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Synthesis of bioactive 2-(2-(difluoromethoxy)aryl)benzo[d]thiazole derivatives via base-promoted one-pot process

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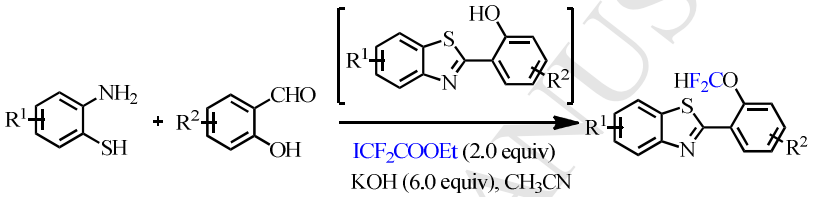
Abstract:



A convenient synthesis of 2-(2-(difluoromethoxy)aryl)benzo[d]thiazoles from 2-(*o*-hydroxyaryl)benzothiazoles and commercially available ethyl difluoroiodoacetate (ICF_2CO_2Et) is described. The transformation was amenable to a one-pot, sequential three-component protocol from *o*-hydroxybenzaldehyde, *o*-aminothiophenol, and ICF_2CO_2Et promoted by KOH. Additionally, some of the prepared compounds exhibited promising activity against human ovarian cancer cells.

Keywords: 2-arylbenzo[d]thiazoles; *O*-difluoromethylation; *o*-hydroxybenzaldehyde; *o*-aminothiophenol; ethyl difluoroiodoacetate.

The introduction of fluorine atom or fluorinated groups into active organic molecules can distinctly modulate their membrane permeability, metabolic stability, and

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bioavailability.[1] Therefore, organofluorine compounds have been widely employed in pharmaceuticals, agrochemicals, and biological molecules.[2] Among these fluorinated molecules, difluoromethyl ethers have attracted great interest as candidates for modern drug discovery.[3] A wide range of OCF_2H-containing organic molecules exhibit anti-inflammary, anti-tumour, anti-bacterial, and antimicrobial activity (Figure 1).[4-7] For instance, Roflumilast is a commercially available drug used in COPD patients.[4,5] Pantoprazole is also a widely used anti-ulcer pharmaceutical agent.[4] Fluoromycin is a fluorescent-labeled derivative of talisomycin S_{10b}, and can be used as a fungicide.[6] Pyroxasulfone was found to be a novel herbicide for soybean, wheat and corn.[7] Consequently, the development of efficient methods for the synthesis of OCF_2H-containing organic molecules from commercially available substrates is highly desired.

2-Arylbenzothiazoles have attracted great attention because such kinds of heterocycles exhibit an extensive range of biological activities, such as antitumor, antiviral, and antimicrobial properties.[8,9] For instance, fluorine-containing compound **I** was discovered to be a potent S1P1 agonist (EC_{50} = 0.017 μM),[8] while compound **II** could suppress the growth of trypanosomes (Figure 2).[9] As part of our interest in C-H functionalization of 2-arylbenzothiazoles,[10] herein we wish to describe a simple and convenient approach for the synthesis of 2-(2-(difluoromethoxy)aryl)benzo[d]thiazoles and examine their bioactivities.

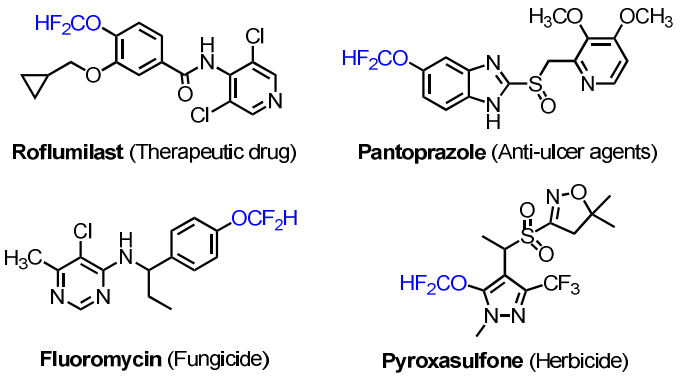


Figure 1. Examples of bioactive compounds possessing an OCF_2H group.

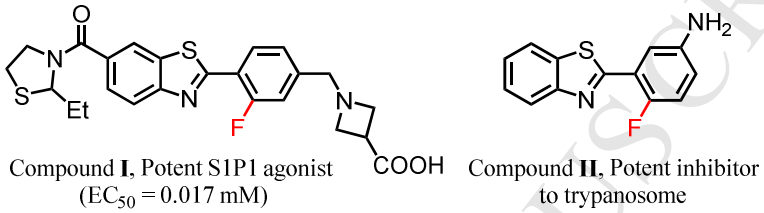
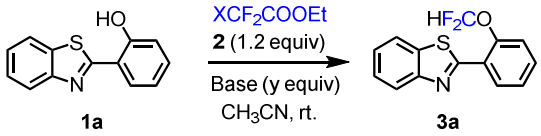


Figure 2. F-containing 2-arylbenzothiazole-based bioactive molecules.

