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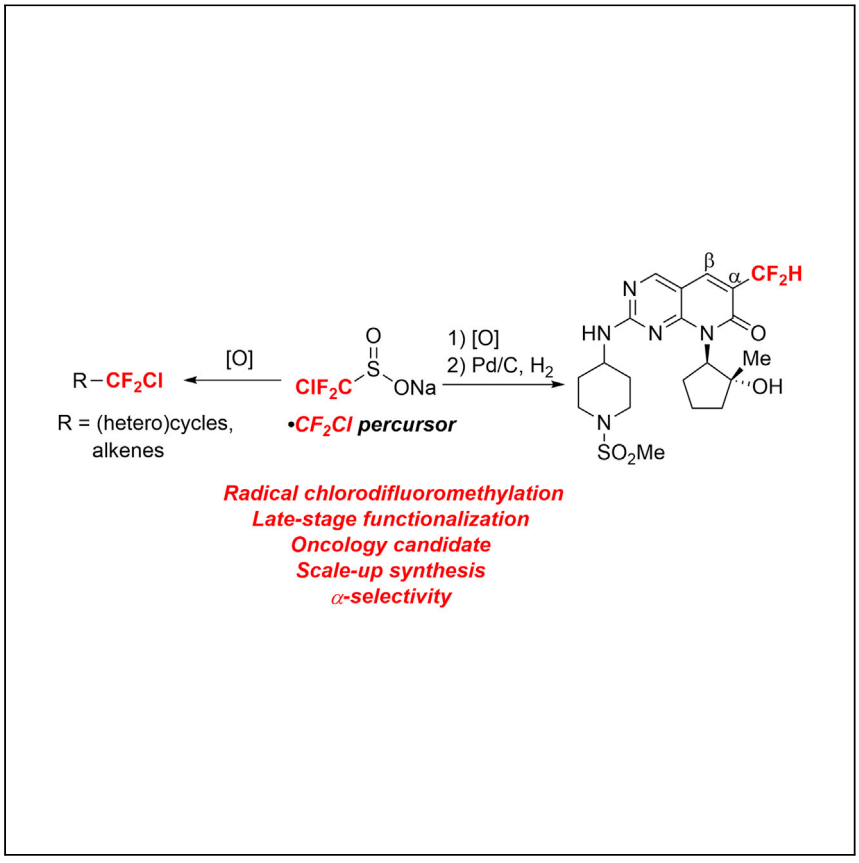
A radical chlorodifluoromethylation protocol for late-stage difluoromethylation and its application to an oncology candidate



Meng et al. develop a radical chlorodifluoromethylation protocol using $ClCF_2SO_2Na$ as a chlorodifluoromethyl radical precursor. The CF_2Cl radical is an electrophilic surrogate for the nucleophilic CF_2H radical. This method is chemoselective and regioselective for the chlorodifluoromethylation of (hetero) arenes and electron-rich alkenes and is applied in the difluoromethylation of an oncology candidate.

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Highlights

A new radical chlorodifluoromethylation reagent ($ClCF_2SO_2Na$) is disclosed

The CF_2Cl radical is a suitable surrogate for accessing the CF_2H group

The reaction is chemo- and regioselective for (hetero)arenes and electron-rich alkenes

The preparation of the sodium chlorodifluoromethanesulfinate is developed

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A radical chlorodifluoromethylation protocol for late-stage difluoromethylation and its application to an oncology candidate

Depei Meng,[1] Lingchun Li,[1] Adam Brown,[2] Jean-Nicolas Desrosiers,[2] Shengquan Duan,[2,*] Cheryl M. Hayward,[2] Zhengbiao He,[1] Jinbo Hu,[1,3,*] Teresa Makowski,[2] Mark Maloney,[2] Sébastien Monfette,[2] Hahdi Perfect,[2] Jared L. Piper,[2] Min Zhou,[1] and Daniel W. Widlicka[2]

SUMMARY

Radical fluoroalkylation is a powerful synthetic tool for the late-stage incorporation of fluorinated moieties into organic molecules, which is widely used in the development of pharmaceuticals and agrochemicals. Here, we report an efficient radical chlorodifluoromethylation protocol with sodium chlorodifluoromethanesulfinate, which is complementary to the existing late-stage difluoromethylation strategies. CF_2Cl radical is a suitable surrogate for accessing the CF_2H group while possessing completely different electronic properties compared to the CF_2H radical. This method is chemoselective and regioselective for the chlorodifluoromethylation of (hetero)arenes and electron-rich alkenes and shows good functionality, tolerance, and generality on scope. The preparation of the sodium chlorodifluoromethanesulfinate is thoroughly investigated and can be scaled up to hundreds of kilograms. The method is successfully implemented on the synthesis of an oncology candidate compound 1.

INTRODUCTION

Cyclin-dependent kinases (CDKs) are important cellular enzymes that regulate eukaryotic cell division and proliferation.[1–3] Highly specific CDK4/6 inhibitors have shown excellent clinical benefit on cancer therapy, especially on breast cancer, as evidenced by the approval of the US Food and Drug Administration (FDA) of palbociclib (PD-0332991),[4] ribociclib (LEE011),[5] and abemaciclib (LY2835219).[6] However, acquired resistance to the combination of CDK4/6 inhibitor and anti-hormonal therapies have been observed in patients following a period of largely stable disease. It is found that the overexpression of CDK2 is usually associated with abnormal regulation of the cell cycle.[7] The development of an inhibitor that selectively inhibits CDK2, -4, and -6 is predicted to drive an efficacious response in patients who have relapsed on the CDK4/6-targeted therapies. Compound 1 is being nominated by Pfizer as a selective CDK2/4/6 inhibitor that is being studied in combination with other cancer therapeutics (Figure 1).[8]

During our development of a commercial route toward compound **1**, it was realized that the lability of the difluoromethyl group would require it to be installed via a late-stage functionalization. Although many difluoromethylation methods have been developed,[9] very few are suitable for late-stage functionalization on an industrial scale.[10] Direct radical C-H functionalization[11–16] was found to be a favorable method for the difluoromethylation to access compound **1** because of the mild nature of the reaction conditions, the convenience of the radical precursor, and the fact that no pre-functionalization

