Synthesis of *N*-[2-(2,4-Difluorophenoxy)trifluoromethyl-3-pyridyl]-sulfonamides and Their Inhibitory Activities against Secretory Phospholipase A_2

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***N*-[2-(2,4-Difluorophenoxy)trifluoromethyl-3-pyridyl]sulfonamide derivatives 3—6 were prepared by the reaction of 3-pyridylamines and sulfonyl chlorides. Inhibitory activities of these compounds toward secretory phospholipase A_2 ($sPLA_2$) were examined and *N*-[2-(2,4-difluorophenoxy)-5-trifluoromethyl-3-pyridyl]-2-naphthalenesulfonamide (5c) was found to be the most potent against $sPLA_2$ with an IC_{50} value of 90 μM.**

Key words trifluoromethylpyridine; sulfonamide; secretory phospholipase A_2 inhibitor; 2,4-difluorophenoxy; naphthalenesulfonamide

Fluoride functions involving trifluoromethyl (CF_3) group have a profound effect on the physical, chemical, and biological properties of organic molecules, including lipophilicity and chemical and metabolic stability.[1)] Due to its strong electron withdrawing property and relatively larger size as compared with a methyl group, the trifluoromethyl group is featured in many important pharmaceuticals[2)] and pesticides.[3)] To date, a great number of CF_3-substituted aromatic and aliphatic compounds have been synthesized.[4—6)] On the other hand, the corresponding CF_3-substituted pyridine derivatives have received relatively less attention among the CF_3-substituted aromatic compounds.[7)] The strong electron withdrawing property of the CF_3 group and the electron deficient pyridine ring confer unique chemical and physical properties to heterocyclic compounds, and therefore, these compounds are quite attractive. In fact, CF_3-substituted pyridines have shown interesting profiles in some biological molecules including agrochemicals[8)] and medicinal candidates.[9)]

CF_3-substituted pyridylsulfonamide **1** was reported to inhibit secretory phospholipase A_2 ($sPLA_2$).[10)] Recently, we have simplified the structure of **1** and synthesized compounds **2**.[11)] The structurally more simple CF_3-substituted 2-pyridylsulfonamides **2a** and **b** possess almost the same level of $sPLA_2$ inhibitory activity (IC_{50} values, 0.58, 0.68 mM, respectively) as that (IC_{50} values, 0.52 to 2.1 mM) of **1**. In order to extend these studies, we have designed *N*-(6- or 5-trifluoromethyl-3-pyridyl)sulfonamides **3**—**6** as a new $sPLA_2$ inhibitors (Fig. 1). They are positional isomers of compound **2**. A nitrogen atom at the N-1 position in the structure of **2c** was moved to the para (C-4) position in the structure of **3**. In addition, we envisaged replacing a hydrogen atom at the C-2 position with a 2,4-difluorophenoxy group on the pyridine ring, and expected an enhancement of its activity, because highly lipophilic 2,4-difluorophenyl aryl or heteroaryl ether is a functional unit, which has often been used for improvement of the activity in drug design. In fact, many successful cases for enhancing an activity have been reported with this substituent.[12—17)]

