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Article

CF_3-Cyclobutanes: Synthesis, Properties, and Evaluation as a Unique *tert*-Butyl Group Analogue

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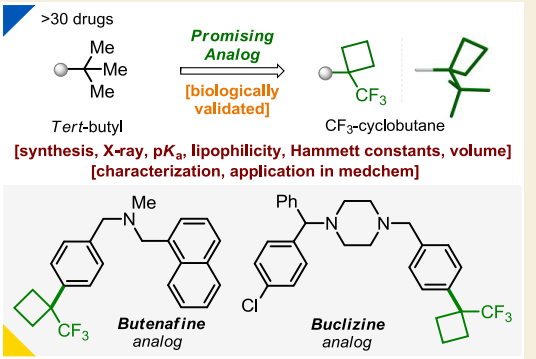
ABSTRACT: Isosteric replacement of functional groups is an emerging strategy for optimizing bioactive molecules in drug discovery. *tert*-Butyl group is a particularly important moiety, yet its isosteric replacement with 1-trifluoromethyl-cyclobutyl group has been rather neglected. To enable the advance of this molecular fragment in drug discovery programs, we report the synthesis of over 30 small-molecule building blocks featuring the trifluoromethyl-cyclobutyl fragment, achieved by reacting sulfur tetrafluoride with cyclobutylcarboxylic acids on a gram-to-multigram scale. Furthermore, we characterized the structural properties of this group through X-ray analysis, studied its effect on acid−base transitions, and evaluated its Hammett parameters. Finally, we evaluated the replacement of *tert*-butyl with 1-trifluoromethyl-cyclobutyl in several bioactive compounds that represent commercial drugs and agrochemicals. Our findings indicate that while the trifluoromethyl-cyclobutyl group exhibited slightly larger steric size and moderately increased lipophilicity, it preserved the original mode of bioactivity in the examined cases and, in some cases, enhanced resistance to metabolic clearance.



KEYWORDS: *bioisostere, medicinal chemistry, tert-butyl, CF_3-cyclopropane, CF_3-cyclobutane*

INTRODUCTION

The trifluoromethyl and difluoromethyl groups are the most popular fluoroalkyl substituents in chemistry.[1] Recent achievements in drug discovery, however, also brought the attention of chemists toward other more sophisticated substituents: difluorocyclobutyl, trifluoroethyl, pentafluoroethyl, trifluoro-*tert*-butyl, and CF_3-cyclopropane (Figure 1).[2] The latter, in particular, was used as a metabolically improved alternative for the labile *tert*-butyl group (Figure 1).[3] This replacement has eventually become common in chemistry, inspiring academic groups to search for novel synthetic approaches toward CF_3-cyclopropanes.[4−7] In parallel, various pharmaceutical companies started routinely using CF_3-cyclopropane substituents in bioactive compounds, as reflected in at least 600 recent patents (Figure 1).[8]

In this work, originally driven by scientific curiosity, we hypothesized that the previously underappreciated chemical substituent—CF_3 cyclobutane (Figure 1) that only appeared in a few previous studies[9−16]—could also be used as a unique *tert*-butyl group analogue. Here, we have developed a practical modular synthesis of this substituent, comprehensively characterized it, and validated our hypothesis with experimental data.

RESULTS AND DISCUSSION

Synthesis

To validate our hypothesis, we first aimed to prepare a library of diverse CF_3-cyclobutanes. Poly-substituted CF_3-cyclobutanes are typically synthesized using linear approaches: thermal and photochemical [2 + 2]-cycloadditions;[17−26] addition of CF_3TMS to imines and ketones;[27−30] among other methods.[31−36] In a search for a modular approach to CF_3-cyclobutanes from commercially available starting materials, we focused our attention on a well-known reaction between carboxylic acids and sulfur tetrafluoride.[37−39]

This transformation has been reported for *poly*-substituted cyclobutane carboxylic acids.[40−46] We envisioned that the same strategy could also be applied to rapidly make a wide

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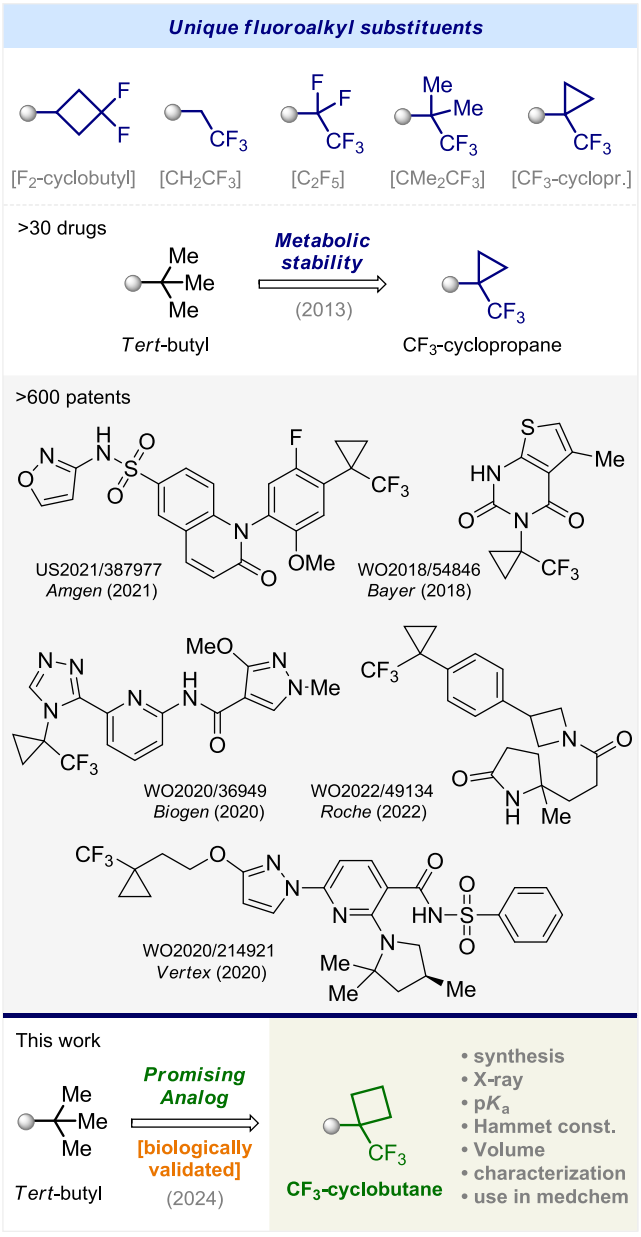

Figure 1. Unique fluoroalkyl substituents. A *tert*-butyl group and its analogues: a CF_3-cyclopropane substituent (previous study) and a CF_3-cyclobutane substituent (this work).

variety of appropriate *mono*-substituted CF_3-cyclobutanes, to subsequently mimic *tert*-butyl groups in drugs.

