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Synthesis of Fluorinated Benzophenones, Xanthones, Acridones, and Thioxanthones by Iterative Nucleophilic Aromatic Substitution

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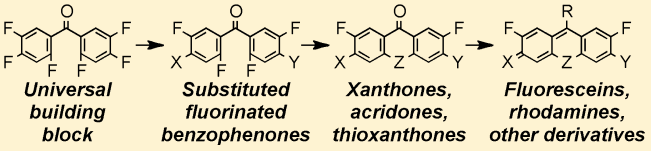
Supporting Information

ABSTRACT: Fluorination of fluorophores can substantially enhance their photostability and improve spectroscopic properties. To facilitate access to fluorinated fluorophores, bis-(2,4,5-trifluorophenyl)methanone was synthesized by treatment of 2,4,5-trifluorobenzaldehyde with a Grignard reagent derived from 1-bromo-2,4,5-trifluorobenzene, followed by oxidation of the resulting benzyl alcohol. This hexafluorobenzophenone was subjected to sequential nucleophilic aromatic substitution reactions, first at one or both of the more reactive 4,4′-fluorines, and second by cyclization through substitution of the less reactive 2,2′-fluorines, using a variety of oxygen, nitrogen, and sulfur nucleophiles, including hydroxide, methoxide, amines, and sulfide. This method yields symmetrical and asymmetrical fluorinated benzophenones, xanthones, acridones, and thioxanthones and provides scalable access to known and novel precursors to fluorinated analogues of fluorescein, rhodamine, and other derivatives. Spectroscopic studies revealed that several of these precursors are highly fluorescent, with tunable absorption and emission spectra, depending on the substituents. This approach should allow access to a wide variety of novel fluorinated fluorophores and related compounds.

A practical approach to access diverse fluorinated fluorophores:



INTRODUCTION

Substitution of hydrogen with fluorine is extensively employed in medicinal chemistry to alter the binding of small molecules to biological targets and modulate metabolic reactivity.[1,2] Fluorination can also alter the photophysical properties of compounds.[3,4] Fluorination of fluorescein (**1**, Figure 1) at the 2′- and 7′-positions yields Oregon Green (**2**),[5] a bright fluorophore with decreased phenol pK_a (4.8 for **2** versus 6.3−6.8[6] for **1**), improving fluorescence in acidic aqueous environments and enhancing photostability. Although a limited number of fluorinated fluorophores have been reported, modification of other dyes[7,8] including Tokyo Green[9] (**3**) to yield Pennsylvania Green (**4**)[10,11] and tetramethylrhodamine (**5**) to yield fluorinated rhodamines (e.g., **6**)[12] can confer beneficial photophysical properties. However, the synthesis and isolation of single isomers of fluorinated fluorophores such as 5-carboxy-Oregon Green[5] is challenging and costly using existing methods.

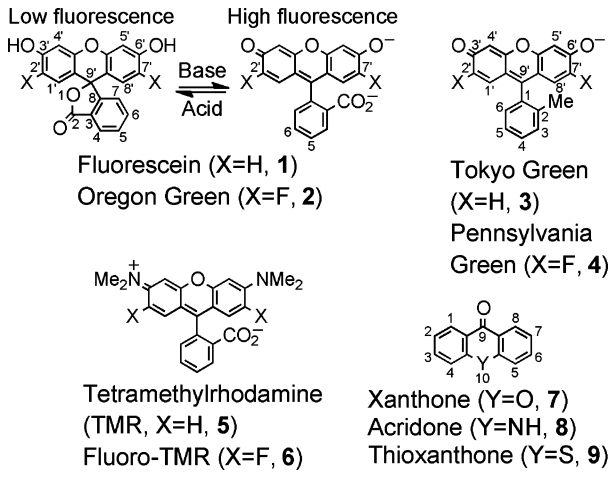


Figure 1. Structures of fluorinated fluorophores and related compounds.

To facilitate access to fluorinated fluorophores, we sought to develop a practical method to synthesize diverse fluorinated xanthone (**7**), acridone (**8**), and thioxanthone (**9**) precursors. Many of these compounds are biologically active,[13−25] some are highly fluorescent,[26] and the addition of Grignard reagents to protected xanthones has been used to prepare 4-carboxy-Tokyo Green,[9] a fluorescent reporter of kinase activity,[27] 4-carboxy-Penn Green,[10] Tokyo Magenta,[28] and other rhodamine and fluorescein analogues.[29−32] Methods for synthesis of derivatives of **7**−**9** have advanced over the past decade,[13,33−41] but only a few reports[27,42−44] describe derivatives with fluorine at the 2- and 7-positions and nitrogen or oxygen at carbons 3 and 6. Because existing syntheses of fluorinated xanthones and similar compounds are lengthy and low yielding, relatively little is known about their cognate photophysical and biological properties.

RESULTS AND DISCUSSION

As shown in Scheme 1, we postulated that repeated S_NAr reactions of the novel benzophenone **10** might allow access to other fluorinated benzophenones (**11** and **12**), as well as xanthones, acridones, and thioxanthones (**13**), as precursors to more highly conjugated fluorophores (**14**).[45] The high selectivity observed for

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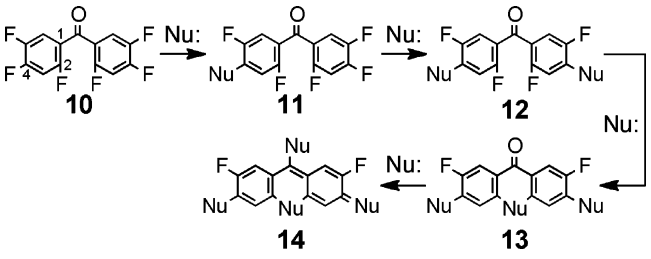
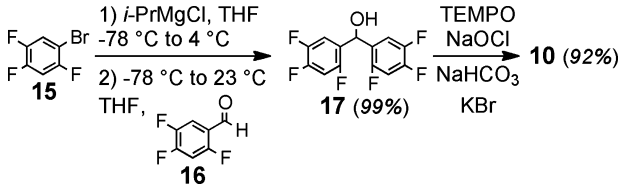
Scheme 1. General Synthesis of Fluorinated Benzophenones, Xanthones, Acridones, Thioxanthones, And Derivatives Involving Iterative Addition of Nucleophiles (Nu:) to Bis(2,4,5-trifluorophenyl)methanone (10)



the sequential addition of multiple nucleophiles to cyanuric chloride[46] and pentafluoropyridine[47] through a similar mechanism offers precedent for this strategy. To evaluate this hypothesis, we synthesized **10** in a two-pot process involving magnesium–halogen exchange of inexpensive 1-bromo-2,4,5-trifluorobenzene (**15**) followed by addition to 2,4,5-trifluorobenzaldehyde (**16**) to generate the alcohol **17** in nearly quantitative yield (Scheme 2).

Scheme 2. Synthesis of Bis(2,4,5-trifluorophenyl)methanone (10)



Oxidation with TEMPO-free radical and sodium hypochlorite[48] produced benzophenone **10** in excellent overall yield. These reactions were scalable, and multiple grams of **10** could be produced in a single run.

Using the strategy outlined in Scheme 1, novel fluorinated benzophenone derivatives (**18**–**29**, shown in Figure 2) were prepared from **10** with a variety of oxygen- and nitrogen-derived nucleophiles in good to excellent yields. As summarized in Table 1, heating of **10** in aqueous KOH/DMSO at 80 °C efficiently substituted both fluorines at the 4,4′-positions with hydroxyl groups to afford **18** (Table 1, entry 1). Sodium methoxide was added to **10** at room temperature in nearly quantitative yield to produce **19** (entry 2).

A wide variety of primary and secondary amines generated similar S_NAr adducts in good to excellent yields (Table 1, entries 3–12). Piperidine and morpholine exhibited particularly high reactivity toward **10**, and dilution was necessary to prevent formation of tri- and tetrasubstituted products. As listed in Table 1, either monosubstituted or disubstituted fluorinated benzophenones derived from ammonia, diethylamine, and piperidine (Table 1, entries 3, 4, 6, 7 10, and 11) were obtained in >70% yield by adjusting reaction concentrations and temperatures, offering additional opportunities for structural diversification.

Symmetrical and asymmetrical xanthones (**30**–**39**) were readily accessed by addition of hydroxide to fluorinated benzophenones using the conditions listed in Table 1. Although previous routes[10,27] to **30**, a valuable precursor for preparation of fluorophores such as Pennsylvania Green, required five to eight steps and achieved only modest overall yields, heating benzophenone **10** with aqueous NaOH either in a sealed tube

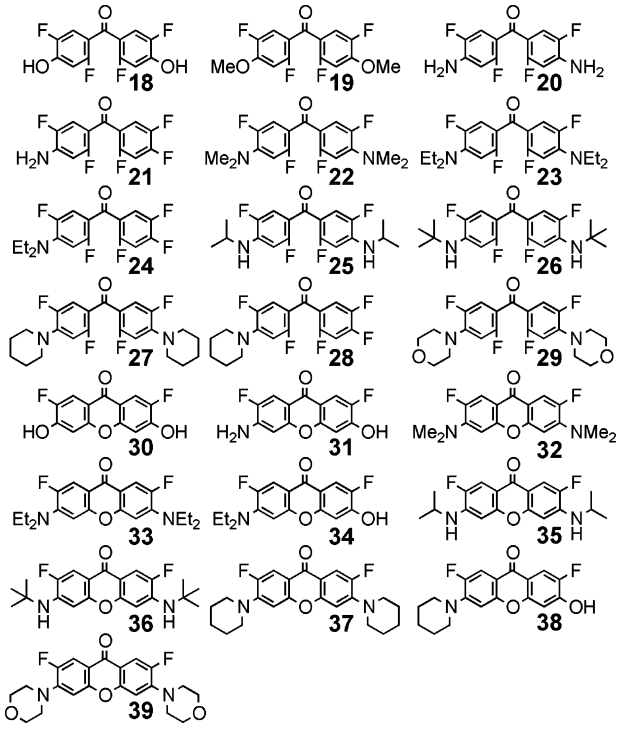


Figure 2. Structures of fluorinated benzophenones and xanthones derived from **10**.

