatic potential on all the Carbon atoms of the four-membered ring and hence creating an X-shaped electrostatic map with opposite potential signs.

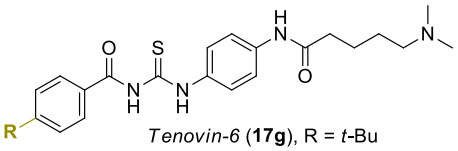
A closer look at the *gem*-CF_2 fragment in **15a** offers a possible explanation for the lowered susceptibility of the fluorinated oxetane ring towards most chemical reagents studied. While the steric size of the Fluorine atom is relatively low, high Fluorine electronegativity causes the formation of a large negatively charged surface near the potential reaction centers. This, in turn, makes the nucleophilic attack at the oxetane ring less feasible, enhancing the chemical stability of the moiety.

The calculated dipole moments of parent cyclobutane **16a** and its fluorinated and/or oxygenated analogs **16b**–**d** revealed the higher effect of the *gem*-CF_2 fragment on the overall polarization of 3,3-*di*Fox moiety, which compensated the effect of the Oxygen atom in the oxetane ring (Figure 9, *D*). In view of its relatively low dipole moment (0.39 D), the 3,3-*di*FOx group can be considered as a better mimic of the non-polar cycloalkyl groups than the corresponding simple *gem*-difluorinated or oxygen-containing counterparts.

Physicochemical and biological evaluation. To demonstrate the potential of 3,3-difluorooxetane for bioisosteric replacements in medicinal chemistry, we have prepared 3,3-*di*FOx-substituted analog **17c** of Tenovin-6 (**17g**), a known selective inhibitor of histone deacetylases SirT1 and SirT2 (Table 1).[57–59] In this case, the 3,3-*di*FOx moiety was introduced instead of *tert*-butyl group. The synthesis of compounds **17c** and **17g** commenced from corresponding benzoic acids **12g** and **9** and followed the procedure reported previously for compound **17g** (see the Supporting Information for more details).[58,60] Evaluation of the obtained products revealed that 3,3-*di*FOx-substituted analog **17c** retained most biological activity of original Tenovin-6 (**17g**) against histone deacetylase SIRT1 (only 4-fold decrease of the IC_{50} value was observed). Furthermore, compound **17c** was by 0.7–1.3 LogP / Log$D_{7.4}$ units less lipophilic than parent Tenovin-6, while aqueous solubility of both compounds was similar (370 and 350 μM, respectively). Caco-2 permeability test demonstrated moderate permeability through the cell membranes for both compounds. Nevertheless, the efflux of Tenovin-6 (**17g**) was strongly affected by P-glycoprotein (P-gp) inhibitor Verapamil, while 3,3-*di*FOx-Tenovin-6 (**17c**) was much less sensitive to the presence of this compound. In other words, introducing the 3,3-

*di*FOx substituent decreased affinity of Tenovin-6 towards P-gp. Finally, metabolic stability (measured as intrinsic clearance, CL_{int}) was somewhat improved for the 3,3-*di*FOx-substituted derivative (CL_{int} = 2 µL/min/mg vs 9 µL/min/mg for Tenovin-6). These results show that 3,3-difluorooxetane can be indeed used as a bioisostere of *tert*-butyl (and likely other) groups to improve pharmacokinetic properties of optimized compounds.

Table 1. Physicochemical and biological assessment of Tenovin-6 (**17g**) and its 3,3-diFOx analog (**17c**).



