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Combinatorial synthesis and biological evaluations of (*E*)- β -trifluoromethyl vinylsulfones as antitumor agents†

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Combinatorial synthesis of (*E*)- β -trifluoromethyl vinylsulfones is accomplished through a reaction of alkynes, Togni reagent, and sodium benzenesulfonates in DMSO under metal-free conditions at room temperature. These compounds are evaluated in several assays against different tumor cells. Some hits are identified against ES-2, HO-8910, and K562.

Introduction

The chalcogen-containing skeleton has become a privileged and attractive scaffold in medicinal chemistry owing to its unique biological activities.¹ In particular, more and more novel biological effects of vinyl sulfone compounds have been discovered recently. It has been reported that structures containing an α,β -unsaturated vinylsulfone moiety exhibit modest inhibitory potencies in inflammation as a novel class toward Parkinson's^{2,3} and arthritis⁴ disease therapy by depressing the expression of endothelial cells of adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), as well as inhibiting the nuclear factor E2-related factor 2 (Nrf2) pathway which is responsible for the cellular defense system against oxidative stress. They also possess other biological activities, such as anti-Gram-positive bacteria as SrtA transpeptidase inhibitors,⁵ anti-parasitic as cysteine protease inhibitors,⁶ and anti-virus as potent inhibitors of HIV-1 integrase.⁷

Since compounds with substitution of fluorine might have a higher stability against metabolic enzymes and a better membranous permeability,^{8,9} we therefore considered to introduce a *trans*-trifluoromethyl group to the α,β -unsaturated vinylsulfone entity (Scheme 1). Thus, we initiated a program for the combinatorial synthesis of trifluoromethyl-substituted (*E*)-vinylsulfones and their biological evaluations as antitumor

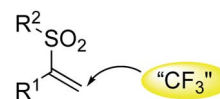
agents. Recently, we and others have involved in the synthesis of sulfonyl compounds,^{10,11} and we identified that (*E*)- β -trifluoromethyl vinylsulfones could be accessed through a three-component reaction of alkynes, Togni reagent, and sodium benzenesulfonates in DMSO under metal-free conditions at room temperature.¹² We envisioned that the library of (*E*)- β -trifluoromethyl vinylsulfones could be constructed *via* this method through diversity-oriented synthesis.

Herein, we report the biological evaluation of a series of *trans*-trifluoromethyl vinylsulfone derivatives by aim to study the structure–activity relationship and identify a hit structure. By initial screening, we found that the introduction of β -*trans*-trifluoromethyl group led to a potent activity against tumor cells proliferation.

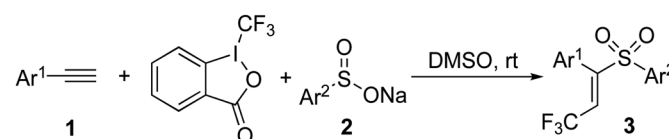
Results and discussion

Chemistry

The synthetic route for the target (*E*)- β -trifluoromethyl vinylsulfones was described in Scheme 2.¹² By treatment of alkynes **1**,



Scheme 1 Generation of (*E*)- β -trifluoromethyl vinylsulfones.



Scheme 2 Synthesis of (*E*)- β -trifluoromethyl vinylsulfones.

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Table 1 *In vitro* antiproliferative activity of the target compounds

$$\text{Ar}^1\text{-C}\equiv\text{C-H} + \text{Phthalimide-CF}_3 + \text{Ar}^2\text{-SO}_2\text{ONa} \xrightarrow{\text{DMSO, rt}} \text{Ar}^1\text{-C}(\text{SO}_2\text{Ar}^2)\text{=C-CF}_3$$

