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C−H Trifluoromethylation of 2-Substituted/Unsubstituted Aminonaphthoquinones at Room Temperature with Bench-Stable $(CF_3SO_2)_2Zn$: Synthesis and Antiproliferative Evaluation

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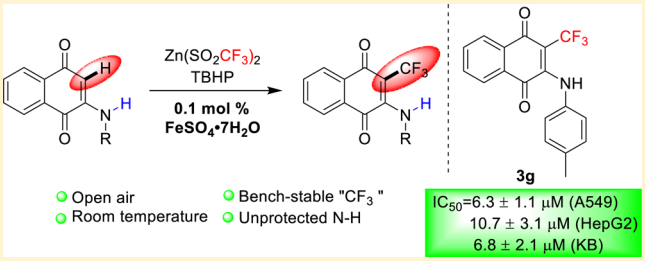
Supporting Information

ABSTRACT: A direct C−H trifluoromethylation of 2-amino-1,4-naphthoquinone analogues is described. This reaction proceeds under mild conditions at open atmosphere, providing a range of CF_3-containing naphthoquinones with good yield and functional group compatibility. All synthetic compounds were screened for antiproliferative activity against three human cancer cell lines. Notably, some of those trifluoromethyl analogs, such as **3a**, **3g**, **3j**, and **3t**, showed good antiproliferative profiles.



INTRODUCTION

The trifluoromethyl group is attractive in the field of medicinal chemistry due to its interesting properties conducive to drug development,[1] such as high electronegativity, lipophilicity, metabolic stability, and bioavailability.[2] Accordingly, substantial efforts have been made toward the incorporation of CF_3 groups into organic molecules to modulate their biological activities.[3] Naphthoquinones, particularly those possessing an amino or substituted amino group at the 2-position, have been a subject of study for many years for a variety of medical and biological applications.[4] Early studies indicated that the cytotoxic activity of these compounds was related to 20S proteasome inhibition (**1** and **PI-083**),[5] histone deacetylase (HDAC) inhibition (**NQN-1**),[6] and reactive oxygen species (ROS) production (**QD242**)[7] (Figure 1). Therefore, introduction of the CF_3 group to naphthoquinones might be very desirable and result in further advances in pharmacological applications.

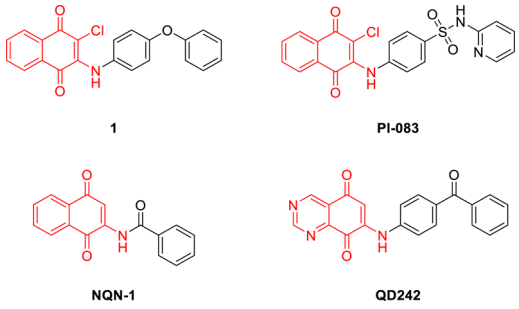


Figure 1. Representative 2-amino-1,4-naphthoquinone-based anticancer agents.

Traditionally, the trifluoromethylation of arenes and/or heteroarenes often needs poisonous fluorinating reagents, such as SbF_4, BrF_3, or HF.[8] While several modern strategies for trifluoromethylation of arenes and/or heteroarenes have been reported,[9] a direct and practical route to C−H functionalization of these structures remains a challenging task and is often hampered by the need for prefunctionalized substrates.[10] Particularly, methods that introduce the CF_3 group onto naphthoquinones are still very limited and most of them need multiple synthetic steps (Scheme 1, eq 1).[11] As far as is known, there is only one method of direct C−H trifluoromethylation of naphthoquinones using unstable, expensive, and explosive Togni's reagent[12] as the CF_3 source in the presence of 20 mol % CuI (Scheme 1, eq 2), in which only one 2-aminonaphthoquinone substrate was explored and the reaction was carried out at 55 °C under argon atmosphere.[13] When the importance and impact of the CF_3 group in drug discovery and the limitations of previous methods are considered, it is still necessary to develop a practical and convenient way to introduce the CF_3 group onto naphthoquinones.

Recently, since the pioneering work by Langlois et al.[14a] on the oxidation of $NaSO_2CF_3$ to the trifluoromethyl radical, the trifluoromethylation of arenes and heterocycles using $NaSO_2CF_3$ or $Zn(SO_2CF_3)_2$ as a stable and inexpensive trifluoromethyl source has been well developed.[14] Inspired by these previous works, we conceived that the Langlois reagent might possibly add CF_3 radical to 2-amino-1,4-naphthoqui-

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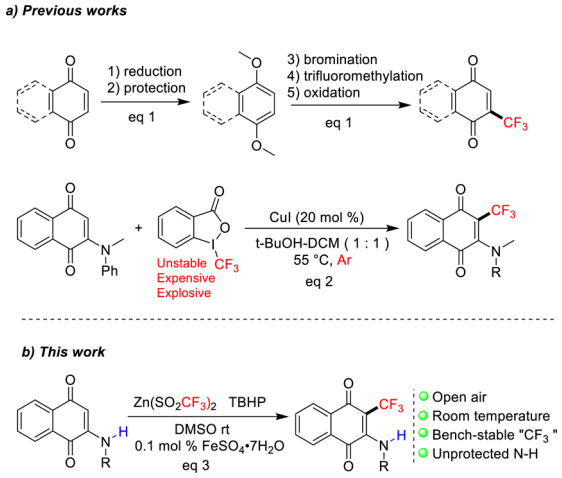
Scheme 1. Trifluoromethylation of 2-Amino-1,4-naphthoquinones: (a) Previous Works and (b) This Work

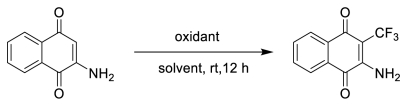


nones (Scheme 1, eq 3). Driven by our continued interest in fluorination of heterocyclic scaffolds,[15] herein we report a trifluoromethylation reaction that proceeds at room temperature in open air using a stable and inexpensive reagent.

