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Synthesis and Anticancer Effect of B-Ring Trifluoromethylated Flavonoids

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Abstract—A series of B-ring trifluoromethylated flavonoids derivatives were prepared and tested in vitro against human gastric adenocarcinoma cell line (SGC-7901). Among these derivatives, 5,7-dipropoxy-2-(4′-trifluoromethylphenyl)-chromen-4-one **5c** had the strongest activity against SGC-7901 cell.

Introduction

Stomach cancer is the type most commonly seen in China.[1] In recent years, there has been a growing interest in the search for anti-stomach cancer substances with high efficacy, low toxicity and minimum side effects. One approach is to search for it from plant origin. Flavonoids are a broad class of polyphenolic secondary metabolites abundant in plants and in a variety of common foods such as apples, onions, tea and red wine. Apart from their important biological roles in nitrogen fixation and chemical defense, flavonoids possess a broad range of pharmacological properties including anti-oxidant, anti-cancer, anti-viral and anti-inflammatory properties.[2] In anti-cancer area, flavonoids can inhibit the metabolism of the carcinogen benzo[α]pyrene by hamster embryo cells in tissue culture[3] and markedly augment the cytotoxicity of TNF (tumor necrosis factor-α).[4] Flavonoids are also found to have tyrosinase inhibitory activity,[5] moderate aromatase inhibitory activity[6] and inhibition of estradiol-induced DNA synthesis.[7] However, most of the anti-cancer activities were low. It is known that fluorine is the most electronegative element and the van der Waals radius of fluorine is close to that of hydrogen, the introduction of the CF_3 group into organic molecules often changes their physiological, physical and chemical properties dramatically, without the introduction of extra steric demand. Many efforts were made to introduce the trifluoromethyl group into different types of organic molecules in order to improve their stability and lipophilicity.[8] To our best knowledge, the introduction of fluorine moiety into the aryl part of the flavonoids molecule can enhance their biological activities including anti-bacterial activity, anti-fungal activity and anti-viral activity.[9] Very recently, newly fluorinated 3,4-dihydroxychalcones have been reported to have interesting biological activities, including anti-peroxidation activity and in vitro anti-tumor activities.[10] However, there were few literature references reported on the synthesis of trifluoromethylated flavonoids. Earlier studies[11] of A-ring trifluoromethylated flavonoids (7-methyl-8-trifluoromethyl-chrysin **1** and 6,8-ditrifluoromethyl-7-acetoxychrysin **2**, Fig. 1) in our laboratory, showed some activities against SGC-7901 tumor cell. As the presence of a hydrophobic substituent on the

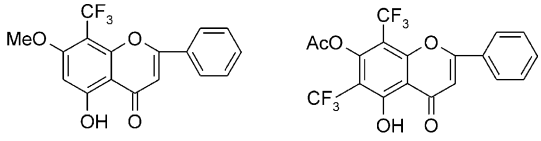

Figure 1.

