



Visible-Light-Promoted Transition-Metal-Free Construction of 3-Perfluoroalkylated Thioflavones

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A visible-light-promoted transition-metal-free perfluoroalkylation/cyclization reaction was developed with 9-mesityl-10-methylacridinium perchlorate ($\text{Acr}^+\text{-Mes}\cdot\text{ClO}_4^-$) as the photocatalyst, by which various perfluoroalkyl-substituted heterocycles including thioflavones, oxindoles, and quinoline-2,4(1*H*,3*H*)-diones were prepared at room temperature. Moreover, the potential of this sustainable method is demonstrated by the excellent *in vitro* anti-lymphoma and cervical carcinoma activity of the novel 3-perfluoroalkylated thioflavone **3m**.

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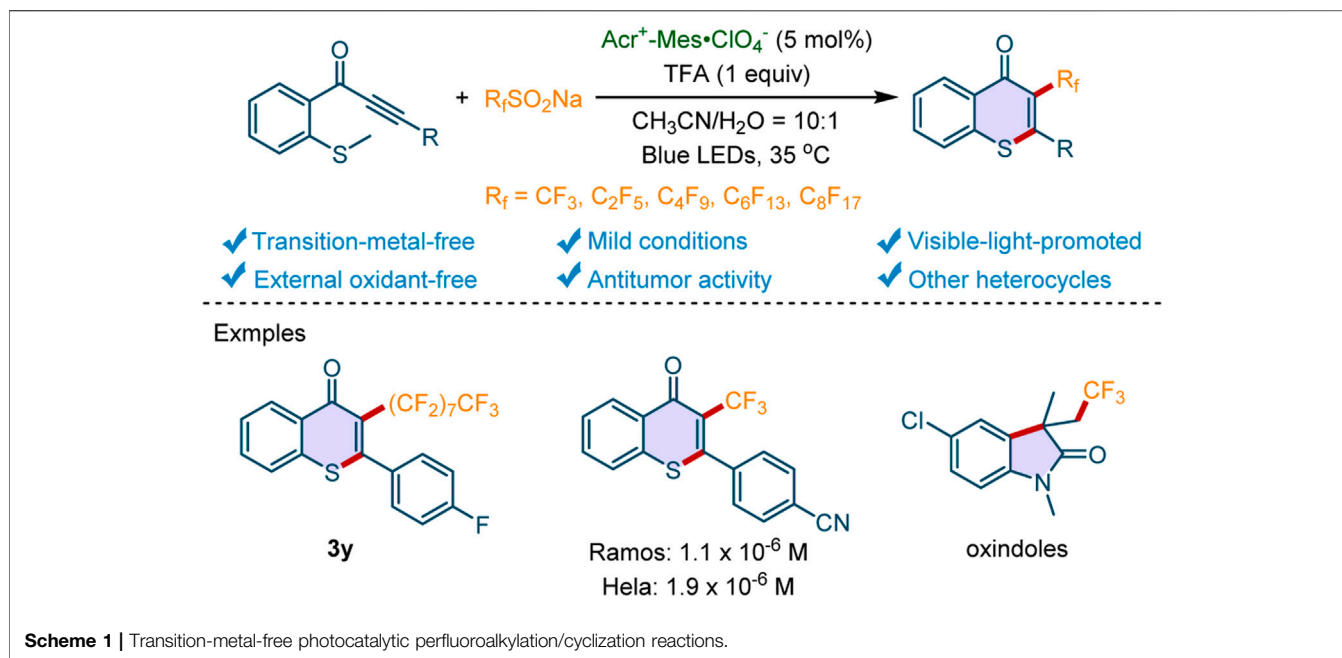
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INTRODUCTION

Thioflavone is a privileged scaffold that is ubiquitous in natural products, bioactive molecules, and functional materials (Dong et al., 2018). The derivatives of thioflavones have been found to exhibit intriguing biological activities, such as anticancer, (Wang et al., 1996), and anti-malarial (Razdan et al., 1978). Consequently, the construction of thioflavones with various substituents has attracted considerable attention (Kumar and Bodas, 2001; Pan et al., 2018; Sangeetha and Sekar, 2019; Yang et al., 2020; Zheng et al., 2020; Wang W. et al., 2021; Lee Jae, 2021). The perfluoroalkyl group, especially trifluoromethyl group, is one of the most prominent substituents in medicinal chemistry, which is essential for more than 70 approved drugs (Schiesser et al., 2020). It may be attributed to the fact that perfluoroalkyl group can remarkably improve the pharmacokinetics properties, lipophilicity and target inhibitory of the parent compounds (Müller et al., 2007; Tang et al., 2015; Tang et al., 2017a; Tang et al., 2017b; Wang et al., 2019; Ma et al., 2021a; Chen et al., 2022). In this context, developing the method to access perfluoroalkyl containing thioflavone is of great significance. However, there are currently no available reports to deliver this fragment.

