

# **Privileged Structures as Peptide Backbone Constraints: Polymer-Supported Stereoselective Synthesis of Benzimidazolinopiperazinone Peptides**

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## Table of Contents

|                                                                             |     |
|-----------------------------------------------------------------------------|-----|
| 1. General Information .....                                                | S2  |
| 2. LC/MS traces of intermediates <b>8</b> and final products <b>9</b> ..... | S3  |
| 3. Analytical data of individual compounds.....                             | S8  |
| 4. Tabular form of NMR data.....                                            | S31 |
| 5. <sup>1</sup> H and <sup>13</sup> C NMR spectra .....                     | S34 |

## Material and Methods

Solvents were used without further purification. The Rink amide resin (100-200 mesh, 1% DVB, 0.68 mmol/g) and Wang resin (100-200 mesh, 1% DVB, 1.0 mmol/g) were used. Synthesis was carried out on Domino Blocks ([www.torvig.com](http://www.torvig.com)) in disposable polypropylene reaction vessels.

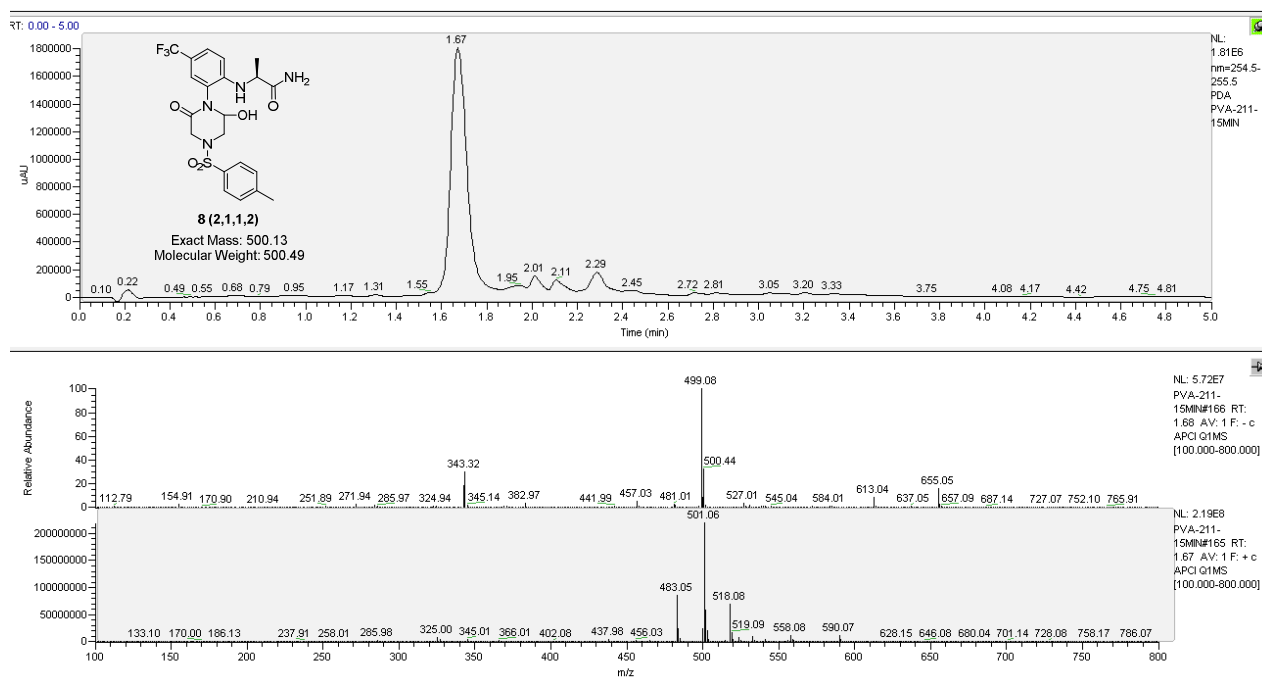
The volume of wash solvent was 10 mL per 1 g of resin (except Mitsunobu alkylation; the volume was 20 mL per 1 g of resin). For washing, resin slurry was shaken with the fresh solvent for at least 1 minute before changing the solvent. After adding a reagent solution, the resin slurry was manually vigorously shaken to break any potential resin clumps. Resin-bound intermediates were dried by a stream of nitrogen for prolonged storage and/or quantitative analysis.

For the LC/MS analysis a sample of resin (~5 mg) was treated by 50% TFA in DCM, the Cleavage cocktail was evaporated by a stream of nitrogen, and cleaved compounds extracted into 1 mL of MeOH. The LC/MS analyses were carried out using two instruments. The first one comprised a 3 x 50 mm C18 reverse phase column, 5  $\mu$ m particles. Mobile phases: 10 mM ammonium acetate in HPLC grade water (A) and HPLC grade acetonitrile (B). A gradient was formed from 5% to 80% of B in 10 minutes, flow rate of 0.7 mL/min. The MS electrospray source operated at capillary voltage 3.5 kV and a desolvation temperature 300 °C. The second instrument comprised a 2.1 x 50 mm C18 reverse phase column, 2.6  $\mu$ m particles, at 30 °C and flow rate of 800  $\mu$ L/min. Mobile phases: 10 mM ammonium acetate in HPLC grade water (A) and HPLC grade acetonitrile (B). A gradient was formed from 10% to 80% of B in 2.5 minutes; kept for 1.5 minute, flow rate of 0.8 mL/min. The column was re-equilibrated with 10% solution B for 1 minute. The APCI source operated at discharge current of 5  $\mu$ A, vaporizer temperature of 400 °C and capillary temperature of 200 °C.

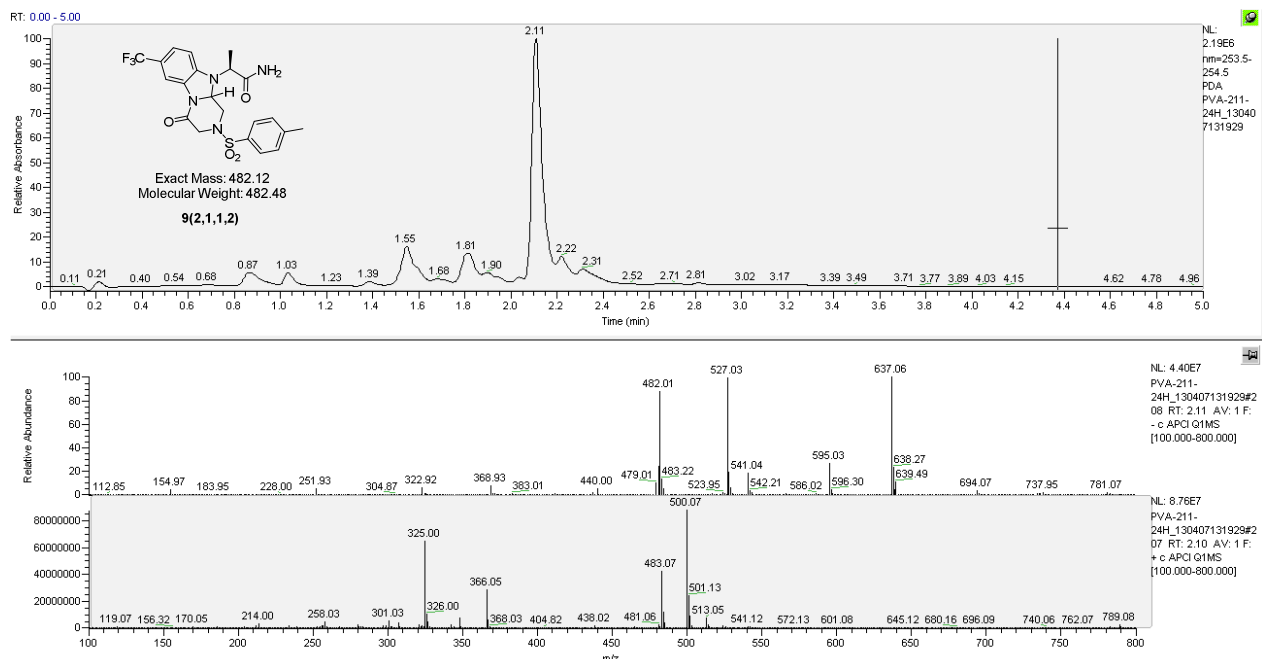
Purification was carried out on C18 reverse phase column 19 x 100 mm, 5  $\mu$ m, gradient was formed from 10 mM aqueous ammonium acetate and acetonitrile, flow rate 15 mL/min.

# HPLC chromatograms and MS traces of intermediate 8(2,1,1,2) after 30 min of cleavage and final product 9(2,1,1,2) after 16 h of cleavage

