

**[3+2] cycloaddition reaction for synthesis of spiro[indoline-3,3'-pyrrolidines]  
and evaluation of cytotoxicity to cancer cells**

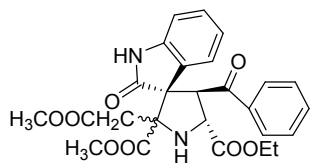
Ying Huang<sup>a,b</sup>, Yi-Xin Huang<sup>b</sup>, Jing Sun<sup>a</sup>, Chao-Guo Yan<sup>a,\*</sup>

**Supporting Information**

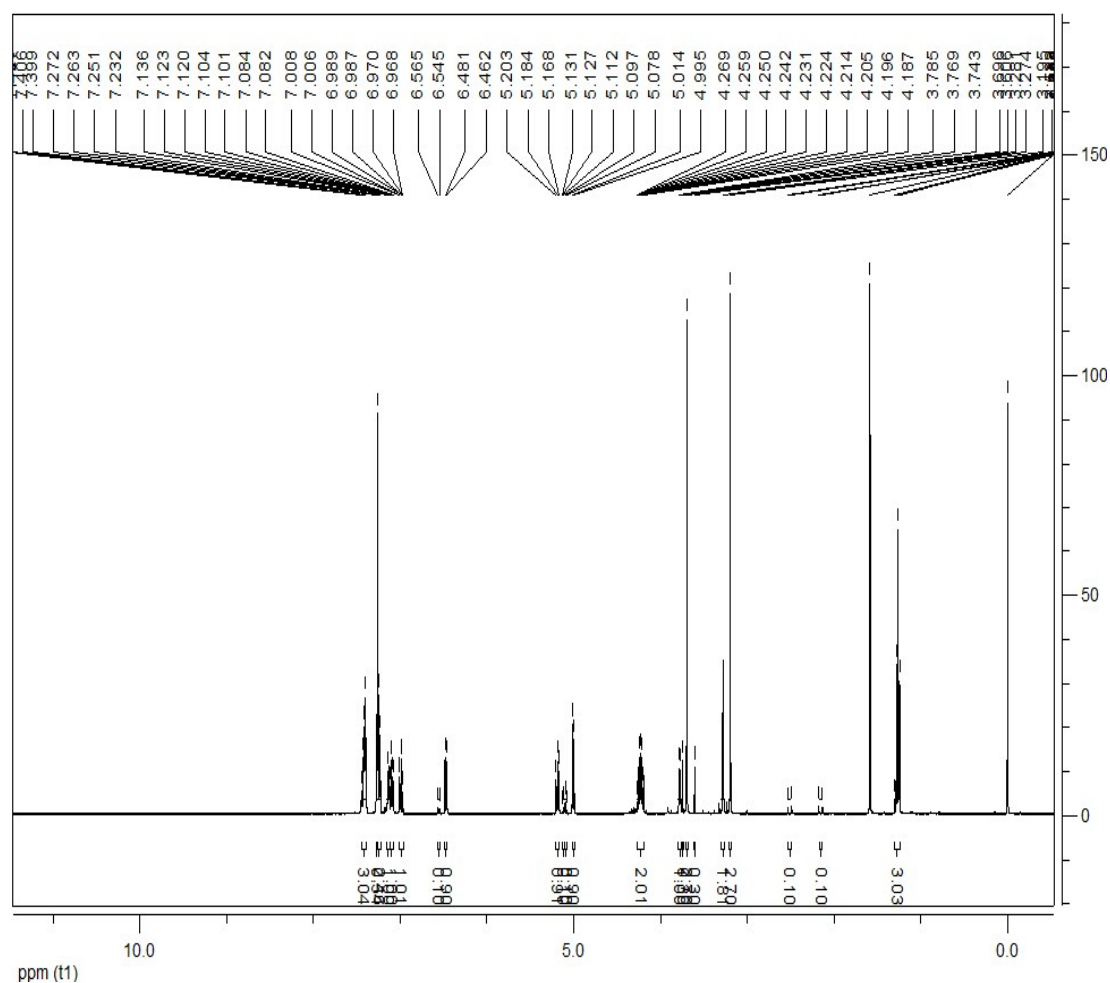
**Characterization data, <sup>1</sup>H, <sup>13</sup>C and HR-MS spectra of the compounds** 2-49

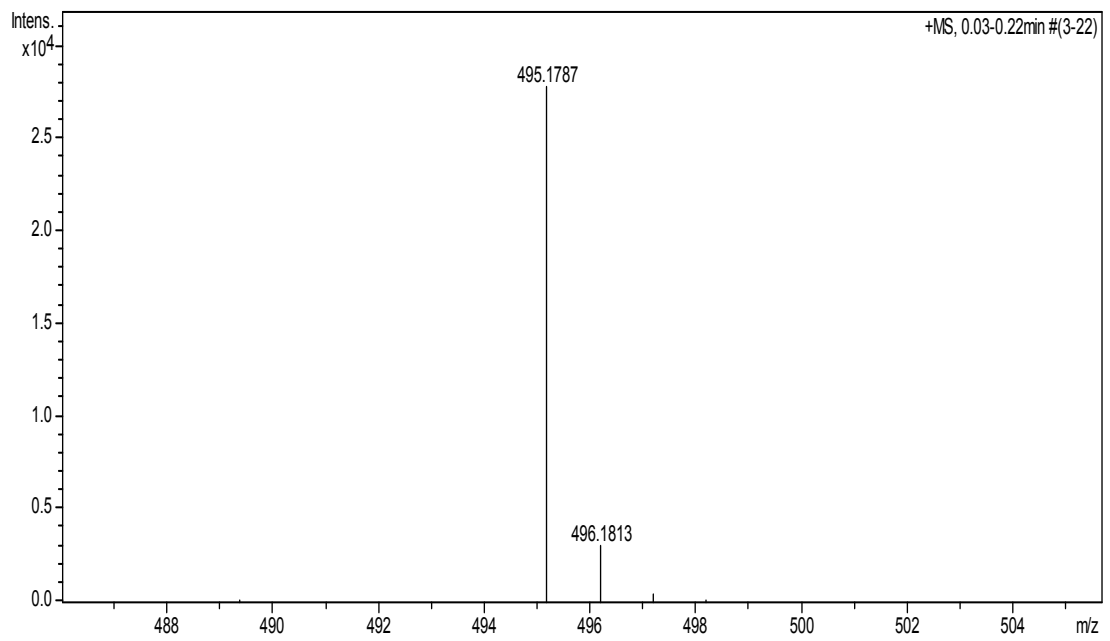
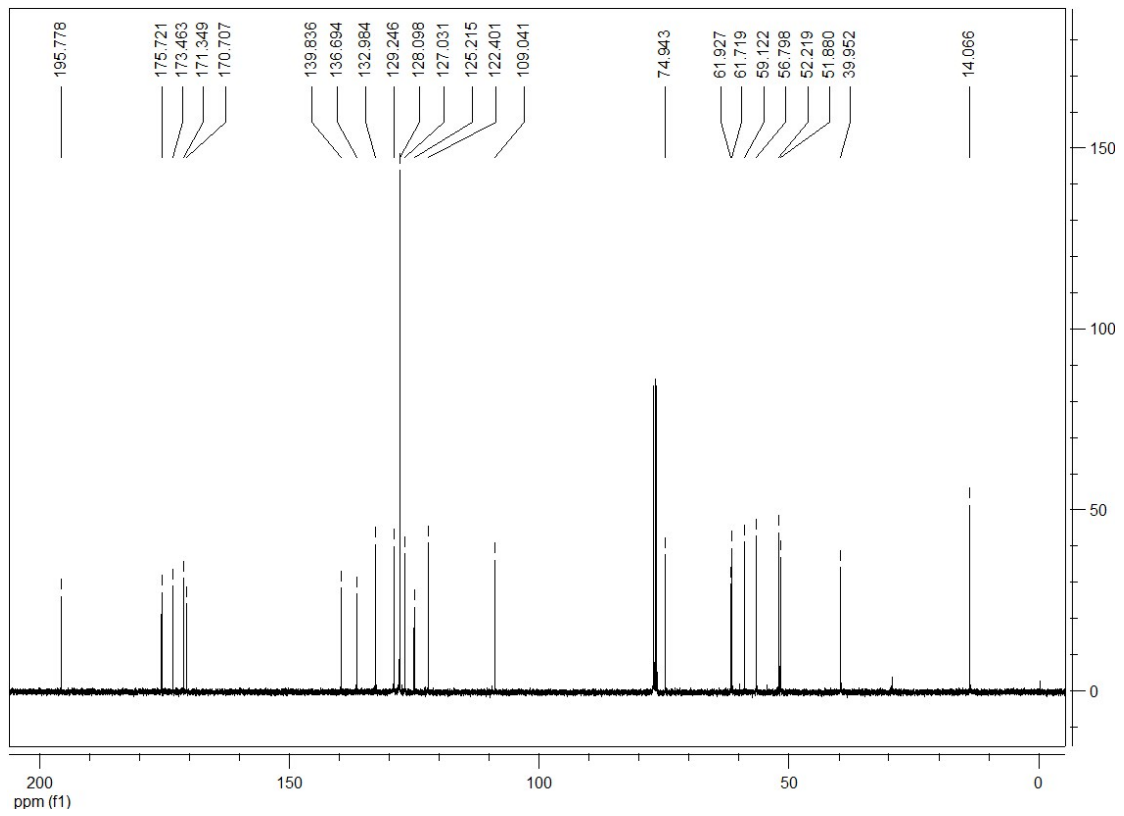
**Preliminary evaluation on the anticancer activities of synthesized compounds  
on 4T1, CT26, HepG2 and A549 cancer cell lines (200 µg·mL<sup>-1</sup>)** 50-52

**5'-ethyl-2'-methyl-(3*S*,4'*R*,5'*R*)-4'-benzoyl-2'-(2-methoxy-2-oxoethyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-2',5'-dicarboxylate (1a)**

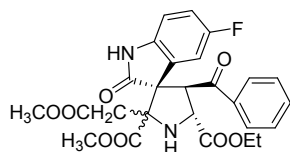


white solid, 71%, m.p. 167~168°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: **Major isomer:** 7.45~7.40 (m, 3H, ArH), 7.27~7.23 (m, 3H, ArH), 7.14 (brs, 1H, NH), 7.12~7.08 (m, 1H, ArH), 7.01~6.97 (m, 1H, ArH), 6.47 (d, *J* = 7.6Hz, 1H, ArH), 5.20~5.17 (m, 1H, CH), 5.00 (d, *J* = 7.6Hz, 1H, CH), 4.27~4.19 (m, 2H, CH), 3.78 (d, *J* = 6.4Hz, 1H, NH), 3.70 (s, 3H, OCH<sub>3</sub>), 3.28 (d, *J* = 2.8Hz, 2H, CH<sub>2</sub>), 3.20 (s, 3H, OCH<sub>3</sub>), 1.30~1.24 (m, 3H, CH<sub>3</sub>); **Minor isomer:** 6.56 (d, *J* = 8.0Hz, 1H, ArH), 5.13~5.11 (m, 1H, CH), 5.06 (d, *J* = 7.6Hz, 1H, CH), 3.74 (s, 3H, OCH<sub>3</sub>), 3.61 (s, 3H, OCH<sub>3</sub>), 2.51 (d, *J* = 16.8Hz, 1H, CH<sub>2</sub>), 2.15 (d, *J* = 16.8Hz, 1H, CH<sub>2</sub>), **ratio of major/minor = 90:10**; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 195.8, 175.7, 173.5, 171.4, 170.7, 139.8, 136.7, 133.0, 129.2, 128.1, 127.0, 125.2, 122.4, 109.0, 74.9, 61.9, 61.7, 59.1, 56.8, 52.2, 51.9, 39.9, 14.1; IR(KBr) ν: 3343, 3147, 1746, 1710, 1193cm<sup>-1</sup>; MS (*m/z*): HRMS (ESI) Calcd. for C<sub>26</sub>H<sub>27</sub>N<sub>2</sub>O<sub>8</sub> ([M+H]<sup>+</sup>): 495.1767, found: 495.1787.





**5'-ethyl-2'-methyl-(3*S*,4'*R*,5'*R*)-4'-benzoyl-5-fluoro-2'-(2-methoxy-2-oxoethyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-2',5'-dicarboxylate (1b)**



viscous oil, 77%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: **Major**

**isomer:** 7.48~7.43 (m, 3H, ArH), 7.30~7.28 (m, 1H, ArH),

7.26~7.20 (m, 2H, ArH, NH), 7.20~7.18 (m, 1H, ArH),

6.93~6.88 (m, 1H, ArH), 6.53~6.50 (m, 1H, ArH), 5.15~5.06

(m, 2H, CH), 4.33~4.21 (m, 2H, CH), 3.91 (s, 1H, NH), 3.74 (s, 3H, OCH<sub>3</sub>), 3.62 (s,

3H, OCH<sub>3</sub>), 2.53 (d, *J* = 16.8Hz, 1H, CH<sub>2</sub>), 2.16 (d, *J* = 16.8Hz, 1H, CH<sub>2</sub>), 1.29~1.24

(m, 3H, CH<sub>3</sub>); **Minor isomer:** 7.09~7.07 (m, 1H, ArH), 6.86~6.81 (m, 1H, ArH),

6.43~6.40 (m, 1H, ArH), 4.98 (d, *J* = 7.6Hz, 1H, CH), 3.70 (s, 3H, OCH<sub>3</sub>), 3.27 (s, 3H,

OCH<sub>3</sub>), 3.31 (d, *J* = 16.8Hz, 1H, CH<sub>2</sub>), 3.22 (d, *J* = 16.8Hz, 1H, CH<sub>2</sub>); **ratio of**

**major/minor = 56:44;** <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 196.2, 195.4, 175.9, 175.1,

173.6, 173.4, 172.4, 171.6, 171.2, 170.6, 158.8 (d, *J* = 240.7Hz), 158.4 (d, *J* =

240.2Hz), 136.7, 136.5, 136.3(d, *J* = 2.1Hz), 136.2 (d, *J* = 2.1Hz), 133.2, 133.0, 128.2,

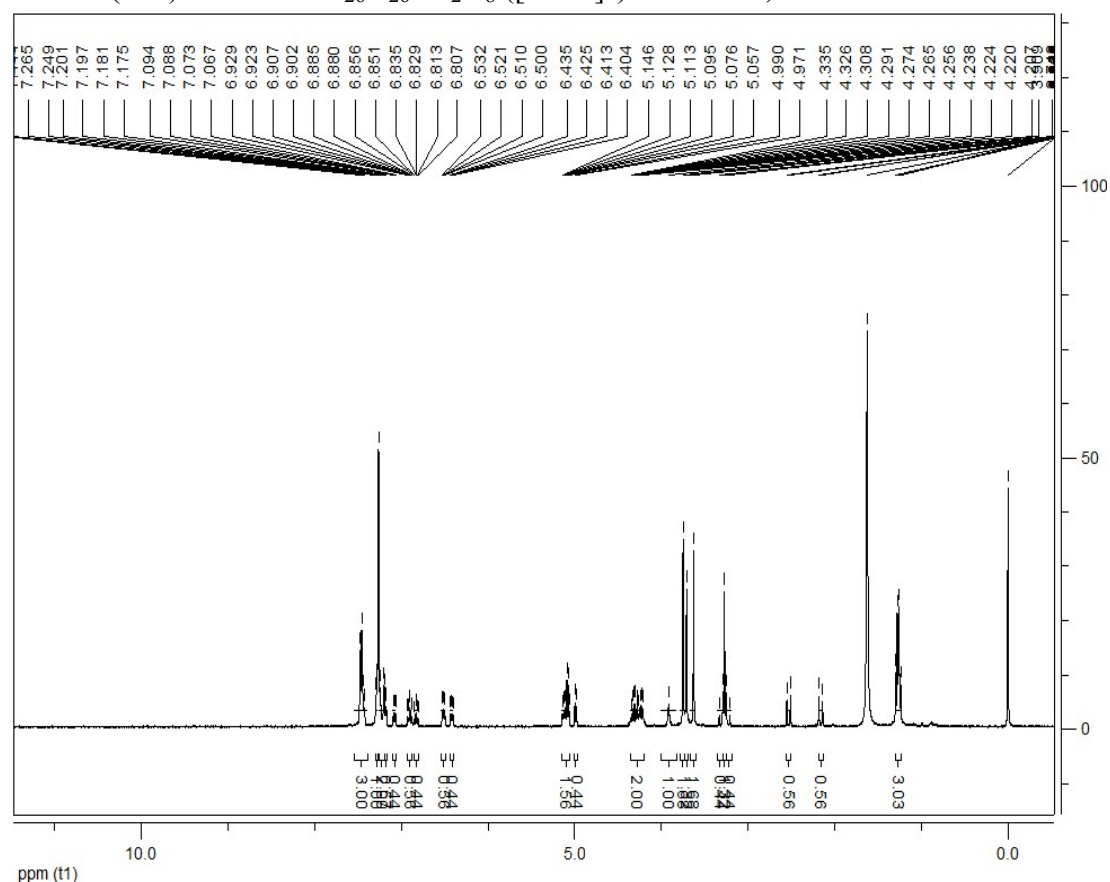
128.1, 128.1, 126.9 (d, *J* = 8.4Hz), 126.8 (d, *J* = 8.4Hz), 116.1 (d, *J* = 23.5Hz), 115.8

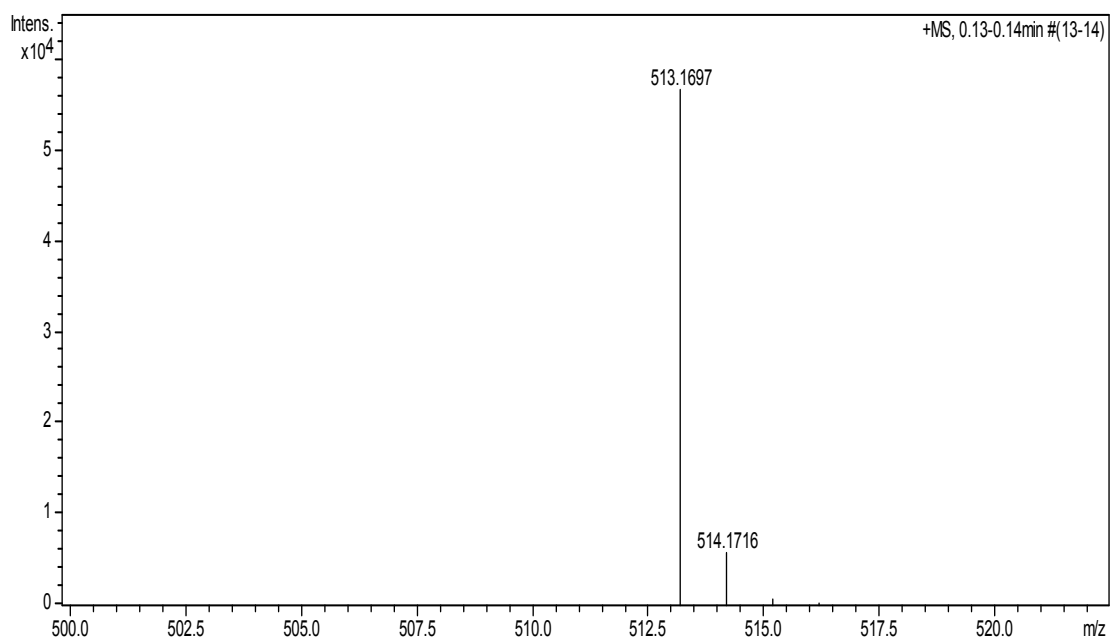
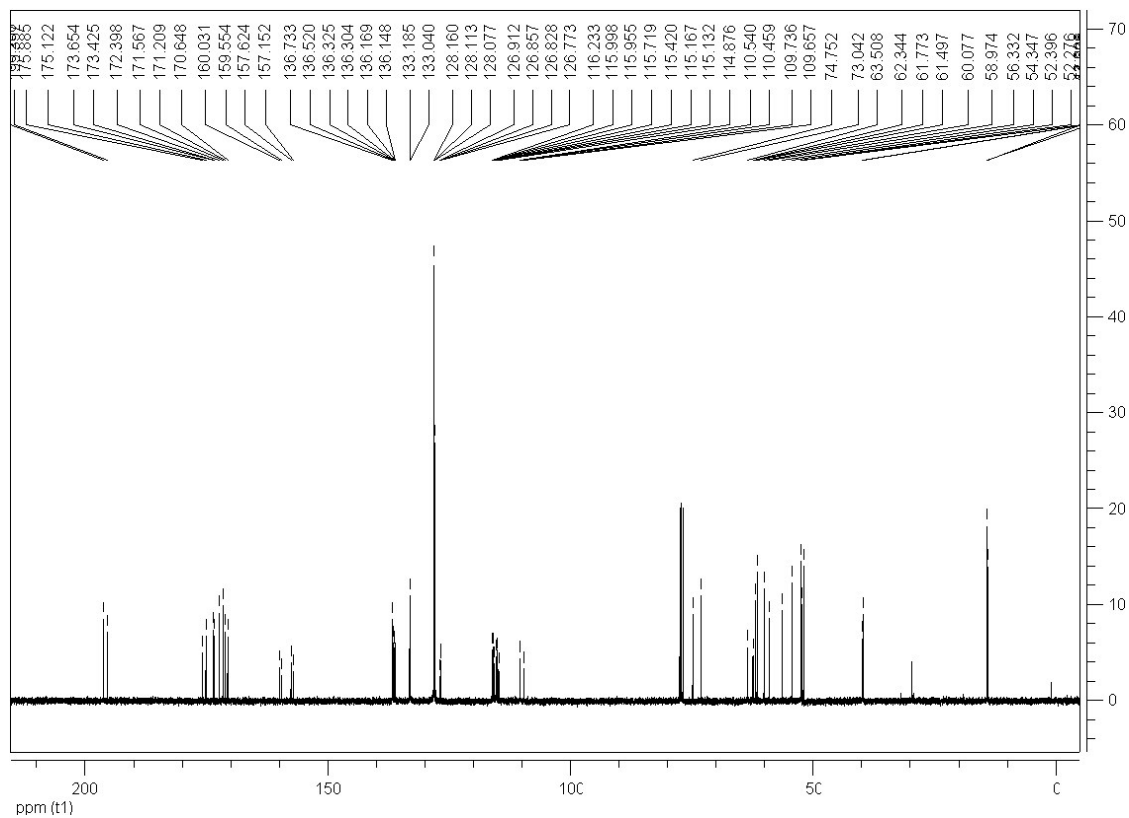
(d, *J* = 23.6Hz), 115.3 (d, *J* = 25.3Hz), 115.0 (d, *J* = 25.6Hz), 110.5 (d, *J* = 8.1Hz),

109.7 (d, *J* = 7.9Hz), 74.8, 73.0, 63.5, 62.3, 61.8, 61.5, 60.1, 59.0, 56.3, 54.3, 52.4,

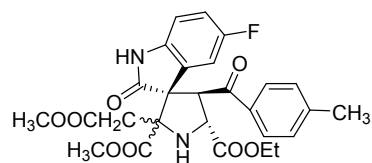
52.3, 51.9, 51.8, 39.8, 39.7, 14.1, 14.0; IR(KBr) ν: 3346, 1724, 1207cm<sup>-1</sup>; MS (*m/z*):

HRMS (ESI) Calcd. for C<sub>26</sub>H<sub>26</sub>FN<sub>2</sub>O<sub>8</sub> ([M+H]<sup>+</sup>): 513.1673, found: 513.1697.





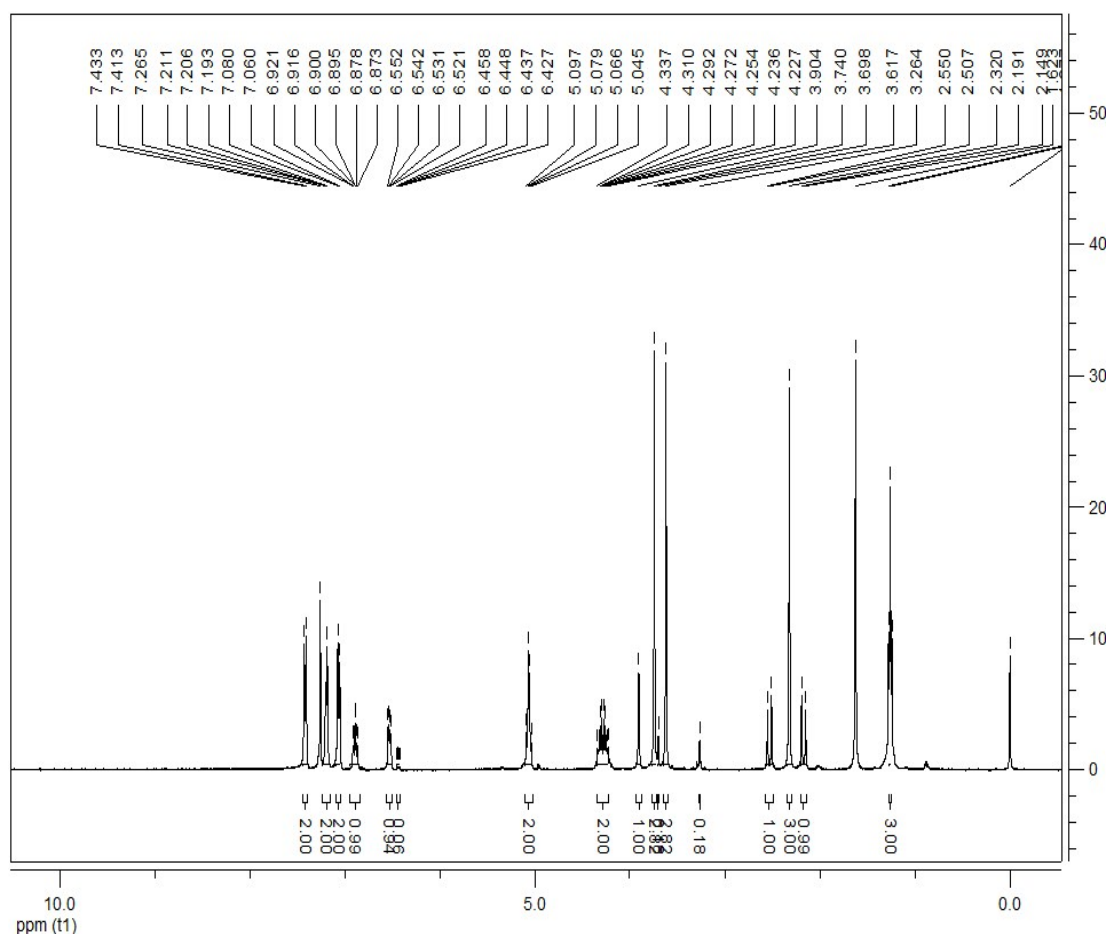
**5'-ethyl-2'-methyl-(3S,4'R,5'R)-5-fluoro-2'-(2-methoxy-2-oxoethyl)-4'-(4-methylbenzoyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-2',5'-dicarboxylate (1c)**

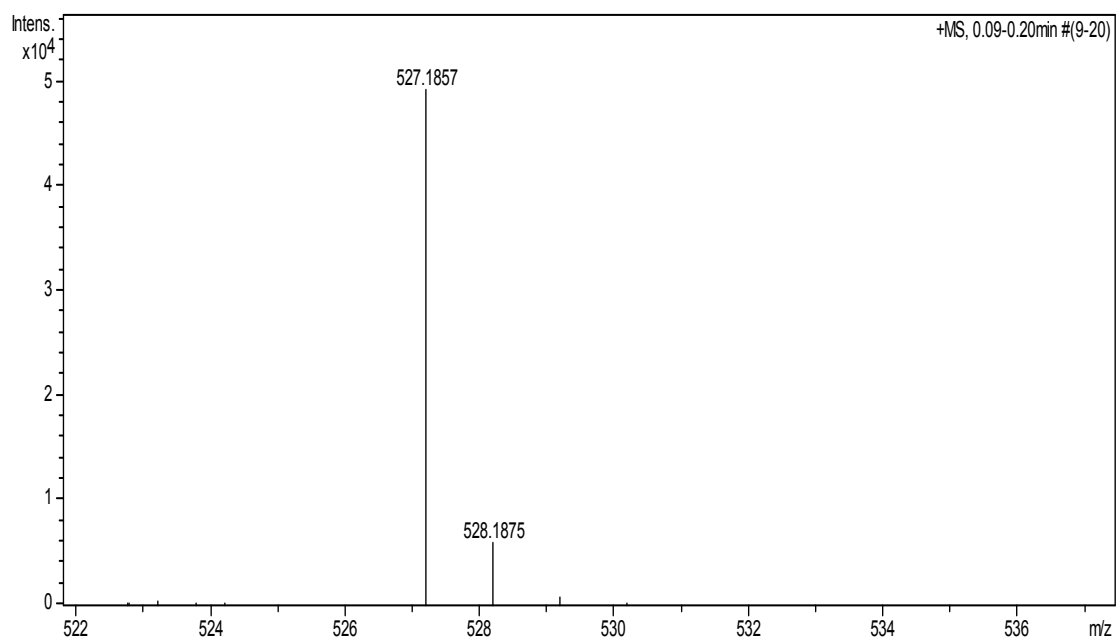
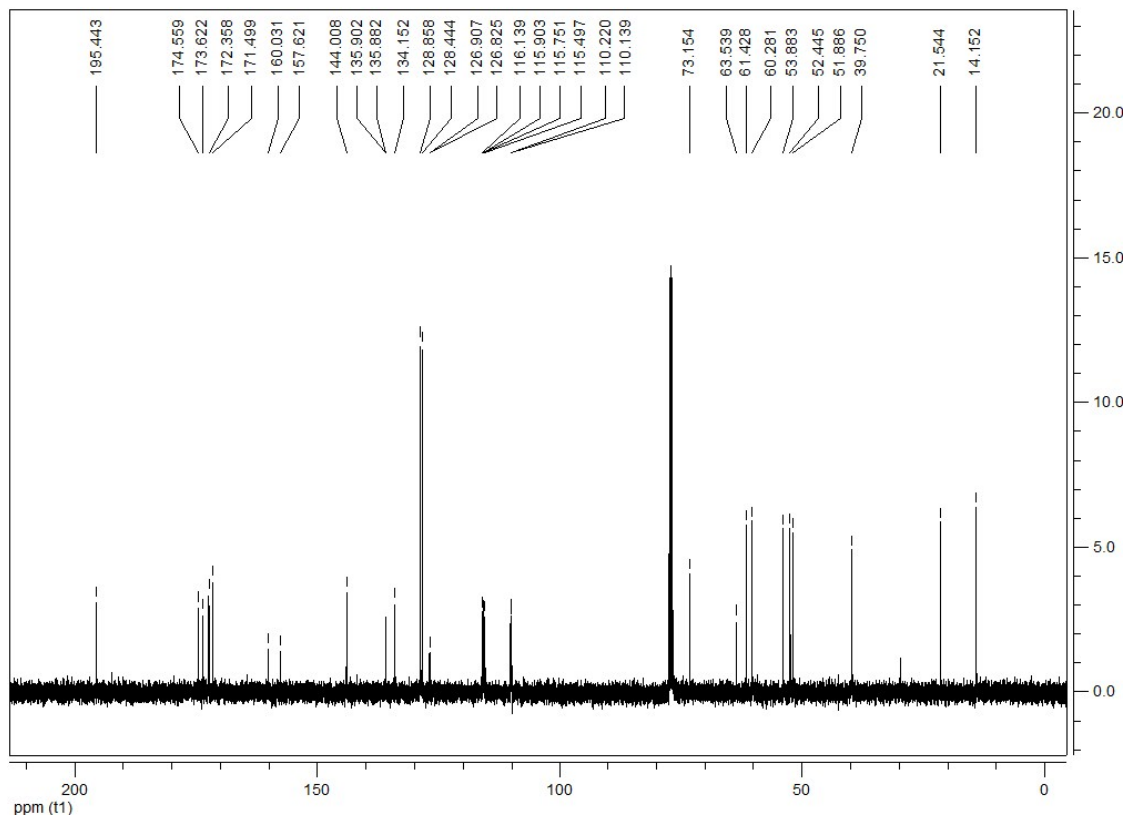


white solid, 50%, m.p. 196~198°C; <sup>1</sup>H NMR (400 MHz,

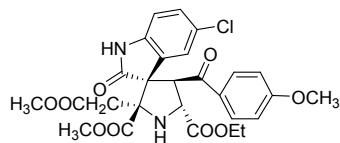
CDCl<sub>3</sub>) δ: **Major isomer:** 7.42 (d, *J* = 8.0Hz, 2H, ArH), 7.21~7.19 (m, 2H, ArH, NH), 7.07 (d, *J* = 8.0Hz, 2H,

ArH), 6.92~6.87 (m, 1H, ArH), 6.55~6.52 (m, 1H, ArH), 5.10~5.04 (m, 2H, CH), 4.34~4.23 (m, 2H, CH), 3.90 (s, 1H, NH), 3.74 (s, 3H, OCH<sub>3</sub>), 3.62 (s, 3H, OCH<sub>3</sub>), 2.53 (d, *J* = 17.2Hz, 1H, CH<sub>2</sub>), 2.32 (s, 3H, CH<sub>3</sub>), 2.17 (d, *J* = 16.8Hz, 1H, CH<sub>2</sub>), 1.26 (t, *J* = 7.2Hz, 3H, CH<sub>3</sub>); **Minor isomer:** 6.46~6.43 (m, 1H, ArH), 3.70 (s, 3H, OCH<sub>3</sub>), 3.26 (s, 3H, OCH<sub>3</sub>), **ratio of major/minor = 94:6**; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 195.4, 174.6, 173.6, 172.4, 171.5, 159.0 (d, *J* = 241Hz), 144.0, 135.9, 135.9, 134.2, 128.9, 128.4, 126.9 (d, *J* = 8.2Hz), 116.0 (d, *J* = 23.6Hz), 115.6 (d, *J* = 25.4Hz), 110.2 (d, *J* = 8.1Hz), 73.2, 63.5, 61.4, 60.3, 53.9, 52.4, 51.9, 39.7, 21.5, 14.2; IR(KBr) ν: 3371, 3184, 1739, 1714, 1208cm<sup>-1</sup>; MS (*m/z*): HRMS (ESI) Calcd. for C<sub>27</sub>H<sub>28</sub>FN<sub>2</sub>O<sub>8</sub> ([M+H]<sup>+</sup>): 527.1830, found: 527.1857.