Recently, methylthiolated alkyne is used as a unique starting material to access thioflavones containing diverse substitutes by the radical-initiated cyclization (Zhou et al., 2006; Alcaide et al., 2017). For instance, Song and coworkers developed a highly efficient approach to synthesizing phosphoryl-, acyl-, and sulfenyl-containing thioflavones from methylthiolated alkynes (Xu et al., 2019). Huang's group realized the reaction of AgSCF_3 with methylthiolated alkynes for the synthesis of 3-trifluoromethylthiolated thioflavones with $(\text{NH}_4)_2\text{S}_2\text{O}_8$ as the oxidant at 80°C (Wang L. et al., 2021). Du and Zhao *et al* reported the synthesis of selenyl/sulfenyl thioflavones with phenyliodine(III) bis(trifluoroacetate) (PIFA) as an oxidant (Ai et al., 2020). Recently, Ye and Wu's group realized an Ir-photocatalyzed radical relay reaction of methylthiolated alkynes and potassium metabisulfite in the presence of sodium methylsulfinate (Liu et al., 2022). With the

**TABLE 1** | Optimization of reaction conditions^a.

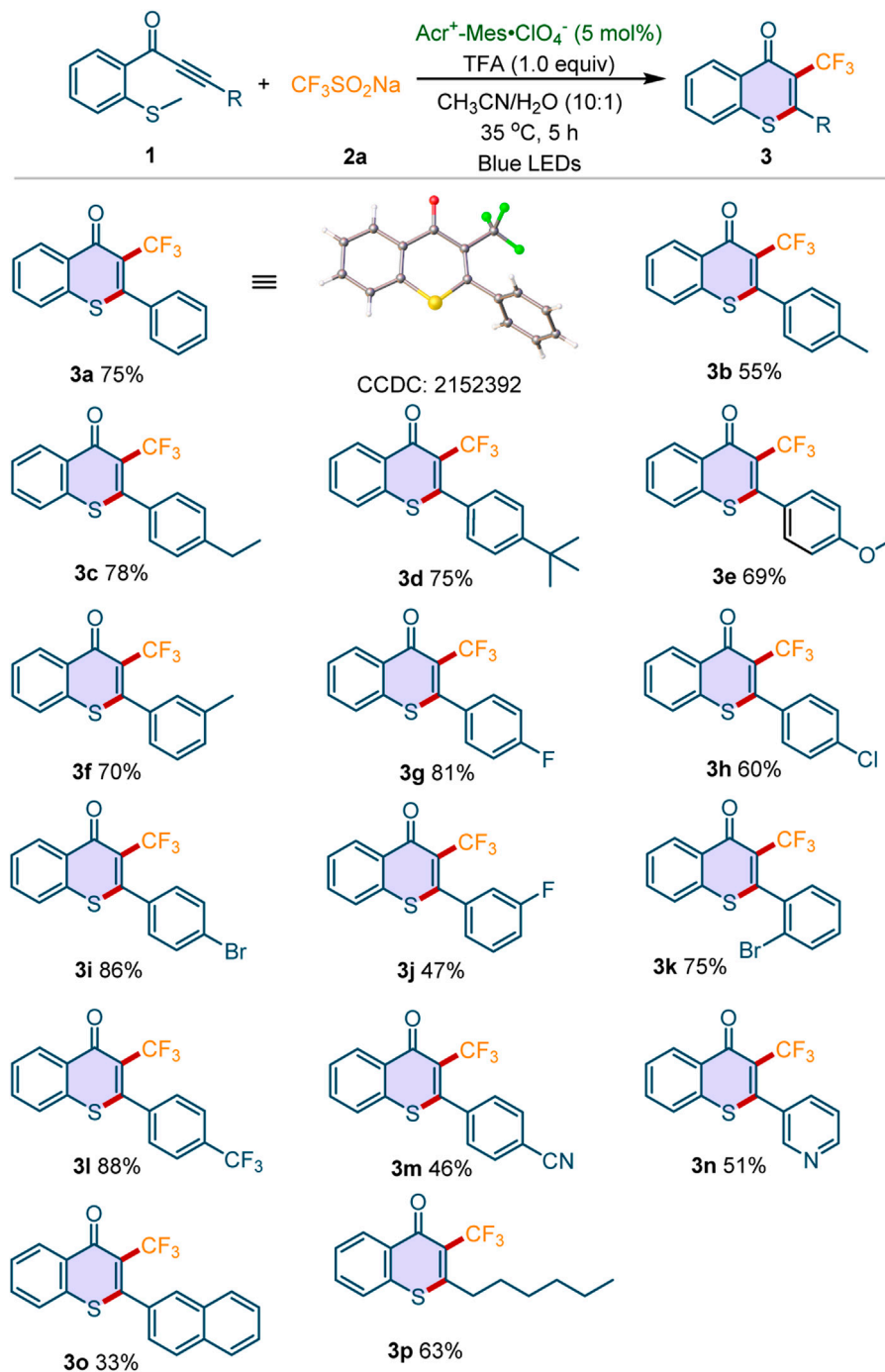
Entry	Catalyst (5 mol%)	Acid (1 equiv)	Solvent	Yield (%) ^b
1	Acr ⁺ -Mes-ClO ₄ ⁻	HCl	MeCN	37
2	Ru(bpy) ₃ Cl ₂	HCl	MeCN	13
