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The organophotocatalytic trifluoromethylation of 6-azauracils†

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An efficient, cost-effective, and metal-free photocatalytic trifluoromethylation of 6-azauracils has been developed using Langlois reagent (CF_3SO_2Na) under ambient air. The present protocol, which utilizes an inexpensive CF_3 reagent and an organophotocatalyst, provides a convenient way to prepare trifluoromethylated azauracil derivatives with a variety of functional groups. The experimental results suggest a radical mechanistic pathway for this methodology.

Introduction

Azauracils are azapyrimidinone analogs of uracils that belong to a privileged group of heterocycles and have important biological applications due to their widespread occurrence in natural products and pharmaceuticals.[1] The core structure of azauracils has been used in a variety of marketed drug molecules and molecules with medicinal properties, such as a c-MeT kinase inhibitor,[1a] an anticoccidial drug,[1b] and a 5-HT_{1A} agonist PET tracer.[1c] Additionally, ribonucleosides of 6-azauracil have been revealed to exhibit diverse biological properties, with examples including diclazuril and 6-azauridine, which shows antiviral activity (Fig. 1).[2] In view of the high value of 6-azauracils, it is important to develop novel synthetic methods for the rapid structural diversification of azauracils. The usual methods for the functionalization of azauracils mainly include cyclization and cross-coupling reactions.[3] Due to their high biological activities, a few processes have been developed for the functionalization of azauracils.[4–8] The reactions demand harsh conditions and there is a need for sustainable development. Hence, recently, the direct C–H bond functionalization of 6-azauracil has gained significant interest.

Fluorinated compounds has found extensive application in pharmaceutical chemistry and the agrochemicals industry, as well as in materials science.[9] Amid the various fluorine-containing groups, the trifluoromethyl group (CF_3) is highly useful in organic synthesis due to its strong electron-withdrawing nature, metabolic stability, and high lipophilicity.[10] Therefore, various trifluoromethyl reagents, such as Umemoto's reagent,[11] Togni's reagent,[12] Ruppert–Prakash reagent,[13] and Langlois reagent,[14] have been created for the incorporation of trifluoromethyl (CF_3) into chosen pharmaceutical molecules, especially heteroarenes. Among these reagents, Langlois reagent has the advantages of good stability, low cost, and easy handling.[15] Hence, with Langlois reagent as a trifluoromethyl source, a series of methodologies has been created.[16]

Considering the importance of both the trifluoromethyl group and the azauracil moiety, we decided to incorporate the trifluoromethyl group into azauracils. Our focus is to advance the reaction by the application of visible-light photocatalysis due to the synthetic versatility, low toxicity, mild reaction conditions, and eco-friendliness of the organic transformations.[17] Visible-light-induced organic reactions have gained a lot of value in organic synthesis.[18] Hence, visible-light-induced transformations are in higher demand for rapid trifluoromethylation when contrasted to metal-catalyzed methods.[19]

In addition, in recent times, various research groups, such as the groups of Kim,[4] Yu,[5] Zhao,[6] Murarka,[7] Zhu,[8d] Huang[8e] and others,[8] have developed several methods for the synthesis of methylated, alkylated, and arylated azauracils *via* C(sp^2)–H bond functionalization. Recently, Zhao *et al.* have demonstrated

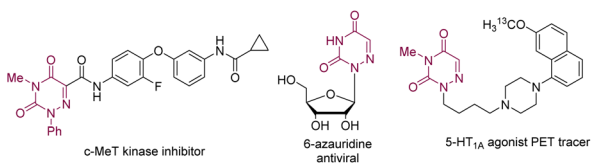

Fig. 1 Bioactive molecules containing azauracil scaffolds.

Scheme 1 The direct trifluoromethylation of 6-azauracils.

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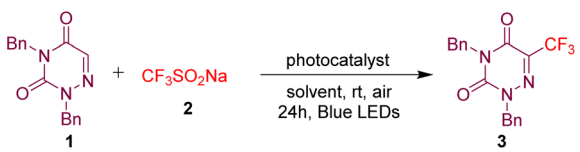
the phosphonation of azauracils.[9f] To the best of our knowledge there is no report on the direct trifluoromethylation of azauracils. Therefore, herein we report the visible-light-mediated organophotocatalytic trifluoromethylation of 6-azauracils (Scheme 1).