RESULTS AND DISCUSSION

To validate the feasibility of the proposed processes, we selected 2-amino-1,4-naphthoquinone (**2a**) as a model substrate to optimize reaction conditions. First, the reaction was carried out with CF_3SO_2Na as CF_3 radical source and *tert*-butyl hydroperoxide (TBHP) in CH_3CN at room temperature (Table 1, entry 1). As per our expectations, the reaction proceeded to give access to the desired trifluoromethylation product **3a** in a moderate yield (65%). Then we screened various solvents (Table 1, entries 1−11) and found that dichloroethane (DCE) and dimethyl sulfoxide (DMSO) both gave good yields (78−83%). DMSO was chosen as the solvent

Table 1. Optimization of Reaction Conditions[a]



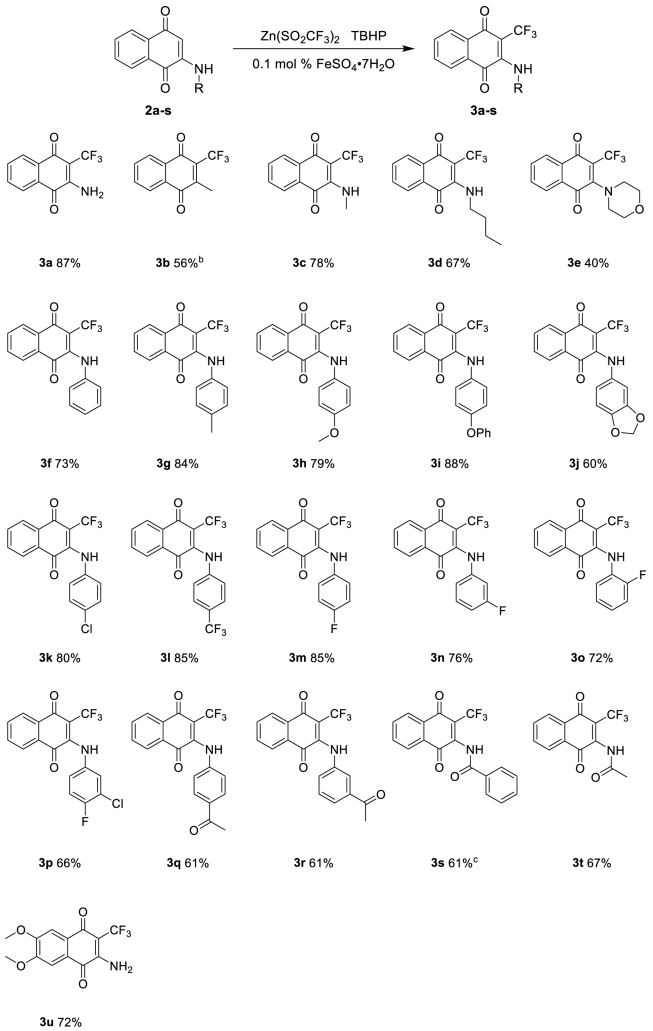
entry	solvent	oxidant	reagent	yield (%)
1	CH_3CN	TBHP	$NaSO_2CF_3$	65
2	MeOH	TBHP	$NaSO_2CF_3$	7
3	DCM	TBHP	$NaSO_2CF_3$	21
4	THF	TBHP	$NaSO_2CF_3$	16
5	$CHCl_3$	TBHP	$NaSO_2CF_3$	25
6	CCl_4	TBHP	$NaSO_2CF_3$	14
7	EtOAc	TBHP	$NaSO_2CF_3$	55
8	H_2O	TBHP	$NaSO_2CF_3$	13
9	toluene	TBHP	$NaSO_2CF_3$	40
10	DMSO	TBHP	$NaSO_2CF_3$	78
11	DCE	TBHP	$NaSO_2CF_3$	83
12[b]	**DMSO**	**TBHP**	**$Zn(SO_2CF_3)_2$**	**87**
13	DMSO	H_2O_2	$Zn(SO_2CF_3)_2$	trace
14	DMSO	DTBP	$Zn(SO_2CF_3)_2$	trace

[a]Conditions: **2a** (0.2 mmol), reagent (0.6 mmol), oxidant (1.0 mmol), solvent (2 mL), 0.1 mol % $FeSO_4·7H_2O$, rt, 12 h. [b]0.3 mmol of $Zn(SO_2CF_3)_2$ was used.

for the 2-amino-1,4-naphthoquinone derivatives that showed poor solubility. We next changed the reagent of the reaction (Table 1, entry 12), and $Zn(SO_2CF_3)_2$ was found to give better result (87%). Finally, other oxidants were examined and only TBHP was effective (Table 1, entries 12−14). Notably, during the optimization of reaction conditions, we found that $FeSO_4·7H_2O$ radical initiator made the reaction more stable and repeatable.[14e]

With the optimized reaction conditions in hand, we next examined a variety of 1,4- naphthoquinones to probe the scope and limitations of this approach (Scheme 2). Both amino (**3a**)

Scheme 2. Substrate Scope of Trifluoromethylation[a]



[a]Conditions: **2** (0.2 mmol), $Zn(SO_2CF_3)_2$ (0.3 mmol), TBHP (1.0 mmol), DMSO (2 mL), 0.1 mol % $FeSO_4·7H_2O$, rt, 12 h. [b]$Zn(SO_2CF_3)_2$ (0.6 mmol) and TBHP (2.0 mmol) were used. [c]83% conversion.

and methyl (**3b**) substituents were suitable substrates. Then we investigated substituted amino analogues. Reactions involving primary and secondary aliphatic amines such as methylamine (**3c**), butylamine (**3d**), and morpholine (**3e**) afforded the desired products in acceptable to moderate yields (40−78%). Beyond aliphatic derivatives, *N*-aryl groups with either electron-donating (methyl **3g**, methoxy **3h**, and phenoxy **3i**) or electron-withdrawing (chloro **3k**, trifluoromethyl **3l**, fluoro **3m**, and acetyl **3q**) substituents at the 4-position of phenyl underwent