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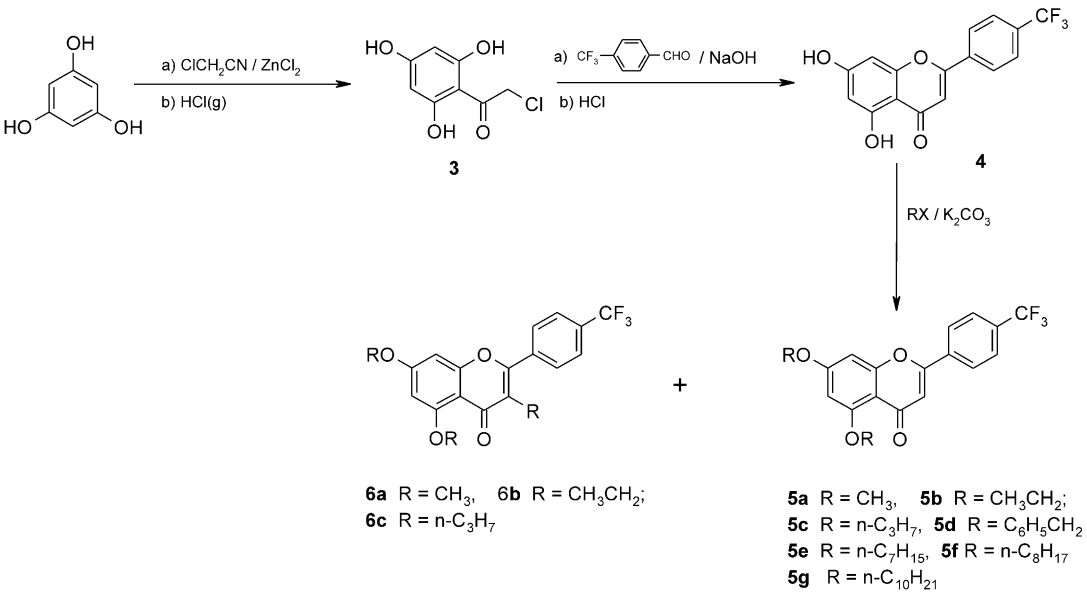
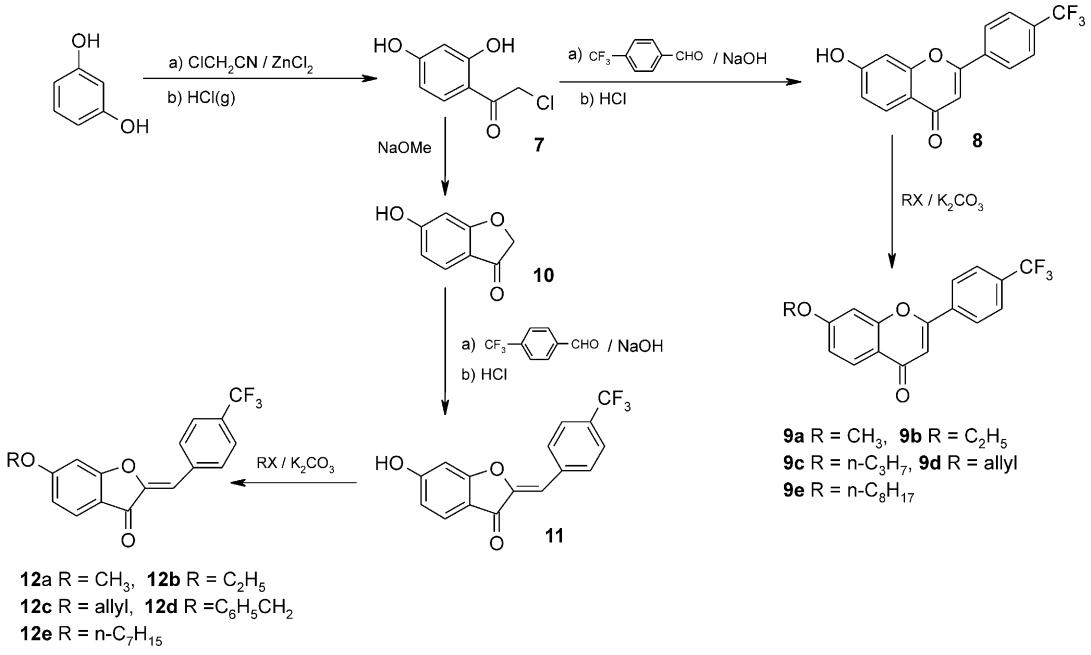


Scheme 1.



Scheme 2.

B-ring of flavonoids considerably enhanced biological activities,[12] we were interested in the introduction of trifluoromethyl group into the B-ring of flavonoids. Herein, we describe the synthesis of B-ring trifluoromethylated flavonoids derivatives and their anticancer activities against human gastric adenocarcinoma cell line (SGC-7901).