3	PC3	HCl	MeCN	24
4	PC4	HCl	MeCN	N. R.
5	Acr ⁺ -Mes-ClO ₄ ⁻	H ₂ SO ₄	MeCN	22
6	Acr ⁺ -Mes-ClO ₄ ⁻	AcOH	MeCN	29
7	Acr ⁺ -Mes-ClO ₄ ⁻	TFA	MeCN	44
8	Acr ⁺ -Mes-ClO ₄ ⁻	Pivalic acid	MeCN	39
9	Acr ⁺ -Mes-ClO ₄ ⁻	TFA	DCM	43
10	Acr ⁺ -Mes-ClO ₄ ⁻	TFA	DCE	37
11	Acr ⁺ -Mes-ClO ₄ ⁻	TFA	CHCl ₃	37
12	Acr ⁺ -Mes-ClO ₄ ⁻	TFA	Dioxane	trace
13	Acr ⁺ -Mes-ClO ₄ ⁻	TFA	DMF	trace
14	Acr ⁺ -Mes-ClO ₄ ⁻	TFA	DMSO	trace
15	Acr ⁺ -Mes-ClO ₄ ⁻	TFA	EtOH	trace
16	Acr ⁺ -Mes-ClO ₄ ⁻	TFA	H ₂ O	trace
17	Acr ⁺ -Mes-ClO ₄ ⁻	TFA	MeCN/H ₂ O = 5:1	41
18	Acr ⁺ -Mes-ClO ₄ ⁻	TFA	MeCN/H ₂ O = 8:1	53
19	Acr ⁺ -Mes-ClO ₄ ⁻	TFA	MeCN/H ₂ O = 10:1	56
20	Acr ⁺ -Mes-ClO ₄ ⁻	TFA	MeCN/H ₂ O = 15:1	53
21 ^c	Acr ⁺ -Mes-ClO ₄ ⁻	TFA	MeCN/H ₂ O = 10:1	75
22 ^c	–	TFA	MeCN/H ₂ O = 10:1	N. R.
23 ^{c,d}	Acr ⁺ -Mes-ClO ₄ ⁻	TFA	MeCN/H ₂ O = 10:1	N. R.
24 ^c	Acr ⁺ -Mes-ClO ₄ ⁻	–	MeCN/H ₂ O = 10:1	35

^aReaction conditions: **1a** (0.2 mmol), **2a** (2 equiv), photocatalyst (5 mol%), acid (1 equiv), solvent (3 ml), 35°C, blue LEDs, 5 h under air atmosphere. **PC3**, 2,4,6-triphenylpyrylium tetrafluoroborate; **PC4**, 10-(3,5-dimethoxyphenyl)-9-mesityl-1,3,6,8-tetramethoxyacridin-10-ium tetrafluoroborate.

^bIsolated yields. N. R., No reaction.

^c**2a** (3 equiv).