Pleasingly, a thermal reaction of sulfur tetrafluoride with various (hetero)aromatic cyclobutane carboxylic acids **1**−**18** efficiently gave trifluoromethyl cyclobutanes **1a**−**18a** in good yields (Scheme 1). The reaction was compatible with nitro groups (**4a**, **5a**), activated chlorine (**7a**, **13a**, and **16a**), and bromine (**8a**) atoms.

This transformation also worked well for aliphatic cyclobutane carboxylic acids with diverse substituents (**19**−**34**) to produce medicinal chemistry-relevant trifluoromethyl cyclobutanes **19a**−**34a**. Among them were compounds with an ester group (**19a**, **20a**, and **27a**), an activated bromine atom (**21a**), and an unprotected amino group (**22a**−**26a**). It is worth noting that the reaction worked for bicyclo[1.1.1]pentanes (**26a**, **28a**), and even for difluoro-substituted bicyclo[1.1.1]-pentanes (**27a**).[47−50] The only two products that could not be obtained even when varying conditions were the *ortho*-substituted bromobenzene and a cubane derivative (Scheme 1). The formation of complex mixtures was observed in both cases.

It is important to note that this method worked equally well on milligram, gram, and even multigram scales (**2a**, **9a**, and **19a**). On a milligram scale, products were purified by silica gel column chromatography. On a gram-to-multigram scale, products were isolated by either crystallization or distillation under reduced pressure. The structures of products **3a**, **5a**, **14a**, **18a**, **28a**, **29a**, and **31a** were confirmed by X-ray crystallographic analysis.[51]

Despite the seeming simplicity of the current approach to CF_3-cyclobutanes, the preparation of only three products **10a**,[33] **22a**,[52] and **26a**[53] from Scheme 1 has been previously reported in the literature by other methods.

Modifications

Representative modifications of the obtained CF_3-cyclobutanes were undertaken to obtain functionalized derivatives (Scheme 2).

Treatment of bromide **1a** with *n*-BuLi followed by an addition of sulfur dioxide and subsequent oxidation with sulfuryl chloride gave sulfonyl chloride **1b**. Reduction of nitro compounds **4a** and **5a** with Raney nickel gave anilines **4c** and **5c**. [Pd]-Catalyzed hydrogenation of the pyridine ring in compounds **6a**, **12a**, and **15a** afforded piperidines **6d**, **12d**, and **15d** respectively. [Pd]-catalyzed carbonylation of the (hetero)-aromatic bromides **1a**, **2a**, **7a**, and **9a**−**11a** in methanol followed by saponification of the intermediate esters resulted in the formation of carboxylic acids **1e**, **2e**, **7e**, and **9e**−**11e**, correspondingly. A standard Curtius reaction of pyridine carboxylic acids **7e**, **9e**−**11e** followed by acidic *N*-Boc deprotection gave amino pyridines **7f**, **9f**−**11f**. Saponification of the ester group in **27a** gave carboxylic acid **27g**. The structures of products **1e**, **10e**, **11e**, and **7f** were confirmed by X-ray crystallographic analysis.[51]

Radical modifications of the obtained compounds were unsuccessful at this point (see SI p. S31−S33).

Chemical Stability

We also checked the chemical stability of three representative trifluoromethyl cyclobutanes, **4a**, **9a**, and **12a** (Scheme 1) because we suspected that some of them could eliminate hydrogen fluoride over time. Treatment of them with aqueous 1 M hydrochloric acid or aqueous 1 M sodium hydroxide at room temperature for 1 day did not lead to any decomposition. We stored all products in closed vials at room temperature on the shelf. The ^{1}H- and ^{19}F-NMR, liquid chromatography−mass spectrometry (LC−MS) inspection after three months revealed no decomposition.

Crystallographic Analysis

Small-molecule X-ray structures representing 1-substituted CF_3-cyclobutanes have been absent in the literature. Therefore, we studied the conformational preferences of the CF_3-cyclobutane ring, based on the X-ray structures solved for eight compounds from this work: **3a**, **5a**, **14a**, **18a**, **1e**, **10e**, **11e**, and **7f** (Figure 2).[51] We examined the axial/equatorial position of the trifluoromethyl substituent and measured the cyclobutane puckering angle γ and dihedral angles φ_1 (C(2)−C−C-CF_3) and φ_2 (C(6)−C−C-CF_3) to determine the alignment of the (hetero)aromatic substituent around the