Chemistry

Condensation of phloroglucinol with chloroacetonitrile catalyzed by $ZnCl_2$ and followed by hydrolysis with HCl gas provided ketone **3** (Scheme 1).[13] Treatment of **3** with α,α,α-trifluoro-*p*-tolualdehyde in the presence of excess NaOH in H_2O/EtOH and followed by acidification with aqueous HCl gave the expected compound **4**. The alkylation of **4** was carried out with alkyl halides in the presence of K_2CO_3 in acetone to afford compounds **5a–g**. When CH_3I, CH_3CH_2Br and $CH_3CH_2CH_2Br$ were used as alkylating agents, it was interesting that the alkylation of **4** gave expected compounds **5a–c** as well as unexpected compounds **6a–c**. The ratio of **5a–c**: **6a–c** was changed from 1:1 (in the case of CH_3I) to 2:1 (in the case of CH_3CH_2Br and $CH_3CH_2CH_2Br$). Treatment of **5a–c** with CH_3I, CH_3CH_2Br and $CH_3CH_2CH_2Br$ in the presence of K_2CO_3 in acetone resulted in no reaction and **5a–c** was recovered. These

Table 1. In vitro cytotoxicity against the SGC-7901 cell line

Compd	IC_{50} (μM)	Compd	IC_{50} (μM)
1	5.90	**8**	17.75
2	8.60	**9a**	8.28
4	6.62	**9b**	28.52
5a	4.37	**9c**	5.61
5b	44.02	**9d**	5.26
5c	2.70	**9e**	4.16
5d	5.00	**11**	4.31
5e	30.83	**12a**	21.19
5f	18.06	**12b**	15.60
5g	9.02	**12c**	3.05
6a	10.08	**12d**	14.72
6b	72.46	**12e**	5.35
6c	8.64		

results indicated **6a–c** was not formed from **5a–c**. The mechanism for the formation of **5a–c** was under investigation.

The same procedure as described above can smoothly convert resorcinol to B-ring trifluoromethylated flavonoids **9a–e** via intermediates **7** and **8** (Scheme 2). We also prepared trifluomethylated aurones from resorcinol (Scheme 2). Treatment of **7** with sodium methoxide in MeOH gave benzofuranone **10**.[14] Condensation of **10** with α,α,α-trifluoro-*p*-tolualdehyde in the presence of excess NaOH in H_2O/EtOH afforded the expected aurone **11**. The alkylation of **11** with alkyl halides in the presence of K_2CO_3 in acetone produced **12a–e**.

Biological Activity

All the above compounds were tested for their in vitro anticancer activity against SGC-7901 cell by MTT-Based Assay. The assays were performed in 96-well plates essentially as described by Mosmann.[15] The IC_{50} concentration represents the concentration which results in a 50% decrease in cell growth after 6 days incubation. The given values are mean values of three experiments.

