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Short communication

Synthesis and fungicidal activity of new fluorine-containing mandelic acid amide compounds

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ABSTRACT

A series of novel fluorine-containing mandelic acid amide compounds were designed and synthesized by a facile method, and their structures were characterized by ^{1}H nuclear magnetic resonance (NMR) and high-resolution mass spectrometry. The preliminary *in vivo* bioassays indicated that some of the title compounds showed excellent fungicidal activities *in vivo* against *Pseudoperonospora cubensis* at the dosage of 25 mg L^{-1}, which were comparable with the control (Mandipropamid).

1. Introduction

Mandipropamid developed by Syngenta is the first mandelic acid amide fungicide [1] on the market. It is belongs to the Carboxylic Acid Amide (CAA) group of fungicides. It exhibited a high level of activity against most foliar Oomycetes pathogens, such as *Plasmopara viticola* in grapes, *Phytophthora infestans* in potatoes and tomatoes and *Pseudoperonospora cubensis* in cucurbits [2]. Blum et al. have reported that the mode of action of Mandipropamid is directly linked to the inhibition of the cellulose synthase-like in the Oomycete plant pathogen [3].

It is well known that the huge success of fluorine-containing drugs will stimulate continued research on fluorine in medicinal chemistry for drug discovery [4] because of the unique properties of fluorine atom, such as the highest electronegativity, high thermal stability and lipophilicity. Bioisosteric substitution for hydrogen by fluorine has become an important strategy [5] for electronic modulation [6], lipophilic modulation [7] and steric parameters [8]. ^{14}C-labeled Mandipropamid showed that the fungicide acts on the cell wall without entering into the cell [3]. Therefore high hydrophobicity may force the immersion of the pesticide into the wax layer of plant surface, which results in long-lasting activity, and does not diminish its fungicidal activity. By taking into account the above-mentioned important contributions, our main interest was to enhance the hydrophobicity of mandelic acid amide compounds by introducing fluorine atoms.

Thus, in this paper, we designed and prepared a series of fluorine-containing mandelic acid amide compounds in which the methyl moiety of catecholamine was replaced by 1,1,1-trifluoromethyl moiety. Among them, compounds **5d**, **5e**, **8a**, **8b** and **8c** displayed excellent fungicidal activity, which were comparable with the control (Mandipropamid) (Fig. 1).

2. Results and discussion

2.1. Synthesis

The intermediate **1** was prepared by *Duff*'s reaction [9], with hexamethylenetetramine (HMTA) in trifluoroacetic acid (TFA). And the intermediates **2a–c**, which were easily obtained from compound **1** by alkylation, were converted to intermediates **3a–c** by Henry Condensation reaction [10]. The intermediates **3a–c** were reduced with lithium aluminum hydride to the corresponding amines, which were then converted into amides **4a** and **b** by treating with ester. The amides **4a** and **b**, which were key intermediates could be transformed by O-alkylation with alkylation reagent into the title mandelamides **5a–e** (Scheme 1).

After synthesizing a series of mandelamides, we wanted to synthesize some mandelamides containing two propargyl groups. Unexpectedly, the β-nitrostyrene **3c** could be reduced to not only the desired phenylethylamine, but also the propargyl cleavage