Recently, much attention has focused on the development of efficient approaches for the synthesis of difluoromethyl ethers via the base-promoted *O*-difluoromethylation of phenols,[11] alcohols,[12] and ketones[13] using various precursors of difluorocarbene. A variety of difluoromethylating agents have also been employed successfully.[11-13] For example, Hartwig and Fier developed a difluoromethylation of phenols with HCF_2OTf in the presence of KOH.[11f] Shen and co-workers described the direct difluoromethylation of alcohols using an electrophilic difluoromethylated sulfonium ylide.[12b] Shibata and co-workers reported the organic base-promoted direct *O*-difluoromethylation of 1,3-diones via the in situ generation of difluorocarbene from bromodifluoromethylating reagents.[13d] However, a number of these fluoromethylating agents (HCF_2Cl, HCF_3, and CHF_2I) are gases, which are difficult to handle. In addition, some of them are low reactivity or difficult to prepare. Therefore, the new,

simple and efficient reagents for the difluoromethylation of alcohols and phenols are also greatly desired.

Table 1 Optimization of reaction conditions[a].



Entry	Base	X (**2**)	y (equiv)	Yield (%)[d]
1	K_2CO_3	Cl (**2a**)	1.0	trace
2	K_2CO_3	Br (**2b**)	1.0	20
3	K_2CO_3	I (**2c**)	1.0	40
4	KOH	I (**2c**)	1.0	51
5	Na_2CO_3	I (**2c**)	1.0	trace
6	KF	I (**2c**)	1.0	trace
7	Cs_2CO_3	I (**2c**)	1.0	40
8	-	I (**2c**)	-	trace
9	KOH	I (**2c**)	3.0	60
10	KOH	I (**2c**)	5.0	65
11	KOH	I (**2c**)	6.0	68
12	KOH	I (**2c**)	7.0	72
13[b]	KOH	I (**2c**)	6.0	82
14[b]	KOH	I (**2c**)	7.0	83
15[c]	KOH	I (**2c**)	6.0	61

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol, 1.2 equiv), base (x equiv), CH_3CN (2 mL), rt, 12 h. [b]In the presence of 2.0 equiv of **2**. [c]At 50 °C. [d]Yield based on **1a**.

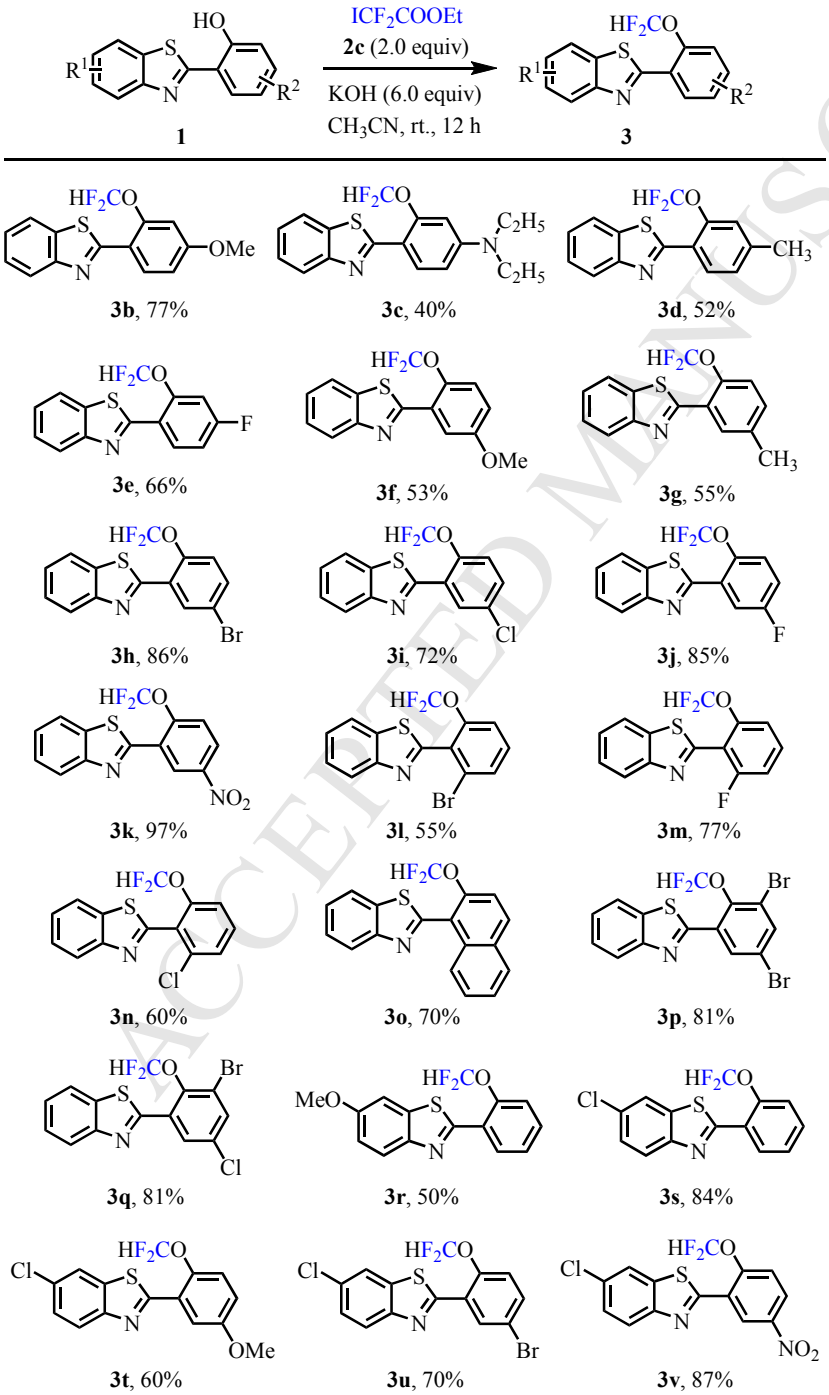
Based on previous work,[11b] the reaction of 2-(2-hydroxyphenyl)benzothiazole **1a** and ethyl chlorodifluoroacetate **2a** (1.2 equiv) was initially chosen as a template to optimize the reaction conditions (Table 1, entry 1). Regretfully, only trace of desired product was observed. Fortunately, when ethyl 2-bromo-2,2-difluoroacetate **2b** and ethyl 2,2-difluoro-2-iodoacetate **2c** were used as difluoromethylating agents in the presence of potassium carbonate (1.0 equiv) in acetonitrile at room temperature, the desired *o*-difluoromethoxylated product **3a** was obtained in 20% and 40% yield, respectively (Table 1, entries 2 and 3). Regrettably, the screening of different solvents