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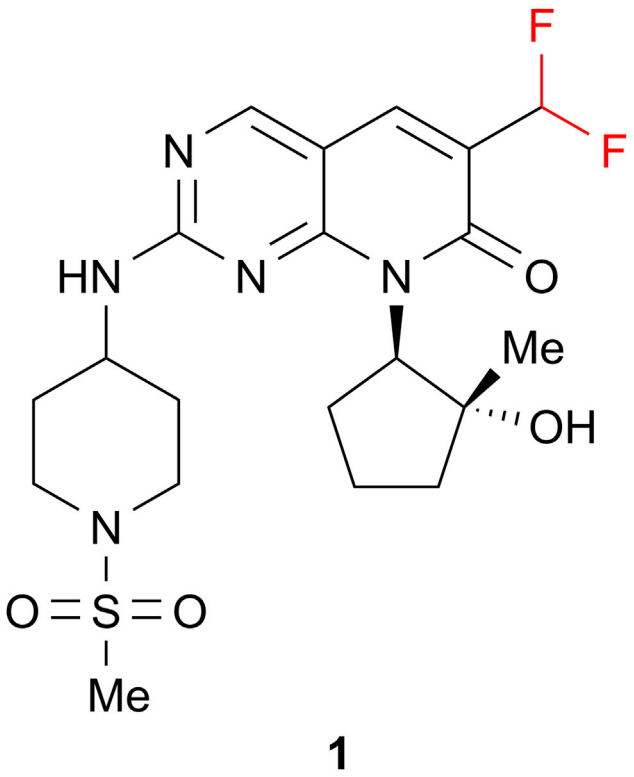

Figure 1. CDK 2/4/6 inhibitor 1
Compound **1** is nominated by Pfizer as a selective CDK2/4/6 inhibitor.

of the substrate was required before the key difluoromethylation. Such a strategy was used with HCF_2SO_2Na as the difluoromethyl radical source[17–20] to provide early clinical supply of compound **1** (Scheme 1, nucleophilic radical).

The poor yield observed for the radical difluoromethylation of **2** was due to indiscriminate reactivity of the difluromethyl radical. While the desired product was favored, the impurity profile indicated the addition of the CF_2H moiety more than once, to the β position, and to different sites of the pyrimidine ring. This poor selectivity led to a complex reaction mixture with numerous low-level impurities, requiring multiple stages of purification (including column chromatography) and culminating in a process with overall poor efficiency.

Considering the electrophilicity of CF_3 radical CF_3SO_2Na (Langlois' reagent)[21,22] and recently reported radical chlorodifluoromethylation with chlorodifluoroacetic anhydride (McAtee et al.[23] and Kawamura et al.[24]) or radical phenylsulfonyldifluoromethylation with $PhSO_2CF_2I$ (Su et al.[16]), we hypothesize that modification of the electronic property of our radical species would improve the selectivity of the desired C-H functionalization reaction. While the difluoromethyl radical is known to react in a nucleophilic manner, the replacement of the hydrogen of the difluoromethyl with an electron-withdrawing group reverses the character of the radical to that of an electrophile.[23–25] Based on this premise, we explore the reactivity of **2** with electrophilic radical species that could be manipulated following the C-H functionalization reaction to provide our desired difluoromethyl species (Scheme 1, electrophilic radical). Furthermore, we establish a system capable of generating the desired electrophilic radical under conditions that are compatible with a highly

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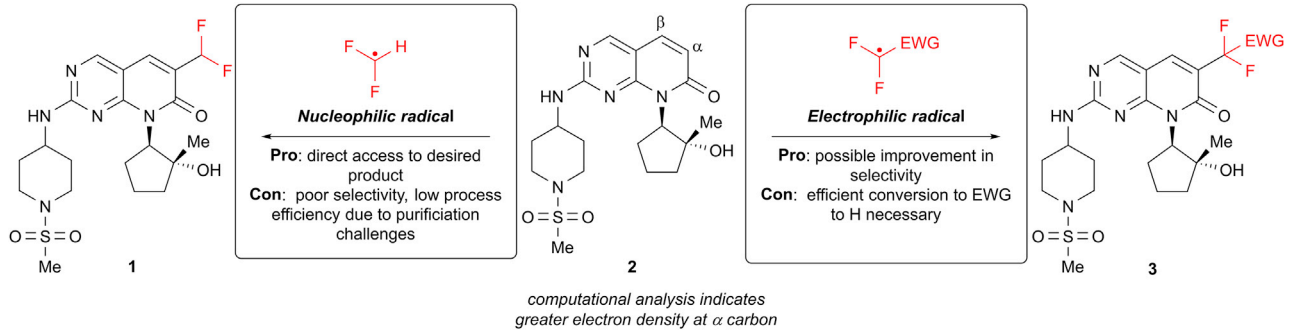

Scheme 1. Varying electronic property of CF_2X radical to improve direct functionalization

Because of different electronic property, the CF_2X (X = H or EWG) radical shows reverse advantages and disadvantages in radical difluoroalkylation with compound **2**.

functionalized molecule such as **2** and that can be carried out on an industrial scale.

RESULTS

Chlorodifluoromethylation of compound 2

Our hypothesis was tested by studying the reactivity of **2** with radicals generated from $ClCF_2SO_2Na$ (**4**) and $PhSO_2CF_2SO_2Na$ (**5**), both of which should have significantly different electronic character and reactivity than the difluoromethyl radical. A variety of reaction conditions were studied to understand the radical difluoromethylation reaction (Table 1).