Tenovin-6 (**17g**), R = *t*-Bu
3,3-diFOx-Tenovin-6 (**17c**), R = 3,3-*di*FOx

Compound	Log*P* / Log$D_{7.4}$	S_w, µM[a]	Efflux ratio,[b] without/with Verapamil	IC_{50}, µM	CL_{int}, µL/min/mg
Tenovin-6 (**17g**)	1.1 / 3.1	350	9.1 / 1.3	14	9
3,3-diFOx-Tenovin-6 (**17c**)	0.4 / 1.8	370	0.9 / 0.3	58	2

[a] Kinetic solubility in phosphate-buffered saline, pH = 7.4 [b] In Caco-2 cells

Conclusion

With the wide spread of the bioisosteric replacement approach in medicinal chemistry, the demand for new functional groups allowing fine-tuning of desirable properties of potential drugs has increased considerably. We propose 3,3-difluoroxetan-2-yl (3,3-*di*FOx) as a promising fluorinated substituent and non-classical isostere of numerous functional groups. We have shown that functionalized derivatives with 3,3-*di*FOx moiety mounted onto an aromatic or saturated heterocyclic ring can be prepared in multigram quantities (up to 64 g scale in a single run). Measurement of pK_a values for model derivatives demonstrated that the 3,3-*di*FOx fragment is a weak acceptor that can be used to fine-tune acidity/basicity by replacing either donor alkyl groups or stronger acceptors like CF_3, CO_2Me, or $C(O)NH_2$. This was confirmed by linear free energy relationship studies, with the Hammet constant value of the title substituent (σ = 0.24) being close to that of chlorine (σ = 0.29).

Lipophilicity measurements for a series of model derivatives showed that the 3,3-*di*FOx moiety slightly increases the compound's lipophilicity when introduced into the parent molecule (ΔLog*P* = +0.5). Again, this effect was intermediate between those of (cyclo)alkyl groups and polar fragments like amide, ester, 1,3-dioxolane, or non-fluorinated oxetane, thus suggesting potential for isosteric replacements of both these categories.

In terms of three-dimensional structure, the 3,3-*di*FOx fragment showed intermediate ring puckering between oxetane and cyclobutane/*gem*-difluorocyclobutane and was the second smallest between these fragments. The molecular electrostatic potential (MEP) map of the 3,3-*di*FOx group was X-shaped, with opposite potential signs at the diagonal ring atoms. As a result, the overall dipole moment of 3,3-difluorooxetane was relatively low (0.39 D), suggesting that the proposed moiety can be a better mimic for (cyclo)alkyl groups than simpler *gem*-difluorinated or oxygen-containing counterparts.

Finally, the 3,3-*di*FOx moiety had reasonable stability towards common chemical reagents, excellent shelf storage stability (over 5 years), and good metabolic stability. The latter fact was confirmed by introducing the title functional group into the molecule of Tenovin-6, a known sirtuin inhibitor, instead of a *tert*-butyl group. This modification retained a significant fraction of the compound's biological activity, increased hydrophilicity, and reduced P-glycoprotein affinity. These data confirm bioisosteric replacement compatibility of the 3,3-*di*FOx moiety for the particular case studied. We hope that along with all other results presented in this work, they will promote applications of 3,3-difluorooxetane as a promising functional group in drug discovery and other areas of science.

Supporting Information

The authors have cited additional works within the Supporting Information.[61–89]

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Conflict of Interest

Most of 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: Fluorine • Oxetane • Building Blocks • Bioisosteres • Functional Groups

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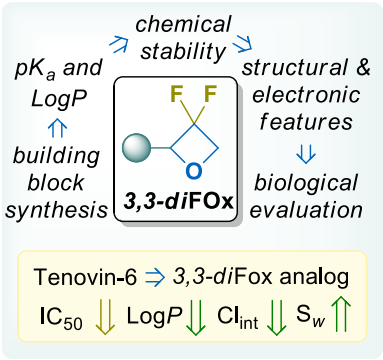
[89] Deposition Number 2377049 contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Bioisosteres



3,3-Difluorooxetane (3,3-*di*FOx) is proposed as a promising functional group for drug discovery and other areas of science. Its applicability is confirmed by a comprehensive study of physicochemical, structural, electronic, and biological properties, assessing chemical stability, as well as multigram synthesis of corresponding building blocks. The compatibility with bioisosteric replacements is demonstrated for the case of *tert*-butyl group in the molecule of Tenovin-6, a known sirtuin inhibitor.

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