Compounds	Ar ¹	Ar ²	IC ₅₀ values (μM)						
			ES-2	HO-8910	Skov3	A2780	K562	A549	Bel-7402
3-1			4.9	3.1	12.8	23.4	4.6	2.1	15.6
3-2			6.3	4.5	23.9	18.3	6.4	4.3	19.1
3-3			10.7	7.0	>25	25.0	11.9	>25	>25
3-4			4.2	3.2	15.5	>25	1.1	3.3	>25
3-5			>25	23.7	>25	>25	12.9	>25	>25
3-6			>25	>25	>25	>25	10.1	>25	>25
3-7			4.4	2.6	>25	14.1	2.4	>25	>25
3-8			>25	9.1	>25	16.6	3.6	19.5	12.4
3-9			19.0	4.7	>25	6.3	4.9	>25	12.2
3-10			3.8	2.4	>25	14.2	2.9	9.7	22.5
3-11			5.6	3.7	>25	>25	8.3	15.1	18.4
3-12			8.9	2.3	16.8	N.D	6.6	14.8	N.D



Table 1 (Contd.)

Compounds	Ar ¹	Ar ²	IC ₅₀ values (μM)						
			ES-2	HO-8910	Skov3	A2780	K562	A549	Bel-7402
3-13			8.6	8.3	>25	>25	4.1	>25	>25
3-14			11.1	6.7	>25	>25	4.1	12.7	>25
3-15			8.2	5.7	>25	>25	7.2	16.6	>25
Doxorubicin			14.5	0.8	14.1	0.004	5.8	>25	24.3

Togni reagent, and sodium benzenesulfonates **2** in DMSO under metal-free conditions at room temperature, a series of (*E*)-β-trifluoromethyl vinylsulfones **3** were obtained in moderate to good yields. On the basis of this strategy, the library of (*E*)-β-trifluoromethyl vinylsulfones was constructed easily with high efficiency.

Biological activity

We chose (*E*)-(3,3,3-trifluoro-1-(phenylsulfonyl)prop-1-en-1-yl)benzene as our structural template and modified the aryl groups. Subsequently, 15 derivatives were synthesized, which included various functional groups on both aryl groups (Ar¹ and Ar²) (Table 1, compounds **3-1** to **3-15**). To our delight, these compounds had an excellent inhibitory activity against different tumor cells and especially against ES-2, HO-8910 and K562 with less than 10 μM of IC₅₀ values. As outlined in Table 1, it was apparent that compounds **3-1** to **3-4** offered reasonable potency profiles when the electron-withdrawing groups were introduced to Ar¹, while the electron-donating groups on Ar¹ (compounds **3-5** and **6**) would result in decreased activities. But the much stronger electron-withdrawing groups of cyano, fluoro, and trifluoromethyl didn't give better activity improvements (compounds **3-4**, **3-7** to **3-9**, and **3-11**). A same electronic effect was also found on Ar² (compounds **3-16** to **3-20**), but the activity changes were much minor than that on Ar¹.

To further validate the activities of electron-withdrawing groups, more substituents were introduced to investigate the structure–activity relations (Table 2, compounds **3-16** to **3-30**). With the same results, the changes of Ar² didn't make significant activity changes (compounds **3-16** to **3-20**). Compound **3-27**, with an acetyl group on *p*-position of Ar¹, all of the IC₅₀

values on ES-2, HO-8910, A2780, and K562 decreased to nM level. However, the compound became more inactive when the acetyl group was connected on the *m*-position (compound **3-28**). When the acetyl group was attached on Ar², the activity was affected very little (compounds **3-20**, **21**, **23**, and **25**). Interestingly, when a strong electron-withdrawing carboxyl group was introduced to Ar¹ (compounds **3-25** and **3-26**), the activity was dramatically decreased. Therefore, it was reasonable to conclude that an acetyl group on the *p*-position of Ar¹ was essential for the inhibitory activity, which might be due to a better noncovalent binding to the biological target by a moderate electronic withdrawing effect of the acetyl group.

Moreover, we synthesized compounds without double bond or trifluoromethyl group to identify the key structure of this skeleton (compounds **3-29** and **30**). The results showed that the proliferation inhibition activities of these two compounds were both obviously inhibited compared with **3-27**, about 40-, 11-, and 43-fold decrease for **3-29**, and 60-, 16-, and 86-fold decrease for **3-30**, on ES-2, HO-8190, and K562, respectively. Therefore, it showed that β-trifluoromethyl vinylsulfone along with an acetyl group on the *p*-position of Ar¹ was essential for the antitumor activity. Subsequently, varies different electron-withdrawing groups were introduced to Ar² with the structure of compound **3-27** as the structural template (Table 3, compounds **31-41**). Unfortunately, no compound showed better profiles than that of compound **3-27**.