Table 1. Reagents and Conditions for Synthesis of Benzophenones 18–29 and Xanthones 30–39

entry	nucleophile	solvent	temp (°C)	time (h)	yield (%)	product (reactant)
1	KOH	DMSO/H_2O	80	12	92	**18** (**10**)
2	NaOMe	MeOH	26	12	99	**19** (**10**)
3	NH_4OH	DMSO/H_2O	110[c]	12	93	**20** (**10**)
4	NH_4OH	DMSO/H_2O	35	12	75	**21** (**10**)
5	DMF/KOH[a]	H_2O	60	12	78	**22** (**10**)
6	$HNEt_2$	*b*	90[c]	12	85	**23** (**10**)
7	$HNEt_2$	*b*	26	12	70	**24** (**10**)
8	H_2NiPr	*b*	60[c]	3	93	**25** (**10**)
9	H_2NtBu	*b*	46	12	82	**26** (**10**)
10	piperidine	THF	26	12	91	**27** (**10**)
11	piperidine	THF	26	3	76	**28** (**10**)
12	morpholine	THF	26	12	81	**29** (**10**)
13	KOH	H_2O	200[c]	3	99	**30** (**10**)
14	KOH	H_2O	110	48	99	**30** (**10**)
15	KOH	DMSO/H_2O	150[c]	12	80	**31** (**21**)
16	KOH	DMSO/H_2O	150[c]	12	85	**32** (**22**)
17	KOH	DMSO/H_2O	170[c]	12	85	**33** (**23**)
18	KOH	DMSO/H_2O	150[c]	12	95	**34** (**24**)
19	KOH	DMSO/H_2O	150[c]	16	92	**35** (**25**)
20	KOH	DMSO/H_2O	150[c]	12	90	**36** (**26**)
21	KOH	DMSO/H_2O	170[c]	12	92	**37** (**27**)
22	KOH	DMSO/H_2O	150[c]	12	95	**38** (**28**)
23	KOH	DMSO/H_2O	170[c]	12	83	**39** (**29**)

[a]Dimethylamine derives from decomposition of DMF. [b]Reaction was performed neat. [c]Reaction performed in a sealed tube.

at 200 °C for 3 h or at reflux for 48 h provided **30** in nearly quantitative yield (Table 1, entries 13 and 14). This latter method was scalable, and multiple grams of **30** could be prepared. Aminobenzophenones (**20**–**29**) were cleanly converted to

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symmetric and asymmetric xanthones via hydroxide-mediated S_NAr reactions with DMSO as a cosolvent (Table 1, entries 15–23).

Cyclization with amine nucleophiles converted fluorinated benzophenones to fluorinated acridones (**40**–**48**, Figure 3).

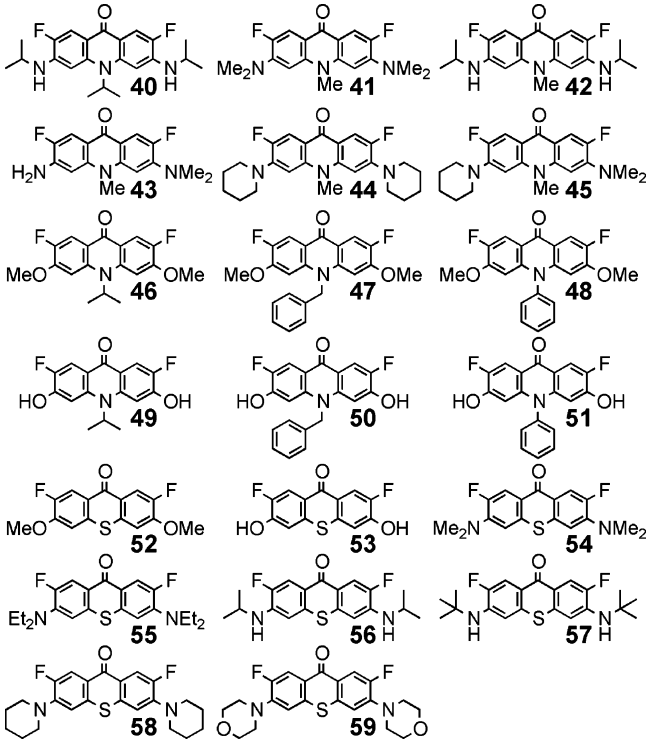

Figure 3. Structures of fluorinated acridones and thioxanthone products.

The conditions for synthesis of **40**–**48** are summarized in Table 2. Heating of **10** in DMF containing KOH provided *N*,*N*-dimethylacridone **41** in 93% yield (Table 2, entry 2). Decomposition of DMF was responsible for generation of the dimethylamine nucleophile. Using the same reaction conditions, acridones **42**–**45** were synthesized from benzophenones **25**, **21**, **27**, and **28** in >90% yield. Dimethoxyacridones **46**, **47**, and **48**, produced by heating **19** with the corresponding amines, required subsequent treatment with NaH or heating in higher-boiling dimethylacetamide for completion. Attempts to demethylate **46**–**48** to generate **49**–**51** with NaSEt or Na_2S cleaved only one of the two methyl groups at 130 °C. Further heating (170 °C) also cleaved the N-linked alkyl group of **46** and **47**. However, reflux with BBr_3 in 1,2-dichloroethane provided **49**–**51** in high yield (Table 2).

To the best of our knowledge, 2,7-difluorinated thioxanthones have not been previously reported. To access these compounds, Na_2S was employed to synthesize **52**–**59** (Figure 3) as summarized in Table 2. By controlling the temperature and concentration of Na_2S, dimethoxybenzophenone **19** was converted into either **52** or **53** (Table 2, entries 13 and 14). Additionally, diaminobenzophenones **22**, **23**, **25**, **26**, **27**, and **29** reacted with Na_2S at 70 °C in greater than 85% yield (Table 2, entries 15–20).

Absorbance (**18**–**59**) and fluorescence emission spectra (**30**–**59**) were acquired on selected compounds. Values for λ_{max}, molar extinction coefficient (ε), determined for compounds with quantum yield (Φ) > 0.2, and Φ relative to

Table 2. Reagents and Conditions for Synthesis of Acridones 40–51 and Thioxanthones 52–59

entry	nucleophile	solvent	temp (°C)	time (h)	yield (%)	product (reactant)
1	H_2NiPr	*b*	100[c]	12	45	**40** (**10**)
2	DMF/KOH[a]	DMF/H_2O	150[c]	6	93	**41** (**10**)
3	DMF/KOH[a]	DMF/H_2O	80	12	95	**42** (**25**)
4	DMF/KOH[a]	DMF/H_2O	150[c]	12	93	**43** (**21**)
5	DMF/KOH[a]	DMF/H_2O	150[c]	4	96	**44** (**27**)
6	DMF/KOH[a]	DMF/H_2O	150[c]	12	91	**45** (**28**)
7	H_2NiPr	*b*	100[c]	12	83	**46** (**19**)
8	H_2NBn	*b*	100	12	86	**47** (**19**)
9	H_2NPh	*b*	130	12	72	**48** (**19**)
10	*d*	$Cl(CH_2)_2Cl$	reflux	12	83	**49** (**46**)
11	*d*	$Cl(CH_2)_2Cl$	reflux	12	91	**50** (**47**)
12	*d*	$Cl(CH_2)_2Cl$	reflux	12	79	**51** (**48**)
13	Na_2S	DMA	26	12	92	**52** (**19**)
14	Na_2S	DMA	90	12	74	**53** (**19**)
15	Na_2S	DMA	70	12	91	**54** (**22**)
16	Na_2S	DMA	70	12	90	**55** (**23**)
17	Na_2S	DMA	70	12	85	**56** (**25**)
18	Na_2S	DMA	70	12	89	**57** (**26**)
19	Na_2S	DMA	70	12	85	**58** (**27**)
20	Na_2S	DMA	70	12	94	**59** (**29**)

[a]Dimethylamine derives from decomposition of DMF. [b]Reaction was performed neat. [c]Reaction performed in a sealed tube. [d]BBr_3 was employed for demethylation.

diphenylanthracene (Φ = 0.95 in EtOH) and anthracene (Φ = 0.27 in EtOH) are listed in Table 3. Absorbance and emission spectra of **30**–**59** are provided in the Supporting Information. Among these compounds, substituents modulated absorbance by up to 77 nm and emission by up to 71 nm, with Stokes shifts of >100 nm in some cases. The ability to readily access multigram quantities of these precursors via iterative S_NAr should have broad utility for the synthesis of diverse fluorinated fluorophores and related molecular probes.

EXPERIMENTAL SECTION

Optical Spectroscopy. Quantum yields (Φ) of the highly emissive compounds **30**, **31**, **35**, **36**, **38**, **40**, and **42** in ethanol were quantified by the method of Williams.[49] Quantum yields for other compounds were determined to be <0.1 by comparison. Diphenylanthracene (Φ = 0.95 in ethanol[50]) and anthracene (Φ = 0.27 in ethanol[51]) were used as standards, and data from these measurements are provided in the Supporting Information. Molar extinction coefficients (ε) of **30**, **31**, **35**, **36**, **38**, **40**, and **42** in ethanol were determined by linear least-squares fitting of Beer's Law plots of absorbance versus concentration, and data from these measurements are provided in the Supporting Information.

Synthesis. In addition to specific methods described below, general procedures A–F were used to access structurally related compounds.

General Procedure A. A mixture of bis(2,4,5-trifluorophenyl)-methanone (**10**, 2.00 g, 6.9 mmol) and the corresponding amine (73.3 mmol) was heated in a sealed tube. The reaction mixture was cooled, and volatiles were removed in vacuo. If impurities were evident, compounds were purified by column chromatography (5% EtOAc in hexanes) to provide viscous oils that typically crystallized when washed with hexanes.