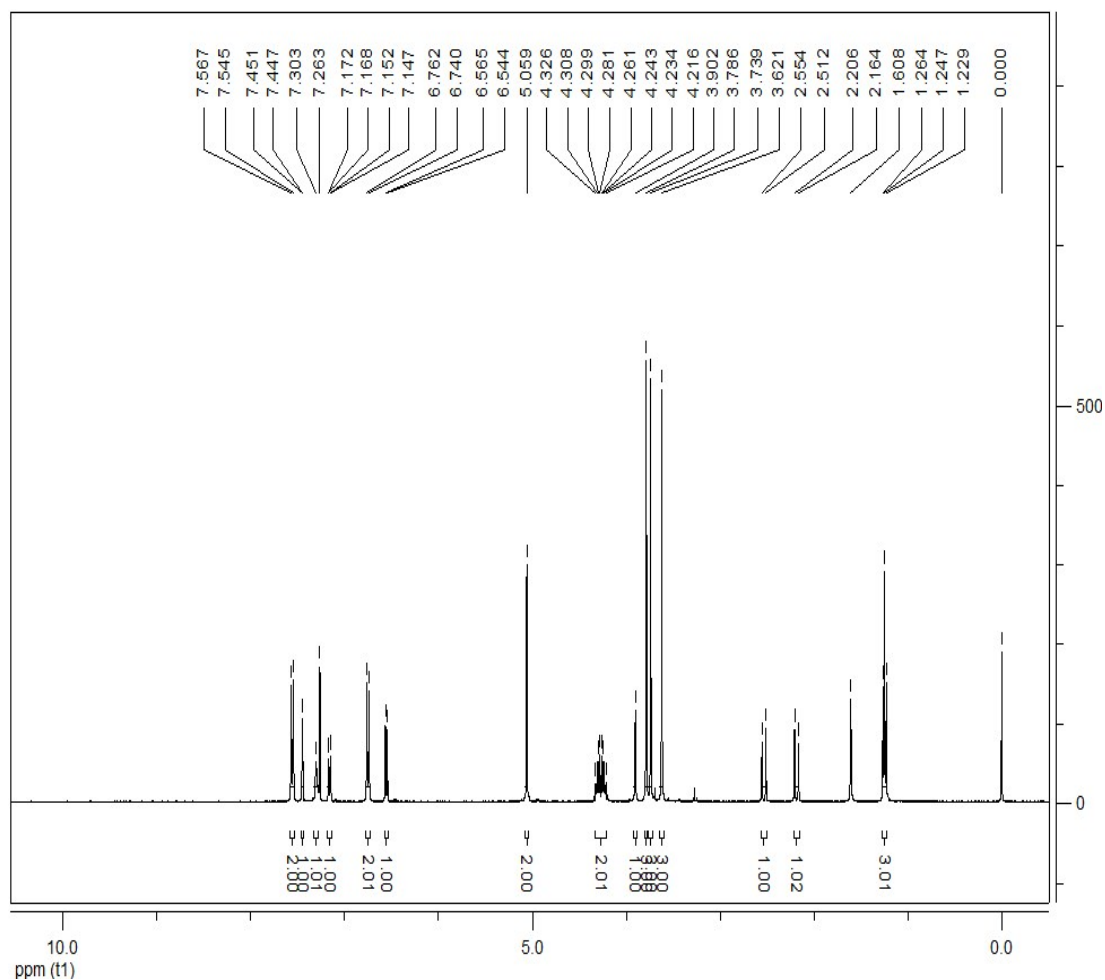




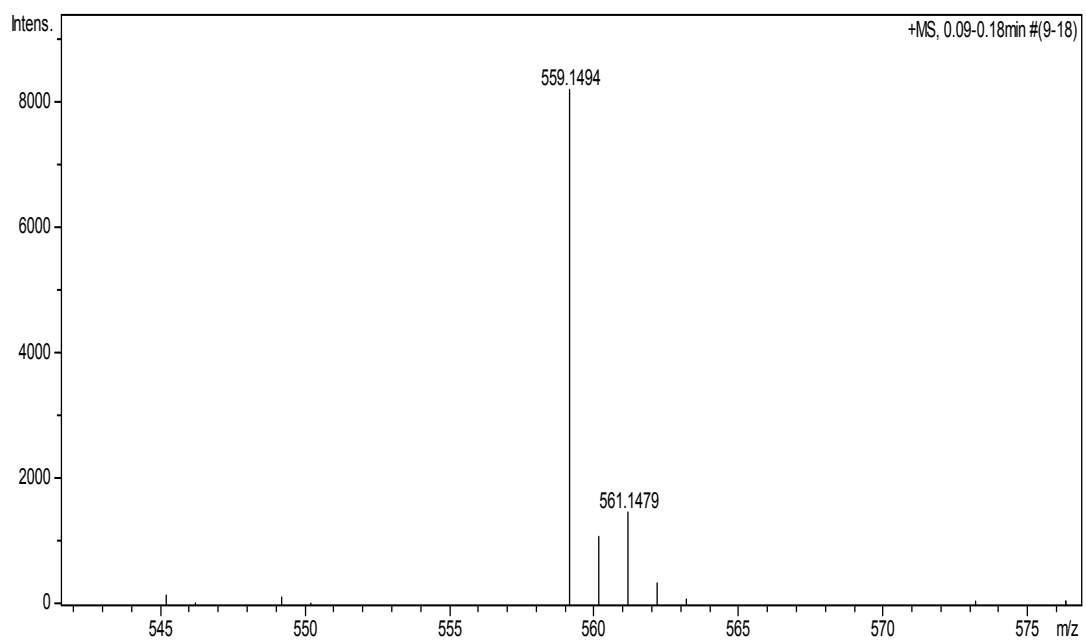
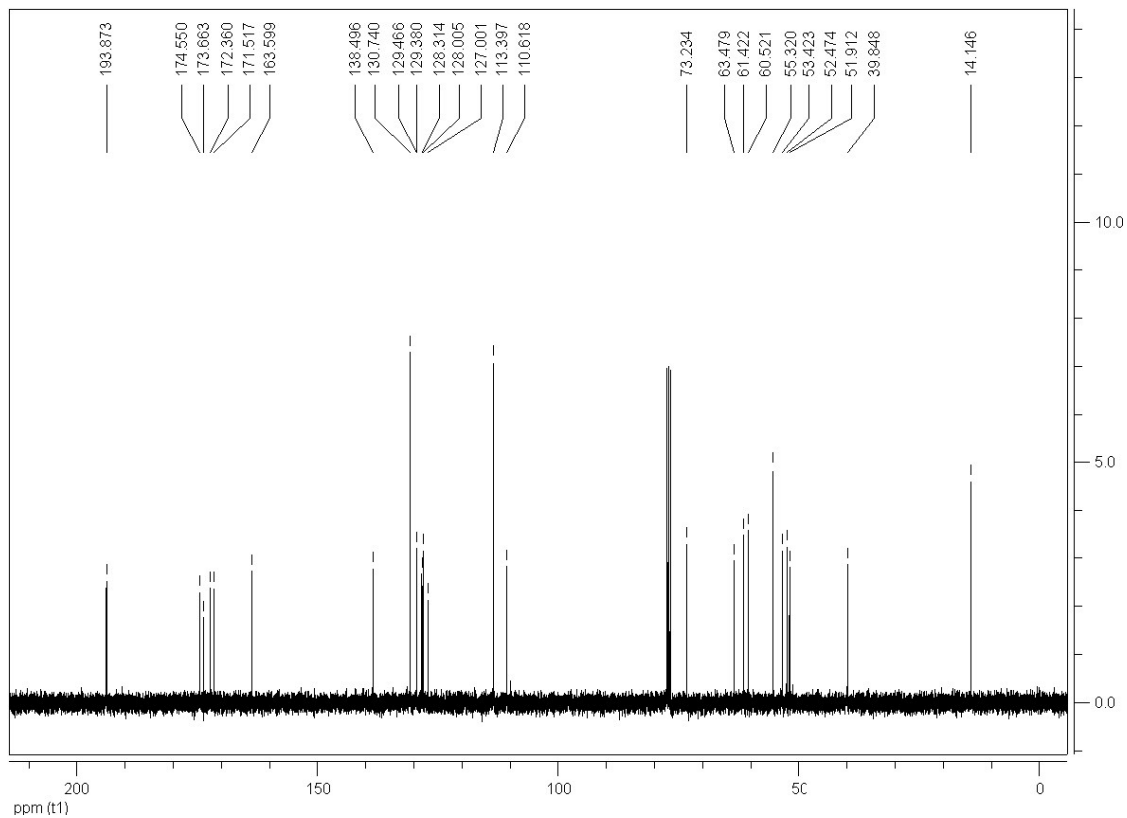
**5'-ethyl-2'-methyl-(2'R,3S,4'R,5'R)-5-chloro-2'-(2-methoxy-2-oxoethyl)-4'-(4-methoxybenzoyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-2',5'-dicarboxylate (1d)**



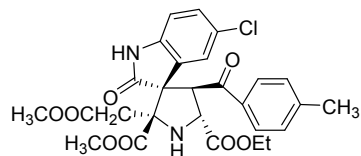
white solid, 51%, m.p. 180~181 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.56 (d, *J* = 8.8Hz, 2H, ArH), 7.45 (d, *J* = 1.6Hz, 1H, ArH), 7.30 (s, 1H, NH), 7.16 (dd, *J*<sub>1</sub> = 8.0Hz, *J*<sub>2</sub> = 1.6Hz, 1H, ArH), 6.75 (d, *J* = 8.8Hz, 2H, ArH), 6.55 (d, *J* = 8.4Hz, 1H, ArH), 5.06 (brs, 2H, CH), 4.33~4.22 (m, 2H, CH), 3.90 (s, 1H, NH), 3.79 (s, 3H, OCH<sub>3</sub>), 3.74 (s, 3H, OCH<sub>3</sub>), 3.62 (s, 3H, OCH<sub>3</sub>), 2.53 (d, *J* = 16.8Hz, 1H, CH<sub>2</sub>), 2.18 (d, *J* = 16.8Hz, 1H, CH<sub>2</sub>), 1.25 (t, *J* = 7.2Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 193.9, 174.5, 173.7, 172.4, 171.5, 163.6, 138.5, 130.7, 129.5, 129.4, 128.3, 128.0, 127.0, 113.4, 110.6, 73.2, 63.5, 61.4, 60.5, 55.3, 53.4, 52.5, 51.9, 39.8, 14.1; IR(KBr) ν: 3383, 3196, 1741, 1710, 1209cm<sup>-1</sup>; MS (*m/z*): HRMS (ESI) Calcd. for C<sub>27</sub>H<sub>28</sub>ClN<sub>2</sub>O<sub>9</sub> ([M+H]<sup>+</sup>): 559.1483, found: 559.1494.



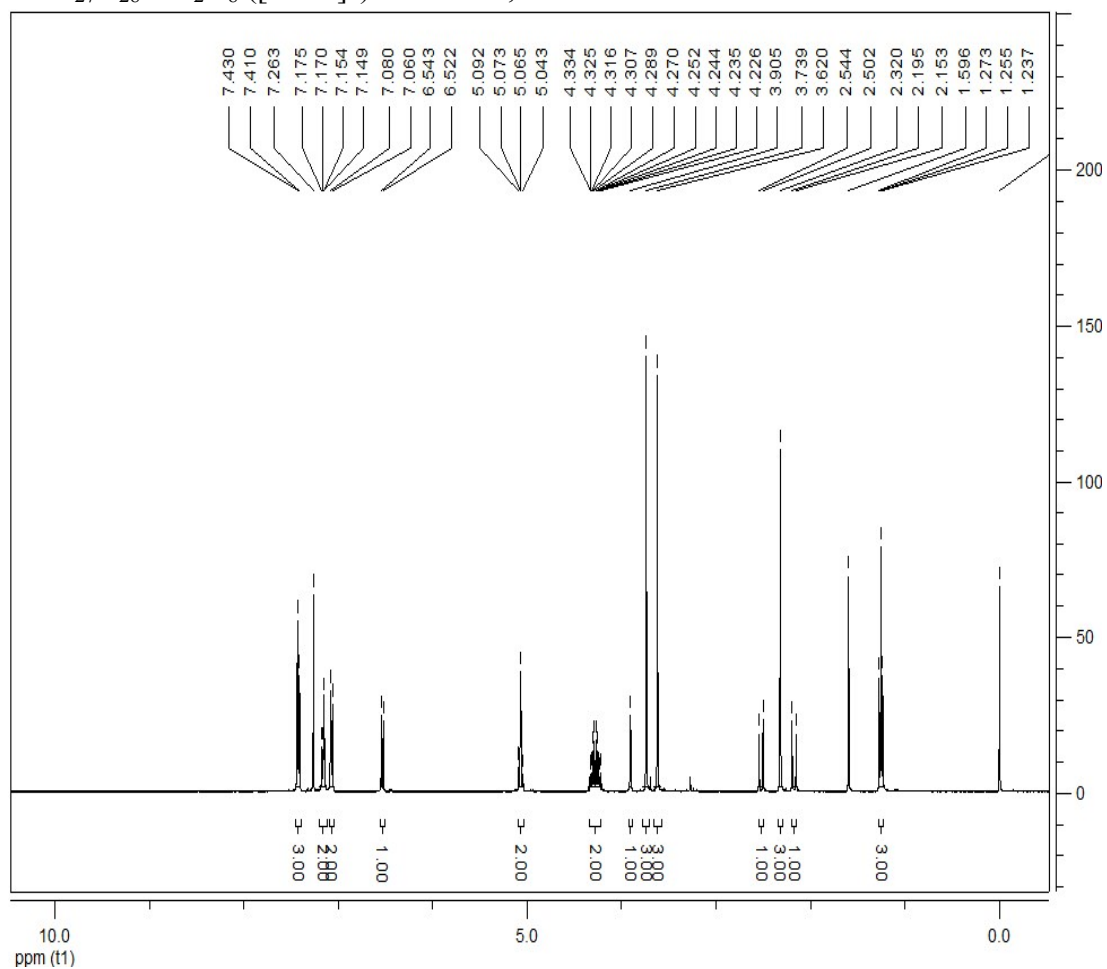


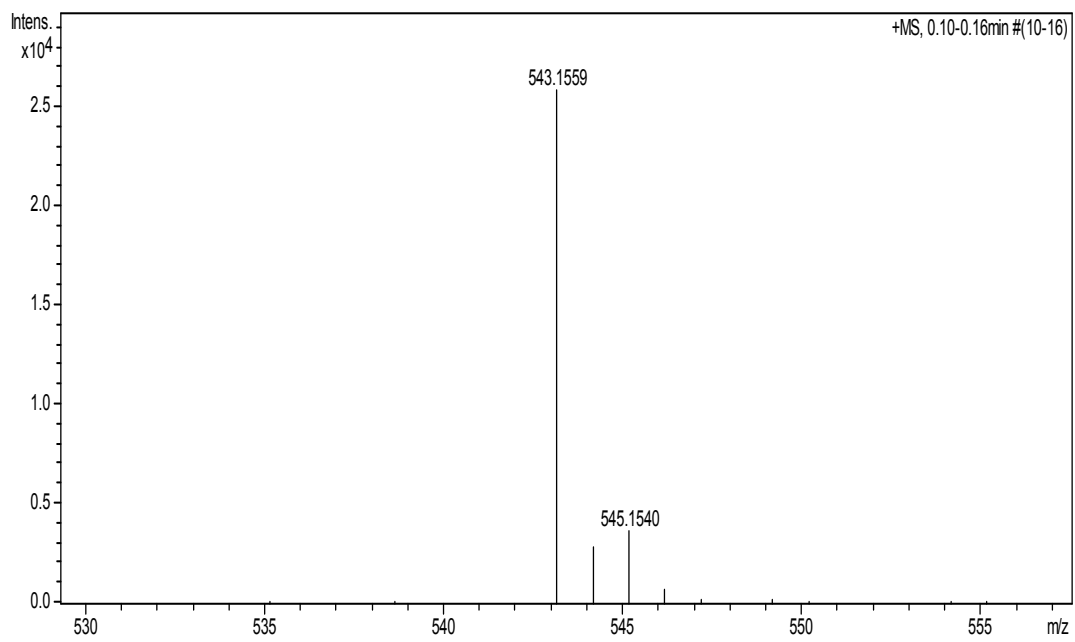
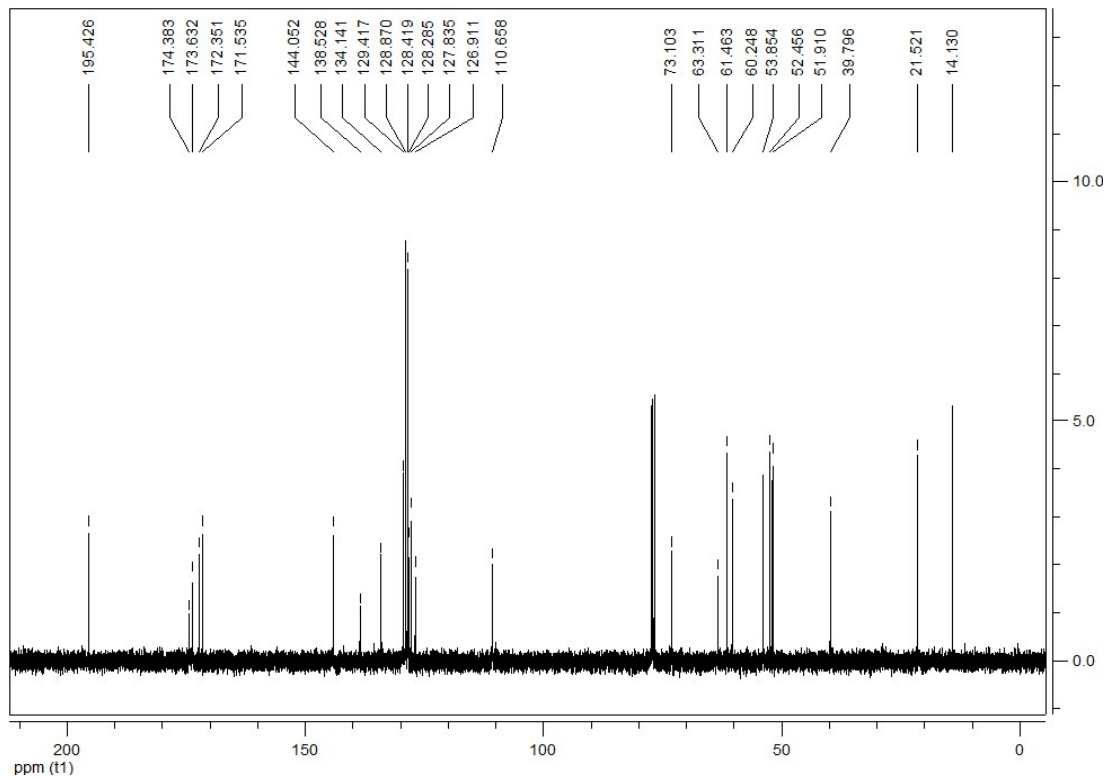


**5'-ethyl-2'-methyl-(2'R,3S,4'R,5'R)-5-chloro-2'-(2-methoxy-2-oxoethyl)-4'-(4-methylbenzoyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-2',5'-dicarboxylate (1e)**

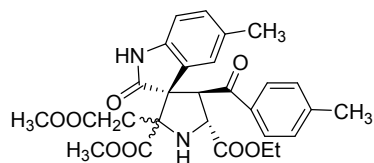


white solid, 61%, m.p. 199~200 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.42 (d, *J* = 8.0Hz, 3H, ArH), 7.18~7.15 (m, 2H, ArH, NH), 7.07 (d, *J* = 8.0Hz, 2H, ArH), 6.53 (d, *J* = 8.4Hz, 1H, ArH), 5.09~5.04 (m, 2H, CH), 4.33~4.23 (m, 2H, CH), 3.90 (s, 1H, NH), 3.74 (s, 3H, OCH<sub>3</sub>), 3.62 (s, 3H, OCH<sub>3</sub>), 2.52 (d, *J* = 16.8Hz, 1H, CH<sub>2</sub>), 2.32 (s, 3H, CH<sub>3</sub>), 2.17 (d, *J* = 16.8Hz, 1H, CH<sub>2</sub>), 1.26 (t, *J* = 6.8Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 195.4, 174.4, 173.6, 172.4, 171.5, 144.0, 138.5, 134.1, 129.4, 128.9, 128.4, 128.3, 127.8, 126.9, 110.7, 73.1, 63.3, 61.5, 60.2, 53.8, 52.5, 51.9, 39.8, 21.5, 14.1; IR(KBr) ν: 3382, 3193, 1740, 1710, 1208cm<sup>-1</sup>; MS (*m/z*): HRMS (ESI) Calcd. for C<sub>27</sub>H<sub>28</sub>ClN<sub>2</sub>O<sub>8</sub> ([M+H]<sup>+</sup>): 543.1534, found: 543.1559.





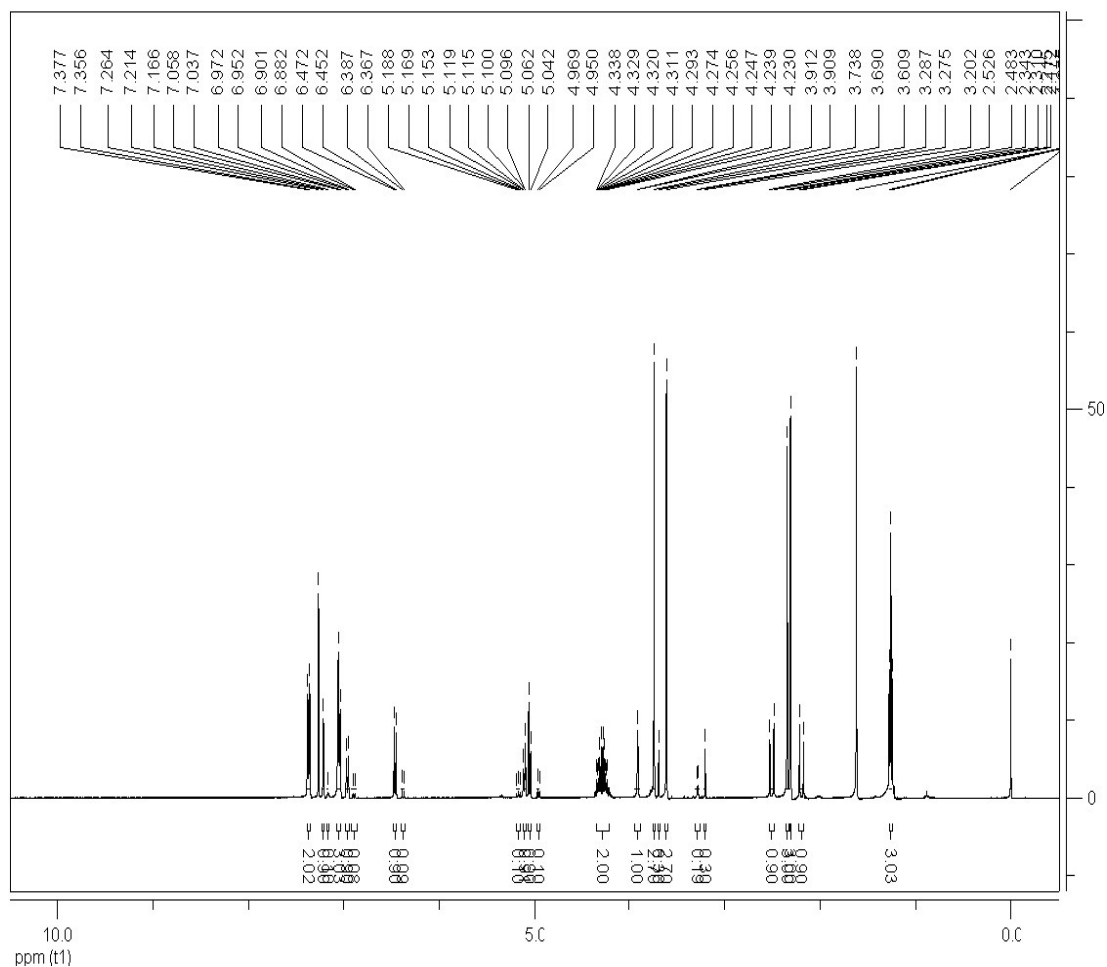
**5'-ethyl-2'-methyl-(3*S*,4'*R*,5'*R*)-2'-(2-methoxy-2-oxoethyl)-5-methyl-4'-(4-methylbenzoyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-2',5'-dicarboxylate (1f)**

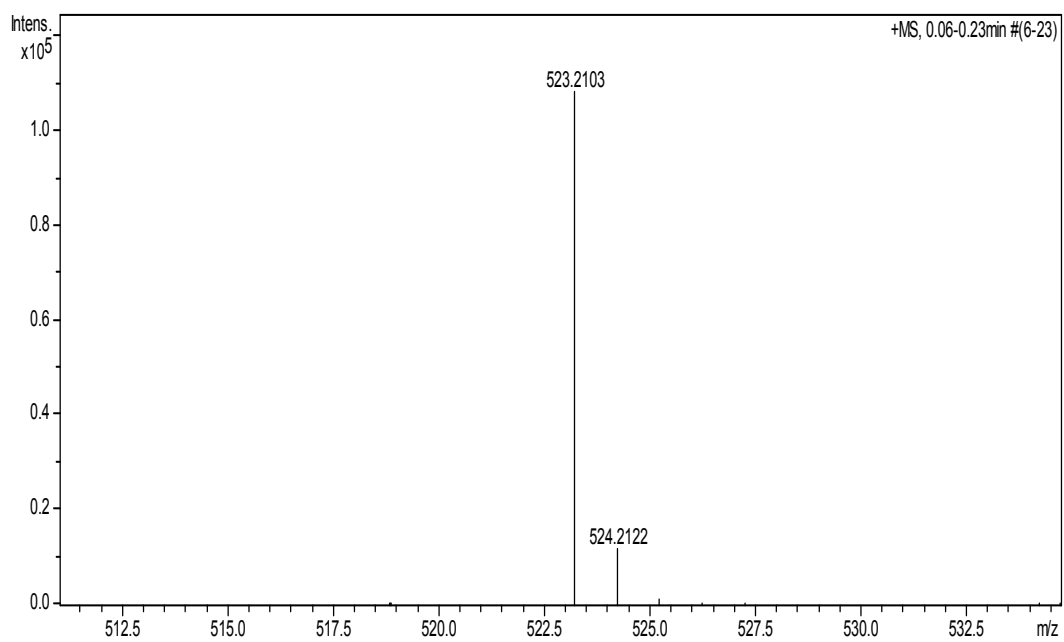
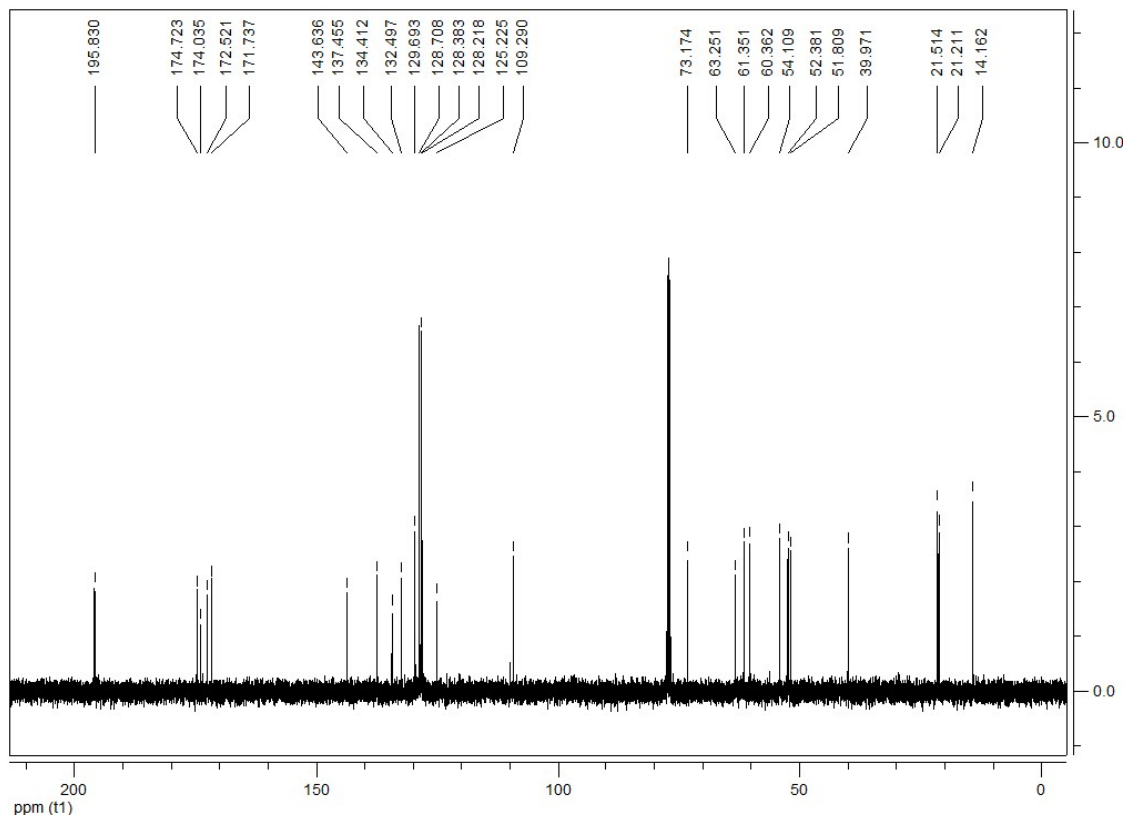


white solid, 55%, m.p. 183~185°C; <sup>1</sup>H NMR (400

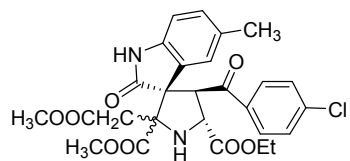
MHz, CDCl<sub>3</sub>) δ: **Major isomer:** 7.37 (d, *J* = 8.4Hz, 2H, ArH), 7.21 (s, 1H, NH), 7.06~7.04 (m, 3H, ArH), 6.96