The further time courses of the proliferation inhibitions on Skov3, HO-8910, ES-2, and K562 cells of compound **3-27** were conducted with different concentrations (10 and 1 μM) for different time periods (12, 24, 36, and 48 h). As shown in Scheme 3, the cellular growth was obviously inhibited in a dose-



Table 2 *In vitro* antiproliferative activity of the target compounds

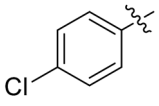
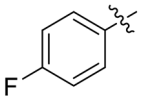
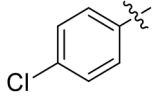
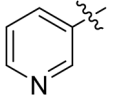
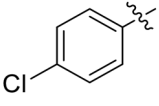
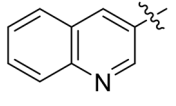
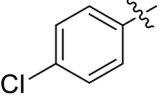
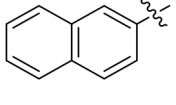
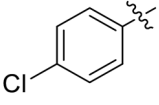
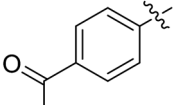
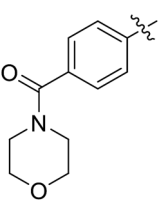
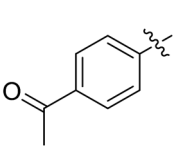
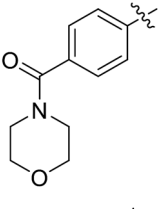
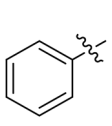
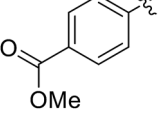
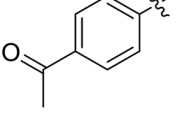
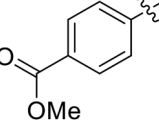
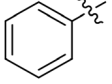
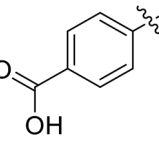
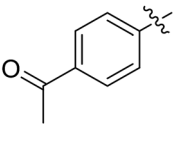
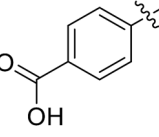
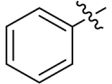
Compounds	Ar ¹	Ar ²	IC ₅₀ values (μM)						
			ES-2	HO-8910	Skov3	A2780	K562	A549	Bel-7402
3-16			4.1	2.0	25.0	21.5	12.4	7.9	>25
3-17			7.1	5.3	21.4	9.9	6.8	12.7	>25
3-18			6.6	4.3	>25	6.6	3.4	12.7	14.2
3-19			6.1	3.9	>25	6.5	>25	12.9	14.1
3-20			6.1	3.4	17.4	14.5	10.0	>25	>25
3-21			N.D	1.5	>25	2.5	2.8	6.0	N.D
3-22			11.3	1.2	17.9	9.2	1.4	8.9	>25
3-23			16	1.9	>25	4.1	2.4	15.7	N.D
3-24			16.8	1.1	12.2	9.8	1.4	5.9	>25
3-25			>25	7.1	>25	>25	6.0	>25	N.D
3-26			>25	2.9	>25	14.9	4.4	12.6	>25



Table 2 (Contd.)

Compounds	Ar ¹	Ar ²	IC ₅₀ values (μM)						
			ES-2	HO-8910	Skov3	A2780	K562	A549	Bel-7402
3-27			0.4	0.4	5.7	0.8	0.2	>25	17.7
3-28			6.2	0.4	8.9	16.4	2.6	0.6	18.1
3-29			17.1	4.3	>25	4.4	8.2	16.6	19.9
3-30			>25	6.3	>25	5.1	16.4	>25	>25
Doxorubicin			14.5	0.8	14.1	0.004	5.8	>25	24.3

and time-dependent manner. All of tested cell lines were more sensitive to compound 3-27 treatment than doxorubicin.