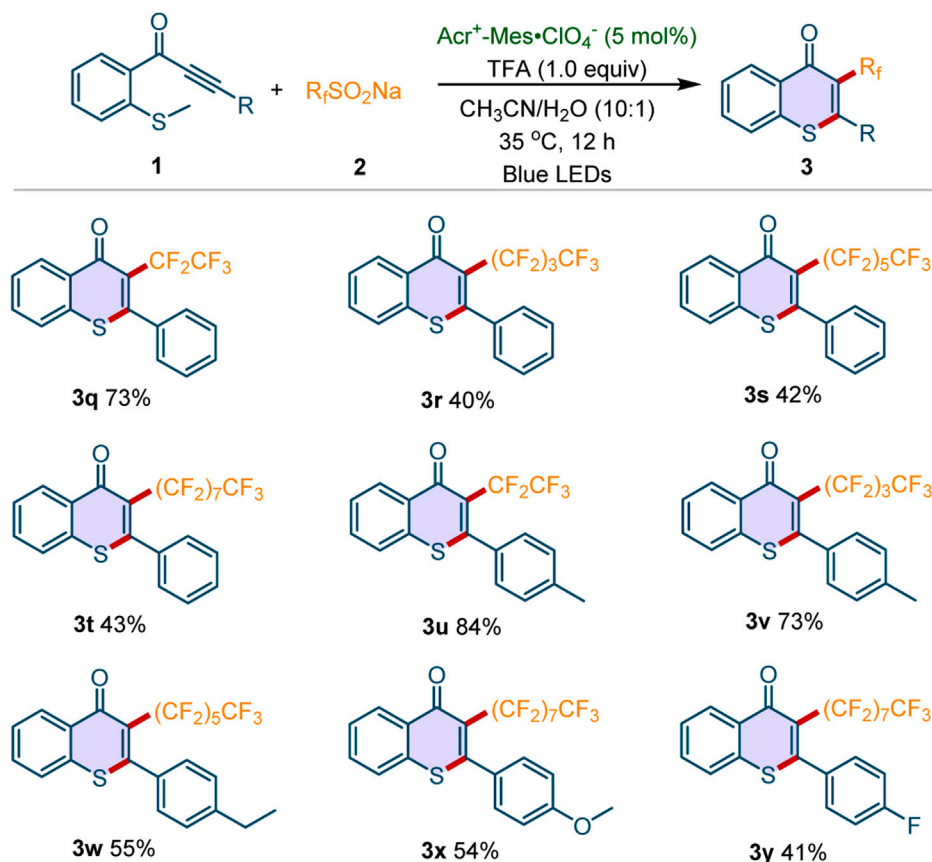
^dWithout light.



Scheme 2 | Scope of methylthiolated alkyne. Reaction conditions: **1** (0.2 mmol), **2a** (3 equiv), $\text{Acr}^+\text{-Mes}\cdot\text{ClO}_4^-$ (5 mol%), TFA (1 equiv), $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (10:1, 3 ml), 35°C, blue LEDs, 5 h under air atmosphere. Isolated yields were given.

radical-initiated cyclization of methylthiolated alkyne, our group has developed some protocols to access the phosphorylated, (Liu et al., 2020), acylated, (Zhu et al., 2021), sulfonated, (Feng et al., 2020; Jiang et al., 2020), and thiocyanated thioflavones (Zeng et al., 2021). Nevertheless, the synthesis of thioflavones bearing perfluoroalkyl-

substituents is rarely reported. Considering the critical roles of F-containing groups in the development of bioactive molecules, we herein disclosed that perfluoroalkyl-containing thioflavones could be accessed through photocatalytic cascade perfluoroalkylation/cyclization reactions in the presence of sodium perfluoroalkanesulfonates ($\text{R}_f\text{SO}_2\text{Na}$) as the



Scheme 3 | Scope of sodium perfluoroalkanesulfonates. Reaction conditions: **1** (0.2 mmol), **2a** (3 equiv), $\text{Acr}^+\text{-Mes-ClO}_4^-$ (5 mol%), TFA (1 equiv), $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (v/v = 10:1, 3 mL), 35°C, blue LEDs, 12 h under air atmosphere. Isolated yields were given.