Initially, a variety of oxidants was explored in combination with $ClCF_2SO_2Na$ (**4**). *m*-CPBA (*meta*-Chloroperoxybenzoic acid), BPO (benzoyl peroxide), and DTBP (di-*tert*-butyl peroxide) were not effective for this reaction. However, cumenehydroperoxide (CHP), (diacetoxyiodo)benzene (PIDA), sodium persulfate, *t*-butyl hydroperoxide (TBHP), and oxone worked well (entries 1–5). TBHP (entry 1) was selected for its low cost, general compatibility with functional groups, and ease of isolation from reaction mixtures.[26] Notably, CHP (entry 2) was also used for larger-scale applications due to the higher temperature onset of this reagent, and therefore higher stability, under the exothermic radical-induced chlorodifluoromethylation process.[27,28] After selecting the optimal oxidant, several reaction parameters were optimized.

The impact of the catalyst was then studied (entries 6–12), and it was found that iron salts were optimal. Very similar results were obtained with different types of iron catalysts, such as $FeCl_2$, $FeCl_3$, $Fe(OTf)_2$, $Fe(acac)_2$, and $(NH_4)_2Fe(SO_4)_2$. Other metal catalysts (e.g., Cu, Ni) were not as active, with the reaction yield decreasing considerably, and a more complicated reaction profile after an extended reaction time. $FeCl_2$ catalyst is selected due to its advantage in cost, handling, and commercial availability.[29,30] The stoichiometry of the $FeCl_2$ does seem to have an impact on the reaction, with a detrimental effect at higher loading (entry 14). Although the chlorodifluoromethyl intermediate is prone to hydrolysis, it is relatively stable in the reaction media, which is typically a mixed aqueous system. Running the reaction at a higher temperature with more water will accelerate the hydrolysis and lower the yield (entries 13 and 14). Polar aprotic solvents (DMSO, sulfolane, and dimethyl formamide [DMF]) are preferred solvents for this reaction. The reaction also works in the acetone or methyl ethyl ketone (MEK), albeit with a lower yield (entries 16–18).

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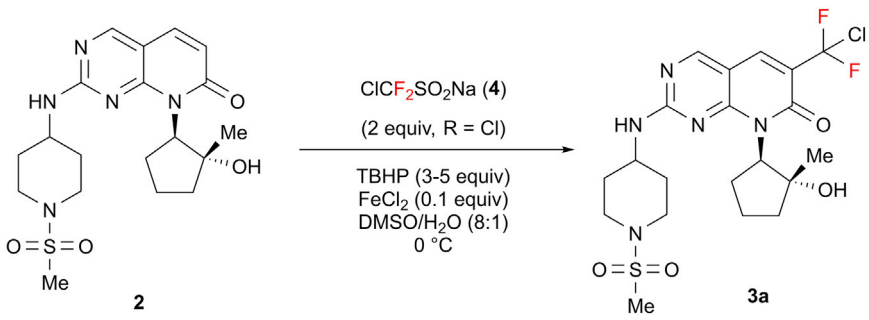
Table 1. Optimization of reaction conditions



Entry[a]	Modifications from standard conditions	Yield (%)[b]
1[c]	none (standard conditions)	82–91
2	CHP (3 equiv) as the oxidant	93
3	$PhI(OAc)_2$ as the oxidant in *t*-BuOH/MeCN (9:1)	76
4	$Na_2S_2O_8$as the oxidant in MeCN/H_2O (9:1)	55
5	oxone as the oxidant	83
6[d]	$Cu(OTf)_2$ (0.3 equiv) as the catalyst	7
7[e]	CuCl (0.3 equiv) as the catalyst	13
8[f]	$NiCl_2$ (0.3 equiv) as the catalyst	12
9	$FeCl_3$ (0.1 equiv) as the catalyst	93
10	$Fe(OTf)_2$ (0.1 equiv) as the catalyst	94
11	$Fe(acac)_2$ (0.1 equiv) as the catalyst	85
12	$NH_4Fe(SO_4)_2$ (0.1 equiv) as the catalyst	91
13[g]	DMSO/H_2O (8:1) as the solvent mixture	54
14[h]	DMSO/H_2O (8:1) as the solvent mixture	77
15	DMSO/H_2O (9:1) as the solvent mixture	84
16[i]	sulfolane/H_2O (8:1) as the solvent mixture	92–99
17	acetone/H_2O (9:1) as the solvent mixture	77
18	MEK/H_2O (9:1) as the solvent mixture	74
19	R=SO_2Ph instead of Cl	86
20	R=H instead of Cl	38

[a]Conditions: **2** (0.5 mmol, 1.0 equiv), **3** (2.5 equiv), CHP (5.0 equiv), cat., solvent/H_2O (8:1, 3.0 mL), $FeCl_2$ (0.1 equiv.), *T*, 15 min.
[b]Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard.
[c]TBHP (2.5 equiv), DMSO/H_2O (8:1, 2.7 mL), 1.5 h, repeated multiple times.
[d]1.5 h.
[e]CHP (3.0 equiv), 10 h.
[f]CHP (3.0 equiv), 12 h.
[g]TBHP (5.0 equiv), $FeCl_2$ (0.5 equiv), 5°C–25°C.
[h]TBHP (5.0 equiv), $FeCl_2$ (0.5 equiv), 0°C–5°C.
[i]TBHP (2.5 equiv), 1.5 h, repeated multiple times.

Substitution of the chlorine with a benzenesulfonyl group was explored (entry 19) and a similar yield was obtained (86%). Gratifyingly, the desired radical functionalization proceeded with much higher efficiency and selectivity with these electrophilic radical species compared to a nucleophilic radical generated from HCF_2SO_2Na (entry 20).

After demonstrating the generation and selective reaction of a masked difluoromethyl radicals with **2** under conditions that are operationally simple, we sought to explore our method in a variety of diverse substrates, and further develop the method for application toward the large-scale synthesis of compound **1**.