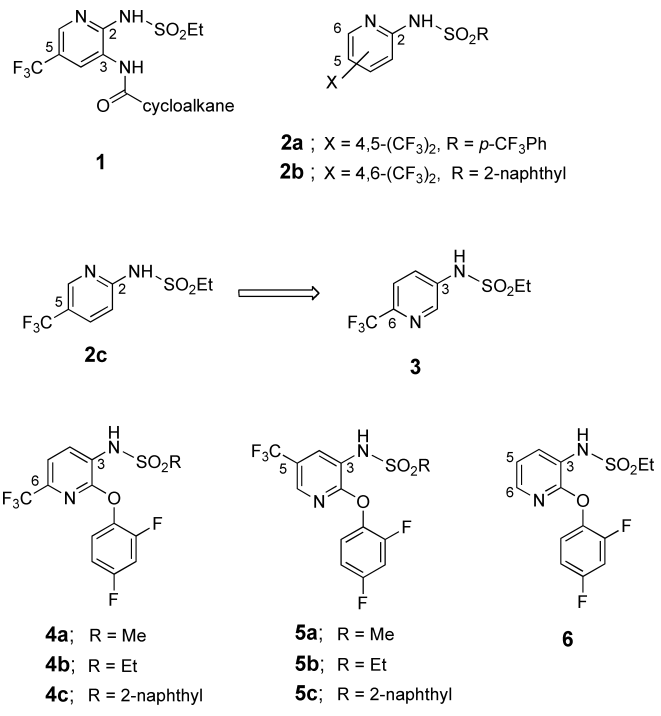

Fig. 1. Structures of Sulfonamides **1**—**6**

In this paper, we report the synthesis of these derivatives **3**—**6** and describe their inhibitory activities against $sPLA_2$.

Results and Discussion

We first prepared a simple sulfonamide **3**. Sulfonylation of 3-amino-6-trifluoromethylpyridine with ethanesulfonyl chloride in pyridine at room temperature gave a mixture of *N*-ethanesulfonamide and *N*,*N*-bisethanesulfonamide, which was heated in aq. KOH and 1,4-dioxane at 90 °C for 30 min to afford **3** in 72% yield (Chart 1).

Inhibitory activity against porcine pancreatic $sPLA_2$ was examined for compounds **2c** and **3** by the same method described in the preceding paper.[11)] Compound **2c** inhibited $sPLA_2$ only weakly by 4.6% at 0.5 mM concentration, while compound **3** inhibited the enzyme by 21.2% at the same con-

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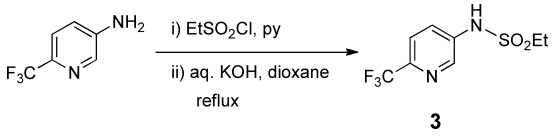
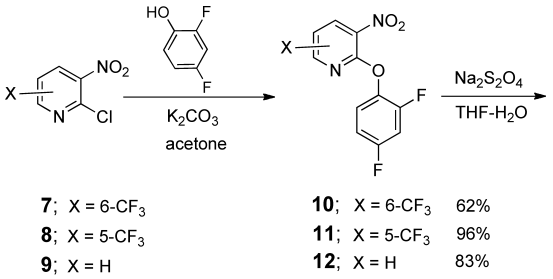
centration. Therefore, we would expect higher inhibitory activity with the *N*-sulfonamide analogues of 3-amino-6-(trifluoromehtyl)pyridine than with the analogues in the series of **2**.

Following the initial plan, the 2,4-difluorophenoxy group was introduced at the C-2 position by substitution reaction of 2-chloropyridine with 2,4-difluorophenol (Chart 2). The reaction of 2-chloro-3-nitro-6-(trifluoromethyl)pyridine with 2,4-difluorophenol in the presence of potassium carbonate in acetone gave 2-pyridyl ether **10** in 62% yield. Due to the anion stabilizing effect of the C-5 CF_3 group in cooperation with the C-3 nitro group under an S*N*Ar reaction mechanism, the reaction of **8** gave **11** in excellent yield. The reaction of 3-nitro-2-pyridyl chloride **9** afforded **12** in 83% yield.[18] Reduction of the nitro group with sodium dithionite in a mixture of tetrahydrofuran (THF) and water gave amines **13**, **14**, and **15**[19] in 89, 97, and 80% yields, respectively.



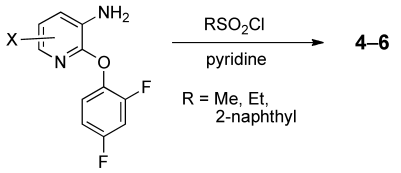
3

Chart 1. Synthesis of **3**



7; X = 6-CF_3
8; X = 5-CF_3
9; X = H

10; X = 6-CF_3 62%
11; X = 5-CF_3 96%
12; X = H 83%



4–6

13; X = 6-CF_3 89%
14; X = 5-CF_3 97%
15; X = H 80%

Chart 2. Synthesis of Sulfonamides **4**—**6**

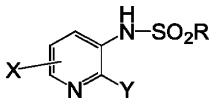
Treatment of 3-pyridylamine **13** and **14** with methane- and 2-naphthalenesulfonyl chloride by the same manner described for the synthesis of **3** gave the corresponding sulfonamides, **4a**, **4c**, **5a** and **5c**, in moderate to excellent yields as shown in Table 1. The reaction of **15** with ethanesulfonyl chloride gave **6** in 97% yield. It is interesting that the electron deficient CF_3-substituted pyridylamine reacted with sulfonyl chloride. In contrast, the reaction with ethanesulfonyl chloride with **13** and **14** gave sulfonamides **4b** and **5b** in low to medium yields with recovery of starting material, probably due to the less reactive ethanesulfonyl chloride and poor nucleophilic reactivity of CF_3-substituted pyridylamine.