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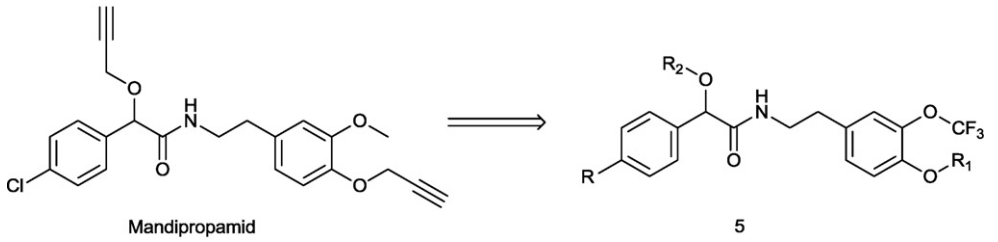
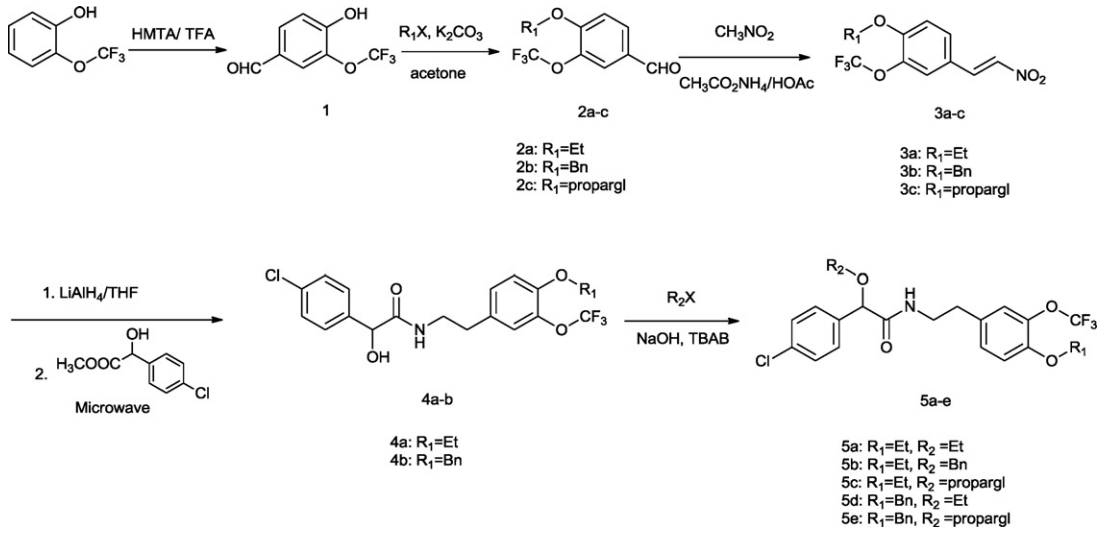


Fig. 1. Structures of Mandipropamid and fluorine-containing mandelic acid amide compounds.



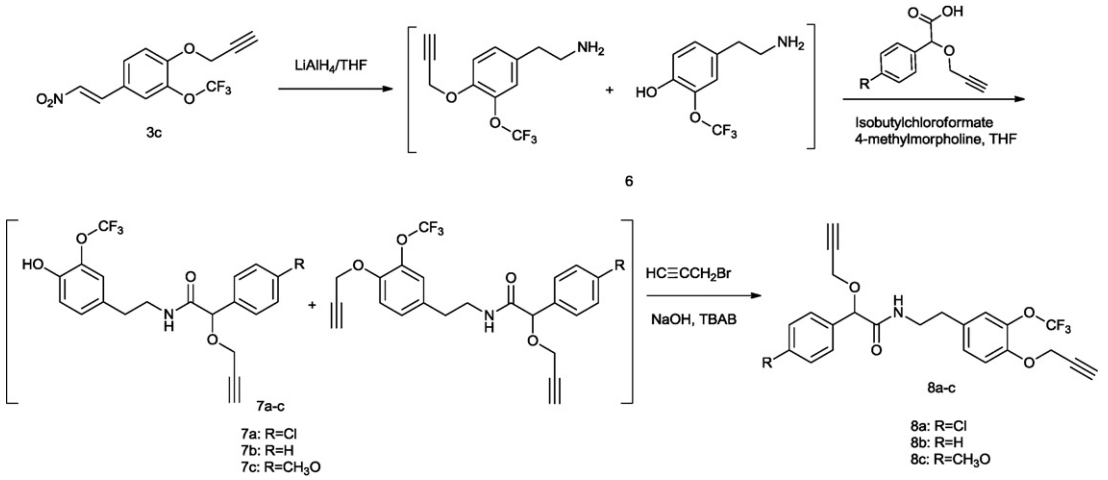
Scheme 1. Synthesis of compounds **5**.

compound. Due to the difficulty of the purification of the mixture **6**, it is immediately used in the next step without further purification. After propargylation in the last step, the title mandelamides **8** were prepared and isolated easily (Scheme 2).