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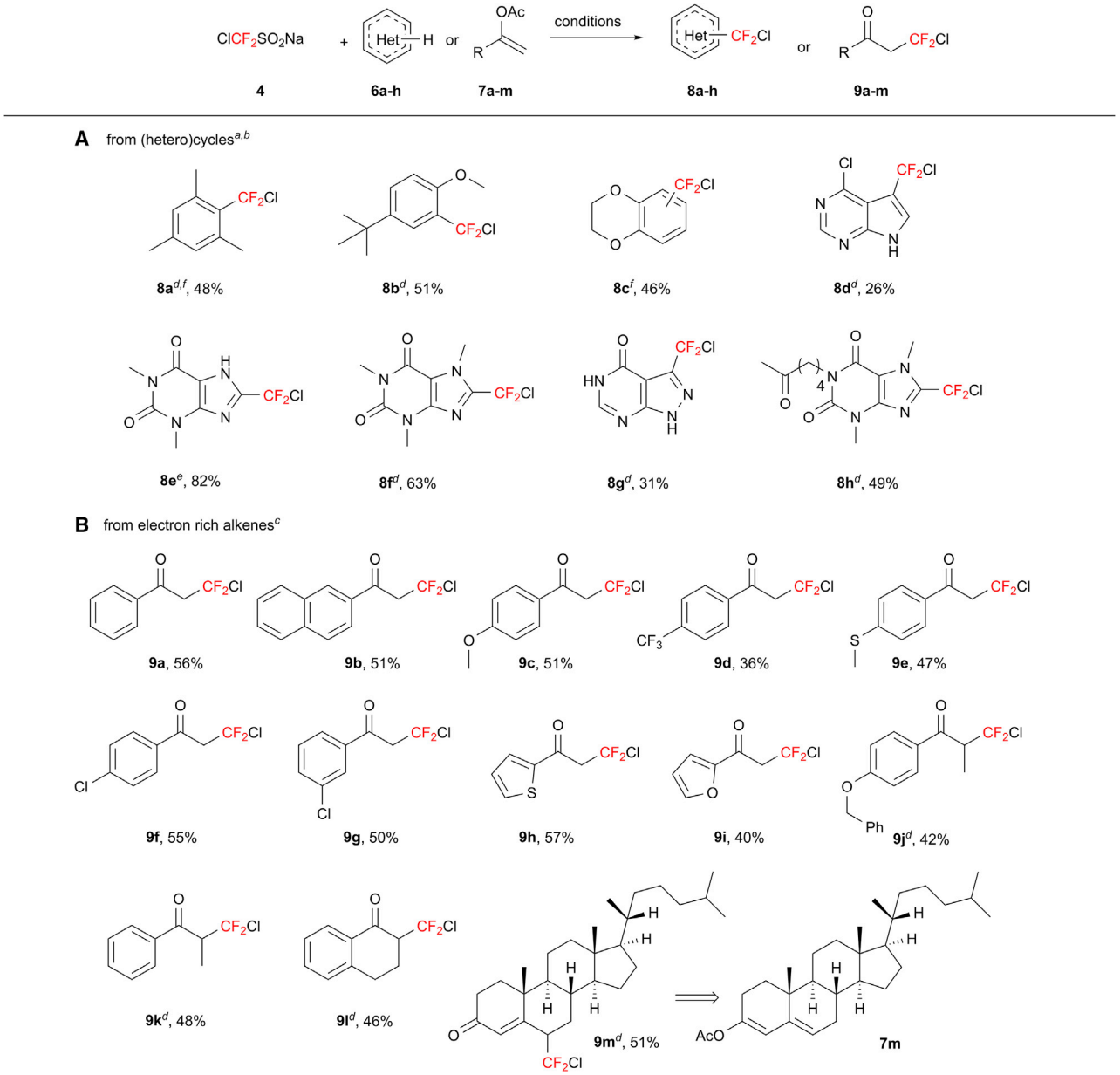

Scheme 2. Substrate scope of chlorodifluoromethylation with corresponding (hetero)cycles and alkenes

Unless otherwise noted, reactions were performed on 0.5 mmol scale and yields of isolated products are given.

[a]Arenes **6a–6c** (1.0 equiv), **4** (2.0 equiv), TBHP (3.0 equiv), $FeCl_2$ (1.0 equiv), and DMSO/H_2O (5:1), 0°C, 4 h.

[b]Heterocycles **6d–6h** (1.0 equiv), **4** (2.0 equiv), TBHP (3.0 equiv), $FeCl_2$ (0.08 equiv), and DCM/H_2O (5:1), 0°C to room temperature (rt), 3 h.

[c]Alkenes **7a–7m** (1.0 equiv), **4** (2.0 equiv), TBHP (3.0 equiv), and DMF, 0°C, 3 h.

[d]Extra **4** and THBP were added after 1 or 2 h.

[e]Reactions were performed on a 10-mmol scale.

[f]The yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

Scope of method with sulfinates 4 and 5

We found that the chlorodifluoromethylation methodology can be applied to various substrates, such as (hetero)cycles or electron-rich alkenes (enol acetates) (Scheme 2; for more details, see Supplemental experimental procedures). When the amount of $FeCl_2$ was increased to 1.0 equiv, because of its ability to accelerate

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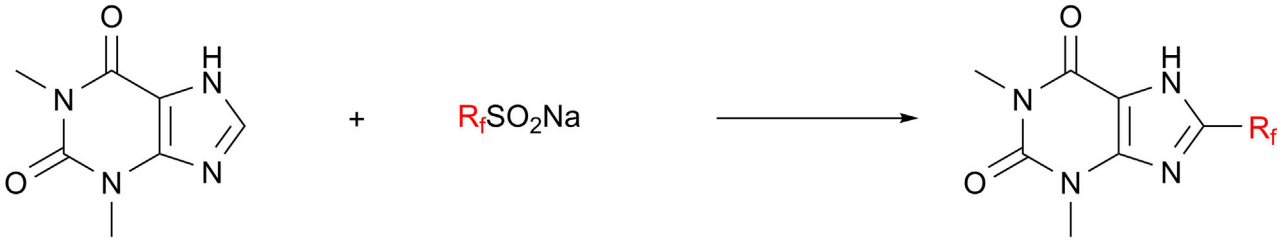
Table 2. Fluoroalkylation of theophylline with different sulfinates