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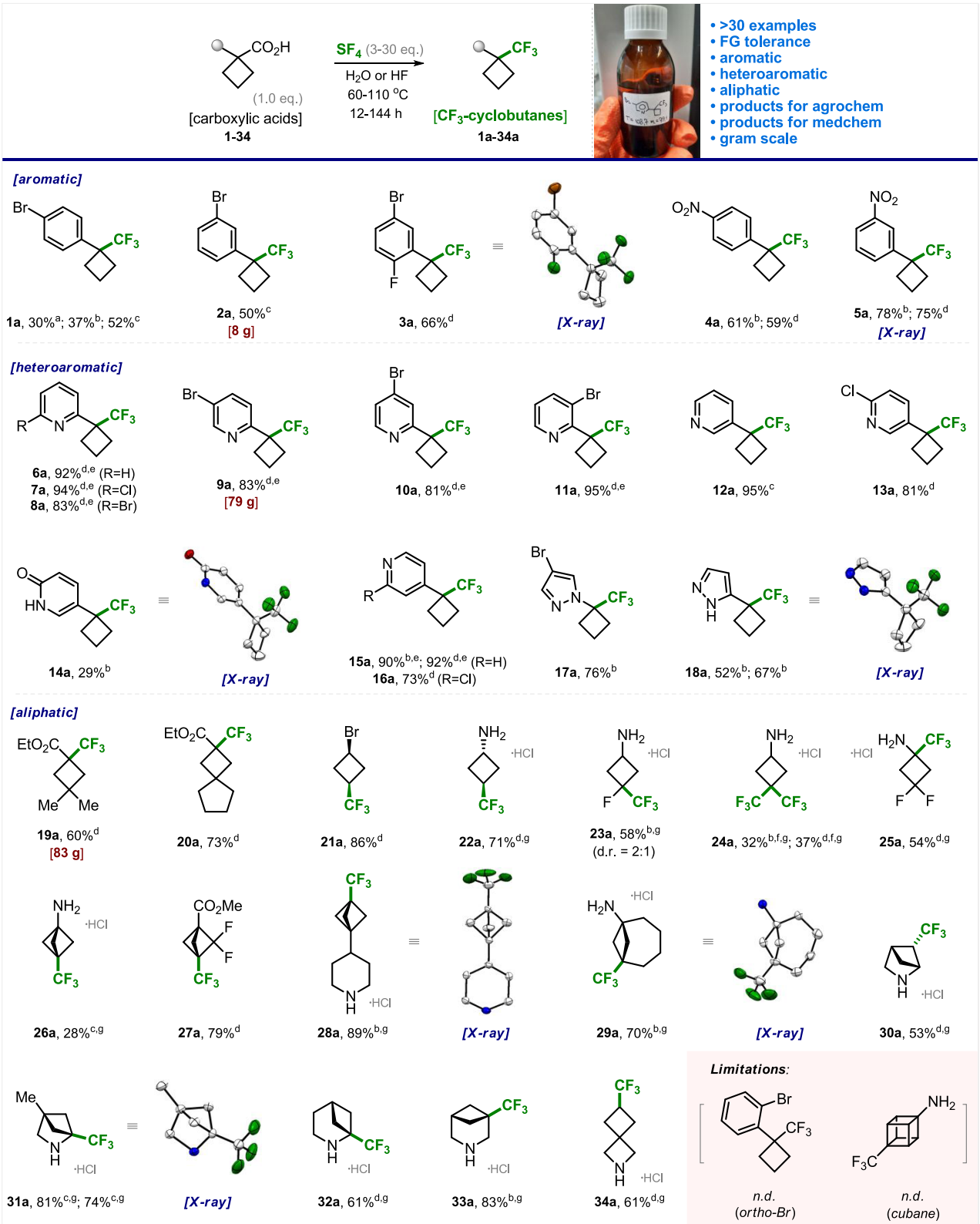
Scheme 1. Synthesis of Trifluoromethyl Cyclobutanes[a]



[a]Reaction conditions: (i) carboxylic acid (1.0 equiv), SF_4 (3−30 equiv), additives (water or HF), 60−110 °C, 12−144 h; (ii) purification (column chromatography or crystallization or vacuum distillation). Scale of the synthesis: [a] 100−300 mg; [b] 500 mg−5 g; [c] 5−10 g; [d] >10 g of the isolated product. [e] The starting carboxylic acids **6**−**11**, and **15** were used in the form of their potassium salts (R-CO_2K). [f] Diisopropyl ester of diacid **24** was directly used in the fluorination reaction. [g] After the reaction, crude products **22a**−**26a**, **28a**−**34a** were converted into the crystalline pure hydrochloride salts with 1 M HCl in MeOH. X-ray crystal structure of compounds **3a**, **14a**, **18a**, **28a**, **29a**, and **31a** are shown as thermal ellipsoids at a 30% probability level; carbon—white, oxygen—red, nitrogen—blue, bromine—orange, fluorine—green; hydrogen and chlorine (for hydrochloride salts **28a**, **29a**, **31a**) atoms are not shown for clarity.

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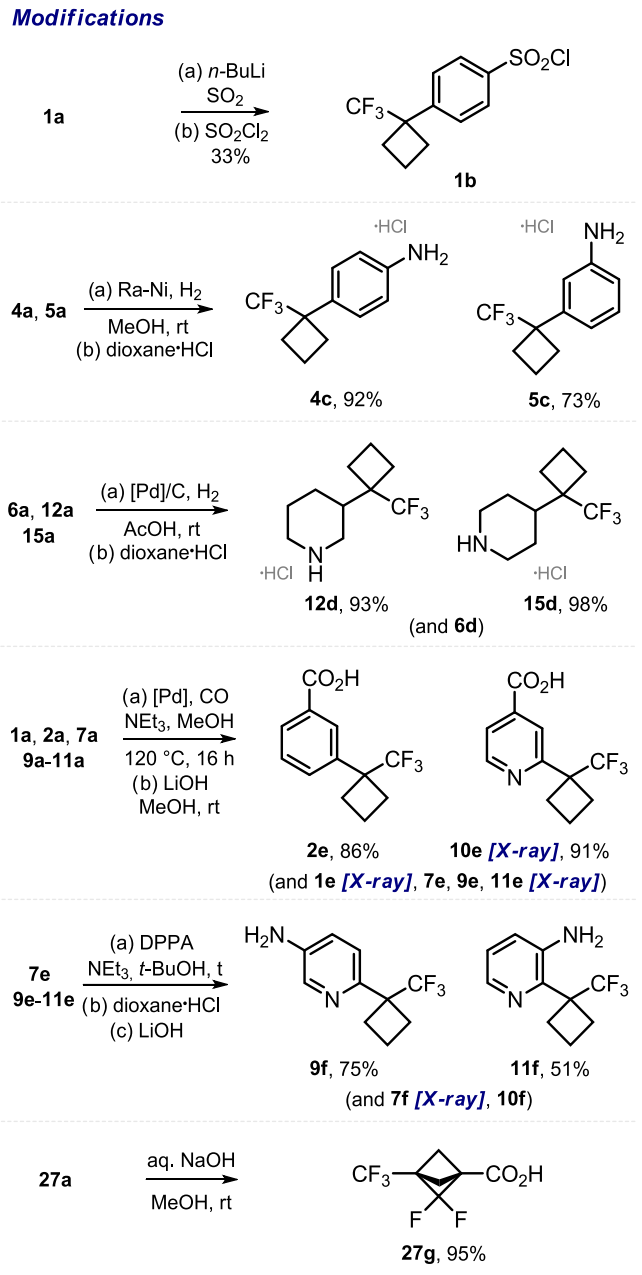
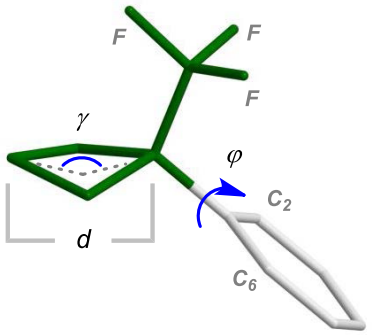
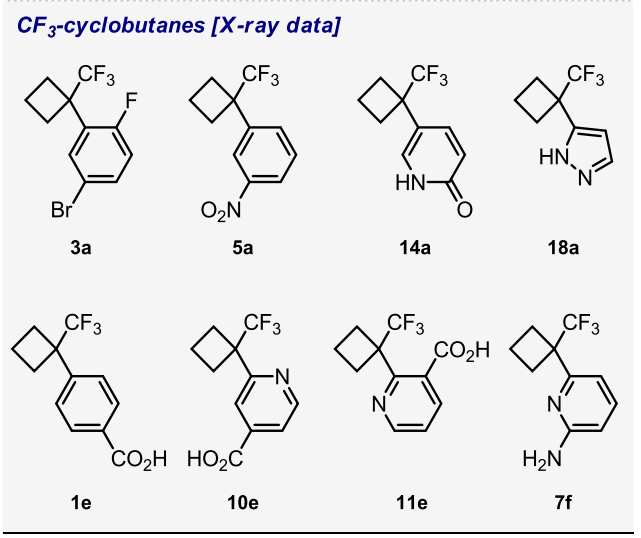
Scheme 2. Modifications of Trifluoromethyl Cyclobutanes "a"