Results and discussion

To start our investigation, we initially selected 2,4-dibenzyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**1a**) as a test substrate and sodium trifluoromethanesulfinate (CF_3SO_2Na) (**2**) as a commercially available trifluoromethylating reagent (Table 1). At first, we performed the reaction between **1a** and 2.0 equiv. of sodium trifluoromethanesulfinate (**2**) with 3 mol% eosin Y as the photocatalyst in 1.5 mL of DMSO with irradiation with blue LEDs at room temperature under an open air atmosphere for 24 h (Table 1, entry 1). Delightfully, we observed the trifluoromethylated product **3a** with 37% yield (Table 1, entry 1). To improve the efficiency of the reaction in terms of yield, we have screened various photocatalysts, such as 4CzIPN (1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene), rose bengal, Mes-$Acr^+ClO_4^-$, and $Ru(bpy)_3Cl_2$ (Table 1, entries 2–5). Among them, 4CzIPN was found to be an effective photocatalyst and gives the desired product **3a** with 83% yield (Table 1, entry 2). Encouraged by this result, we have tested various solvents like DCE, CH_3CN, DMF, toluene and 1,4-dioxane (Table 1, entries 7–11), but no improvement was found. Without a photocatalyst, it was not possible to afford the desired product (**3a**) (Table 1, entry 6). Moreover, reducing the amount of sodium trifluoromethanesulfinate (**2**) to 1.0 equiv., resulted in a lower yield (Table 1, entry 12). Next, we checked the reaction under a nitrogen atmosphere, but no desired product was formed (Table 1, entry 13). Finally, the optimized reaction conditions were determined to involve 3 mol% 4CzIPN as the organophotocatalyst and 2.0 equiv. of sodium trifluoromethanesulfinate (**2**) in 2 mL of DMSO with irradiation with blue LEDs at room temperature under an open air atmosphere for 24 h (Table 1, entry 2).

After optimizing the reaction conditions, the substrate scope of the visible-light mediated trifluoromethylation was explored, as shown in Table 2. We investigated the scope for a variety of N_2,N_4-disubstituted azauracils by reacting them with Langlois reagent (CF_3SO_2Na) (**2**) under the optimal conditions. Various N_4-benzylated azauracils with diverse N_2-substituents, such as benzyl, phenacyl, –CH_2COOEt, *n*-butyl, and methyl groups afforded the desired products **3a–3e** in 59–94% yields. Furthermore, N_2,N_4-disubstituted azauracils (**1f–1i**) fruitfully delivered the expected products in good to excellent yields. Several N_4-4-nitro benzylated 6-azauracils connecting different N_2-substituents, such as 4-nitro benzyl, 4-bromo benzyl, 2-bromo benzyl, and 3,5-dimethyl benzyl, afforded the desired products **3j–3m** in 57–76% yields. The diverse disubstituted azauracils **1n**, **1o** and **1p** were also reacted with **2a** to produce the desired products (**3n**, **3o** and **3p**) in good yields. The use of ethyl and *n*-butyl groups as N_2,N_4-substituents was also

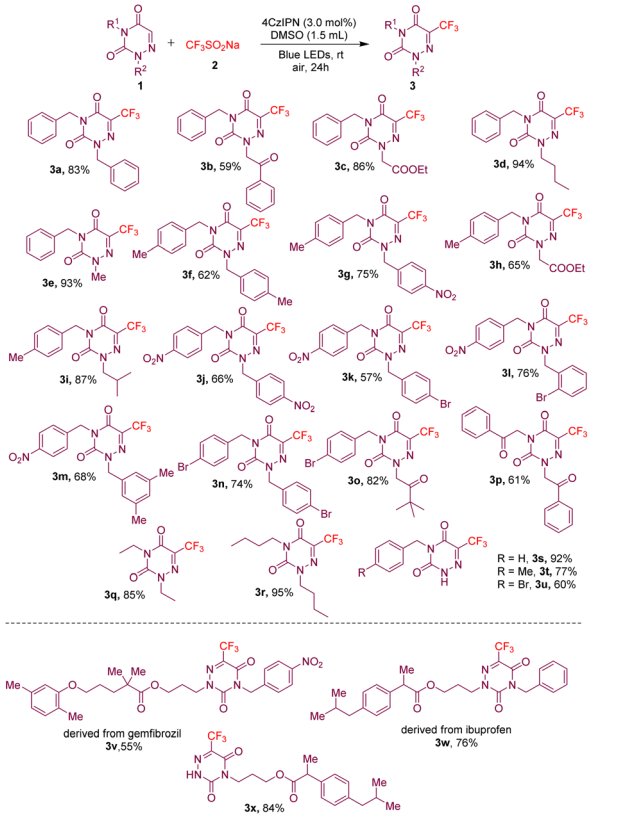
Table 1 Optimization of the reaction conditions[a]