6e

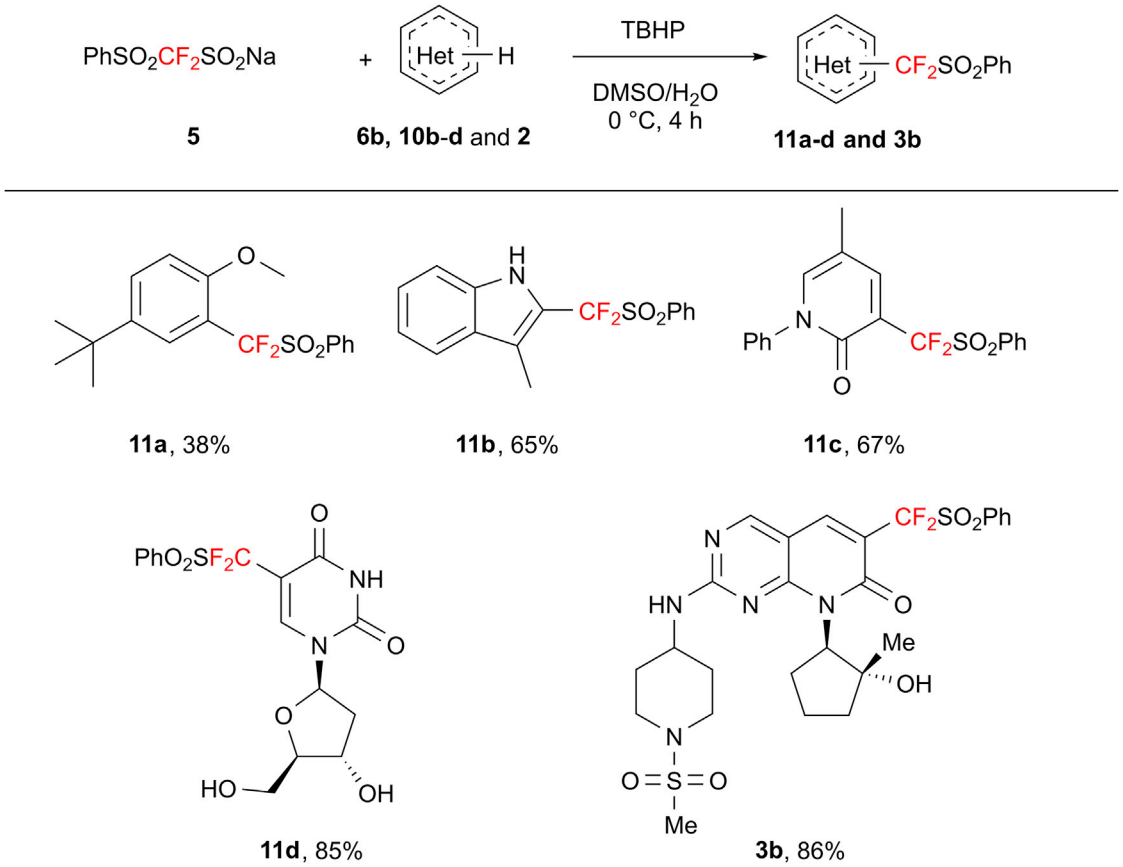
Entry[a]	R_f	Yield (%)[b]
1	CF_3	75
2	CF_2Cl	81
3	CF_2H	17
4	CFH_2	9

[a]Conditions: **6e** (0.1 mmol, 1.0 equiv), R_fSO_2Na (2.0 equiv), TBHP (3.0 equiv), $FeCl_2$ (0.08 equiv), and DCM/H_2O (0.5 mL/0.1 mL), 0°C, 3 h.
[b]The yield was determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

the generation of $ClCF_2$ radical and promote the conversion of the reaction intermediate, mesitylene, anisole or 1,4-benzodioxane gave a corresponding single product (**6a** and **6b**) or a mixture of regioisomers (**6c**) in moderate yields (see Table S1). Deazapurine (**6d**), xanthines (**6e**, **6f**, and **6h**), and pyrazolino-pyrimidine (**6g**) can be directly chlorodifluoromethylated when the solvent was changed from DMSO to dichloromethane (DCM) (see Table S2). A gram-scale reaction was successfully performed with theophylline (**6e**). Besides reacting with (hetero)cycles, the $ClCF_2$ radical could also react with electron-rich alkenes to form α-chlorodifluoromethylketone in DMF without the $FeCl_2$ catalyst (see Table S3). Phenylvinyl acetate (**7a**), naphthyl acetate (**7b**), and arylvinyl acetates (**7c–7g**) with electron-donating groups or electron-withdrawing groups worked well under the optimal conditions and gave medium yields analogously. The trifluoromethyl substituted substrate (**7d**) was more reluctant to react than others because of the strong electron-withdrawing capacity of the trifluoromethyl group. Both thienyl and furyl could be used instead of aryl to provide the addition products (**7h and 7i**), and non-terminal olefins were also compatible under similar conditions (**7j–7l**). Enol acetate from 4-cholesten-3-one, a precursor to a range of steroid hormone drugs, can also be used as a substrate, and the γ-chlorodifluoromethylated product was obtained in a 51% yield (**7m**). The moderate yields may be attributed to the stability of the products or to the activity of substrates. An extra portion of sulfinate and oxidant was needed for parts of substrates due to the incomplete conversion of substrates. Because of the electrophilicity of the CF_2Cl radical, the reaction typically occurred at the electron-rich site and no regio-isomers were observed except **6c**.

The fluoroalkylation of theophylline was carried out to further substantiate the hypothesis that the CF_2Cl radical was more likely to react in an electrophilic manner compared to the CF_2H radical. As shown in Table 2, higher reactivity of the CF_3 and CF_2Cl radicals was observed at the electron-rich site of the theophylline, which was not the case for the nucleophilic CF_2H and CH_2F radicals. It is evident that the CF_2Cl radical is very similar to the electrophilic CF_3 radical, but far different from CF_2H and CH_2F radicals.