Cleavage time = 30 min

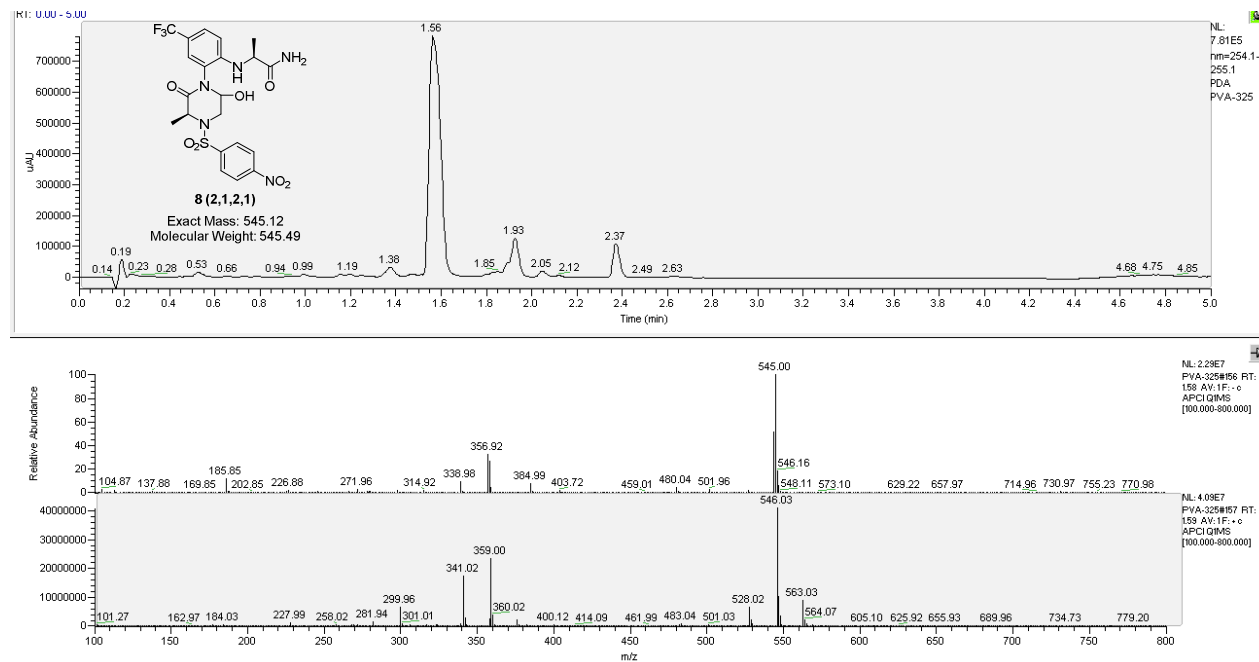


Cleavage time = 16 h

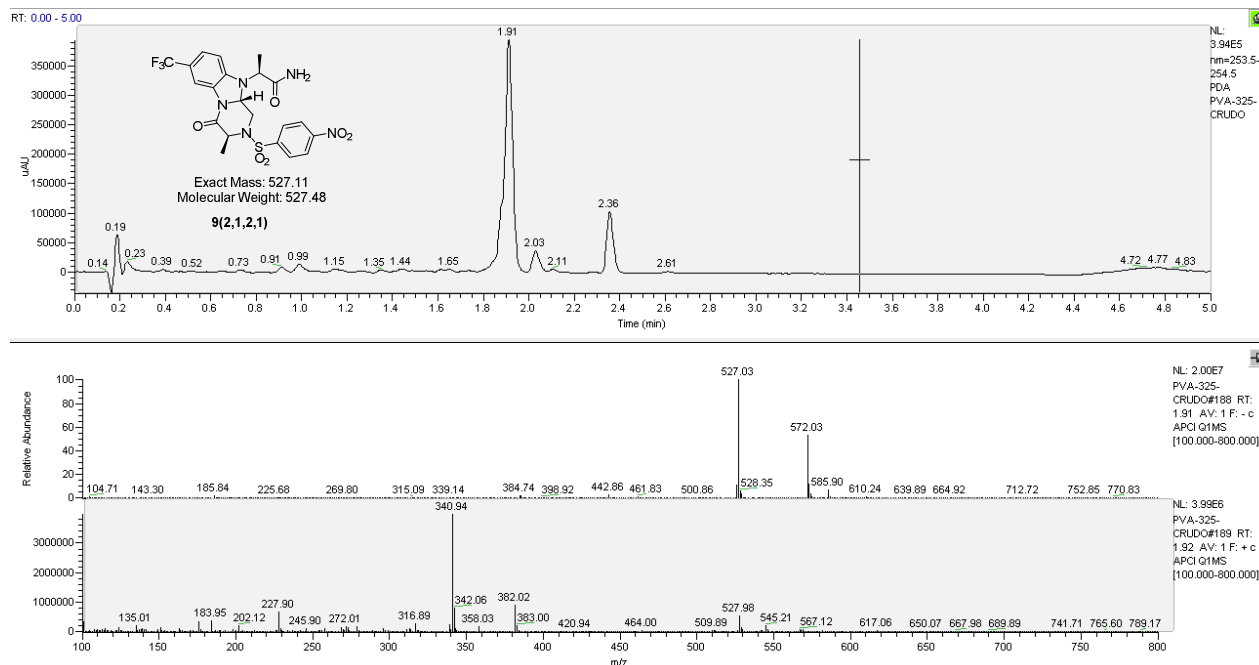


# HPLC chromatograms and MS traces of intermediate 8(2,1,2,1) after 30 min of cleavage and final product 9(2,1,2,1) after 16 h of cleavage

Cleavage time = 30 min

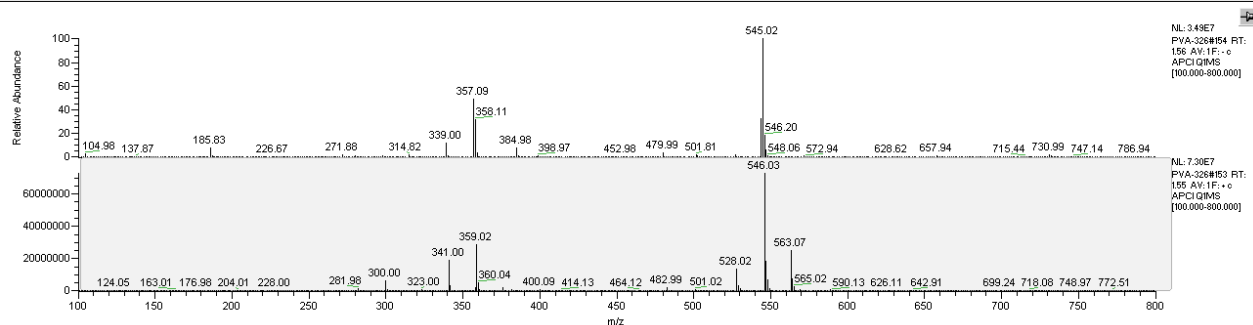
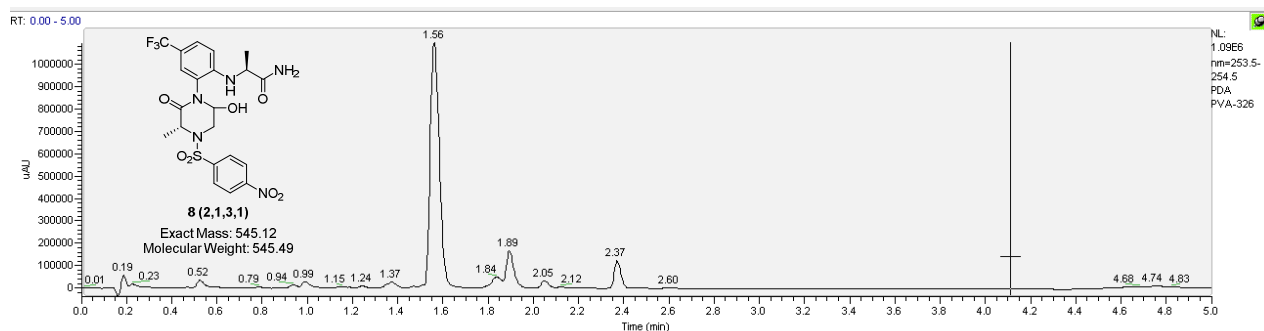


Cleavage time = 16 h

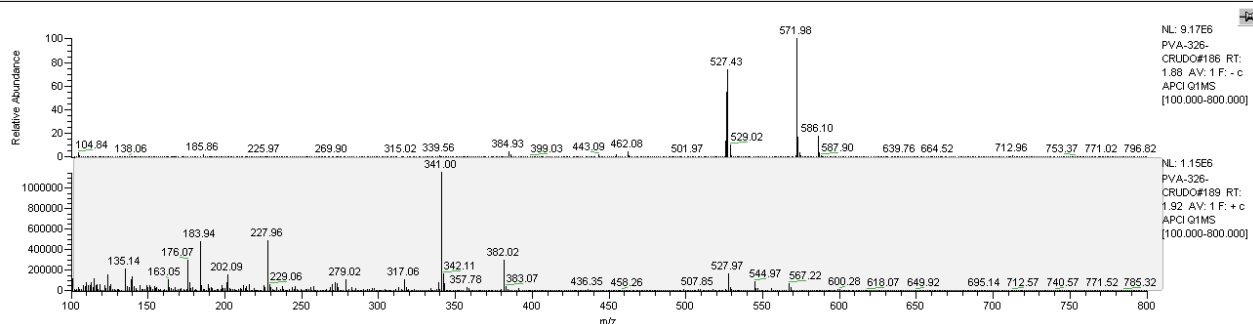
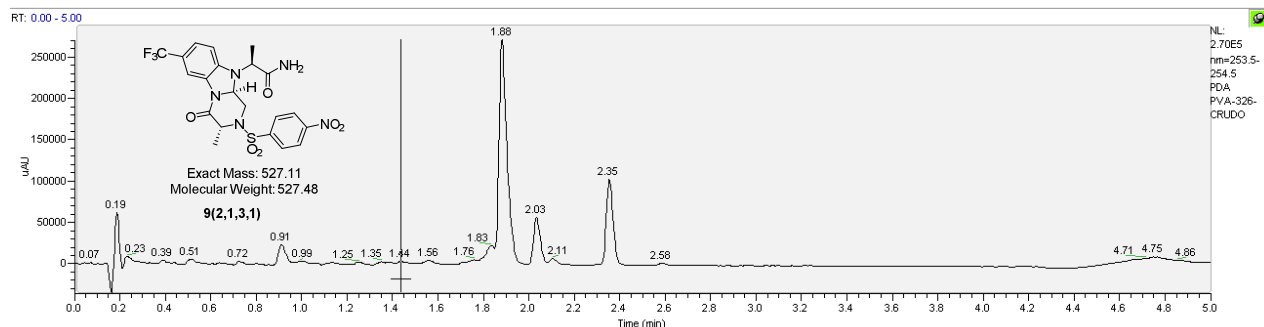


# HPLC chromatograms and MS traces of intermediate 8(2,1,3,1) after 30 min of cleavage and final product 9(2,1,3,1) after 16 h of cleavage