2.2. Biological activities

To determine the efficacy of the new fluorine-containing compounds as a potential fungicide, the upper leaf surfaces of three-week-old cucumber plants were treated with the test compounds in a spray chamber. Each test compound was prepared at a terminal concentration of 100, 50 and 25 mg L^{-1}, respectively. One day later, the treated and controlled plants were inoculated with *P. cubensis* by spraying a sporangial suspension. Disease incidence was assessed after an incubation period of 5 days in a greenhouse. Mandipropamid was chosen as the comparison fungicide. The results of the fungicidal experiments are presented in Table 1.

The SAR picture of fluorine-containing mandelic acid amide compounds is completely different from that of mandelic acid amide compounds. The alkylation of the phenol in the *para* position of the catecholamine moiety has a negative effect on the fungicidal efficacy, and leads to inactive compounds at 100 mg L^{-1}, as **5a**, **5b** and **5c**. A comparison between the ethylated title compounds (**5a**, **5b** and **5c**) and their propargyl and benzyl derivatives reveals that the biological activitives are closely related



Scheme 2. Synthesis of compounds **8**.

Table 1
Fungicidal activities of title compounds.

No.	*Pseudoperonospora cubensis*		
	100 mg L^{-1}	50 mg L^{-1}	25 mg L^{-1}
5a	0	0	0
5b	0	0	0
5c	0	0	0
5d	98	90	85
5e	98	90	90
8a	98	98	95
8b	98	98	90
8c	98	98	90
Mandipropamid	98	85	75

to the degree of unsaturation of the substituent groups, and propargylation here leads to the best result. For example, compounds **5d**, **5e** and **8a** exhibited 85, 90 and 95% inhibition effect against *P. cubenis*, at 25 mg L^{-1} respectively. The propargyl substitution of the free hydroxyl function of mandelic acid generally leads to higher fungicidal activity than the benzyl substitution.

The fungicidal activity of compound **8c**, whose methoxyl is introduced into the *para* position of the mandelic acid phenyl ring, was equivalent to that of the unsubstituted compound **8b**. The 4-chloro substituent (**8a**) gave the best results.

3. Conclusion

A series of novel fluorine-containing mandelic acid amide compounds were designed based on the theory of bioisoterism. Some of the title compounds showed excellent fungicidal activities *in vivo* against *P. cubensis* at the dosage of 25 mg L^{-1}, which were comparable with the control (Mandipropamid). After introducing of fluorine atoms into the catecholamine moiety, their fungicidal activities had close relation with the degree of unsaturation of the substituent R_1. The compounds where R_1 is either propargyl or benzyl have good fungicidal activities, whereas compounds **5a**–**c** (R_2 is ethyl) are inactive.

4. Experimental

^{1}H NMR spectra were obtained at 400 MHz, ^{19}F NMR spectra were obtained at 376 MHz, ^{13}C NMR spectra were obtained at 100 MHz on a Bruker Avance 400 spectrometer with tetramethylsilane (TMS) as an internal standard. ^{1}H NMR spectra of some intermediates were obtained at 300 MHz on a Bruker AV300 spectrometer with tetramethylsilane (TMS) as an internal standard. High resolution mass spectrometry (HRMS) data were obtained on a VG ZAB HS instrument. CEM Discover focused microwave (2450 MHz, 300 W) were used wherever mentioned. Melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. Yields were not optimized. All chemicals or reagents were purchased from standard commercial suppliers. All solvents and liquid reagents were dried by standard methods in advance and distilled before use.

5. Chemistry

5.1. Synthesis of 4-hydroxy-3-(trifluoromethoxy)benzaldehyde (1)

A solution of 2-(trifluoromethoxy)phenol (10 g, 56.1 mmol) and hexamethylenetetramine (16 g, 112.3 mmol) in trifluoroacetic acid (50 mL) was heated at 65 °C for 10 h. Then the mixture was concentrated and diluted with a 2 N aqueous solution of hydrochloric acid. The acid phase was extracted twice with ethyl acetate and the combined organic extract was dried over magnesium sulfate, and concentrated. The residue was purified by flash chromatography on silica gel [elution solvent:ethyl acetate/petroleum ether (60–90 °C), 1:10 (v/v)] to afford compound **1**. White solid, m.p. 74–75 °C (76–78 °C [11]), yield 45%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.25 (s, 1H, OH), 9.95 (s, 1H, CHO), 7.57–7.50 (m, 2H, Ar–H), 7.07–7.03 (m, 1H, Ar–H).