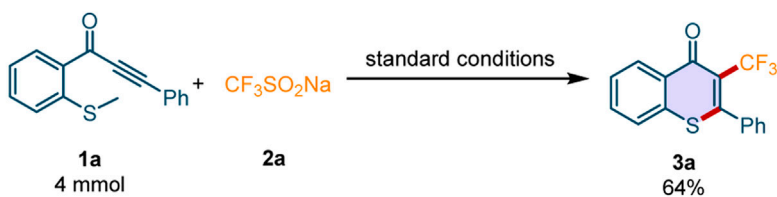
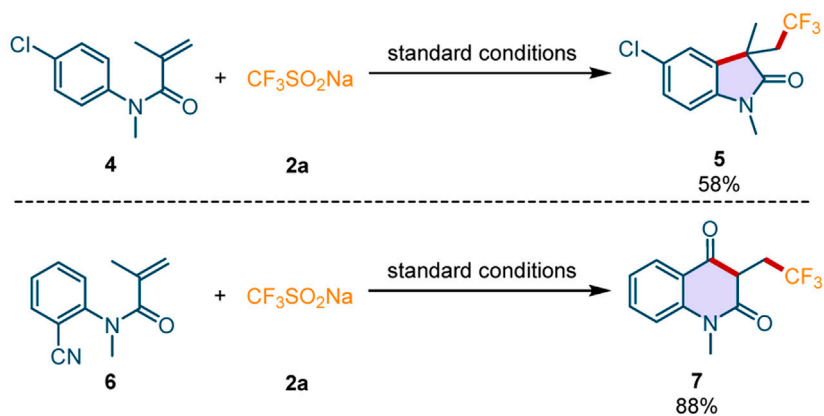
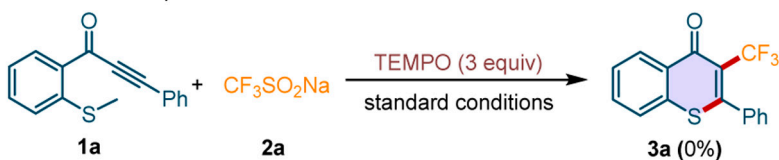
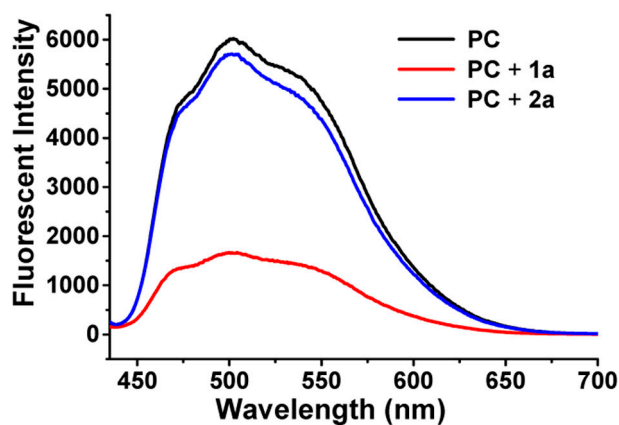
perfluoroalkyl source ($\text{R}_f = \text{CF}_3, \text{C}_2\text{F}_5, \text{C}_4\text{F}_9, \text{C}_6\text{F}_{13}, \text{C}_8\text{F}_{17}$) and 9-mesityl-10-methylacridinium perchlorate ($\text{Acr}^+\text{-Mes-ClO}_4^-$) as a transition-metal-free photocatalyst (**Scheme 1**). More importantly, the synthesized compounds exhibited excellent *in vitro* antitumor properties, which indicated that the unique protocol could be used to deliver novel antitumor hit compounds.