Results and Discussion

The pharmacological activity against the SGC-7901 cell is summarized in Table 1. It appeared that these closely related molecules displayed a remarkable difference in cytotoxicity. As shown in Table 1, we disclosed that **5a**, **5c**, **5d**, **9c**, **9d**, **9e**, **11**, **12c** and **12e** showed stronger cytotoxicity towards SGC-7901 cell than **1**, and **4**, **5a**, **5c**, **5d**, **9a**, **9c**, **9d**, **9e**, **11**, **12c** and **12e** showed stronger cytotoxicity towards SGC-7901 cell than **2**. 5,7-Dipropoxy-2-(4′-trifluoromethylphenyl)-chromen-4-one **5c** was identified as the most potent inhibitor of SGC-7901 tumor cell. Although general structure–activity relationship of those compounds was not elucidated from these data, the following points were noteworthy: (1) Compound **4** had stronger activity against SGC-7901 tumor cell than **8**. This was probably due to the formation of intramolecular hydrogen bond of 5-hydroxyl group in **4**. (2) Compounds **5a**, **5b** and **5c** had stronger activities than **6a**, **6b** and **6c**, respectively, suggesting that introduction of an alkyl group at the 3-position of the C-ring resulted in a significant decrease in anti-SGC-7901 tumor cell activity. (3) Comparing **5e–g** with **4**, we found that alkylated compounds had less activities than compound **4**, meanwhile among them, compounds with longer alkyl chain showed better activity. (4) When the hydroxy group of flavonoids was transformed into propoxy or allyloxy group, the resulted compounds **5c**, **9c**, **9d** and **12c** were more active for inhibition of SGC-7901 cell than parent compounds **4**, **8** and **11**, respectively. However, the anti-tumor activity of the ethylated compounds **5b**, **9b**, and **12b** decreased dramatically. (5) Comparing **9a–e** with **8**, the results showed that, apart from **9b**, the alkylated compounds were more active than **8**, the activity was enhanced with longer alkyl chain. (6) Comparing **12a–e** with **11**, we disclosed that 6-alkoxy (except allyloxy compound **12c**) substituted products **12a**, **12b**, **12d** and **12e** had less activity than compound **11**. However, it may increase activity when the alkyl chain was prolonged. (7) It was known that flavonoid containing a γ-pyrone ring was necessary for their anti-bacterial property.[9] However, for the flavonoids that we obtained with trifluoromethyl group bound on B-ring, apart from that **9a** had stronger activities against SGC-7901 tumor cell than **12a**, compounds **8**, **9b**, **9d** had less activities than **11**, **12b** and **12c**, respectively.

In conclusion, we have designed and synthesized a series of trifluoromethylated flavonoids.[16] The preliminary biological activity screening tests indicated that 5,7-Dipropoxy-2-(4′-trifluoromethyl phenyl)-chromen-4-one **5c** was the most active compound against SGC-7901 tumor cell.

Acknowledgements

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References and Notes

1. King, R. J. B., *Cancer Biology*. 2nd ed.; Pearson Education, 2000.
2. (a) *Flavonoids in Health and Disease*, Rice-Evans, C. A.; Packer, L. Eds. Marcel Dekker: New York, NY, 1997. (b) Bertrand, A.; Olivier, D. *Helv. Chim. Acta* **1999**, *82*, 2201.
3. Liu, Y. L.; Ho, D. K.; Cassady, J. M. *J. Nat. Prod.* **1992**, *55*, 357.
4. Hebtemariam, S. *J. Nat. Prod.* **1997**, *60*, 775.
5. Kubo, I.; Kinst-Hori, I.; Chaudhuri, S. K.; Kubo, Y.; Sanchez, Y.; Ogura, T. *Bioorg. Med. Chem.* **2000**, *8*, 1749.
6. Suresh, C. T.; Leena, S.; Sari, M.; Risto, S. *J. Med. Food* **1999**, *2*, 235.
7. Wang, C. F.; Kurzer, M. S. *Nutr. Cancer* **1998**, *31*, 90.
8. (a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (b) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613.
9. Sachchar, S. P.; Tripathi, N. N.; Singh, A. K. *Ind. J. Chem.* **1987**, *26B*, 493.
10. Nakamura, C.; Kawasaki, N.; Miyataka, H.; Jayachan-