showed that almost no reaction occurred in toluene, dimethyl sulfoxide, glacial acetic acid, methanol, 1,4-dioxane, DMF, and DMAc. Next, the screening of bases revealed that potassium hydroxide was better than others (Table 1, entries 4-7). Trace amounts of the desired product were observed in the absence of base (Table 1, entry 8). Increasing the amount of KOH from 1.0 to 7.0 equivalents gave higher yields of the desired product; the yield increased to 72% when 7.0 equivalent of KOH was used (Table 1, entry 12). Further studies showed that the yield of **3a** could be increased to 82% when 2.0 equivalents of **2c** were employed (Table 1, entry 13). When the reaction temperature was increased to 50 ^{o}C, the desired product was obtained in only 61% yield, showing that reaction temperature has a significant impact on product yield (Table 1, entry 15).

With the optimized reaction conditions in hand (Table 1, entry 13), we explored the substrate scope of the 2-(2-hydroxyaryl)benzothiazoles **1** (Table 2). The results show that the methodology can be applied to a broad range of substrates. Substrates bearing electron-withdrawing or electron-donating groups underwent reaction smoothly. The reaction was compatible with various substituents, such as methoxy, *N*,*N*-diethyl, methyl, fluoro, chloro, bromo, and nitro groups. In comparison, substrates bearing electron-donating groups gave their corresponding products in moderate yields, whereas substrates bearing electron-withdrawing groups gave the desired products with good to excellent yields. For instance, the reaction of *N*,*N*-diethyl substituted substrate **1c** with ethyl difluoroiodoacetate **2c** gave the corresponding product **3c** in only 40% yield. However, the nitro substituted 2-(2-hydroxyphenyl)benzothiazole **1k**

reacted smoothly with **2c** to give the corresponding target product **3k** in 97% yield. Similarly, the analogue 1-(benzo[d]thiazol-2-yl)naphthalen-2-ol **1o** gave the corresponding difluoromethoxylated product **3o** in 70% yield.

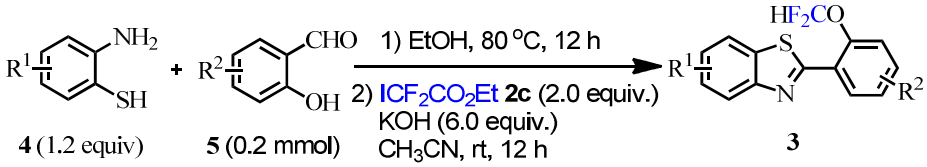
Table 2 Substrate scope for difluoromethylation of 2-(2-hydroxyaryl)benzothiazoles **1**[a]



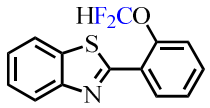
[a]Reaction conditions: **1** (0.2 mmol), **2c** (0.24 mmol, 1.2 equiv), KOH (6.0 equiv), CH_3CN (2 mL), rt, 12 h.