Several radical phenylsulfonyldifluoromethylation with (hetero)cycles, including compound **2** (Scheme 3), were explored. All of the substrates showed good



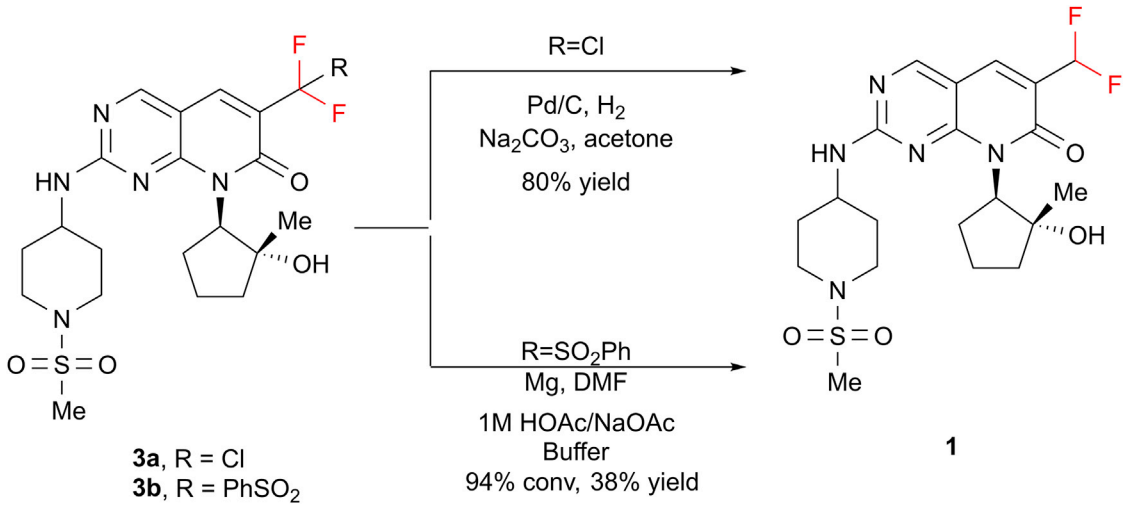
Scheme 3. Reaction of (hetero)cycles with $PhSO_2CF_2SO_2Na$ (5)[a,b,c]

[a]Conditions: (hetero)cycles (0.25 or 0.5 mmol, 1.0 equiv), **5** (2.0 equiv), TBHP (2.0 equiv), and DMSO/H_2O (2.5:1).
[b]**2** (0.25 mmol, 1.0 equiv), **5** (2.0 equiv), TBHP (2.0 equiv), $FeCl_2$ (0.1 equiv), and DMSO/H_2O (10:1).
[c]Isolated yields.

reactivity under the standard reaction conditions. The electron-rich arene (**6b**), which was difficult to react with the HCF_2 radical,[23] could provide the addition product (**10a**) in a 38% yield. The nitrogen-containing heterocycles, such as skatole (**10b**), pirfenidone (**10c**), 2′-deoxyuridine (**10d**), and compound **2**, performed better to afford corresponding difluoroalkylation products in good yields (65%–86%).

Application toward compound 1 and considerations for large-scale synthesis

With two high-yielding difluoroalkylation processes of **2** in hand with either benzenesulfonyl or chloro electron-withdrawing substituents on the difluoromethyl radical, we evaluated the downstream chemistry required to unmask the precursor to compound **1** (Scheme 4). Unexpectedly, the desulfonylation of **3b** was not straightforward.[31] Although high conversion was observed, only a 38% yield of **1** was obtained due to defluorination and, likely, reduction of the methanesulfonyl (SO_2Me) group. In contrast, hydrodechlorination of **3a** is efficient, proceeding in the presence of either homogeneous or heterogenous Pd catalyst to provide **1** in a good yield (see Table S4).[23] Chlorodifluoromethylation was therefore selected for application in our synthesis, and further development of both the reaction conditions and reagent synthesis were carried out.



Scheme 4. Method toward compound 1

Hydrodechlorination of **3a** with Pd/C and desulfonylation of **3b** with Mg.

Preparation of $ClCF_2SO_2Na$ (4)

Multiple methods were developed for the preparation of the sodium sulfinate reagent, considering that a large quantity will be needed for this reagent.

As shown in Scheme 5A the key for the synthesis of **4** is to obtain either of the intermediates $BTSO_2CF_2Cl$ (**12**) or $BTSCF_2Cl$ (**14**) (BT [2-benzothiazolyl]), as the oxidation reaction from sulfide to sulfone has been well established.[32] In the first attempt, we decided to prepare $BTSO_2CF_2Cl$ (**12**) by decarboxylative chlorination of $BTSCF_2CO_2Na$ (**15**). Based on the reported method of preparation of aryloxydifluoroacetic acids from the sodium salts of phenols,[33] the reaction conditions were further optimized to provide $BTSCF_2CO_2Na$ from BTSH in a 94% ^{19}F NMR yield (Scheme 5B; Table S5).[34] The desired product **12** was obtained in a 77% ^{19}F NMR yield when $BTSO_2CF_2CO_2Na$ was treated with CCl_4 in DMF at room temperature (see Table S6). During the optimization of this reaction, we found it infeasible that the above-mentioned procedure involved multiple reaction steps and several unstable intermediates, so we continued to develop another method to prepare **14** (Scheme 5C). Thus, we designed a new procedure for the preparation of the sodium sulfinate, as shown in Scheme 5D (for more details, see Supplemental experimental procedures). BTSNa was reacted with difluorocarbene to generate $BTSCF_2^-$. Then, a suitable Cl^+ reagent (i.e., CCl_4 or C_2Cl_6) was used to quench the *in situ*-generated $BTSCF_2^-$ species to yield **14**, which could be directly oxidized to **12** in a 56% yield over 2 steps. In the final step, $ClCF_2SO_2Na$ (**4**) was obtained in a 79% yield via the reduction of **12** by $NaBH_4$.[17]