Entry	Photocatalyst	Solvent	Yield (%)
1	Eosin Y	DMSO	37
2	4CzIPN	DMSO	83
3	Rose bengal	DMSO	nr
4	Mes-$Acr^+ClO_4^-$	DMSO	55
5	$Ru(bpy)_3Cl_2$	DMSO	nr
6	—	DMSO	nr
7	4CzIPN	DCE	19
8	4CzIPN	CH_3CN	40
9	4CzIPN	DMF	45
10	4CzIPN	Toluene	nr
11	4CzIPN	1,4-Dioxane	<10
12	4CzIPN	DMSO	49[b]
13	4CzIPN	DMSO	nr

[a] Reaction conditions: reactions were carried out with **1a** (0.3 mmol) and **2** (2.0 equiv.) in the presence of 3 mol% photocatalyst in 1.5 mL of solvent, with irradiation with blue LEDs at room temperature for 24 h under air. [b] 1.0 equiv. of CF_3SO_2Na was used. nr = no reaction.

Table 2 The substrate scope for the synthesis of 6-azauracils[a]

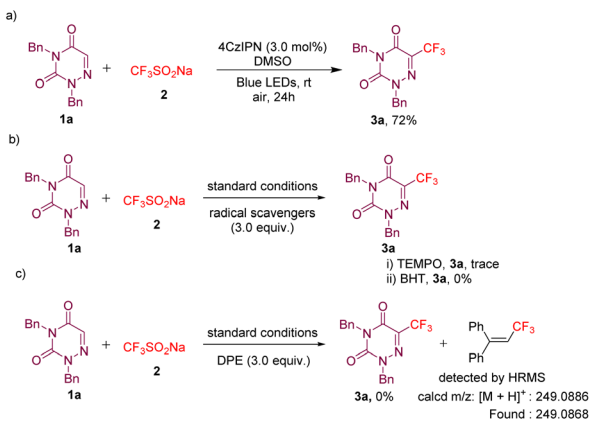


[a] Reaction conditions: 0.3 mmol of **1** and 2.0 equiv. of **2** in the presence of 3.0 mol% 4CzIPN in 1.5 mL of DMSO, with irradiation with blue LEDs at room temperature for 24 h under air.

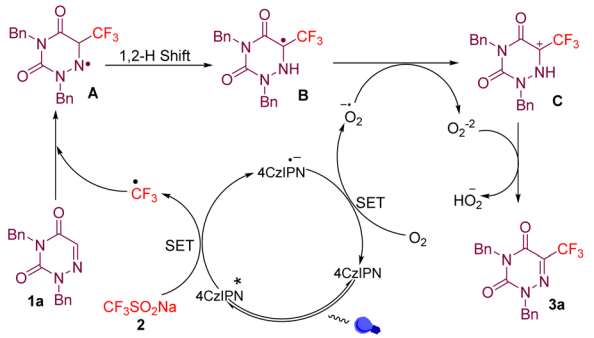
tolerated, giving the corresponding products **3q** and **3r** in 85% and 95% yields, respectively. In addition, 1,2,4-triazine-3,5(2*H*,4*H*)-diones with an N_4-monosubstituted compound (**1s**, **1t** and **1u**) were well-suited to the transformation and produced the trifluoromethylated products in moderate to good yields. Interestingly, azauracils contained within some pharmaceuticals, such as gemfibrozil and ibuprofen, resulted in the respective products (**3v–3x**) in good yields (55–84%).

To help determine the scalability, a scaled-up reaction was carried out using 2,4-dibenzyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**1**) and Langlois reagent (CF_3SO_2Na) with the presented laboratory setup on a 5 mmol scale. Delightfully, the reaction offered the corresponding product (**3a**) with a yield of 72%, which clearly shows the practical applicability of the presented methodology (Scheme 2a). To determine the mechanistic pathway of the proposed trifluoromethylation reaction, some control experiments were performed to explore the reaction pathway. The reaction did not progress in the presence of radical scavengers like 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) (Scheme 2b). However, the radical scavenger 1,1-diphenylethylene (DPE) formed an adduct with the trifluoromethyl radical species generated from Langlois reagent (CF_3SO_2Na), which was detected using HRMS (Scheme 2c, see ESI S6†). These results point toward the fact that the present reaction follows a radical mechanistic pathway. Moreover, fluorescence quenching experiments were performed to investigate the reaction mechanism. Stern–Volmer fluorescence quenching studies of the reaction components show that the excited-state photocatalyst was most effectively quenched by sodium trifluoromethanesulfinate (CF_3SO_2Na) (**2**), with an observed K_{SV} value of $5.93 \times 10^3\ M^{-1}$ (see the ESI† for more information).