5.2. General synthetic procedures for 3-trifluoromethoxy-4-alkoxylbenzaldehyde (2a–c)

The 4-hydroxy-3-(trifluoromethoxy)benzaldehyde (2.0 g, 9.7 mmol), 1-bromopropane (1.3 g, 10.7 mmol), and anhydrous K_2CO_3 (2.0 g, 14.6 mmol) were stirred together under reflux in 30 mL dry acetone for 6 h. The mixture was filtered, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel [elution solvent:ethyl acetate/petroleum ether (60–90 °C), 1:20 (v/v)] to afford compound **2a**. Compounds **2b** and **2c** were prepared through the same process, the alkylation reagent was benzyl bromide and 3-bromopropyne, respectively. Data for **2a**. Colorless oil, yield 60%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (s, 1H, O=C–H), 7.83–7.60 (m, 2H, Ar–H), 7.02 (d, J = 8.3 Hz, 1H, Ar–H), 4.12 (q, J = 7.0 Hz, 2H, $\underline{CH_2}CH_3$), 1.41 (t, J = 7.0 Hz, 3H, $CH_2\underline{CH_3}$).

Data for **2b**. White solid, m.p. 57–59 °C, yield 51%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.87 (s, 1H, CHO), 7.88–7.71 (m, 2H, Ar–H), 7.59–7.32 (m, 5H, Ph–H), 7.14 (d, J = 8.4 Hz, 1H, Ar–H), 5.25 (s, 2H, O–CH_2).

Data for **2c**. Yellow oil. Yield 62.2%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.90 (s, 1H, CHO), 7.91–7.74 (m, 2H, Ph–H), 7.30 (d, J = 8.6 Hz, 1H, Ph–H), 4.89 (s, 2H, OCH_2), 2.61 (s, 1H, C≡CH).

5.3. General synthetic procedures for 3-trifluoromethoxy-4-alkoxy-β-nitrostyrene (3a–c)

A mixture of 4-ethoxy-3-trifluoromethoxybenzaldehyde (**2a**, 3.3 g, 14.1 mmol), nitromethane (2.6 g, 42.3 mmol), glacial acetic acid (14 mL) and ammonium acetate (1.1 g, 14.1 mmol) was refluxed for 6 h. Upon cooling to room temperature, the crude product was filtrated as a yellow solid, then recrystallized from ethanol to give **3a**. Compounds **3b** and **3c** were prepared through the same process.

Data for **3a**. Yellow solid, m.p. 101–103 °C, yield 53.8%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 13.6 Hz, 1H, C=C–H), 7.43 (d, J = 13.6 Hz, 1H, C=C–H), 7.42–6.95 (m, 3H, Ar–H), 4.10 (q, J = 7.0 Hz, 2H, $\underline{CH_2}CH_3$), 1.41 (t, J = 7.0 Hz, 3H, $CH_2\underline{CH_3}$).

Data for **3b**. Yellow solid, m.p. 97–99 °C, yield 43.3%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, J = 13.6 Hz, 1H, C=C–H), 7.50 (d, J = 13.6 Hz, 1H, C=C–H), 7.45–7.06 (m, 8H, Ar–H), 5.23 (s, 2H, OCH_2).

Data for **3c**. Yellow solid, m.p. 80–81 °C, yield 31.0%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, J = 13.7 Hz, 1H, C=C–H), 7.52 (d, J = 13.7 Hz, 1H, C=C–H), 7.52–7.21 (m, 3H, Ar–H), 4.85 (d, J = 2.4 Hz, 2H, OCH_2), 2.59 (t, J = 2.4 Hz, 1H, C≡CH).