It is well-known that 2-(*o*-hydroxyphenyl)benzothiazoles can be easily prepared via the cyclocondensation/oxidation of *o*-amino thiophenol **4a** and *o*-hydroxybenzaldehyde **5a**. Therefore, we envisaged that a cyclocondensation/oxidation and a subsequent difluoromethyl etherification could be conducted in one-pot. Thus, we performed a three-component reaction of *o*-hydroxybenzaldehyde **5a**, *o*-aminothiophenol **4a** (1.2 equiv), and ICF_2COOEt **2c** (2.0 equiv) in EtOH/acetonitrile in the presence of KOH (6.0 equiv). The in situ formed 2-(*o*-hydroxyphenyl)benzothiazole was converted to the difluoromethyl ether product **3a** in 75% yield. A range of *o*-amino thiophenols **4** and *o*-hydroxybenzaldehydes **5** were amenable to the cascade reaction conditions, giving the corresponding products **3** in good yields (Table 3).

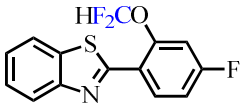
Table 3 One-pot three-component reaction[a]



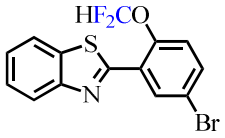
4 (1.2 equiv) **5** (0.2 mmol) **3**



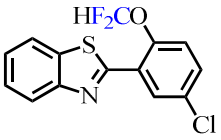
3a, 75%



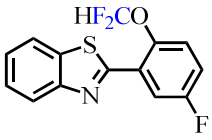
3e, 60%



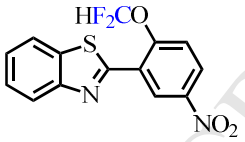
3h, 66%



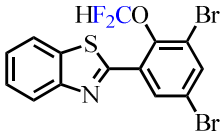
3i, 66%



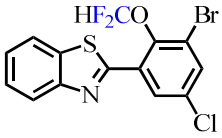
3j, 73%



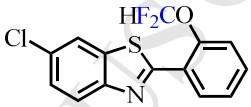
3k, 50%



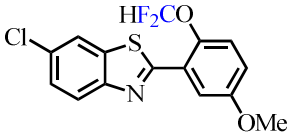
3p, 61%



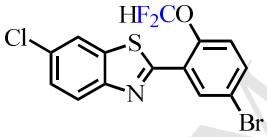
3q, 86%



3s, 65%



3t, 64%

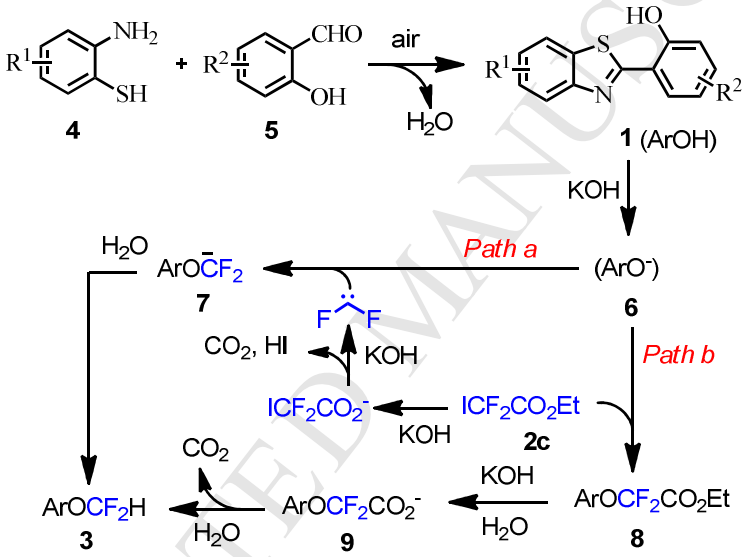


3u, 60%

[a]Reaction conditions: (1) **5** (0.2 mmol), **4** (0.24 mmol, 1.2 equiv), KOH (6.0 equiv), EtOH (2 mL), 80 °C, 12 h. (2) **2c** (0.4 mmol, 2 equiv), KOH (6.0 equiv), CH_3CN (2 mL), rt, 12 h.

According to previous reports,[11-13] a plausible mechanism of this cascade reaction has been proposed, as shown in Scheme 1. First, the cyclocondensation/oxidation of *o*-amino thiophenol **4** and *o*-hydroxybenzaldehyde **5** under an air atmosphere affords 2-(*o*-hydroxyphenyl)benzothiazole **1**. Subsequently, the transformation may involve the traditional catalytic model via generation of a difluorocarbene intermediate, which is formed in situ from ethyl difluoroiodoacetate **2c** in the presence of KOH. The difluorocarbene is attacked by a phenoxide (ArO^-) species to give the intermediate **7** ($ArOCF_2^-$), which is then converted to the target product **3** in the presence of water

(Path a). Alternatively, **1** undergoes an intermolecular nucleophilic substitution reaction with ethyl difluoroiodoacetate **2c** upon treatment with KOH, yielding ethyl 2-(2-(benzo[d]thiazol-2-yl)phenoxy)-2,2-difluoroacetate **8**. Next, the 2-(2-(benzo[d]thiazol-2-yl)phenoxy)-2,2-difluoroacetic acid anion **9** is generated via the alkaline hydrolysis of compound **8** using KOH as a base. Finally, the decarboxylation of **9** produces the desired product **3** (Path b).[14] Compounds **8** and **9** haven't been isolated in our reaction system, although they were observed by LC-MS.