Based on literature reports[19b,20] and the results of the control experiments, a plausible mechanism for the reaction pathway is shown in Scheme 3. We suggest that a radical mechanism occurs *via* an oxidative quenching pathway. First of all, photoexcitation of 4CzIPN, which is irradiated under blue light, generates the excited state of 4CzIPN*. Next, a single electron transfers from the excited photocatalyst 4CzIPN* to sodium trifluoromethanesulfinate (**2**) to form a trifluoromethyl radical



Scheme 2 Scaled-up and control experiments.



Scheme 3 A plausible mechanistic pathway.

and 4CzIPN$^{\bullet-}$ species. The subsequent attack by this radical of 2,4-dibenzyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**1a**) forms intermediate **A**, which undergoes a 1,2-hydrogen shift process to produce intermediate **B**. Now, another single electron transfer (SET) process takes place between the 4CzIPN$^{\bullet-}$ species and O_2 to provide an $O_2^{\bullet-}$ species, by which 4CzIPN is regenerated. Afterward, the intermediate **B** is consequently oxidized by the $O_2^{\bullet-}$ species to give the intermediate **C** and O_2^{2-}. Lastly, the deprotonation of intermediate **C** affords the desired product **3a**.

Conclusions

We have developed the metal-free visible-light-induced organophotoredox-catalyzed radical trifluoromethylation of 6-azauracils using 4CzIPN as a photocatalyst under aerobic reaction conditions. Both the trifluoromethyl source and organophotocatalyst are low-cost and readily available. A variety of trifluoromethylated 6-azauracil derivatives have been produced in moderate to good yields under mild conditions. The present photocatalytic trifluoromethylation reaction possibly follows a radical pathway. We believe this approach will gain much significance in medicinal chemistry, organic synthesis, and materials science.

Experimental section

Experimental procedures

Typical experimental procedure for 3a. A mixture of 2,4-dibenzyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**1a**) (0.3 mmol, 88.1 mg), Langlois reagent (CF_3SO_2Na) (**2**) (2.0 equiv., 93.6 mg) and 4CzIPN (3 mol%, 7.0 mg) was taken in an oven-dried reaction tube. Then, DMSO (2 mL) was added to an oven-dried reaction vessel (tube) equipped with a magnetic stirrer, and the reaction vessel was irradiated with a Kessil 34 W blue LED at room temperature under an open-air atmosphere for 24 h. The progress of the reaction was monitored by TLC, and extraction was with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4. The crude residue was obtained after evaporating the solvent under vacuum and it was purified by column chromatography on silica gel using a mixture of petroleum ether and ethyl acetate.

*2,4-Dibenzyl-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3a**).* White solid (83%, 89.9 mg); $R_f = 0.50$ (PE/EA = 90 : 10); mp:

107–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.49 (m, 2H), 7.45–7.42 (m, 2H), 7.41–7.37 (m, 3H), 7.36–7.31 (m, 3H), 5.01 (s, 2H), 5.08 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.2, 148.3, 134.6, 134.3, 131.4 (q, J = 36.0 Hz), 129.9, 129.1, 129.0, 128.9, 128.8, 128.6, 119.3 (q, J = 273.0 Hz), 55.4 44.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.74; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{18}H_{15}F_3N_3O_2]^+$: 362.1111; found: 362.1103.

*4-Benzyl-2-(2-oxo-2-phenylethyl)-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3b**).* Colorless gummy mass (59%, 68.9 mg); R_f = 0.50 (PE/EA = 83 : 17); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 7.6 Hz, 2H), 7.67 (t, J = 7.6 Hz, 1H), 7.53 (t, J = 8.0 Hz, 2H), 7.49–7.47 (m, 2H), 7.36–7.29 (m, 3H), 5.45 (s, 2H), 5.13 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 190.5, 152.3, 148.7, 134.7, 134.5, 134.0, 131.9 (q, J = 37.0 Hz), 129.9, 129.2, 128.8, 128.6, 128.2, 119.2 (q, J = 273.0 Hz), 58.2, 44.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.85; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{19}H_{15}F_3N_3O_3]^+$: 390.1060; found: 390.1049.