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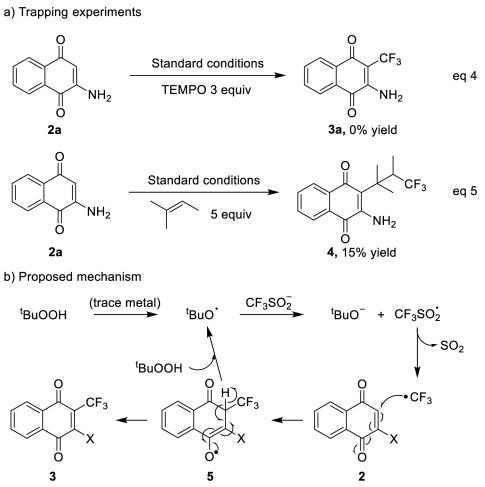
trifluoromethylation in good yield (60−88%). Ortho or meta substituents and disubstituents also worked well (**3j**, **3n**, **3o**, **3p**, and **3r**). In addition, *N*-acetyl (**3t**) or *N*-benzoyl (**3s**) substituents afforded products in moderate yields (61−67%). Meanwhile, 2-amino-6,7-dimethoxy-1,4-naphthoquinone could react satisfactorily and gave the product (**3u**) in good yield (72%).

For further exploring the reaction mechanism, some control experiments were carried out (Scheme 3). When the reaction proceeded in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), the transformation was found to be inhibited and no product was detected (Scheme 3, eq 4). We next investigated the reaction with 2-methyl-2-butene and obtained the desired product **4** (Scheme 3, eq 5). These results indicated that a CF_3 radical might be involved in the reaction, which was consistent with the literature precedent.[14e,16]

Scheme 3. Trapping Experiments and Proposed Mechanism



With these results, we proposed a reasonable mechanism for this reaction (Scheme 3). First, the interaction of $Zn(SO_2CF_3)_2$ with TBHP generated the CF_3 radical. It would be attracted to naphthoquinone **2**, and subsequently **2** would produce trifluoromethylated naphthoquinone **3** through the intermediate **5**.

With these novel CF_3-containing naphthoquinones in hand, we subsequently decided to evaluate their preliminary biological activities. In recent years, many reports have shown that 2-amino-1,4- naphthoquinones derivatives have good anticancer potential, such as compounds **1** and **PI-083**.[5b,17] Inspired by these works, we tested some synthesized naphthoquinone analogues for their antiproliferative activities against human alveolar basal epithelial cell line A549, human liver cancer cell line HepG2, and human KB cell line by using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and sulforhodamine B (SRB) assays.[18] A summary of the IC_{50} values is shown in Table 2. Excitingly, the results showed that the tested CF_3-containing naphthoquinones displayed antiproliferative effects against three different types of tumor cell lines with IC_{50} values ranging from 3.2 to 61.2 μM. Among the tested compounds, **3a**, **3g**, **3j**, and **3t** exhibited the best values of IC_{50}. Obviously, relative to nonfluorinated naphthoquinone analogue **1**, the CF_3-containing compounds showed superior activity against all three cell lines, revealing that the incorporation of the CF_3 group into the naphthoquinone scaffold indeed increased their bioactivities.

Table 2. Inhibitory Activities of Selected Compounds against Tumor Cell Growth

	IC_{50} (μM)		
compd	A549	HepG2	KB
3a	3.2 ± 0.4	8.6 ± 1.6	61.2 ± 13.1
3c	26.1 ± 2.7	52.2 ± 6.4	>100.0
3d	8.7 ± 0.8	23.6 ± 2.4	87.3 ± 3.4
3e	8.6 ± 2.1	16.5 ± 5.9	50.0 ± 21.0
3f	27.2 ± 5.9	46.2 ± 12.2	20.3 ± 9.4
3g	6.3 ± 1.1	10.7 ± 3.1	6.8 ± 2.1
3h	12.4 ± 4.4	17.1 ± 6.0	10.7 ± 4.1
3i	23.1 ± 5.2	38.1 ± 6.3	33.8 ± 8.3
3j	6.7 ± 0.5	11.5 ± 3.6	9.5 ± 3.8
3k	15.9 ± 3.6	24.9 ± 4.5	12.6 ± 3.2
3l	18.8 ± 1.9	31.4 ± 5.1	27.0 ± 12.8
3m	20.5 ± 6.0	29.0 ± 6.1	22.5 ± 4.6
3n	10.8 ± 4.4	15.2 ± 5.0	9.6 ± 3.2
3o	22.4 ± 1.8	32.9 ± 3.3	38.5 ± 16.7
3p	20.2 ± 3.4	35.6 ± 9.0	27.0 ± 9.5
3q	14.5 ± 2.9	29.0 ± 8.2	18.7 ± 3.8
3r	21.0 ± 6.3	40.3 ± 9.7	27.9 ± 13.9
3s	10.5 ± 3.5	14.9 ± 4.4	52.7 ± 19.5
3t	4.1 ± 1.3	7.4 ± 1.4	39.8 ± 21.1
1	11.9 ± 4.5	>100.0	>100.0
VP16	1.1 ± 0.3	0.9 ± 0.4	0.6 ± 0.1

CONCLUSIONS

In summary, we have developed a new method for 3-trifluoromethylation of 2-amino-1,4-naphthoquinone analogues. The reaction used stable trifluoromethylation reagent and was performed under mild conditions without excluding air and water. A wide range of trifluoromethylated products were efficiently synthesized in moderate to excellent yields. Notably, some CF_3-contaning compounds (**3g** and **3j**) showed good antiproliferative activity against different cancer cell lines. The result suggests that incorporating CF_3 into naphthoquinone might be a promising strategy for further development of this type of anticancer agents. Further investigation is ongoing in our laboratories.

EXPERIMENTAL SECTION

General Information. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a standard spectrometer operating at 300, 400, and 500 MHz (^1H 300/400/500 MHz, ^{13}C 125 MHz, and ^{19}F 471 MHz). Chemical shifts of ^1H and ^{13}C NMR were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Chemical shifts of ^{19}F NMR are reported as δ values relative to 0.05% TFA in D_2O (δ −74.2 ppm) as internal standard (−76.5 ppm for pure TFA). Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). High-resolution mass spectra were recorded by the electron ionization (EI) method with a double-focusing magnetic mass analyzer. Infrared spectra were recorded on an IR spectrometer, and absorption frequencies were reported in reciprocal centimeters (cm^{-1}). Melting points were measured uncorrected. Reactions were monitored by thin-layer chromatographic (TLC) or liquid chromatographic/mass spectrometric (LC/MS) analysis. Column chromatography (petroleum ether/ethyl acetate) was performed on silica gel (200−300 mesh). Unless otherwise noted, all solvents and other reagents are commercially available and were used without further purification. All reagents were weighed and handled in air at room temperature.