Although the above method provided quick access to the sulfinate reagent, the use of CCl_4 has been largely prohibited in the industry due to its high toxicity.[35] The effort to replace CCl_4 with other chlorination reagents was not successful and that forced us to develop a new stepwise method for the chlorination reaction (Scheme 6). To this end, the benzothiazole thiol was alkylated by a difluorocarbene ($BrCF_2CO_2Na$ is shown in the scheme; $ClCF_2H$ can also be used) to give compound **17** in a 85% yield. The sulfide was oxidized to sulfone using aqueous H_2O_2 with ammonium heptamolybdate as a catalyst. The chlorination was achieved by deprotonation with lithium hexamethyldisilazide (LiHMDS) and treatment with

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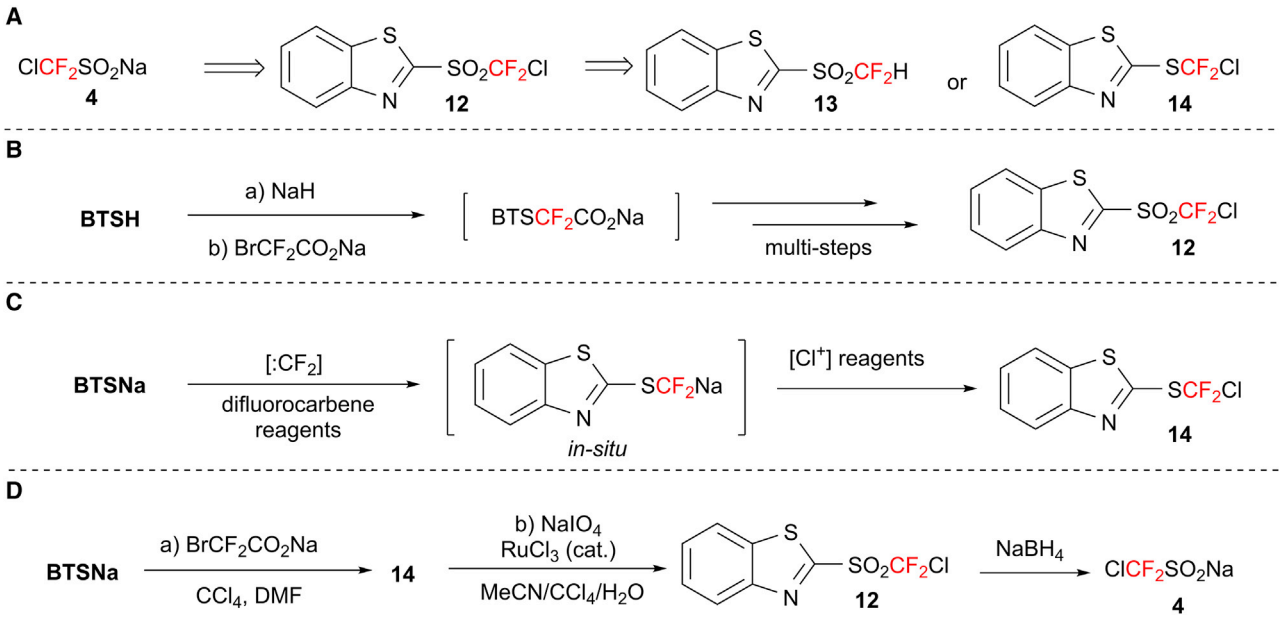

Scheme 5. Laboratory method

(A) Retrosynthetic analysis for preparing $ClCF_2SO_2Na$ (**4**).

(B) Preparation of $BTSO_2CF_2Cl$ (**12**) by decarboxylative chlorination (BT, 2-benzothiazolyl).

(C) Preparation of $BTSCF_2Cl$ (**14**) by difluorocarbene insertion.

(D) Preparation of $ClCF_2SO_2Na$ (**4**) in laboratory.

N-chlorosuccinimide (NCS) (trichloroisocyanuric acid could also be used instead of NCS). This chlorination was more challenging than the carbon tetrachloride condition, but with careful control of the reaction temperature and the stoichiometry of LiHMDS and NCS, the impurity formation can be minimized and a 77% yield can be obtained. The most significant improvement of the process was achieved when we used NaOMe for the final C-S cleavage instead of $NaBH_4$, as the isolation of the final product became much easier without the need to deal with the boron side products.

Preparation of compound 1

The newly developed radical chlorodifluoromethylation methodology allows quick access to compound **1** in a large quantity. Based on this key strategy, a short synthetic route (shown in Scheme 7) was developed and used for the clinical supply manufacturing of **1**. This route has the potential to be used for commercial manufacture due to the scalability of the two-step late-stage difluoromethylation. The synthesis starts from commercially available 5-bromo-2,4-dichloropyrimidine (**18**) and the chiral amino alcohol building block **19** (synthesis of **19** will be reported independently). The first S_NAr reaction is straightforward and the regioselectivity is typically ~95:5, favoring the desired product. The second S_NAr reaction between **20** and the aminopiperidine is slower and requires the use of polar aprotic solvents and elevated temperatures. Both steps give products in excellent yield and purity. The subsequent Heck coupling and cyclization sequence provides compound **2**, the substrate used for the chlorodifluoromethylation.[36] The Heck coupling usually gives a mixture of E/Z isomer at 95:5 ratio and only the E-isomer is obtained if an isolation is carried out. The isomerization/cyclization can be achieved using KOt-Bu as base. Finally, the chlorodifluoromethylation/hydrodechlorination affords the active pharmaceutical ingredient (API) in high