(d, *J* = 8.0Hz, 1H, ArH), 6.46 (d, *J* = 8.0Hz, 1H, ArH), 5.11 (dd, *J*<sub>1</sub> = 7.6Hz, *J*<sub>2</sub> = 1.6Hz, 1H, CH), 5.05 (d, *J* = 8.0Hz, 1H, CH), 4.34~4.23 (m, 2H, CH), 3.91 (d, *J* = 1.2Hz, 1H, NH), 3.74 (s, 3H, OCH<sub>3</sub>), 3.61 (s, 3H, OCH<sub>3</sub>), 2.55 (d, *J* = 17.2Hz, 1H, CH<sub>2</sub>), 2.34 (s, 3H, CH<sub>3</sub>), 2.31 (s, 3H, CH<sub>3</sub>), 2.19 (d, *J* = 17.2Hz, 1H, CH<sub>2</sub>), 1.26 (t, *J* = 7.2Hz, 3H, CH<sub>3</sub>); **Minor isomer:** 7.17 (s, 1H, NH), 6.89 (d, *J* = 7.6Hz, 1H, ArH), 6.38 (d, *J* = 8.0Hz, 1H, ArH), 5.19~5.15 (m, 1H, CH), 4.96 (d, *J* = 7.6Hz, 1H, CH), 3.69 (s, 3H, OCH<sub>3</sub>), 3.28 (d, *J* = 4.8Hz, 2H, CH), 3.20 (s, 3H, OCH<sub>3</sub>), **ratio of major/minor = 90:10**; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 195.8, 174.7, 174.0, 172.5, 171.7, 143.6, 137.4, 134.4, 132.5, 129.7, 128.7, 128.4, 128.2, 125.2, 109.3, 73.2, 63.2, 61.4, 60.4, 54.1, 52.4, 51.8, 39.9, 21.5, 21.2, 14.2; IR(KBr) ν: 3382, 3176, 1740, 1705, 1205cm<sup>-1</sup>; MS (*m/z*): HRMS (ESI) Calcd. for C<sub>28</sub>H<sub>31</sub>N<sub>2</sub>O<sub>8</sub> ([M+H]<sup>+</sup>): 523.2080, found: 523.2103.

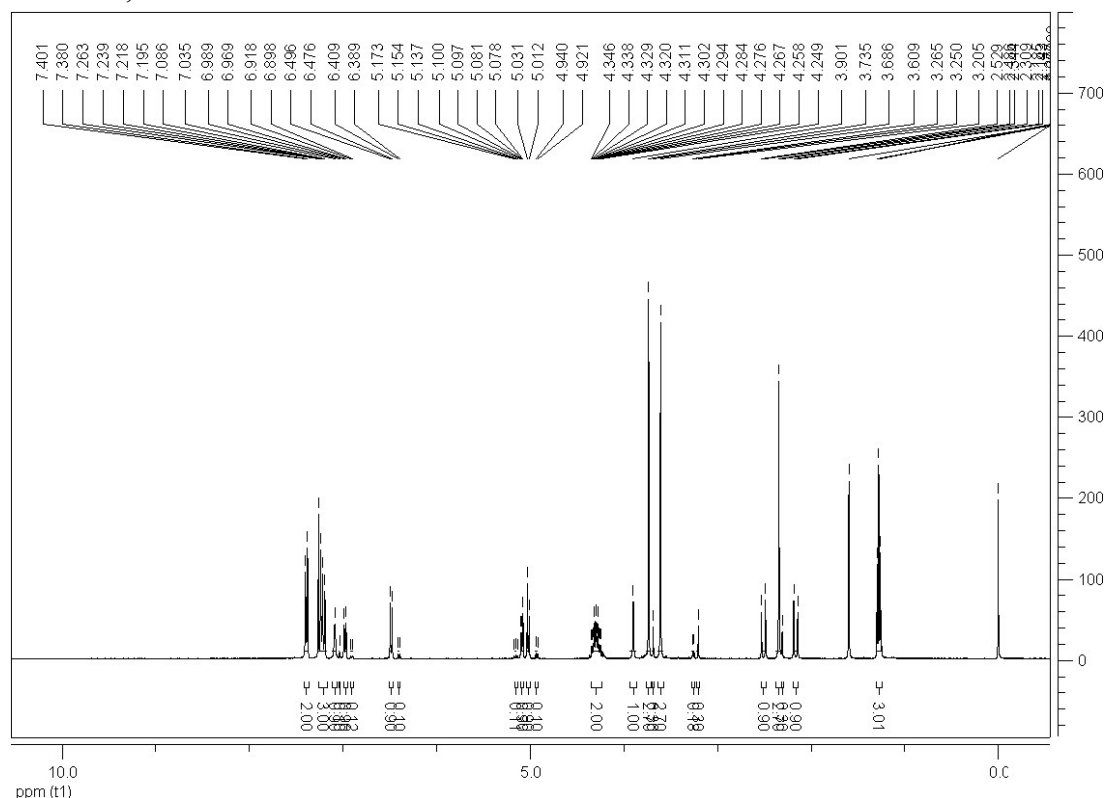


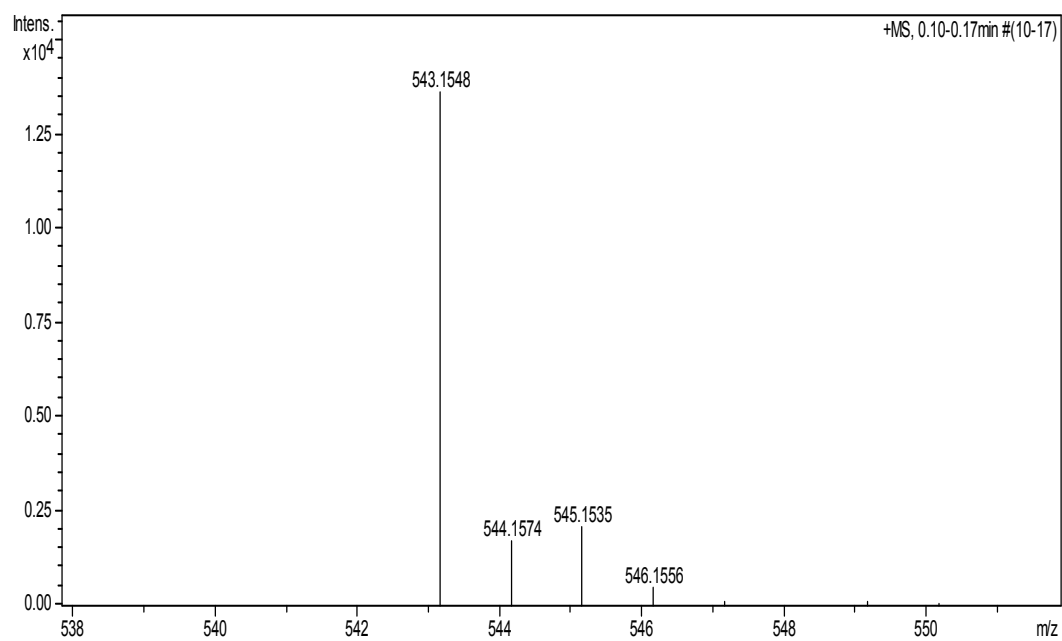
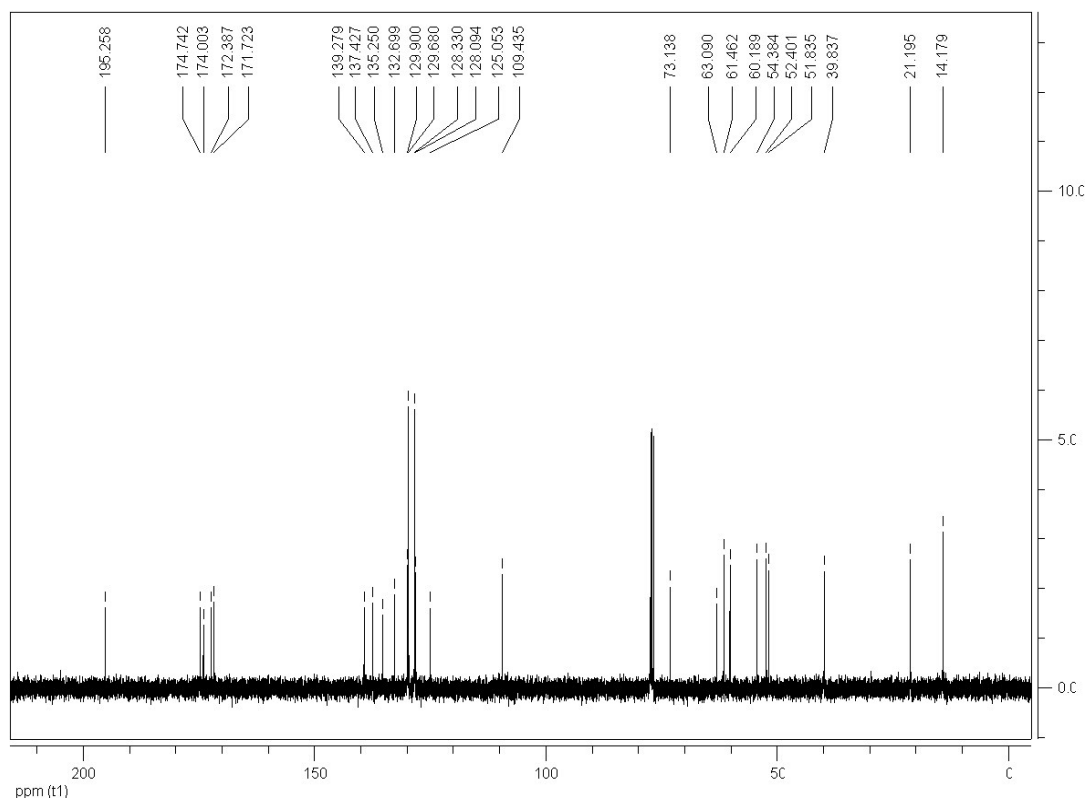


**5'-ethyl-2'-methyl-(3S,4'R,5'R)-4'-(4-chlorobenzoyl)-2'-(2-methoxy-2-oxoethyl)-5-methyl-2-oxospiro[indoline-3,3'-pyrrolidine]-2',5'-dicarboxylate (1g)**

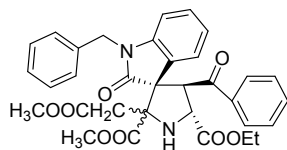


white solid, 75%, m.p. 182~184°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: **Major isomer:** 7.39 (d, *J* = 8.4Hz, 2H, ArH), 7.23 (d, *J* = 8.4Hz, 2H, ArH), 7.20 (brs, 1H, NH), 7.09 (brs, 1H, ArH), 6.98 (d, *J* = 8.0Hz, 1H, ArH), 6.49 (d, *J* = 8.0Hz, 1H, ArH), 5.10~5.08 (m, 1H, CH), 5.02 (d, *J* = 7.6Hz, 1H, CH), 4.35~4.25 (m, 2H, CH), 3.90 (s, 1H, NH), 3.74 (s, 3H, OCH<sub>3</sub>), 3.61 (s, 3H, OCH<sub>3</sub>), 2.51 (d, *J* = 17.2Hz, 1H, CH<sub>2</sub>), 2.34 (s, 3H, CH<sub>3</sub>), 2.16 (d, *J* = 16.8Hz, 1H, CH<sub>2</sub>), 1.28 (t, *J* = 7.2Hz, 3H, CH<sub>3</sub>); **Minor isomer:** 7.04 (brs, 1H, ArH), 6.91 (d, *J* = 8.0Hz, 1H, ArH), 6.40 (d, *J* = 8.0Hz, 1H, ArH), 5.17~5.14 (m, 1H, CH), 4.93 (d, *J* = 7.6Hz, 1H, CH), 3.69 (s, 3H, OCH<sub>3</sub>), 3.26 (d, *J* = 6.0Hz, 2H, CH), 3.20 (s, 3H, OCH<sub>3</sub>), 2.31 (s, 3H, CH<sub>3</sub>), **ratio of major/minor = 90:10**; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 195.3, 174.7, 174.0, 172.4, 171.7, 139.3, 137.4, 135.3, 132.7, 129.9, 129.7, 128.3, 128.1, 125.0, 109.4, 73.1, 63.1, 61.5, 60.2, 54.4, 52.4, 51.8, 39.8, 21.2, 14.2; IR(KBr) ν: 3378, 3175, 1740, 1703, 1207cm<sup>-1</sup>; MS (*m/z*): HRMS (ESI) Calcd. for C<sub>27</sub>H<sub>28</sub>ClN<sub>2</sub>O<sub>8</sub> ([M+H]<sup>+</sup>): 543.1534, found: 543.1548.

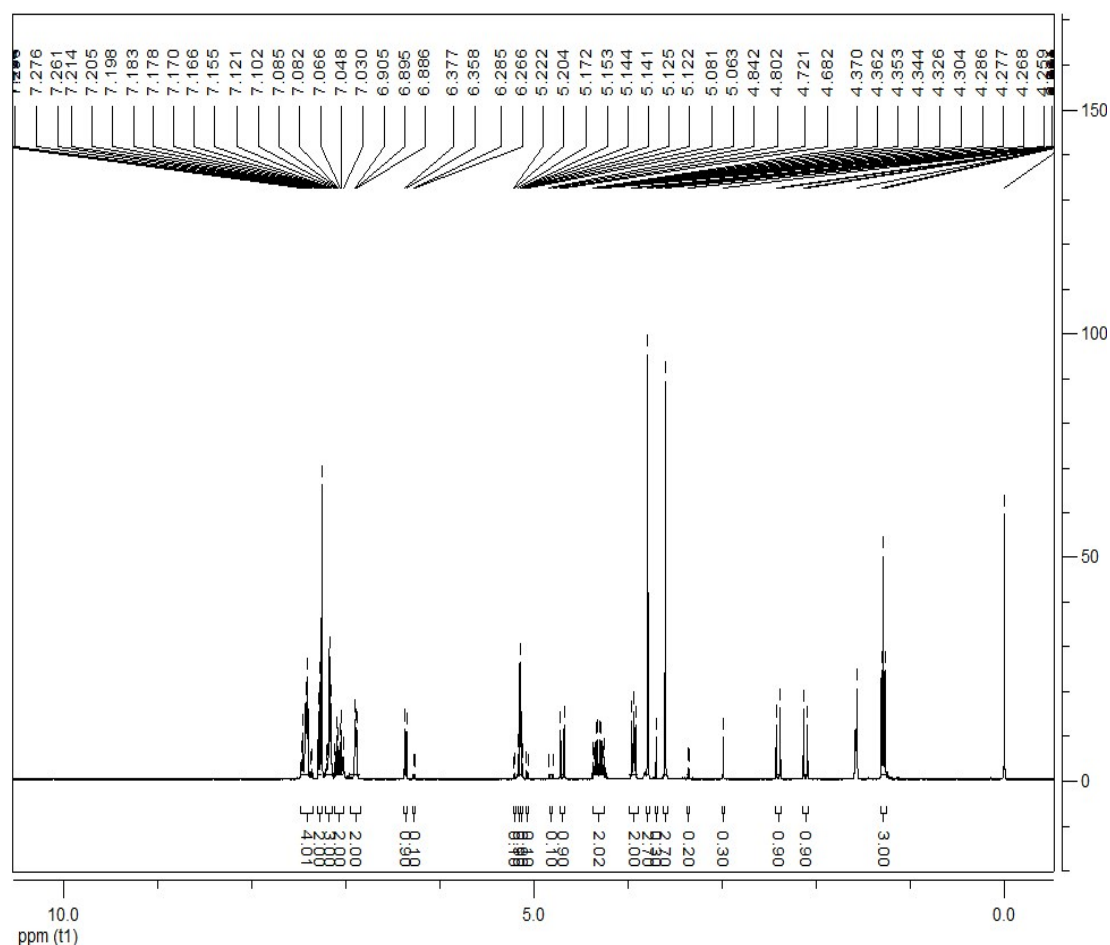




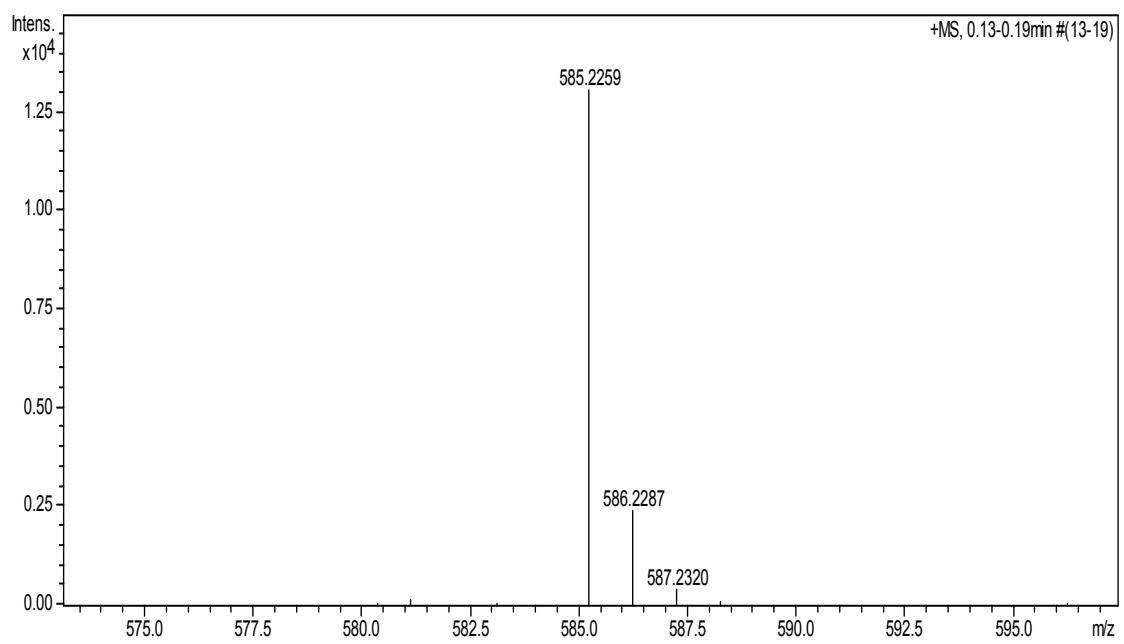
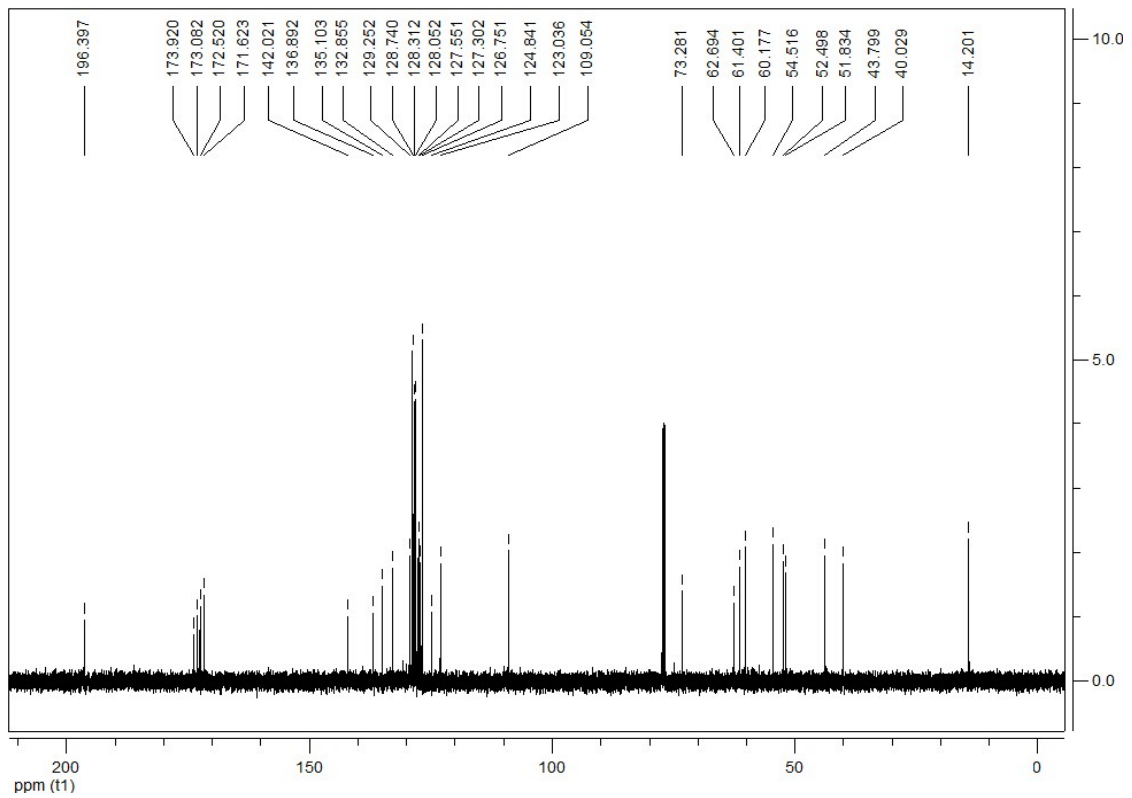
**5'-ethyl-2'-methyl-(3S,4'R,5'R)-4'-benzoyl-1-benzyl-2'-(2-methoxy-2-oxoethyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-2',5'-dicarboxylate (1h)**



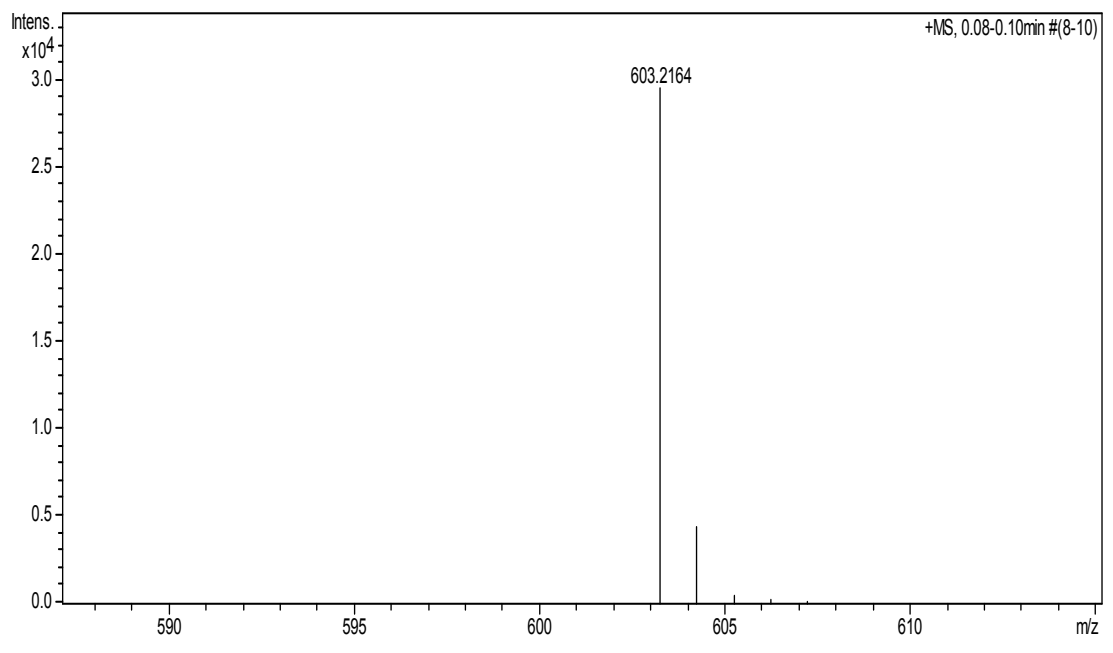
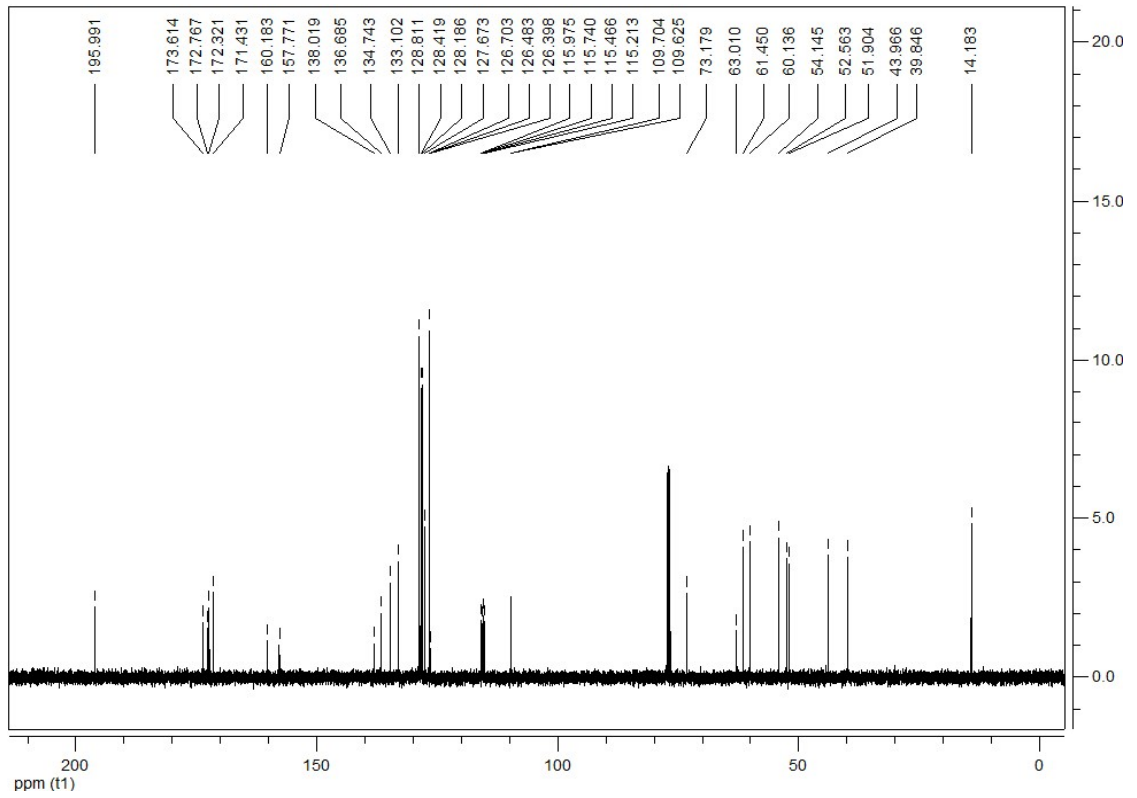
white solid, 80%, m.p. 157~158°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: **Major isomer:** 7.48~7.36 (m, 4H, ArH), 7.29 (d, *J* = 8.0Hz, 2H, ArH), 7.21~7.16 (m, 3H, ArH), 7.12~7.03 (m, 2H, ArH), 6.90~6.89 (m, 2H, ArH), 6.37 (d, *J* = 7.6Hz, 1H, ArH), 5.16 (d, *J* = 7.6Hz, 1H, CH), 5.14~5.12 (m, 1H, CH), 4.70 (d, *J* = 15.6Hz, 1H, CH), 4.37~4.26 (m, 2H, CH), 3.96~3.92 (m, 2H, CH, NH), 3.79 (s, 3H, OCH<sub>3</sub>), 3.61 (s, 3H, OCH<sub>3</sub>), 2.40 (d, *J* = 16.8Hz, 1H, CH<sub>2</sub>), 2.11 (d, *J* = 17.2Hz, 1H, CH<sub>2</sub>), 1.31~1.26 (m, 3H, CH<sub>3</sub>); **Minor isomer:** 6.28 (d, *J* = 7.6Hz, 1H, ArH), 5.21 (d, *J* = 7.2Hz, 1H, CH), 5.07 (d, *J* = 7.2Hz, 1H, CH), 4.82 (d, *J* = 16.0Hz, 1H, CH), 3.70 (s, 3H, OCH<sub>3</sub>), 3.36 (d, *J* = 4.0Hz, 2H, CH), 2.99 (s, 3H, OCH<sub>3</sub>), **ratio of major/minor = 90:10**; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 196.4, 173.9, 173.1, 172.5, 171.6, 142.0, 136.9, 135.1, 132.8, 129.2, 128.7, 128.3, 128.0, 127.6, 127.3, 126.8, 124.8, 123.0, 109.0, 73.3, 62.7, 61.4, 60.2, 54.5, 52.5, 51.8, 43.8, 40.0, 14.2; IR(KBr) ν: 3375, 1740, 1210cm<sup>-1</sup>; MS (*m/z*): HRMS (ESI) Calcd. for C<sub>33</sub>H<sub>33</sub>N<sub>2</sub>O<sub>8</sub> ([M+H]<sup>+</sup>): 585.2237, found: 585.2259.