dran, E.; Kim, I. H.; Kirk, K. L.; Taguchi, T.; Takeuchi, Y.; Hori, H.; Satoh, T. *Bioorg. Med. Chem.* **2002**, *10*, 699.
11. Zheng, X.; Meng, W. D.; Xu, Y. Y.; Cao, J. G.; Qing, F. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 881.
12. Boumendjel, A.; Bois, F.; Beney, C.; Mariotte, A. M.; Conseil, A.; Pietro, A. D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 75.
13. Chen, J. J.; Yang, W. W.; Pan, X. F.; Tan, Z. *Acta Chimica Sin.* **1987**, *45*, 503.
14. Beney, C.; Mariotte, A. M.; Boumendjel, A. *Heterocycles* **2001**, *55*, 967.
15. Mosman, T. J. *Immunol. Methods* **1983**, *65*, 55.
16. All the new compounds were characterized by detailed spectroscopic analysis. **4** MS (EI, 70 ev) *m/z*: 322; IR υ_{max} (cm^{-1}, KBr): 1682 (C=O), 3096, 3312 (OH); ^1H NMR (300 MHz, DMSO-d_6): 6.100 (1H, d, $J=1.5$ Hz), 6.230 (1H, d, $J=1.5$ Hz), 6.688 (1H, s), 7.801 (2H, d, $J=8.1$ Hz), 8.076 (2H, d, $J=8.1$ Hz), 11.006 (1H, s), 11.082 (1H, s). ^{19}F NMR (300 MHz) −70.95. Anal. calcd for $C_{16}H_9F_3O_4$: C, 59.64, H, 2.82; Found C, 59.44, H, 2.85. **5a** MS (EI, 70 ev) *m/z*: 350; IR υ_{max} (cm^{-1}, KBr): 1705 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 3.952 (3H, s), 3.972 (3H, s), 6.156 (1H, d, $J=1.8$ Hz), 6.412 (1H, d, $J=1.8$ Hz), 6.755 (1H, s), 7.671 (2H, d, $J=8.4$ Hz), 7.958 (2H, d, $J=8.4$ Hz). ^{19}F NMR (300 MHz) −62.686. **5b** MS (EI, 70 ev) *m/z*: 378; IR υ_{max} (cm^{-1}, KBr): 1699 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 1.447–1.596 (6H, m), 4.162–4.293 (4H, m), 6.184 (1H, d, $J=1.5$ Hz), 6.412 (1H, d, $J=1.5$ Hz), 6.765 (1H, s), 7.717 (2H, d, $J=8.1$ Hz), 8.004 (2H, d, $J=8.1$ Hz). ^{19}F NMR (300 MHz) −76.240. **5c** MS (EI, 70 ev) *m/z*: 406; IR υ_{max} (cm^{-1}, KBr): 1699 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 1.066–1.114 (6H, m), 1.839–1.970 (4H, m), 4.014–4.111 (4H, m), 6.147 (1H, s), 6.373 (1H, s), 6.708 (1H, s), 7.670 (2H, d, $J=8.1$ Hz), 7.958 (2H, d, $J=8.1$ Hz). ^{19}F NMR (300 MHz) −63.108. Anal. calcd for $C_{22}H_{21}F_3O_4$: C, 65.02, H, 5.21; Found C, 64.57, H, 5.19. **5d** MS (EI, 70 ev) *m/z*: 502; IR υ_{max} (cm^{-1}, KBr): 1702 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 5.137 (2H, s), 5.298 (2H, s), 6.277 (1H, d, $J=1.8$), 6.480 (1H, d, $J=1.8$), 6.757 (1H, s), 7.333–7.507 (10H, m), 7.685 (2H, d, $J=8.1$ Hz), 7.968 (2H, d, $J=8.1$ Hz). ^{19}F NMR (300 MHz) −62.768. Anal. calcd for $C_{30}H_{21}F_3O_4$: C, 71.71, H, 4.21; Found C, 71.69, H, 4.17. **5e** MS (EI, 70 ev) *m/z*: 518; IR υ_{max} (cm^{-1}, KBr): 1707 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 0.683–1.896 (26H, m), 4.038–4.108 (4H, m), 6.132 (1H, d, $J=1.2$ Hz), 6.363 (1H, d, $J=1.2$ Hz), 6.704 (1H, s), 7.661 (2H, d, $J=8.4$ Hz), 7.950 (2H, d, $J=8.4$). ^{19}F NMR (300 MHz) −62.709. HRMS calcd for $C_{30}H_{37}F_3O_4$: 518.26158; Found: 518.26439. **5f** MS (EI, 70 ev) *m/z*: 546; IR υ_{max} (cm^{-1}, KBr): 1699 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 