Compound	CF_3	γ (°)	$\lvert\varphi_1\rvert$ (°)	$\lvert\varphi_2\rvert$ (°)	d (Å)
3a	axial	160.4(3)	87.1(3)	92.7(3)	2.170(4)
5a	axial	163.6(3)	86.4(3)	92.7(3)	2.165(5)
14a	axial	174.0(4)	86.9(3)	91.0(3)	2.172(5)
18a	equatorial	158.4(6)	85.2(6)	93.6(5)	2.127(8)
1e	axial	163.8(2)	85.5(2)	94.0(2)	2.187(3)
10e	axial	161.2(3)	87.7(3)	90.4(3)	2.184(5)
11e	axial	162.3(7)	82.5(5)	100.1(5)	2.19(1)
7f (A)[a]	axial	165(1)	87.7(6)	92.2(6)	2.20(2)
7f (B)[a]	axial	174.7(7)	82.9(6)	97.4(6)	2.184(9)

Figure 2. Definition of angles γ, φ, and distance d (1-Ph trifluoromethyl cyclobutane is shown as an example). φ_1 = C(F_3)−C-C(Ph)-C_2. φ_2 = C(F_3)−C-C(Ph)-C_6. C_2 and C_6 atoms are chosen so that $|\varphi_1|<|\varphi_2|$. Geometric parameters γ, $|\varphi_1|$, $|\varphi_2|$, and d are for trifluoromethyl cyclobutanes **3a**, **5a**, **14a**, **18a**, **1e**, **10e**, **11e**, and **7f**. [a] Two molecules of **7f** (A, B) are present in the crystalline lattice.

cyclobutane ring; and the distance d between two distal carbon atoms in the cyclobutane ring (Figure 2).

Interestingly, in seven of eight studied CF_3-cyclobutanes, the trifluoromethyl substituent adopted the axial position. Only in compound **18a**, the trifluoromethyl substituent adopted the equatorial position (Figure 2).

The cyclobutane puckering angle γ was within the 158−175° range, suggesting an almost flattened cyclobutane ring. The dihedral angles $|\varphi|$ were in the range of 83−100°, indicating the "perpendicular" alignment of the (hetero)aromatic and the trifluoromethyl substituents in all compounds. The distance d between the carbon atoms in the cyclobutane ring was 2.1−2.2 Å.

Steric Volume

To estimate the size of the CF_3-cyclobutane substituent compared to the *tert*-butyl group, we calculated[54] and compared a steric volume of three molecules: *t*Bu-, CF_3-cyclopropane-, and CF_3-cyclobutane-benzenes (Figure 3a). The obtained data show that the CF_3-cyclobutane substituent is somewhat bigger than the *tert*-butyl group: 171 Å^3 (CF_3-cyclobutane) vs 155 Å^3 (CF_3-cyclopropane) vs 150 Å^3 (*t*-Bu). For a more detailed comparison including other substitutes, see the SI (p. S354).

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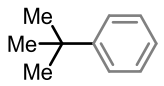
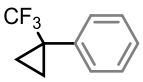
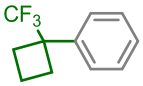
(a) Substituent	Compound	Volume (Å^3)
t-Bu		150
CF_3-cyclopropane		155
CF_3-cyclobutane		171

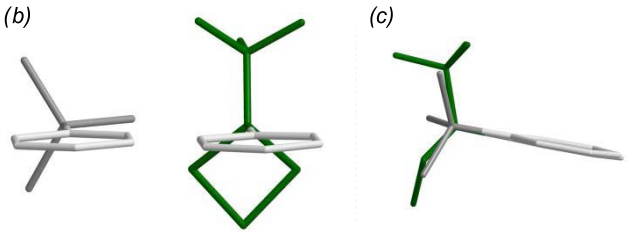


Figure 3. (a) Calculated molecular volume (Å^3) of *t*Bu-Ph, CF_3-cyclopropane-Ph, and CF_3-cyclobutane-Ph. (b) Visual comparison of *t*Bu-Ph (left) and CF_3-cyclobutane-Ph (right, the CF_3-cyclobutane residue is green). (c) Superposition of *t*Bu-Ph and CF_3-cyclobutane-Ph (the CF_3-cyclobutane residue is green).

The visual comparison of *t*Bu-Ph and CF_3-cyclobutane-Ph (Figure 3b) also shows the bigger steric size of the CF_3-cyclobutane substituent compared to the *tert*-butyl group.

The Acidity of Functional Groups

To better understand the electron-withdrawing effect elicited by the CF_3-cyclobutyl substituent, we studied the acid−base transition of pivalic acid and *tert*-butyl amine as compared to their CF_3-cyclopropyl and CF_3-cyclobutyl analogues. Toward this goal, we measured experimental pK_a values of the corresponding carboxylic acids and amine hydrochlorides (Figure 4).