General Procedure B. A mixture of bis(2,4,5-trifluorophenyl)-methanone (**10**, 1.00 g, 3.45 mmol), the corresponding amine (10.1 mmol), and THF (10.0 mL) was stirred for 12 h at 26 °C. The reaction mixture was concentrated in vacuo. If impurities were evident,

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Table 3. Spectral Properties of Compounds in Ethanol (18−51 and 53−59) or DMSO (52) (Values Not Determined Are Indicated by −)

compd	abs λ_{max} (nm)	ε (M^{-1} cm^{-1})	fluorescenc λ_{max} (nm)	Φ
18	306	–	–	–
19	301	–	–	–
20	340	–	–	–
21	335	–	–	–
22	358	–	–	–
23	369	–	–	–
24	361	–	–	–
25	357	–	–	–
26	348	–	–	–
27	354	–	–	–
28	350	–	–	–
29	342	–	–	–
30	369	13300 @ 369 nm	439	0.26
31	366	39200 @ 366 nm	425	0.44
32	378	–	446	<0.1
33	389	–	452	<0.1
34	379	–	438	<0.1
35	370	36200 @ 370 nm	422	0.41
36	368	48600 @ 368 nm	418	0.31
37	369	–	457	<0.1
38	373	15300 @ 373 nm	445	0.23
39	344	–	448	<0.1
40	376	36800 @ 376 nm	423	0.32
41	384	–	441	<0.1
42	377	56700 @ 377 nm	421	0.31
43	369	–	432	<0.1
44	368	–	455	<0.1
45	364	–	443	<0.1
46	383	–	425	<0.1
47	381	–	416	<0.1
48	378	–	424	<0.1
49	379	–	438	<0.1
50	381	–	431	<0.1
51	377	–	454	<0.1
52	316	–	416	<0.1
53	377	–	465	<0.1
54	382	–	477	<0.1
55	393	–	475	<0.1
56	377	–	446	<0.1
57	373	–	432	<0.1
58	377	–	487	<0.1
59	361	–	481	<0.1

compounds were purified by column chromatography (5% EtOAc in hexanes) to give viscous oils that typically crystallized upon standing.

General Procedure C. A mixture of the corresponding diaminoxanthone (**21**−**29**, 1.0 mmol), aqueous KOH (10 M, 1.5 mL, 15.0 mmol), and DMSO (1.5 mL) was heated in a sealed tube. After the time indicated, the reaction mixtures were cooled and transferred to ice water (150 mL). The resulting precipitate was collected by vacuum filtration and washed with water (3 × 100 mL). If impurities were evident, products were purified by washing with an organic solvent or by column chromatography.

General Procedure D. The corresponding benzophenone (**10**, **21**, **25**, **27**, or **28**, 1.0 mmol) was dissolved in a solution of DMF (2.0 mL, 25.9 mmol) and aqueous KOH (10 M, 2.0 mL, 20.0 mmol). This mixture was heated in a sealed tube and at 150 °C for the time indicated, cooled, and transferred to ice water (100 mL). The resulting precipitate was filtered, washed with water (3 × 50 mL), and washed with either diethyl ether or acetone to afford the product.

General Procedure E. The corresponding dimethoxyacridone (**46**−**48**, 0.10 mmol) was dissolved in 1,2-dichloroethane (4.0 mL) and treated with BBr_3 in CH_2Cl_2 (0.57 mL of a 0.7 M solution, 0.40 mmol). The reaction mixture was heated to reflux for 12 h, cooled to room temperature, and quenched with methanol (1.00 mL). The product was concentrated and purified by column chromatography (0−3% MeOH in CH_2Cl_2).

General Procedure F. A solution of diaminoxanthone (**19**, **22**, **23**, **25**−**27**, and **29**, 1.0 mmol) in DMA (5.0 mL) was vigorously purged with Ar for 30 min followed by treatment with finely ground Na_2S (0.375 g, 5.0 mmol). The resulting yellow-orange slurry was heated to 70 °C for 12 h with stirring. The hot reaction mixture was poured into ice-cold water (150 mL), and the precipitate was collected by vacuum filtration. The crude yellow solid was air-dried and further purified by column chromatography or by washing with an organic solvent to give the corresponding thioxanthone.

Bis(2,4,5-trifluorophenyl)methanone (10). To a solution of **17** (400 mg, 1.37 mmol) in CH_2Cl_2 (12 mL) were added KBr (33.2 mg, 0.28 mmol), TEMPO (11.0 mg, 0.07 mmol, 5 mol %), and saturated aqueous $NaHCO_3$. The biphasic mixture was vigorously stirred, and aqueous NaOCl (6.0 mL, 0.7 M) was added. The resulting bright orange mixture was stirred for 3 h, and the orange color dissipated. The colorless biphasic layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 12 mL), and the combined organic fractions were dried over anhydrous Na_2SO_4 and concentrated to give a crude yellow solid. The solid was purified elution through a plug of silica gel (10% EtOAc in hexanes). The filtrate was concentrated to yield **10** as a colorless solid (370 mg, 92%): mp 80−81 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (qd, J = 8.8, 6.4 Hz, 2H), 6.95 (qd, J = 9.2, 6.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.7 (s), 156.8 (dd, J = 254.7, 9.8 Hz), 153.3 (ddd, J = 260.0, 14.5, 12.2 Hz), 147.1 (ddd, J = 248.1, 12.7, 3.1 Hz), 123.2 (d, J = 14.9 Hz), 118.8 (d, J = 20.1 Hz), 111.6−98.1 (m); IR (thin film) 3073, 1667, 1623, 1509, 1437, 1420, 1333, 1293, 1208, 1138, 889 cm^{-1}; HRMS (ESI) m/z 291.0263 ($M + H^+$, $C_{13}H_5F_6O$ requires 291.0245).

Bis(2,4,5-trifluorophenyl)methanol (17). To a solution of 1-bromo-2,4,5-trifluorobenzene (2.34 mL, 20.0 mmol) in THF (30 mL) at −78 °C was added *i*-PrMgCl (1.3 M in Et_2O, 16.1 mL, 21.0 mmol), dropwise. The resulting pale yellow solution was stirred at −78 °C for 10 min, was warmed to 4 °C, and was maintained at 4 °C for 1 h. This solution was cooled again to −78 °C and treated with 2,4,5-trifluorobenzaldehyde (2.55 mL, 22.0 mmol). This mixture was allowed to slowly warm to ambient temperature (23 °C). After stirring at room temperature for 3 h, the reaction mixture was slowly quenched with saturated aqueous NH_4Cl solution (20 mL). The resulting phases were separated, the aqueous fraction was extracted with Et_2O (2 × 30 mL), the combined organic phases were dried over anhydrous Na_2SO_4, and the solution was concentrated to give a crude oil that was purified by flash chromatography (5% EtOAc in hexanes) to provide pure **17** (5.74 g, 99%): mp 81−83 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (qd, J = 10.0, 6.4 Hz, 2H), 6.95 (qd, J = 9.2, 6.4 Hz, 2H), 6.29 (d, J = 3.2 Hz, 1H), 2.46 (d, J = 3.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6 (ddd, J = 246.9, 9.3, 2.8 Hz), 151.5−148.5 (m), 148.4−145.2 (m), 125.4 (d, J = 15.7 Hz), 116.5−114.1 (m), 105.8 (dd, J = 27.4, 21.1 Hz), 62.8 (s); IR (thin film) 3364, 1631, 1513, 1430, 1337, 1200, 1147, 1096 cm^{-1}; HRMS (ESI) m/z 291.0263 (M − H, $C_{13}H_5F_6O$ requires 291.0245).

Bis(2,5-difluoro-4-hydroxyphenyl)methanone (18). A mixture of **10** (3.0 g, 10.3 mmol), aqueous KOH (10 M, 10 mL, 100 mmol), and DMSO (10 mL) was heated to 80 °C for 12 h. This solution was transferred to a mixture of concentrated aqueous HCl (15 mL) and ice (200 g) to generate a fine precipitate that was collected by vacuum filtration. This colorless precipitate was washed with cold water (3 × 100 mL) and dried overnight (16 h) under high vacuum to provide pure **18** (2.71 g, 92%): mp 170−171 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.40 (br s, 2H), 7.45 (dd, J = 10.8, 7.0 Hz, 2H), 6.83 (dd, J = 11.6, 7.0 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 184.7 (s), 157.1 (d, J = 249.8 Hz), 150.6 (t, J = 13.5 Hz), 147.4

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(d, J = 239.6 Hz), 117.4 (dd, J = 15.1, 4.9 Hz), 117.2 (dd, J = 21.5, 3.9 Hz), 104.9 (dd, J = 27.3, 3.0 Hz); IR (film) 3162, 3071, 2964, 1621, 1514, 1303, 1199, 1143, 789 cm^{-1}; HRMS (ESI) m/z 285.0161 (M − H, $C_{13}H_5F_4O_3$ requires 285.0175).

Bis(2,5-difluoro-4-methoxyphenyl)methanone (19). A mixture of **10** (2.00 g, 6.8 mmol) and methanol (28 mL) was treated with NaOMe in methanol (5.4 M, 5.50 mL, 29.6 mmol), dropwise. This mixture was stirred for 12 h, and water (300 mL) was added. A colorless precipitate was collected by vacuum filtration, washed with water (2 × 150 mL), and dried under high vacuum to provide of pure **19** (2.11 g, 99%): mp 158−160 °C; ^{1}H NMR (400 MHz, 10% CD_3OD in $CDCl_3$) δ 7.47 (dd, J = 10.8, 7.0 Hz, 2H), 6.70 (dd, J = 11.2, 7.0 Hz, 2H); ^{13}C NMR (126 MHz, 10% CD_3OD in $CDCl_3$) δ 185.5 (s), 157.9 (d, J = 252.5 Hz), 152.3 (dd, J = 12.8, 10.6 Hz), 148.4 (dd, J = 244.5, 2.2 Hz), 120.4−118.0 (m), 117.1 (dd, J = 21.4, 3.7 Hz), 103.6−99.7 (m), 56.6 (s); IR (film) 3066, 2951, 1663, 1621, 1513, 1346, 1145, 794 cm^{-1}; HRMS (ESI) m/z 337.0474 (M + Na^+, $C_{15}H_{10}F_4O_3Na$ requires 337.0464).