0.884–0.920 (6H, m), 1.501–1.274 (20H, m), 1.826–1.941 (4H, m), 4.057–4.150 (4H, m), 6.151 (1H, d, $J=1.2$), 6.382 (1H, d, $J=1.2$ Hz), 6.722 (1H, s), 7.682 (2H, d, $J=8.4$ Hz), 7.972 (2H, d, $J=8.4$ Hz). ^{19}F NMR (300 MHz) −76.194. HRMS calcd for $C_{32}H_{41}F_3O_4$: 546.29234; Found: 546.29570. **5g** MS (EI, 70 ev) *m/z*: 602; IR υ_{max} (cm^{-1}, KBr): 1703 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 0.884–0.920 (6H, m), 1.298–1.496 (28H, m), 1.822–1.938 (4H, m), 4.053–4.145 (4H, m), 6.146 (1H, d, $J=1.2$ Hz), 6.378 (1H, d, $J=1.2$), 6.717 (1H, s), 7.679 (2H, d, $J=8.1$ Hz), 7.967 (2H, d, $J=8.1$ Hz). ^{19}F NMR (300 MHz) −76.194. HRMS calcd for $C_{36}H_{49}F_3O_4$: 602.35545; Found: 602.35829. **6a** MS (EI, 70 ev) *m/z*: 364; IR υ_{max} (cm^{-1}, KBr): 1696 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 2.079 (3H, s), 3.965 (3H, s), 4.185 (3H, s), 6.530 (1H, s), 6.730 (1H, s), 7.675 (2H, d, $J=8.1$ Hz), 7.947 (2H, d, $J=8.1$ Hz). ^{19}F NMR (300 MHz) −76.261. HRMS. calcd for $C_{19}H_{15}F_3O_4$: 364.08929; Found: 364.09225. **6b** MS (EI, 70 ev) *m/z*: 406; IR υ_{max} (cm^{-1}, KBr): 1699 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 1.081 (3H, t, $J=7.2$), 1.433 (3H, t, $J=6.9$), 1.501 (3H, t, $J=6.9$), 2.655 (2H, q, $J=7.2$ Hz), 4.163 (2H, q, $J=6.9$ Hz), 4.456 (2H, q, $J=6.9$ Hz), 6.491 (1H, s), 6.703 (1H, s), 7.665 (2H, d, $J=8.1$ Hz), 7.953 (2H, d, $J=8.1$ Hz). ^{19}F NMR (300 MHz) −76.214. HRMS calcd for $C_{22}H_{21}F_3O_4$: 406.14311; Found: 406.13919. **6c** MS (EI, 70 ev) *m/z*: 448; IR υ_{max} (cm^{-1}, KBr): 1699 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 0.941–1.951 (15H, m), 2.637 (2H, m), 4.062 (2H, m), 4.381 (2H, m), 6.507 (1H, s), 6.720 (1H, s), 7.686 (2H, d, $J=7.8$ Hz), 7.971 (2H, d, $J=7.8$ Hz). ^{19}F NMR (300 MHz) −63.107. HRMS calcd for $C_{25}H_{27}F_3O_4$: 448.18953; Found: 448.19087. **8** MS (EI, 70 ev) *m/z*: 306; IR υ_{max} (cm^{-1}, KBr): 1683 (C=O), 3072 (OH); ^1H NMR (300 MHz, CD_3COCD_3): 6.818 (1H, s), 6.857 (1H, dd, $J=2.1$, 8.4), 6.899 (1H, d, $J=2.1$ Hz), 7.692 (1H, d, $J=8.4$ Hz), 7.774 (2H, d, $J=6.8$ Hz), 8.220 (2H, d, $J=6.8$ Hz), 10.138 (1H, s). ^{19}F NMR (300 MHz) −68.627. Anal. calcd for $C_{16}H_9F_3O_3$: C, 62.75, H, 2.96; Found C, 62.90, H, 3.44. **9a** MS (EI, 70ev) *m/z*: 320; IR υ_{max} (cm^{-1}, KBr): 1702 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 3.972 (3H, s), 6.806 (1H, dd, $J=2.1$, 9.3 Hz), 6.821 (1H, s), 7.709 (2H, d, $J=8.4$ Hz), 7.726 (1H, d, $J=2.1$ Hz), 7.745 (1H, d, $J=9.3$ Hz), 8.009 (2H, d, $J=8.4$ Hz). ^{19}F NMR (300 MHz) −71.206. **9b** MS (EI, 70 ev) *m/z*: 334; IR υ_{max} (cm^{-1}, KBr): 1693 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 1.492 (3H, t, $J=6.9$ Hz), 4.163 (2H, q, $J=6.9$ Hz), 6.759 (1H, dd, $J=2.1$ Hz, 6.6), 6.780 (1H, s), 7.680 (2H, d, $J=8.4$ Hz), 7.697 (1H, d, $J=2.1$ Hz), 7.705 (1H, d, $J=6.6$ Hz), 7.975 (2H, d, $J=8.4$ Hz). ^{19}F NMR (300 MHz) −71.206. Anal. calcd for $C_{18}H_{13}F_3O_3$: C, 64.67, H, 3.92; Found C, 65.23, H, 4.21. **9c** MS (EI, 70 ev) *m/z*: 348; IR υ_{max} (cm^{-1}, KBr): 1706 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 1.086 (3H, t, $J=7.5$), 1.856–1.925 (2H, m), 4.059 (2H, t, $J=6.6$ Hz), 6.763 (1H, dd, $J=2.4$, 6.6 Hz), 6.781 (1H, d, $J=6.6$ Hz), 6.794 (1H, s), 7.690 (2H, d, $J=8.1$ Hz), 7.704 (1H, d, $J=2.4$ Hz), 7.988 (2H, d, $J=8.1$ Hz). ^{19}F NMR (300 MHz) −71.203. Anal. calcd for $C_{19}H_{15}F_3O_3$: C, 65.52, H, 4.34; Found C, 65.32, H, 4.32. **9d** MS (EI, 70 ev) *m/z*: 346; IR υ_{max} (cm^{-1}, KBr): 1707 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 4.681–4.652 (2H, m), 5.505–5.363 (2H, m), 6.028–6.120 (1H, m), 6.770 (1H, s), 6.786 (1H, dd, $J=2.1$, 7.5 Hz), 6.798 (1H, d, $J=7.5$ Hz), 7.670 (2H, d, $J=7.8$ Hz), 7.709 (1H, d, $J=2.1$ Hz), 7.960 (2H, d, $J=7.8$ Hz). ^{19}F NMR (300 MHz) −67.021. Anal. calcd for $C_{19}H_{13}F_3O_3$: C, 65.90, H, 3.70; Found C, 65.89, H, 3.89. **9e** MS (EI, 70 ev) *m/z*: 418; IR υ_{max} (cm^{-1}, KBr): 1701 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 0.909 (3H, t, $J=6.6$ Hz), 1.313–1.880 (12H, m), 4.088 (2H, t, $J=6.6$ Hz), 6.764 (1H, dd, $J=2.1$, 6.6 Hz), 6.779 (1H, d, $J=2.1$ Hz), 6.789 (1H, s), 7.688 (2H, d, $J=6.8$ Hz), 7.712 (1H, d, $J=6.6$ Hz), 7.985 (2H, d, $J=6.8$ Hz). ^{19}F NMR (300 MHz) −68.437. Anal. calcd for $C_{24}H_{25}F_3O_3$: C, 68.89, H, 6.02; Found C, 69.10, H, 6.13. **11** MS (EI, 70 ev) *m/z*: 306; IR υ_{max} (cm^{-1}, KBr): 1778 (C=O); ^1H NMR (300 MHz, CD_3COCD_3): 6.781 (1H, s), 6.822 (1H, dd, $J=2.1$, 7.8 Hz), 6.864 (1H, d, $J=2.1$ Hz), 7.656 (2H, d, $J=8.4$ Hz), 7.821 (1H, d, $J=7.8$), 8.174 (2H, d, $J=8.4$ Hz), 10.118 (1H, s). ^{19}F NMR (300 MHz) −70.772. Anal. calcd for $C_{16}H_9F_3O_3$: C, 62.75, H, 2.96; Found C, 62.69, H, 2.97. **12a** MS (EI, 70 ev) *m/z*: 320; IR υ_{max} (cm^{-1}, KBr): 1702 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 3.974 (3H, s), 6.798 (1H, s), 6.818 (1H, dd, $J=2.1$, 7.8 Hz), 7.710 (1H, d, $J=2.1$), 7.715 (2H, d, $J=8.4$), 7.747 (1H, d, $J=7.8$ Hz), 8.004 (2H, d, $J=8.4$ Hz). ^{19}F NMR (300 MHz) −70.493. **12b** MS (EI, 70 ev) *m/z*: 334; IR υ_{max} (cm^{-1}, KBr): 1700 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 1.499 (3H, t, $J=6.9$ Hz), 4.175 (2H, q, $J=6.9$ Hz), 6.760 (1H, dd, $J=2.1$, 7.8 Hz), 6.784 (1H, d, $J=2.1$ Hz), 6.799 (1H, s), 7.690 (2H, d, $J=8.4$ Hz), 7.715 (1H, d, $J=7.8$ Hz), 7.990 (2H, d, $J=8.4$ Hz). ^{19}F NMR (300 MHz) −73.059. Anal. calcd for $C_{18}H_{13}F_3O_3$: C, 64.67, H, 3.92; Found C, 65.45, H, 4.22. **12c** MS (EI, 70 ev) *m/z*: 346; IR υ_{max} (cm^{-1}, KBr): 1707 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 4.664–4.691 (2H, m), 5.369–5.515 (2H, m), 6.033–6.126 (1H, m), 6.787 (1H, s), 6.814 (1H, d, $J=2.1$), 7.671 (2H, d, $J=7.8$ Hz), 7.675 (1H, d, $J=7.5$ Hz), 7.719 (1H, dd, $J=2.1$, 7.5 Hz), 7.978 (2H, d, $J=7.8$ Hz). ^{19}F NMR (300 MHz) −56.761. Anal. calcd for $C_{19}H_{13}F_3O_3$:

C, 65.89, H, 3.78; Found C, 65.76, H, 3.99. **12d** MS (EI, 70 ev) *m*/*z*: 396; IR υ_{max} (cm^{-1}, KBr): 1699 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 5.221 (2H, s), 6.815 (1H, s), 6.880 (1H, dd, $J=2.1$,9.0), 7.425–7.470 (5H, m), 7.456 (1H, d, $J=2.1$ Hz), 7.703 (2H, d, $J=7.8$), 7.747 (1H, d, $J=9.0$ Hz), 7.996 (2H, d, $J=7.8$ Hz). ^{19}F NMR (300 MHz) −74.146. Anal. calcd for $C_{23}H_{15}F_3O_3$: C, 69.70, H, 3.81; Found C, 69.76, H, 3.91. **12e** MS (EI, 70 ev) *m*/*z*: 404; IR υ_{max} (cm^{-1}, KBr): 1699 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 0.887 (3H, t, $J=6.9$ Hz), 0.925–1.873 (10H, m), 4.079 (2H, t, $J=6.9$ Hz), 6.756 (1H, dd, $J=2.1$, 9.0 Hz), 6.773 (1H, d, $J=2.1$ Hz), 6.777 (1H, s), 7.677 (2H, d, $J=7.8$ Hz), 7.696 (1H, d, $J=9.0$ Hz), 7.972 (2H, d, $J=7.8$ Hz). ^{19}F NMR (300 MHz) −67.871. Anal. calcd for $C_{23}H_{23}F_3O_3$: C, 68.31, H, 5.73; Found C, 68.92, H, 6.21.