Replacement of the *tert*-butyl group in pivalic acid for the fluoroalkyl substituents increased the acidity by ca. 2 pK_a units: 4.79 (*t*Bu) vs 2.99 (CF_3-cyclopropane) vs 2.92 (CF_3-cyclobutane). Analogous replacement in the *tert*-butyl amine hydrochloride increased the acidity even stronger, pK_a: 10.69 (*t*Bu) vs 4.06 (CF_3-cyclopropane) vs 5.29 (CF_3-cyclobutane). The significant difference of about 1 pK_a unit between the cyclopropane and cyclobutane compounds can be explained by a conjugative effect within the aminocyclopropane unit.

These results demonstrate that the CF_3-cyclobutane substituent is innately electron-withdrawing, but it is a weaker acceptor than the CF_3-cyclopropane (Figure 4).

Hammett Parameters

To further characterize the electronic properties of the CF_3-cyclobutane substituent, we also determined its Hammett parameters by adapting the ^{19}F NMR approach developed by Taft.[55−57] For comparison, the corresponding parameters for the CF_3-cyclopropane substituent were measured, as well.

To this end, we first synthesized the fluorobenzenes substituted with the CF_3-cyclobutane at the *meta*- (**35a**) and

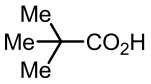
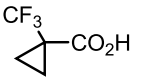
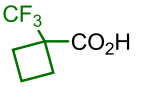
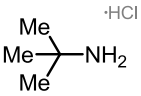
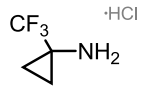
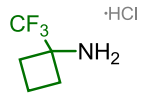
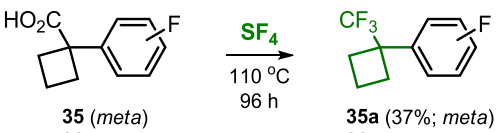
Substituent	Compound	pK_a (exp.)
t-Bu		4.79 ± 0.05
CF_3-cyclopropane		2.99 ± 0.05
CF_3-cyclobutane		2.92 ± 0.05
t-Bu		10.69 ± 0.05
CF_3-cyclopropane		4.06 ± 0.05
CF_3-cyclobutane		5.29 ± 0.05

Figure 4. Experimental pK_a values of carboxylic acids and amine hydrochlorides that are *para*-substituted with *tert*-butyl, CF_3-cyclopropane, and CF_3-cyclobutane groups.

Hammett parameters



35 (*meta*)
36 (*para*)

35a (37%; *meta*)
36a (43%; *para*)

Substituent	$\delta_H^{p\text{-}X}$	$\delta_H^{m\text{-}X}$	σ_I	σ_R^0	σ_m^0	σ_p^0
	0.16	-0.01	0.09	-0.01	0.08	0.08
	1.76	0.08	0.07	-0.06	0.04	0.02

Figure 5. Experimental Hammett parameters of CF_3-cyclopropane and CF_3-cyclobutane substituents. Negative values of $\delta_H^{p\text{-}X}$ and $\delta_H^{m\text{-}X}$ denote downfield ^{19}F NMR shifts (deshielding) of *para*- and *meta*-substituted fluorobenzene derivatives, respectively, relative to a fluorobenzene standard in <0.02 M solutions in CD_3CN. The σ_I and σ_R^0 parameters were calculated by the method of Taft and used to estimate σ_m^0 and σ_p^0 constants (see SI, p. S355−S356).

para-positions (**36a**) (Figure 5) and the corresponding CF_3-cyclopropanes (see SI p. S34−S35). By measuring the chemical shift differences between *meta*- or *para*-substituted fluorobenzenes and a fluorobenzene internal standard, we determined inductive (σ_I) and resonance (σ_R) parameters, and thus *meta*- and *para*-σ constants (σ_m and σ_p; see SI p. S355−

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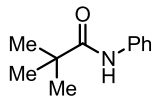
Model compounds



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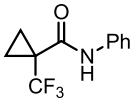

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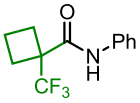

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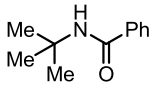

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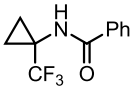

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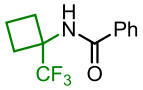

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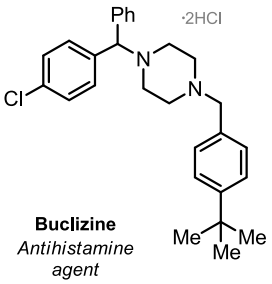
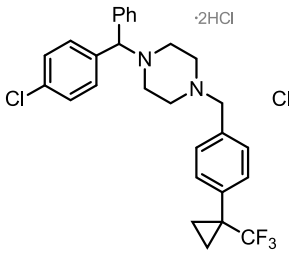
Compound	Sol.	logD	CL_{int}	$t_{1/2}$
37	≥400	2.11	11	157
38	369	2.27	14	120
39	≥400	2.51	16	106

Compound	Sol.	logD	CL_{int}	$t_{1/2}$
40	313	2.01	12	138
41	395	1.90	16	103
42	338	2.48	1*	1212*

Analogs of drugs and agrochemicals



Buclizine
Antihistamine agent



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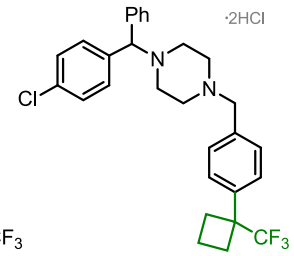
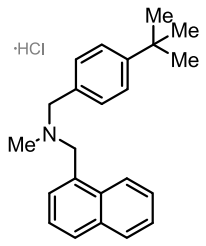
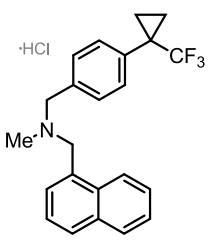


44

Compound	Sol.	pK_a	logD	CL_{int}	$t_{1/2}$
Buclizine	3	3.73	≥4.5	6*	284*
43	3	3.41	≥4.5	3*	497*
44	7	3.52	≥4.5	0*	6026*