Cleavage time = 30 min

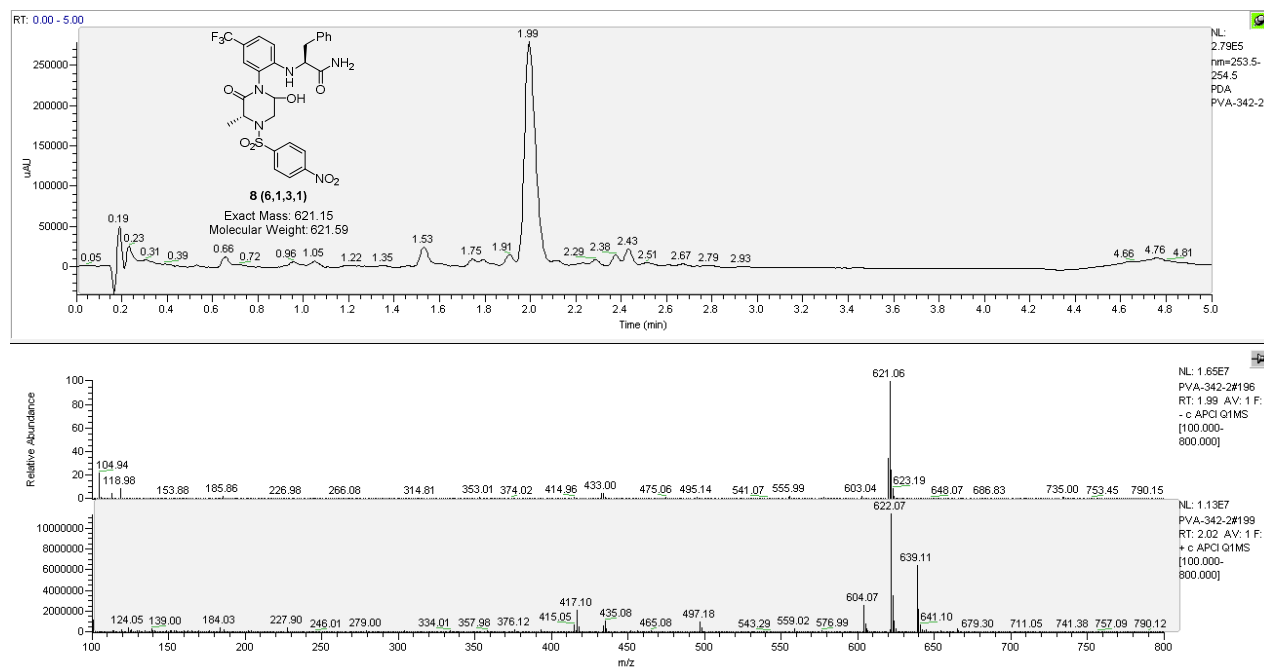


Cleavage time = 16 h

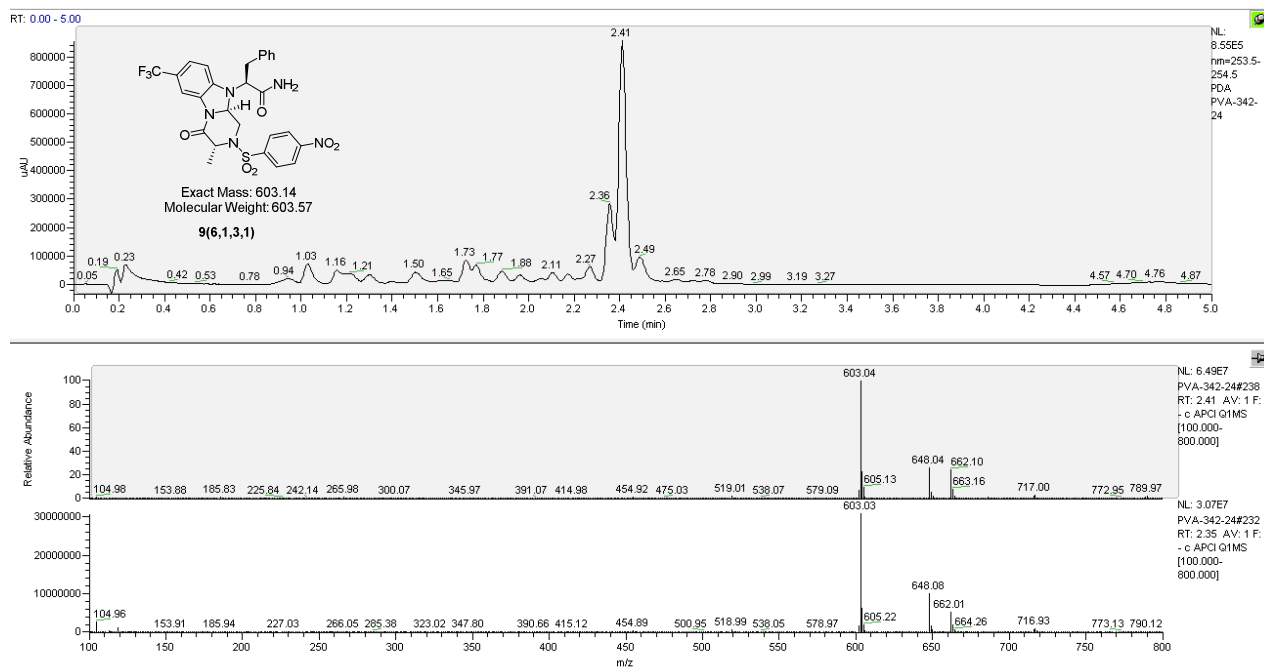


# HPLC chromatograms and MS traces of intermediate 8(6,1,3,1) after 30 min of cleavage and final product 9(6,1,3,1) after 16 h of cleavage

Cleavage time = 30 min

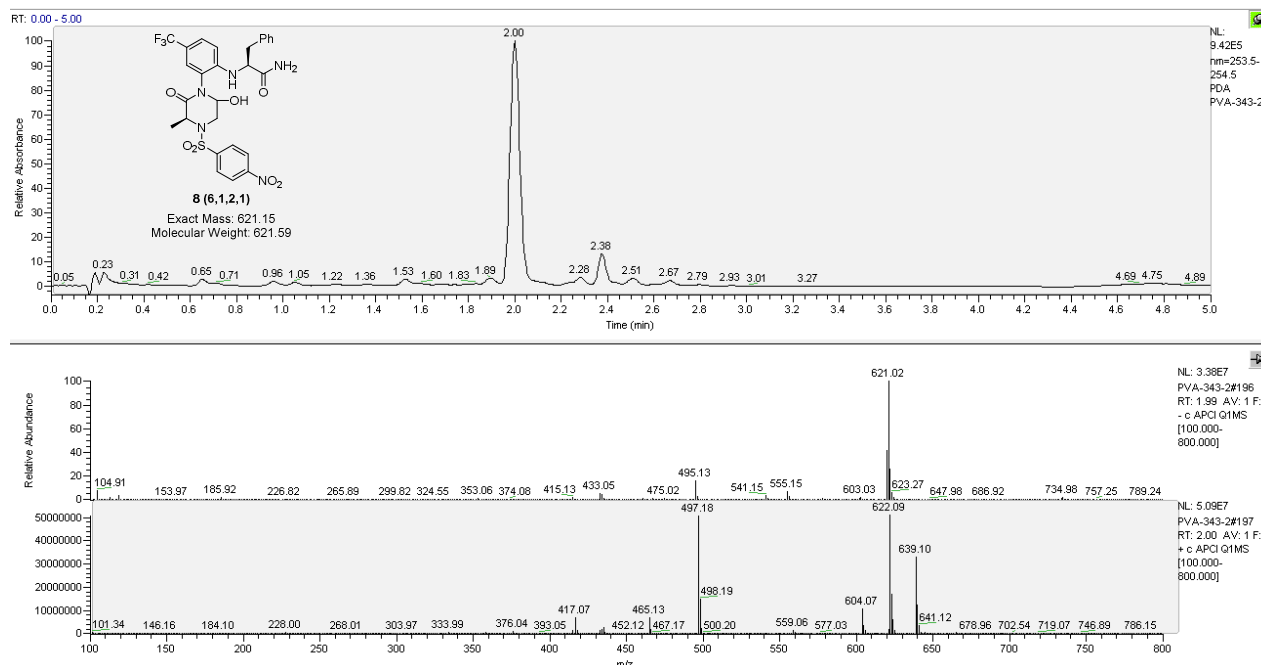


Cleavage time = 16 h

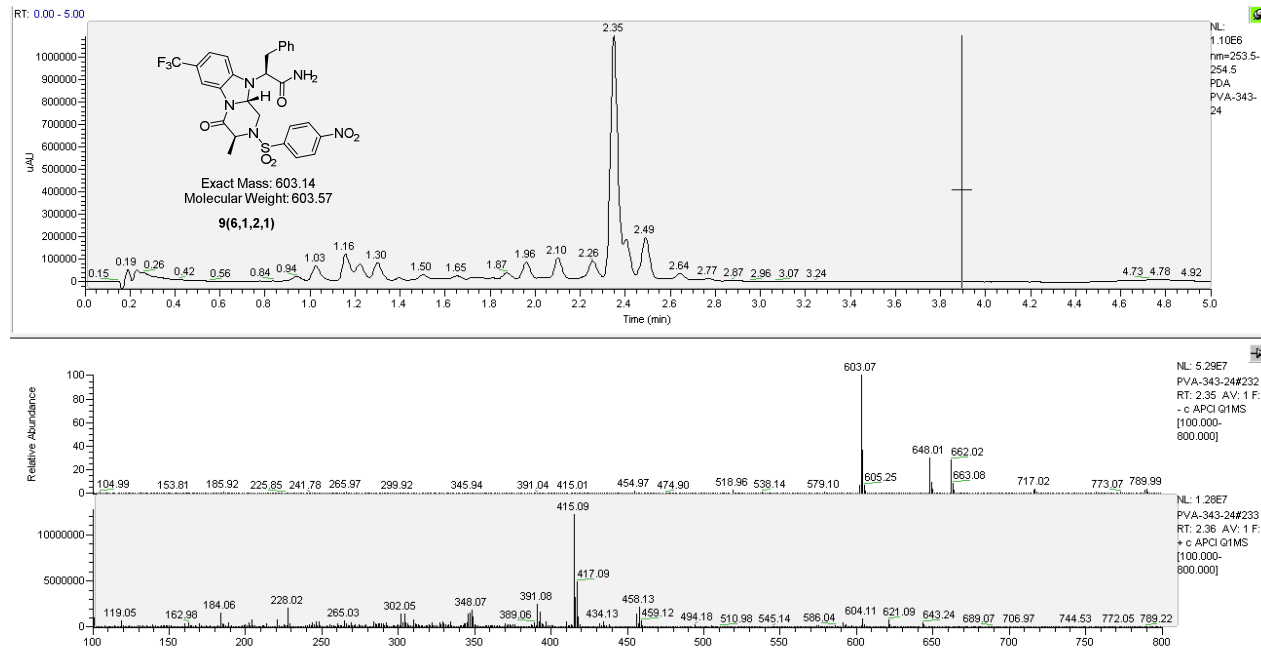


# HPLC chromatograms and MS traces of intermediate 8(6,1,2,1) after 30 min of cleavage and final product 9(6,1,2,1) after 16 h of cleavage

Cleavage time = 30 min

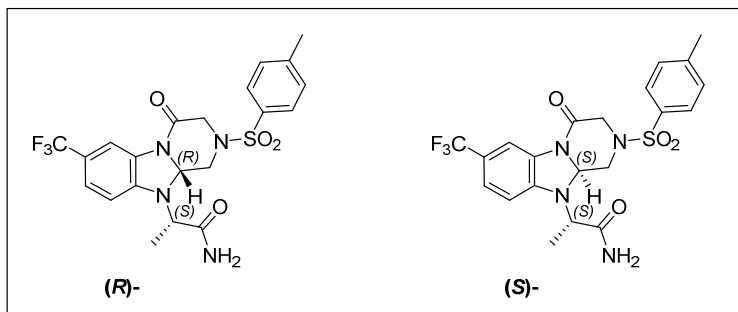


Cleavage time = 16 h



## Analytical Data of Individual Compounds

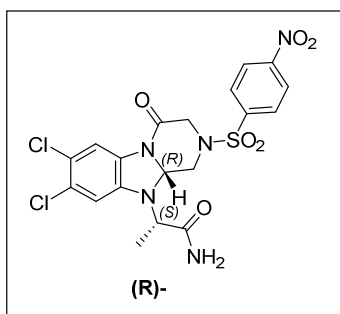
### (S)-2-((RS)-4-oxo-2-tosyl-7-(trifluoromethyl)-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-10(2H)-yl)propanamide 9(2,1,1,2)