Materials. $NaSO_2CF_3$ was purchased from commercial sources, and $(CF_3SO_2)_2Zn$ and substrates was prepared according to the literature.[14c,19]

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General Procedure for Preparation of 2-Amino-3-trifluoromethyl-1,4-naphthoquinones (3a–3u). A solution of 2-amino-1,4-naphthoquinone (0.2 mmol) and $(CF_3SO_2)_2Zn$ (0.3 mmol) in DMSO (2.5 mL) was cooled to 0 °C, followed by slow addition of *tert*-butyl hydroperoxide (70% solution in water, 1 mmol) by an eppendorf pipet. Then 0.1 mol % $FeSO_4·7H_2O$ was added to the mixture, which was stirred at room temperature overnight. Upon consumption of the starting material, the reaction was partitioned between CH_2Cl_2 (20.0 mL) and saturated $NaHCO_3$ (20.0 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20.0 mL). The organic layers were dried with Na_2SO_4, concentrated, and purified by column chromatography on silica gel, with ethyl acetate/petroleum ether mixture (ratio ca. 1:2) as the eluent, to afford the corresponding 2-amino-3-trifluoromethyl-1,4-naphthoquinones.

*2-Amino-3-trifluoromethyl-1,4-naphthoquinone (**3a**).* Yellow solid (42 mg, 87%), mp 187–188 °C. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.19 (d, *J* = 8.3 Hz, 1H), 8.11 (d, *J* = 7.7 Hz, 1H), 7.82 (t, *J* = 8.2 Hz, 1H), 7.70 (t, *J* = 7.0 Hz, 1H), 6.50 (s, 1H), 6.03 (s, 1H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 180.2, 178.9, 145.8, 135.8, 132.9, 132.8, 129.4, 126.9, 126.7, 124.8 (q, *J* = 274.2 Hz), 102.6 (d, *J* = 27.4 Hz). ^{19}F NMR (471 MHz, chloroform-*d*) δ −56.0. FT-IR (ν) 3475, 3374, 1610, 1577, 1420, 1348, 1292, 1111, 798, 726, and 699 cm^{-1}. HRMS (EI) *m*/*z* M$^+$ calcd for $[C_{11}H_6NO_2F_3]$, 241.0351; found, 241.0349.

*2-Methyl-3-trifluoromethyl-1,4-naphthoquinone (**3b**).* Yellow solid (27 mg, 56%), mp 84–85 °C. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.15–8.11 (m, 2H), 7.83–7.75 (m, 2H), 2.44 (q, *J* = 3.3 Hz, 3H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 183.9, 180.1, 148.8, 134.6, 134.2, 133.2 (d, *J* = 28.2 Hz), 131.8, 131.2, 126.9, 126.7, 122.5 (d, *J* = 277.9 Hz), 13.1 (q, *J* = 3.6 Hz). ^{19}F NMR (471 MHz, chloroform-*d*) δ −57.5. FT-IR (ν) 3360, 2961, 2850, 1659, 1632, 1468, 1260, and 800 cm^{-1}. HRMS (EI) *m*/*z* M$^+$ calcd for $[C_{12}H_7F_3O_2]$, 240.0398; found, 240.0399.

*2-Methylamino-3-trifluoromethyl-1,4-naphthoquinone (**3c**).* Yellow soild (40 mg, 78%), mp 241–243 °C. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.17 (d, *J* = 7.7 Hz, 1H), 8.07 (d, *J* = 7.7 Hz, 1H), 7.80 (t, *J* = 7.0 Hz, 1H), 7.67 (t, *J* = 8.1 Hz, 1H), 6.89 (s, 1H), 3.20 (s, 3H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 181.2, 179.2, 148.1, 135.8, 133.4, 132.7, 129.14, 126.8, 126.8, 123.8 (d, *J* = 273.5 Hz), 101.6 (d, *J* = 30.1 Hz), 34.0 (q, *J* = 6.6 Hz). ^{19}F NMR (471 MHz, chloroform-*d*) δ −51.4. FT-IR (ν) 3360, 3275, 2922, 2850, 1606, 1578, 1533, 1420, 1300, 1102, and 727 cm^{-1}. HRMS (EI) *m*/*z* M$^+$ calcd for $[C_{12}H_8F_3NO_2]$, 255.0507; found, 255.0509.

*2-Butylamino-3-trifluoromethyl-1,4-naphthoquinone (**3d**).* Yellow solid (40 mg, 67%), mp 97–99 °C. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.18 (d, *J* = 7.7 Hz, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.71–7.61 (m, 1H), 6.62 (s, 1H), 3.45 (s, 2H), 1.69 (q, *J* = 7.3 Hz, 2H), 1.44 (heptet, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).^{13}C NMR (151 MHz, chloroform-*d*) δ 181.3, 179.3, 147.1, 135.8, 133.4, 132.6, 129.2, 126.8, 123.9 (d, *J* = 274.3 Hz), 101.6 (d, *J* = 28.4 Hz), 46.9 (q, *J* = 5.8 Hz), 32.2, 19.8, 13.6. ^{19}F NMR (471 MHz, chloroform-*d*) δ −52.2. FT-IR (ν) 3274, 2961, 2923, 2877, 2851, 1686, 1599, 1576, 1530, 1296, 1102, and 724 cm^{-1}. HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $[C_{15}H_{15}F_3NO_2]$, 298.1049; found, 298.1048.