Butenafine
Antifungal agent



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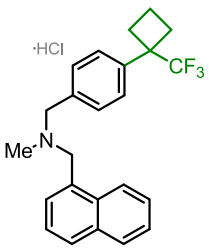
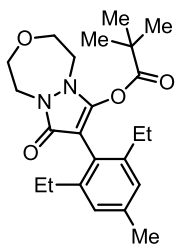
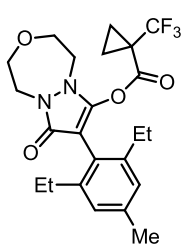


46

Compound	Sol.	logD	CL_{int}	$t_{1/2}$
Butenafine	10	4.2	30	57
45	3	4.3	15	111
46	8	≥4.5	21	65



Pinoxaden
Herbicide



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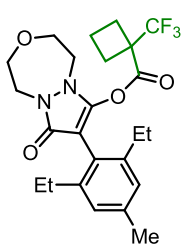
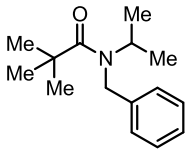
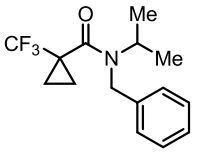


48

Compound	Sol.	logD	CL_{int}	$t_{1/2}$
Pinoxaden	358	3.8	1023	1.6
47	333	3.9	3343**	0.5**
48	282	≥4.5	3380**	0.5**



Tebutam
Herbicide



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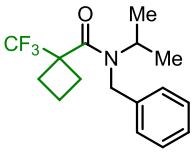
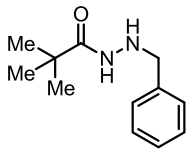
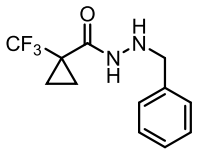


50

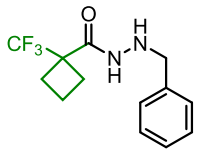
Compound	Sol.	logD	CL_{int}	$t_{1/2}$
Tebutam	324	3.4	57	30
49	284	3.6	24	70
50	233	4.1	107	16



Pivhydrazine
Antidepressant



51



52

Compound	Sol.	pK_a	logD	CL_{int}	$t_{1/2}$
Pivhydrazine	≥400	2.64	1.8	1*	1502*
51	≥400	2.07	2.0	1*	2690*
52	371	1.90	2.3	6*	277*

Figure 6. Physicochemical properties of model compounds **37**−**42**; drugs *Buclizine*, *Butenafine*, *Pyvhydrazine*; agrochemicals *Pinoxaden*, *Tebutatam*; and their CF_3-cyclopropane/CF_3-cyclobutane analogues **43**−**52**. *Sol.*: the experimental kinetic solubility in phosphate-buffered saline, pH 7.4 (μM). log *D* (7.0) for compounds **37**−**42**: the experimental distribution coefficient in *n*-octanol/water. Reliable log *D* values could be obtained within the range of 1.0−3.0 log *D* (7.4) for all other compounds: the experimental distribution coefficient in *n*-octanol/phosphate-buffered saline, pH 7.4. Reliable log *D* values could be obtained within the range of 1.0−4.5. CL_{int}: experimental metabolic stability in human liver microsomes (μL min^{-1} mg^{-1}). $t_{1/2}$ (min): the experimental half-time of a metabolic decomposition in human liver microsomes. *Parameter should be considered as approximate due to the high stability of compounds. ** Parameter should be considered as approximate due to the high instability of compounds.

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S356). The electron-withdrawing effect of the CF_3-cyclobutane group was rather weak, with $\sigma_m \approx 0.04$ and $\sigma_p \approx 0.02$ (Figure 5), and can be benchmarked against that of the CH_2OH group ($\sigma_m \approx 0.00$ and $\sigma_p \approx 0.00$) and that of the CH_2F group ($\sigma_m \approx 0.12$ and $\sigma_p \approx 0.11$).[58] For the CF_3-cyclopropane group, we determined similar values of $\sigma_m \approx 0.08$ and $\sigma_p \approx 0.08$. In full accordance with the pK_a data (Figure 4), the Hammett parameters show that the inductive influence of CF_3-cyclobutane is slightly weaker than that of the CF_3-cyclopropane substituent.

Incorporation into Drugs and Agrochemicals

With numerous building blocks in hand (Schemes 1 and 2), we were curious to study the effects of a *tert*-butyl-to-CF_3-cyclobutane replacement on the experimental physicochemical and biological properties of bioactive compounds. Toward this goal, we synthesized CF_3-cyclopropane- and CF_3-cyclobutane-containing analogues of three drugs and two agrochemicals. CF_3-cyclopropanes were included for comparison, representing an already established isosteric substitute. The examined bioactive structures included the antihistamine agent *Buclizine*, the antifungal agent *Butenafine*, the antidepressant drug *Pyvhydrazine*, and the herbicide agrochemicals *Pinoxaden* and *Tebutam*. We also synthesized small model amides **37**−**42** (Figure 2, see SI p. S35−S45).

Physicochemical Properties

Having synthesized the CF_3-cyclobutane analogues of model and bioactive compounds (Figure 6), we studied their experimental physicochemical properties, water solubility, lipophilicity (see SI p. S357−S365), and metabolic stability (see SI p. S375−S382), and compared the data with those of the parent models, drugs, and agrochemicals.

Water Solubility. Replacement of the *tert*-butyl group in model compound **40**, *Butenafine* and *Pivhydrazine* with the CF_3-cyclobutane showed a negligible impact on the water solubility: 313 μM (**40**) vs 338 μM (**42**); 10 μM (*Butenafine*) vs 8 μM (**46**); ≥400 μM (*Pivhydrazine*) vs 371 μM (**52**). In *Pinoxaden* and *Tebutam*, such replacement led to a notable 20−30% decrease in the solubility: 358 μM (*Pinoxaden*) vs 282 μM (**48**); 324 μM (*Tebutam*) vs 233 μM (**50**). In model compounds **39** and *Buclizine*, an effect was not detected due to either too high (**39**) or too low (*Buclizine*) solubility outside the sensitivity range of the experimental method.

In three studied compounds—**40**, *Butenafine*, and *Pivhydrazine*—the replacement of the *tert*-butyl group with the CF_3-cyclobutane did not significantly affect the water solubility. In another two compounds studied—*Pinoxaden* and *Tebutam*—such replacement led to a notable decrease in solubility.