*Ethyl 2-(4-benzyl-3,5-dioxo-6-(trifluoromethyl)-4,5-dihydro-1,2,4-triazin-2(3H)-yl)acetate (**3c**).* White solid (86%, 92.1 mg); R_f = 0.50 (PE/EA = 85 : 15); mp: 109–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.45 (m, 2H), 7.35–7.28 (m, 3H), 5.10 (s, 2H), 4.73 (s, 2H), 4.28–4.23 (m, 2H), 1.28 (t, J = 7.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.5, 152.1, 148.4, 134.4, 132.1 (q, J = 36.0 Hz), 129.6, 128.8, 128.6, 119.1 (q, J = 272.0 Hz), 62.4, 53.4, 44.7, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.92; HRMS (ESI-TOF) m/z: $[M + K]^+$ calcd for $[C_{15}H_{14}F_3N_2O_2K]^+$: 396.0568; found: 396.0574.

*4-Benzyl-2-butyl-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3d**).* Colorless gummy mass (94%, 92.2 mg); R_f = 0.50 (PE/EA = 90 : 9); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.50 (m, 2H), 7.36–7.29 (m, 3H), 5.10 (s, 2H), 4.03 (t, J = 7.6 Hz, 2H), 1.79–1.71 (m, 2H), 1.42–1.33 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.3, 148.3, 134.8, 131.1 (q, J = 36.0 Hz), 129.8, 128.8, 128.5, 119.4 (q, J = 273.0 Hz), 52.6, 44.6, 30.1, 19.7, 13.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.77; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{15}H_{17}F_3N_3O_2]^+$: 328.1267; found: 328.1257.

*4-Benzyl-2-methyl-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3e**).* Colorless gummy mass (90%, 77.0 mg); R_f = 0.50 (PE/EA = 90 : 10); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.49 (m, 2H), 7.36–7.26 (m, 3H), 5.10 (s, 2H), 3.69 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.4, 148.5, 134.7, 131.2 (d, J = 37.0 Hz), 129.9, 128.8, 128.6, 119.4 (q, J = 272.0 Hz), 44.6, 40.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.83; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{12}H_{11}F_3N_3O_2]^+$: 286.0798; found: 286.0793.

*2,4-Bis(4-methylbenzyl)-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3f**).* White solid (62%, 72.4 mg); R_f = 0.50 (PE/EA = 91 : 9); mp: 112–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 5.10 (s, 2H), 5.03 (s, 2H), 2.35 (s, 3H), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.3, 148.3, 138.9, 138.5, 131.7, 131.6 (q, J = 36.0 Hz), 131.3, 129.9, 129.7, 129.5, 129.1, 119.3 (q, J = 273.0 Hz), 56.2, 44.5, 21.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.77; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{20}H_{19}F_3N_3O_2]^+$: 390.1424; found: 390.1411.

*4-(4-Methylbenzyl)-2-(4-nitrobenzyl)-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3g**).* White solid (75%, 94.5 mg); R_f = 0.50 (PE/EA = 86 : 14); mp: 118–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22–8.19 (m, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 5.23 (s, 2H), 5.04 (s, 2H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.9, 148.3, 148.2, 141.1, 138.7, 132.1 (q, J = 37.0 Hz), 131.5, 129.97, 129.92, 129.5, 124.3, 119.2 (q, J = 273.0 Hz), 55.4, 44.7, 21.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.82; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{19}H_{16}F_3N_4O_4]^+$: 421.1118; found: 421.1129.

*Ethyl 2-(4-(4-methylbenzyl)-3,5-dioxo-6-(trifluoromethyl)-4,5-dihydro-1,2,4-triazin-2(3H)-yl)acetate (**3h**).* Colorless gummy mass (65%, 72.4 mg); R_f = 0.50 (PE/EA = 865 : 15); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 5.07 (s, 2H), 4.73 (s, 2H), 4.29–4.23 (m, 2H), 2.32 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.5, 152.1, 148.4, 138.5, 132.3 (q, J = 36.0 Hz), 131.5, 129.7, 129.5, 119.2 (q, J = 273.0 Hz), 62.4, 53.4, 44.6, 21.2, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.92; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{16}H_{17}F_3N_3O_4]^+$: 372.1166; found: 372.1155.