Yield 16.9 mg (45%) of amorphous solid. Purified by semi-preparative HPLC. (*R*):(*S*) ratio of the crude = 77:23. (*R*):(*S*) ratio of the purified product = 75:25. HPLC: RT = 2.12 min. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) *R*-epimer (75%) 7.79 (d, *J* = 8.4 Hz, 2H, Tos), 7.74 (d, *J* = 1.9 Hz, 1H, 6-H), 7.55 (bs, 1H, NH), 7.46 (d, *J* = 8.4 Hz, 2H, Tos), 7.30 (d, *J* = 8.2 Hz, 1H, 8-H), 7.27 (bs, 1H, NH), 6.61 (d, *J* = 8.2 Hz, 1H, 9-H), 5.65 (dd, *J* = 9.5, 3.6 Hz, 1H, 10a-H), 4.41 (dd, *J* = 11.8, 3.6 Hz, 1H, 1-H), 4.25 (q, *J* = 7.0 Hz, 1H, α-H-Ala), 4.24 (d, *J* = 16.9 Hz, 1H, 3-H), 3.54 (d, *J* = 17.0 Hz, 1H, 3-H), 3.15 (dd, *J* = 11.9, 9.6 Hz, 1H, 1-H), 2.39 (s, 1H, CH<sub>3</sub>-Tos), 1.32 (d, *J* = 7.1 Hz, 1H, CH<sub>3</sub>-Ala); *S*-epimer (25%) 7.77 (d, *J* = 8.4 Hz, 2H, Tos), 7.74 (d, *J* = 1.9 Hz, 1H, 6-H), 7.61 (bs, 1H, NH), 7.44 (d, *J* = 8.4 Hz, 1H), 7.34 (bs, 1H, NH), 7.30 (d, *J* = 8.2 Hz, 1H, 8-H), 6.75 (d, *J* = 8.3 Hz, 1H, 9-H), 5.57 (dd, *J* = 9.5, 3.5 Hz, 1H, 10a-H), 4.32 (q, *J* = 7.1 Hz, 1H, α-H-Ala), 4.31 – 4.26 (m, 1H, 1-H), 4.22 (d, *J* = 17.0 Hz, 1H, 3-H), 3.63 (d, *J* = 17.0 Hz, 1H, 3-H), 3.15 (dd, *J* = 12.7, 8.9 Hz, 1H, 1-H), 2.39 (s, 1H, CH<sub>3</sub>-Tos), 1.32 (d, *J* = 7.1 Hz, 1H, CH<sub>3</sub>-Ala). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) *R*-epimer 172.1 (C, CONH<sub>2</sub>-Ala), 161.5 (C, C<sub>4</sub>), 144.3 (C, C<sub>9a</sub>), 132.9 (C, Tos), 131.9 (C, Tos), 130.1 (2CH, Tos), 127.5 (2CH, Tos), 124.6 (q, *J* = 270.8 Hz, C, CF<sub>3</sub>), 122.8 (q, *J* = 4.2 Hz, CH, C<sub>8</sub>), 118.8 (q, *J* = 31.9 Hz CH, C<sub>7</sub>), 110.8 (q, *J* = 3.8 Hz CH, C<sub>6</sub>), 108.4 (CH, C<sub>9</sub>), 76.1 (CH, C<sub>10a</sub>), 53.0 (CH, C<sub>α</sub>-Ala), 48.0 (CH<sub>2</sub>, C<sub>3</sub>), 46.7 (CH<sub>2</sub>, C<sub>1</sub>), 21.0 (CH<sub>3</sub>, Tos), 12.3 (CH<sub>3</sub>, CH<sub>3</sub>-Ala); *S*-epimer 170.0 (CONH<sub>2</sub>-Ala), 161.5 (C, C<sub>4</sub>), 143.6 (C, C<sub>9a</sub>), 133.3 (C, Tos), 131.0 (C, Tos),

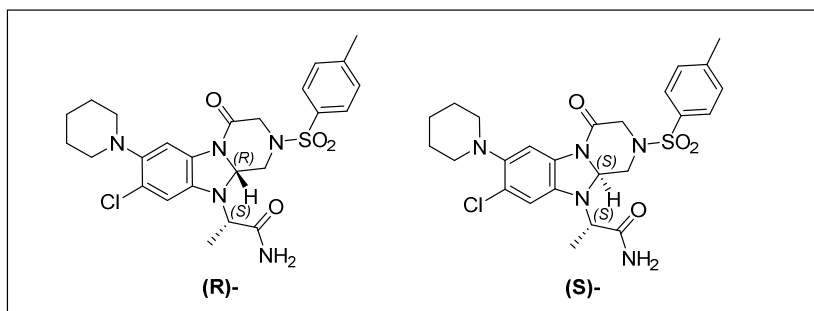
130.1 (2CH, Tos), 127.3 (2CH, Tos), 125.0 (q,  $J = 270.8$  Hz, C, CF<sub>3</sub>), 123.3 (q,  $J = 4.2$  Hz, CH, C<sub>8</sub>), 118.3 (q,  $J = 32$  Hz, CH, C<sub>7</sub>), 110.6 (q,  $J = 3.8$  Hz, CH, C<sub>6</sub>), 107.0 (CH, C<sub>9</sub>), 74.9 (CH, C<sub>10a</sub>), 53.6 (CH, C<sub>α</sub>-Ala), 47.8 (CH<sub>2</sub>, C<sub>3</sub>), 46.9 (CH<sub>2</sub>, C<sub>1</sub>), 21.0 (CH<sub>3</sub>, Tos), 13.1 (CH<sub>3</sub>, CH<sub>3</sub>-Ala). HRMS (ESI-TOF)  $m/z$  calcd for C<sub>21</sub>H<sub>22</sub>F<sub>3</sub>N<sub>4</sub>O<sub>4</sub>S [M + H]<sup>+</sup> 482.1308, found 482.1317.

**(S)-2-((R)-7,8-dichloro-2-((4-nitrophenyl)sulfonyl)-4-oxo-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-10(2H)-yl)propanamide 9(2,2,1,1)**



Yield 21.6 mg (52%) of amorphous solid. Purified by precipitation in MeOH. (*R*):(*S*) ratio of the crude = 65:35. (*R*):(*S*) ratio of the purified product = 90:10. RT = 1.91 min. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 8.38 (d,  $J = 8.9$  Hz, 2H, 4-Nos), 8.13 (d,  $J = 8.9$  Hz, 2H, 4-Nos), 7.59 (s, 1H, 9-H), 7.58 (bs, 1H, NH), 7.31 (bs, 1H, NH), 6.78 (s, 1H, 6-H), 5.68 (dd,  $J = 9.3, 3.6$  Hz, 1H, 10a-H), 4.40 (dd,  $J = 12.1, 3.6$  Hz, 1H, 1-H), 4.29 (d,  $J = 16.9$  Hz, 1H, 3-H), 4.19 (q,  $J = 7.0$  Hz, 1H,  $\alpha$ -H-Ala), 3.73 (d,  $J = 17.0$  Hz, 1H, 3-H), 3.29 (dd,  $J = 12.0, 9.5$  Hz, 1H, 1-H), 1.31 (t,  $J = 8.6$  Hz, 3H, CH<sub>3</sub>-Ala). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  172.5 (C, CONH<sub>2</sub>-Ala), 161.7 (C, C<sub>4</sub>), 150.6 (C, 4-Nos), 142.1 (C, 4-Nos), 141.3 (C, C<sub>9a</sub>), 131.9 (C, C<sub>5a</sub>), 129.5 (2CH, 4-Nos), 126.8 (CH, C<sub>8</sub>), 125.2 (2CH, 4-Nos), 120.2 (C, C<sub>7</sub>), 115.6 (CH, C<sub>9</sub>), 110.4 (CH, C<sub>6</sub>), 76.6 (CH, C<sub>10a</sub>), 53.8 (CH, C<sub>α</sub>-Ala), 48.2 (CH<sub>2</sub>, C<sub>3</sub>), 47.5 (CH<sub>2</sub>, C<sub>1</sub>), 13.7 (CH<sub>3</sub>, CH<sub>3</sub>-Ala). HRMS (ESI-TOF)  $m/z$  calcd for C<sub>19</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>5</sub>O<sub>6</sub>S [M + H]<sup>+</sup> 514.0349, found 514.0346.

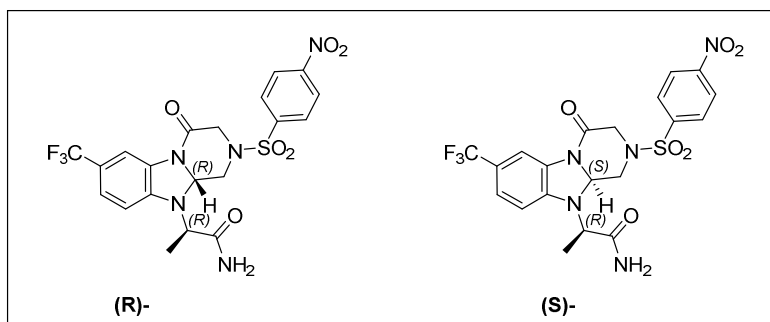
**(S)-2-((R)-8-chloro-4-oxo-7-(piperidin-1-yl)-2-tosyl-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-10(2H)-yl)propanamide 9(2,3,1,2)**



Yield 6.4 mg (32%) of amorphous solid. Purified by semi-preparative HPLC. (*R*):(*S*) ratio of the crude = 66:34. (*R*):(*S*) ratio of the purified product = 62:38. HPLC: RT = 2.54 min. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) (*R*)-epimer (62%) 7.77 (d, *J* = 8.3 Hz, 2H, Tos), 7.54 (bs, 1H, NH), 7.48 (s, 1H, 9-H), 7.44 (d, *J* = 8.3 Hz, 2H, Tos), 7.22 (bs, 1H, NH), 6.39 (s, 1H, 6-H), 5.49 (dd, *J* = 9.5, 3.7 Hz, 1H, 10-H), 4.36 (dd, *J* = 12.0, 3.5 Hz, 1H, 1-H), 4.18 (d, *J* = 17.0 Hz, 1H, 3-H), 4.12 (q, *J* = 6.9 Hz, 1H, α-H-Ala), 3.49 (d, *J* = 17.0 Hz, 1H, 3-H), 3.04 (dd, *J* = 12.0, 9.6 Hz, 1H, 1-H), 2.85 – 2.72 (m, 4H, pip), 2.38 (s, 3H, CH<sub>3</sub>-Tos), 1.65 – 1.56 (m, 4H, pip), 1.54 – 1.41 (m, 2H, pip), 1.25 (d, *J* = 7.0 Hz, 3H, CH<sub>3</sub>-Ala); (*S*)-epimer (38%) 7.72 (d, *J* = 8.3 Hz, 2H, Tos), 7.59 (bs, 1H, NH), 7.49 (s, 1H, 9-H), 7.43 (d, *J* = 8.3 Hz, 2H, Tos), 7.29 (bs, 1H, NH), 6.52 (s, 1H, 6-H), 5.36 (dd, *J* = 9.5, 3.5 Hz, 1H, 10a-H), 4.30 – 4.22 (m, 2H, 1-H and α-H-Ala), 4.16 (d, *J* = 17.0 Hz, 1H, 3-H), 3.56 (d, *J* = 17.0 Hz, 1H, 3-H), 3.01 (dd, *J* = 12.2, 9.6 Hz, 1H, 1-H), 2.84 – 2.72 (m, 4H, pip), 2.37 (s, 3H, CH<sub>3</sub>-Tos), 1.67 – 1.57 (m, 4H, pip), 1.53 – 1.39 (m, 2H, pip), 1.20 (d, *J* = 7.0 Hz, 1H, CH<sub>3</sub>-Ala). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) (*R*)-epimer 172.6 (C, CONH<sub>2</sub>-Ala), 160.7 (C, C<sub>4</sub>), 147.2 (C, C<sub>9a</sub>), 144.2 (C, C<sub>7</sub>), 140.1 (C, Tos), 133.0 (C, Tos), 130.2 (2CH, Tos), 127.5 (C, C<sub>5a</sub>), 127.03 (2CH<sub>2</sub>, Tos), 125.5 (C, C<sub>8</sub>), 116.1 (s, CH, C<sub>9</sub>), 102.7 (CH, C<sub>6</sub>), 76.0 (CH, C<sub>10a</sub>), 53.2 (CH, C<sub>α</sub>-Ala), 52.6 (2CH<sub>2</sub>, pip), 47.9 (CH<sub>2</sub>, C<sub>3</sub>), 46.9 (CH<sub>2</sub>, C<sub>1</sub>), 25.8 (2CH<sub>2</sub>, pip), 23.7 (CH<sub>3</sub>-Tos), 21.1 (CH<sub>2</sub>, pip), 12.0 (CH<sub>3</sub>, CH<sub>3</sub>-Ala); (*S*)-epimer 172.8 (C, CONH<sub>2</sub>-Ala), 160.7 (C, C<sub>4</sub>), 147.5 (C, C<sub>9a</sub>), 144.2 (C, C<sub>7</sub>), 141.4 (C, Tos), 133.4 (C, Tos), 130.2 (2CH, Tos), 128.1 (s, C, C<sub>5a</sub>), 127.3 (2CH<sub>2</sub>, Tos), 126.1 (C, C<sub>8</sub>), 115.9 (CH, C<sub>9</sub>), 101.5 (CH, C<sub>6</sub>), 74.4 (CH, C<sub>10a</sub>), 54.0 (CH, C<sub>α</sub>-Ala), 52.6 (2CH<sub>2</sub>, pip), 47.7 (CH<sub>2</sub>, C<sub>3</sub>), 47.2 (CH<sub>2</sub>, C<sub>1</sub>), 25.8 (2CH<sub>2</sub>, pip), 23.7 (CH<sub>3</sub>-Tos), 21.1 (CH<sub>2</sub>, pip),

12.3 (CH<sub>3</sub>, CH<sub>3</sub>-Ala). HRMS (ESI-TOF)  $m/z$  calcd for C<sub>25</sub>H<sub>31</sub>ClN<sub>5</sub>O<sub>4</sub>S [M + H]<sup>+</sup> 532.1785, found 532.1882.