All new sulfonamides were evaluated for their inhibitory activity against $sPLA_2$.[20] We determined IC_{50} values for all the sulfonamides. The values were generated from at least three trials, and each trial consisted of a mean value generated from duplicate assays. These results are summarized in Table 1.

Compound **3** was a poor inhibitor, an IC_{50} value of >3 mM (entry 1). The introduction of a 2,4-difluorophenoxy group at the C-2 position of 3-amino-6-(trifluoromehtyl)pyridine greatly increased the inhibitory potency of the corresponding methanesulfonamide **4a**, which inhibited $sPLA_2$ with an $IC_{50}=0.81$ mM. When the methanesulfonamide was replaced with ethanesulfonamide, the potency of compound **4b** increased by 2 times (entries 2 and 3). In the previous investigation with compounds **2**, 2-naphthalenesulfonamide indicated an excellent profile in $sPLA_2$ inhibition. Indeed, the 6-CF_3-susbutitued 2-naphthalenesulfonamide **4c** exhibited the highest inhibition activity, with an IC_{50} value of 0.12 mM (entry 4). In the series of 5-CF_3 analogues, a similar trend of inhibition was observed (entries 5—7). 2-Naphthalenesulfonamide **5c** exhibited an IC_{50} value of 0.09 mM, which was the highest value in this series and 6.4- and 7.5-fold more potent than **2a** and **b**. On the other hand, the corresponding analogue lacking the CF_3 group was a poor inhibitor with an IC_{50} value of >3 mM (entry 8). Therefore, the CF_3 as well as 2,4-difluorophenoxy groups appear to perform an essentially important role in enhancing the inhibitory activity against $sPLA_2$.

In conclusion, we have synthesized *N*-[2-(2,4-difluoro-

Table 1. Chemical Yields of Sulfonamides **3**—**6** and Their $sPLA_2$ Inhibitory Activities



Entry	Compound No.	X	R	Y	Yield[a] (%)	mp (°C)	IC_{50} (mM)
1	**3**	6-CF_3	Et	H	72	101—102	>3
2	**4a**	6-CF_3	Me	$OC_6H_3(2,4\text{-}F_2)$	58	104—105	0.81
3	**4b**	6-CF_3	Et	$OC_6H_3(2,4\text{-}F_2)$	39	89—90	0.44
4	**4c**	6-CF_3	2-Naphthyl	$OC_6H_3(2,4\text{-}F_2)$	79	90—92	0.12
5	**5a**	5-CF_3	Me	$OC_6H_3(2,4\text{-}F_2)$	72	88—90	1.03
6	**5b**	5-CF_3	Et	$OC_6H_3(2,4\text{-}F_2)$	26	75—77	0.41
7	**5c**	5-CF_3	2-Naphthyl	$OC_6H_3(2,4\text{-}F_2)$	91	44—49	0.09
8	**6**	H	Et	$OC_6H_3(2,4\text{-}F_2)$	97	109—110	>3
9	**2a**	4,5-$(CF_3)_2$	—[b]	$NHSO_2\text{-}4\text{-}CF_3C_6H_4$	—	—	0.58
10	**2b**	4,6-$(CF_3)_2$	—[b]	$NHSO_2$-2-naphthyl	—	—	0.68

a) Isolated yields. *b*) C-3 substituent is H instead of $NHSO_2R$.

phenoxy)-6- and 5-trifluoromethyl-3-pyridyl]sulfonamides **4** and **5**, and revealed their inhibitory activity against sPLA$_2$. The potency of **4c** and **5c** increased by 5—7 fold as compared to the previous series of compounds **2a** and **2b**.