*2-Isobutyl-4-(4-methylbenzyl)-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3i**).* White solid (87%, 89.0 mg); R_f = 0.50 (PE/EA = 93 : 7); mp: 68–69 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 7.6 Hz, 2H), 5.07 (s, 2H), 3.84 (d, J = 7.6 Hz, 2H), 2.33 (s, 3H), 2.23–2.13 (m, 1H), 0.94 (d, J = 6.8 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.2, 148.6, 138.4, 131.8, 131.2 (q, J = 36.0 Hz), 129.8, 129.4, 119.4 (q, J = 273.0 Hz), 59.5, 44.6, 27.8, 21.2, 19.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.78; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{16}H_{19}F_3N_3O_2]^+$: 342.1424; found: 342.1425.

*2,4-Bis(4-nitrobenzyl)-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3j**).* White solid (66%, 89.3 mg); R_f = 0.50 (PE/EA = 81 : 19); mp: 208–209 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 5.25 (s, 2H), 5.15 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 151.9, 148.2, 148.0, 141.1, 140.7, 132.2 (q, J = 37.0 Hz), 130.8, 130.0, 124.2, 124.0, 119.0 (q, J = 274.0 Hz), 55.6, 44.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.79; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{18}H_{13}F_3N_5O_6]^+$: 452.0812; found: 452.0790.

*2-(4-Bromobenzyl)-4-(4-nitrobenzyl)-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3k**).* White solid (57%, 82.9 mg); R_f = 0.50 (PE/EA = 85 : 15); mp: 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 5.14 (s, 2H), 5.11 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.0, 148.1, 148.0, 141.2, 132.8, 132.3, 131.9 (q, J = 36.0 Hz), 130.9, 130.7, 124.0, 123.4, 119.1 (q, J = 274.0 Hz), 55.9, 44.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.76; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $[C_{18}H_{12}BrF_3N_4O_4Na]^+$: 506.9886; found: 506.9871.

*2-(2-Bromobenzyl)-4-(4-nitrobenzyl)-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3l**).* White solid (76%, 110.6 mg); R_f = 0.50 (PE/EA = 85 : 15); mp: 111–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 8.8 Hz, 2H), 7.65–7.59 (m, 3H), 7.34–7.26 (m, 2H), 7.24–7.20 (m, 1H), 5.33 (s, 2H), 5.18 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.0, 148.2, 148.0, 141.4, 133.5, 133.3, 131.5 (q, J = 36.0 Hz), 130.78, 130.70, 130.4, 127.9, 124.0, 123.9, 119.1 (q, J = 273.0 Hz), 56.1, 44.0; ^{19}F NMR (376 MHz,

$CDCl_3$) δ: −67.77; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{18}H_{13}BrF_3N_4O_4]^+$: 485.9994; found: 485.0089.

*2-(3,5-Dimethylbenzyl)-4-(4-nitrobenzyl)-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3m**).* White solid (68%, 88.5 mg); $R_f = 0.50$ (PE/EA = 85 : 15); mp: 126–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, $J = 8.8$ Hz, 2H), 7.65 (d, $J = 8.4$ Hz, 2H), 7.00 (d, $J = 8.0$ Hz, 2H), 5.15 (s, 2H), 5.09 (s, 2H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.1, 148.1, 148.0, 141.4, 138.8, 133.9, 131.3 (q, $J = 36.0$ Hz), 130.7, 130.6, 126.7, 124.0, 119.2 (q, $J = 273.0$ Hz), 56.6, 43.9, 21.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.72; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{20}H_{18}F_3N_4O_4]^+$: 435.1275; found: 435.1281.

*2,4-Bis(4-bromobenzyl)-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3n**).* White solid (74%, 115.2 mg); R_f = 0.50 (PE/EA = 91 : 9); mp: 132–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, $J = 8.4$ Hz, 2H), 7.46–7.43 (m, 2H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 8.4$ Hz, 2H), 5.09 (s, 2H), 5.01 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.0, 148.1, 133.4, 133.0, 132.2, 132.0, 131.7, 131.6 (q, $J = 36.0$ Hz), 130.8, 123.3, 122.9, 119.2 (q, $J = 273.0$ Hz), 55.8, 44.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.76; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $[C_{18}H_{12}BrF_3N_3O_2Na]^+$: 539.9141; found: 539.9125.