*2-Morpholino-3-trifluoromethyl-1,4-naphthoquinone (**3e**).* Yellow oil (25 mg, 40%). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.11 (dd, *J* = 7.7, 0.9 Hz, 1H), 8.01 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.76 (td, *J* = 7.5, 1.3 Hz, 1H), 7.70 (td, *J* = 7.5, 1.3 Hz, 1H), 3.90–3.86 (m, 4H), 3.74–3.69 (m, 4H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 183.3, 180.9, 151.7, 134.7, 133.2, 132.1, 131.5, 126.8, 126.1, 123.3 (d, *J* = 274.2 Hz), 111.3 (q, *J* = 28.7 Hz), 67.4, 54.0 (q, *J* = 2.4 Hz). ^{19}F NMR (471 MHz, chloroform-*d*) δ −56.8. FT-IR (ν) 3358, 2922, 2851, 1646, 1565, 1332, 1284, 1114, 986, and 727 cm^{-1}. HRMS (EI) *m*/*z* M$^+$ calcd for $[C_{15}H_{12}F_3NO_3]$, 311.0769; found, 311.0770.

*2-Phenylamino-3-trifluoromethyl-1,4-naphthoquinone (**3f**).* Red solid (46 mg, 73%), decomposed at 257 °C. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.23 (d, *J* = 7.7 Hz, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 8.12 (s, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.25–7.19 (m, 3H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 181.5, 179.9, 143.5, 139.6, 135.9, 133.2, 132.8, 129.4 (d, *J* = 3.3 Hz), 127.0, 126.9, 126.4, 122.8 (d, *J* = 274.4 Hz), 122.2, 105.9 (d, *J* = 30.4 Hz). ^{19}F NMR (471 MHz, chloroform-*d*) δ −56.2. FT-IR (ν) 3360, 3254, 1642, 1570, 1518, 1260, 1094, 799, and 694 cm^{-1}. HRMS (ESI) *m*/*z* [M − H]$^-$ calcd for $[C_{17}H_9F_3NO_2]$, 316.0591; found, 316.0598.

*2-(p-Tolylamino)-3-trifluoromethyl-1,4-naphthoquinone (**3g**).* Red solid (55 mg, 84%), mp 248–250 °C. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.22 (d, *J* = 7.7 Hz, 1H), 8.16 (d, *J* = 7.7 Hz, 1H), 8.10 (s, 1H), 7.84 (td, *J* = 7.6, 1.2 Hz, 1H), 7.73 (td, *J* = 7.6, 1.2 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 181.6, 179.9, 143.6, 137.0, 136.4, 135.9, 133.1, 132.9, 129.9, 129.4, 127.0, 126.9, 122.9 (q, *J* = 274.3 Hz), 122.1, 105.4 (d, *J* = 30.2 Hz), 21.1. ^{19}F NMR (471 MHz, chloroform-*d*) δ −56.0. FT-IR (ν) 3288, 2920, 2850, 1678, 1598, 1522, 1292, 1127, 729, and 700 cm^{-1}. HRMS (ESI) *m*/*z* [M − H]$^-$ calcd for $[C_{18}H_{11}F_3NO_2]$, 330.0747; found, 330.0754.

*2-[(4-Methoxyphenyl)amino]-3-trifluoromethyl-1,4-naphthoquinone (**3h**).* Red solid (55 mg, 79%), decomposed at 250 °C. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.22 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 8.09 (s, 1H), 7.84 (td, *J* = 7.6, 1.3 Hz, 1H), 7.72 (td, *J* = 7.6, 1.2 Hz, 1H), 7.15–7.11 (m, 2H), 6.92–6.87 (m, 2H), 3.83 (s, 3H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 181.6, 179.8, 158.0, 143.9, 135.9, 133.0, 132.4, 129.3, 126.9, 126.9, 123.9, 123.0 (d, *J* = 274.4 Hz), 114.5, 104.8 (d, *J* = 30.4 Hz), 55.5.^{19}F NMR (471 MHz, chloroform-*d*) δ −55.6. FT-IR (ν) 3442, 3264, 2920, 2850, 1682, 1597, 1520, 1292, 1244, 1147, 826, and 733 cm^{-1}. HRMS (ESI) *m*/*z* [M − H]$^-$ calcd for $[C_{18}H_{11}F_3NO_3]$, 346.0697; found, 346.0702.

*2-[(4-Phenoxyphenyl)amino]-3-trifluoromethyl-1,4-naphthoquinone (**3i**).* Black solid (72 mg, 88%), decomposed at 210 °C. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.22 (d, *J* = 7.7 Hz, 1H), 8.16 (d, *J* = 7.7 Hz, 1H), 8.10 (s, 1H), 7.85 (td, *J* = 7.6, 1.2 Hz, 1H), 7.73 (td, *J* = 7.6, 1.2 Hz, 2H), 7.39–7.32 (m, 2H), 7.18–7.10 (m, 3H), 7.06–6.99 (m, 4H). ^{13}C NMR (151 MHz, chloroform-*d*) δ 181.5, 179.8, 156.8, 155.6, 143.7, 135.9, 134.6, 133.1, 132.9, 129.9, 129.3, 127.0, 126.9, 124.0 (d, *J* = 2.2 Hz), 123.6, 122.9 (d, *J* = 274.5 Hz), 119.4, 119.0, 105.3 (d, *J* = 30.3 Hz). ^{19}F NMR (471 MHz, chloroform-*d*) δ −55.7. FT-IR (ν) 3359, 3253, 2920, 2850, 1678, 1574, 1522, 1239, 1145, 1126, 792, and 688 cm^{-1}. HRMS (ESI) *m*/*z* [M − H]$^-$ calcd for $[C_{23}H_{13}F_3NO_3]$, 408.0853; found, 408.0859.