Furthermore, special attention was paid to potential cell toxicities caused by the tested compounds. The cell toxicities of several active compounds were evaluated on human bone marrow mesenchymal stem cells (hBMSCs), compared with doxorubicin (Table 4). Except compound 3-31, all of these tested compounds had much lower toxicities on hBMSCs. A representative example, compound 3-27 had much higher inhibition activities on tumor cells with only 1/5 toxicity on hBMSCs than doxorubicin, which indicates a potential development of such a new kind of skeleton as an alternative chemo drug.

Conclusions

In summary, we have identified several hits with a structural β -*trans*-trifluoromethyl vinylsulfone, which shows promising biological effects on antitumor with low cell toxicities, even the biological target is still unknown. The moderate electron-withdrawing groups, such as chloro, bromo, or acetyl group, on the *p*-position of Ar¹ and with Ar² unsubstituted both benefit the activity. More studies of structure–activity relationship,

biological mechanism, and *in vivo* activity are likely to be subsequently conducted on such a lead compound.

Experimental

Cell culture

Human ovarian cancer cells (ES-2, HO-8910, Skov3, and A2780), human alveolar basal epithelial cells (A549), human hepatocellular carcinoma cells (Bel-7402), human myelogenous leukemia cells (K562) and human bone marrow mesenchymal stem cell (hBMSCs) were obtained from the Type Culture Collection of Chinese Academy of Sciences (Shanghai, China). Cancer cells were maintained in RPMI-1640 supplemented with antibiotics (100 units per mL penicillin A and 100 μg mL⁻¹ streptomycin) and 10% FBS in an atmosphere of 5% CO₂ at 37 °C. hBMSCs was maintained in high glucose DMEM with 10% FBS. The medium was changed every three days. Exponentially growing cells were plated at a final concentration of 1 × 10⁴ cells per well in 96-well plates for cell proliferation assay.

Cell viability

The cell growth inhibitory effect of tested compounds determined using the MTT assay. After incubation for 24 h in 96-well



Table 3 *In vitro* antiproliferative activity of the target compounds

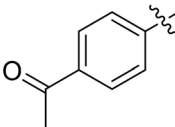
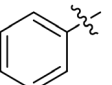
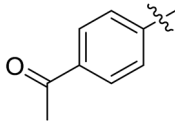
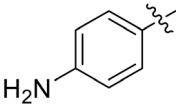
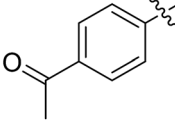
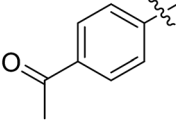
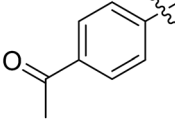
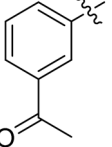
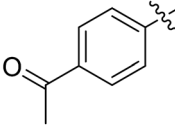
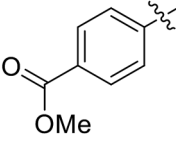
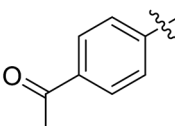
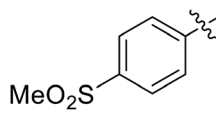
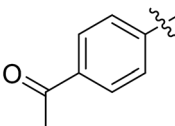
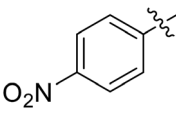
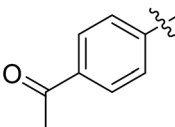
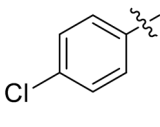
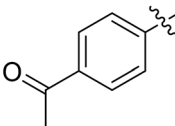
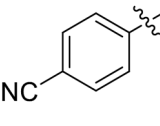
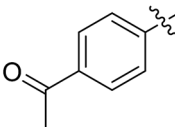
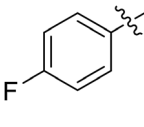
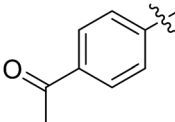
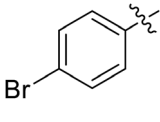
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3-31			>25	9.9	>25	14.6	5.9	>25	>25
3-32			4.5	4.8	4.6	N.D	0.8	5.3	N.D
3-33			13.1	1.5	17.5	4.1	0.4	14.7	15.3
3-34			>25	7.7	>25	18.4	4.2	>25	>25
3-35			>25	2.2	>25	15.5	6.5	20.2	>25
3-36			14.6	8.9	>25	13.4	12.1	13.6	20.2
3-37			>25	2.0	12.8	15.2	5.6	>25	13.6
3-38			2	2.5	3.7	18.9	>25	>25	>25
3-39			6.5	4.2	7.2	3.7	7.9	8.6	5.7
3-40			3.2	2.2	4.2	2.7	5.6	>25	13.5