*4-(4-Bromobenzyl)-2-(3,3-dimethyl-2-oxobutyl)-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3o**).* White solid (82%, 110.2 mg); $R_f = 0.50$ (PE/EA = 82 : 18); mp: 102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.43 (m, 2H), 7.33 (d, $J = 8.4$ Hz, 2H), 5.02 (s, 2H), 5.96 (s, 2H), 1.25 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 206.5, 152.1, 148.3, 133.4, 132.1, 131.3, 131.9 (q, $J = 37.0$ Hz), 122.7, 119.2 (q, $J = 273.0$ Hz), 56.8, 44.0, 43.4, 26.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.85; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{17}H_{18}BrF_3N_3O_3]^+$: 448.0478; found: 448.0490.

*2,4-Bis(2-oxo-2-phenylethyl)-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3p**).* White solid (61%, 76.3 mg); $R_f = 0.50$ (PE/EA = 80 : 20); mp: 198–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99–7.96 (m, 4H), 7.67–7.62 (m, 2H), 7.54–7.49 (m, 4H), 5.50 (s, 2H), 5.40 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 190.5, 189.5, 151.9, 148.4, 134.6, 134.4, 134.3, 134.0, 132.1 (q, $J = 37.0$ Hz), 129.2, 129.1, 128.3, 128.2, 119.2 (q, $J = 273.0$ Hz), 58.2, 46.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.83; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{20}H_{15}F_3N_3O_4]^+$: 418.1009; found: 418.1010.

*2,4-Diethyl-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3q**).* White solid (85%, 60.4 mg); $R_f = 0.50$ (PE/EA = 90 : 10); mp: 96–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12–4.07 (m, 2H), 4.04–3.98 (m, 2H), 1.37 (t, $J = 7.2$ Hz, 2H), 1.26 (t, $J = 7.2$ Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.2, 148.0, 131.1 (d, $J = 36.0$ Hz), 119.5 (q, $J = 272.0$ Hz), 48.0, 36.8, 13.3, 12.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.89; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_8H_{11}F_3N_3O_2]^+$: 238.0798; found: 238.0793.

*2,4-Dibutyl-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3r**).* Colorless gummy mass (95%, 83.5 mg); $R_f = 0.50$ (PE/EA = 91 : 9); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.02 (t, $J = 7.6$ Hz, 2H), 3.92 (t, $J = 7.6$ Hz, 2H), 1.78–1.70 (m, 2H), 1.66–1.57 (m, 2H), 1.41–1.31 (m, 4H), 0.96–0.91 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.3, 148.3, 130.9 (q, $J = 36.0$ Hz), 119.5 (q, $J = 273.0$ Hz), 52.5, 41.3, 30.1, 29.1, 20.2, 19.7, 13.68, 13.64; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.93; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{12}H_{19}F_3N_3O_2]^+$: 294.1424; found: 294.1405.

*4-Benzyl-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3s**).* White solid (92%, 74.8 mg); $R_f = 0.50$ (PE/EA = 80 : 20); mp: 133–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.88 (s, 1H), 7.50–7.48 (m, 2H), 7.35–7.30 (m, 3H), 5.08 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.1, 149.3, 134.2, 133.0 (q, $J = 35.0$ Hz), 129.8, 128.9, 128.7, 119.2 (q, $J = 273.0$ Hz), 44.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −68.19; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{11}H_9F_3N_3O_2]^+$: 272.0641; found: 272.0652.

*4-(4-Methylbenzyl)-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3t**).* White solid (77%, 65.8 mg); $R_f = 0.50$ (PE/EA = 80 : 20); mp: 142–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.67 (s, 1H), 7.39 (d, $J = 7.6$ Hz, 2H), 7.13 (d, $J = 8.0$ Hz, 2H), 5.05 (s, 2H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.1, 149.2, 138.7, 133.1 (q, $J = 37.0$ Hz), 131.4, 129.8, 129.5, 119.2 (q, $J = 273.0$ Hz), 43.9, 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −68.19; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{12}H_{11}F_3N_3O_2]^+$: 286.0798; found: 286.0780.

*4-(4-Bromobenzyl)-6-(trifluoromethyl)-1,2,4-triazine-3,5(2H,4H)-dione (**3u**).* White solid (60%, 63.0 mg); $R_f = 0.50$ (PE/EA = 80 : 20); mp: 164–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.60 (s, 1H), 7.45 (d, $J = 8.4$ Hz, 2H), 7.37 (d, $J = 8.4$ Hz, 2H), 5.03 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.0, 149.0, 133.23, 133.20 (q, $J = 36.0$ Hz), 132.1, 131.6, 123.0, 119.1 (q, $J = 273.0$ Hz), 43.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −68.18; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{11}H_8BrF_3N_3O_2]^+$: 349.9747; found: 349.9735.