Experimental

General Melting points were determined on a Yanagimoto micro-melting point apparatus and were not corrected. ^{1}H-NMR spectra were recorded on a JEOL JNM-GSX 400 (400 MHz) or JNM-AL 300 (300 MHz) spectrometers in $CDCl_3$ with tetramethylsilane as an internal standard. IR spectra were recorded on JASCO FT/IR-410 instrument. Column chromatography was carried out using Merck silica gel 60 (70—230 mesh). Mass spectra were recorded on a JEOL JMS-GCmate spectrometer.

Preparation of 2-(2,4-Difluorophenoxy)pyridine To a solution of 2-chloropyridine (3.0 mmol) and 2,4-difluorophenol (3.0 mmol) in anhydrous acetone (20 ml) was added powdered K_2CO_3 (480 mg, 3.45 mmol). The mixture was stirred for 1—2 h at room temperature and refluxed for 3 h. After cooling, ice water (50 ml) was added to the reaction mixture and the mixture was extracted with ether (100 ml). The organic layer was dried over Na_2SO_4, and condensed. The crude product was purified by flash chromatography on silica gel eluted with 10 to 20% EtOAc in hexane to give the aryl ether.

Compound **10** was obtained from **7** in 62% yield. Oil, *Rf*=0.31 (10% EtOAc in hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.91—7.02 (2H, m), 7.22—7.30 (1H, m), 7.57 (1H, d, *J*=8.1 Hz), 8.54 (1H, dd, *J*=8.1, 0.73 Hz). Electron ionization (EI)-MS *m/z*: 320 (M^+), 129, 101, 63. EI-high resolution (HR)-MS *m/z*: 320.0212 (Calcd for $C_{12}H_5F_5N_2O_3$: 320.0220).

Compound **11** was obtained from **8** in 96% yield. Yellow prisms, mp 66—68 °C. *Rf*=0.39 (10% EtOAc in hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.92—7.03 (2H, m), 7.22 (1H, m), 7.44 (1H, s), 8.57 (1H, s). *Anal.* Calcd for $C_{12}H_5F_5N_2O_3$: C, 45.02; H, 1.57; N, 8.75. Found: C, 45.22; H, 1.60; N, 8.62.

Compound **12** was obtained from **9** in 83% yield.[18] Pale yellow solid, mp 53—54 °C, *Rf*=0.32 (20% EtOAc in hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.92—7.01 (2H, m), 7.18—7.29 (2H, m), 8.30—8.43 (2H, m).

Reduction of Nitro Group to Amine To a solution of $Na_2S_2O_4$ (6.3 g, 36 mmol) in water (60 ml) was added a solution of 2-(2,4-difluorophenoxy)-3-nitropyridine (2.5 mmol) in THF (15 ml) with dropwise at room temperature. The reaction mixture was stirred for 2.5 h at the same temperature. Then, THF (50 ml) was added to the mixture. THF layer was separated and it was washed with brine and dried over $MgSO_4$. The solvent was removed to give solid product, which was purified by recrystalization from a mixture of EtOAc and hexane to give pure amine.

Compound **13** was obtained from **10** in 89% yield. White needles, mp 78—81 °C. *Rf*=0.42 (20% EtOAc in hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.20 (2H, bs), 6.90—7.01 (2H, m), 7.18 (1H, dd, *J*=2.1, 0.3 Hz), 7.24 (1H, m), 7.74 (1H, dd, *J*=2.1, 1.2 Hz). *Anal.* Calcd for $C_{12}H_7F_5N_2O$: C, 49.67; H, 2.43; N, 9.65. Found: C, 49.89; H, 2.44; N, 9.67. EI-MS *m/z*: 290 (M^+), 271, 193, 141. EI-HR-MS *m/z*: 290.0484 (Calcd for $C_{12}H_7F_5N_2O$: 290.0478).