Bis(4-amino-2,5-difluorophenyl)methanone (20). Bis(2,4,5-trifluorophenyl)methanone (**10**, 3.00 g, 10.3 mmol) was dissolved in DMSO (10.0 mL) and treated with concentrated aqueous NH_4OH (10.0 mL, 145 mmol). This mixture was stirred at 110 °C for 12 h (sealed tube), followed by addition to ice water (400 mL). A yellow precipitate was collected by vacuum filtration, washed with water (3 × 150 mL), and dried under high vacuum for 12 h to provide pure **20** (2.73 g 93%): mp 180−182 °C; ^{1}H NMR (400 MHz, 10% CD_3OD in $CDCl_3$) δ 7.22 (dd, J = 11.2, 7.0 Hz, 2H), 6.37 (dd, J = 11.2, 7.0 Hz, 2H); ^{13}C NMR (10% CD_3OD in $CDCl_3$) δ 187.7 (s), 160.1 (d, J = 250.1 Hz), 148.2 (d, J = 236.3 Hz), 142.6 (dd, J = 15.2, 12.7 Hz), 118.0 (dd, J = 21.0, 3.7 Hz), 117.2 (d, J = 13.7 Hz), 104.9−101.4 (m); IR (film) 3343, 3087, 1627, 1599, 1523, 1459, 1362, 1314, 1371, 750 cm^{-1}; HRMS (ESI) m/z 307.0450 (M + Na^+, $C_{13}H_8F_4N_2ONa$ requires 307.0470).

(4-Amino-2,5-difluorophenyl)-(2,4,5-trifluorophenyl)-methanone (21). Bis(2,4,5-trifluorophenyl)methanone (**10**, 1.00 g, 3.43 mmol) in DMSO (2.50 mL) was treated with concentrated aqueous NH_4OH (2.50 mL, 36.3 mmol). This mixture was stirred at 35 °C for 12 h, diluted with ice-cold water (100 mL), and extracted with EtOAc (3 × 50 mL). The combined organic fractions were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a crude yellow oil that was purified by column chromatography (10% to 20% EtOAc in hexanes) to provide pure **21** (0.738 g, 75%): mp 134−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.60 (m, 2H), 7.00 (ddd, J = 15.6, 6.0, 3.6 Hz, 1H), 6.43 (dd, J = 11.6, 6.8 Hz, 2H), 4.45 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.9 (s), 159.4 (d, J = 252.3 Hz), 155.9 (ddt, J = 252.5, 9.9, 2.5 Hz), 152.2 (ddd, J = 257.0, 14.5, 12.2 Hz), 147.0 (d, J = 239.1 Hz), 148.1−145.5 (m), 141.7 (dd, J = 15.2, 12.9 Hz), 127.4−123.0 (m), 119.7−117.0 (m), 116.8 (dd, J = 21.5, 4.0 Hz), 115.1 (dd, J = 13.4, 5.5 Hz), 106.1 (dd, J = 28.3, 21.1 Hz), 102.2 (dd, J = 28.8, 3.5 Hz); IR (film) 3489, 3343, 3218, 1661, 1593, 1511, 1456, 1425, 1331, 1249, 1144, 900, 787 cm^{-1}; HRMS (ESI) m/z 286.0276 (M − H, $C_{13}H_5F_5NO$ requires 286.0291).

Bis(4-(dimethylamino)-2,5-difluorophenyl)methanone (22). Bis(2,4,5-trifluorophenyl)methanone (**10**, 291 mg, 1.00 mmol) was dissolved in DMF (2.00 mL, 25.9 mmol), treated with aqueous KOH (10 M, 2.00 mL, 20.0 mmol), and stirred at 60 °C for 12 h. This mixture was cooled to room temperature (23 °C), transferred to ice water (50 mL), extracted with EtOAc (3 × 20 mL), and the combined organic fractions were washed with water (2 × 30 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by flash chromatography (5−10% EtOAc in hexanes) to provide pure **22** (265 mg, 78%) as a yellow solid: mp 120−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 14.1, 7.0 Hz, 2H), 6.39 (dd, J = 12.8, 7.0 Hz, 2H), 3.01 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.2 (s), 158.2 (d, J = 249.8 Hz), 148.9 (d, J = 240.7 Hz), 144.7 (s), 120.4−116.9 (m), 117.1−115.6 (m), 106.9−99.3 (m), 42.1 (d, J = 6.1 Hz); IR (film) 2954, 2807, 1619, 1526, 1446, 1359, 1121, 782 cm^{-1}; HRMS (ESI) m/z 341.1259 (M + H^+, $C_{17}H_{17}F_4N_2O$ requires 341.1277).

Bis(4-(diethylamino)-2,5-difluorophenyl)methanone (23). Using General Procedure A at 90 °C for 12 h, bis(2,4,5-trifluorophenyl)methanone **10** (1.00 g, 3.45 mmol) and diethylamine (7.0 mL, 71.0 mmol) afforded **23** (1.07 g, 85%): mp 60−62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 12.4, 5.6 Hz, 2H), 6.54 (dd, J = 12.8, 5.6 Hz, 2H), 4.50 (d, J = 3.6 Hz, 2H), 1.46 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.9 (s), 158.4 (d, J = 249.6 Hz), 148.3 (d, J = 239.2 Hz), 142.5 (s), 118.22 (dd, J = 25.9, 5.2 Hz), 116.4−115.5 (m), 102.7 (d, J = 28.7 Hz), 46.0 (d, J = 5.7 Hz), 13.6−12.5 (m); IR (film) 2976, 2934, 1618, 1523, 1443, 1394, 1356, 1279, 1234, 1192, 1077, 779 cm^{-1}; HRMS (ESI) m/z 397.1877 (M + H^+, $C_{21}H_{25}F_4N_2O$ requires 397.1903).

(4-(Diethylamino)-2,5-difluorophenyl)-(2,4,5-trifluorophenyl)-methanone (24). Using General Procedure A at 26 °C for 12 h, bis(2,4,5-trifluorophenyl)methanone (**10**, 2.60 g, 6.90 mmol) and diethylamine (1.02 mL, 10.3 mmol) afforded **24** (1.65 g, 70%) after column chromatography (5−10% EtOAc in hexanes): mp 74−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.50 (m, 2H), 6.96 (ddd, J = 15.7, 6.2, 3.4 Hz, 1H), 6.32 (dd, J = 14.1, 7.2 Hz, 2H), 3.41 (q, J = 6.2 Hz, 2H), 1.23 (t, J = 6.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.3 (s), 162.6−156.0 (m), 155.6 (ddt, J = 252.5, 9.9, 2.5 Hz), 149.4−146.1 (m), 147.9−145.2 (m),146.6 (d, J = 239.1 Hz), 141.4 (dd, J = 15.2, 12.9 Hz), 127.2−122.7 (m), 118.4 (d, J = 4.5 Hz), 116.4 (dd, J = 21.5, 4.0 Hz), 114.9 (dd, J = 13.4, 5.5 Hz), 105.9 (dd, J = 28.4, 21.1 Hz), 103.0−99.5 (m), 46.3 (d, J = 6.3 Hz), 13.1 (d, J = 1.8 Hz); IR (film) 3067, 2980, 2938, 1650, 1607, 1528, 1511, 1424, 1392, 1329, 1280, 1131, 1076, 887, 791 cm^{-1}; HRMS (ESI) m/z 366.0889 (M + Na^+, $C_{17}H_{14}F_5NONa$ requires 366.0893).

Bis(2,5-difluoro-4-(isopropylamino)phenyl)methanone (25). Using General Procedure A, **10** (2.0 g), isopropylamine (6.00 mL, 73.3 mmol), and heating in a sealed tube at 60 °C for 3 h provided pure **25** (2.32 g, 92%): mp 91− 92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J = 12.0, 5.2 Hz, 2H), 6.30 (dd, J = 12.4, 5.6 Hz, 2H), 4.32 (d, J = 5.2 Hz, 2H), 3.66 (hept, J = 6.8 Hz, 2H), 1.30 (s, J = 6.4 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.4 (s), 159.2 (d, J = 249.5 Hz), 146.7 (d, J = 235.7 Hz), 140.9 (dd, J = 14.0, 12.2 Hz), 115.7 (dd, J = 21.7, 4.8 Hz), 114.8−113.2 (m), 98.4−96.9 (m), 44.2 (s), 22.6 (s); IR (film) 3433, 3366, 2972, 2934, 1625, 1607, 1534, 1456, 1368, 1280, 1156, 907, 727 cm^{-1}; HRMS (ESI) m/z 391.1402 (M + Na^+, $C_{19}H_{20}F_4N_2ONa$ requires 391.1409).

Bis(4-(*tert*-butylamino)-2,5-difluorophenyl)methanone (26). Using General Procedure A, **10** (500 mg, 1.72 mmol), *t*-butylamine (7.00 mL, 71.0 mmol), and heating at 46 °C for 12 h afforded **26** (560 mg, 82%): mp 135−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 12.4, 5.6 Hz, 2H), 6.54 (dd, J = 12.8, 5.6 Hz, 2H), 4.50 (d, J = 3.6 Hz, 2H), 1.46 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.3 (s), 157.5 (d, J = 249.0 Hz), 146.2 (d, J = 235.6 Hz), 139.2 (s), 114.2 (d, J = 4.5 Hz), 113.4−112.4 (m), 99.5−97.6 (m), 50.3 (s), 28.3 (s); IR (film) 3436, 2979, 1626, 1534, 1462, 1371, 1288, 1211, 796 cm^{-1}; HRMS (ESI) m/z 397.1877 (M + H^+, $C_{21}H_{25}F_4N_2O$ requires 397.1903).