*3-(4-(4-Nitrobenzyl)-3,5-dioxo-6-(trifluoromethyl)-4,5-dihydro-1,2,4-triazin-2(3H)-yl)propyl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (**3v**).* Yellow gummy mass (55%, 100.0 mg); $R_f = 0.50$ (PE/EA = 74 : 26); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, $J = 8.8$ Hz, 2H), 7.63 (d, $J = 8.4$ Hz, 2H), 6.97 (d, $J = 7.2$ Hz, 1H), 6.63 (d, $J = 7.6$ Hz, 1H), 6.59 (s, 1H), 5.14 (s, 2H), 4.15–4.10 (m, 4H), 3.92 (s, 2H), 2.29 (s, 3H), 2.14–2.09 (m, 5H), 1.71 (d, $J = 2.8$ Hz, 4H), 1.21 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 177.6, 156.9, 152.0, 148.2, 148.0, 141.3, 136.6, 131.5 (q, $J = 36.0$ Hz), 130.7, 130.4, 124.0, 123.5, 120.8, 119.2 (q, $J = 273.0$ Hz), 112.0, 67.9, 60.8, 49.8, 43.9, 42.2, 37.1, 27.4, 25.27, 25.21, 21.5, 15.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.74; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{29}H_{34}F_3N_4O_7]^+$: 607.2374; found: 607.2381.

*3-(4-Benzyl-3,5-dioxo-6-(trifluoromethyl)-4,5-dihydro-1,2,4-triazin-2(3H)-yl)propyl 2-(4-isobutylphenyl)propanoate (**3w**).* Yellow gummy mass (76%, 117.9 mg); R_f = 0.50 (PE/EA = 75 : 24); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51–7.49 (m, 2H), 7.36–7.29 (m, 3H), 7.18 (d, $J = 8.0$ Hz, 2H), 7.09 (d, $J = 8.0$ Hz, 2H), 5.08 (s, 2H), 4.13 (d, $J = 6.0$ Hz, 2H), 4.06–3.94 (m, 2H), 3.68–3.63 (m, 1H), 2.43 (d, $J = 6.8$ Hz, 2H), 2.10–2.03 (m, 2H), 1.86–1.79 (m, 1H), 1.47 (d, $J = 7.2$ Hz, 3H), 0.87 (d, $J = 6.4$ Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.6, 152.1, 148.2, 140.7, 137.6, 134.6, 131.4 (q, $J = 36.0$ Hz), 129.9, 129.5, 128.8, 128.6, 127.2, 119.3 (q, $J = 273.0$ Hz), 61.3, 49.8, 45.17, 45.13, 44.7, 30.2, 27.3, 22.4, 18.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −67.76; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{27}H_{31}F_3N_3O_4]^+$: 518.2261; found: 518.2272.

*3-(3,5-Dioxo-6-(trifluoromethyl)-2,5-dihydro-1,2,4-triazin-4(3H)-yl)propyl 2-(4-isobutylphenyl)propanoate (**3x**).* Yellow gummy mass (84%, 107.7 mg); $R_f = 0.50$ (PE/EA = 74 : 25); ^{1}H NMR (400

MHz, $CDCl_3$): δ 10.93 (s, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 4.19–4.07 (m, 2H), 4.01–3.90 (m, 2H), 3.77–3.67 (m, 1H), 2.42 (d, J = 7.2 Hz, 2H), 2.02–1.96 (m, 2H), 1.85–1.77 (m, 1H), 1.48 (d, J = 7.2 Hz, 3H), 0.87 (d, J = 6.8 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 175.1, 152.1, 149.1, 140.7, 137.4, 132.6 (q, J = 37.0 Hz), 129.4, 127.2, 119.2 (q, J = 273.0 Hz), 62.1, 45.1, 45.0, 38.1, 30.2, 26.3, 22.4, 18.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −68.22; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{20}H_{25}F_3N_3O_4]^+$: 428.1792; found: 428.1786.

Data availability

All data including experimental procedures, compound characterization and NMR spectra are recorded in the ESI.†

Conflicts of interest

There are no conflicts of interest to declare.

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