Table 3 (Contd.)

Compounds	Ar ¹	Ar ²	IC ₅₀ values (μM)						
			ES-2	HO-8910	Skov3	A2780	K562	A549	Bel-7402
3-41			2.3	3.1	4.8	12.6	9.2	>25	>25
Doxorubicin			14.5	0.8	14.1	0.004	5.8	>25	24.3

plates, cells were treated with various concentrations (25, 12.5, 6.25, 3.12, 1.56, 0.78, 0.39, and 0.20 μM) of tested compounds for 48 hours, and the MTT solution (0.5 mg mL⁻¹) was added. After 4 h of incubation at 37 °C for MTT-formazan formation, the supernatant was removed and 100 μL of dimethyl sulfoxide (DMSO) was added into each well. Absorbance at 490 nm was determined spectrophotometrically by using a microplate reader (Epoch, BioTek Instruments, Inc., VT, USA). Each concentration was performed in triplicate. Antitumor activity was evaluated using IC₅₀ determined by non-linear regression analysis.

General experimental procedure for the synthesis of (*E*)-β-trifluoromethyl vinylsulfones from alkyne, Togni reagent, and sodium benzenesulfinate

Under nitrogen atmosphere, a mixture of alkyne **1** (0.2 mmol) and Togni reagent (0.22 mmol) in DMSO (1.0 mL) was stirred for several minutes. Then sodium benzenesulfinate **2** (0.4 mmol) in DMSO (2.0 mL) was added to the solution. The mixture was stirred overnight at room temperature. After completion of reaction as indicated by TLC, water (10 mL) was added and the mixture was extracted by EtOAc (3 × 10 mL). The solvent was evaporated and the residue was purified by flash column chromatography (EtOAc/*n*-hexane, 1 : 8) to give the desired product **3**. Data of typical examples are shown below.

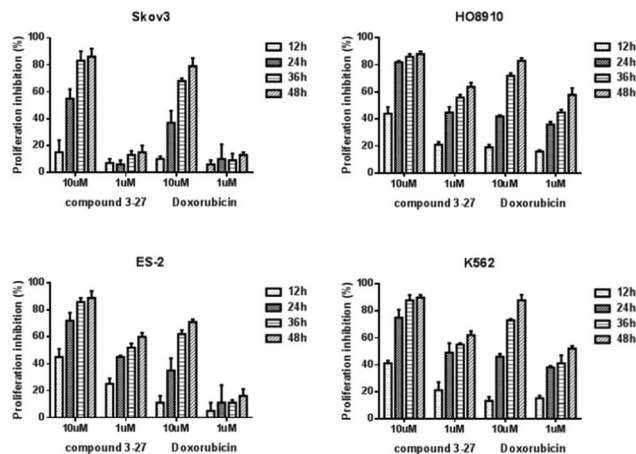
(*E*)-1-Bromo-4-(3,3,3-trifluoro-1-(phenylsulfonyl)prop-1-en-1-yl)benzene (3-1). White solid, 59.4 mg, 76.3% yield, ¹H NMR (400 MHz, CDCl₃) δ 7.67–7.54 (m, 3H), 7.50–7.37 (m, 4H), 7.17 (q, *J* = 7.1 Hz, 1H), 6.91–6.82 (m, 2H); ¹⁹F NMR (376 MHz, CDCl₃) δ –58.2 (d, *J* = 7.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 152.2 (d, *J* = 4.8 Hz), 136.0, 134.5, 131.4, 131.1 (d, *J* = 1.3 Hz), 129.2, 129.1, 126.7, 125.8 (q, *J* = 36.0 Hz), 124.9, 121.4 (q, *J* = 273.5 Hz); LC-MS: >97% purity; HRMS (ESI) calcd for C₁₅H₁₁BrF₃O₂S: 390.9610 (M + H⁺), found: 390.9634.