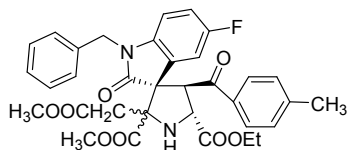








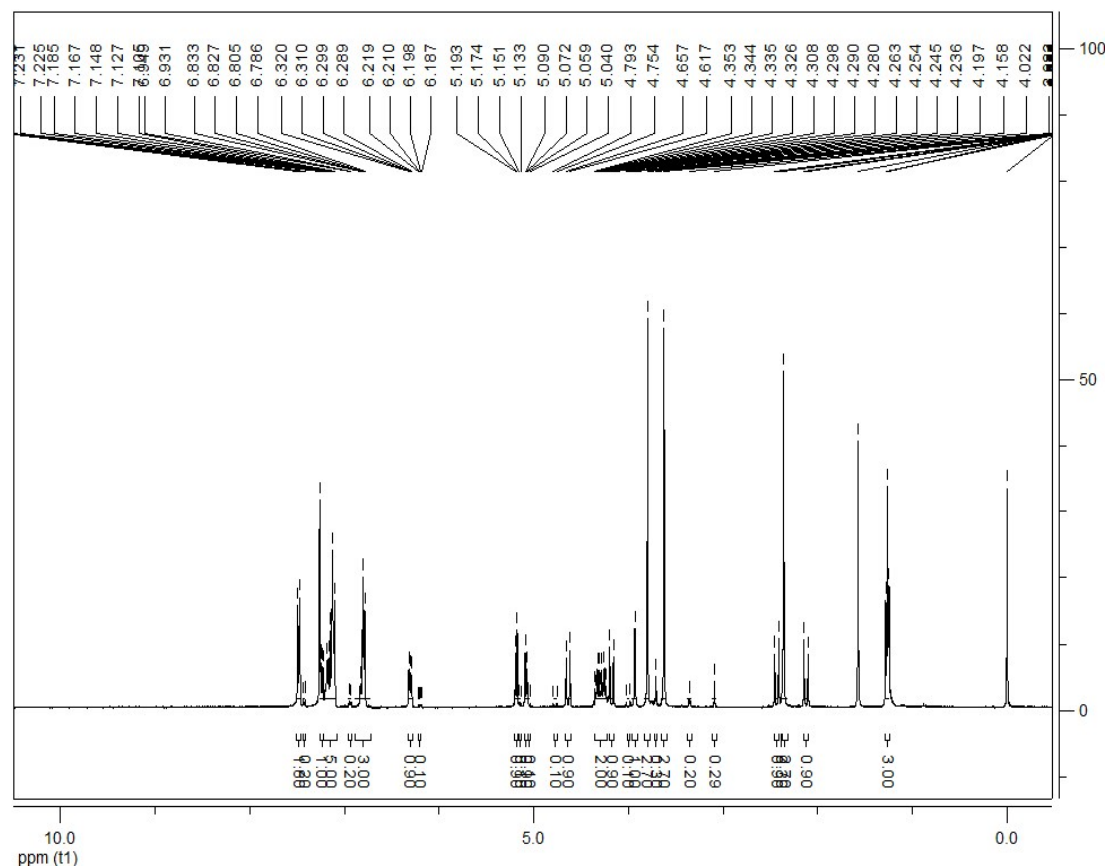
**5'-ethyl-2'-methyl-(3*S*,4'*R*,5'*R*)-1-benzyl-5-fluoro-2'-(2-methoxy-2-oxoethyl)-4'-(4-methylbenzoyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-2',5'-dicarboxylate (1j)**

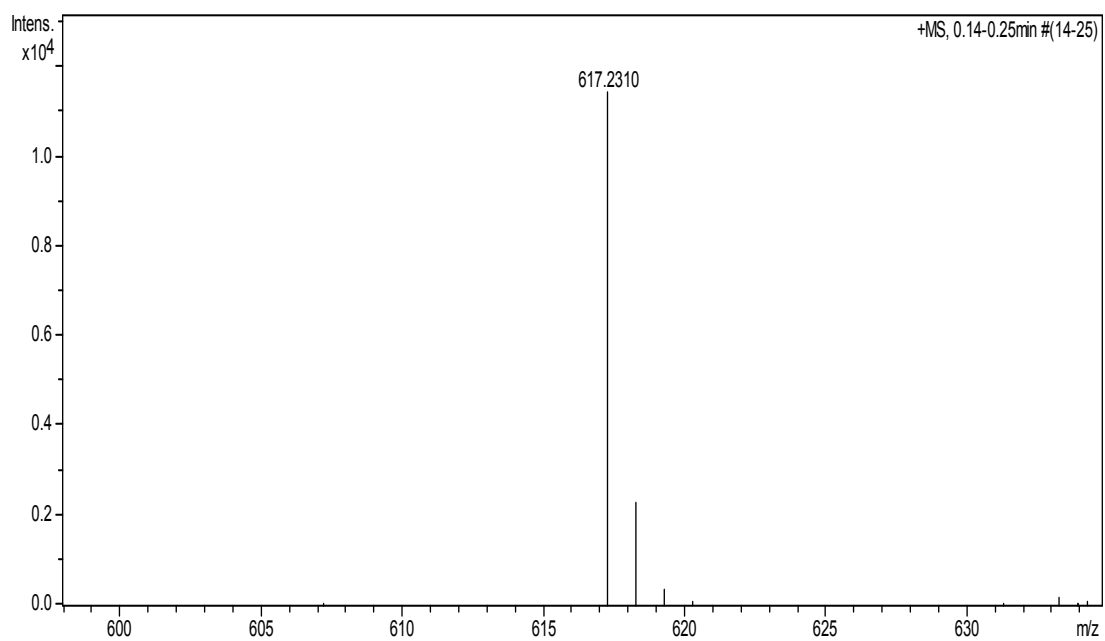
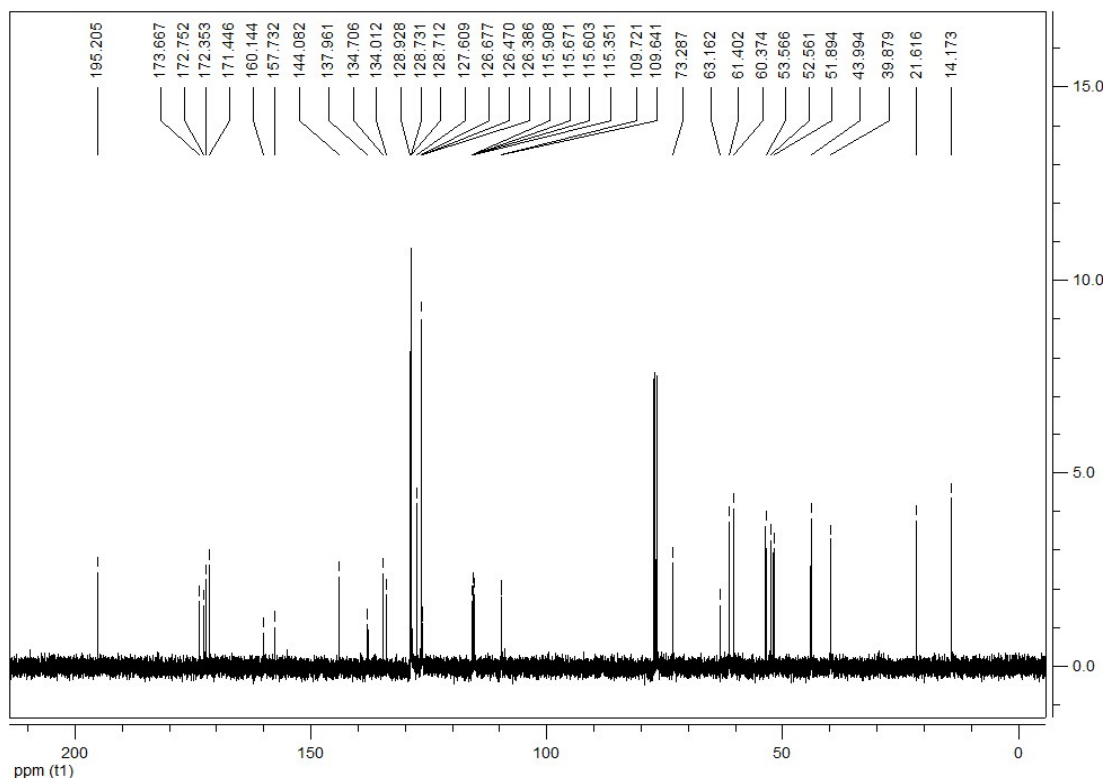


white solid, 60%, m.p. 182~183 °C; <sup>1</sup>H NMR (400 MHz,

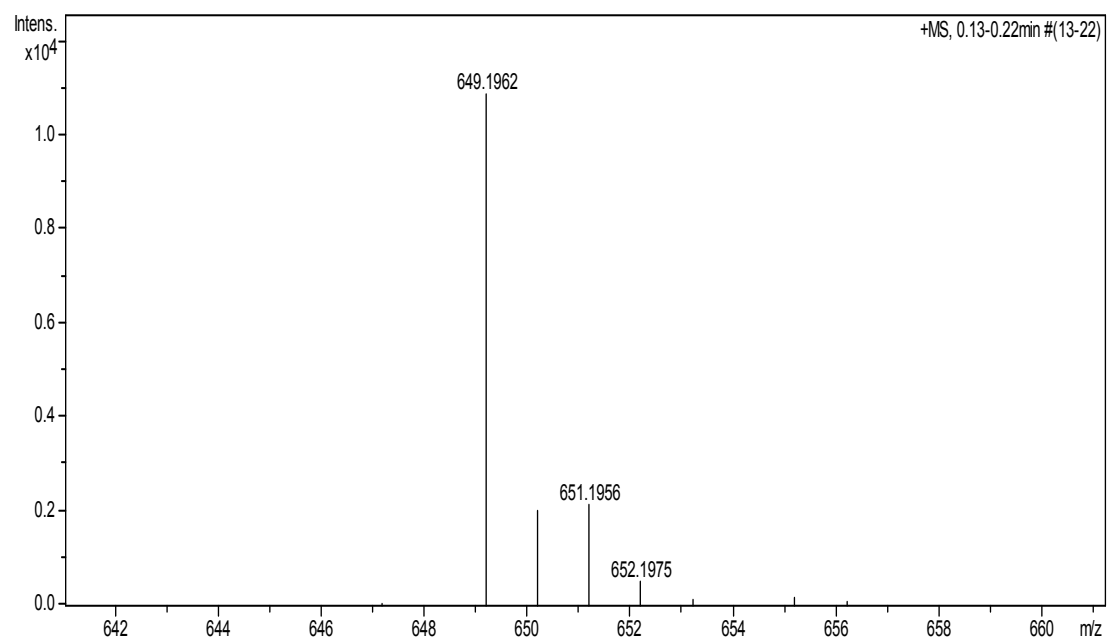
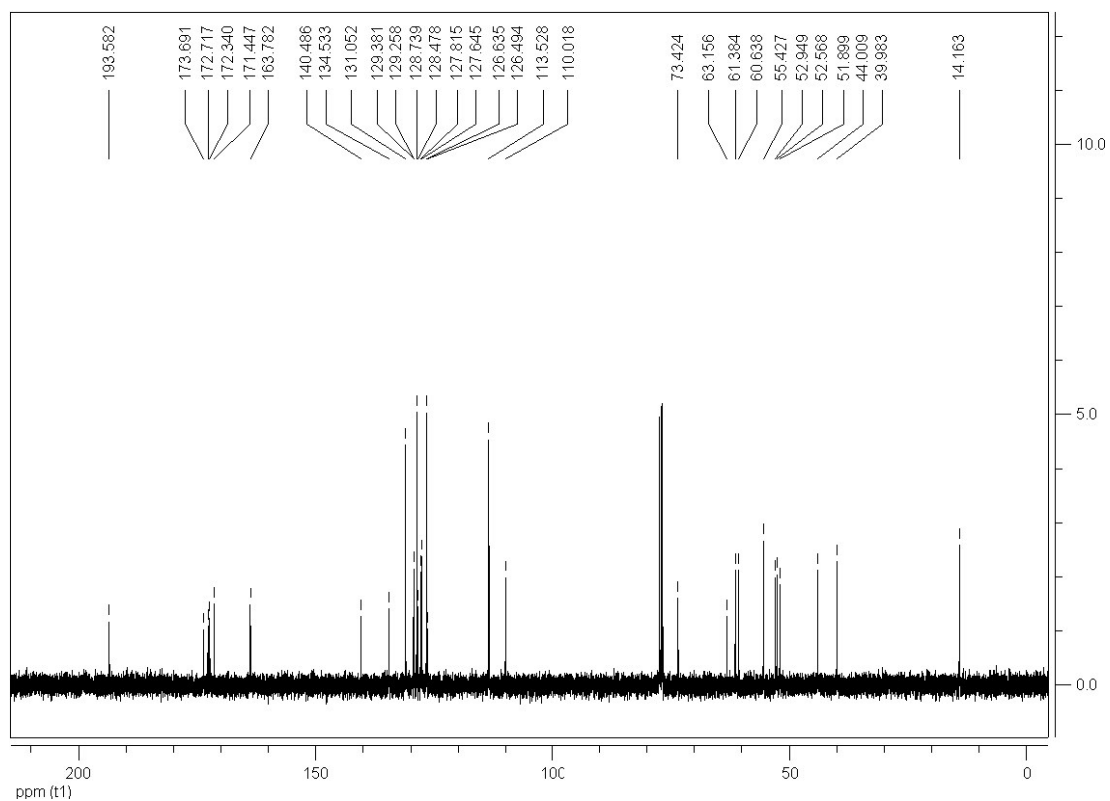
CDCl<sub>3</sub>) δ: **Major isomer:** 7.48 (d, *J* = 8.0Hz, 2H, ArH), 7.25~7.22 (m, 1H, ArH), 7.18~7.10 (m, 5H, ArH),

6.83~6.88 (m, 3H, ArH), 6.32~6.29 (m, 1H, ArH), 5.18 (d, *J* = 7.6Hz, 1H, CH), 5.08 (d, *J* = 7.2Hz, 1H, CH), 4.64 (d, *J* = 16.0Hz, 1H, CH), 4.35~4.24 (m, 2H, CH), 4.18 (d, *J* = 15.6Hz, 1H, CH), 3.93 (s, 1H, NH), 3.80 (s, 3H, OCH<sub>3</sub>), 3.64 (s, 3H, OCH<sub>3</sub>), 2.43 (d, *J* = 17.2Hz, 1H, CH<sub>2</sub>), 2.36 (s, 3H, CH<sub>3</sub>), 2.12 (d, *J* = 16.8Hz, 1H, CH<sub>2</sub>), 1.28~1.25 (m, 3H, CH<sub>3</sub>); **Minor isomer:** 7.42 (d, *J* = 8.4Hz, 2H, ArH), 6.94 (d, *J* = 7.2Hz, 2H, ArH), 6.22~6.19 (m, 1H, ArH), 5.14 (d, *J* = 7.2Hz, 1H, CH), 5.05 (d, *J* = 7.6Hz, 1H, CH), 4.77 (d, *J* = 15.6Hz, 1H, CH), 4.00 (d, *J* = 15.6Hz, 1H, CH), 3.71 (s, 3H, OCH<sub>3</sub>), 3.35 (d, *J* = 4.0Hz, 2H, CH), 3.09 (s, 3H, OCH<sub>3</sub>), 2.37 (s, 3H, CH<sub>3</sub>), **ratio of major/minor = 90:10**; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 195.2, 173.7, 172.8, 172.4, 171.4, 158.9 (d, *J* = 241Hz), 144.1, 138.0, 134.7, 134.0, 128.9, 128.7, 128.7, 127.6, 126.7, 126.4 (d, *J* = 8.4Hz), 115.8 (d, *J* = 23.7Hz), 115.5 (d, *J* = 25.2Hz), 109.7 (d, *J* = 8.0Hz), 73.3, 63.2, 61.4, 60.4, 53.6, 52.6, 51.9, 44.0, 39.9, 21.6, 14.2; IR(KBr) ν: 3368, 1738, 1715, 1207cm<sup>-1</sup>; MS (*m/z*): HRMS (ESI) Calcd. for C<sub>34</sub>H<sub>34</sub>FN<sub>2</sub>O<sub>8</sub> ([M+H]<sup>+</sup>): 617.2299, found: 617.2310.

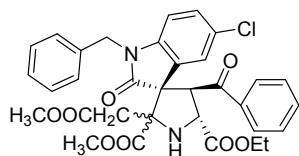








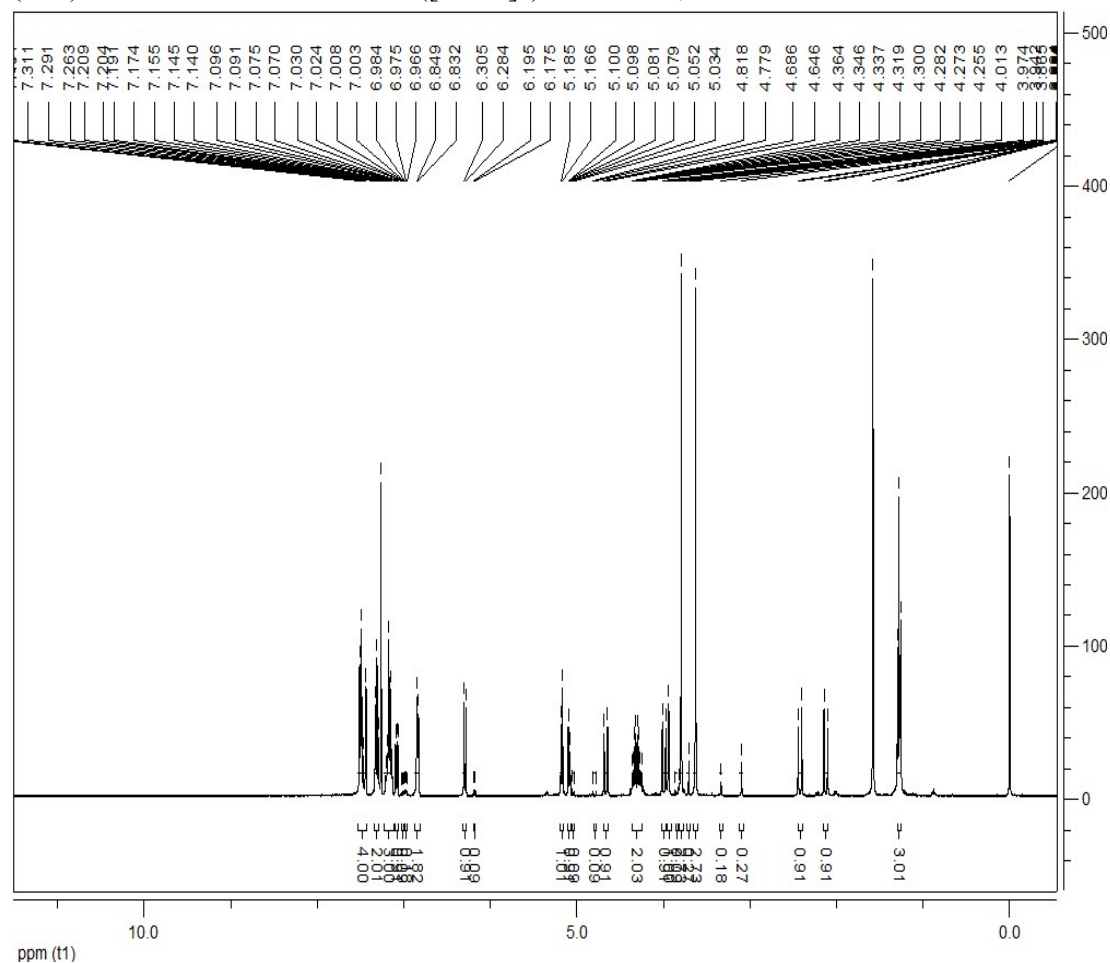
**5'-ethyl-2'-methyl-(3*S*,4'*R*,5'*R*)-4'-benzoyl-1-benzyl-5-chloro-2'-(2-methoxy-2-oxoethyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-2',5'-dicarboxylate (11)**



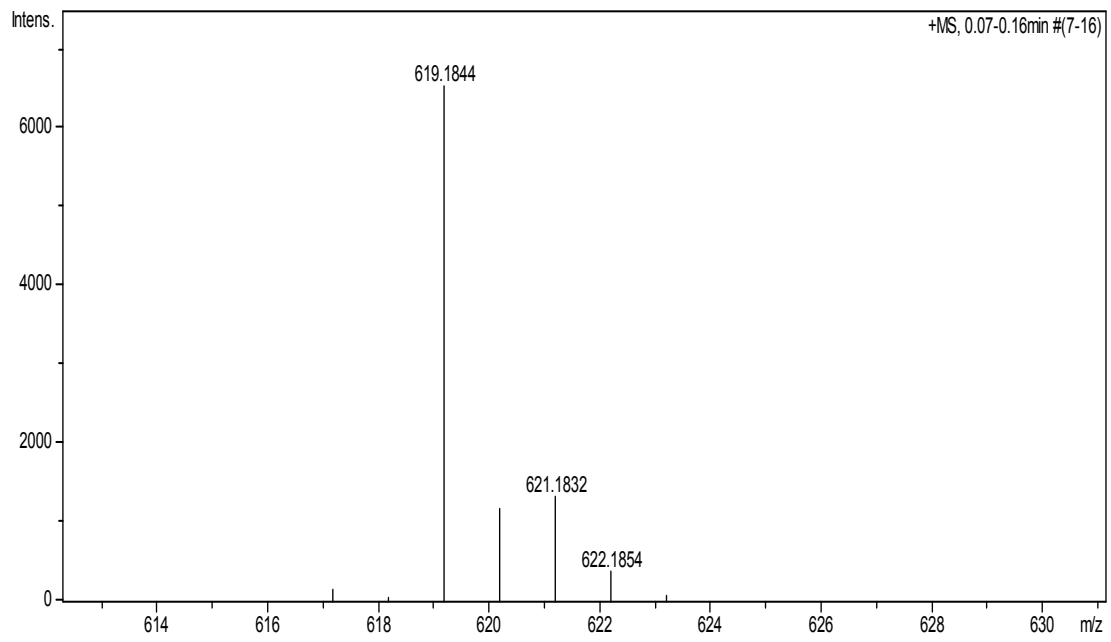
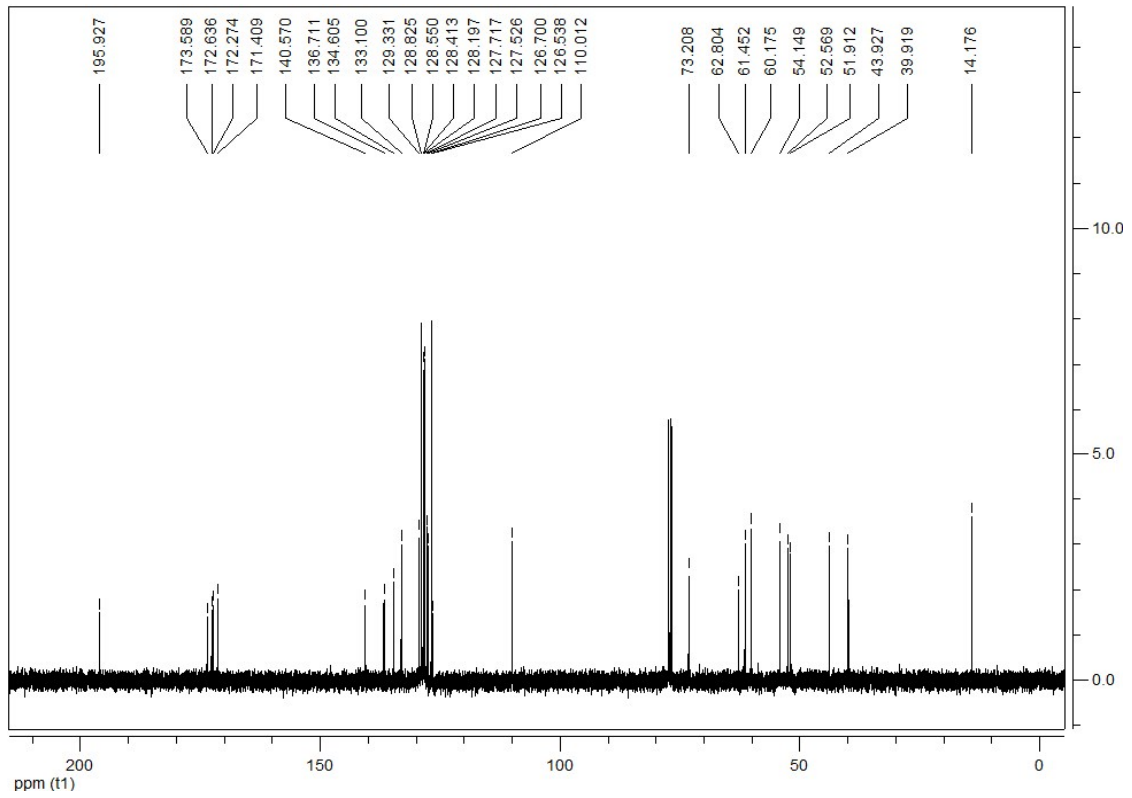
white solid, 72%, m.p. 138~140°C; <sup>1</sup>H NMR (400 MHz,

CDCl<sub>3</sub>) δ: **Major isomer:** 7.51~7.44 (m, 4H, ArH), 7.33~7.29 (m, 2H, ArH), 7.21~7.14 (m, 3H, ArH), 7.10~7.07 (m, 1H, ArH), 6.85~6.83 (m, 2H, ArH), 6.29 (d, *J*

= 8.4Hz, 1H, ArH), 5.18 (d, *J* = 7.6Hz, 1H, CH), 5.10~5.08 (m, 1H, CH), 4.67 (d, *J* = 16.0Hz, 1H, CH), 4.36~4.26 (m, 2H, CH), 3.99 (d, *J* = 15.6Hz, 1H, CH), 3.94 (s, 1H, NH), 3.80 (s, 3H, OCH<sub>3</sub>), 3.63 (s, 3H, OCH<sub>3</sub>), 2.42 (d, *J* = 16.8Hz, 1H, CH<sub>2</sub>), 2.12 (d, *J* = 17.2Hz, 1H, CH<sub>2</sub>), 1.30~1.26 (m, 3H, CH<sub>3</sub>); **Minor isomer:** 7.03~7.00 (m, 1H, ArH), 6.98~6.97 (m, 2H, ArH), 6.18 (d, *J* = 8.0Hz, 1H, ArH), 5.04 (d, *J* = 7.2Hz, 1H, CH), 4.80 (d, *J* = 15.6Hz, 1H, CH), 3.84 (d, *J* = 16.4Hz, 1H, CH), 3.71 (s, 3H, OCH<sub>3</sub>), 3.34 (brs, 2H, CH), 3.10 (s, 3H, OCH<sub>3</sub>), **ratio of major/minor = 91:9**; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 195.9, 173.6, 172.6, 172.3, 171.4, 140.6, 136.7, 134.6, 133.1, 129.3, 128.8, 128.5, 128.4, 128.2, 127.7, 127.5, 126.7, 126.5, 110.0, 73.2, 62.8, 61.4, 60.2, 54.1, 52.6, 51.9, 43.9, 39.9, 14.2; IR(KBr) ν: 3368, 1721, 1206cm<sup>-1</sup>; MS (*m/z*): HRMS (ESI) Calcd. for C<sub>33</sub>H<sub>32</sub>ClN<sub>2</sub>O<sub>8</sub> ([M+H]<sup>+</sup>): 619.1847, found: 619.1844.