5.4. General synthetic procedures for 2-(4-chlorophenyl)-N-(4-alkoxy-3-(trifluoromethoxy)phenethyl)-2-hydroxyacetamide (4a and b)

To a stirred solution of $LiAlH_4$ (1.1 g, 30.0 mmol) in dry THF (35 mL) was slowly added a solution of 3-(trifluoromethoxy)-4-(ethoxy)-β-nitrostyrene (**3a**, 2.8 g, 10.0 mmol) in dry THF (15 mL). The solution was refluxed for 7 h. The mixture was cooled to 0 °C and quenched carefully with water (3 mL), 15% aqueous NaOH (3 mL), and then water (6 mL). The solution was stirred 30 min at room temperature. After removal of white precipitates by

filtration, the filtrate was dried over K_2CO_3, and evaporated under reduced pressure to afford colorless oil, which was used in the subsequent step without further purification.

The mixture of methyl 2-(4-chlorophenyl)-2-hydroxyacetate (2.0 g, 10.0 mmol) and the crude product obtained above was heated under microwave condition (120 °C, 135 W) for 1 h. Upon cooling to room temperature, the mixture was diluted with CH_2Cl_2 (20 mL), and then washed with water (10 mL), dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica gel [elution solvent:ethyl acetate/petroleum ether (60–90 °C), 1:2 (v/v)] to afford compound **4a**. Compound **4b** was prepared through the same process.

Data for **4a**. White solid, m.p. 83–84 °C, yield 62.5%. Rf = 0.39 (PE:EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.20 (m, 4H, Ar–H), 6.97 (s, 1H, Ar–H), 6.87–6.81 (m, 2H, Ar–H), 6.16 (s, 1H, NH), 4.95 (s, 1H, CH), 4.07 (q, J = 6.8 Hz, 2H, $\underline{CH_2}CH_3$), 3.59–3.33 (m, 2H, $\underline{CH_2}CH_2$), 2.70 (m, 2H, $CH_2\underline{CH_2}$), 1.43 (t, J = 6.8 Hz, 3H, $CH_2\underline{CH_3}$). HRMS (ESI) m/z Calcd for $C_{19}H_{19}ClF_3NO_4Na^+$ [M+Na$^+$] 440.0847, found 440.0850.

Data for **4b**. White solid, m.p. 87–88 °C, yield 56.2%. Rf = 0.22 (PE:EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.21 (m, 9H, Ar–H), 7.00 (s, 1H, Ar–H), 6.87–6.79 (m, 2H, Ar–H), 6.13 (s, 1H, NH), 5.13 (s, 2H, Ph–CH_2), 4.96 (s, 1H, CH), 3.40–3.55 (m, 2H, $\underline{CH_2}CH_2$), 2.80–2.60 (m, 2H, $CH_2\underline{CH_2}$). HRMS (ESI) m/z Calcd for $C_{24}H_{21}ClF_3NO_4Na^+$ [M+Na$^+$] 502.1030, found 502.0997.

5.5. General synthetic procedures for 2-(4-chlorophenyl)-2-alkoxy-N-(4-alkoxy-3-(trifluoromethoxy)phenethyl)acetamide (5a–e)

1-Bromopropane (3 mmol) was added slowly at room temperature to a mixture of **5a** (0.5 g, 1.2 mmol), 30% aqueous sodium hydroxide solution (0.8 g, 6 mmol) and catalytic amounts of tetrabutylammonium bromide (TBAB) in 10 mL of dichloromethane. The reaction mixture was stirred for 16 h at 40 °C. The mixture was concentrated under vancum. Water was added, dichloromethane (3 × 50) was used to extract the crude product. The combines organic layers were dried over magnesium sulfate and evaporated to give a crude product, which was purified by flash chromatography on silica gel [elution solvent:ethyl acetate/petroleum ether (60–90 °C), 1:1 (v/v)] to afford compound **5a**. Compounds **5b**, **5c**, **5d**, and **5e** were prepared through the same process, using benzyl bromide, 3-bromopropyne, 3-bromopropyne and diethyl sulfate separately. Data for **5a**. Colorless oil, yield 55.9%. Rf = 0.28 (PE:EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (s, 4H, Ar–H), 6.95 (s, 1H, Ar–H), 6.92–6.78 (m, 2H, Ar–H), 6.75 (s, 1H, NH), 4.57 (s, 1H, CH), 3.98 (q, J = 7.0 Hz, 2H, $CH_3\underline{CH_2}$), 3.46–3.31 (m, 4H, $CH_3\underline{CH_2}$ + $\underline{CH_2}CH_2$), 2.67 (t, J = 6.9 Hz, 2H, $CH_2\underline{CH_2}$), 1.34 (t, J = 7.0 Hz, 3H, $\underline{CH_3}CH_2$), 1.09 (t, J = 7.0 Hz, 3H, $\underline{CH_3}CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.46, 150.04, 138.12, 136.11, 134.10, 131.16, 128.63, 128.10, 127.94, 123.44, 121.94, 119.38, 114.24, 81.20, 65.38, 64.71, 39.98, 34.58, 15.09, 14.65. ^{19}F NMR (376 MHz, $CDCl_3$): −58.12 (3F). HRMS (ESI) m/z Calcd for $C_{21}H_{23}ClF_3NO_4Na^+$ [M+Na$^+$] 468.1160, found 468.1165.