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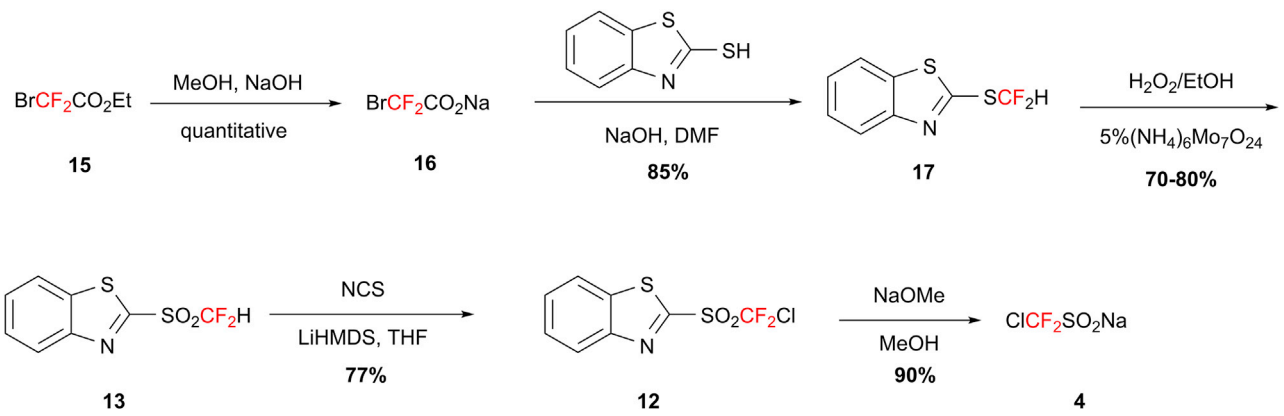


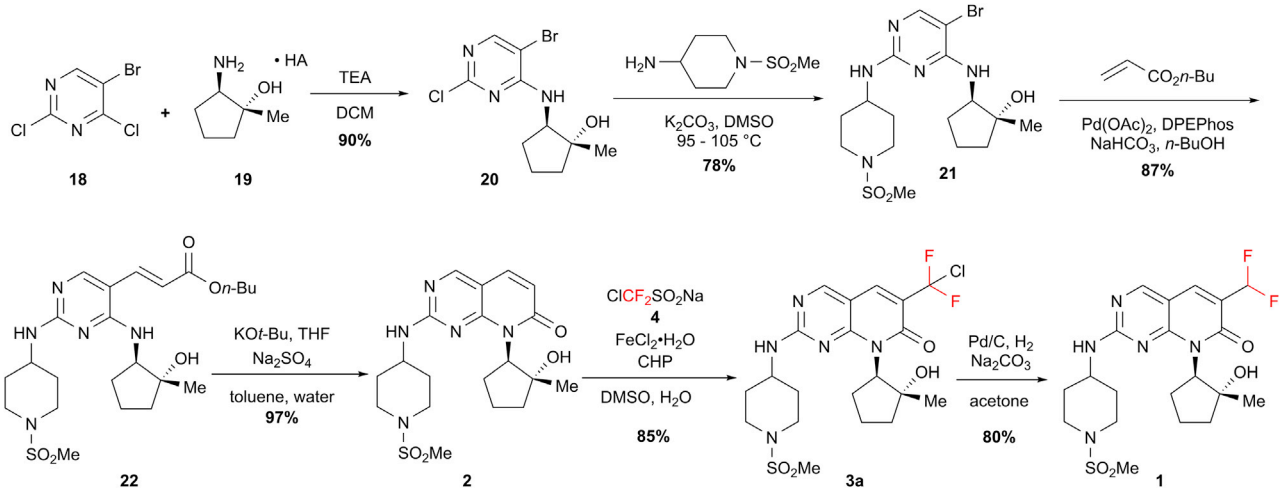
Scheme 6. Method for large-scale preparation

Preparation of $ClCF_2SO_2Na$ (**4**) from $BrCF_2CO_2Et$ (**15**) on industrial scale (for more details, see supplemental experimental procedures).

yield. The chlorodifluoromethylation can be carried out under batch or flow conditions. The hydrodechlorination works under both homogeneous and heterogeneous catalysis conditions.[37] For this specific substrate, the ketone type of solvents is preferred. An overall 40%–45% yield is obtained over the 6-step sequence.

DISCUSSION

In summary, we have successfully developed a radical chlorodifluoromethylation method, which is complementary to the existing late-stage difluoromethylation strategies reported in the literature. The CF_2Cl radical is a suitable surrogate for accessing the CF_2H group, while possessing completely different electronic properties compared to the CF_2H radical. This novel method is highly chemoselective and regioselective for the chlorodifluoromethylation of (hetero)arenes and electron-rich alkenes and shows good functionality tolerance and generality on scope. The preparation of the sodium chlorodifluoromethanesulfinate is thoroughly investigated and can be scaled up to hundreds of kilograms. The newly developed



Scheme 7. Synthetic application of 4

$ClCF_2SO_2Na$ (**4**) was used as a building block in the synthesis of oncology candidate **1**.

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method has been successfully implemented on the synthesis of an oncology candidate compound **1**.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Jinbo Hu (jinbohu@sioc.ac.cn).

Materials availability

The reagents generated in this study are available from the lead contact upon reasonable request.

Data and code availability

The authors declare that data supporting the findings of this study are available within the article and the Supplemental information.

Synthetic details and characterization

For further experimental descriptions, see the Supplemental experimental procedures. In addition, see Figures S1–S92 for all ^{1}H, ^{13}C, and ^{19}F NMR spectra. Tables S1–S3 show the optimization of chlorodifluoromethylation with (hetero)cycles and alkenes. Table S4 shows the optimization of the hydrodechlorination reaction. Tables S5 and S6 show the optimization for preparing $BTSCF_2Cl$ from $BTSCF_2CO_2Na$.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.xcrp.2021.100394.

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AUTHOR CONTRIBUTIONS

J.H. and S.D. conceived and led the project (J.H. for the synthetic methodology and S.D. for the application to the oncology candidate). D.M., L.L., Z.H., and M.Z. performed the synthetic and mechanistic experiments for the synthetic methodology and the preliminary application to the oncology candidate. A.B., J.-N.D., C.M.H., T.M., M.M., S.M., H.P., J.L.P., and D.W.W. were involved in the detailed experiments related to the oncology candidate. D.M., J.H., S.D., and A.B. co-wrote the manuscript. All of the authors discussed the results and commented on the manuscript. J.H. finalized the whole manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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