Scheme 1 Possible mechanism for the difluoromethoxylation.

To evaluate the bioactivities of the 2-(2-(difluoromethoxy)aryl)benzo[d]thiazoles, a general screening of their antitumor activities was performed using an MTT assay. Preliminary results showed that some of the compounds exhibited good activity against human ovarian cancer cells (SKOV3). For example, compound **3l**, bearing a bromo group at the *ortho*- position of the 2-phenyl ring, displayed promising activity (IC_{50} = 92.0 μM, 48 h) against human ovarian cancer cells (SKOV3), comparing

favourably with cisplatin (IC_{50} =135.2 μM, 48 h).[15]

Conclusion

In summary, we have developed a simple and efficient method for the synthesis of 2-(2-(difluoromethoxy)aryl)benzo[d]thiazoles via the reaction of 2-(*o*-hydroxyaryl)benzothiazoles with commercially available and easily handled ethyl difluoroiodoacetate (ICF_2COOEt). In addition, the methodology was successfully employed in a one-pot, three-component process involving *o*-hydroxybenzaldehyde, *o*-aminothiophenol, and ICF_2COOEt in the presence of KOH. Furthermore, some of the target compounds exhibited good anti-ovarian cancer cell activity.

EXPERIMENTAL SECTION

Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane on the δ scale. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AV-400 spectrometer operating at 400 MHz, 100 MHz and 376 MHz respectively. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. High resolution mass spectrometry (HRMS) spectra were obtained on a micrOTOF II instrument.

*General Procedure for difluoromethylation of of 2-(2-hydroxyaryl)benzothiazoles **3**.*

2-(*o*-Hydroxyphenyl)benzothiazoles were synthesized according to the reported procedures.[16]

2-(*o*-Hydroxyaryl)benzo[*d*]thiazole **1** (0.2 mmol), potassium hydroxide (6 equiv,

67.3 mg), acetonitrile (2 mL) and ethyl difluoroiodoacetate **2** (2.0 equiv, 100 mg) were continuously added to a 20 mL reaction tube. The reaction was stirred at 25 °C for 12 h. After completion of the reaction, it was detected by a TLC thin-layer silica gel plate, evaporation of the solvent under reduced pressure followed purification by silica gel chromatography using petroleum ether: ethyl acetate = 50:1 as eluent to give 2-(*o*-difluoromethoxyphenyl) benzo[*d*]thiazole **3**.

*Experimental data for compounds **3***

*2-(2-(Difluoromethoxy)phenyl)benzo[d]thiazole (**3a**).* Colorless solid, 45.5 mg (82%), mp 51-53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (dd, *J* =1.6, 7.6 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.43 – 7.36 (m, 2H), 7.29 (d, *J* = 8.4 Hz, 1H), 6.69 (t, *J* = 73.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 152.4, 148.8, 136.1, 131.6, 130.6, 126.2, 125.9, 125.7, 125.3, 123.3, 121.4, 119.6, 116.1 (t, $^{1}J_{C\text{-}F}$ = 260 Hz).^{19}F NMR (376 MHz, $CDCl_3$) δ -80.42. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{10}F_2NOS^+$: 278.0446; found: 278.0450.

*2-(2-(Difluoromethoxy)-4-methoxyphenyl)benzo[d]thiazole (**3b**).* Colorless solid, 47.5 mg (77%), mp 102-104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.8 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.76 (d, *J* = 2.0 Hz, 1H), 6.66 (d, *J* = 73.2 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 162.0, 152.4, 149.9 (t, $J_{C\text{-}F}$ = 3.0 Hz), 135.6, 131.6, 126.1, 124.9, 122.9, 121.3, 118.3, 116.1 (t, $^{1}J_{C\text{-}F}$ = 260 Hz), 111.4, 105.6, 55.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.50. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{12}F_2NO_2S^+$: 308.0551; found: 308.0556.

*4-(Benzo[d]thiazol-2-yl)-3-(difluoromethoxy)-N,N-diethylaniline (**3c**).* Yellow solid, 28 mg (40%), mp 69-71 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.8 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 6.64 (t, *J* = 74.0 Hz, 1H), 6.62 (dd, *J* = 9.6, 2.8 Hz, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 3.42 (q, *J* = 7.2 Hz, 4H), 1.22 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 152.7, 150.7, 150.4, 135.4, 131.4, 125.9, 124.2, 122.3, 121.2, 116.5 (t, $^{1}J_{C-F}$ = 259 Hz), 112.5, 109.0, 101.9, 44.7, 12.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -79.62. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{18}F_2N_2OS^+$: 349.1181; found: 349.1188.

*2-(2-(Difluoromethoxy)-4-methylphenyl)benzo[d]thiazole (**3d**).* Colorless solid, 30.3 mg (52%) , mp 129-131 ^{o}C . ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.08 (s, 1H), 6.67 (t, *J* = 73.2 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 152.4, 148.8, 142.8, 135.9, 130.3, 126.8, 126.2, 125.1, 123.1, 122.9, 121.4, 120.1, 116.2 (t, $^{1}J_{C-F}$ = 260 Hz), 21.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.21. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{12}F_2NOS^+$: 293.0602; found: 293.0648.