Data for **5b**. White solid, m.p. 94–96 °C, yield 75.8%. Rf = 0.31 (PE:EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.20 (m, 9H, Ar–H), 7.03 (s, 1H, Ar–H), 6.99–6.82 (m, 2H, Ar–H), 6.83 (s, 1H, NH), 4.76 (s, 1H, CH), 4.51 (d, J = 11.5 Hz, 1H, Ph–CH_2), 4.37 (d, J = 11.5 Hz, 1H, Ph–CH_2), 4.05 (q, J = 7.0 Hz, 2H, $CH_3\underline{CH_2}$), 3.58–3.40 (m, 2H, $\underline{CH_2}CH_2$), 2.74 (t, J = 6.9 Hz, 2H, $CH_2\underline{CH_2}$), 1.43 (t, J = 7.0 Hz, 3H, $\underline{CH_3}CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.11, 150.06, 138.13, 136.64, 135.60, 134.35, 131.07, 128.79, 128.63, 128.59, 128.37, 128.27, 127.96, 123.44, 114.19, 80.47, 71.35, 64.67, 40.00, 34.54, 14.67. ^{19}F NMR (376 MHz, $CDCl_3$): −58.08 (3F). HRMS (ESI) m/z Calcd for $C_{26}H_{25}ClF_3NO_4Na^+$ [M+Na$^+$] 530.1316, found 530.1321.

Data for **5c**. Colorless oil, yield 82.3%. Rf = 0.22 (PE:EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.15 (m, 4H, Ar–H), 6.95 (s, 1H, Ar–H), 6.93–6.79 (m, 2H, Ar–H), 6.71 (s, 1H, NH), 4.89 (s, 1H, NH), 4.11 (dd, J = 15.8, 2.4 Hz, 1H, $\underline{CH}$–C≡CH), 3.98 (q, J = 7.0 Hz, 2H, $CH_3\underline{CH_2}$), 3.88 (dd, J = 15.8, 2.4 Hz, 1H, $\underline{CH}$–C≡CH), 3.57–3.29 (m, 2H, $CH_2\underline{CH_2}$), 2.68 (td, J = 6.9, 2.6 Hz, 2H, $\underline{CH_2}CH_2$), 2.40 (t, J = 2.4 Hz, 1H, C≡CH), 1.34 (t, J = 7.0 Hz, 3H, $\underline{CH_3}CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.59, 150.07, 134.64, 131.08, 128.85, 128.66, 127.94, 123.49, 114.26, 79.59, 78.05, 75.85, 64.69, 56.39, 40.12, 34.59, 14.67. ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.10 (3F). HRMS (ESI) m/z Calcd for $C_{22}H_{21}ClF_3NO_4Na^+$ [M+Na$^+$] 478.1003, found 478.1006.