Lipophilicity. To estimate the influence of a replacement of a *tert*-butyl group with a CF_3-cyclobutane on lipophilicity, we used the experimental index log *D*.

In model compounds **37** and **40**, the replacement of the *tert*-butyl group with the CF_3-cyclobutane led to an increase of the log *D* index by 0.4−0.5 units: 2.11 (**37**) vs 2.51 (**39**); 2.01 (**40**) vs 2.48 (**42**).

An analogous impact was observed in four bioactive compounds—*Butenafine*, *Pinoxaden*, *Tebutam*, and *Pivhydrazine*—the replacement of *tert*-butyl groups with CF_3-cyclobutanes resulted in a notable increase in log *D* by ca. 0.5 units. In *Buclizine*, an effect could not be detected due to the high lipophilicity outside the sensitivity range of the experimental method.

Metabolic Stability. The effect of CF_3-cyclobutane on the metabolic stability of the bioactive compounds varied among the analogues tested. In model compound **37** and *Tebutam*, the incorporation of CF_3-cyclobutane led to a decrease in the metabolic stability, CL_{int} (mg min^{-1} μL^{-1}): 11 (**37**) vs 16 (**39**); 57 (*Tebutam*) vs 107 (**50**).

In model compounds **40** and *Butenafine*, the analogous replacement led to an increase in the metabolic stability, CL_{int} (mg min^{-1} μL^{-1}): 12 (**40**) vs 1 (**42**); 30 (*Butenafine*) vs 21 (**46**).

In *Buclizine*, *Pinoxaden*, and *Pivhydrazine*, effects were not observed because of either too high (*Buclizine*, *Pivhydrazine*) or too low (*Pinoxaden*) stability of bioactive compounds and their analogues outside the sensitivity range of the experimental method.

In summary, the replacement of the *tert*-butyl group with the CF_3-cyclobutane in model/bioactive compounds tended to preserve/slightly decrease the water solubility and increase the lipophilicity. The effect on metabolic stability was inconsistent.

Biological Activity

Finally, we wanted to answer the key question of whether the CF_3-cyclobutane motif indeed acts as an analogue of the *tert*-butyl group in bioactive compounds. To this end, we studied the biological properties of the antifungal agent *Butenafine* with its CF_3-cyclobutane analogue **46**; and the antihistamine agent *Buclizine* with its CF_3-cyclobutane analogue **44**. For comparison, we also studied the corresponding CF_3-cyclopropane analogues **45** and **43**.

Testing the antifungal activity *Butenafine* and its fluoroalkyl-substituted analogues **45**, **46** against two fungal strains—*Trichophyton mentagrophytes* and *Trichophyton rubrum*—using the disk diffusion method was undertaken (for details, see SI, p. S383−S386).

Although the original drug was slightly more potent against both fungal strains (Figure 7), the patent-free CF_3-cyclobutane analogue **46** was found to be reasonably active and showed high growth inhibition of both *T. mentagrophytes* and *T. rubrum* (Figure 7).

Buclizine is an antihistamine agent used as a drug for the treatment of allergy symptoms and the prevention of nausea and vomiting. Recently, *Buclizine* was suggested for repurposing for cancer treatment, following an observation that the original target (histamine-releasing factor) and the suggested one (translationally controlled tumor protein) were identical.[59] Subsequently, *Buclizine* was found to exhibit a cytostatic effect in the MCF-7 human cancer cell line. The cell growth arrest was observed in a suppression of cell respiration, followed by the resazurin reduction assay. *Buclizine* also induced cell differentiation, which was seen in an accumulation of intracellular lipid droplets. In our study, we tested the analogues, **43** and **44**, for their ability to arrest cell growth and induce lipid droplets and compared them to the parent *Buclizine* molecule (for details, see SI, p. S387−S389). By doing so, we expected to characterize indirectly the interaction of the compounds with the tumor protein depending on the nature of the *tert*-butyl group analogue in the molecule.

In the resazurin reduction assay, the original drug, *Buclizine*, showed moderate effectiveness (IC_{50} = 31 μM), while the CF_3-cyclopropane analogue **43** was found to be inactive (Figure 8). Conversely, the patent-free CF_3-cyclobutane analogue **44** was active and showed a micromolar inhibition (IC_{50} = 102 μM). Furthermore, in an experiment assisted by fluorescence