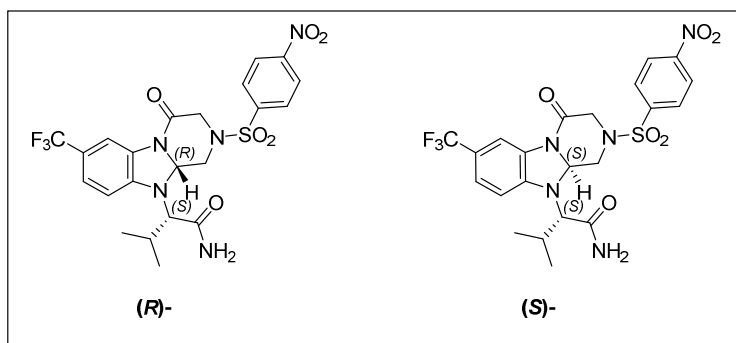
**(*R*)-2-((*RS*)-2-((4-nitrophenyl)sulfonyl)-4-oxo-7-(trifluoromethyl)-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)propanamide 9(3,1,1,1)**



Yield 46.7 mg (55%) of amorphous solid. Purified by precipitation in MeOH. (*R*):(*S*) ratio of the crude = 57:43. (*R*):(*S*) ratio of the purified product = 54:46. HPLC: RT = 1.88 min. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) (*R*)-epimer (54%) 8.38 (d, *J* = 8.8 Hz, 2H, 4-Nos), 8.15 (d, *J* = 8.9 Hz, 2H, 4-Nos), 7.70 (d, *J* = 1.6 Hz, 1H, 6-H), 7.53 (bs, 1H, NH), 7.28 – 7.22 (m, 2H, 8-H and NH), 6.62 (d, *J* = 8.3 Hz, 1H, 9-H), 5.67 (dd, *J* = 9.4, 3.6 Hz, 1H, 10a-H), 4.43 (dd, *J* = 12.0, 3.5 Hz, 1H, 1-H), 4.29 (d, *J* = 16.5 Hz, 1H, 3-H), 4.23 (q, *J* = 7.3 Hz, 1H, α-H-Ala), 3.70 (d, *J* = 17.0 Hz, 1H, 3-H), 3.30 (dd, *J* = 12.1, 9.6 Hz, 1H, 1-H), 1.31 (d, *J* = 7.2 Hz, 3H, CH<sub>3</sub>-Ala); (*S*)-epimer (46%) 8.39 (d, *J* = 8.8 Hz, 2H, 4-Nos), 8.14 (d, *J* = 8.9 Hz, 2H, 4-Nos), 7.72 (d, *J* = 1.6 Hz, 1H, 6-H), 7.66 (bs, 1H, NH), 7.36 (bs, 1H, NH), 7.32 – 7.26 (m, 1H, 8-H), 6.74 (d, *J* = 8.3 Hz, 1H, 9-H), 5.60 (dd, *J* = 9.2, 3.6 Hz, 1H, 10a-H), 4.36 (dd, *J* = 12.4, 3.4 Hz, 1H, 1-H), 4.32 (d, *J* = 16.0 Hz, 1H, 3-H), 4.31 (q, *J* = 7.0 Hz, 1H, α-H-Ala), 3.80 (d, *J* = 17.0 Hz, 1H, 3-H), 3.37 (dd, *J* = 12.5, 9.3 Hz, 1H, 1-H), 1.33 (d, *J* = 7.3 Hz, 3H, CH<sub>3</sub>-Ala). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) (*R*)-epimer 172.2 (C, CONH<sub>2</sub>-Ala), 161.4 (C, C<sub>4</sub>), 150.1 (C, 4-Nos), 144.4 (C, C<sub>9a</sub>), 141.9 (C, 4-Nos), 130.9 (C, C<sub>6a</sub>), 129.0 (2CH, 4-Nos), 124.8 (2CH, 4-Nos), 124.6 (q, *J* = 270.5 Hz, C, CF<sub>3</sub>), 122.9 (q, *J* = 4.4 Hz, CH, C<sub>8</sub>), 118.5 (q, *J* = 32.0 Hz, C, C<sub>7</sub>), 110.5 (d, *J* = 3.8 Hz, CH, C<sub>6</sub>), 107.0 (CH, C<sub>9</sub>), 74.8 (CH, C<sub>10a</sub>), 53.7 (CH, C<sub>α</sub>-Ala), 47.8 (CH<sub>2</sub>, C<sub>3</sub>), 46.9 (CH<sub>2</sub>, C<sub>1</sub>), 13.3 (CH<sub>3</sub>, CH<sub>3</sub>-Ala); (*S*)-epimer 172.1 (C, CONH<sub>2</sub>-Ala), 161.3 (C,

C<sub>4</sub>), 150.2 (C, 4-Nos), 143.6 (C, C<sub>9a</sub>), 141.7 (C, 4-Nos), 131.8 (C, C<sub>6a</sub>), 129.1 (2CH, 4-Nos), 124.8 (2CH, 4-Nos), 124.6 (q,  $J = 270.8$  Hz, C, CF<sub>3</sub>), 122.9 (q,  $J = 4.2$  Hz, CH, C<sub>8</sub>), 118.9 (q,  $J = 32.0$  Hz, C, C<sub>7</sub>), 110.7 (q,  $J = 3.6$  Hz, CH, C<sub>6</sub>), 108.4 (CH, C<sub>9</sub>), 75.9 (CH, C<sub>10a</sub>), 53.1 (CH, C<sub>α</sub>-Ala), 47.8 (CH<sub>2</sub>, C<sub>3</sub>), 47.0 (CH<sub>2</sub>, C<sub>1</sub>), 12.8 (CH<sub>3</sub>, CH<sub>3</sub>-Ala). HRMS (ESI-TOF)  $m/z$  calcd for C<sub>20</sub>H<sub>19</sub>F<sub>3</sub>N<sub>5</sub>O<sub>6</sub>S [M + H]<sup>+</sup> 514.1003, found 514.1017.

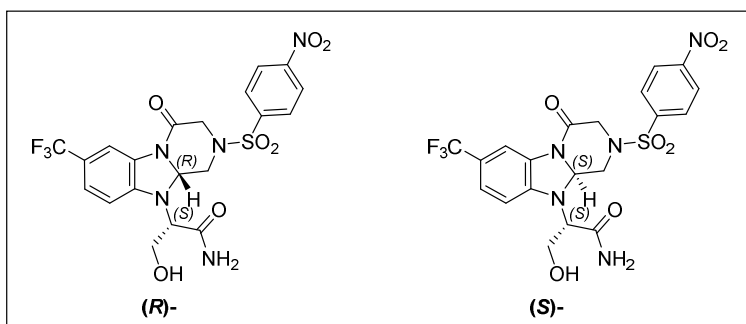
**(S)-3-methyl-2-((RS)-2-((4-nitrophenyl)sulfonyl)-4-oxo-7-(trifluoromethyl)-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-10(2H)-yl)butanamide 9(4,1,1,1)**



Yield 82.9 mg (86%) of amorphous solid. Purified by semi-preparative HPLC. (*R*):(*S*) ratio of the crude = 65:35. (*R*):(*S*) ratio of the purified product = 63:37. HPLC: RT = 2.20 min. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) (*R*)-epimer (63%) 8.42 (d,  $J = 8.8$  Hz, 2H, 4-Nos), 8.18 (d,  $J = 8.8$  Hz, 2H, 4-Nos), 7.79 (bs, 1H, NH), 7.76 (d,  $J = 2.1$  Hz, 1H, 6-H), 7.40 (bs, 1H, NH), 7.28 (d,  $J = 8.5$  Hz, 1H, 8-H), 7.00 (d,  $J = 8.3$  Hz, 1H, 9-H), 5.57 (dd,  $J = 9.4, 3.4$  Hz, 1H, 10a-H), 4.65 (dd,  $J = 11.9, 3.8$  Hz, 1H, 1-H), 4.28 (d,  $J = 17.0$  Hz, 1H, 3-H), 3.79 (d,  $J = 17.1$  Hz, 1H, 3-H), 3.72 (d,  $J = 11.0$  Hz, 1H,  $\alpha$ -H-Val), 3.40 – 3.32 (m, 1H, 1-H), 2.22 – 2.10 (m, 2H,  $\beta$ -H-Val), 0.97 (d,  $J = 6.7$  Hz, 3H,  $\gamma$ -CH<sub>3</sub>-Val), 0.90 (d,  $J = 6.6$  Hz, 3H,  $\gamma$ -CH<sub>3</sub>-Val); (*S*)-epimer (37%) 8.41 (d,  $J = 8.8$  Hz, 2H, 2-H), 8.13 (d,  $J = 8.8$  Hz, 2H, 2-H), 7.85 (bs, 1H, NH), 7.76 (d,  $J = 2.7$  Hz, 1H, 6-H), 7.34 (bs, 1H, NH), 7.25 (d,  $J = 8.8$  Hz, 1H, 8-H), 7.00 (d,  $J = 8.3$  Hz, 1H, 9-H), 5.52 (dd,  $J = 9.4, 3.4$  Hz, 1H, 10a-H), 4.65 (dd,  $J = 12.1, 4.5$  Hz, 1H, 1-H), 4.29 (d,  $J = 16.8$  Hz, 1H, 3-H), 3.79 (d,  $J = 16.8$  Hz, 1H, 3-H), 3.70 (d,  $J = 10.8$  Hz, 1H,  $\alpha$ -H-Val), 3.21 (dd,  $J = 12.1, 9.5$  Hz, 1H, 1-H), 2.36 – 2.26 (m, 1H,  $\beta$ -H-Val), 0.95 (d,  $J = 7.0$  Hz, 3H,  $\gamma$ -CH<sub>3</sub>-Val), 0.76 (d,  $J = 6.6$  Hz, 1H,  $\gamma$ -CH<sub>3</sub>-Val). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm)