Data for **5d**. White solid, m.p. 72–73 °C, yield 65.6%. Rf = 0.32 (PE:EA = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–7.23 (m, 9H, Ar–H), 7.06 (s, 1H, Ar–H), 6.97–6.90 (m, 2H, Ar–H), 6.78 (s, 1H, NH), 5.12 (s, 2H, Ph–CH_2), 4.65 (s, 1H, CH), 3.55–3.37 (m, 4H, $CH_2\underline{CH_2}$ + $CH_3\underline{CH_2}$), 2.75 (t, J = 6.8 Hz, 2H, $\underline{CH_2}CH_2$), 1.17 (t, J = 6.9 Hz, 3H, $\underline{CH_3}CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.48, 149.72, 138.28, 136.45, 136.10, 134.11, 131.74, 128.64, 128.09,128.04, 127.99, 127.02, 126.98, 123.59, 114.83, 81.19, 70.82, 65.39, 39.97, 34.59, 15.10. ^{19}F NMR (376 MHz, $CDCl_3$): −57.99 (3F). HRMS (ESI) m/z Calcd for $C_{26}H_{25}ClF_3NO_4Na^+$ [M+Na$^+$] 530.1316, found 530.1313.

Data for **5e**. Colorless oil, yield 79.2%. Rf = 0.24 (PE:EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51–7.23 (m, 9H, Ar–H), 7.07 (s, 1H, Ar–H), 6.99–6.91 (m, 2H, Ar–H), 6.73 (s, 1H, NH), 5.13 (s, 2H, Ph–CH_2), 4.96 (s, 1H, CH), 4.19 (d, J = 15.8 Hz, 1H, $\underline{CH}$–C≡CH), 3.96 (d, J = 15.8 Hz, 1H, $\underline{CH}$–C≡CH), 3.74–3.36 (m, 2H, $CH_2\underline{CH_2}$), 2.77 (t, J = 6.9 Hz, 2H, $\underline{CH_2}CH_2$), 2.46 (s, 1H, C≡CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.64, 149.75, 136.45, 134.66, 131.67, 128.86, 128.66, 128.64, 128.04, 128.00, 127.04, 123.62, 114.87, 79.59, 78.04, 75.87, 70.83, 56.40, 40.12, 34.59. ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.97 (3F). HRMS (ESI) m/z Calcd for $C_{27}H_{23}ClF_3NO_4Na^+$ [M+Na$^+$] 540.1160, found 540.1162.

5.6. General synthetic procedures for 2-(4-substituted phenyl)-2-(prop-2-ynyloxy)-N-(4-(prop-2-ynyloxy)-3-(trifluoromethoxy)phenethyl)acetamide (8a–c)

To a stirred solution of $LiAlH_4$ (1.1 g, 30.0 mmol) in dry THF (50 mL) was slowly added a solution of 3-(trifluoromethoxy)-4-(propynyloxy)-β-nitrostyrene **3c** (2.9 g, 10.0 mmol) in dry THF (35 mL). The solution was refluxed for 7 h. The mixture was cooled to 0 °C and quenched carefully with water (3 mL), 15% aqueous NaOH (3 mL), and then water (6 mL). The solution was stirred 30 min at room temperature. After removal of white precipitates by filtration, the filtrate was dried over K_2CO_3, and evaporated under reduced pressure to afford colorless oil, which was used in the subsequent step without further purification. This mixture **6** was 4-propynyloxy-3-trifluoromethoxyphenethylamine and the propargyl cleavage product 4-hydroxy-3-trifluoromethoxyphenethylamine.

To a cooled (−20 °C) solution of compound **6a** (2.9 g, 12.9 mmol) in anhydrous THF (100 mL) was added 4-methylmorpholine (1.4 g, 13.8 mmol) during 20 min. After 10 min isobutyl chloroformate (1.8 g, 13.2 mmol) was added at the same temperature during 10 min. After 20 min, the crude product obtained above was added. The resulting mixture was stirred for an additional 12 h at room temperature. The mixture was concentrated under reduced pressure, the residue was diluted with H_2O (10 mL) and extracted twice with ethyl acetate and the combined organic extract dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica gel [elution solvent:ethyl acetate/petroleum ether (60–90 °C), 1:3 (v/v)] to afford a mixture. The mixture cannot be separated further, because both compounds had the same retention times on TLC. This mixture can be converted to pure title compound **8** by further propargylation.

Propargyl bromide (1.4 g, 12.0 mmol) was added slowly at room temperature to the mixture obtained above, 30% aqueous sodium hydroxide solution (3.2 g, 24.0 mmol) and catalytic amounts of tetrabutylammonium bromide in 150 mL of dichloromethane. The reaction mixture was stirred for 16 h at 40 °C. The mixture was concentrated under vacuum. Ethyl acetate (3 × 50 mL) was used to extract the product; then, the combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to give a crude product, which was purified by flash chromatography on silica gel [elution solvent:ethyl acetate/petroleum ether (60–90 °C), 1:3 (v/v)] to afford compound **8a**. Compounds **8b** and **8c** were prepared through the same process.