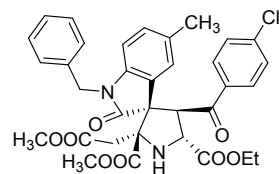




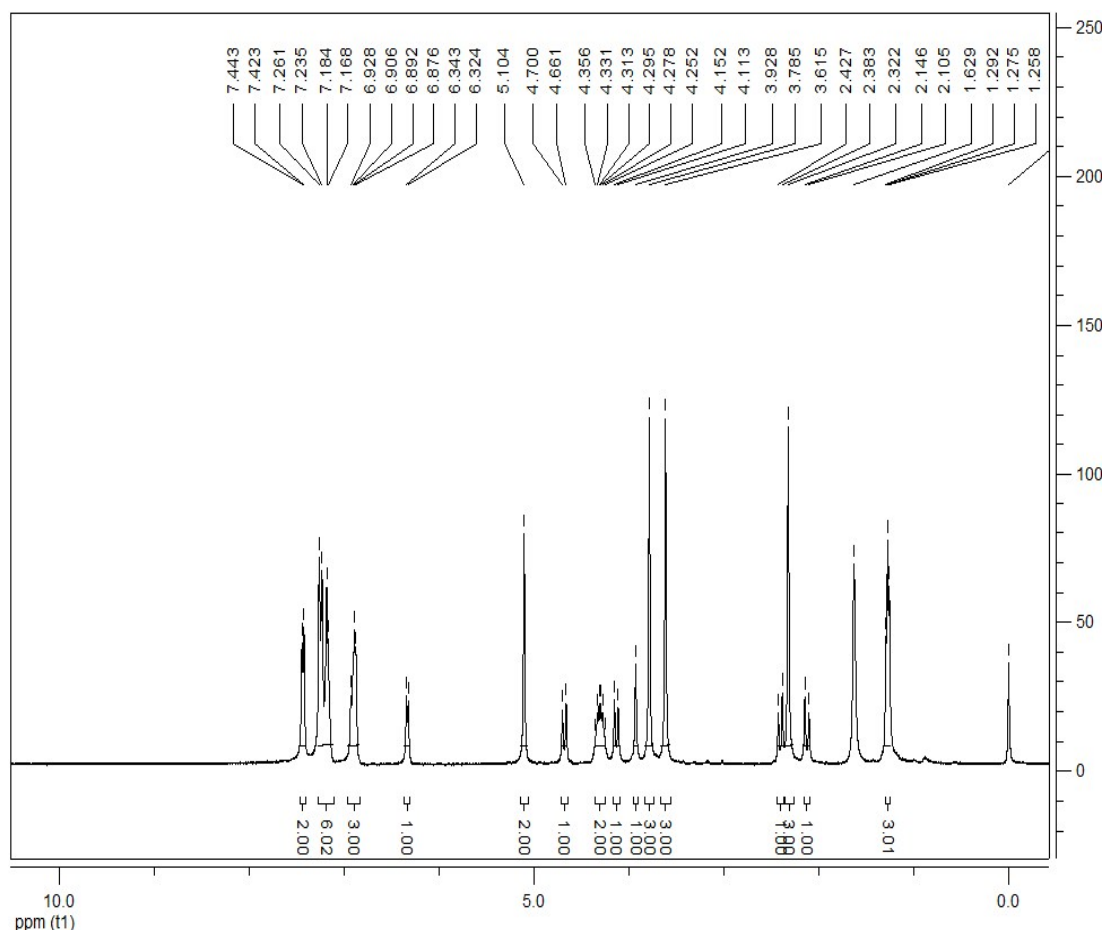
(1m, 1m') Ratio of major/minor = 67:33

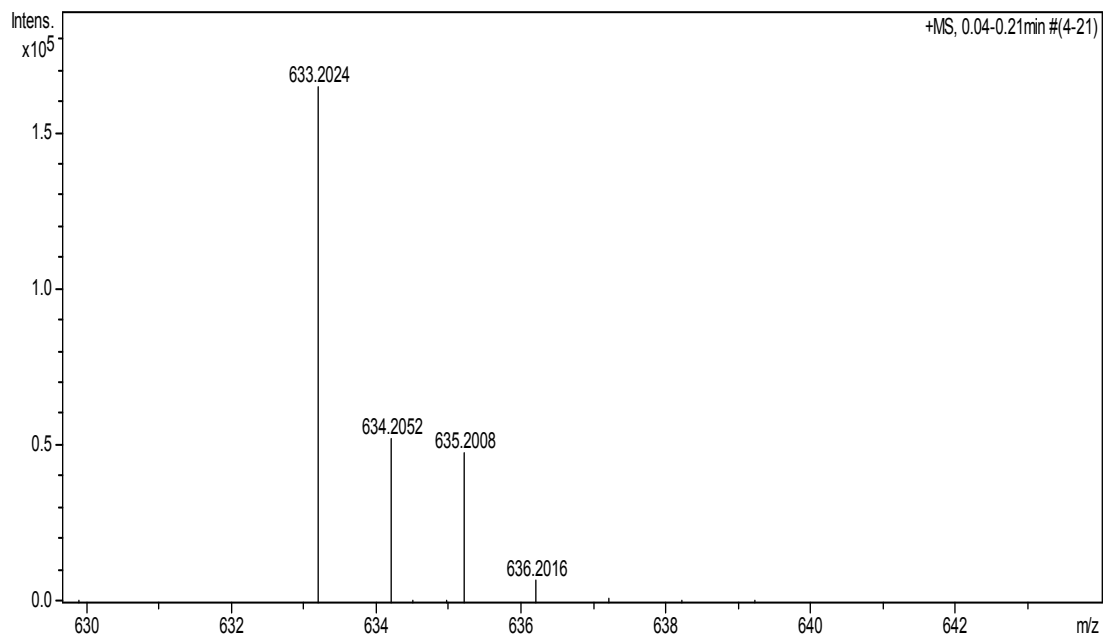
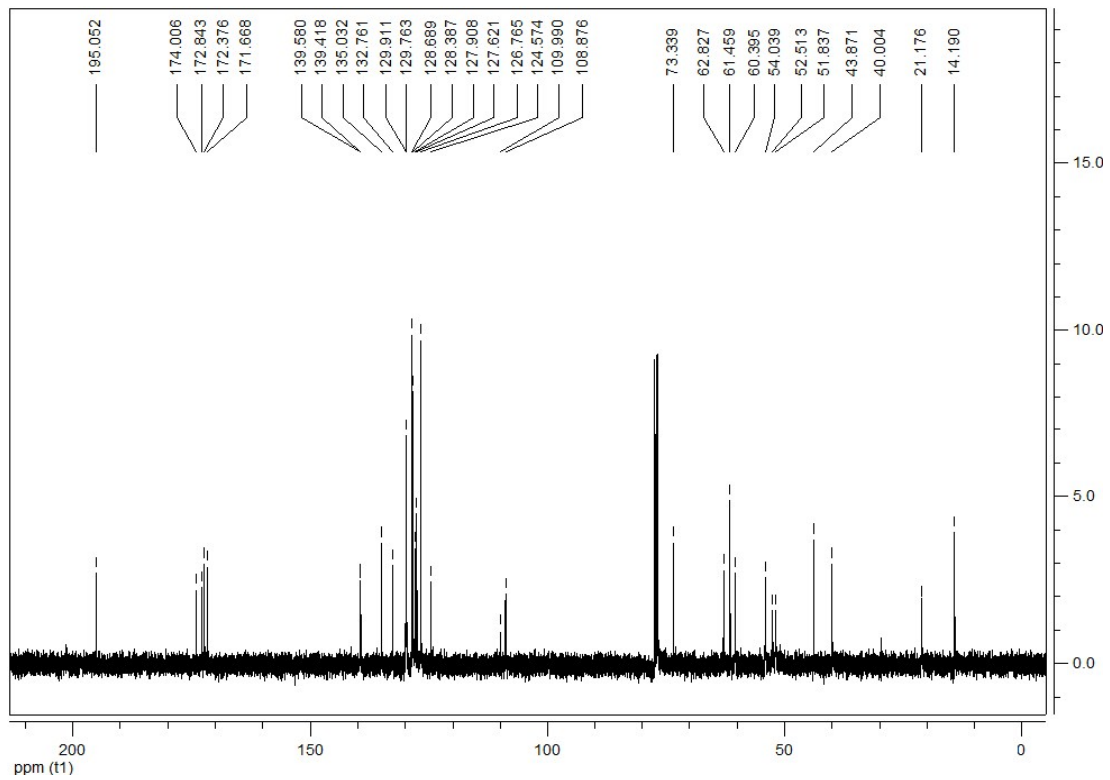
5'-ethyl-2'-methyl-(2'R,3S,4'R,5'R)-1-benzyl-4'-(4-chlorobenzoyl)-2'-(2-methoxy-2-oxoethyl)-5-methyl-2-oxospiro[indoline-3,3'-pyrrolidine]-2',5'-dicarboxylate

(1m) Major isomer:

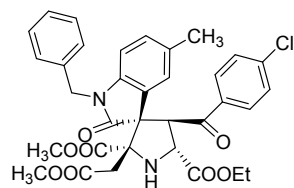


viscous oil, 50%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.43 (d,  $J = 8.0\text{Hz}$ , 2H, ArH), 7.24~7.17 (m, 6H, ArH), 6.93~6.88 (m, 3H, ArH), 6.33 (d,  $J = 7.6\text{Hz}$ , 1H, ArH), 5.10 (s, 2H, CH), 4.78 (d,  $J = 15.6\text{Hz}$ , 1H, CH), 4.36~4.25 (m, 2H, CH), 4.13 (d,  $J = 15.6\text{Hz}$ , 1H, CH), 3.93 (s, 1H, NH), 3.78 (s, 3H,  $\text{OCH}_3$ ), 3.62 (s, 3H,  $\text{OCH}_3$ ), 2.40 (d,  $J = 17.6\text{Hz}$ , 1H,  $\text{CH}_2$ ), 2.32 (s, 3H,  $\text{CH}_3$ ), 2.12 (d,  $J = 16.4\text{Hz}$ , 1H,  $\text{CH}_2$ ), 1.28 (t,  $J = 6.8\text{Hz}$ , 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 195.0, 174.0, 172.8, 172.4, 171.7, 139.6, 139.4, 135.0, 132.8, 129.9, 129.8, 128.7, 128.4, 127.9, 127.6, 126.8, 124.4, 110.0, 108.9, 73.4, 62.8, 61.5, 60.4, 54.0, 52.5, 51.8, 43.9, 40.0, 21.2, 14.2; IR(KBr)  $\nu$ : 3374, 1741, 1712,  $1204\text{cm}^{-1}$ ; MS ( $m/z$ ): HRMS (ESI) Calcd. for  $\text{C}_{34}\text{H}_{34}\text{ClN}_2\text{O}_8$  ( $[\text{M}+\text{H}]^+$ ): 633.2004, found: 633.2024.

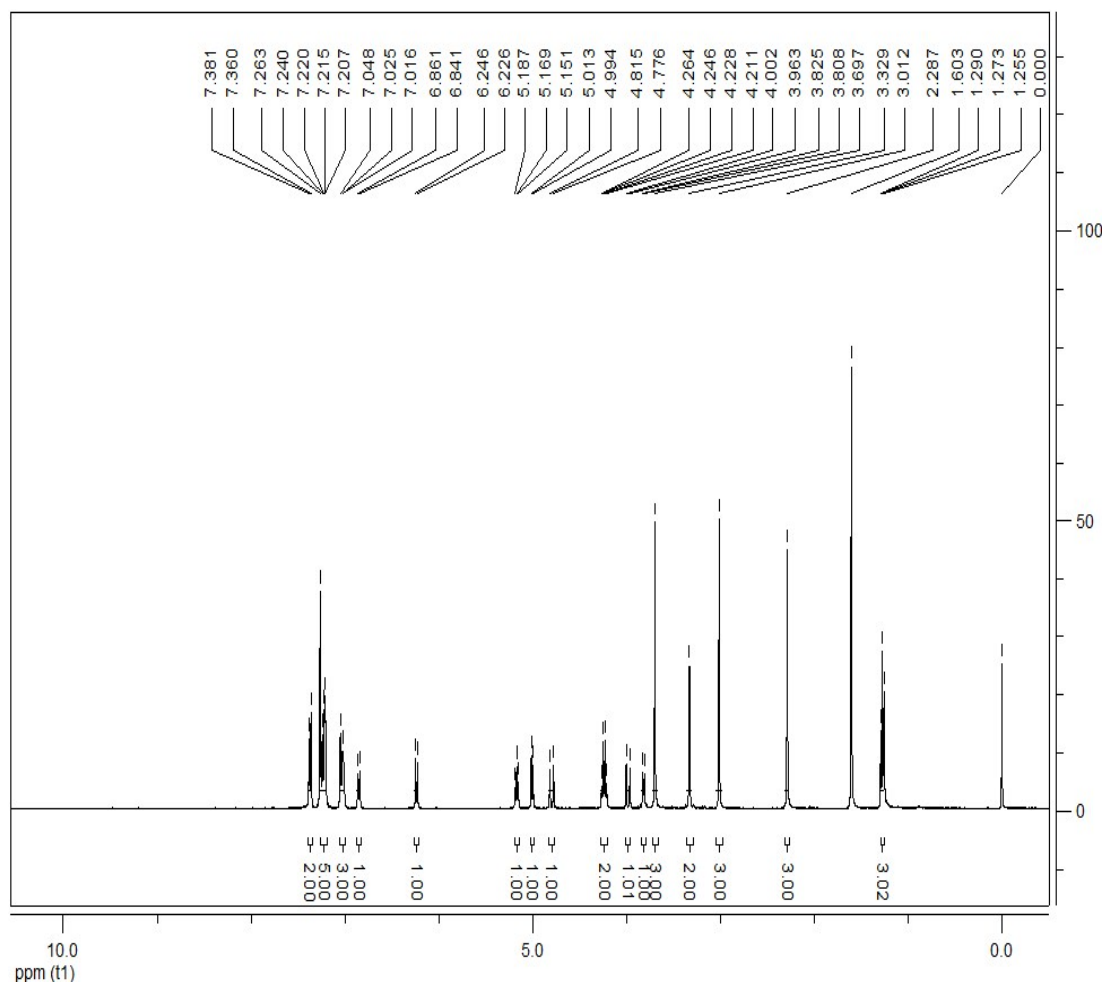


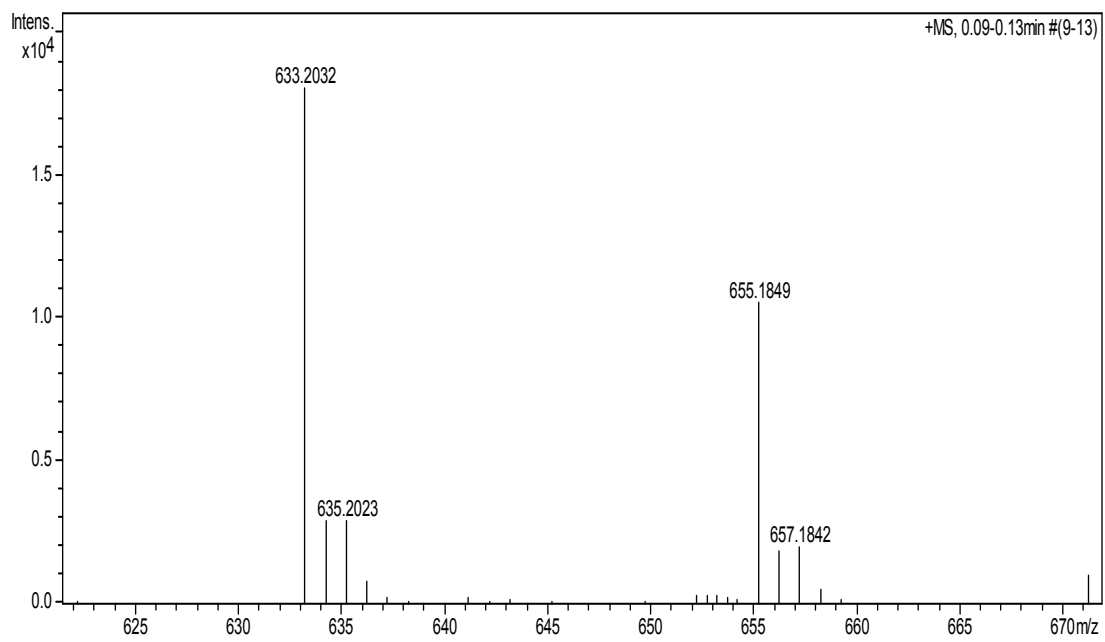
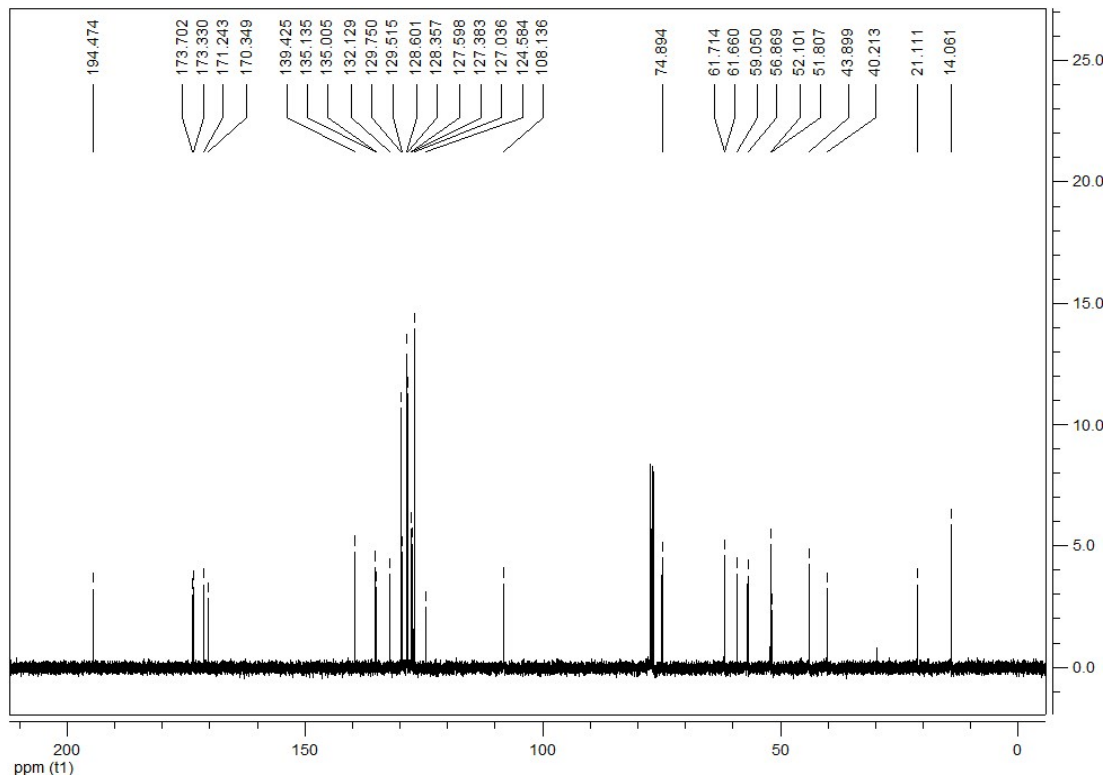


**5'-ethyl-2'-methyl-(2'S,3S,4'R,5'R)-1-benzyl-4'-(4-chlorobenzoyl)-2'-(2-methoxy-2-oxoethyl)-5-methyl-2-oxospiro[indoline-3,3'-pyrrolidine]-2',5'-dicarboxylate (1m')** Minor isomer:

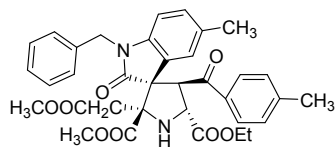


white solid, 25%, m.p. 169~170°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.37 (d, *J* = 8.4Hz, 2H, ArH), 7.26~7.21 (m, 5H, ArH), 7.05~7.02 (m, 3H, ArH), 6.85 (d, *J* = 8.0Hz, 1H, ArH), 6.24 (d, *J* = 8.0Hz, 1H, ArH), 5.17 (t, *J* = 7.6Hz, 1H, CH), 5.00 (d, *J* = 7.6Hz, 1H, CH), 4.80 (d, *J* = 15.6Hz, 1H, CH), 4.24 (q, *J*<sub>1</sub> = 14.2Hz, *J*<sub>2</sub> = 7.2Hz, 2H, CH), 3.98 (d, *J* = 15.6Hz, 1H, CH), 3.82 (d, *J* = 6.8Hz, 1H, NH), 3.70 (s, 3H, OCH<sub>3</sub>), 3.33 (brs, 2H, CH), 3.01 (s, 3H, OCH<sub>3</sub>), 2.29 (s, 3H, CH<sub>3</sub>), 1.27 (t, *J* = 6.8Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 194.5, 173.7, 173.3, 171.2, 170.3, 139.4, 135.1, 135.0, 132.1, 129.8, 129.5, 128.6, 128.4, 127.6, 127.4, 127.0, 124.6, 108.1, 74.9, 61.7, 61.7, 59.0, 56.9, 52.1, 51.8, 43.9, 40.2, 21.1, 14.1; IR(KBr) ν: 3355, 1747, 1694, 1201cm<sup>-1</sup>; MS (*m/z*): HRMS (ESI) Calcd. for C<sub>34</sub>H<sub>34</sub>ClN<sub>2</sub>O<sub>8</sub> ([M+H]<sup>+</sup>): 633.2004, found: 633.2032.

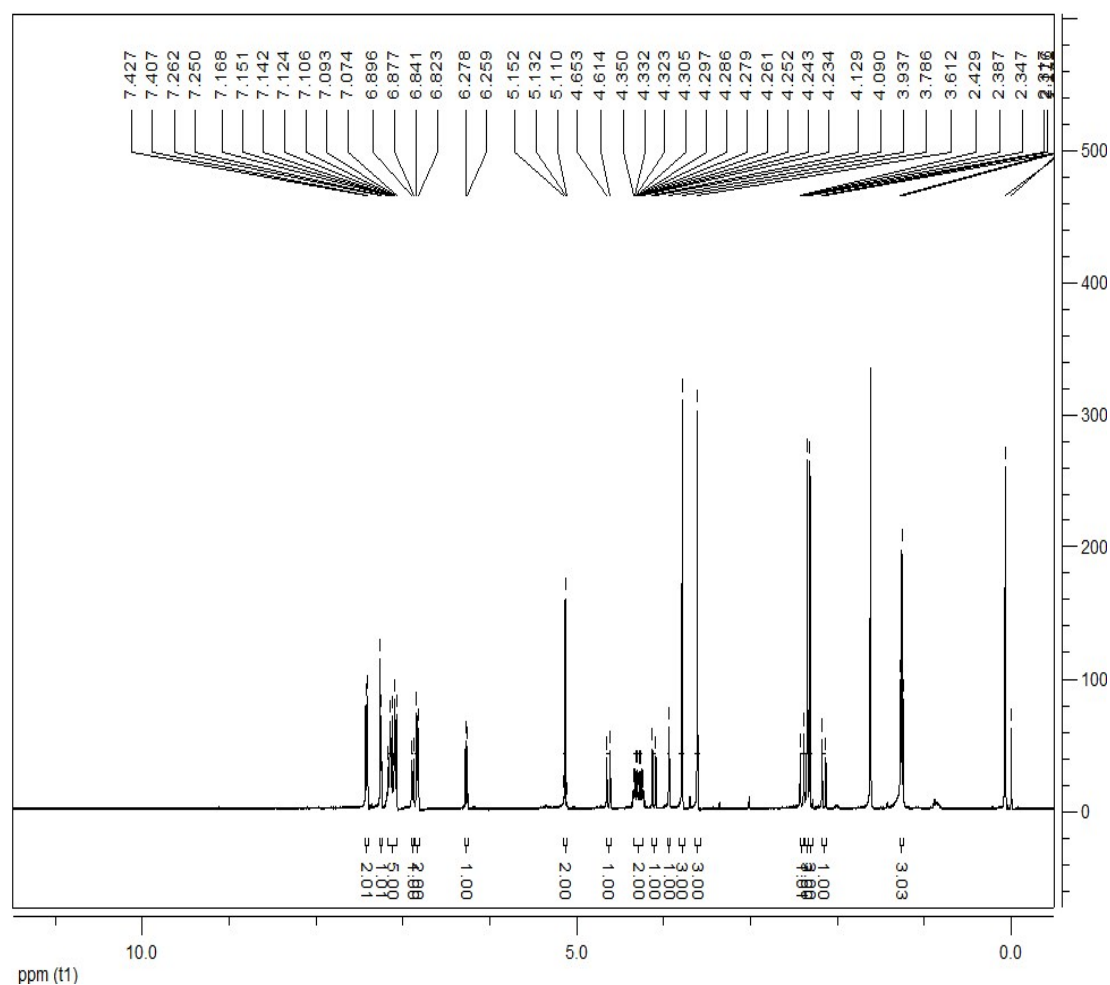


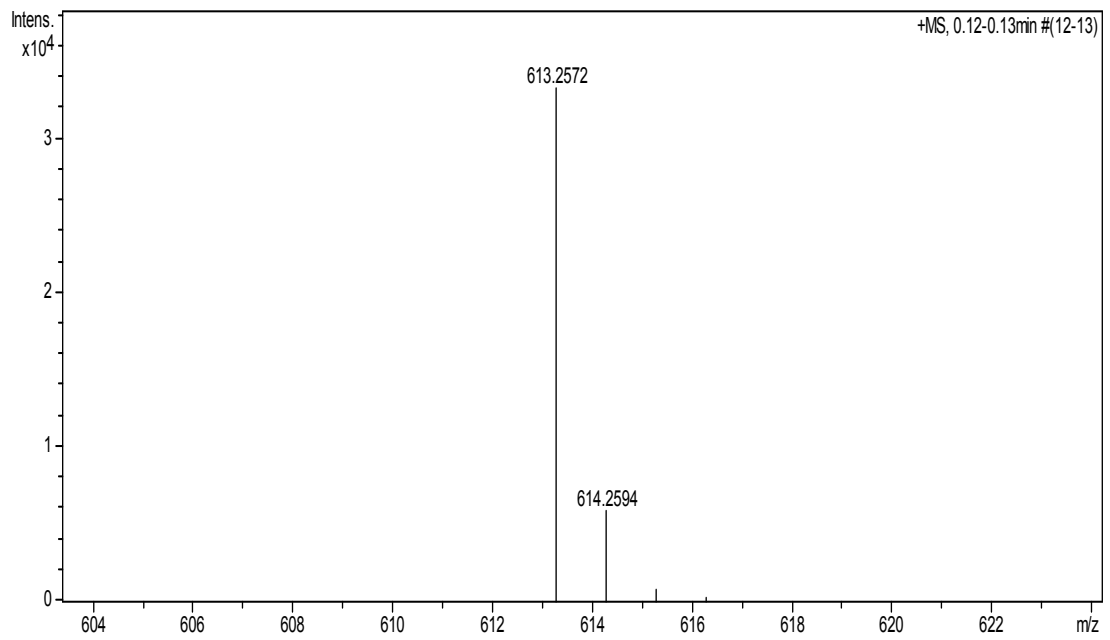
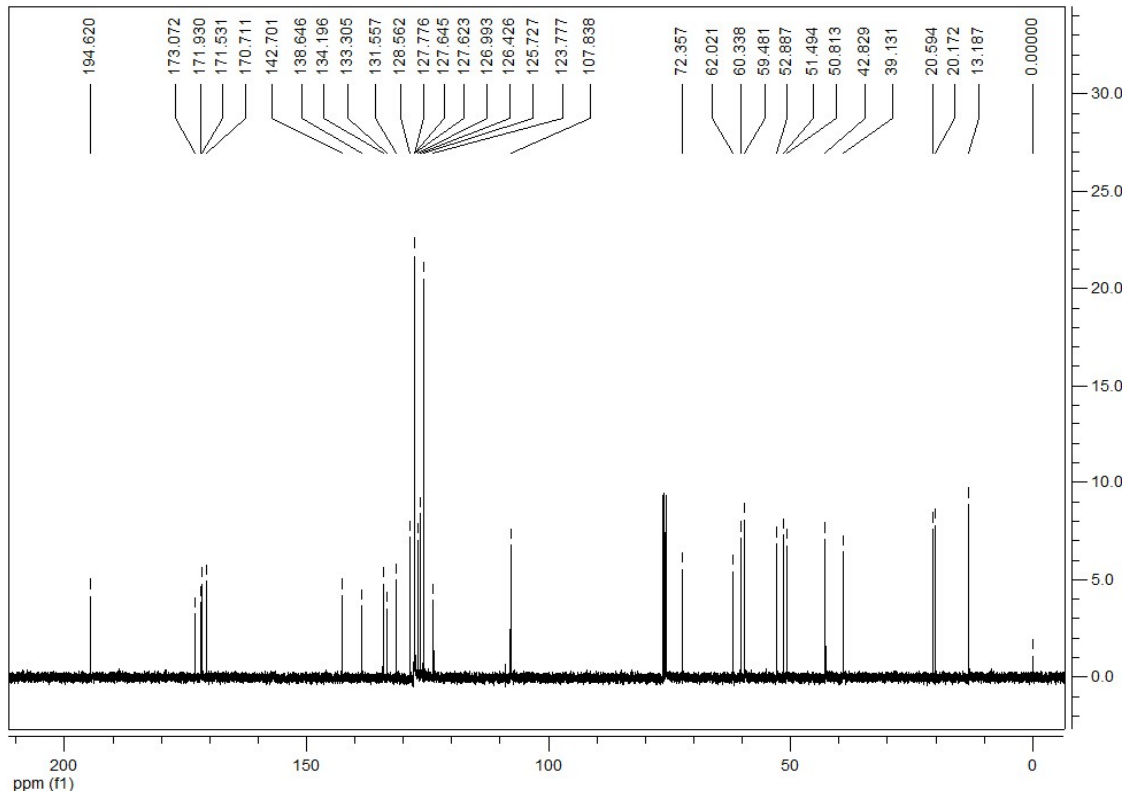


**5'-ethyl-2'-methyl-(2'R,3S,4'R,5'R)-1-benzyl-2'-(2-methoxy-2-oxoethyl)-5-methyl-4'-(4-methylbenzoyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-2',5'-dicarboxylate (1n)**



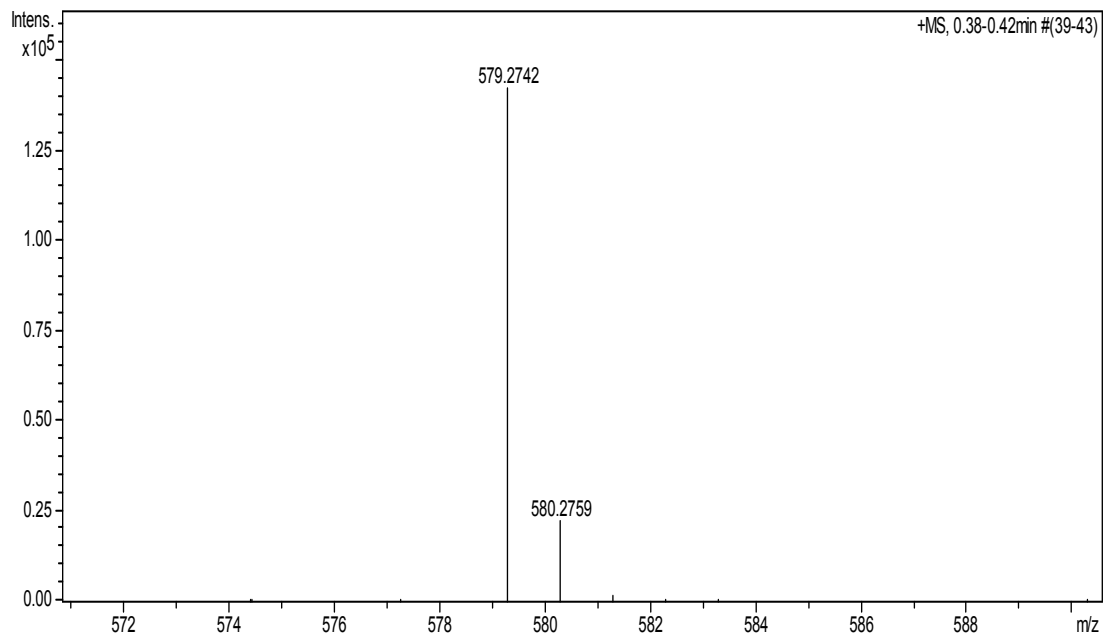
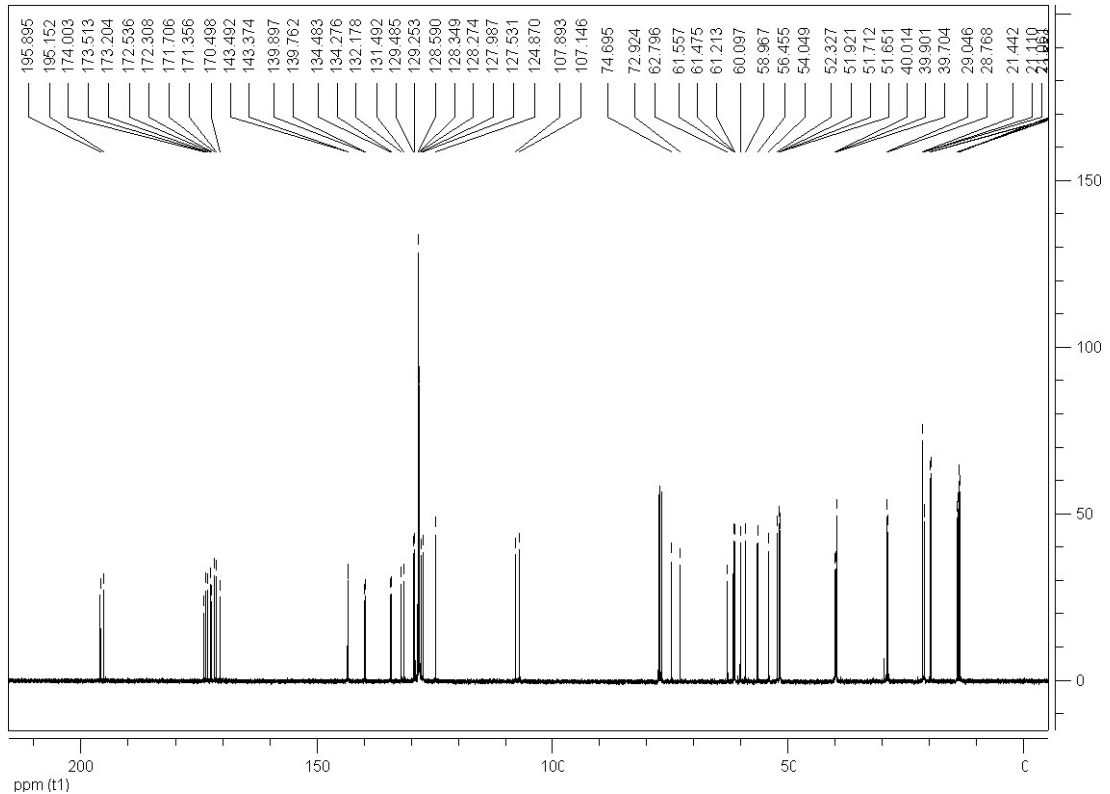
white solid, 71%, m.p. 127~128°C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.42 (d,  $J = 8.0\text{Hz}$ , 2H, ArH), 7.25 (brs, 1H, ArH), 7.17~7.07 (m, 5H, ArH), 6.89 (d,  $J = 7.6\text{Hz}$ , 1H, ArH), 6.83 (d,  $J = 7.2\text{Hz}$ , 1H, ArH), 6.27 (d,  $J = 7.6\text{Hz}$ , 1H, ArH), 5.15~5.11 (m, 2H, CH), 4.63 (d,  $J = 15.6\text{Hz}$ , 1H, CH), 4.35~4.23 (m, 2H, CH), 4.11 (d,  $J = 15.6\text{Hz}$ , 1H, CH), 3.94 (s, 1H, NH), 3.79 (s, 3H,  $\text{OCH}_3$ ), 3.61 (s, 3H,  $\text{OCH}_3$ ), 2.41 (d,  $J = 16.8\text{Hz}$ , 1H,  $\text{CH}_2$ ), 2.35 (s, 3H,  $\text{CH}_3$ ), 2.32 (s, 3H,  $\text{CH}_3$ ), 2.16 (d,  $J = 16.8\text{Hz}$ , 1H,  $\text{CH}_2$ ), 1.68 (t,  $J = 7.2\text{Hz}$ , 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 194.6, 173.1, 171.9, 171.5, 170.7, 142.7, 138.6, 134.2, 133.3, 131.6, 128.6, 127.8, 127.6, 127.6, 127.0, 126.4, 125.7, 123.8, 107.8, 72.4, 62.0, 60.3, 59.5, 52.9, 51.5, 50.8, 42.8, 39.1, 20.6, 20.2, 13.2; IR(KBr)  $\nu$ : 3382, 1741, 1206 $\text{cm}^{-1}$ ; MS ( $m/z$ ): HRMS (ESI) Calcd. for  $\text{C}_{35}\text{H}_{37}\text{N}_2\text{O}_8$  ( $[\text{M}+\text{H}]^+$ ): 613.2550, found: 613.2572.