(R)-epimer 170.3 (C, CONH<sub>2</sub>-Val), 161.6 (C, C<sub>4</sub>), 150.7 (C, 4-Nos), 144.9 (C, C<sub>9a</sub>), 142.6 (C, 4-Nos), 131.3 (C, C<sub>6a</sub>), 129.5 (2CH, 4-Nos), 125.3 (2CH, 4-Nos), 125.1 (q, *J* = 270.8 Hz, C, CF<sub>3</sub>), 123.4 (q, *J* = 4.2 Hz, CH, C<sub>8</sub>), 118.9 (q, *J* = 32.0 Hz, C, C<sub>7</sub>), 111.2 (q, *J* = 3.6 Hz, CH, C<sub>6</sub>), 108.0 (CH, C<sub>9</sub>), 76.8 (CH, C<sub>10a</sub>), 65.3 (CH, C<sub>α</sub>-Val), 48.0 (CH<sub>2</sub>, C<sub>3</sub>), 47.0 (CH<sub>2</sub>, C<sub>1</sub>), 28.9 (CH, C<sub>β</sub>-Val), 19.8 (2CH<sub>3</sub>, CH<sub>3</sub>-Val), 19.4 (s); (S)-epimer 171.3 (C, CONH<sub>2</sub>-Val), 161.9 (C, C<sub>4</sub>), 150.7 (C, 4-Nos), 144.5 (C, C<sub>9a</sub>), 142.5 (C, 4-Nos), 130.8 (C, C<sub>6a</sub>), 129.5 (2CH, 4-Nos), 125.3 (2CH, 4-Nos), 125.1 (q, *J* = 270.8 Hz, C, CF<sub>3</sub>), 123.3 (q, *J* = 4.2 Hz, CH, C<sub>8</sub>), 118.6 (q, *J* = 32.0 Hz, C, C<sub>7</sub>), 111.0 (q, *J* = 3.6 Hz, CH, C<sub>6</sub>), 108.4 (CH, C<sub>9</sub>), 75.35 (CH, C<sub>10a</sub>), 65.5 (CH, C<sub>α</sub>-Val), 48.2 (CH<sub>2</sub>, C<sub>3</sub>), 47.4 (CH<sub>2</sub>, C<sub>1</sub>), 26.73 (CH, C<sub>β</sub>-Val), 20.05 (2CH<sub>3</sub>, CH<sub>3</sub>-Val), 19.98 (s). HRMS (ESI-TOF) *m/z* calcd for C<sub>22</sub>H<sub>23</sub>F<sub>3</sub>N<sub>5</sub>O<sub>6</sub>S [M + H]<sup>+</sup> 542.1316, found 542.1302.

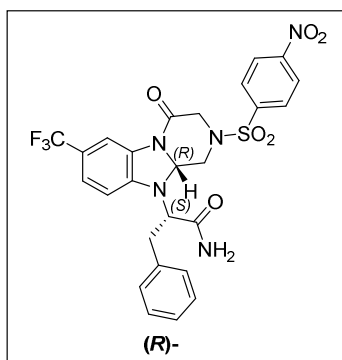
**(S)-3-hydroxy-2-((RS)-2-((4-nitrophenyl)sulfonyl)-4-oxo-7-(trifluoromethyl)-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-10(2H)-yl)propanamide 9(5,1,1,1)**



Yield 16.8 mg (27%) of amorphous solid. Purified by precipitation in MeOH. (*R*):(*S*) ratio of the crude = 47:53. (*R*):(*S*) ratio of the purified product = 55:45. HPLC: RT = 1.78 min. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) (R)-epimer (45%) 8.39 (d, *J* = 9.0 Hz, 2H, 4-Nos), 8.17 (d, *J* = 9.0 Hz, 2H, 4-Nos), 7.74 (d, *J* = 1.9 Hz, 1H, 6-H), 7.62 (bs, 1H, NH), 7.33 (bs, 1H, NH), 7.29 – 7.25 (m, 1H, 8-H), 6.67 (d, *J* = 8.3 Hz, 1H, 9-H), 5.84 (dd, *J* = 9.3, 3.5 Hz, 1H, 10a-H), 4.58 (dd, *J* = 12.1, 3.5 Hz, 1H, 1-H), 4.33 (d, *J* = 17.0 Hz, 1H, 3-H), 4.29 (dd, *J* = 7.4, 4.2 Hz, 1H, α-H-Ser), 3.99 – 3.79 (m, 2H, β-H-Ser), 3.75 (d, *J* = 17.0 Hz, 1H, 3-H), 3.41 (dd, *J* = 12.4, 9.3 Hz, 1H, 1-H); (S)-epimer (55%) 8.41 (d, *J* = 9.0 Hz, 2H, 4-Nos), 8.13 (d, *J* = 8.7 Hz, 2H, 4-

Nos), 7.72 (d,  $J = 1.8$  Hz, 1H, 6-H), 7.68 (bs, 1H, NH), 7.36 (bs, 1H, NH), 7.29 – 7.22 (m, 1H, 8-H), 6.73 (d,  $J = 8.3$  Hz, 1H, 9-H), 5.67 (dd,  $J = 9.2, 3.5$  Hz, 1H, 10a-H), 4.46 (dd,  $J = 12.4, 3.6$  Hz, 1H, 1-H), 4.32 (d,  $J = 16.9$  Hz, 1H, 3-H), 4.25 (dd,  $J = 8.2, 5.0$  Hz, 1H,  $\alpha$ -H-Ser), 3.97 – 3.86 (m, 2H,  $\beta$ -H-Ser), 3.82 (d,  $J = 17.0$  Hz, 1H, 3-H), 3.33 (dd,  $J = 12.1, 9.4$  Hz, 2H, 1-H).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  (ppm) (*R*)-*epimer* 170.0, 161.3, 150.1, 144.3, 142.0, 131.6, 129.0, 124.8, 124.7 (q,  $J=270.0$  Hz), 122.8 - 123.0 (m), 118.2 (q,  $J=32.0$  Hz), 110.6 (q,  $J=4.2$  Hz), 107.9, 77.0, 59.5, 58.6, 47.8, 46.6 (*S*)-*epimer* 170.4, 161.3, 150.1, 145.0, 142.1, 130.5, 128.9, 124.6 (q,  $J=270.0$  Hz), 122.7 - 123.1 (m), 118.5 (q,  $J=32.0$  Hz), 110.5 (q,  $J=4.2$  Hz), 106.6, 75.2, 60.3, 57.9, 47.8, 47.0. HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_5\text{O}_7\text{S}$  [ $\text{M} + \text{H}$ ] $^+$  530.0952, found 530.0964.

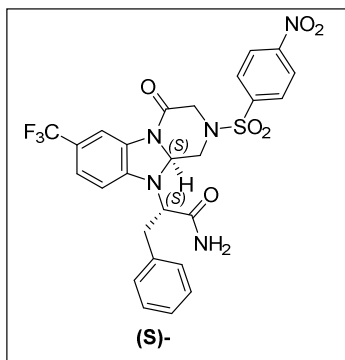
**(*S*)-2-((*R*)-2-((4-nitrophenyl)sulfonyl)-4-oxo-7-(trifluoromethyl)-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)-3-phenylpropanamide 9(6,1,1,1)**



Yield 11.9 mg (20%) of amorphous solid. Purified by semi-preparative HPLC. (*R*):(*S*) ratio of the crude = 64:34. HPLC: RT = 2.37 min.  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 8.42 (d,  $J = 9.0$  Hz, 2H), 8.12 (d,  $J = 9.0$  Hz, 2H), 7.72 (d,  $J = 1.9$  Hz, 1H), 7.61 (s, 1H), 7.35 (s, 1H), 7.33 – 7.15 (m, 6H), 6.96 (d,  $J = 8.3$  Hz, 1H), 5.30 (dd,  $J = 9.3, 3.6$  Hz, 1H), 4.52 (dd,  $J = 12.1, 3.6$  Hz, 1H), 4.44 (t,  $J = 7.7$  Hz, 1H), 4.26 (d,  $J = 17.0$  Hz, 1H), 3.68 (d,  $J = 17.0$  Hz, 1H), 3.31 (dd,  $J = 13.9, 6.6$  Hz, 1H), 3.22 (dd,  $J = 12.0, 9.5$  Hz, 1H), 3.04 (dd,  $J = 13.9, 7.9$  Hz, 1H).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 170.7, 161.6, 150.7, 143.9, 142.2, 137.9, 131.9, 129.5, 129.0, 129.0, 127.0, 125.24, 125.0 (q,  $J = 270.7$  Hz) 123.3 (q,  $J = 4.2$  Hz), 119.1 (q,  $J = 31.9$

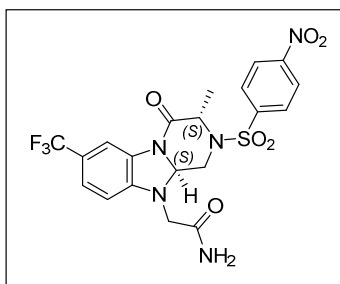
Hz), 111.1 (q,  $J = 3.6$  Hz), 109.0, 76.9, 59.7, 48.1, 46.8, 34.1. HRMS (ESI-TOF)  $m/z$  calcd for  $C_{26}H_{22}F_3N_5NaO_6S$   $[M + Na]^+$  612.1135, found 612.1135.

**(S)-2-((S)-2-((4-nitrophenyl)sulfonyl)-4-oxo-7-(trifluoromethyl)-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-10(2H)-yl)-3-phenylpropanamide 9(6,1,1,1)**



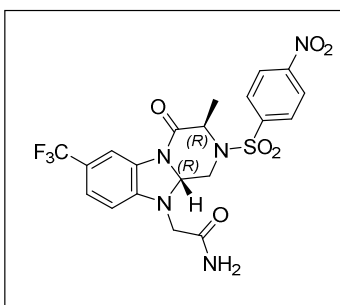
Yield 3 mg (12%) of amorphous solid. Purified by semi-preparative HPLC. (*R*):(*S*) ratio of the crude = 64:36. HPLC: RT = 2.32 min.  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 8.41 (d,  $J = 9.0$  Hz, 2H), 7.97 (d,  $J = 9.0$  Hz, 2H), 7.67 (d,  $J = 1.9$  Hz, 1H), 7.64 (s, 1H), 7.38 (s, 1H), 7.30 – 7.22 (m, 3H), 7.20 – 7.10 (m, 3H), 6.86 (d,  $J = 8.3$  Hz, 1H), 5.60 (dd,  $J = 9.2, 3.5$  Hz, 1H), 4.40 (dd,  $J = 8.9, 6.9$  Hz, 1H), 4.19 (d,  $J = 16.9$  Hz, 1H), 4.05 (dd,  $J = 11.9, 3.4$  Hz, 1H), 3.62 (d,  $J = 16.9$  Hz, 1H), 3.22 (dd,  $J = 13.7, 6.6$  Hz, 1H), 2.91 (dd,  $J = 13.6, 9.0$  Hz, 1H).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 170.7, 161.5, 150.62, 144.0, 141.7, 138.2, 131.3, 129.6, 129.4, 128.8, 127.0, 125.23, 123.5 – 123.2 (m), 111.0 – 110.5 (m), 108.1, 76.0, 60.5, 48.1, 46.7, 33.7. HRMS (ESI-TOF)  $m/z$  calcd for  $C_{26}H_{23}F_3N_5O_6S$   $[M + H]^+$  590.1316, found 590.1297.