Bis(2,5-difluoro-4-(piperidin-1-yl)phenyl)methanone (27). Using General Procedure B, **10** (1.00 g, 3.45 mmol), piperidine (1.0 mL, 10.1 mmol), and THF (6.00 mL), and a reaction time of 12 h afforded **27** (1.28 g, 91%): mp 141−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, J = 13.3, 6.4 Hz, 2H), 6.53 (dd, J = 12.4, 5.5 Hz, 2H), 3.17 (t, J = 5.2 Hz, 8H), 1.72 (p, J = 5.7 Hz, 8H), 1.61 (p, J = 5.4 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.6 (s), 158.0 (d, J = 251.1 Hz), 150.4 (dd, J = 242.6, 1.6 Hz), 145.7 (s), 119.5−117.9 (m), 118.3−116.5 (m), 105.1 (s), 51.0 (d, J = 5.0 Hz), 25.8 (s), 24.1 (s); IR (film) 2937, 2854, 2821, 1614, 1508, 1437, 1385, 1255, 1164, 1123, 782 cm^{-1}; HRMS (ESI) m/z 421.1877 (M + H^+, $C_{23}H_{25}F_4N_2O$ requires 421.1903).

(2,5-Difluoro-4-(piperidin-1-yl)phenyl)(2,4,5-trifluorophenyl)-methanone (28). Using General Procedure B, **10** (640 mg, 2.20 mmol), piperidine (0.24 mL, 2.40 mmol), THF (10 mL), and a reaction time of 3 h afforded **28** (600 mg, 76%): mp 71−73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.52 (m, 2H), 6.96 (ddd, J = 15.7, 6.1, 3.5 Hz, 1H), 6.50 (dd, J = 13.1, 7.0 Hz, 1H), 3.24 (t, J = 5.2 Hz, 4H), 1.71 (p, J = 5.4 Hz, 8H), 1.65 (p, J = 5.2 Hz, 4H); ^{13}C NMR

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(125 MHz, $CDCl_3$) δ 184.8 (s), 159.0 (d, J = 315.0 Hz), 154.2 (dd, J = 163.8, 12.5 Hz), 150.3 (dd, J = 312.5, 12.3 Hz), 149.5 (d, J = 225.3 Hz), 146.9 (dd, J = 325.3, 9.8 Hz), 146.5−146.8 (m), 122.2−122.7 (m), 118.3 (d, J = 23.7 Hz), 117.4 (dd, J = 31.6, 5.1 Hz), 116.0−116.5 (m), 106.1 (dd, J = 35.5, 26.4 Hz), 104.9 (dd, J = 35.3, 5.0 Hz), 50.8 (s), 25.7 (s), 24.1 (s); IR (film) 3070, 2940, 2856, 1665, 1614, 1509, 1438, 1256, 1126, 878, 758 cm^{-1}; HRMS (ESI) m/z 356.1067 ($M + H^+$, $C_{18}H_{15}F_5NO$ requires 356.1074).

Bis(2,5-difluoro-4-morpholinophenyl)methanone (29). Using General Procedure B, **10** (1.00 g, 3.45 mmol), morpholine (0.75 mL, 8.62 mmol), THF (8 mL), and a reaction time of 12 h afforded **29** (1.18 g, 81%): mp 189−191 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, J = 6.7, 5.6 Hz, 2H), 6.54 (dd, J = 12.0, 5.2 Hz, 2H), 3.86 (t, J = 4.6 Hz, 8H), 3.21 (t, J = 4.6 Hz, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.3 (s), 158.0 (d, J = 314.7 Hz), 150.5 (d, J = 305.0 Hz), 144.7 (d, J = 12.1 Hz), 119.2−119.8 (m), 117.7 (d, J = 30.6 Hz), 105.1 (d, J = 34.4 Hz), 66.6 (s), 49.9 (s); IR (film) 2960, 2916, 2861, 1620, 1509, 1267, 1170, 1115, 782 cm^{-1}; HRMS (ESI) m/z 447.1300 ($M + Na^+$, $C_{21}H_{20}F_4N_2O_3Na$ requires 447.1308).

2,7-Difluoro-3,6-dihydroxyxanthen-9-one (30). A mixture of **10** (4.46 g, 15.4 mmol) and aqueous KOH (10 M, 30 mL, 0.300 mol) was heated to reflux for 48 h. During this time, **10** slowly dissolved to give a bright yellow-orange solution. This hot solution was poured onto acidic ice (20 mL of 12 M HCl and 200 g of ice) and was allowed to stand for 3 h. The resulting colorless slurry was filtered via vacuum, and the filtrate was washed with cool water (3 × 100 mL), ethanol (2 × 50 mL), and dried under high vacuum to yield pure colorless difluoroxanthone **30** (3.91 g, 96%). Xanthone **30** had spectral properties identical to those previously reported.[27]

3-Amino-2,7-difluoro-6-hydroxy-9*H*-xanthen-9-one (31). Using General Procedure C, **21** (1.17 g, 4.07 mmol), and heating at 150 °C for 12 h afforded **31** (726 mg, 80%): mp 247−250 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 7.69 (d, J = 10.9 Hz, 1H), 7.56 (d, J = 11.3 Hz, 1H), 7.04 (d, J = 7.0 Hz, 1H), 6.67 (d, J = 7.2 Hz, 1H), 6.55 (s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.7 (s), 154.0 (s), 152.8 (s), 151.3 (d, J = 14.8 Hz), 149.2 (d, J = 85.9 Hz), 147.2 (d, J = 83.7 Hz), 144.1 (d, J = 15.9 Hz), 112.8 (d, J = 5.5 Hz), 110.9 (d, J = 19.9 Hz), 109.7 (d, J = 19.8 Hz), 109.0−108.2 (m), 104.7 (d, J = 2.5 Hz), 100.1 (d, J = 4.5 Hz); IR (film) 3369, 3221, 2986, 1614, 1481, 1288, 773 cm^{-1}; HRMS (ESI) m/z 262.0291 (M − H, $C_{13}H_6F_2NO_3$ requires 262.0316).

3,6-Bis(dimethylamino)-2,7-difluoro-9*H*-xanthen-9-one (32). Using General Procedure C, **22** (2.00 g, 5.05 mmol), and heating to 150 °C for 12 h afforded **32** (1.61 g, 85%): mp 211−213 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 7.59 (d, J = 14.0 Hz, 2H), 6.76 (d, J = 7.6 Hz, 2H), 3.03 (s, 12H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.4 (s), 153.2 (s), 150.7 (s), 149.5−144.7 (m), 111.4 (d, J = 6.7 Hz), 110.8 (d, J = 23.7 Hz), 103.1 (d, J = 4.1 Hz), 41.8 (d, J = 6.0 Hz); IR (film) 3450, 2922, 2850, 2798, 1615, 15221, 1447, 1371, 1332, 1257, 1132, 777 cm^{-1}; HRMS (ESI) m/z 341.1087 ($M + Na^+$, $C_{17}H_{16}F_2N_2O_2Na$ requires 341.1078).

3,6-Bis(diethylamino)-2,7-difluoro-9*H*-xanthen-9-one (33). Using General Procedure C, **23** (1.50 g, 3.78 mmol), and heating at 170 °C for 12 h afforded **33** (1.20 g, 85%): mp 108−109 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 14.4 Hz, 2H), 6.31 (d, J = 7.3 Hz, 2H), 3.42 (q, J = 7.0 Hz, 8H), 1.23 (t, J = 7.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0 (s), 152.9 (s), 148.9 (d, J = 219.2 Hz), 142.5 (d, J = 10.5 Hz), 111.1(d, J = 24.9 Hz), 110.8 (d, J = 7.1 Hz), 101.5 (s), 45.1 (d, J = 5.9 Hz), 11.9 (d, J = 1.5 Hz); IR (film) 2976, 2934, 1615, 1519, 1457, 1274, 1246, 1071, 773 cm^{-1}; HRMS (ESI) m/z 375.1857 ($M + H^+$, $C_{21}H_{25}F_2N_2O_2$ requires 375.1884).

3-(Diethylamino)-2,7-difluoro-6-hydroxy-9*H*-xanthen-9-one (34). Using General Procedure C, **24** (1.00 g, 2.92 mmol), and heating at 150 °C for 12 h afforded **34** (884 mg, 95%): mp 299−300 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.41 (br s, 1 H), 7.71 (d, J = 10.8 Hz, 1H), 7.59 (d, J = 12.8 Hz, 1H), 7.00 (d, J = 7.0 Hz, 1H), 6.80 (d, J = 7.3 Hz, 1H), 3.43 (q, J = 6.5 Hz, 4H), 1.17 (t, J = 6.5 Hz, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.6 (s), 153.6 (s), 152.9 (s), 151.6 (s), 151.5 (s), 149.9 (d, J = 84.3 Hz), 148.0 (d, J = 84.6 Hz), 143.3 (d, J = 10.1 Hz), 112.8 (d, J = 5.4 Hz), 111.8−110.31 (m), 110.3 (s), 104.6 (d, J = 2.6 Hz), 102.4 (s), 45.7 (d, J = 5.9 Hz), 12.8 (s); IR (film) 3069, 2975, 2733, 1618, 1578, 1475, 1398, 1275, 1213, 1080, 775 cm^{-1}; HRMS (ESI) m/z 318.0916 (M − H, $C_{17}H_{14}F_2NO_3$ requires 318.0942).