(*E*)-1-Chloro-4-(3,3,3-trifluoro-1-(phenylsulfonyl)prop-1-en-1-yl)benzene (3-2). White solid, 51.4 mg, 74.3% yield, ¹H NMR (400 MHz, CDCl₃) δ 7.62 (t, *J* = 7.4 Hz, 1H), 7.61–7.59 (m, 2H), 7.49–7.42 (m, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 7.17 (q, *J* = 7.1 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 2H); ¹⁹F NMR (376 MHz, CDCl₃) δ –58.3 (d, *J* = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 152.2, 136.5, 136.0, 134.5, 130.9 (d, *J* = 1.2 Hz), 129.2, 129.1, 128.4, 126.2, 125.8 (q, *J* = 36.0 Hz), 121.4 (q, *J* = 273.6 Hz); LC-MS: >97% purity; HRMS (ESI) calcd for C₁₅H₁₁ClF₃O₂S: 347.0115 (M + H⁺), found: 347.0104.

(*E*)-1-(3,3,3-Trifluoro-1-(phenylsulfonyl)prop-1-en-1-yl)-4-(trifluoromethoxy)benzene (3-3). White solid, 50.0 mg, 63.1% yield, ¹H NMR (400 MHz, CDCl₃) δ 7.62 (t, *J* = 7.4 Hz, 1H), 7.58–7.55 (m, 2H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.18 (q, *J* = 7.1 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H); ¹⁹F NMR (376 MHz, CDCl₃) δ –57.9 (s, 3F), –58.4 (d, *J* = 7.0 Hz, 3F); ¹³C NMR (100 MHz, CDCl₃) δ 152.0 (d, *J* = 4.9 Hz), 150.4, 135.9, 134.5, 131.3 (d, *J* = 1.0 Hz), 129.2, 129.1, 126.3, 125.8 (q, *J* = 36.0 Hz), 121.3 (q, *J* = 267.2 Hz), 120.2 (q, *J* = 258.4 Hz), 120.1; LC-MS: >97% purity; HRMS (ESI) calcd for C₁₆H₁₁F₆O₃S: 397.0328 (M + H⁺), found: 397.0314.

(*E*)-1-(3,3,3-Trifluoro-1-(phenylsulfonyl)prop-1-en-1-yl)-4-(trifluoromethyl)benzene (3-4). White solid, 53.5 mg, 70.4% yield, ¹H NMR (400 MHz, CDCl₃) δ 7.66 (d, *J* = 7.0 Hz, 1H), 7.63–7.52 (m, 4H), 7.51–7.48 (m, 2H), 7.29–7.22 (m, 1H), 7.14 (d, *J* = 7.3 Hz, 2H); ¹⁹F NMR (376 MHz, CDCl₃) δ –58.3 (d, *J* = 6.8 Hz), –63.0 (s); ¹³C NMR (100 MHz, CDCl₃) δ 152.0, 135.8, 134.7, 131.9, 131.6, 130.1, 129.3, 129.1, 126.1 (q, *J* = 36.3 Hz), 125.0, 121.3 (q, *J* = 273.2 Hz); LC-MS: >97% purity; HRMS (ESI) calcd for C₁₆H₁₁F₆O₂S: 381.0378 (M + H⁺), found: 381.0369.

(*E*)-4-(3,3,3-Trifluoro-1-(phenylsulfonyl)prop-1-en-1-yl)-1,1'-biphenyl (3-5). Pale yellow solid, 55.0 mg, 70.9% yield, ¹H NMR



Scheme 3 Dose- and time-dependent effect of compound **3-27** on cancer cells (Skov3, HO-8910, ES-2, and K562). Cell proliferation inhibitions were examined by the MTT method as described in Experimental. The data has been plotted using means S.E. of triplicate determinations.