*2-(2-(Difluoromethoxy)-4-fluorophenyl)benzo[d]thiazole (**3e**).* Yellow solid, 39 mg (66%), mp 82-84 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51-8.47 (m, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 6.8 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 9.2 Hz, 1H), 6.68 (t, *J* = 72.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (d, J_{C-F} = 253 Hz), 161.0, 152.3, 149.4 (d, J_{C-F} = 11 Hz), 135.7, 132.1 (d, J_{C-F} = 10 Hz), 126.3, 125.3, 123.2, 122.0, 121.4, 115.8 (t, J_{C-F} = 262

Hz), 113.2 (d, J_{C-F} = 21 Hz), 107.5 (d, J_{C-F} = 25 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.25, -106.06. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_9F_3NOS^+$: 296.0351; found: 296.0357.

*2-(2-(Difluoromethoxy)-5-methoxyphenyl)benzo[d]thiazole (**3f**)*. Colorless solid, 32.6 mg (53.2%), mp 85-87 ^oC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 3.2 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 7.00 (dd, *J* = 9.2, 3.2 Hz, 1H), 6.59 (t, *J* = 73.6 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 157.3, 152.3, 142.4, 136.1, 126.8, 126.3, 125.4, 123.3, 121.9, 121.4, 118.2, 116.4 (t, *J* = 261 Hz), 55.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.32. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{12}F_2NO_2S^+$: 308.0551; found: 308.0564.

2-(2-(Difluoromethoxy)-5-methylphenyl)benzo[d]thiazole (**3g**). Colorless solid, 32 mg (55%) mp 70-72 ^oC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 2.0 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.51 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.28 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.64 (t, *J* = 73.6 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 152.4, 146.7, 136.0, 135.9, 132.3, 130.6, 126.2, 125.3, 125.2, 123.2, 121.4, 119.8, 116.3 (t, $^1J_{C-F}$ = 260 Hz), 20.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.35. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{12}F_2NOS^+$: 296.0602; found: 296.0596.

2-(5-Bromo-2-(difluoromethoxy)phenyl)benzo[d]thiazole (**3h**). Yellow solid, 61.3 mg (86%), mp 103-105 ^oC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 2.4 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.42 (t, *J* = 7.6

Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 6.66 (t, *J* = 72.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 152.2, 147.6, 136.1, 134.2, 133.0, 127.4, 126.5, 125.7, 123.5, 121.4, 121.3, 119.2, 115.8 (t, $^{1}J_{C-F}$ = 262 Hz), 29.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.76. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_9BrF_2NOS^+$: 355.9551; found: 355.9560.

2-(5-Chloro-2-(difluoromethoxy)phenyl)benzo[d]thiazole (**3i**). Colorless solid, 44.9 mg (72%), mp 84-86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 2.4 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.24 (d, *J* = 8.8 Hz, 1H), 6.66 (t, *J* = 72.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 152.2, 147.0, 136.1, 131.7, 131.3, 130.1, 127.1, 126.5, 125.7, 123.5, 121.4, 121.2, 115.9 (t, $^{1}J_{C-F}$ = 262 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.80. HRMS (ESI) : m/z $[M + H]^+$ calcd for $C_{14}H_9ClF_2NOS^+$: 312.0056; found: 312.0066.

*2-(2-(Difluoromethoxy)-5-fluorophenyl)benzo[d]thiazole (**3j**)*. Colorless solid, 50.2 mg (85%), mp 99-101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 9.2, 3.2 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.52 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.28 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.19-7.14 (m, 1H), 6.64 (t, *J* = 72.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5 (d, $^{4}J_{C-F}$ = 2.4 Hz), 160.0 (d, $^{1}J_{C-F}$ = 244 Hz), 152.2, 144.5 (d, $^{4}J_{C-F}$ = 2.7 Hz), 136.1, 127.7 (d, $^{4}J_{C-F}$ = 8.0 Hz), 126.5, 125.7, 123.5, 121.9 (d, ^{4}J = 8.5 Hz), 121.5, 118.2 (d, $^{2}J_{C-F}$ = 24 Hz), 116.7 (d, $^{2}J_{C-F}$ = 25.6 Hz), 116.1 (t, $^{1}J_{C-F}$ = 261 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.69, -115.50. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_9F_3NOS^+$: 296.0351; found: 296.0361.

*2-(2-(Difluoromethoxy)-5-nitrophenyl)benzo[d]thiazole (**3k**).* Red solid, 62.5 mg (97%), mp 169-170 °C. ^{1}H NMR (400 MHz, CDCl3) δ 9.45 (d, *J* = 3.2 Hz, 1H), 8.34

(dd, *J* = 2.8, 9.2 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.57 (dt, *J* = 1.2, 9.2 Hz,1H), 7.47 (dt, *J* = 0.8, 8.0 Hz,1H), 7.45 (d, *J* = 9.2 Hz,1H), 6.84 (t, *J* = 71.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 152.3, 152.1, 145.1, 136.1, 126.8, 126.4, 126.2, 126.0, 123.8, 121.5, 119.2, 115.3 (t, $^{1}J_{C-F}$ = 265.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.73. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_8F_2N_2O_3S^+$: 323.0296; found: 323.0298.