*2-(Benzo[d][1,3]dioxol-5-ylamino)-3-trifluoromethyl-1,4-naphthoquinone (**3j**).* Black solid (43 mg, 60%), mp 227–229 °C. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.22 (d, *J* = 7.7 Hz, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 8.03 (s, 1H), 7.84 (td, *J* = 7.6, 1.3 Hz, 1H), 7.73 (td, *J* = 7.6, 1.3 Hz, 2H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 2.2 Hz, 1H), 6.67 (ddd, *J* = 8.3, 2.2, 0.8 Hz, 1H), 6.01 (s, 2H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 181.5, 179.8, 148.3, 146.1, 143.8, 135.9, 133.6, 133.1, 132.9, 129.3, 127.0, 126.9, 122.9 (d, *J* = 274.3 Hz), 116.0, 108.4, 105.3 (d, *J* = 30.1 Hz), 104.2, 101.8. ^{19}F NMR (471 MHz, chloroform-*d*) δ −55.8. FT-IR (ν) 3442, 3287, 2921, 2851, 1681, 1601, 1578, 1488, 1342, 1293, 1124, 1038, 796, and 728 cm^{-1}. HRMS (ESI) *m*/*z* [M − H]$^-$ calcd for $[C_{18}H_9F_3NO_4]$, 360.0489; found, 360.0496.

*2-[(4-Chlorophenyl)amino]-3-trifluoromethyl-1,4-naphthoquinone (**3k**).* Red solid (56 mg, 70%), decomposed at 257 °C. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.22 (d, *J* = 7.8 Hz, 1H), 8.16 (d, *J* = 7.7 Hz, 1H), 8.03 (s, 1H), 7.86 (td, *J* = 7.6, 1.2 Hz, 1H), 7.75 (td, *J* = 7.6, 1.2 Hz, 2H), 7.37–7.34 (m, 2H), 7.14 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 181.3, 179.8, 143.3, 138.2, 136.0, 133.3, 132.7, 131.8, 129.6, 129.3, 127.1, 127.0, 123.5, 122.7 (d, *J* = 274.6 Hz), 106.4 (d, *J* = 30.2 Hz).. ^{19}F NMR (471 MHz, chloroform-*d*) δ −56.2. FT-IR (ν) 3357, 3252, 1677, 1602, 1569, 1518, 1298, 1259, 1129, 1011 794, and 687 cm^{-1}. HRMS (ESI) *m*/*z* [M − H]$^-$ calcd for $[C_{17}H_8ClF_3NO_2]$, 350.0201; found, 350.0205.

*2-{[(4-Trifluoromethyl)phenyl]amino}-3-trifluoromethyl-1,4-naphthoquinone (**3l**).* Red solid (65 mg, 85%), mp 209–211 °C. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.24 (d, *J* = 7.6 Hz, 1H), 8.18 (d, *J* = 7.7 Hz, 1H), 8.08 (s, 1H), 7.88 (t, *J* = 7.6 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 181.2, 179.9, 142.8, 136.1, 133.5, 132.6, 129.3, 128.0 (d, *J* = 32.9 Hz), 127.1, 127.0, 126.7 (q, *J* = 3.7 Hz), 123.8

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(d, J = 271.8 Hz), 122.6 (d, J = 275.0 Hz), 121.8, 107.8 (d, J = 30.0 Hz).^{19}F NMR (471 MHz, chloroform-d) δ −56.7, −62.34. FT-IR (ν) 3362, 3266, 1676, 1645, 1574, 1526, 1327, 1294, 1108, 844, and 725 cm^{-1}. HRMS (ESI) m/z [M − H]$^-$ calcd for [$C_{18}H_8F_6NO_2$], 384.0465; found, 384.0471.

*2-[(4-Fluorophenyl)amino]-3-trifluoromethyl-1,4-naphthoquinone (**3m**).* Red solid (57 mg, 85%), decomposed at 254 °C. ^{1}H NMR (500 MHz, chloroform-d) δ 8.22 (d, J = 7.8 Hz, 1H), 8.16 (d, J = 7.7 Hz, 1H), 8.05 (s, 1H), 7.85 (td, J = 7.6, 1.3 Hz, 1H), 7.74 (td, J = 7.6, 1.2 Hz, 1H), 7.20−7.16 (m, 2H), 7.10−7.05 (m, 2H). ^{13}C NMR (126 MHz, chloroform-d) δ 181.4, 179.9, 160.7 (d, J = 246.6 Hz), 143.8, 136.0, 135.6, 133.2, 132.8, 129.3, 127.0, 126.9, 124.3 (d, J = 8.5 Hz), 122.8 (d, J = 274.5 Hz), 116.3 (d, J = 23.1 Hz), 105.7 (d, J = 30.7 Hz). ^{19}F NMR (471 MHz, chloroform-d) δ −55.9, −114.7. FT-IR (ν) 3358, 3252, 1678, 1641, 1611, 1573, 1525, 1260, 1127, 836, and 728 cm^{-1}. HRMS (ESI) m/z [M − H]$^-$ calcd for [$C_{17}H_8F_4NO_2$], 334.0497; found, 334.0503.

*2-[(3-Fluorophenyl)amino]-3-trifluoromethyl-1,4-naphthoquinone (**3n**).* Red solid (51 mg, 76%), decomposed at 213 °C. ^{1}H NMR (500 MHz, chloroform-d) δ 8.24 (d, J = 7.8 Hz, 1H), 8.18 (d, J = 7.7 Hz, 1H), 8.07 (s, 1H), 7.88 (td, J = 7.6, 1.3 Hz, 1H), 7.77 (td, J = 7.6, 1.3 Hz, 1H), 7.36 (td, J = 8.7, 6.3 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 6.98−6.94 (m, 2H). ^{13}C NMR (126 MHz, chloroform-d) δ 181.3, 179.9, 163.1 (d, J = 247.9 Hz), 143.2, 141.2 (d, J = 10.0 Hz), 136.0, 133.3, 132.6, 130.6 (d, J = 9.2 Hz), 129.3, 127.1, 127.0, 122.7 (q, J = 274.8 Hz), 117.8, 113.3 (d, J = 21.2 Hz), 109.7 (d, J = 24.5 Hz), 107.0 (q, J = 30.3 Hz). ^{19}F NMR (471 MHz, chloroform-d) δ −56.6, −110.9 (q, J = 8.3 Hz). FT-IR (ν) 3254, 1676, 1594, 1573, 1520, 1304, 1129, 780, and 686 cm^{-1}. HRMS (ESI) m/z [M − H]$^-$ calcd for [$C_{17}H_8F_4NO_2$], 334.0497; found, 334.0504.