Compound **14** was obtained from **11** in 97% yield. White prisms, mp 68—70 °C. *Rf*=0.28 (20% EtOAc in hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.32 (2H, bs), 6.90—7.04 (2H, m), 7.02 (1H, d, *J*=7.8 Hz), 7.22 (1H, d, *J*=7.8 Hz), 7.28 (1H, m). *Anal.* Calcd for $C_{12}H_7F_5N_2O$: C, 49.67; H, 2.43; N, 9.65. Found: C, 49.91; H, 2.21; N, 9.59. EI-MS *m/z*: 290 (M^+). EI-HR-MS *m/z*: 290.0473 (Calcd for $C_{12}H_7F_5N_2O$: 290.0478).

Compound **15** was obtained from **12** in 80% yield.[19] Pale yellow powder, mp 87—89 °C. *Rf*=0.21 (20% EtOAc in hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.97 (2H, bs), 6.84 (1H, dd, *J*=7.5, 4.8 Hz), 6.87—6.97 (2H, m), 7.30 (1H, dd, *J*=7.5, 1.5 Hz), 7.23 (1H, m), 7.49 (1H, dd, *J*=4.8, 1.5 Hz).

General Synthesis of Sulfonamide To a stirred solution of 3-aminopyridine **13**, **14**, or **15** (3.0 mmol) in pyridine (3 ml) were added dropwise methane-, ethane-, or 2-naphthalenesulfonyl chloride (9 mmol) at room temperature, and the mixture was stirred for 2—6 h at the same temperature. Then, the mixture was quenched with cold 2 N hydrochloric acid (50 ml), and extracted with EtOAc (50 ml). The organic extract was washed with brine and the solvent was removed. The residual oil was dissolved in a mixture of 3 M aqueous KOH (5 ml) and 1,4-dioxane (13 ml) and heated at 90 °C for 30 min. After cooling, ice water (60 ml) was added to the reaction mixture, and the pH was adjusted to 5 with 1 N hydrochloric acid. The mixture was extracted with EtOAc (50 ml×2) and the combined extract was washed with brine, and dried over $MgSO_4$. Evaporation of solvent and purification of the crude product by recrystalization or column chromatography on silica gel provided sulfonamides.

N-(6-Trifluoromethyl-3-pyridyl)ethanesulfonamide (**3**): White needles, mp 101—102 °C. Recrystallization from a mixture of Et_2O and hexane. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.42 (3H, t, *J*=7.5 Hz), 3.24 (2H, q, *J*=7.5 Hz), 5.99 (1H, bs), 7.67 (1H, d, *J*=8.4 Hz), 7.85 (1H, dd, *J*=8.4, 2.1 Hz), 8.53 (1H, d, *J*=2.1 Hz). IR (KBr) cm^{-1}: 1321, 1146. *Anal.* Calcd for $C_8H_9F_3N_2O_2S$: C, 37.79; H, 3.57; N, 11.02. Found: C, 37.73; H, 3.42; N, 10.92.

N-[2-(2,4-Difluorophenoxy)-6-trifluoromethyl-3-pyridyl]methanesulfonamide (**4a**): White powder, mp 104—105 °C. Purification by flash chromatography on silica gel eluted with 20% EtOAc in hexane. *Rf*=0.37 (33% EtOAc in hexane). ^{1}H-NMR($CDCl_3$) δ: 3.16 (3H, s), 6.91—7.01 (2H, m), 7.13 (1H, bs), 7.29 (1H, m), 7.44 (1H, d, *J*=8.0 Hz), 8.04 (1H, d, *J*=8.0 Hz). IR (KBr) cm^{-1}: 1331, 1164. *Anal.* Calcd for $C_{13}H_9F_5N_2O_3S$: C, 42.40; H, 2.46; N, 7.61. Found: C, 42.64; H, 2.45; N, 7.58.

N-[2-(2,4-Difluorophenoxy)-5-trifluoromethyl-3-pyridyl]methanesulfonamide (**5a**): Pale yellow powder, mp 88—90 °C. Purification by flash chromatography on silica gel eluted with 20% EtOAc in hexane. *Rf*=0.17 (20% EtOAc in hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.16 (3H, s), 6.94—7.03 (3H, m), 7.22 (1H, m), 8.13 (2H, s). IR (KBr) cm^{-1}: 1330, 1139. *Anal.* Calcd for $C_{13}H_9F_5N_2O_3S$: C, 42.40; H, 2.46; N, 7.61. Found: C, 42.57; H, 2.48; N, 7.63.