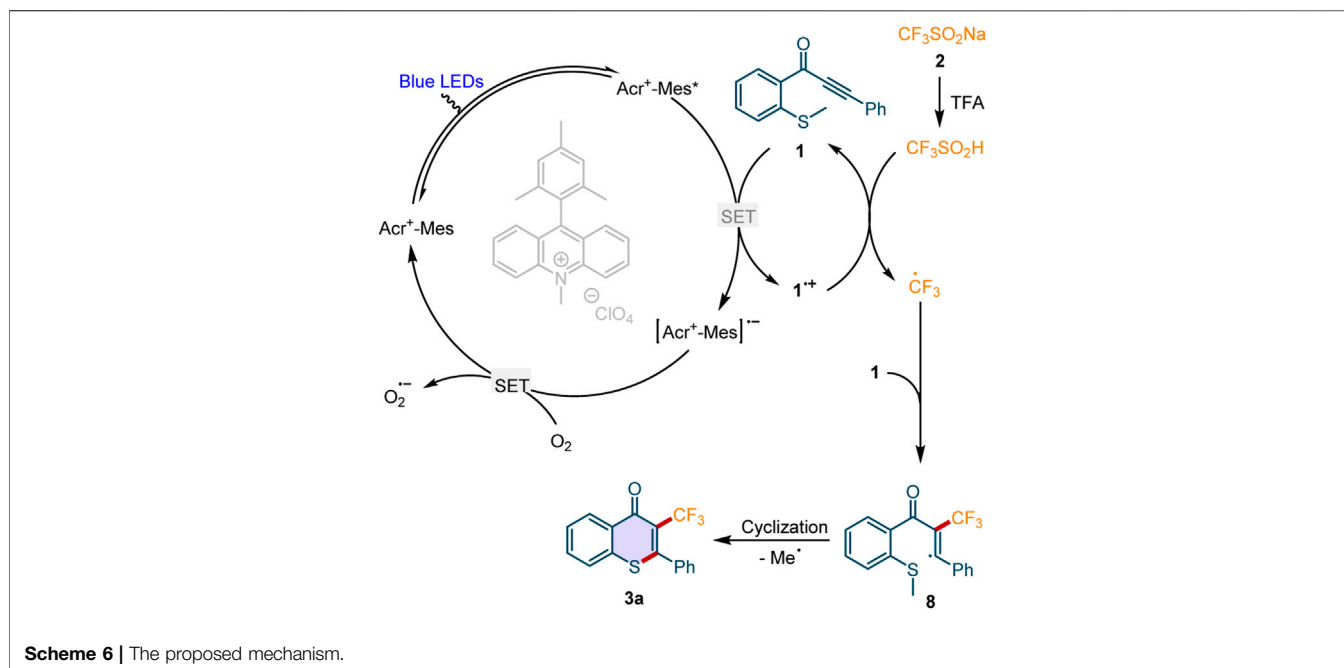
RESULTS AND DISCUSSION

We chose methylthiolated alkynone (**1a**) and $\text{CF}_3\text{SO}_2\text{Na}$ (**2a**) as model substrates to investigate the perfluoroalkylation/cyclization reaction in CH_3CN under 18 W blue LEDs irradiation at 35°C. Fortunately, when $\text{Acr}^+\text{-Mes-ClO}_4^-$ was used as the photocatalyst and HCl as the acid additive, **1a** and **2a** could be converted into the corresponding trifluoromethylated thioflavone **3a** in 37% yield (**Table 1**, entry 1). Evaluation of the different photocatalysts showed that $\text{Acr}^+\text{-Mes-ClO}_4^-$ was the best photocatalyst for this process (**Table 1**, entries 2-4). Different acidic additives were screened to further improve the efficiency of this transformation (**Table 1**, entries 5-8). The experimental

results indicated that trifluoroacetic acid (TFA) showed the highest reactivity, affording **3a** in 44% yield (**Table 1**, entry 7). To further improve the yield, a range of solvents, including DCM, DCE, CHCl_3 , 1,4-dioxane, DMF, DMSO, EtOH, H_2O , and acetonitrile aqueous were evaluated (**Table 1**, entries 9-20). The mixed solvent $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (v/v = 10:1) was found to be the optimal solvent system, and the desired product **3a** could be obtained in 56% yield (**Table 1**, entry 19). Furthermore, increasing the amount of **2a** to 3 equiv afforded the highest yield (**Table 1**, entry 21). The control experiments confirmed the photochemical nature of this transformation, as no product was observed in the absence of photocatalyst or visible light (**Table 1**, entries 22-23). The reaction efficiency was decreased to 35% in the absence of TFA, which indicated that the acid plays an important role in promoting the transformation (**Table 1**, entry 24). Taken together, the optimal reaction conditions were established as follows: **1a** (0.2 mmol), **2a** (3 equiv), $\text{Acr}^+\text{-Mes-ClO}_4^-$ (5 mol%) as catalyst, TFA (1 equiv) as additive, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (v/v = 10:1) as solvent, at 35°C under the irradiation of blue LEDs ($\lambda_{\text{max}} = 460 \text{ nm}$) for 5 h.

With the optimal conditions in hand, we further explored the scope and generality of this cascade perfluoroalkylation/

A Gram scale reaction**B** Synthesis of trifluoromethylated oxindoles and quinoline-2,4(1*H*,3*H*)-diones**Scheme 4** | The gram-scale synthesis and the application of this perfluoroalkylation/cyclization reactions.**A** The control experiments**B** Fluorescence quenching experiments**Scheme 5** | The control experiment and fluorescence quenching experiment.



cyclization reaction. Firstly, the reactivities of electron-rich or electron-deficient methylthiolated alkynes were investigated. As depicted in **Scheme 2**, the electron-donating groups (4-Me, 4-Et, 4-*t*Bu, 4-MeO, 3-Me) were well tolerant, giving the desired products **3b-3f** in 55–78% yields. For the substrates with electron-withdrawing groups, we found that both halogen substitutions (4-F, 4-Cl, 4-Br, 3-F, 2-Br) and CF₃ group were compatible with this transformation, and the corresponding products **3g-3l** were obtained in moderate to good yields. Moreover, the methylthiolated alkyne containing a strong electron-withdrawing substituent (4-CN) worked well under the standard conditions (**3m**). The pyridine or naphthalene analogs (**1n-1o**) were also found to be tolerant to the optimized condition. To our delight, the substrate containing alkyl group instead of aryl ring is well tolerant, affording the desired product **3p** in 63% yield. Moreover, the structure of **3a** was unambiguously confirmed by X-ray crystallographic analysis.