*2-[(2-Fluorophenyl)amino]-3-trifluoromethyl-1,4-naphthoquinone (**3o**).* Red solid (48 mg, 72%), mp 240−242 °C. ^{1}H NMR (500 MHz, chloroform-d) δ 8.21 (d, J = 7.8 Hz, 1H), 8.15 (d, J = 7.7 Hz, 1H), 7.92 (s, 1H), 7.84 (td, J = 7.6, 1.3 Hz, 1H), 7.74 (td, J = 7.6, 1.3 Hz, 1H), 7.28−7.21 (m, 2H), 7.19−7.15 (m, 2H). ^{13}C NMR (126 MHz, chloroform-d) δ 181.1, 179.8, 155.8 (d, J = 249.3 Hz), 144.1, 135.9, 133.3, 132.7, 129.4, 127.8 (d, J = 7.6 Hz), 127.5 (d, J = 12.1 Hz), 127.0, 126.9, 124.5 (d, J = 3.8 Hz), 124.3, 122.8 (d, J = 274.9 Hz), 116.4 (d, J = 19.2 Hz), 106.8 (d, J = 30.0 Hz). ^{19}F NMR (471 MHz, chloroform-d) δ −56.4, −123.5 (d, J = 7.3 Hz). FT-IR (ν) 3443, 3249, 1679, 1645, 1575, 1518, 1302, 1125, 1107, 754, and 724 cm^{-1}. HRMS (ESI) m/z [M − H]$^-$ calcd for [$C_{17}H_8F_4NO_2$], 334.0497; found, 334.0502.

*2-[(4-Fluoro-3-chlorophenyl)amino]-3-trifluoromethyl-1,4-naphthoquinone (**3p**).* Red solid (49 mg, 66%), mp 235−237 °C. ^{1}H NMR (500 MHz, chloroform-d) δ 8.22 (d, J = 7.7 Hz, 1H), 8.16 (d, J = 7.7 Hz, 1H), 7.98 (s, 1H), 7.86 (td, J = 7.6, 1.2 Hz, 1H), 7.76 (dd, J = 7.6, 1.2 Hz, 1H), 7.28 (dd, J = 6.2, 2.6 Hz, 1H), 7.16 (t, J = 8.6 Hz, 1H), 7.13−7.06 (m, 1H). ^{13}C NMR (126 MHz, chloroform-d) δ 181.1, 179.8, 156.2 (d, J = 249.5 Hz), 143.5, 136.2, 136.1, 133.4, 132.6, 129.2, 127.10, 127.0, 124.9, 122.3 (d, J = 7.2 Hz), 122.0 (d, J = 19.1 Hz). 122.6 (d, J = 274.7 Hz), 117.2 (d, J = 22.6 Hz), 106.6 (d, J = 30.0 Hz). ^{19}F NMR (471 MHz, chloroform-d) δ −56.2, −117.2. FT-IR (ν) 3447, 3252, 1674, 1643, 1594, 1517, 1312, 1117, 724, and 713 cm^{-1}. HRMS (ESI) m/z [M − H]$^-$ calcd for [$C_{17}H_7ClF_4NO_2$], 368.0107; found, 368.0111.

*2-[(4-Acetylphenyl)amino]-3-trifluoromethyl-1,4-naphthoquinone (**3q**).* Yellow solid (44 mg, 61%), mp 195−197 °C. ^{1}H NMR (500 MHz, chloroform-d) δ 8.23 (d, J = 7.8 Hz, 1H), 8.18 (d, J = 7.7 Hz, 1H), 8.12 (s, 1H), 7.99 (d, J = 8.6 Hz, 2H), 7.87 (td, J = 7.6, 1.2 Hz, 1H), 7.77 (td, J = 7.6, 1.2 Hz, 1H), 7.27 (d, J = 8.5 Hz, 2H). 2.61 (s, 3H). ^{13}C NMR (126 MHz, chloroform-d) δ 196.6, 181.2, 179.9, 143.9, 142.6, 136.1, 134.4, 133.5, 132.6, 129.8, 129.3, 127.1, 127.0, 122.6 (d, J = 274.8 Hz), 121.2 (d, J = 2.3 Hz), 108.1 (d, J = 30.1 Hz), 26.5. ^{19}F NMR (471 MHz, chloroform-d) δ −56.8. FT-IR (ν) 3288, 1681, 1576, 1524, 1291, 1155, 1127, and 727 cm^{-1}. HRMS (ESI) m/z [M − H]$^-$ calcd for [$C_{19}H_{11}F_3NO_3$], 358.0697; found, 358.0703.

*2-[(3-Acetylphenyl)amino]-3-trifluoromethyl-1,4-naphthoquinone (**3r**).* Yellow solid (44 mg, 61%), mp 245−246 °C. ^{1}H NMR (500 MHz, chloroform-d) δ 8.24 (d, J = 8.3 Hz, 1H), 8.18 (d, J = 8.3 Hz, 1H), 8.14 (s, 1H), 7.87 (t, J = 8.2 Hz, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.79−7.74 (m, 2H), 7.50 (t, J = 7.9 Hz, 1H), 7.41 (d, J = 9.5 Hz, 1H), 2.61 (s, 3H). ^{13}C NMR (126 MHz, chloroform-d) δ 197.0, 181.3, 179.9, 143.2, 140.2, 138.3, 136.0, 133.3, 132.7, 129.7, 129.3, 127.1, 127.0, 126.5, 126.1, 122.7 (d, J = 274.7 Hz), 121.8, 106.7 (d, J = 29.9 Hz), 26.7. ^{19}F NMR (471 MHz, chloroform-d) δ −56.2. FT-IR (ν) 3359, 3261, 1674, 1642, 1558, 1260, 1122, 791, and 688 cm^{-1}. HRMS (ESI) m/z [M − H]$^-$ calcd for [$C_{19}H_{11}F_3NO_3$], 358.0697; found, 358.0704.