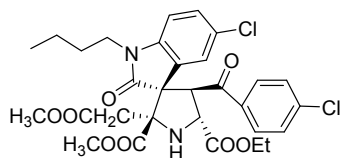




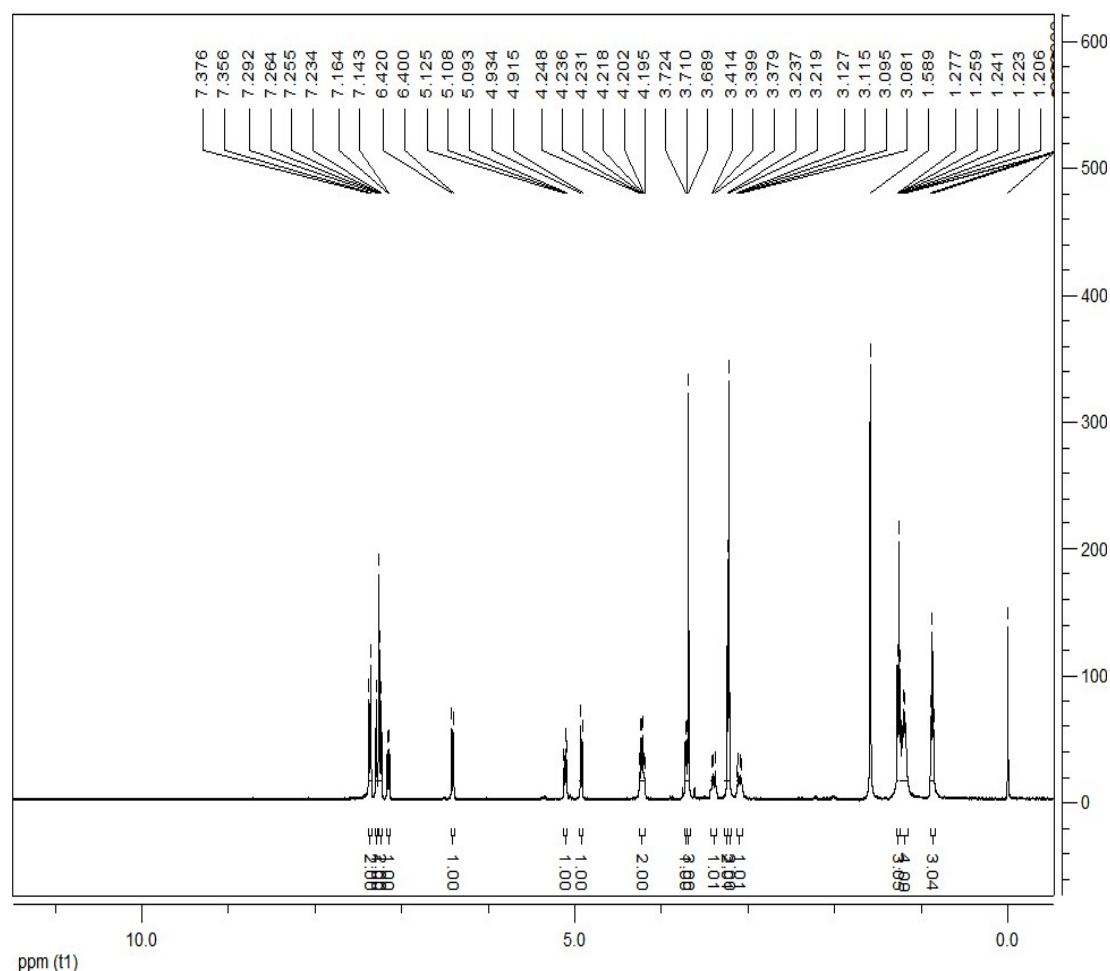


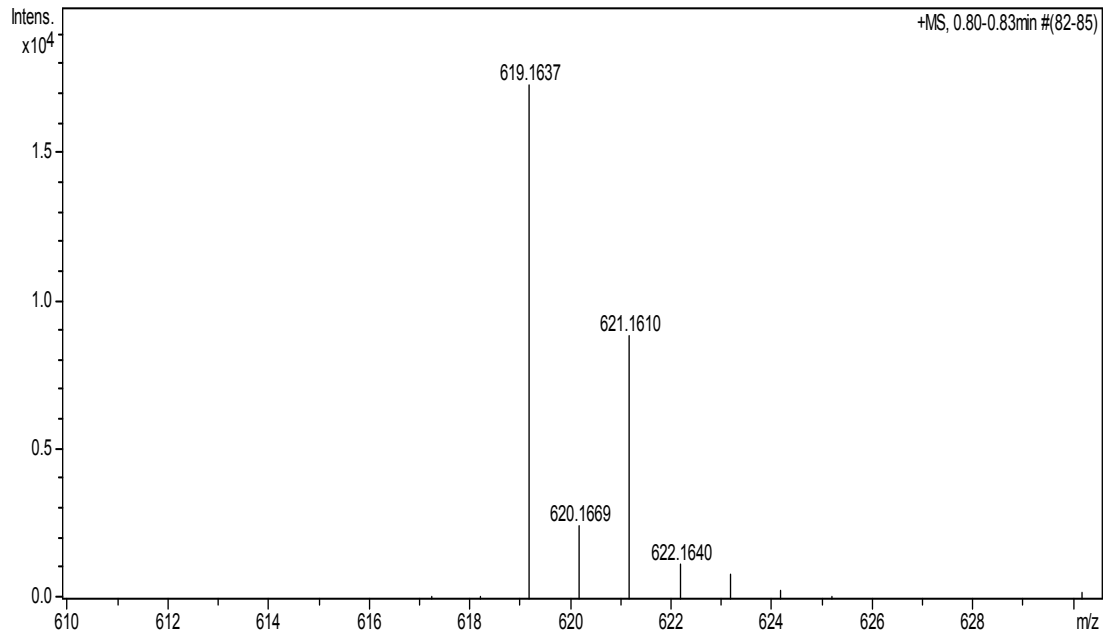
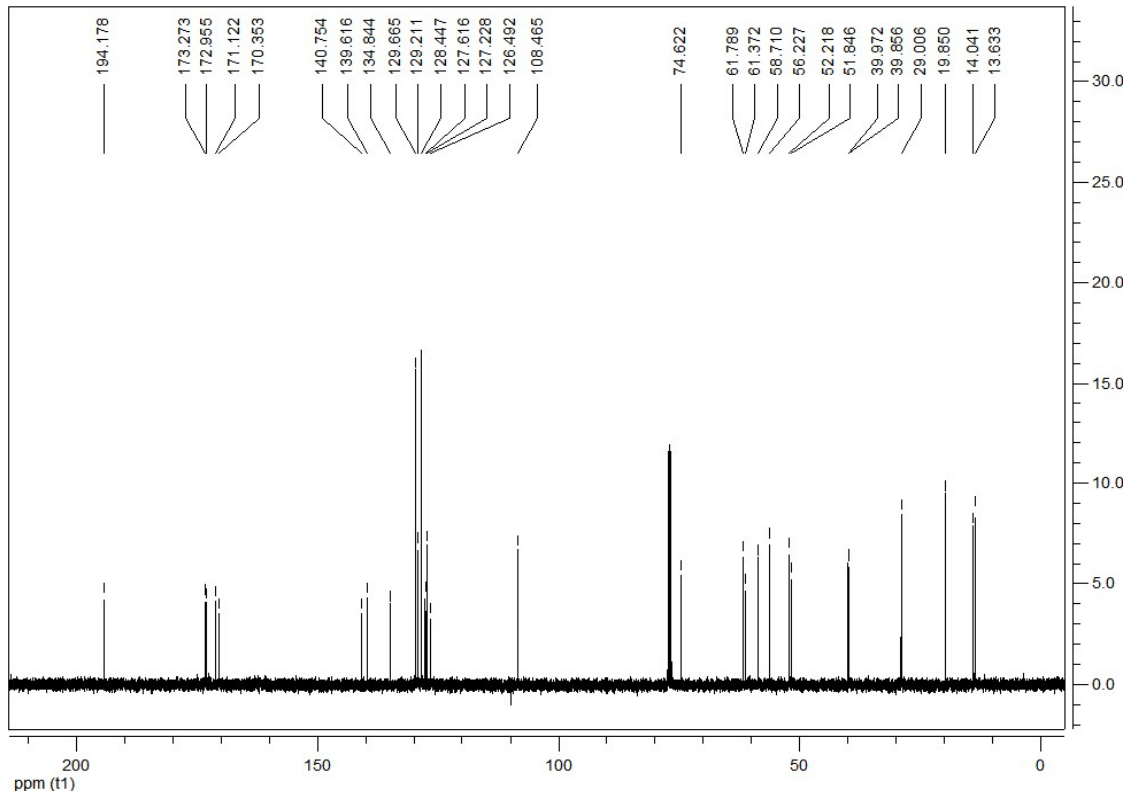


**5'-ethyl-2'-methyl-(2'R,3S,4'R,5'R)-1-butyl-5-chloro-4'-(4-chlorobenzoyl)-2'-(2-methoxy-2-oxoethyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-2',5'-dicarboxylate (1p)**

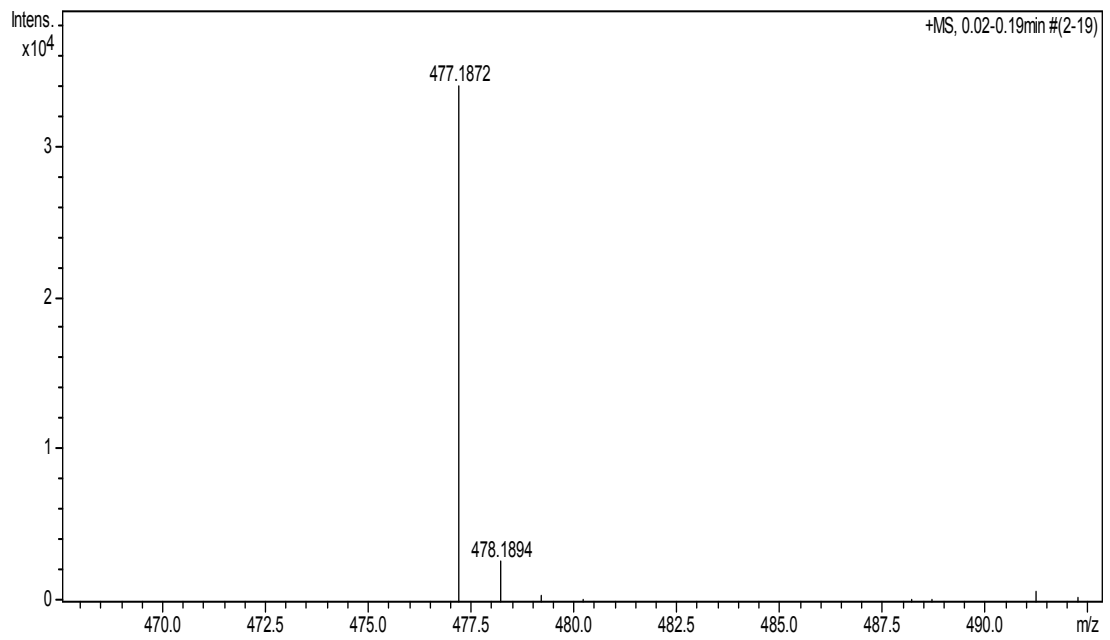
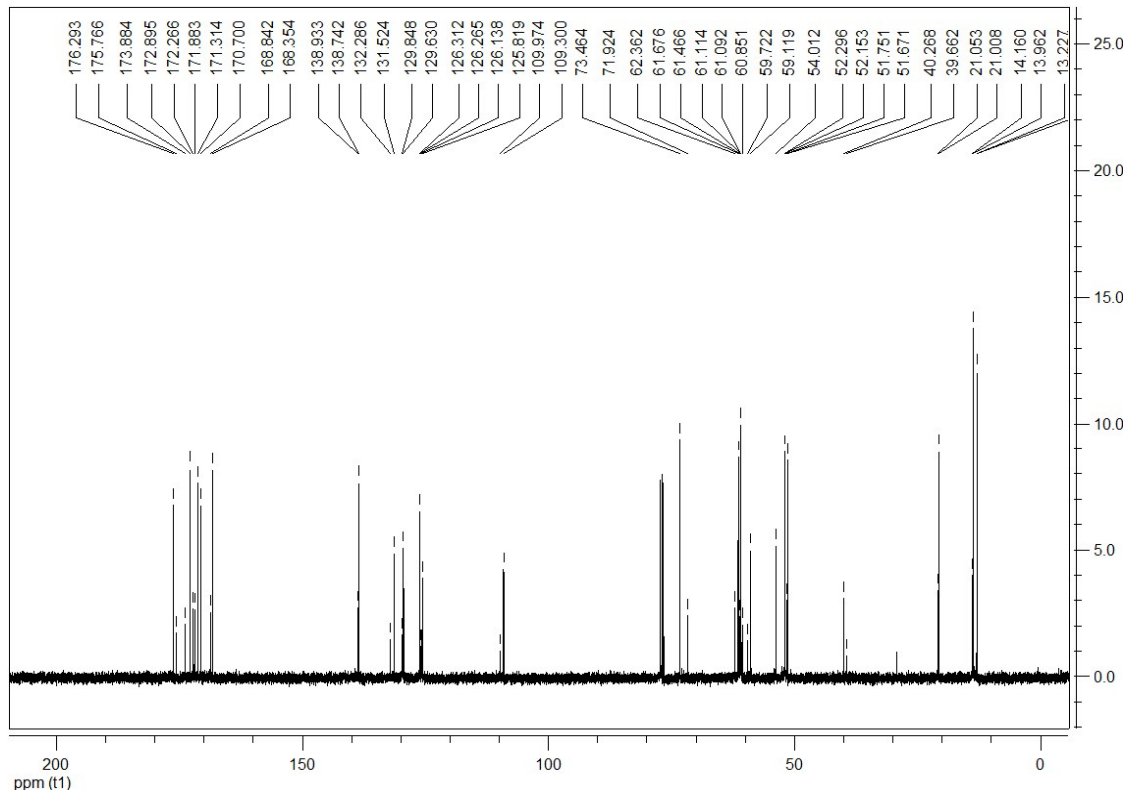


white solid, 66%, m.p. 117~119°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.37 (d, *J* = 8.0Hz, 2H, ArH), 7.29 (brs, 1H, ArH), 7.24 (d, *J* = 8.4Hz, 2H, ArH), 7.15 (d, *J* = 8.4Hz, 1H, ArH), 6.41 (d, *J* = 8.0Hz, 1H, ArH), 5.12~5.09 (m, 1H, CH), 4.92 (d, *J* = 7.6Hz, 1H, CH), 4.25~4.20 (m, 2H, CH), 3.72 (d, *J* = 5.6Hz, 1H, NH), 3.69 (s, 3H, OCH<sub>3</sub>), 3.41~3.38 (m, 1H, CH), 3.24 (brs, 2H, CH), 3.22 (s, 3H, OCH<sub>3</sub>), 3.13~3.08 (m, 1H, CH), 1.26 (t, *J* = 7.2Hz, 3H, CH<sub>3</sub>), 1.22~1.18 (m, 4H, CH), 0.87 (t, *J* = 6.8Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 194.2, 173.3, 172.9, 171.1, 170.4, 140.8, 139.6, 134.8, 129.7, 129.2, 128.4, 127.6, 127.2, 126.5, 108.5, 74.6, 61.8, 61.4, 58.7, 56.2, 52.2, 51.8, 40.0, 39.9, 29.0, 19.9, 14.0, 13.6; IR(KBr) ν: 3350, 1751, 1697, 1191cm<sup>-1</sup>; MS (*m/z*): HRMS (ESI) Calcd. for C<sub>30</sub>H<sub>33</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>8</sub> ([M+H]<sup>+</sup>): 619.1614, found: 619.1637.

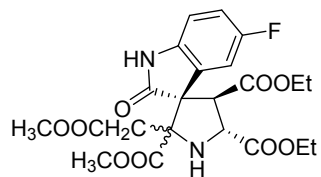




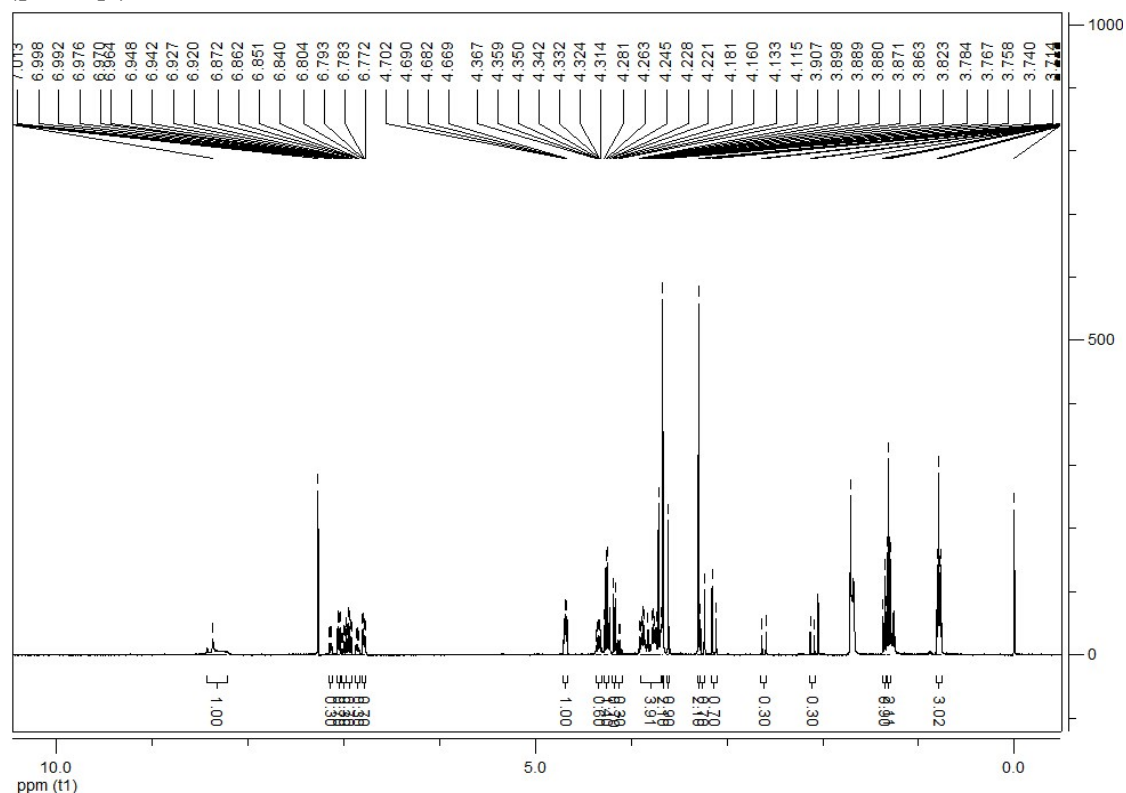


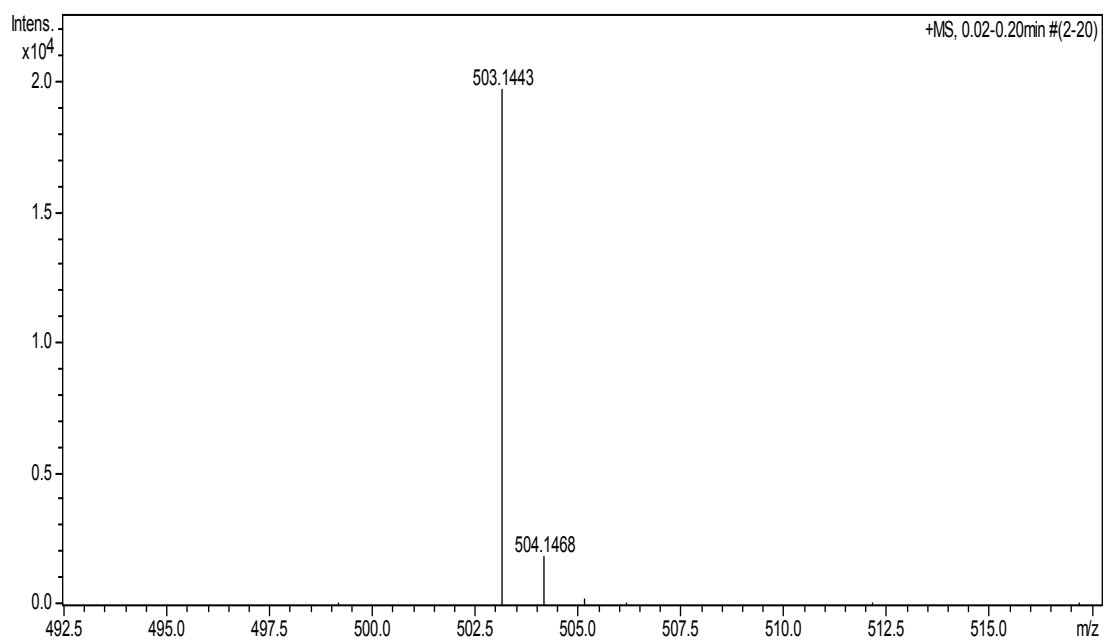
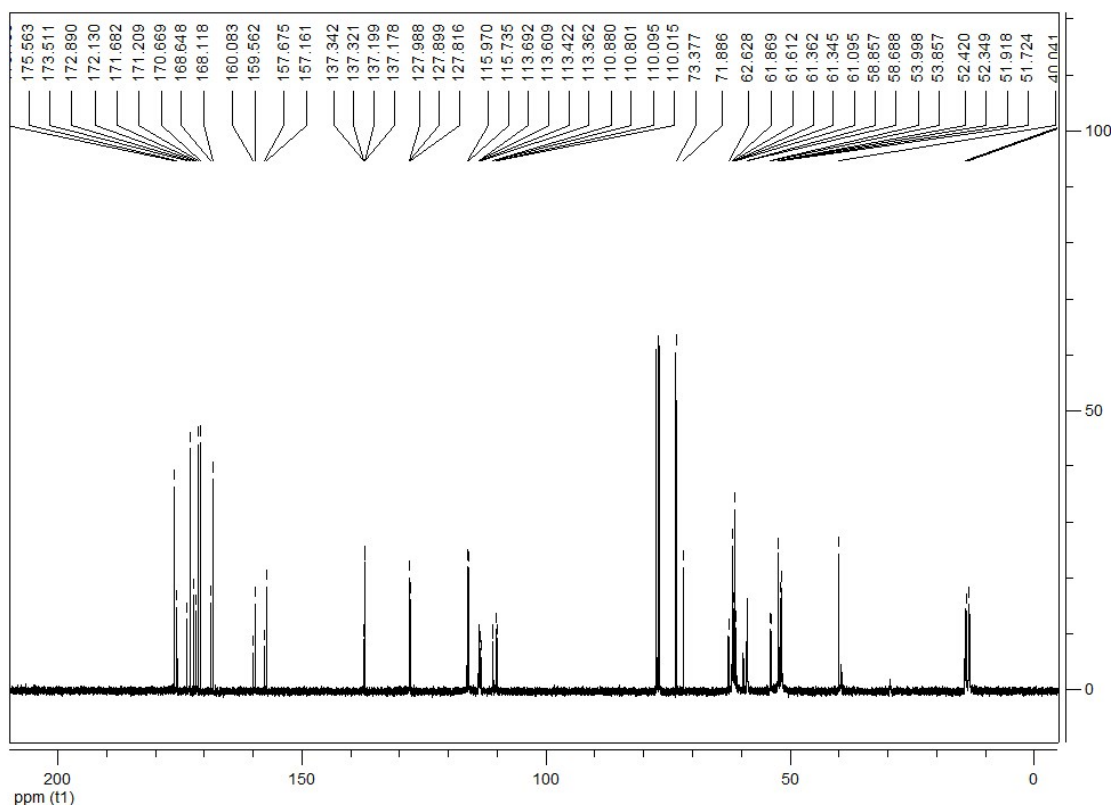


**4',5'-diethyl-2'-methyl-(3S,4'R,5'R)-5-fluoro-2'-(2-methoxy-2-oxoethyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-2',4',5'-tricarboxylate (1r)**

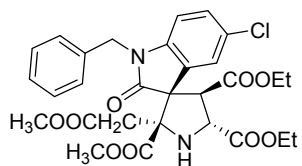


viscous oil, 68%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : **Major isomer:** 8.37 (brs, 1H, NH), 7.06~7.04 (m, 1H, ArH), 6.97~6.92 (m, 1H, ArH), 6.80~6.77 (m, 1H, ArH), 4.70~4.67 (m, 1H, CH), 4.25 (q,  $J = 7.2\text{Hz}$ , 2H, CH), 4.17 (d,  $J = 8.4\text{Hz}$ , 1H, CH), 3.91~3.69 (m, 3H, 2CH, NH), 3.67 (s, 3H,  $\text{OCH}_3$ ), 3.30 (s, 3H,  $\text{OCH}_3$ ), 3.26 (d,  $J = 16.8\text{Hz}$ , 1H,  $\text{CH}_2$ ), 3.13 (d,  $J = 16.4\text{Hz}$ , 1H,  $\text{CH}_2$ ), 1.31 (t,  $J = 7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 0.81~0.76 (m, 3H,  $\text{CH}_3$ ); **Minor isomer:** 7.15~7.13 (m, 1H, ArH), 7.02~6.98 (m, 1H, ArH), 6.87~6.84 (m, 1H, ArH), 4.37~4.31 (m, 2H, CH), 4.15~4.10 (m, 1H, CH), 3.71 (s, 3H,  $\text{OCH}_3$ ), 3.61 (s, 3H,  $\text{OCH}_3$ ), 2.61 (d,  $J = 17.2\text{Hz}$ , 1H,  $\text{CH}_2$ ), 2.11 (d,  $J = 17.2\text{Hz}$ , 1H,  $\text{CH}_2$ ), 1.36 (t,  $J = 7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), **ratio of major/minor = 70:30**;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 176.1, 175.6, 173.5, 172.9, 172.1, 171.7, 171.2, 170.7, 168.6, 168.1, 158.9 (d,  $J = 240.8\text{Hz}$ ), 158.4 (d,  $J = 240.1\text{ Hz}$ ), 137.3 (d,  $J = 2.1\text{ Hz}$ ), 137.2 (d,  $J = 2.1\text{Hz}$ ), 128.0, 127.9, 127.8, 115.8 (d,  $J = 23.5\text{ Hz}$ ), 113.5 (d,  $J = 8.3\text{ Hz}$ ), 113.4 (d,  $J = 8.0\text{ Hz}$ ), 110.8 (d,  $J = 7.9\text{ Hz}$ ), 110.1 (d,  $J = 8.0\text{ Hz}$ ), 73.4, 71.9, 62.6, 61.9, 61.6, 61.4, 61.3, 61.1, 58.9, 58.7, 54.0, 53.9, 52.4, 52.3, 51.9, 51.7, 40.0, 14.1, 13.9, 13.4, 13.4; IR(KBr)  $\nu$ : 3360, 1740, 1197  $\text{cm}^{-1}$ ; MS ( $m/z$ ): HRMS (ESI) Calcd. for  $\text{C}_{22}\text{H}_{25}\text{FN}_2\text{O}_9$  ( $[\text{M}+\text{H}]^+$ ): 503.1442, found: 503.1443.