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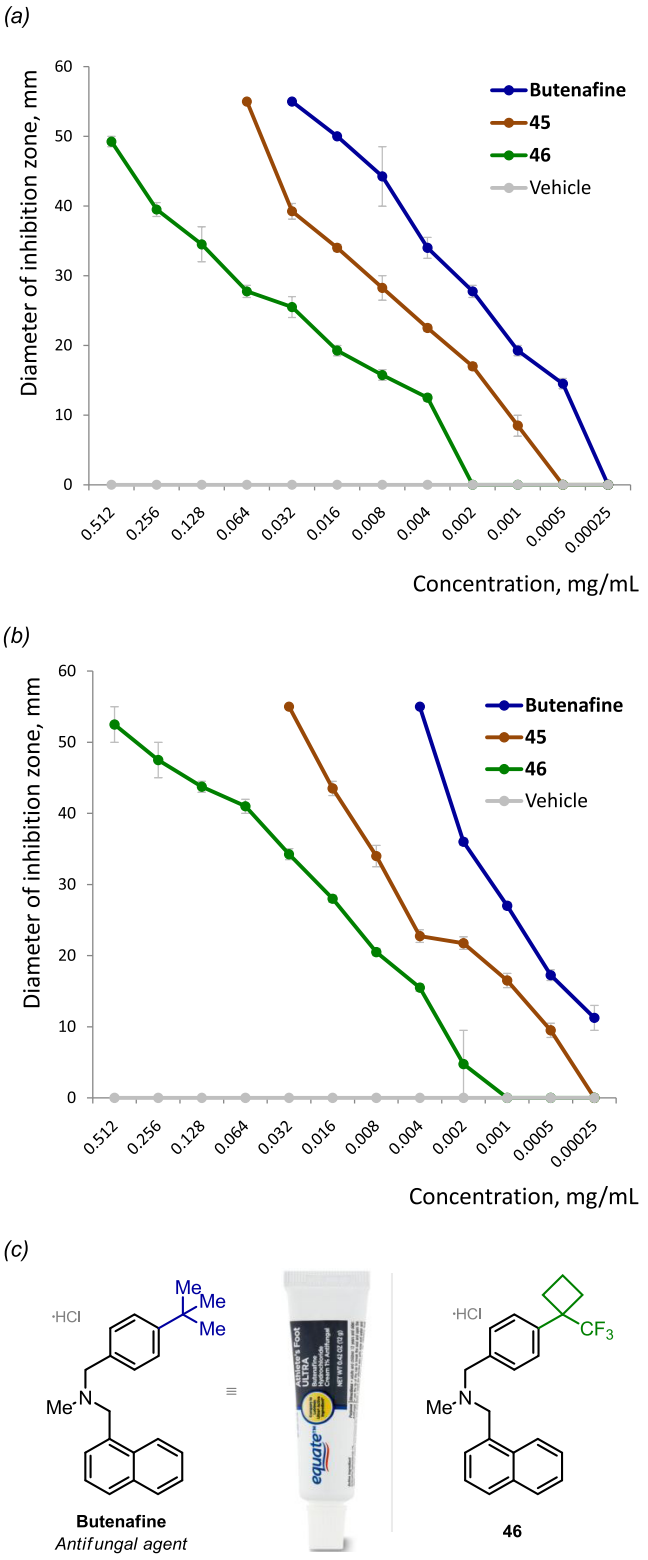
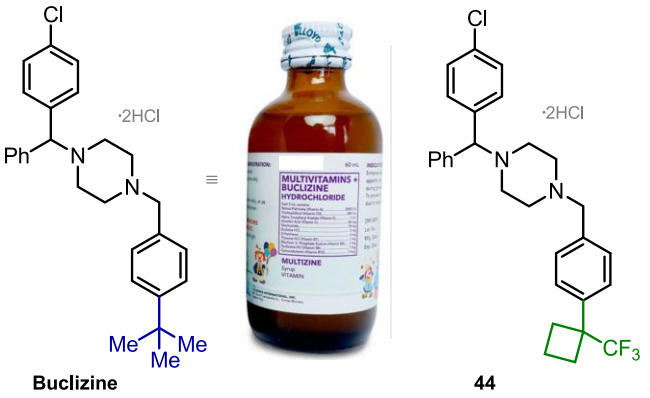


Figure 7. Inhibition of growth of (a) *T. mentagrophytes* (strain ATCC 18748) and (b) *T. rubrum* (strain ATCC 28188) (measured as a diameter *d* of the inhibition zone, in millimeters) by *Butenafine* and its analogues **45** and **46**. (c) Structures of *Butenafine* and compound **46**.

imaging (Figure 9), the CF_3-cyclobutane analogue **44** (EC_{50} = 15 μM) showed the earliest onset of lipid droplet formation among the tested substances (EC_{50} = 19 μM for *Buclizine*; and 21 μM for **43**) (Figure 8).



Compound	*IC_{50}*	*EC_{50}*
Buclizine (*tert*-butyl)	31.3 ± 7.8 μM	19.11 ± 1.45 μM
43 (CF_3-cyclopropane)	inactive	21.04 ± 1.71 μM
44 (CF_3-cyclobutane)	101.6 ± 13.4 μM	14.69 ± 0.39 μM

Figure 8. Effectiveness of inhibition of (a) the growth of the human cancer cell line MCF-7 (IC_{50} index) and (b) lipid droplet formation (EC_{50} index) by *Buclizine* and its analogues **43** and **44**.

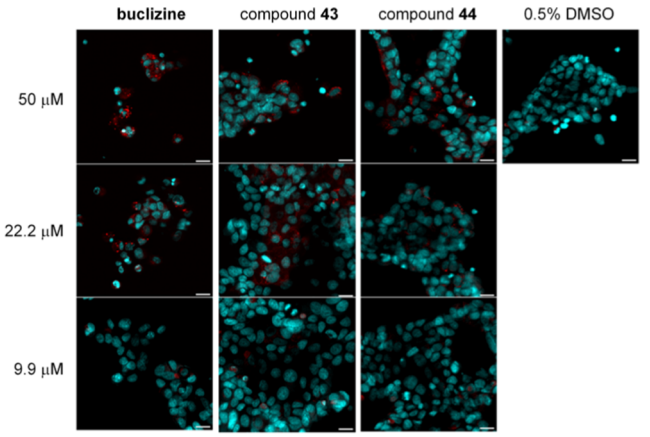


Figure 9. Confocal images of the lipid droplet formation in MCF-7 cells upon incubation with *Buclizine* and analogues **43** and **44** for 72 h. Nuclei were stained with Hoechst 33342 (cyan), and lipid droplets were stained with Nile Red (red). Scale bars: 20 μm.

The data presented in this study highlights the CF_3-cyclobutane unit as a promising analogue to a *tert*-butyl group, resulting in a valuable expansion of the structural repertoire available to medicinal chemists.

CONCLUSIONS

In this work, we have developed a modular practical approach toward a previously neglected class of compounds containing the CF_3-cyclobutane group. We have comprehensively studied the impact of this substituent (pK_a, lipophilicity, X-ray, Hammett constants, volume, ADME), and we demonstrated that it can mimic the *tert*-butyl group in drugs (*Buclizine*, *Butenafine*).

It is important to note that while the CF_3-cyclopropane analogue **43** of *Buclizine* was inactive, the CF_3-cyclobutane **44** exhibited a reasonable activity, suggesting that the CF_3-cyclobutane is a more optimal replacement in this case.

We believe that expanding the repertoire of available analogues of the *tert*-butyl group will ease the job of medicinal

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chemists in designing and making new drugs. We anticipate that in the forthcoming decade, CF_3-cyclobutyl-containing compounds will become common in chemistry.[60]

■ ASSOCIATED CONTENT

Data Availability Statement

The authors declare that data supporting the findings of this study are available within the paper and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c00864.

Details on chemical synthesis procedures including a photo session of the experimental setup with sulfur tetrafluoride; characterization of compounds; copies of the NMR spectra; crystal structures; data on the molecular volume of different substituents; determination of the Hammett parameters; protocols for determination of compound's solubility, lipophilicity, and acid−base transition constants; and details of the biochemical studies of the metabolic clearance, antifungal activity, and cytostatic effect of the buclizine analogues (PDF)

Crystallographic data (ZIP)

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Notes

The authors declare the following competing financial interest(s): Authors of this work are emploees of a chemical supplier Enamine.

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