*2-Benzoylamino-3-trifluoromethyl-1,4-naphthoquinone (**3s**).* Yellow solid (35 mg, 61% yield, 83% conversion), decomposed at 210 °C. ^{1}H NMR (500 MHz, chloroform-d) δ 8.82 (s, 1H), 8.23 (d, J = 8.7 Hz, 1H), 8.16 (d, J = 8.7 Hz, 1H), 8.00 (d, J = 6.2 Hz, 1H), 7.90−7.85 (m, 1H), 7.83−7.76 (m, 1H), 7.70−7.63 (m, 1H), 7.56 (t, J = 7.7 Hz, 2H). ^{13}C NMR (126 MHz, chloroform-d) δ 181.2, 180.0, 165.5, 138.5, 135.9, 134.1, 133.6, 132.2, 131.9, 129.4, 129.1, 128.1, 127.2, 127.0, 121.7 (d, J = 275.4 Hz), 121.2 (d, J = 30.7 Hz) . ^{19}F NMR (471 MHz, chloroform-d) δ −61.3. FT-IR (ν) 3358, 3311, 1672, 1662, 1487, 1261, 1164, 1025, 796, and 708 cm^{-1}. HRMS (ESI) m/z [M − H]$^-$ calcd for [$C_{18}H_9F_3NO_3$], 344.0540; found, 344.0548.

*2-Acetylamino-3-trifluoromethyl-1,4-naphthoquinone (**3t**).* Yellow solid (37 mg, 67%), decomposed at 229 °C. ^{1}H NMR (500 MHz, chloroform-d) δ 8.20 (d, J = 8.7 Hz, 1H), 8.17−8.09 (m, 2H), 7.85 (d, J = 6.3 Hz, 1H), 7.81−7.76 (m, 1H), 2.32 (s, 3H). ^{13}C NMR (126 MHz, chloroform-d) δ 181.2, 180.0, 168.1, 137.5, 135.9, 134.1, 131.8, 129.4, 127.2, 126.9, 121.8 (d, J = 30.6 Hz), 121.6 (d, J = 275.3 Hz), 24.3. ^{19}F NMR (471 MHz, chloroform-d) δ −61.4. FT-IR (ν) 3358, 3294, 2960, 2850, 1710, 1673, 1661, 1470, 1259, 1121, 1019, 800, and 739 cm^{-1}. HRMS (ESI) m/z [M − H]$^-$ calcd for [$C_{13}H_7F_3NO_3$], 282.0384; found, 282.0383.

*2-Amino-6,7-dimethoxy-3-trifluoromethyl-1,4-naphthoquinone (**3u**).* Yellow solid (43 mg, 72%), decomposed at 285 °C. ^{1}H NMR (500 MHz, chloroform-d) δ 7.61 (s, 1H), 7.49 (s, 1H), 6.51 (s, 1H), 5.97 (s, 1H), 4.04 (s, 3H), 4.01 (s, 3H). ^{13}C NMR (126 MHz, chloroform-d) δ 176.3, 176.1, 152.7, 149.9, 143.4, 125.7, 122.2 (d, J = 273.9 Hz), 120.8, 105.7, 105.1, 98.9 (d, J = 27.7 Hz), 54.0, 53.8. ^{19}F NMR (471 MHz, chloroform-d) δ −55.7. FT-IR (ν) 3519, 3383, 1619, 1578, 1506. 1322, 1276, 1119, 772, and 623 cm^{-1}. HRMS (ESI) m/z [M + H]$^+$ calcd for [$C_{13}H_{11}F_3NO_4$], 302.0635; found, 302.0640.

Mechanistic Experiments. A solution of 2-amino-1,4-naphthoquinone (0.2 mmol), $(CF_3SO_2)_2Zn$ (0.3 mmol), and TEMPO or 2-methyl-2-butene in DMSO (2.5 mL) was cooled to 0 °C, followed by a slow addition of *tert*-butyl hydroperoxide (70% solution in water, 1 mmol) by an eppendorf pipet. Then 0.1 mol % $FeSO_4.7H_2O$ was added to the mixture, which was stirred at room temperature overnight. The reaction was monitored by HPLC, and the mixture was partitioned between CH_2Cl_2 (20.0 mL) and saturated $NaHCO_3$ (20.0 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20.0 mL). The organic layers were dried with Na_2SO_4, concentrated, and purified by column chromatography on silica gel with ethyl acetate/petroleum ether mixture (ratio ca. 1:2) as the eluent.

*2-Amino-3-(2-trifluoromethyl-2,3-dimethylbutan-2-)-1,4-naphthoquinone (**4**).* Yellow oil (9 mg, 15%). ^{1}H NMR (500 MHz, chloroform-d) δ 8.03 (d, J = 7.7 Hz, 1H), 7.99 (d, J = 7.6 Hz, 1H), 7.69 (t, J = 7.0 Hz, 1H), 7.59 (t, J = 8.1 Hz, 1H), 5.70 (s, 1H), 3.76−3.65 (m, 1H), 1.62−1.53 (m, 6H), 1.17 (d, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, chloroform-d) δ 184.3, 182.2, 145.1, 134.6, 134.5, 131.9, 129.5, 128.9 (d, J = 282.2 Hz), 126.4, 125.7, 120.8, 43.1 (q, J = 23.3 Hz), 40.9, 27.9, 26.1, 9.7 (d, J = 3.5 Hz). ^{19}F NMR (471 MHz, chloroform-d) δ −65.4. FT-IR (ν) 3551, 3382, 2961, 2923, 2851, 1680, 1602. 1579, 1296, 1262, 1160, and 727 cm^{-1}. HRMS (ESI) m/z [M − H]$^-$ calcd for [$C_{16}H_{15}F_3NO_2$], 310.1060; found, 310.106.

Proliferation Inhibition Assays. The IC_{50} values of different agents in adherent and suspension cells were measured by the sulforhodamine B (SRB; Sigma, St. Louis, MO) assay and luminescent cell viability assay (Promega, Madison, WI) respectively, as reported previously. Cells were seeded into 96-well plates, cultured overnight, and treated with gradient concentrations of the tested agents for 72 h. Optic density for both assays was read with an EnVision Multilabel

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Reader (PerkinElmer, Waltham, MA). The average IC_{50} values were determined with the Logit method from three independent experiments.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00940.

Characterization of new compounds **3a**−**3u** and **4** by ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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