Table 4 Cell toxicities of the selected compounds on hBMSCs

Compounds	3-27	3-32	3-36	3-37	3-39	3-40	Doxorubicin
IC ₅₀ (μM)	5.4 ± 0.61	0.65 ± 0.45	15.3 ± 0.72	6.5 ± 0.56	6.8 ± 1.57	8.4 ± 0.91	0.96 ± 0.24

(400 MHz, CDCl₃) δ 7.67–7.56 (m, 5H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.50–7.42 (m, 4H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.22 (q, *J* = 7.1 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 2H); ¹⁹F NMR (376 MHz, CDCl₃) δ –58.1 (d, *J* = 7.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 153.1, 142.7, 139.7, 136.3, 134.3, 130.03, 129.1, 128.9, 128.0, 127.0, 126.6, 125.3 (q, *J* = 35.9 Hz), 124.8, 121.6 (q, *J* = 284.1 Hz); LC-MS: >97% purity; HRMS (ESI) calcd for C₂₁H₁₆F₃O₂S: 389.0818 (M + H⁺), found: 389.0803.

(E)-1-(3,3,3-Trifluoro-1-(phenylsulfonyl)prop-1-en-1-yl)naphthalene (3-6). Yellow oil, 32.3 mg, 44.6% yield, ¹H NMR (400 MHz, CDCl₃) δ 7.88 (d, *J* = 8.3 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.51–7.46 (m, 3H), 7.44 (d, *J* = 7.0 Hz, 1H), 7.42–7.39 (m, 1H), 7.38–7.33 (m, 2H), 7.32–7.27 (m, 3H), 7.03 (d, *J* = 7.1, 1H); ¹⁹F NMR (376 MHz, CDCl₃) δ –60.1 (d, *J* = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 152.0, 134.3, 132.9, 131.4, 130.6, 129.7, 129.4, 129.2, 128.9, 128.6, 128.1, 127.2 (q, *J* = 35.9 Hz), 126.7, 126.2, 124.6, 124.3, 121.4 (q, *J* = 273.6 Hz); LC-MS: >97% purity; HRMS (ESI) calcd for C₁₉H₁₄F₃O₂S: 363.0661 (M + H⁺), found: 363.0659.

(E)-1-Chloro-4-((1-(4-chlorophenyl)-3,3,3-trifluoroprop-1-en-1-yl)sulfonyl)benzene (3-12). White solid, 34.0 mg, 44.8% yield, ¹H NMR (400 MHz, CDCl₃) δ 7.53–7.45 (m, 4H), 7.33–7.28 (m, 2H), 7.23–7.13 (m, 1H), 7.05–6.89 (m, 2H); ¹⁹F NMR (376 MHz, CDCl₃) δ –58.3 (d, *J* = 6.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 151.8, 141.5, 136.8, 134.6, 130.9, 130.5, 129.6, 128.6, 126.2 (q, *J* = 36.2 Hz), 126.0, 121.3 (q, *J* = 274.1 Hz); LC-MS: >97% purity; HRMS (ESI) calcd for C₁₅H₁₀Cl₂F₃O₂S: 380.9725 (M + H⁺), found: 380.9708.

(E)-1-(4-(3,3,3-Trifluoro-1-(phenylsulfonyl)prop-1-en-1-yl)phenyl)ethanone (3-27). White solid, 56.6 mg, 79.9% yield, ¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, *J* = 8.5 Hz, 2H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.58–7.55 (m, 2H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.19 (q, *J* = 7.1 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 2H), 2.59 (s, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ –58.3 (d, *J* = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 197.2, 152.3, 137.9, 135.9, 134.6, 132.5, 129.9, 129.3, 129.1, 127.8, 125.8 (q, *J* = 36.1 Hz), 121.3 (q, *J* = 273.5 Hz), 26.6; LC-MS: >97% purity; HRMS (ESI) calcd for C₁₇H₁₄F₃O₃S: 355.0610 (M + H⁺), found: 355.0617.

Conflicts of interest

There are no conflicts to declare.

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