**2-((3S,10aS)-3-methyl-2-((4-nitrophenyl)sulfonyl)-4-oxo-7-(trifluoromethyl)-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-10(2H)-yl)acetamide 9(1,1,2,1)**



Yield 10 mg (19.5%) of amorphous solid. Purified by semi-preparative HPLC. HPLC: RT =1.78 min;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  (ppm) 8.27 (d,  $J$  = 8.9 Hz, 2H, 4-Nos), 8.09 (d,  $J$  = 8.7 Hz, 2H, 4-Nos), 7.60 (bs, 1H, NH), 7.54 (d,  $J$  = 1.7 Hz, 1H, 6-H), 7.28 (bs, 1H, NH), 7.23 (d,  $J$  = 8.0 Hz, 1H, 8-H), 6.59 (d,  $J$  = 8.2 Hz, 1H, 9-H), 5.79 (dd,  $J$  = 7.8, 4.0 Hz, 1H, 10a-H), 4.29 (dd,  $J$  = 11.3, 3.7 Hz, 1H, 1-H), 4.22 (q,  $J$  = 7.1 Hz, 1H, 3-H), 4.01 (q,  $J$  = 17.4 Hz, 2H,  $\alpha$ -Gly), 3.48 (dd,  $J$  = 11.6, 8.0 Hz, 1H, 1-H), 1.54 (d,  $J$  = 7.2 Hz, 3H, 3- $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  (ppm) 170.1 (C, CONH-Gly), 164.8 (C,  $\text{C}_4$ ), 150.3 (C, 4-Nos), 145.6 (C,  $\text{C}_{9a}$ ), 141.9 (C, 4-Nos), 130.8 (C,  $\text{C}_{6a}$ ), 129.5 (2CH, 4-Nos), 125.0 (q,  $J$  = 270.6 Hz, C,  $\text{CF}_3$ ), 124.9 (2CH, 4-Nos), 118.5 (q,  $J$  = 31.9 Hz, C,  $\text{C}_7$ ), 110.6 (q,  $J$  = 4.3 Hz, CH,  $\text{C}_6$ ), 106.4 (CH,  $\text{C}_9$ ), 76.1 (CH,  $\text{C}_{10a}$ ), 55.8 (CH,  $\text{C}_3$ ), 47.6 ( $\text{CH}_2$ ,  $\text{C}_\alpha$ -Gly), 47.1 ( $\text{CH}_2$ ,  $\text{C}_1$ ), 19.6 ( $\text{CH}_3$ , 3- $\text{CH}_3$ ); HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_5\text{O}_6\text{S}$  [ $\text{M} + \text{H}$ ] $^+$  514.1003, found 514.1011.

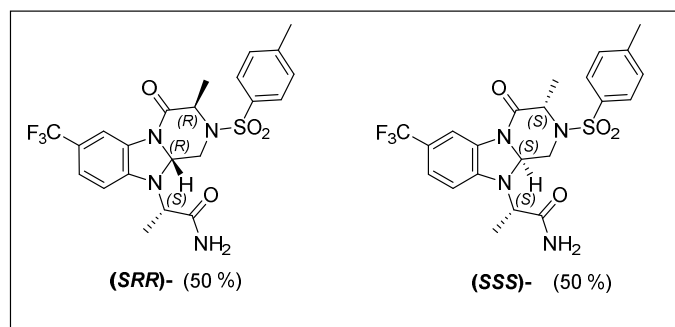
**2-((3*R*,10a*R*)-3-methyl-2-((4-nitrophenyl)sulfonyl)-4-oxo-7-(trifluoromethyl)-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)acetamide 9(1,1,3,1)**



Yield 13 mg (21%) of amorphous solid. Purified by semi-preparative HPLC. HPLC: RT =1.76 min;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  (ppm) 8.27 (d,  $J$  = 8.9 Hz, 2H, 4-Nos), 8.09 (d,  $J$  = 8.9 Hz, 2H, 4-Nos), 7.60 (bs, 1H, NH), 7.54 (d,  $J$  = 1.7 Hz, 1H, 6-H), 7.28 (bs, 1H, NH), 7.23 (d,  $J$

= 7.7 Hz, 1H, 8-H), 6.59 (d,  $J$  = 8.2 Hz, 1H, 9-H), 5.79 (dd,  $J$  = 7.8, 4.0 Hz, 1H, 10a-H), 4.29 (dd,  $J$  = 11.6, 4.0 Hz, 1H, 1-H), 4.21 (q,  $J$  = 7.1 Hz, 1H, 3-H), 4.01 (q,  $J$  = 17.4 Hz, 2H,  $\alpha$ -Gly), 3.48 (dd,  $J$  = 11.6, 7.9 Hz, 1H, 1-H), 1.54 (d,  $J$  = 7.2 Hz, 1H, 3-CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 170.1 (C, CONH-Gly), 164.8 (C, C<sub>4</sub>), 150.3 (C, 4-Nos), 145.6 (C, C<sub>9a</sub>), 141.9 (C, 4-Nos), 130.8 (C, C<sub>6a</sub>), 129.5 (2CH, 4-Nos), 125.0 (q,  $J$  = 270.6 Hz, C, CF<sub>3</sub>), 124.9 (2CH, 4-Nos), 118.5 (q,  $J$  = 31.9 Hz, C, C<sub>7</sub>), 110.5 (q,  $J$  = 4.3 Hz, CH, C<sub>6</sub>), 106.4 (CH, C<sub>9</sub>), 76.1 (CH, C<sub>10a</sub>), 55.81 (CH, C<sub>3</sub>), 47.56 (CH<sub>2</sub>, C $\alpha$ -Gly), 47.09 (CH<sub>2</sub>, C<sub>1</sub>), 19.59 (CH<sub>3</sub>, 3-CH<sub>3</sub>). HRMS (ESI-TOF)  $m/z$  calcd for C<sub>20</sub>H<sub>19</sub>F<sub>3</sub>N<sub>5</sub>O<sub>6</sub>S [M + H]<sup>+</sup> 514.1003, found 514.0991.

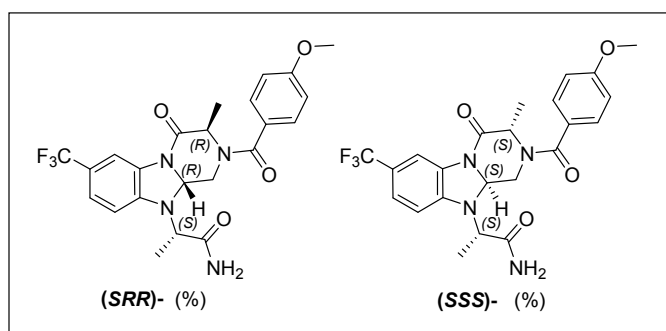
**(S)-2-((3*R*,10a*R*)-3-methyl-4-oxo-2-tosyl-7-(trifluoromethyl)-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)propanamide 9(2,1,3,2) and (S)-2-((3*S*,10a*S*)-3-methyl-4-oxo-2-tosyl-7-(trifluoromethyl)-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)propanamide 9(2,1,2,2)**



Yield 18.5 mg (27%) of amorphous solid. Purified by semi-preparative HPLC. (*R*):(*S*) ratio of the crude = 58:42. (*R*):(*S*) ratio of the purified product = 50:50. HPLC: RT =2.20 min; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) (SRR)-epimer (50%) 7.72 (d,  $J$  = 8.3 Hz, 2H, Tos), 7.63 (d,  $J$  = 1.9 Hz, 1H, 6-H), 7.58 (s, 1H, NH), 7.37 (d,  $J$  = 8.5, 2H, Tos), 7.28 – 7.24 (m, 2H, 8-H and NH), 6.56 (d,  $J$  = 8.2 Hz, 1H, 9-H), 5.95 (dd,  $J$  = 9.0, 3.5 Hz, 1H, 10a-H), 4.31 (q,  $J$  = 7.2 Hz, 1H,  $\alpha$ -H-Ala), 4.25 (dd,  $J$  = 10.8, 3.4 Hz, 1H, 1-H), 4.04 (d,  $J$  = 7.1 Hz, 1H, 3-H), 3.26 (dd,  $J$  = 11.1, 8.1 Hz, 1H, 1-H), 2.32 (s, 1H, CH<sub>3</sub>-Tos), 1.54 (d,  $J$  = 7.2 Hz, 3H, 3-CH<sub>3</sub>), 1.35 (d,  $J$  = 7.1 Hz, 3H, CH<sub>3</sub>-Ala); (SSS)-epimer (50%) 7.67 (d,  $J$  = 8.3 Hz, 2H, Tos), 7.60 (d,  $J$  = 1.9 Hz, 1H, 6-H), 7.58 (s, 1H, NH), 7.32 (d,  $J$  = 8.6, 2H, Tos), 7.28 – 7.24 (m, 2H, 8-H and NH), 6.64

(d,  $J = 8.3$  Hz, 1H, 9-H), 5.92 (dd,  $J = 8.6, 3.6$  Hz, 1H, 10a-H), 4.27 (d,  $J = 7.2$  Hz, 1H,  $\alpha$ -H-Ala), 4.17 (dd,  $J = 11.3, 3.6$  Hz, 1H, 1-H), 4.06 (q,  $J = 7.1$  Hz, 1H, 3-H), 3.24 (dd,  $J = 10.8, 7.7$  Hz, 1H, 1-H), 1.53 (q,  $J = 7.1$  Hz, 3H, 3-CH<sub>3</sub>), 1.35 (d,  $J = 7.1$  Hz, 3H, CH<sub>3</sub>-Ala); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) (SRR)-epimer 172.5 (C, CONH<sub>2</sub>-Ala), 164.9 (C, C<sub>4</sub>), 144.4 (C, C<sub>9a</sub>), 133.4 (C, Tos), 131.0 (C, Tos), 130.4 (2CH, Tos), 127.8 (2CH, Tos), 125.0 (q,  $J = 270.8$  Hz, C, CF<sub>3</sub>), 123.2 (d,  $J = 4.2$  Hz, CH, C<sub>8</sub>), 119.1 (q,  $J = 32$  Hz, CH, C<sub>7</sub>), 110.6 (q,  $J = 3.8$  Hz, CH, C<sub>6</sub>), 108.9 (CH, C<sub>9</sub>), 75.4 (CH, C<sub>10a</sub>), 55.8 (CH, C<sub>3</sub>), 54.3 (CH, C $\alpha$ -Ala), 48.9 (CH<sub>2</sub>, C<sub>1</sub>), 21.4 (CH<sub>3</sub>, Tos), 20.8 (CH<sub>3</sub>, 3-CH<sub>3</sub>), 13.0 (CH<sub>3</sub>, CH<sub>3</sub>-Ala); (SSS)-epimer 172.6 (C, CONH<sub>2</sub>-Ala), 165.0 (C, C<sub>4</sub>), 144.5 (C, C<sub>9a</sub>), 133.5 (C, Tos), 132.1 (C, Tos), 130.5 (2CH, Tos), 127.9 (2CH, Tos), 125.1 (q,  $J = 270.8$  Hz, C, CF<sub>3</sub>), 123.4 (d,  $J = 4.2$  Hz, CH, C<sub>8</sub>), 118.4 (q,  $J = 32$  Hz, CH, C<sub>7</sub>), 110.7 (q,  $J = 3.8$  Hz, CH, C<sub>6</sub>), 107.0 (CH, C<sub>9</sub>), 74.0 (CH, C<sub>10a</sub>), 55.6 (CH, C<sub>3</sub>), 55.8 (CH, C $\alpha$ -Ala), 48.9 (CH<sub>2</sub>, C<sub>1</sub>), 21.4 (CH<sub>3</sub>, Tos), 20.2 (CH<sub>3</sub>, 3-CH<sub>3</sub>), 14.0 (CH<sub>3</sub>, CH<sub>3</sub>-Ala); HRMS (ESI-TOF)  $m/z$  calcd for C<sub>22</sub>H<sub>24</sub>F<sub>3</sub>N<sub>4</sub>O<sub>4</sub>S [M + H]<sup>+</sup> 497.1465, found 497.1443.