*2-(2-Bromo-6-(difluoromethoxy)phenyl)benzo[d]thiazole (**3l**)*. Colorless oil, 39 mg (55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.58 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 6.48 (t, *J* = 73.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 152.9, 150.2, 136.4, 132.0, 130.2, 128.5, 126.3, 125.8, 124.8, 123.9, 121.6, 119.2, 115.9 (t, $^{1}J_{C-F}$ = 261 Hz), 29.71.^{19}F NMR (376 MHz, $CDCl_3$) δ -81.46. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_9BrF_2NOS^+$: 355.9551; found: 355.9554.

*2-(2-(Difluoromethoxy)-6-fluorophenyl)benzo[d]thiazole (**3m**)*. Yellow oil, 34 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.52 (dt, *J* = 1.2, 8.0 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.15-7.10 (m, 2H), 6.62 (t, *J* = 73.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8 (d, $^{1}J_{C-F}$ = 253 Hz), 156.7, 153.0, 149.7, 136.1, 131.8 (d, $^{3}J_{C-F}$ = 10 Hz), 126.2, 125.7, 123.8, 121.4, 116.4 (d, $^{4}J_{C-F}$ = 3 Hz), 116.2 (t, $^{2}J_{C-F}$ = 15 Hz), 116.1 (t, $^{1}J_{C-F}$ = 261 Hz), 113.6 (d, $^{2}J_{C-F}$ = 22 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.90, -109.49. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_9F_3NOS^+$: 296.0351; found: 296.0355.

*2-(2-Chloro-6-(difluoromethoxy)phenyl)benzo[d]thiazole (**3n**)*. Yellow oil, 37.4 mg (60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.49-7.41 (m, 3 H), 7.27-7.24 (m, 1H), 6.50 (t, *J* = 73.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 153.0, 150.3, 136.5, 135.6, 131.6, 127.1, 126.6, 126.3, 125.7, 123.9, 121.6, 118.7, 115.9 (t, $^{1}J_{C-F}$ = 262 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.54. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_9ClF_2NOS^+$: 312.0056; found: 312.0066.

*2-(2-(Difluoromethoxy)naphthalen-1-yl)benzo[d]thiazole (**3o**)*. Yellow solid, 45.8 mg (70%), mp 71-73 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.0 Hz, 1H), 8.01 (t, *J* = 8.4 Hz, 2H), 7.92-7.90 (m, 1H), 7.86 - 7.84 (m, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.54-7.47 (m, 4H), 6.58 (t, *J* = 73.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 153.3, 146.9, 136.5, 132.9, 132.3, 131.3, 128.1, 128.0, 126.3, 126.2, 125.6, 125.5, 123.8, 122.4, 121.5, 119.4, 116.4 (t, $^{1}J_{C-F}$ = 260 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.40. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{12}F_2NOS^+$: 328.0602; found: 328.0609.

*2-(3,5-Dibromo-2-(difluoromethoxy)phenyl)benzo[d]thiazole (**3p**)*. Colorless solid, 70.5 mg (81%), mp 118-120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 2.4 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 2.4 Hz, 1H), 7.55 (dt, *J* = 1.2, 7.2 Hz, 1H), 7.46 (dt, *J* = 0.8, 7.6 Hz, 1H), 6.73 (t, *J* = 74.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 152.4, 144.7, 137.7, 136.2, 132.9, 131.7, 126.6, 126.1, 123.7, 121.6, 120.6, 118.92, 116.4 (t, $^{1}J_{C-F}$ = 260 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -82.19. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_8Br_2F_2NOS^+$: 433.8656;

found: 433.8658.

*2-(3-Bromo-5-chloro-2-(difluoromethoxy)phenyl)benzo[d]thiazole (**3q**)*. Colorless solid, 51.6 mg (81%), mp 120-121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 2.4 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 6.73 (t, *J* = 74.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 152.4, 144.2, 136.2, 134.9, 133.2, 131.3, 130.0, 126.6, 126.1, 123.8, 121.6, 118.7. 116.5 (t, $^{1}J_{C\text{-}F}$ = 265 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -82.18. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_8BrClF_2NOS^+$: 389.9161; found: 389.9162.

*2-(2-(Difluoromethoxy)phenyl)-5-methoxybenzo[d]thiazole (**3r**)*. Colorless solid, 30.7 mg (50%) mp 103-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.46 (dt, *J* = 2.0, 8.4 Hz, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.36 (dt, *J* = 1.2, 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.11 (dd, *J* = 2.0, 8.8 Hz, 1H), 6.68 (t, *J* = 73.4 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 157.9, 148.5, 147.1, 137.5, 131.2, 130.2, 125.9, 125.8, 123.8, 119.6, 116.2 (t, $^{1}J_{C\text{-}F}$ = 260 Hz), 116.0, 103.5, 55.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.38. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{12}F_2NO_2S^+$: 308.0551; found: 308.0556.