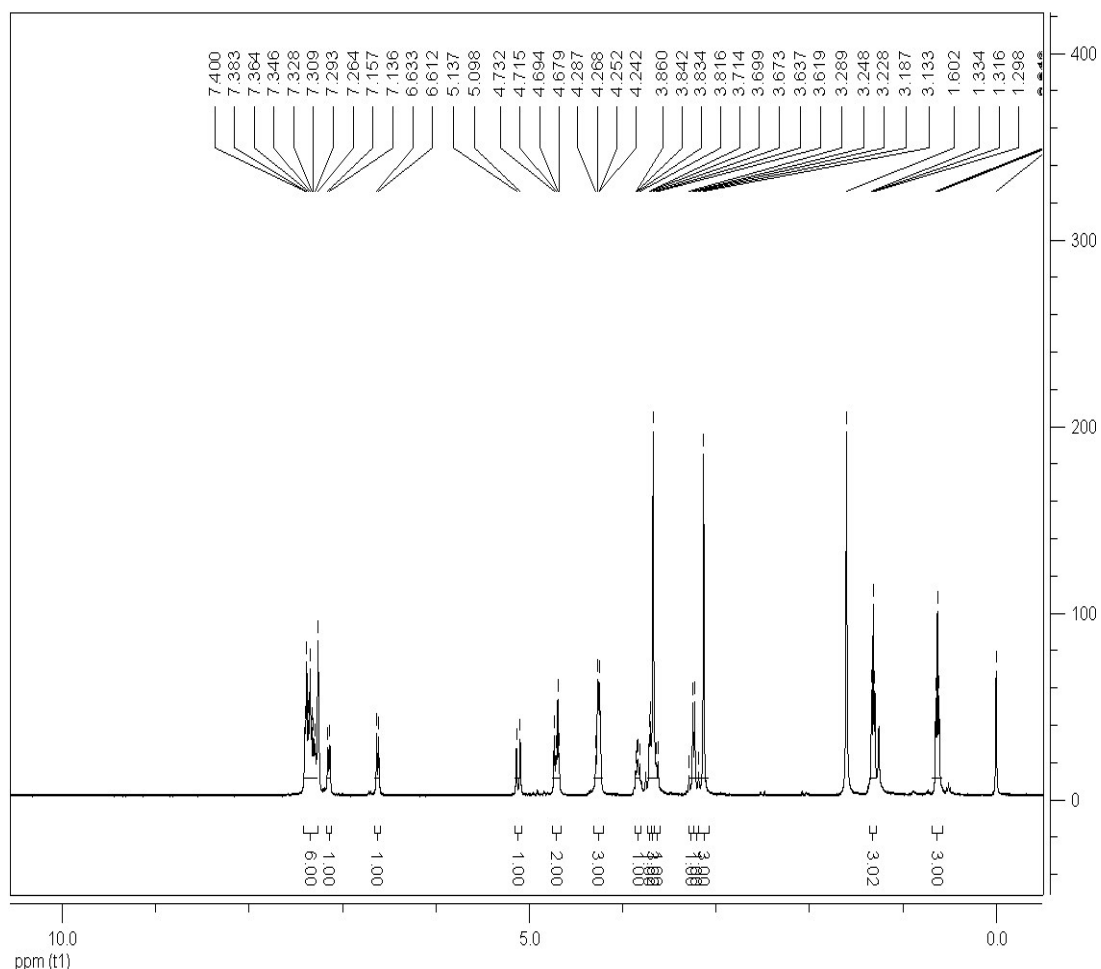




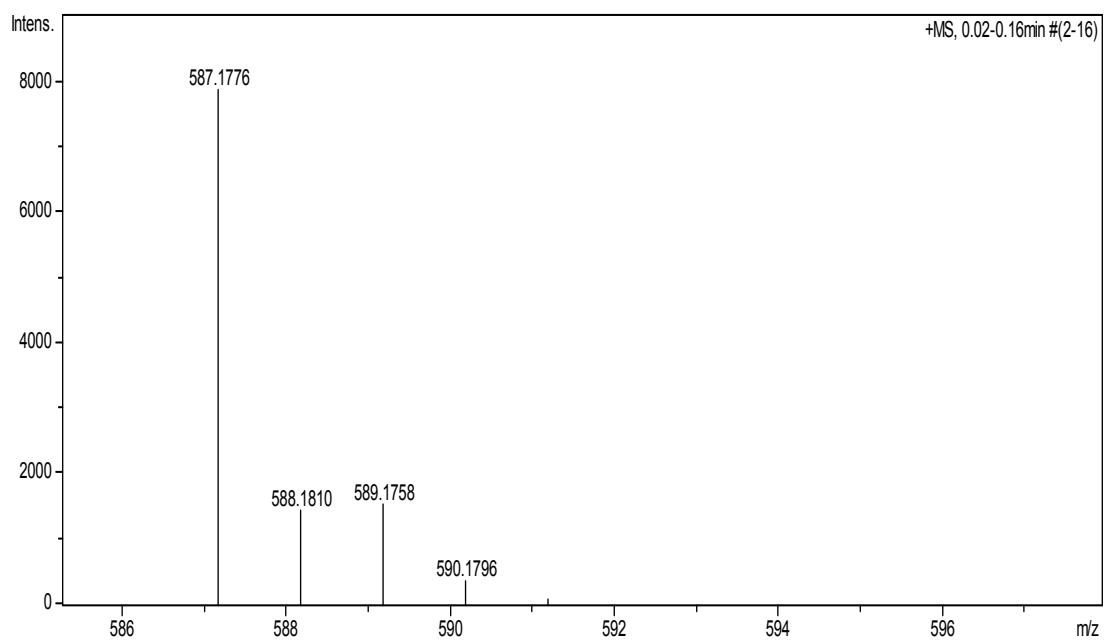
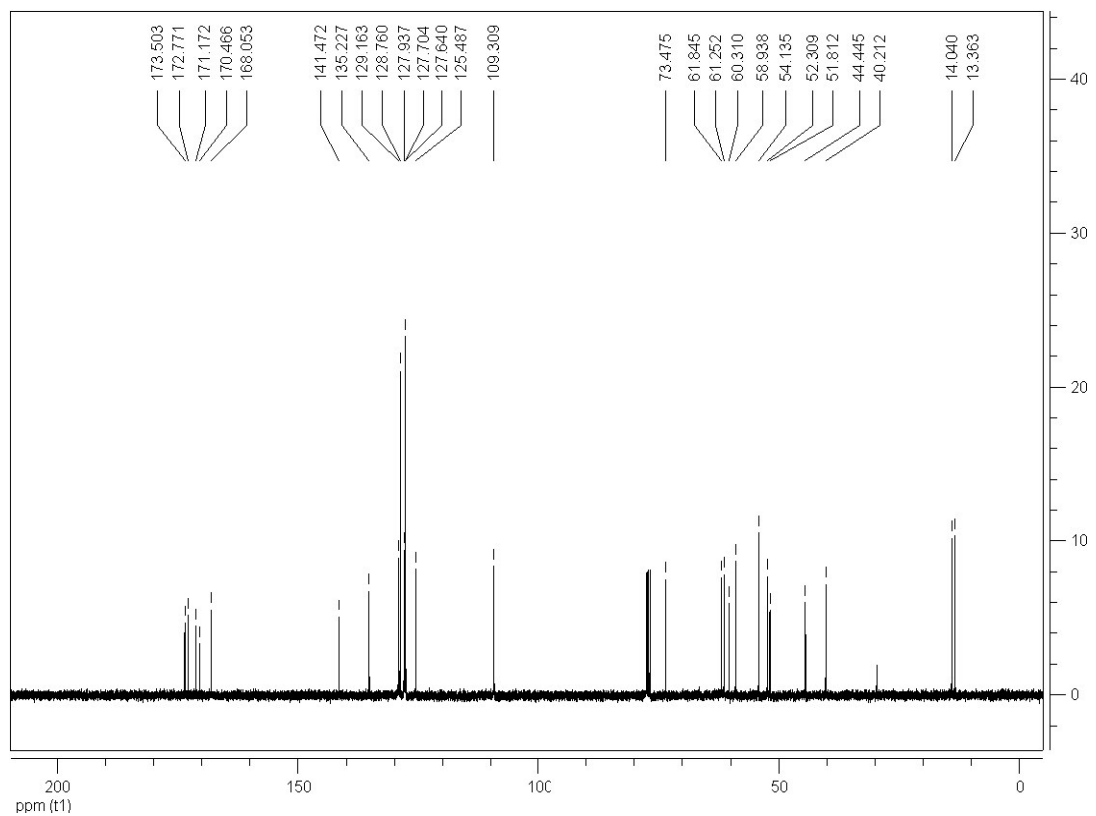
**4',5'-diethyl-2'-methyl-(2'R,3S,4'R,5'R)-1-benzyl-5-chloro-2'-(2-methoxy-2-oxoethyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-2',4',5'-tricarboxylate (1s)**



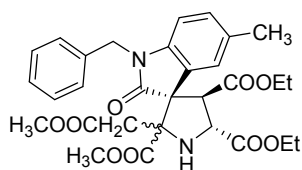
white solid, 57%, m.p. 134~135°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.40~7.29 (m, 6H, ArH), 7.15 (d, *J* = 8.4Hz, 1H, ArH), 6.62 (d, *J* = 8.4Hz, 1H, ArH), 5.12 (d, *J* = 15.6Hz, 1H, CH), 4.73~4.68 (m, 2H, CH), 4.29~4.24 (m, 3H, CH), 3.86~3.82 (m, 1H, CH), 3.71 (d, *J* = 6.0Hz, 1H, NH), 3.67 (s, 3H, OCH<sub>3</sub>), 3.64~3.62 (m, 1H, CH), 3.27 (d, *J* = 16.4Hz, 1H, CH<sub>2</sub>), 3.21 (d, *J* = 16.4Hz, 1H, CH<sub>2</sub>), 3.13 (s, 3H, OCH<sub>3</sub>), 1.32 (t, *J* = 7.2Hz, 3H, CH<sub>3</sub>), 0.63 (t, *J* = 7.2Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 173.5, 172.8, 171.2, 170.5, 168.0, 141.5, 135.2, 129.2, 128.8, 127.9, 127.7, 127.6, 125.5, 109.3, 73.5, 61.8, 61.2, 60.3, 58.9, 54.1, 52.3, 51.8, 44.4, 40.2, 14.0, 13.4; IR(KBr) ν: 3353, 1748, 1705, 1187cm<sup>-1</sup>; MS (*m/z*): HRMS (ESI) Calcd. for C<sub>29</sub>H<sub>32</sub>ClN<sub>2</sub>O<sub>9</sub> ([M+H]<sup>+</sup>): 587.1796, found: 587.1776.



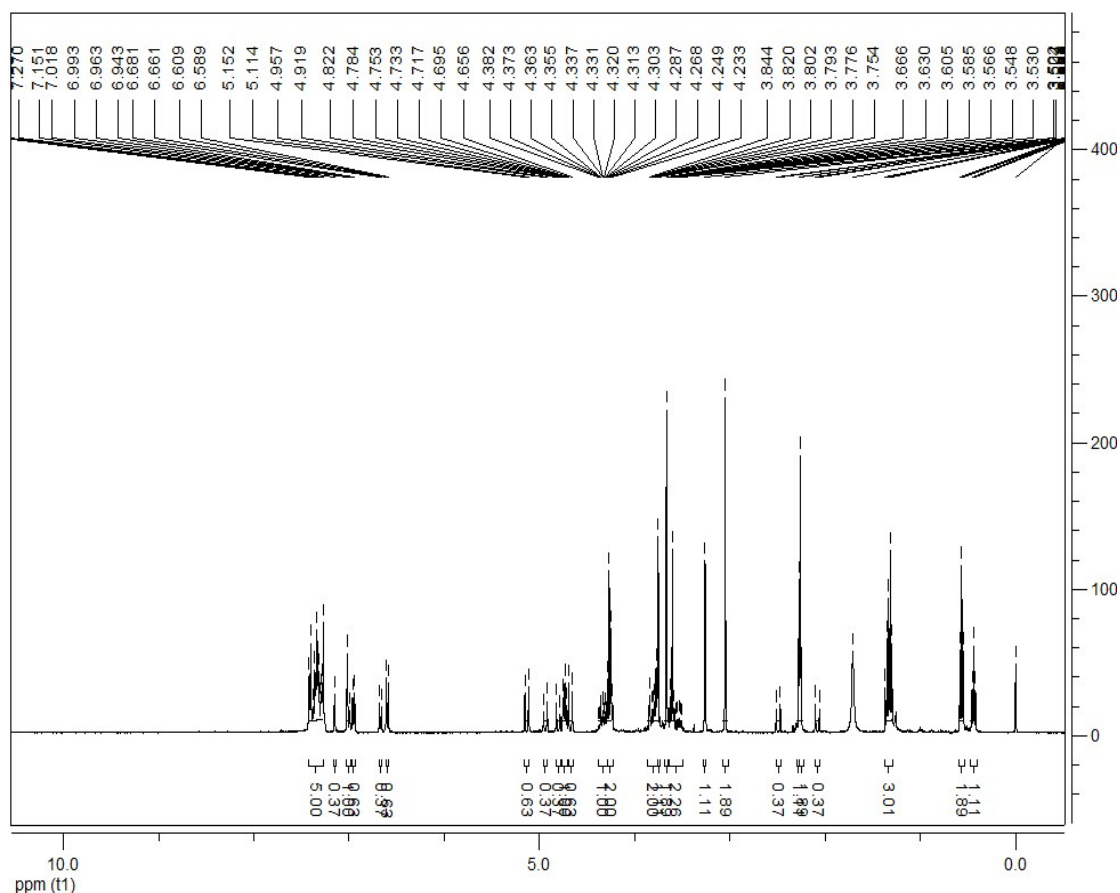


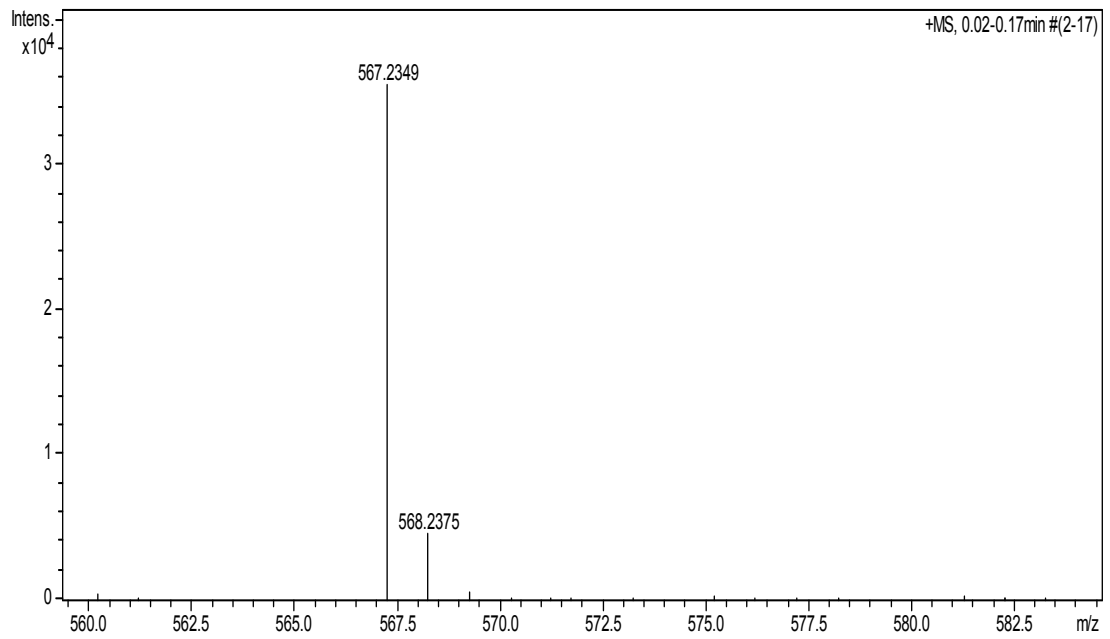
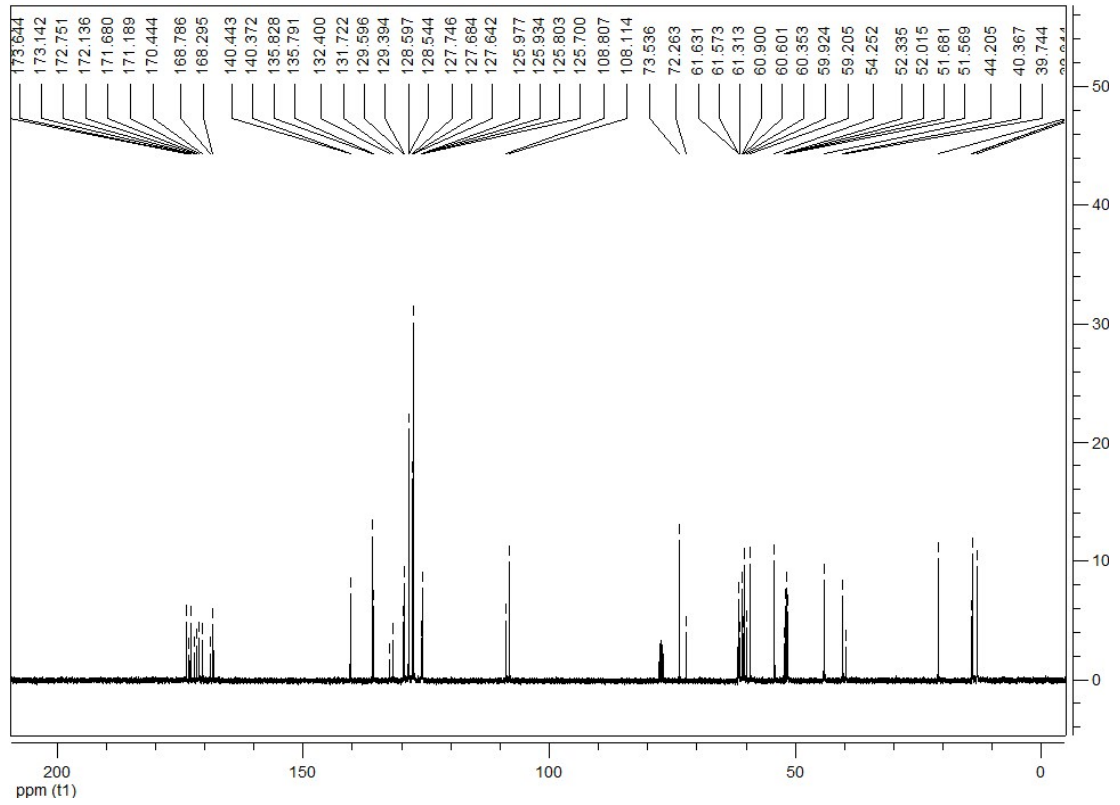


**4',5'-diethyl-2'-methyl-(3*S*,4'*R*,5'*R*)-1-benzyl-2'-(2-methoxy-2-oxoethyl)-5-methyl-2-oxospiro[indoline-3,3'-pyrrolidine]-2',4',5'-tricarboxylate (1t)**

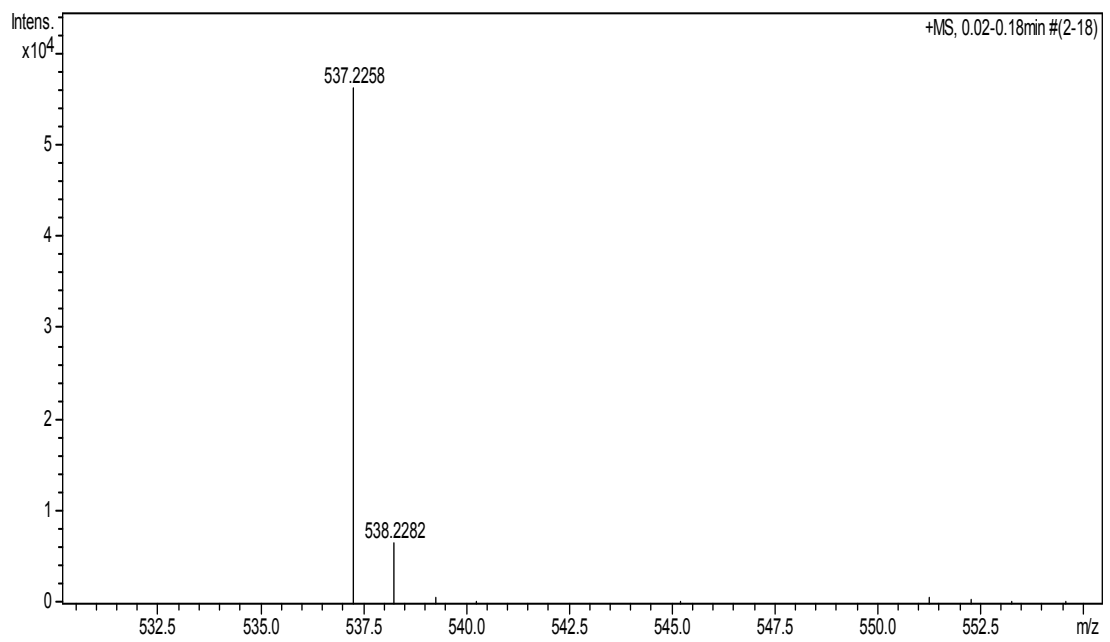
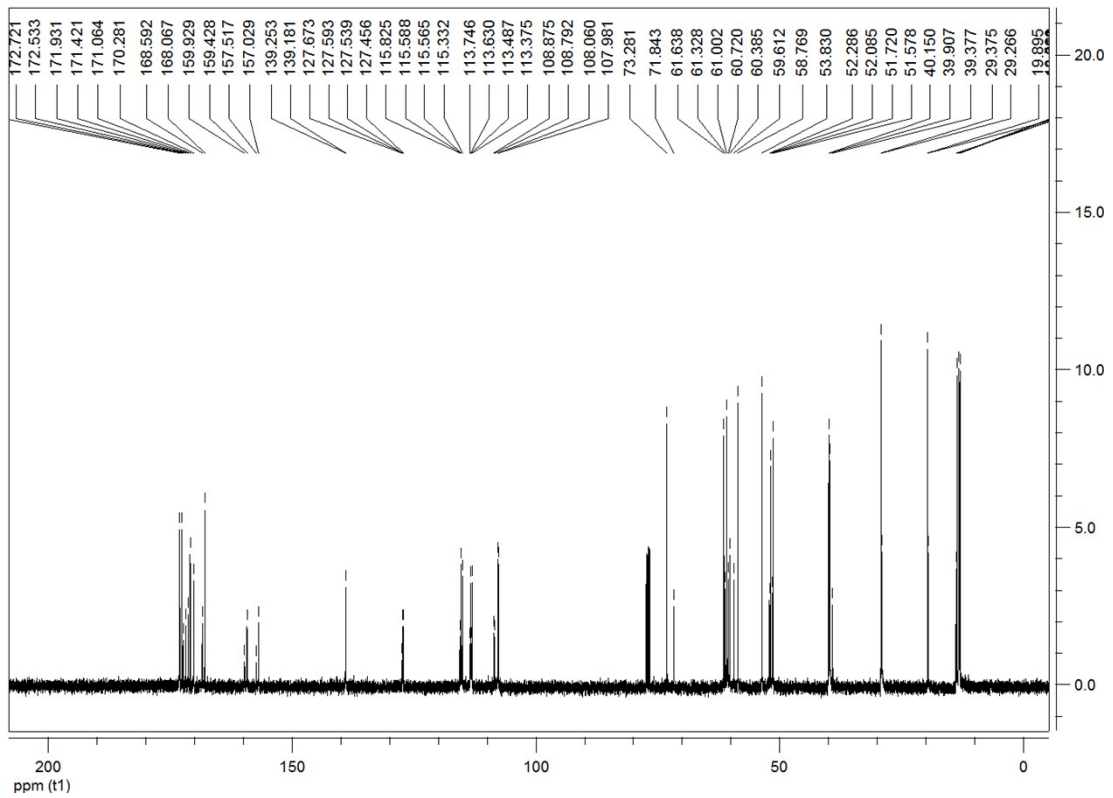


viscous oil, 75%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : **Major isomer:** 7.42~7.28 (m, 5H, ArH), 7.02~6.99 (m, 1H, ArH), 6.95 (d,  $J = 8.0\text{Hz}$ , 1H, ArH), 6.60 (d,  $J = 8.0\text{Hz}$ , 1H, ArH), 5.13 (d,  $J = 15.2\text{Hz}$ , 1H, CH), 4.75~4.72 (m, 1H, CH), 4.68 (d,  $J = 15.6\text{Hz}$ , 1H, CH), 4.38~4.30 (m, 1H, CH), 4.29~4.23 (m, 2H, CH), 3.84~3.78 (m, 2H, CH), 3.67 (s, 3H,  $\text{OCH}_3$ ), 3.63~3.50 (m, 3H, 2CH, NH), 3.05 (s, 3H,  $\text{OCH}_3$ ), 2.26 (s, 3H,  $\text{CH}_3$ ), 1.37~1.30 (m, 3H,  $\text{CH}_3$ ), 0.57 (t,  $J = 7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ); **Minor isomer:** 7.15 (brs, 1H, ArH), 6.67 (d,  $J = 8.0\text{Hz}$ , 1H, ArH), 4.94 (d,  $J = 15.2\text{Hz}$ , 1H, CH), 4.80 (d,  $J = 15.2\text{Hz}$ , 1H, CH), 3.75 (s, 3H,  $\text{OCH}_3$ ), 3.26 (s, 3H,  $\text{OCH}_3$ ), 2.49 (d,  $J = 17.2\text{Hz}$ , 1H,  $\text{CH}_2$ ), 2.28 (s, 3H,  $\text{CH}_3$ ), 2.08 (d,  $J = 16.8\text{Hz}$ , 1H,  $\text{CH}_2$ ), 0.44 (t,  $J = 7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), **ratio of major/minor = 63:37**;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 173.8, 173.6, 173.1, 172.8, 172.1, 171.7, 171.2, 170.4, 168.8, 168.3, 140.4, 140.4, 135.8, 135.8, 132.4, 131.7, 129.6, 129.4, 128.6, 128.5, 127.7, 127.7, 127.6, 126.0, 125.9, 125.8, 125.7, 108.8, 108.1, 73.5, 72.3, 61.6, 61.6, 61.3, 60.9, 60.6, 60.4, 59.9, 59.2, 54.2, 52.3, 52.0, 51.7, 51.6, 44.2, 40.4, 39.7, 20.9, 14.2, 14.0, 13.2, 13.1; IR(KBr)  $\nu$ : 3362, 1740, 1197 $\text{cm}^{-1}$ ; MS ( $m/z$ ): HRMS (ESI) Calcd. for  $\text{C}_{30}\text{H}_{35}\text{N}_2\text{O}_9$  ( $[\text{M}+\text{H}]^+$ ): 567.2343, found: 567.2349.