N-[2-(2,4-Difluorophenoxy)-6-trifluoromethyl-3-pyridyl]ethanesulfonamide (**4b**): White powder, mp 89—90 °C. Purification by flash chromatography on silica gel eluted with 20% EtOAc in hexane. *Rf*=0.48 (33% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, t, *J*=7.3 Hz), 3.24 (2H, q, *J*=7.3 Hz), 6.92—7.00 (2H, m), 7.01 (1H, bs), 7.27 (1H, m), 7.41 (1H, d, *J*=8.3 Hz), 8.06 (1H, d, *J*=8.3 Hz). IR (KBr) cm^{-1}: 1328, 1162. *Anal.* Calcd for $C_{14}H_{11}F_5N_2O_3S$: C, 43.98; H, 2.90; N, 7.33. Found: C, 44.00; H, 2.96; N, 7.31.

N-[2-(2,4-Difluorophenoxy)-5-trifluoromethyl-3-pyridyl]ethanesulfonamide (**5b**): White powder, mp 75—77 °C. Purification by flash chromatography on silica gel eluted with 20% EtOAc in hexane.*Rf*=0.34 (20% EtOAc in hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.46 (3H, t, *J*=7.3 Hz), 3.24 (2H, q, *J*=7.3 Hz), 6.95—7.19 (3H, m), 7.24 (1H, m), 8.10 (1H, s), 8.15 (1H, s). IR (KBr) cm^{-1}: 1345, 1138. *Anal.* Calcd for $C_{14}H_{11}F_5N_2O_3S$: C, 43.98; H, 2.90; N, 7.33. Found: C, 44.07; H, 3.00; N, 7.27.

N-[2-(2,4-Difluorophenoxy)-6-trifluoromethyl-3-pyridyl]-2-naphthalenesulfonamide (**4c**): White powder, mp 90—92 °C. Purification by flash chromatography on silica gel eluted with 10% EtOAc in hexane. *Rf*=0.40 (20% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 6.83—6.95 (2H, m), 7.01 (1H, m), 7.38 (1H, d, *J*=8.0 Hz), 7.62 (1H, bs), 7.66—7.75 (2H, m), 7.90 (1H, dd, *J*=8.6, 1.8 Hz), 7.95 (1H, d, *J*=8.0 Hz), 8.00 (1H, s), 8.02 (1H, m), 8.11 (1H, d, *J*=8.0 Hz), 8.54 (1H, s). *Anal.* Calcd for $C_{22}H_{13}F_5N_2O_3S$: C, 55.00; H, 2.73; N, 5.83. Found: C, 55.26; H, 2.66; N, 5.76.

N-[2-(2,4-Difluorophenoxy)-5-trifluoromethyl-3-pyridyl]-2-naphthalenesulfonamide (**5c**): White powder, mp 44—49 °C. Purification by flash chromatography on silica gel eluted with 20% EtOAc in hexane. *Rf*=0.27 (20% EtOAc in hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.77—6.98 (3H, m), 7.37 (1H, bs), 7.61—7.70 (2H, m), 7.82 (1H, dd, *J*=8.4, 1.8 Hz), 7.90—8.00 (4H, m), 8.22 (1H, d, *J*=1.8 Hz), 8.45 (1H, s). *Anal.* Calcd for $C_{22}H_{13}F_5N_2O_3S$: C, 55.00; H, 2.73; N, 5.83. Found: C, 54.75; H, 2.45; N, 5.76.

N-[2-(2,4-Difluorophenoxy)-3-pyridyl]ethanesulfonamide (**6**): White powder, mp 109—110 °C. Purification by flash chromatography on silica gel eluted with 5% Et_2O in hexane. *Rf*=0.18 (20% EtOAc in hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.43 (3H, t, *J*=7.5 Hz), 3.18 (2H, q, *J*=7.5 Hz), 6.86 (1H, bs), 6.94—6.98 (2H, m), 7.04 (1H, m), 7.24 (1H, m), 7.86 (1H, m), 7.96 (1H, m). *Anal.* Calcd for $C_{13}H_{12}F_2N_2O_3S$: C, 49.68; H, 3.85; N, 8.91. Found: C, 49.83; H, 4.14; N, 8.90.

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