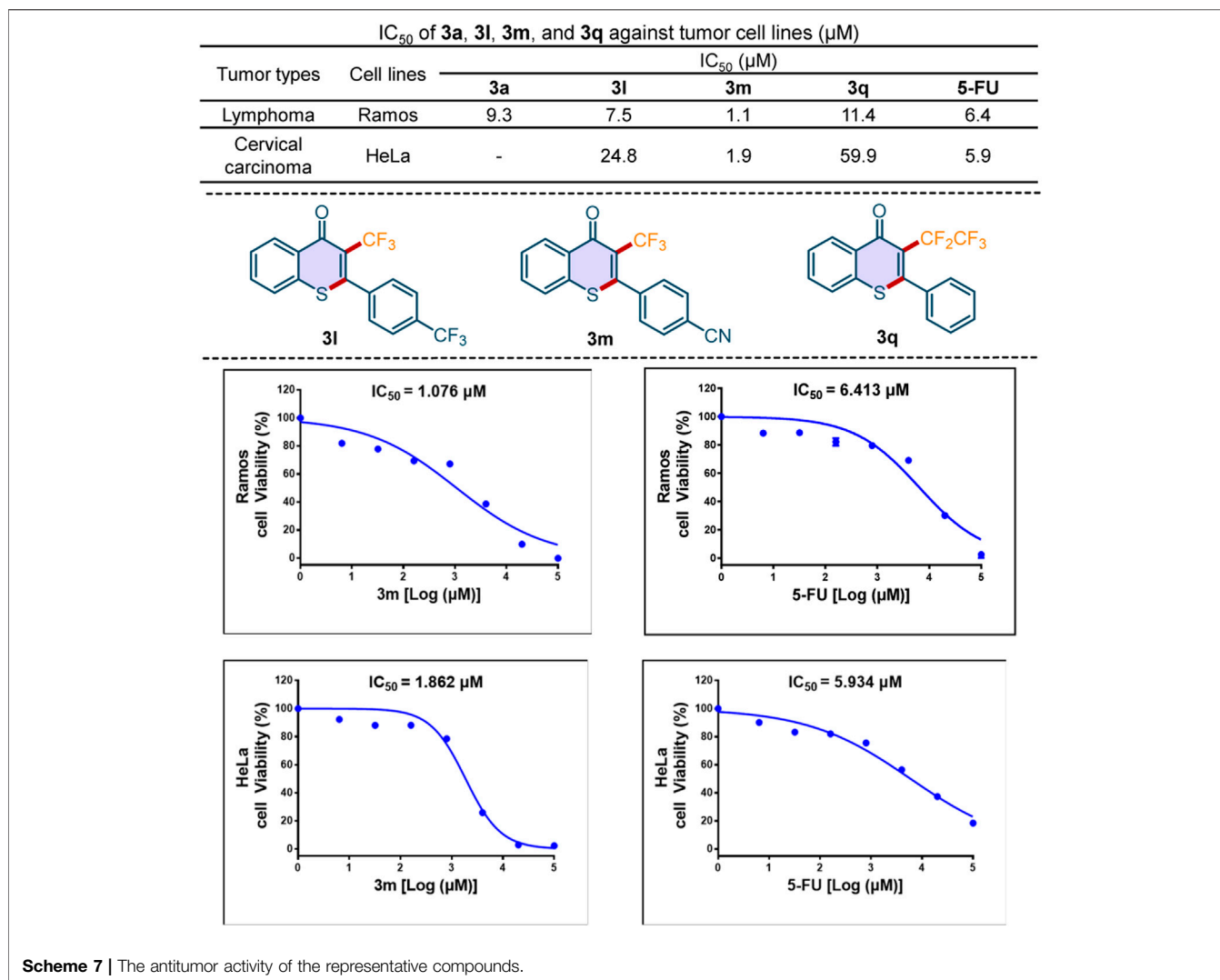
Subsequently, the scope of sodium perfluoroalkanesulfonates **2** was examined. As shown in **Scheme 3**, a variety of sodium perfluoroalkanesulfonates were well tolerated in this protocol. For example, CF₃CF₂SO₂Na, CF₃(CF₂)₃SO₂Na, CF₃(CF₂)₅SO₂Na and CF₃(CF₂)₇SO₂Na reacted well with **1a**, furnishing the perfluoroalkyl-substituted thioflavones **3q-3t** in moderate to good yields. Meanwhile, the sodium perfluoroalkanesulfonates reacted well with methylthiolated alkynes **1** bearing different substituents (Me, Et, OMe, F), affording the desired products **3u-3y** in 41–84% yields. Notably, all the synthesized 3-perfluoroalkylated thioflavones are new compounds.