2,7-Difluoro-3,6-bis(isopropylamino)-9*H*-xanthen-9-one (35). Using General Procedure C, **25** (2.50 g, 6.79 mmol), and heating at 150 °C for 16 h afforded **35** (2.15 g, 92%): mp 238−239 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 7.54 (d, J = 12.0 Hz, 2H), 6.64 (d, J = 7.2 Hz, 2H), 6.45 (dd, J = 2, 8.0 Hz, 2H), 3.76 (hept, J = 6.4 Hz, 2H), 1.22 (d, J = 6.4 Hz, 12H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.3 (s), 154.2 (s), 147.7 (d, J = 129.2 Hz), 142.0 (s), 141.8 (s), 110.8−106.0 (m), 96.9 (d, J = 3.8 Hz), 43.5 (s), 21.7 (s); IR (film) 3435, 2392, 3968, 2837, 1645, 1610, 1531, 1461, 1296, 1016 cm^{-1}; HRMS (ESI) m/z 347.1592 ($M + H^+$, $C_{19}H_{21}F_2N_2O_2$ requires 347.1571).

3,6-Bis(*tert*-butylamino)-2,7-difluoro-9*H*-xanthen-9-one (36). Using General Procedure C, **26** (1.00 g, 2.52 mmol), and heating at 150 °C for 12 h afforded **36** (848 mg, 90%): mp 289−291 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 12.0 Hz, 2H), 6.75 (d, J = 6.7 Hz, 2H), 4.60 (d, J = 4.9 Hz, 2H), 1.48 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3 (s), 154.1 (s), 148.8 (d, J = 239.0 Hz), 140.8 (d, J = 13.0 Hz), 110.1 (d, J = 6.7 Hz), 109.4 (d, J = 21.7 Hz), 99.1 (d, J = 2.2 Hz), 51.4 (s), 29.2 (s); IR (film) 3451, 2972, 1623, 1527, 1491, 1294, 1217, 887, 821 cm^{-1}; HRMS (ESI) m/z 375.1897 ($M + H^+$, $C_{21}H_{25}F_2N_2O_2$ requires 375.1884).

2,7-Difluoro-3,6-di(piperidin-1-yl)-9*H*-xanthen-9-one (37). Using General Procedure C, **27** (840 mg, 2.00 mmol), and heating to 170 °C for 12 h afforded **37** (733 mg, 92%): mp 200−201 °C; ^1H NMR (400 MHz, 10% CD_3OD in $CDCl_3$) δ 7.45 (d, J = 13.2 Hz, 2H), 6.58 (d, J = 6.8 Hz, 2H), 2.99 (t, J = 4.8 Hz, 8H), 1.49 (p, J = 4.8 Hz, 8H), 1.41 (hept, J = 4.8 Hz, 4H); ^{13}C NMR (125 MHz, 10% CD_3OD in $CDCl_3$) δ 175.2 (s), 153.9 (s), 151.9 (d, J = 252.0 Hz), 147.3 (d, J = 10.1 Hz), 113.5 (d, J = 6.3 Hz), 111.0 (d, J = 23.9 Hz), 105.4 (d, J = 3.8 Hz), 51.1 (d, J = 5.0 Hz), 25.6 (s), 24.0 (s); IR (film) 2931, 1619, 1461, 1234, 1130, 776 cm^{-1}; HRMS (ESI) m/z 421.1714 ($M + Na^+$, $C_{23}H_{24}F_2N_2O_2Na$ requires 421.1704).

2,7-Difluoro-3-hydroxy-6-(piperidin-1-yl)-9*H*-xanthen-9-one (38). Using General Procedure C, **28** (710 mg, 2.01 mmol), and heating at 150 °C for 12 h afforded **38** (630 mg, 95%): mp 230−231 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.48 (s, 2H), 7.73 (d, J = 10.8 Hz, 1H), 7.64 (d, J = 13.3 Hz, 1H), 7.03 (d, J = 6.9 Hz, 1H), 7.01 (d, J = 6.9 Hz, 1H), 3.21 (t, J = 5.4 Hz, 1H), 1.65 (p, J = 5.2 Hz, 1H), 1.58 (p, J = 5.4 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.9 (s), 152.6 (d, J = 161.3 Hz), 155.0 (d, J = 155.0 Hz), 152.1 (s), 150.1 (s), 149.7 (s), 147.7 (s), 146.5 (d, J = 10.1 Hz), 113.1−112.5 (m), 111.0 (d, J = 20.2 Hz), 110.7 (d, J = 23.5 Hz), 105.9 (s), 104.6 (s), 50.5 (d, J = 5.0 Hz), 25.3 (s), 23.6 (s); IR (film) 3126, 2936, 1625, 1587, 1484, 1296, 1090, 832, 778 cm^{-1}; HRMS (ESI) m/z 330.0925 (M − H, $C_{18}H_{14}F_2NO_3$ requires 330.0942).

2,7-Difluoro-3,6-dimorpholino-9*H*-xanthen-9-one (39). Using General Procedure C, **29** (1.00 g, 2.36 mmol), and heating at 170 °C for 12 h afforded **39** (787 mg, 83%): mp 236−237 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 13.0 Hz, 2H), 6.80 (d, J = 6.8 Hz, 2H), 3.90 (t, J = 5.0 Hz, 8H), 3.26 (t, J = 5.0 Hz, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4 (s), 153.6 (s), 151.9 (d, J = 245.9 Hz), 146.1 (d, J = 10.6 Hz), 114.9 (d, J = 7.2 Hz), 112.0 (d, J = 23.5 Hz), 105.5 (d, J = 3.0 Hz), 66.6 (s), 50.1 (d, J = 4.8 Hz); IR (film) 2921, 2863, 1619, 1473, 1259, 1198, 1123, 1030, 900, 777 cm^{-1}; HRMS (ESI) m/z 403.1490 ($M + H^+$, $C_{21}H_{21}F_2N_2O_4$ requires 403.1469).

2,7-Difluoro-10-isopropyl-3,6-bis(isopropylamino)acridin-9-(10*H*)-one (40). Bis(2,4,5-trifluorophenyl)methanone **10** (291 mg, 1.00 mmol) was dissolved in isopropylamine (3.00 mL, 36.7 mmol) and transferred to a sealed tube. The reaction was stirred at 100 °C for 12 h, and all volatiles were removed under reduced pressure. The residual oil was purified by flash chromatography to yield **40** (170 mg, 45%) as a white solid: mp 160−162 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 12.0 Hz, 2H), 6.56 (d, J = 8.0 Hz, 2H), 5.01 (hept, J = 7.0 Hz, 1H), 4.34 (br s, 2H), 3.75 (hept, J = 5.92 Hz, 2H), 1.75 (d, J = 7.0 Hz, 6H), 1.33 (d, J = 7.0 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$)

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δ 173.9 (s), 146.5 (d, J = 238.3 Hz), 140.1 (s), 138.9 (d, J = 13.7 Hz), 112.4 (d, J = 5.8 Hz), 109.7 (d, J = 19.5 Hz), 95.4 (s), 50.8 (s), 43.0 (s), 21.6 (s), 20.5 (s); IR (film) 3437, 3304, 2970, 2934, 1622, 1599, 1498, 1281 cm^{-1}; HRMS (ESI) m/z 388.2204 (M + H^+, $C_{22}H_{28}F_2N_3O$ requires 388.2200).

3,6-Bis(dimethylamino)-2,7-difluoro-10-methylacridin-9-(10*H*)-one (41). Using General Procedure D, **10** (291 mg, 1.00 mmol), a reaction time of 6 h, purification by washing with acetone, and removal of solvent in vacuo afforded **41** (307 mg, 93%): mp 200−203 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 14.2 Hz, 2H), 6.51 (d, J = 6.5 Hz, 2H), 3.73 (s, 3H), 3.06 (s, 12H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.8 (s), 149.3 (d, J = 241.6 Hz), 144.9 (d, J = 10.3 Hz), 140.4 (s), 113.5 (s), 111.3 (d, J = 22.3 Hz), 102.2 (d, J = 3.3 Hz), 42.0 (d, J = 5.5 Hz), 34.2 (s); IR (film) 2916, 1602, 1329, 1267, 750 cm^{-1}; HRMS (ESI) m/z 332.1548 (M + H^+, $C_{18}H_{20}F_2N_3O$ requires 332.1574).

2,7-Difluoro-3,6-bis(isopropylamino)-10-methylacridin-9-(10*H*)-one (42). Using General Procedure D, **25** (1.70 g, 4.62 mmol), heating to 80 °C for 12 h, and purification by washing with ether and removal of solvent in vacuo afforded **42** (1.58 g, 95%) mp 232−233 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 12.2 Hz, 2H), 6.33 (d, J = 6.8 Hz, 2H), 4.33 (d, J = 4.0 Hz, 2H), 3.73 (hept, J = 6.6 Hz, 2H), 3.69 (s, 3H), 1.31 (d, J = 6.3 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.5 (s), 146.9 (d, J = 244.4 Hz), 141.3 (s), 140.8 (d, J = 13.9 Hz), 110.4 (d, J = 5.1 Hz), 109.3 (d, J = 18.9 Hz), 94.9 (d, J = 3.1 Hz), 43.1 (s), 34.3 (s), 21.9 (s); IR (film) 3405, 3302, 2970, 1623, 1596, 1505, 1284, 1034, 800 cm^{-1}; HRMS (ESI) m/z 360.1866 (M + H^+, $C_{20}H_{24}F_2N_3O$ requires 360.1887).

3-Amino-6-(dimethylamino)-2,7-difluoro-10-methylacridin-9(10*H*)-one (43). Using General Procedure D, **21** (300 mg, 1.05 mmol), a reaction time of 12 h, and purification by washing with ether and removal of solvent in vacuo afforded **43** (295 mg, 93%): mp 263−264 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, J = 14.3 Hz, 1H), 7.71 (d, J = 11.7 Hz, 1H), 6.89 (d, J = 7.4 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.24 (s, 2H), 3.75 (s, 3H), 3.03 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.3 (s), 149.8 (d, J = 200.6 Hz), 147.4 (d, J = 250.7 Hz), 145.1 (d, J = 10.3 Hz), 143.3 (s), 143.1 (s), 141.5 (s), 140.5 (s), 113.9 (d, J = 6.3 Hz), 111.8 (d, J = 22.3 Hz), 110.6 (d, J = 18.6 Hz), 102.5 (d, J = 3.3 Hz), 99.0 (d, J = 3.9 Hz), 42.5 (s), 34.4 (s); IR (film) 3322, 3176, 1619, 1493, 1309, 1256, 1026, 902, 777 cm^{-1}; HRMS (ESI) m/z 304.1260 (M + H^+, $C_{16}H_{16}F_2N_3O$ requires 304.1261).