Data for **8a**. White solid, m.p. 80–81 °C, yield 60.6%. Rf = 0.21 (PE:EA = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.26 (m, 4H, Ar–H), 7.09–7.03 (m, 3H, Ar–H), 6.76 (s, 1H, NH), 4.97 (s, 1H, OCH), 4.76 (s, 2H, CH_2–C≡CH), 4.21 (d, J = 15.8 Hz, 1H, CH–C≡CH), 3.97 (d, J = 15.8 Hz, 1H, CH–C≡CH), 3.62–3.43 (m, 2H, $\underline{CH_2}CH_2$), 2.79 (t, J = 7.0 Hz, 2H, $CH_2\underline{CH_2}$), 2.54 (s, 1H, C≡CH), 2.48 (s, 1H, C≡CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.64, 148.53, 134.67, 134.62, 132.56, 128.88, 128.67, 127.84, 123.45, 115.20, 79.58, 76.21, 75.89, 56.79, 56.39, 40.09, 34.64. ^{19}F NMR (376 MHz, $CDCl_3$): −58.04 (3F). HRMS (ESI) m/z Calcd for $C_{23}H_{19}ClF_3NO_4Na^+$ $[M+Na]^+$ 488.0847, found 488.0840.

Data for **8b**. Colorless oil, yield 64.2%. Rf = 0.29 (PE:EA = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.31 (m, 5H, Ar–H), 7.08–7.04 (m, 3H, Ar–H), 6.80 (s, 1H, NH), 5.00 (s, 1H, CH), 4.75 (s, 2H, $\underline{CH_2}$–C≡CH), 4.20 (d, J = 15.8 Hz, 1H, $\underline{CH}$–C≡CH), 3.97 (d, J = 15.8 Hz, 1H, $\underline{CH}$–C≡CH), 3.57–3.43 (m, 2H, $\underline{CH_2}CH_2$), 2.79 (t, J = 7.0 Hz, 2H, $CH_2\underline{CH_2}$), 2.54 (s, 1H, C≡CH), 2.47 (s, 1H, C≡CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.08, 148.49, 136.05, 132.73, 128.77, 128.70, 127.89, 127.37, 123.47, 115.23, 80.36, 76.19, 75.60, 56.81, 56.20, 40.13, 34.70. ^{19}F NMR (376 MHz, $CDCl_3$): −58.03 (3F). HRMS (ESI) m/z Calcd for $C_{23}H_{20}ClF_3NO_4Na^+$ $[M+Na]^+$ 454.1237, found 454.1236.

Data for **8c**. Colorless oil, yield 45.8%. Rf = 0.34 (PE:EA = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–6.87 (m, 7H, Ar–H), 6.78 (s, 1H, NH), 4.95 (s, 1H, CH), 4.75 (s, 2H, $\underline{CH_2}$–C≡CH), 4.17 (d, J = 15.8 Hz, 1H, $\underline{CH}$–C≡CH), 3.94 (d, J = 15.8 Hz, 1H, $\underline{CH}$–C≡CH), 3.80 (s, 3H, OCH_3), 3.63–3.43 (m, 2H, $\underline{CH_2}CH_2$), 2.80 (t, J = 7.0 Hz, 2H, $CH_2\underline{CH_2}$), 2.54 (s, 1H, C≡CH), 2.46 (s, 1H, C≡CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.34, 159.99, 148.49, 138.41, 132.75, 128.79, 128.04, 127.87, 123.49, 121.67, 115.22, 114.14, 79.92, 78.46, 77.96, 76.20, 75.46, 56.81, 55.86, 55.31, 40.08, 34.72. ^{19}F NMR (376 MHz, $CDCl_3$): -58.03 (3F). HRMS (ESI) m/z Calcd for $C_{24}H_{21}ClF_3NO_5^-$ $[M-H]^-$ 460.1377, found 460.1369.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2012.02.011.

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