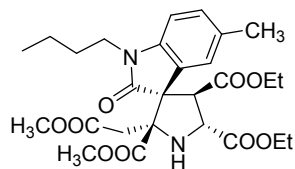




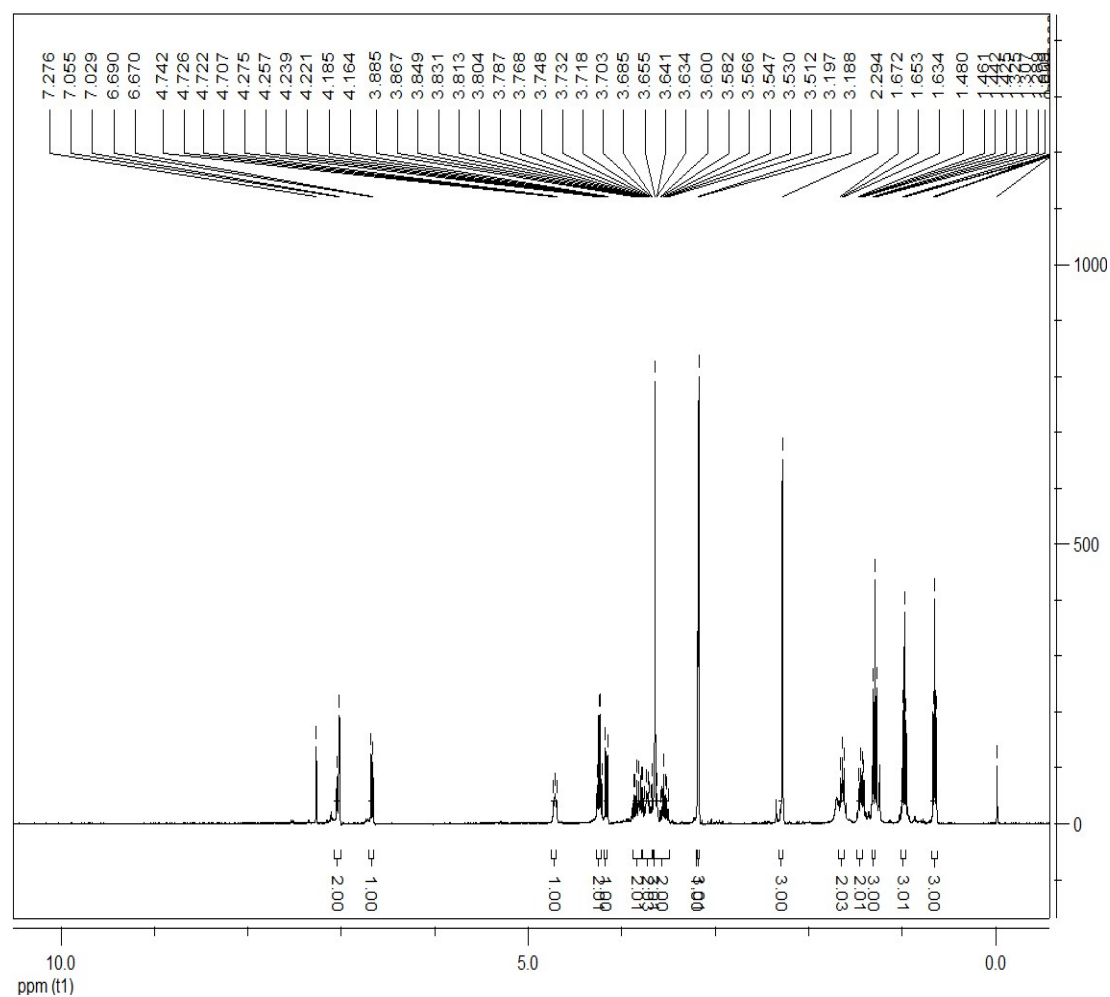


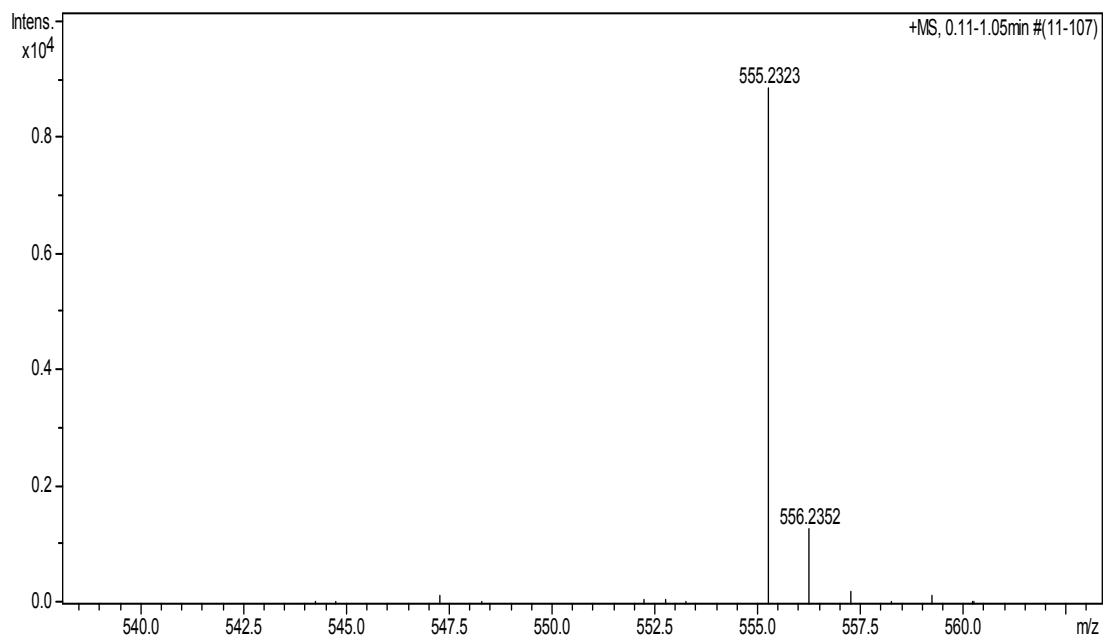
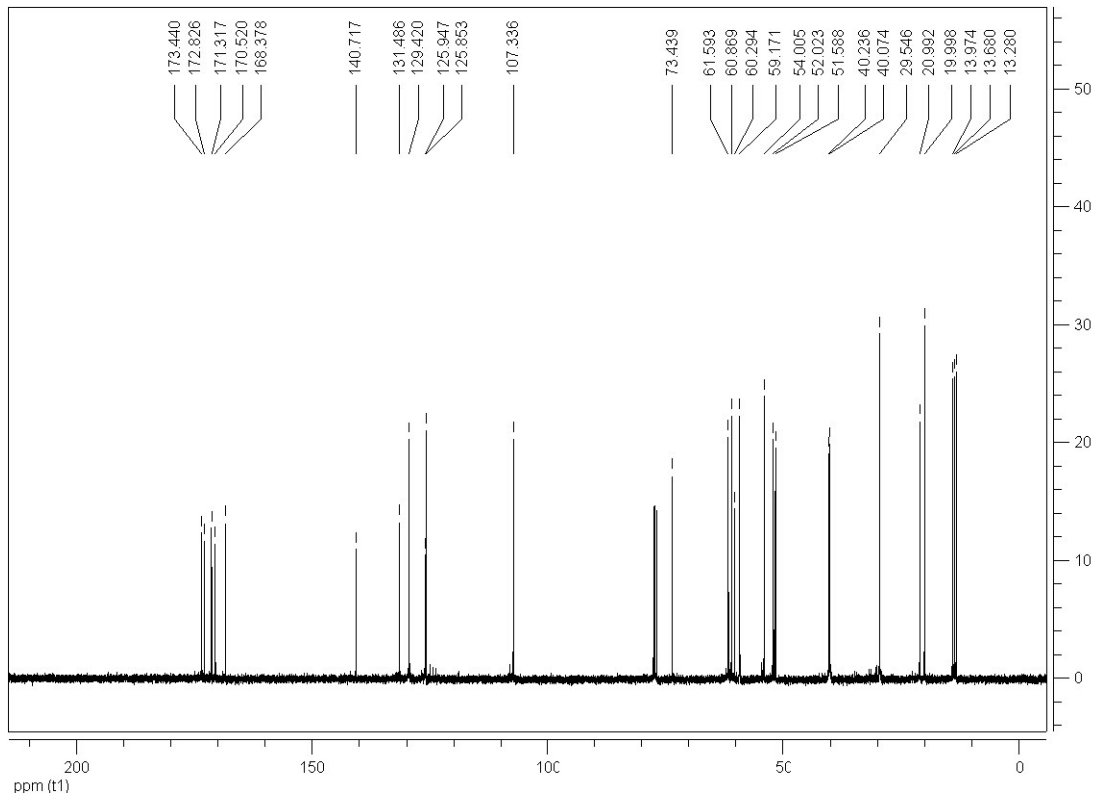
(1v, 1v') Ratio of major/minor = 81:19

**4',5'-diethyl-2'-methyl-(2'R,3S,4'R,5'R)-1-butyl-2'-(2-methoxy-2-oxoethyl)-5-methyl-2-oxospiro[indoline-3,3'-pyrrolidine]-2',4',5'-tricarboxylate (1v) Major isomer:**

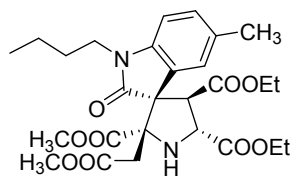


viscous oil, 59%;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.06~7.03 (m, 2H, ArH), 6.68 (d,  $J = 8.0\text{Hz}$ , 1H, ArH), 4.72 (dd,  $J_1 = 8.0\text{Hz}$ ,  $J_2 = 6.4\text{Hz}$ , 1H, CH), 4.25 (q,  $J = 8.4\text{Hz}$ , 2H, CH), 4.17 (d,  $J = 8.4\text{Hz}$ , 1H, CH), 3.88~3.79 (m, 2H, CH), 3.77~3.69 (m, 2H, CH), 3.66 (s, 3H,  $\text{OCH}_3$ ), 3.65~3.51 (m, 2H, CH), 3.20 (s, 1H, NH), 3.19 (s, 3H,  $\text{OCH}_3$ ), 2.29 (s, 3H,  $\text{CH}_3$ ), 1.67~1.63 (m, 2H, CH), 1.48~1.42 (m, 2H, CH), 1.31 (t,  $J = 7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 0.99 (t,  $J = 7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 0.67 (t,  $J = 7.2\text{Hz}$ , 3H,  $\text{CH}_3$ );  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 173.4, 172.8, 171.3, 170.5, 168.4, 140.7, 131.5, 129.4, 125.9, 125.8, 107.3, 73.4, 61.6, 60.9, 60.3, 59.2, 54.0, 52.0, 51.6, 40.2, 40.1, 29.5, 21.0, 20.0, 14.0, 13.7, 13.3; IR(KBr)  $\nu$ : 3479, 1739, 1196 $\text{cm}^{-1}$ ; MS ( $m/z$ ): HRMS (ESI) Calcd. for  $\text{C}_{27}\text{H}_{36}\text{NaN}_2\text{O}_9$  ( $[\text{M}+\text{H}]^+$ ): 555.2319, found: 555.2323.

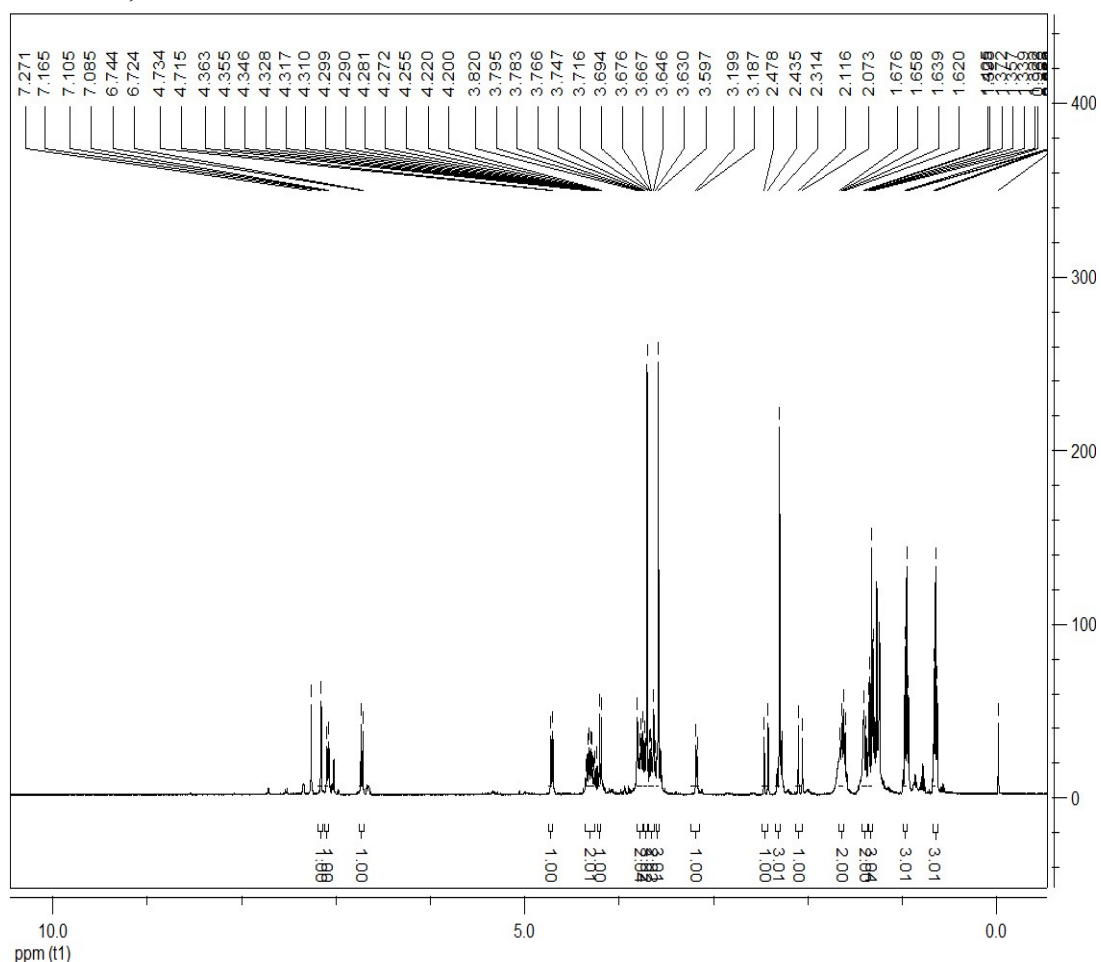




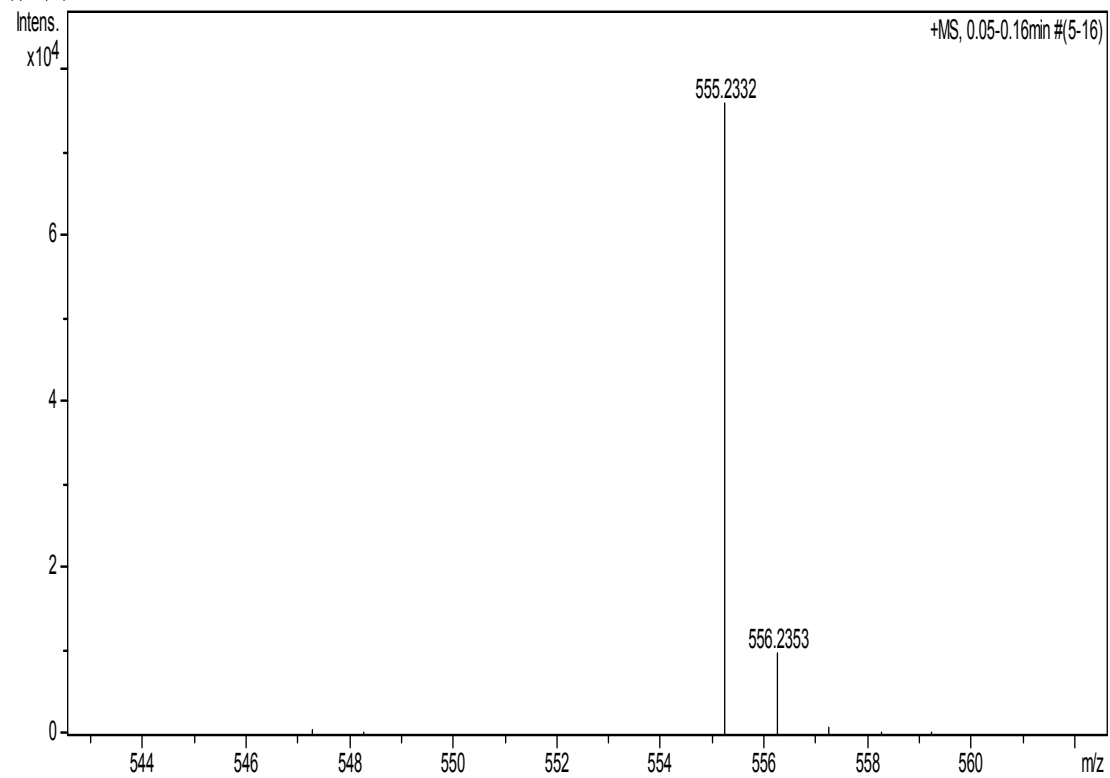
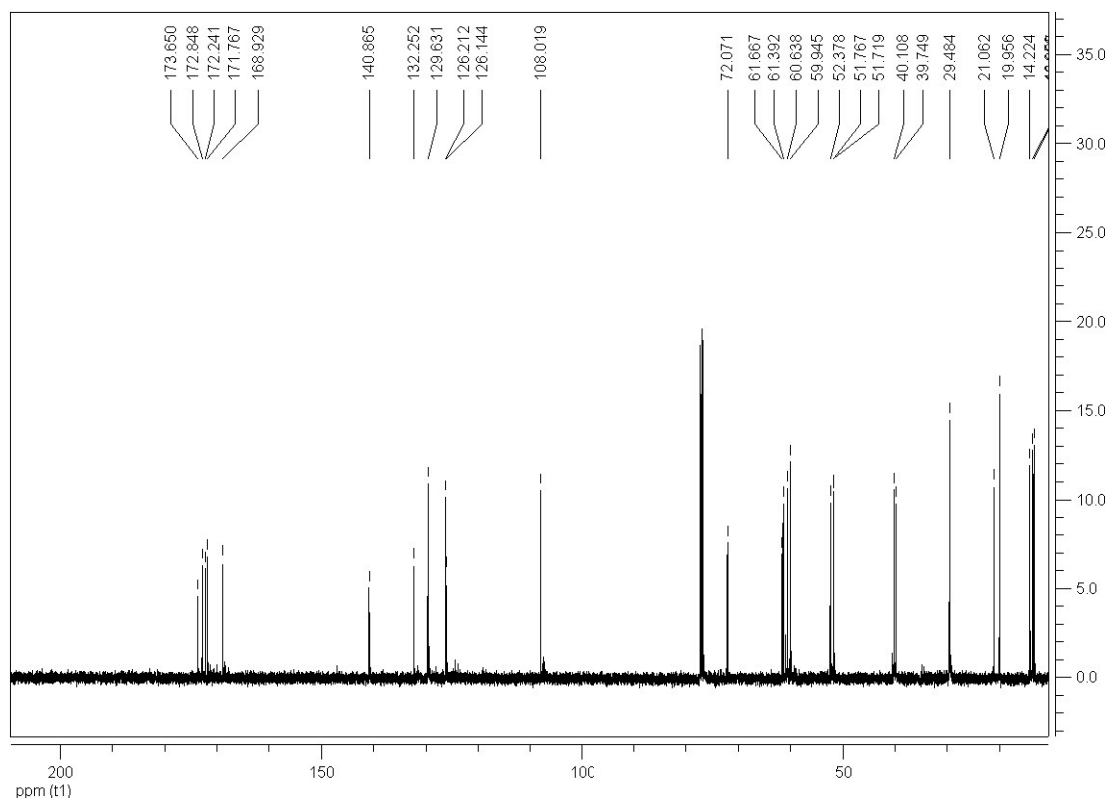
**4',5'-diethyl-2'-methyl-(2'S,3S,4'R,5'R)-1-butyl-2'-(2-methoxy-2-oxoethyl)-5-methyl-2-oxospiro[indoline-3,3'-pyrrolidine]-2',4',5'-tricarboxylate (1v') Minor isomer:**



viscous oil, 14%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.16 (s, 1H, ArH), 7.10 (d,  $J = 8.0\text{Hz}$ , 1H, ArH), 6.73 (d,  $J = 8.0\text{Hz}$ , 1H, ArH), 4.72 (d,  $J = 7.6\text{Hz}$ , 1H, CH), 4.36~4.26 (m, 2H, CH), 4.21 (d,  $J = 8.0\text{Hz}$ , 1H, CH), 3.82~3.75 (m, 2H, CH), 3.72 (s, 3H,  $\text{OCH}_3$ ), 3.70~3.63 (m, 2H, CH), 3.60 (s, 3H,  $\text{OCH}_3$ ), 3.19 (d,  $J = 4.8\text{Hz}$ , 1H, NH), 2.46 (d,  $J = 17.2\text{Hz}$ , 1H,  $\text{CH}_2$ ), 2.31 (s, 3H,  $\text{CH}_3$ ), 2.09 (d,  $J = 17.2\text{Hz}$ , 1H,  $\text{CH}_2$ ), 1.68~1.62 (m, 2H, CH), 1.42~1.37 (m, 2H, CH), 1.34 (t,  $J = 7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 0.97 (t,  $J = 7.6\text{Hz}$ , 3H,  $\text{CH}_3$ ), 0.66 (t,  $J = 7.2\text{Hz}$ , 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 173.6, 172.8, 172.2, 171.8, 168.9, 140.9, 132.2, 129.6, 126.2, 126.1, 108.0, 72.1, 61.7, 61.4, 60.6, 59.9, 52.4, 51.8, 51.7, 40.1, 39.7, 29.5, 21.1, 20.0, 14.2, 13.7, 13.4; IR(KBr)  $\nu$ : 3355, 1740, 1200 $\text{cm}^{-1}$ ; MS ( $m/z$ ): HRMS (ESI) Calcd. for  $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_9$  ( $[\text{M}+\text{H}]^+$ ): 555.2319, found: 555.2332.







**Table S1.** Preliminary evaluation on the anticancer activities of synthesized compounds **1a-1v** on 4T1, CT26, HepG2 and A549 cancer cell lines (200  $\mu\text{g}\cdot\text{mL}^{-1}$ )

Compound		4T1		CT26		HepG2		A549	
		Cell inhibition		Cell inhibition		Cell inhibition		Cell inhibition	
		%	Mean $\pm$ SD	%	Mean $\pm$ SD	%	Mean $\pm$ SD	%	Mean $\pm$ SD
<b>1a</b>	24 h	4.43	0.639 $\pm$ 0.012	/	0.404 $\pm$ 0.015	6.41	0.301 $\pm$ 0.006	3.32	0.467 $\pm$ 0.037
	48 h	5.12	0.746 $\pm$ 0.023	11.06	0.522 $\pm$ 0.040	10.16	0.335 $\pm$ 0.015	2.70	0.675 $\pm$ 0.081
<b>1b</b>	24 h	/	0.708 $\pm$ 0.032	14.38	0.379 $\pm$ 0.006	24.32	0.255 $\pm$ 0.008	2.11	0.475 $\pm$ 0.010
	48 h	0.92	0.769 $\pm$ 0.045	14.76	0.475 $\pm$ 0.033	39.57	0.252 $\pm$ 0.008	38.32	0.448 $\pm$ 0.024
<b>1c</b>	24 h	11.67	0.587 $\pm$ 0.023	3.06	0.421 $\pm$ 0.017	8.89	0.286 $\pm$ 0.014	/	0.501 $\pm$ 0.026
	48 h	5.29	0.734 $\pm$ 0.019	10.14	0.579 $\pm$ 0.038	23.72	0.295 $\pm$ 0.006	7.99	0.643 $\pm$ 0.002
<b>1d</b>	24 h	6.47	0.623 $\pm$ 0.018	10.95	0.406 $\pm$ 0.017	5.95	0.305 $\pm$ 0.019	/	0.495 $\pm$ 0.005
	48 h	2.67	0.757 $\pm$ 0.030	1.01	0.540 $\pm$ 0.032	/	0.369 $\pm$ 0.003	5.05	0.656 $\pm$ 0.003
<b>1e</b>	24 h	38.45	0.434 $\pm$ 0.003	3.73	0.364 $\pm$ 0.015	22.63	0.287 $\pm$ 0.017	1.89	0.475 $\pm$ 0.014
	48 h	27.86	0.587 $\pm$ 0.043	3.88	0.408 $\pm$ 0.007	23.19	0.298 $\pm$ 0.005	21.81	0.554 $\pm$ 0.016
<b>1f</b>	24 h	18.19	0.559 $\pm$ 0.023	4.69	0.336 $\pm$ 0.010	/	0.323 $\pm$ 0.007	19.03	0.398 $\pm$ 0.011
	48 h	16.45	0.658 $\pm$ 0.043	8.32	0.262 $\pm$ 0.008	25.33	0.294 $\pm$ 0.006	15.60	0.586 $\pm$ 0.014
<b>1g</b>	24 h	4.44	0.489 $\pm$ 0.006	16.46	0.341 $\pm$ 0.026	4.52	0.800 $\pm$ 0.068	/	0.472 $\pm$ 0.005
	48 h	18.13	0.800 $\pm$ 0.033	/	0.256 $\pm$ 0.009	/	0.892 $\pm$ 0.023	1.89	0.598 $\pm$ 0.033
<b>1h</b>	24 h	/	0.535 $\pm$ 0.037	/	0.332 $\pm$ 0.022	/	0.884 $\pm$ 0.035	0.37	0.373 $\pm$ 0.013
	48 h	2.29	0.944 $\pm$ 0.017	/	0.244 $\pm$ 0.008	/	0.927 $\pm$ 0.031	0.67	0.671 $\pm$ 0.018
<b>1i</b>	24 h	14.53	0.443 $\pm$ 0.048	4.63	0.376 $\pm$ 0.003	5.25	0.798 $\pm$ 0.009	/	0.446 $\pm$ 0.014
	48 h	7.74	0.894 $\pm$ 0.041	/	0.565 $\pm$ 0.043	/	0.897 $\pm$ 0.030	4.60	0.634 $\pm$ 0.039
<b>1j</b>	24 h	5.90	0.482 $\pm$ 0.015	4.72	0.446 $\pm$ 0.022	/	0.842 $\pm$ 0.056	12.59	0.415 $\pm$ 0.009
	48 h	15.95	0.828 $\pm$ 0.027	/	0.599 $\pm$ 0.003	/	0.896 $\pm$ 0.018	14.66	0.529 $\pm$ 0.019
<b>1k</b>	24 h	/	0.507 $\pm$ 0.047	1.89	0.423 $\pm$ 0.008	2.17	0.829 $\pm$ 0.044	/	0.468 $\pm$ 0.009
	48 h	25.75	0.737 $\pm$ 0.037	3.31	0.552 $\pm$ 0.027	33.19	0.628 $\pm$ 0.027	/	0.617 $\pm$ 0.009
<b>1l</b>	24 h	/	0.548 $\pm$ 0.034	/	0.417 $\pm$ 0.002	6.00	0.804 $\pm$ 0.018	11.19	0.422 $\pm$ 0.011
	48 h	23.32	0.768 $\pm$ 0.036	/	0.543 $\pm$ 0.002	34.43	0.617 $\pm$ 0.042	/	0.626 $\pm$ 0.019
<b>1m</b>	24 h	14.56	0.444 $\pm$ 0.016	0.56	0.423 $\pm$ 0.021	/	0.853 $\pm$ 0.018	/	0.475 $\pm$ 0.019
	48 h	26.38	0.743 $\pm$ 0.010	/	0.500 $\pm$ 0.002	/	0.940 $\pm$ 0.010	8.43	0.568 $\pm$ 0.014
<b>1n</b>	24 h	/	0.809 $\pm$ 0.024	/	0.495 $\pm$ 0.016	/	1.028 $\pm$ 0.058	/	0.471 $\pm$ 0.001
	48 h	/	1.228 $\pm$ 0.051		0.587 $\pm$ 0.033	6.11	0.836 $\pm$ 0.013	/	0.674 $\pm$ 0.017
<b>1o</b>	24 h	/	0.735 $\pm$ 0.039	/	0.433 $\pm$ 0.018	/	0.875 $\pm$ 0.053	24.30	0.368 $\pm$ 0.002
	48 h	/	1.257 $\pm$ 0.035	4.06	0.563 $\pm$ 0.022	52.77	0.455 $\pm$ 0.032	27.87	0.458 $\pm$ 0.003
<b>1p</b>	24 h	27.91	0.385 $\pm$ 0.028	14.57	0.503 $\pm$ 0.007	/	0.851 $\pm$ 0.019	/	0.472 $\pm$ 0.004
	48 h	41.18	0.629 $\pm$ 0.048	/	0.656 $\pm$ 0.044	1.83	0.869 $\pm$ 0.016	/	0.650 $\pm$ 0.002
<b>1q</b>	24 h	/	0.622 $\pm$ 0.016	3.19	0.436 $\pm$ 0.006	10.94	0.792 $\pm$ 0.037	/	0.465 $\pm$ 0.016

	48 h	4.65	0.941±0.008	9.86	0.497±0.021	28.31	0.790±0.013	/	0.604±0.008
<b>1r</b>	24 h	2.53	0.603±0.020	6.09	0.383±0.012	14.03	0.770±0.018	/	0.458±0.003
	48 h	15.54	0.844±0.071	8.63	0.525±0.028	29.50	0.784±0.019	0.58	0.584±0.003
<b>1s</b>	24 h	21.90	0.495±0.019	13.10	0.435±0.009	/	0.891±0.026	/	0.450±0.046
	48 h	29.39	0.734±0.038	18.91	0.505±0.009	24.44	0.837±0.016	14.02	0.521±0.018
<b>1t</b>	24 h	/	0.820±0.014	/	0.404±0.015	/	1.112±0.040	4.90	0.446±0.001
	48 h	/	1.263±0.056	/	0.522±0.040	47.62	0.623±0.042	3.02	0.578±0.015
<b>1u</b>	24 h	/	0.872±0.024	4.00	0.379±0.006	24.94	0.682±0.080	6.76	0.430±0.001
	48 h	7.22	0.923±0.114	6.28	0.475±0.033	67.14	0.408±0.038	13.79	0.517±0.010
<b>1v</b>	24 h	/	0.712±0.042	17.64	0.421±0.017	40.39	0.545±0.051	/	0.468±0.019
	48 h	9.05	0.910±0.045	28.84	0.579±0.038	10.44	0.875±0.021	2.36	0.575±0.028

/ : no activity

**Table S2.** Preliminary evaluation on the anticancer activities of synthesized compounds **2a-2n** on 4T1, CT26, HepG2 and A549 cancer cell lines (200 µg·mL<sup>-1</sup>)

Compound		4T1		CT26		HepG2		A549	
		Cell inhibition		Cell inhibition		Cell inhibition		Cell inhibition	
		%	Mean ± SD	%	Mean ± SD	%	Mean ± SD	%	Mean ± SD
<b>2a</b>	24 h	41.62	0.389±0.043	14.72	0.336±0.010	28.22	0.308±0.007	39.95	0.306±0.010
	48 h	37.37	0.534±0.020	23.60	0.262±0.008	<b>52.91</b>	0.184±0.008	39.28	0.483±0.022
<b>2b</b>	24 h	36.64	0.415±0.005	/	0.341±0.026	20.48	0.215±0.003	33.19	0.320±0.008
	48 h	38.90	0.522±0.034	3.84	0.256±0.009	37.90	0.331±0.005	30.89	0.325±0.013
<b>2c</b>	24 h	2.63	0.598±0.027	0.28	0.332±0.022	/	0.318±0.004	27.03	0.556±0.025
	48 h	8.01	0.745±0.038	16.64	0.244±0.008	7.86	0.370±0.008	26.63	0.560±0.106
<b>2d</b>	24 h	1.53	0.618±0.140	5.05	0.376±0.003	13.09	0.278±0.005	18.22	0.383±0.011
	48 h	12.67	0.711±0.009	7.84	0.565±0.043	24.43	0.317±0.005	18.39	0.617±0.015
<b>2e</b>	24 h	/	0.893±0.210	28.98	0.446±0.022	3.31	0.299±0.020	/	0.507±0.004
	48 h	/	0.919±0.045	26.11	0.599±0.003	<b>55.47</b>	0.231±0.027	42.24	0.461±0.002
<b>2f</b>	24 h	32.64	0.457±0.006	12.06	0.423±0.008	16.71	0.266±0.011	23.47	0.334±0.011
	48 h	33.04	0.566±0.024	23.30	0.552±0.027	17.35	0.344±0.007	28.48	0.572±0.002
<b>2g</b>	24 h	24.51	0.488±0.011	13.40	0.417±0.002	32.25	0.237±0.016	25.21	0.325±0.021
	48 h	34.30	0.560±0.041	31.95	0.543±0.002	23.97	0.329±0.010	18.82	0.598±0.021
<b>2h</b>	24 h	29.56	0.486±0.010	17.21	0.423±0.021	22.08	0.197±0.010	14.83	0.384±0.016
	48 h	31.17	0.601±0.059	30.26	0.500±0.002	<b>50.59</b>	0.360±0.016	17.56	0.642±0.041
<b>2i</b>	24 h	38.94	0.417±0.013	2.41	0.495±0.016	21.07	0.213±0.005	35.90	0.304±0.009
	48 h	34.45	0.553±0.043	21.59	0.587±0.033	42.58	0.329±0.007	39.80	0.507±0.03
<b>2j</b>	24 h	/	0.673±0.040	<b>62.84</b>	0.433±0.018	21.15	0.268±0.019	2.28	0.455±0.024
	48 h	25.76	0.620±0.057	<b>88.58</b>	0.563±0.022	43.48	0.267±0.006	40.89	0.460±0.035

<b>2k</b>	24 h	5.14	0.636±0.097	0.41	0.503±0.007	13.72	0.298±0.005	5.23	0.452±0.035
	48 h	24.18	0.630±0.033	14.66	0.656±0.044	21.05	0.302±0.008	5.82	0.646±0.013
<b>2l</b>	24 h	/	1.035±0.005	12.11	0.436±0.006	2.77	0.329±0.019	/	0.474±0.006
	48 h	/	0.859±0.088	9.57	0.497±0.021	14.94	0.319±0.009	16.40	0.580±0.006
<b>2m</b>	24 h	/	0.716±0.035	18.64	0.383±0.012	18.82	0.267±0.018	/	0.497±0.022
	48 h	2.79	0.749±0.093	16.19	0.525±0.028	45.80	0.239±0.003	20.71	0.564±0.005
<b>2n</b>	24 h	6.23	0.621±0.028	19.83	0.435±0.009	<b>57.58</b>	0.199±0.019	0.20	0.452±0.010
	48 h	6.98	0.724±0.048	25.54	0.505±0.009	<b>59.86</b>	0.194±0.026	5.52	0.683±0.014

/ : no activity