2,7-Difluoro-10-methyl-3,6-di(piperidin-1-yl)acridin-9(10*H*)-one (44). Using General Procedure D, **27** (1.50 g, 3.58 mmol), a reaction time of 4 h, and purification by washing the product with ether and removal of solvent in vacuo afforded **44** (1.37 g, 93%): mp 243−244 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 12.1 Hz, 2H), 6.69 (d, J = 6.9 Hz, 2H), 3.74 (s, 3H), 3.21 (t, J = 5.2 Hz, 8H), 1.79 (p, J = 5.2 Hz, 8H), 1.64 (hept, J = 5.2 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9 (s), 151.1 (d, J = 245.7 Hz), 146.5 (d, J = 10.4 Hz), 140.3 (s), 115.9 (d, J = 6.7 Hz), 112.6 (d, J = 22.5 Hz), 102.9 (d, J = 2.7 Hz), 51.5 (d, J = 4.5 Hz), 34.2 (s), 26.0 (s), 24.2 (s); IR (film) 2938, 2846, 1624, 1597, 1494, 1274, 1225, 1145, 783 cm^{-1}; HRMS (ESI) m/z 412.2196 (M + H^+, $C_{24}H_{28}F_2N_3O$ requires 412.2200).

3-(Dimethylamino)-2,7-difluoro-10-methyl-6-(piperidin-1-yl)-acridin-9(10*H*)-one (45). Using General Procedure D, **28** (355 mg, 1.00 mmol), a reaction time of 12 h, and purification by washing with ether and removal of solvent in vacuo afforded **45** (338 mg, 91%): mp 227−229 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 12.6 Hz, 1H), 7.96 (d, J = 14.2 Hz, 1H), 6.65 (d, J = 6.9 Hz, 1H), 6.43 (d, J = 7.2 Hz, 1H), 3.67 (s, 3H), 3.19 (t, J = 5.2 Hz, 4H), 3.05 (s, 6H), 1.78 (p, J = 5.4 Hz, 4H), 1.65 (p, J = 5.4 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.6 (s), 151.3 (d, J = 138.6 Hz), 149.5 (d, J = 127.8 Hz), 146.1 (d, J = 10.4 Hz), 145.5 (d, J = 10.0 Hz), 141.1 (s), 141.0 (s), 115.5 (s), 114.2 (s), 111.9 (d, J = 22.5 Hz), 111.7 (d, J = 22.6 Hz), 104.7 (d, J = 2.6 Hz), 102.4 (d, J = 3.4 Hz), 51.5 (d, J = 4.7 Hz), 42.5 (d, J = 5.8 Hz), 34.7 (s), 26.0 (s), 24.2 (s); IR (film) 2836, 1626, 1601, 1503, 1280, 1011, 895 cm^{-1}; HRMS (ESI) m/z 372.1889 (M + H^+, $C_{21}H_{24}F_2N_3O$ requires 372.1887).

2,7-Difluoro-10-isopropyl-3,6-dimethoxyacridin-9(10*H*)-one (46). A solution of **19** (100 mg, 0.32 mmol) in isopropylamine (3.00 mL, 36.6 mmol) was heated to 100 °C in a sealed tube for 12 h. This mixture was cooled and residual isopropylamine removed in vacuo. The resulting crude yellow oil was dissolved in THF (7.00 mL), treated with NaH (60%, 77.0 mg, 1.92 mmol), and heated to 60 °C for 12 h. The reaction mixture was cooled in an ice bath and carefully neutralized with saturated aqueous $NaHCO_3$ (20 mL). Extraction with THF (3 × 20 mL), drying of the combined organic fractions over anhydrous Na_2SO_4, and removal of solvent in vacuo provided a crude yellow oil that was purified by column chromatography (CH_2Cl_2) to provide dimethoxyacridone **46** (88.4 mg, 83%): mp 158−159 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 11.2 Hz, 2H), 7.04 (d, J = 6.8 Hz, 2H), 5.09 (p, J = 7.2 Hz, 1H), 4.06 (s, 6H), 1.83 (d, J = 7.2 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3 (s), 152.1 (d, J = 12.9 Hz), 148.5 (d, J = 245.9 Hz), 140.2 (s), 117.0 (d, J = 5.4 Hz), 112.8 (d, J = 18.9 Hz), 100.1 (s), 56.4 (s), 52.4 (s), 21.4 (s); IR (film) 2924, 2851, 1736, 1626, 1603, 1488, 1263, 1091, 796 cm^{-1}; HRMS (ESI) m/z 334.1255 (M + H^+, $C_{18}H_{18}F_2NO_3$ requires 334.1255).

10-Benzyl-2,7-difluoro-3,6-dimethoxyacridin-9(10*H*)-one (47). A solution of **19** (1.50 g, 4.78 mmol) in benzylamine (8.00 mL, 73.3 mmol) was heated to 100 °C for 12 h. This mixture was cooled and residual benzylamine removed by vacuum distillation (36 °C, 1 mmHg). The resulting crude yellow oil was dissolved in THF (30 mL), treated with NaH (60%, 574 mg, 14.4 mmol), and heated to 60 °C for 12 h. The reaction mixture was cooled in an ice bath and carefully neutralized with saturated aqueous $NaHCO_3$ (20 mL). The resulting biphasic mixture was extracted with THF (3 × 20 mL), and the combined organic fractions were dried over anhydrous Na_2SO_4 and concentrated to give a crude yellow oil that was purified by column chromatography (CH_2Cl_2) to provide dimethoxyacridone **47** (1.56 g, 86%): mp 205−206 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 11.2 Hz, 2H), 7.45−7.30 (m, 3H), 7.22 (d, J = 6.8 Hz, 2H), 6.93 (d, J = 6.8 Hz, 2H), 5.70 (s, 2H), 4.82 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9 (s), 153.0 (d, J = 13.0 Hz), 148.7 (d, J = 246.0 Hz), 140.1 (s), 135.1 (s), 129.5 (s), 128.22 (s), 125.6 (s), 115.6 (d, J = 5.4 Hz), 112.5 (d, J = 19.1 Hz), 98.5 (s), 56.21 (s), 51.6 (s); IR (film) 2989, 2938, 1607, 1498, 1273, 1042 cm^{-1}; HRMS (ESI) m/z 382.1278 (M + H^+, $C_{22}H_{18}F_2NO_3$ requires 382.1255).

2,7-Difluoro-3,6-dimethoxy-10-phenylacridin-9(10*H*)-one (48). A solution of **19** (100 mg, 0.320 mmol) in aniline (2.00 mL, 21.9 mmol) was heated to 130 °C for 12 h in a sealed tube. The reaction mixture was cooled, and the residual aniline was removed by vacuum distillation (40 °C, 1 mmHg). The resulting crude yellow oil was dissolved in DMA (3.5 mL) and heated at 170 °C for 12 h. The reaction mixture was cooled, diluted with water (30 mL), and extracted with THF (3 × 20 mL). The combined organic fractions were dried over anhydrous Na_2SO_4 and concentrated to give a crude yellow oil that was purified by column chromatography (CH_2Cl_2) to provide dimethoxyacridone **48** (84.5 mg, 72%): mp 256−257 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, J = 11.6 Hz, 2H), 7.74−7.87 (m, 3H), 7.59 (d, J = 7.2 Hz, 2H), 6.17 (d, J = 7.2 Hz, 2H), 3.62 (s, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.5 (s), 151.8 (d, J = 13.1 Hz), 148.0 (d, J = 244.2 Hz), 140.7 (s), 138.0 (s), 131.4 (s), 130.3 (s), 129.6 (s), 113.9 (d, J = 5.1 Hz), 111.0 (d, J = 18.7 Hz), 100.1 (s), 55.8 (s); IR (film) 3057, 2939, 1612, 1580, 1479, 1306, 1256, 1084, 823, 701 cm^{-1}; HRMS (ESI) m/z 368.1098 (M + H^+, $C_{21}H_{16}F_2NO_3$ requires 368.1098).

2,7-Difluoro-3,6-dihydroxy-10-isopropylacridin-9(10*H*)-one (49). Using General Procedure E, **46** (20.0 mg, 0.0601 mmol) afforded dihydroxylacridone **49** (15.2 mg, 83%): mp 172−173 °C; ^1H NMR (400 MHz, CD_3OD) δ 7.95 (d, J = 11.6 Hz, 2H), 7.29 (d, J = 7.2 Hz, 2H), 5.18 (p, J = 7.2 Hz, 2H), 1.75 (d, J = 7.2 Hz, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 177.2 (s), 152.4 (d, J = 15.4 Hz), 149.6 (d, J = 242.1 Hz), 142.1 (s), 116.7 (d, J = 5.1 Hz), 112.8 (d, J = 19.2 Hz), 105.2 (s), 53.6 (s), 20.9 (s); IR (film) 3357, 3075, 2977, 1701, 1627, 1542, 1490, 1448, 1406, 1277, 1199, 889, 770 cm^{-1}; HRMS (ESI) m/z 304.0765 (M − H, $C_{16}H_{12}F_2NO_3$ requires 304.0785).