To evaluate the applicability of this perfluoroalkylation/cyclization reaction in the pharmaceutical industry, it was scaled up to 4 mmol under standard conditions. Delightfully, the desired

product **3a** was obtained in 64% yield (**Scheme 4A**), which indicates that the transformation may be used in drug development. Inspired by the successful usage of this photocatalytic system in the synthesis of perfluoroalkylated thioflavones, we then applied the sustainable system in the construction of other perfluoroalkylated heterocycles under the standard conditions (**Scheme 4B**). The substrates *N*-(4-chlorophenyl)-*N*-methylmethacrylamide **4** and *N*-(2-cyanophenyl)-*N*-methylmethacrylamide **6** could be converted into the corresponding trifluoromethylated oxindole **5** and trifluoromethylated quinoline-2,4(1*H*,3*H*)-dione **7** in 58 and 88% yields, respectively.

To explore the reaction mechanism, the control experiment and the Stern–Volmer fluorescence quenching experiments were performed (**Scheme 5**). The addition of radical quencher, 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO), to the standard conditions completely prevented the reaction (**Scheme 5A**). It indicated that a radical pathway may be involved in this photocatalytic transformation. We conducted the Stern–Volmer fluorescence quenching experiment by mixing the photocatalyst Acr⁺-Mes·ClO₄[−] (PC) with methylthiolated alkyne **1a** and CF₃SO₂Na **2a**, respectively. The results were depicted in **Scheme 5B**. The luminescence effect was obviously quenched by the addition of **1a**, while it is hardly changed by the addition of **2a**. Moreover, a strong linear relationship was observed between I₀/I and the concentration of **1a**, indicating that **1a** could act as an available quencher of the excited state of the photocatalyst (for details see the **Supplementary Material**).

Based on the above experimental results and the previous reports, (Neogi et al., 2020; Ma et al., 2021b; Yang et al., 2021; Ma et al., 2022; Shen et al., 2022; Zhu et al., 2022), we proposed a plausible reaction mechanism for this photocatalyzed



perfluoroalkylation/cyclization reaction (**Scheme 6**). Under the visible light irradiation, Acr⁺-Mes was activated into the excited state Acr⁺-Mes*, which then oxidized the substrate **1** to afford the radical cation **1**^{•+} and the radical anion [Acr⁺-Mes]^{•-}. CF₃SO₂Na **2a** was *in situ* converted into CF₃SO₂H in the presence of the acid TFA. Then the radical cation **1**^{•+} reacted with CF₃SO₂H *via* a single-electron transfer (SET) process to generate the CF₃ radical and regenerate the substrate **1**. The desired product **3** was afforded by the addition of CF₃ radical to the triple bond of **1** and a subsequent intramolecular demethylation cyclization. On the other hand, the [Acr⁺-Mes]^{•-} could be oxidized by the O₂ in the air to regenerate the ground state of the photocatalyst and complete the photoredox cycle.

To highlight this sustainable method in drug development, we evaluated the *in vitro* antitumor activity of the novel 3-perfluoroalkylated thioflavones. As shown in **Scheme 7**, compound **3m** exhibited better antitumor activities against Ramos cell and HeLa cell than that of broad-spectrum antitumor drug 5-fluorouracil (5-FU), which indicated that

our compound has the potential to treat human B cell lymphoma and human cervical carcinoma. Because tumor resistance to chemotherapeutic drugs is a significant issue in the clinical treatment of carcinoma, the development of novel chemical entries, such as the 3-perfluoroalkylated thioflavones, is of great value.

CONCLUSION

In summary, we have developed a visible-light-induced perfluoroalkylation/cyclization of methylthiolated alkynes for the mild and rapid construction of 3-perfluoroalkylated thioflavones. It has been demonstrated that this radical involved strategy is tolerant of a variety of functional groups and could be applied to the construction of other perfluoroalkylated heterocycles, such as oxindoles and quinoline-2,4-(1*H*,3*H*)-diones. Moreover, compound **3m** exhibited robust antitumor activity, which provides a novel chemical entry for the clinical treatment of human

lymphoma and cervical carcinoma. The structural modification of these novel compounds is currently underway in our laboratory.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fchem.2022.953978/full#supplementary-material>

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