*5-Chloro-2-(2-(difluoromethoxy)phenyl)benzo[d]thiazole (**3s**)*. Colorless solid, 52.4 mg (84%), mp 157-159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 1.6, 8.0 Hz, 1H), 8.08 (d, *J* = 1.6 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.51 (dt, *J* = 1.6, 8.0 Hz, 1H), 7.40 – 7.36 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 1H), 6.70 (t, *J* = 73.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 153.2, 148.9, 134.3, 132.2, 132.0, 130.5, 125.9, 125.8,

125.1, 123.0, 122.1, 119.3, 116.1 (t, $^{1}J_{C\text{-}F}$ = 260 Hz).^{19}F NMR (376 MHz, $CDCl_3$) δ -80.47. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_9ClF_2NOS^+$: 312.0056; found: 312.0067.

*5-Chloro-2-(2-(difluoromethoxy)-5-methoxyphenyl)benzo[d]thiazole (**3t**)*. Colorless solid, 41mg (60%), mp 133-135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 2.0 Hz, 1H), 7.96 (d, *J* = 3.2 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.37 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.02 (dd, *J* = 3.2, 9.2 Hz, 1H), 6.59 (t, *J* = 73.6 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 157.3, 153.1, 142.5, 134.4, 132.3, 126.3, 125.9, 123.0, 122.2, 121.7, 118.6, 116.4 (t, $^{1}J_{C\text{-}F}$ = 261 Hz), 113.6, 55.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.79. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{12}ClF_2NO_2S^+$: 342.0162; found: 342.0168.

*2-(5-Bromo-2-(difluoromethoxy)phenyl)-5-chlorobenzo[d]thiazole (**3u**)*. Yellow solid, 54.7 mg (70%), mp 160-162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 2.4 Hz, 1H), 8.09 (d, *J* = 1.6 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.61 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.40 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 1H), 6.68 (t, *J* = 72.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 153.0, 147.6, 134.6, 134.3, 133.0, 132.5, 126.9, 126.2, 123.2, 122.2, 121.1, 119.2, 115.8 (t, $^{1}J_{C\text{-}F}$ = 262 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.82. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_8BrClF_2NOS^+$: 389.9161; found: 389.9159.

*5-Chloro-2-(2-(difluoromethoxy)-5-nitrophenyl)benzo[d]thiazole (**3v**)*. Yellow solid, 36.4 mg (51%), mp 130-132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (d, *J* = 2.8 Hz, 1H), 8.37 (dd, *J* = 2.8, 8.8 Hz, 1H), 8.15 (d, *J* = 1.6 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 1H),

7.47 – 7.43 (m, 2H), 6.84 (t, J = 71.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 152.9, 145.1, 134.4, 132.9, 126.6, 126.4, 126.2, 125.9, 123.5, 122.2, 119.0, 115.3 (t, $^{1}J_{C\text{-}F}$ = 265 Hz), 29.70. ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.79. HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_8ClF_2N_2O_3S^+$: 356.9907; found: 356.9911.

General procedure for three-component reaction.

To the sealed tube, 1.0 equivalent (0.2 mmol) of *o*-hydroxybenzaldehyde **5** and 1.2 equivalents (0.24 mmol) of *o*-aminothiophenol **4** were added, and 2 mL of EtOH was further added thereto, and the temperature was slowly raised to 80 ^{o}C, and the reaction was carried out for 12 hours. After completion of the reaction, evaporation of the solvent under reduced pressure, and then ICF_2COOEt **2** (2.0 equiv), KOH (6.0 equiv), 2 mL of acetonitrile were added to the mixture, then stirred at room temperature for 12 hours. After completion of the reaction, evaporation of the solvent under reduced pressure followed purification by silica gel chromatography using petroleum ether: ethyl acetate = 50:1 as eluent to give 2-(*o*-difluoromethoxyaryl) benzothiazole **3**.

Evaluation of anticancer activity

The anticancer activity of prepared compounds **3** was determined against human ovarian cancer cell (SKOV-3). The cell line was cultured in DMEM (TBD) supplemented with 10% heat inactivated foetal bovine serum (FBS) (PAA Laboratories) and 1% penicillin/streptomycin (PAA Laboratories). Culture was maintained in a humidified incubator at 37 ^{o}C in an atmosphere of 5% CO_2. Anticancer activity of prepared compounds **3** and cisplatin at various concentrations was assessed using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide

(MTT) (Sigma) assay, as described by Mosmann, but with minor modification, following 48 h of incubation. Assay plates were read using a spectrophotometer at 490 nm. Data generated were used to plot a dose–response curve of which the concentration of test compounds required to kill 50% of cell population (IC_{50}) was determined. Anticancer activity was expressed as the mean IC_{50} of three independent experiments.

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3. Exhibition promising activity against human ovarian cancer cells