10-Benzyl-2,7-difluoro-3,6-dihydroxyacridin-9(10*H*)-one (50). Using General Procedure E, **47** (20.0 mg, 0.0526 mmol)

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afforded dihydroxyacridone **50** (17.0 mg, 91%): mp 247−249 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 11.2 Hz, 2H), 7.25−7.45 (m, 3H), 7.18 (d, J = 7.2 Hz, 2H), 6.97 (d, J = 7.2 Hz, 2H), 5.53 (s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.6 (s), 151.2 (s), 147.8 (d, J = 241.4 Hz), 140.3 (s), 135.6 (s), 129.0 (s), 127.4 (s), 125.7 (s), 113.8 (s), 111.6 (d, J = 18.9 Hz), 102.8 (s), 50.3 (s); IR (film) 3369, 3050, 3007, 1629, 1574, 1490, 1276, 750 cm^{-1}; HRMS (ESI) m/z 352.0776 (M − H, $C_{20}H_{12}F_2NO_3$ requires 352.0785).

2,7-Difluoro-3,6-dihydroxy-10-phenylacridin-9(10*H*)-one (51). Using General Procedure E, **48** (20.0 mg, 0.0545 mmol) afforded dihydroxylacridone **51** (14.6 mg, 79%): mp 257−259 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (d, J = 11.2 Hz, 2H), 7.75−7.90 (m, 3H), 7.49 (d, J = 6.8 Hz, 2H), 6.36 (d, J = 7.2 Hz, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 174.4 (s), 154.1 (d, J = 15.5 Hz), 150.7 (d, J = 245.7 Hz), 143.3 (s), 140.1 (s), 132.6 (s), 131.6 (s), 130.6 (s), 113.6 (d, J = 6.2 Hz), 112.0 (d, J = 20.4 Hz), 104.8 (d, J = 2.4 Hz); IR (film) 3369, 3064, 2924, 1727, 1624, 1547, 1489, 1395, 1268, 1193, 893 cm^{-1}; HRMS (ESI) m/z 338.0609 (M − H, $C_{19}H_{10}F_2NO_3$ requires 338.0629).

2,7-Difluoro-3,6-dimethoxy-9*H*-thioxanthen-9-one (52). Using General Procedure F, **19** (3.15 g, 10.0 mmol), 26 °C, and purification by washing with water (3 × 100 mL), methanol (3 × 50 mL), acetone (3 × 50 mL), and removal of solvent in vacuo afforded **52** (2.74 g, 92%): mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 12.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 4.032 (s, 2H); IR (film) 3047, 2967, 1603, 1419, 1346, 1263, 1046, 894, 771 cm^{-1}; HRMS (ESI) m/z 309.0407 (M + H$^+$, $C_{15}H_{11}F_2O_3S$ requires 309.0397).

2,7-Difluoro-3,6-dihydroxy-9*H*-thioxanthen-9-one (53). Using General Procedure F, **19** (1.58 g, 5.00 mmol), heating to 90 °C, and purification by column chromatography (1−3% MeOH in CH_2Cl_2) afforded **53** (1.04 g, 74%): mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, J = 12.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 3.42 (br s, 2H); ^{13}C NMR (126 MHz, DMSO) δ 175.7 (s), 150.5 (d, J = 243.2 Hz), 150.2 (d, J = 14.1 Hz), 133.4 (d, J = 1.9 Hz), 120.1 (d, J = 5.0 Hz), 115.3 (d, J = 19.5 Hz), 112.7 (d, J = 2.7 Hz); IR (film) 3393, 3064, 1617, 1553, 1502, 1413, 1391, 1303, 1287, 1182, 1114, 903 cm^{-1}; HRMS (ESI) m/z 278.9924 (M − H, $C_{13}H_5F_2O_3S$ requires 278.9927).

3,6-Bis(dimethylamino)-2,7-difluoro-9*H*-thioxanthen-9-one (54). Using General Procedure F, **22** (150 mg, 0.440 mmol), and purification by column chromatography (10−20% EtOAc in hexanes) afforded **54** (134 mg, 91%): mp 218−220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 15.1 Hz, 2H), 6.63 (d, J = 8.0 Hz, 2H), 3.02 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8 (s), 151.4 (d, J = 246.1 Hz), 142.7 (d, J = 10.0 Hz), 132.9 (s), 119.5 (d, J = 6.3 Hz), 114.8 (d, J = 23.5 Hz), 110.0 (d, J = 3.7 Hz), 41.1 (d, J = 6.0 Hz); IR (film) 2907, 2898, 2853, 1682, 1601, 1583, 1354, 1256, 1116, 722 cm^{-1}; HRMS (ESI) m/z 335.1042 (M + H$^+$, $C_{17}H_{17}F_2N_2OS$ requires 335.1030).

3,6-Bis(diethylamino)-2,7-difluoro-9*H*-thioxanthen-9-one (55). Using General Procedure F, **23** (1.10 g, 2.77 mmol), and purification by column chromatography (10−20% EtOAc in hexanes) afforded **55** (973 mg, 90%): mp 145−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 15.6 Hz, 2H), 6.66 (d, J = 8.0 Hz, 2H), 3.40 (q, J = 7.0 Hz, 8H), 1.21 (t, J = 7.0 Hz, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.7 (s), 152.1 (d, J = 312.5 Hz), 141.8 (d, J = 9.9 Hz), 134.0 (d, J = 1.5 Hz), 119.7 (s), 116.3 (d, J = 24.3 Hz), 110.6 (s), 46.0 (d, J = 5.8 Hz), 13.0 (d, J = 1.5 Hz); IR (film) 2972, 2931, 2872, 1590, 1504, 1426, 1352, 1264, 1238, 1071, 901, 790 cm^{-1}; HRMS (ESI) m/z 391.1662 (M + H$^+$, $C_{21}H_{25}F_2N_2OS$ requires 391.1656).

2,7-Difluoro-3,6-bis(isopropylamino)-9*H*-thioxanthen-9-one (56). Using General Procedure F, **25** (1.00 g, 2.71 mmol), and purification by column chromatography (CH_2Cl) afforded **56** (834 mg, 85%): mp 164−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 12.8 Hz, 2H), 6.59 (d, J = 7.6 Hz, 2H), 4.41 (br s, 2H), 3.74 (hept, J = 6.4 Hz, 2H), 1.33 (d, J = 6.4 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) 176.9 (s), 150.4 (d, J = 225.5 Hz), 139.3 (d, J = 41.6 Hz), 134.8 (s), 118.2 (s), 113.8 (d, J = 18.9 Hz), 104.9 (s), 44.0 (s), 22.6 (s); IR (film) 3435, 3322, 2969, 1610, 1592, 1515, 1426, 1287, 1326, 1026, 774 cm^{-1}; HRMS (ESI) m/z 363.1338 (M + H$^+$, $C_{19}H_{21}F_2N_2OS$ requires 363.1343).

3,6-Bis(*tert*-butylamino)-2,7-difluoro-9*H*-thioxanthen-9-one (57). Using General Procedure F, **26** (300 mg, 0.762 mmol), and purification by column chromatography (10−20% EtOAc in hexanes) afforded **57** (263 mg, 89%): mp 199−201 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 13.2 Hz, 2H), 6.33 (d, J = 7.8 Hz, 2H), 4.57 (d, J = 4.6 Hz, 2H), 1.47 (s, 18H), 1.31 (d, J = 6.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9 (s), 150.9 (d, J = 241.0 Hz), 139.2 (d, J = 12.2 Hz), 135.6−132.8 (m), 118.0 (d, J = 6.1 Hz), 113.6 (d, J = 21.3 Hz), 106.6 (s), 51.4 (s), 29.3 (s); IR (film) 3437, 2978, 1598, 1514, 1420, 1364, 1202 cm^{-1}; HRMS (ESI) m/z 391.1649 (M + H$^+$, $C_{21}H_{25}F_2N_2OS$ requires 391.1656).

2,7-Difluoro-3,6-di(piperidin-1-yl)-9*H*-thioxanthen-9-one (58). Using General Procedure F, **27** (400 mg, 1.00 mmol), and purification by column chromatography (10−20% EtOAc in hexanes) afforded **58** (352 mg, 85%): mp 205−206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 14.3 Hz, 2H), 6.87 (d, J = 7.7 Hz, 2H), 3.23 (t, J = 5.2 Hz, 8H), 1.75 (p, J = 5.2 Hz, 8H), 1.63 (hept, J = 5.2 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.1 (s), 153.9 (d, J = 238.1 Hz), 145.1 (d, J = 10.0 Hz), 133.9 (s), 122.0 (d, J = 6.5 Hz), 115.8 (d, J = 23.2 Hz), 113.3 (d, J = 3.0 Hz), 51.2 (d, J = 4.8 Hz), 25.8 (s), 24.2 (s); IR (film) ν_{max} 2936, 2852, 1624, 1597, 1497, 1420, 1350, 1269, 1252, 1240, 1115, 750 cm^{-1}; HRMS (ESI) m/z 415.1650 (M + H$^+$, $C_{23}H_{25}F_2N_2OS$ requires 415.1656).

2,7-Difluoro-3,6-dimorpholino-9*H*-thioxanthen-9-one (59). Using General Procedure F, **29** (213 mg, 0.500 mmol), and purification by column chromatography (15−30% EtOAc in hexanes) afforded **59** (195 mg, 94%): mp 275−276 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 14.2 Hz, 2H), 6.86 (d, J = 7.6 Hz, 2H), 3.90 (t, J = 4.7 Hz, 8H), 3.26 (t, J = 4.7 Hz, 8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0 (s), 152.9 (d, J = 258.3 Hz), 143.1 (d, J = 9.9 Hz), 132.8 (d, J = 2.0 Hz), 122.0 (d, J = 6.7 Hz), 115.1 (d, J = 23.1 Hz), 112.1 (d, J = 2.8 Hz), 65.6 (s), 49.1 (d, J = 4.7 Hz); IR (film) 2990, 2923, 2887, 1602, 1499, 1426, 1271, 1122, 1006 cm^{-1}; HRMS (ESI) m/z 441.1056 (M + Na$^+$, $C_{21}H_{20}F_2N_2O_3SNa$ requires 441.1060).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Methods and data used to determine quantum yields and molar extinction coefficients, and absorption, fluorescence emission, ^{1}H NMR, and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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