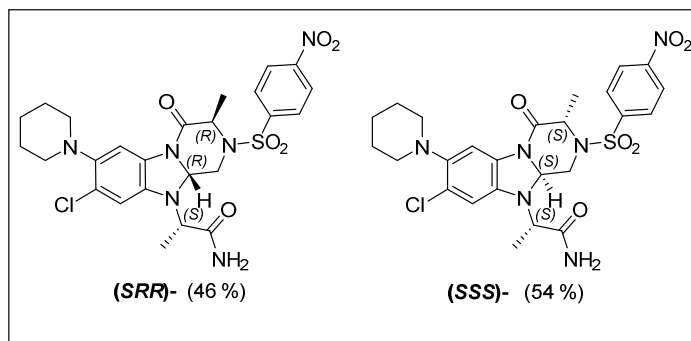
**(S)-2-((3*R*,10*aR*)-2-(4-methoxybenzoyl)-3-methyl-4-oxo-7-(trifluoromethyl)-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)propanamide 9(2,1,3,4) and (S)-2-((3*S*,10*aS*)-2-(4-methoxybenzoyl)-3-methyl-4-oxo-7-(trifluoromethyl)-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)propanamide 9(2,1,2,4)**



Yield 13 mg (35%) of amorphous solid. Purified by semi-preparative HPLC. (*R*):(*S*) ratio of the crude = 55:45. (*R*):(*S*) ratio of the purified product = 37:63. HPLC: RT = 1.57 min; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) (SRR)-epimer (37%) 7.83 (d,  $J = 2.5$  Hz, 1H, 6-H), 7.55 (s, 1H, NH), 7.47 (d,  $J = 8.8$  Hz, 2H, CO-Ph-OMe), 7.31 (d,  $J = 8.2$  Hz, 1H, 8-H), 7.26 (s, 1H, NH),

7.00 (d,  $J = 8.9$  Hz, 2H, CO-Ph-OMe), 6.63 (d,  $J = 8.2$  Hz, 1H, 9-H), 6.12 (dd,  $J = 9.6, 3.5$  Hz, 1H, 10a-H), 4.59 (q,  $J = 7.0$  Hz, 1H, 3-H), 4.28 – 4.12 (m, 2H, 1-H and  $\alpha$ -H-Ala), 3.81 (s, 3H, CO-Ph-OMe), 3.75 (dd,  $J = 11.7, 9.7$  Hz, 1H, 1-H), 1.50 (d,  $J = 6.9$  Hz, 3H, 3-CH<sub>3</sub>), 1.32 (d,  $J = 7.1$  Hz, 3H, CH<sub>3</sub>-Ala); (SSS)-epimer (63%) 7.83 (d,  $J = 2.1$  Hz, 1H, 6-H), 7.54 (s, 1H, NH), 7.47 (d,  $J = 8.8$  Hz, 1H, CO-Ph-OMe), 7.31 (d,  $J = 8.2$  Hz, 1H, 8-H), 7.21 (s, 1H, NH), 6.99 (d,  $J = 8.9$  Hz, 2H, CO-Ph-OMe), 6.66 (d,  $J = 8.2$  Hz, 2H, 9-H), 6.04 (dd,  $J = 9.9, 3.1$  Hz, 1H, 10a-H), 4.55 (q,  $J = 7.6$  Hz, 1H, 3-H), 4.24 (q,  $J = 7.2$  Hz, 1H,  $\alpha$ -H-Ala), 4.21 (dd,  $J = 11.4, 3.6$  Hz, 1H, 1-H), 3.81 (s, 3H, CO-Ph-OMe), 3.65 (dd,  $J = 11.8, 9.9$  Hz, 1H, 1-H), 1.51 (d,  $J = 7.0$  Hz, 3H, 3-CH<sub>3</sub>), 1.32 (d,  $J = 7.1$  Hz, 3H, CH<sub>3</sub>-Ala); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) (SRR)-epimer 172.8 (C, CONH<sub>2</sub>-Ala), 170.1 (C, C<sub>4</sub>), 166.2 (C, CO-Ph-OMe), 160.8 (C, CO-Ph-OMe), 144.7 (C, C<sub>9a</sub>), 132.4 (C, C<sub>5a</sub>), 128.4 (2CH, CO-Ph-OMe), 125.1 (q,  $J = 270.7$  Hz, C, CF<sub>3</sub>), 123.1 (q,  $J = 4.6$  Hz, CH, C<sub>8</sub>), 119.3 (q,  $J = 31.9$  Hz, C, C<sub>7</sub>), 114.1 (2CH, CO-Ph-OMe), 110.5 (q,  $J = 4.1$  Hz, CH, C<sub>6</sub>), 108.8 (CH, C<sub>9</sub>), 75.4 (CH, C<sub>10a</sub>), 55.7 (CH<sub>3</sub>, CO-Ph-OMe), 55.1 (CH, C<sub>3</sub>), 54.3 (CH, C $\alpha$ -Ala), 50.6 (CH<sub>2</sub>, C<sub>1</sub>), 18.5 (CH<sub>3</sub>, 3-CH<sub>3</sub>), 13.9 (CH<sub>3</sub>, CH<sub>3</sub>-Ala); (SSS)-epimer 172.3 (C, CONH<sub>2</sub>-Ala), 170.1 (C, C<sub>4</sub>), 166.3 (C, CO-Ph-OMe), 160.8 (C, CO-Ph-OMe), 144.9 (C, C<sub>9a</sub>), 131.5 (C, C<sub>5a</sub>), 129.4 (2CH, CO-Ph-OMe), 125.2 (d,  $J = 270.5$  Hz, C, CF<sub>3</sub>), 123.3 (q,  $J = 4.2$  Hz, CH, C<sub>8</sub>), 118.5 (q,  $J = 32.2$  Hz, C, C<sub>7</sub>), 114.1 (2CH, CO-Ph-OMe), 110.4 (q,  $J = 4.3$  Hz, CH, C<sub>6</sub>), 107.0 (CH, C<sub>9</sub>), 74.6 (CH, C<sub>10a</sub>), 55.7 (CH<sub>3</sub>, CO-Ph-OMe), 55.2 (CH, C<sub>3</sub>), 54.3 (CH, C $\alpha$ -Ala), 50.6 (CH<sub>2</sub>, C<sub>1</sub>), 18.6 (CH<sub>3</sub>, 3-CH<sub>3</sub>), 14.3 (CH<sub>3</sub>, CH<sub>3</sub>-Ala); HRMS (ESI-TOF)  $m/z$  calcd for C<sub>23</sub>H<sub>24</sub>F<sub>3</sub>N<sub>4</sub>O<sub>4</sub> [M + H]<sup>+</sup> 477.1744, found 477.1734.

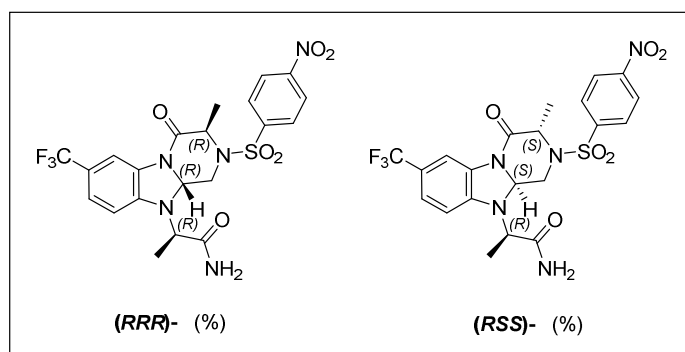
**(S)-2-((3*R*,10a*R*)-8-chloro-3-methyl-2-((4-nitrophenyl)sulfonyl)-4-oxo-7-(piperidin-1-yl)-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)propanamide 9(2,3,3,1) and (S)-2-((3*S*,10a*S*)-8-chloro-3-methyl-2-((4-nitrophenyl)sulfonyl)-4-oxo-7-(piperidin-1-yl)-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)propanamide 9(2,3,2,1)**



Yield 30 mg (58%) of amorphous solid. Purified by semi-preparative HPLC. (*R*):(*S*) ratio of the crude = 52:47. (*R*):(*S*) ratio of the purified product = 58:42. HPLC: RT = 2.44 min; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) (*SSS*)- epimer (54%) 8.22 (d, *J* = 8.9 Hz, 2H, 4-Nos), 8.01 (d, *J* = 8.9 Hz, 2H, 4-Nos), 7.69 (s, 1H, NH), 7.35 (s, 1H, 9-H), 7.28 (s, 1H, NH), 6.40 (s, 1H, 6-H), 5.73 (dd, *J* = 7.6, 4.2 Hz, 1H, 10a-H), 4.30- 4.08 (m, 3H, 1-H, 3-H and α-H-Ala), 3.48 (dd, *J* = 12.0, 7.7 Hz, 1H, 1-H), 2.85- 2.67 (m, 4H, pipe), 1.70 – 1.55 (m, 2H, pipe), 1.51 (d, *J* = 7.2 Hz, 3H, 3-CH<sub>3</sub>), 1.55- 1.40 (m, 2H, pipe), 1.25 (t, *J* = 6.6 Hz, 3H, CH<sub>3</sub>-Ala); (*SRR*)- epimer (46%) 8.32 (d, *J* = 8.9 Hz, 2H, 4-Nos), 8.10 (d, *J* = 8.9 Hz, 2H, 4-Nos), 7.58 (s, 1H, NH), 7.35 (s, 1H, NH), 7.27 (s, 1H, 9-H), 6.38 (s, 1H, 6-H), 5.89 (dd, *J* = 8.4, 3.9 Hz, 1H, 10a-H), 4.30- 4.10 (m, 3H, 1-H, 3-H and α-H-Ala), 3.40- 3.34 (m, 1H, 1-H), 2.85- 2.69 (m, 4H, pipe), 1.69-1.58 (m, 2H, pipe), 1.54 (d, *J* = 7.2 Hz, 3H, 3-CH<sub>3</sub>), 1.56- 1.44 (m, 2H, pipe), 1.34 (d, *J* = 7.1 Hz, 3H, CH<sub>3</sub>-Ala); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) (*SSS*)-epimer 173.1 (C, CONH<sub>2</sub>-Ala), 164.2 (C, C<sub>4</sub>), 150.1 (C, C<sub>9a</sub>), 147.9 (C, C<sub>7</sub>), 141.9 (C, 4-Nos), 140.9 (C, 4-Nos), 129.4 (2CH, 4-Nos), 125.9b (C, C<sub>5a</sub>), 124.9 (2CH, 4-Nos), 116.5 (C, C<sub>8</sub>), 115.6 (CH, C<sub>9</sub>), 101.6 (CH, C<sub>6</sub>), 73.1 (CH, C<sub>10a</sub>), 55.7 (CH, C<sub>3</sub>), 54.9 (CH, C<sub>α</sub>-Ala), 52.9 (2CH<sub>2</sub>, pipe), 48.3 (CH<sub>2</sub>, C<sub>1</sub>), 26.2 (2CH<sub>2</sub>, pipe), 24.2 (CH<sub>2</sub>, pipe), 18.9 (CH<sub>3</sub>, 3-CH<sub>3</sub>), 13.5 (s, CH<sub>3</sub>, CH<sub>3</sub>-Ala); (*SRR*)-epimer 173.3 (C, CONH<sub>2</sub>-Ala), 163.9 (C, C<sub>4</sub>), 150.4 (C, C<sub>9a</sub>), 147.7 (s, C, C<sub>7</sub>), 141.8 (C, 4-Nos), 140.2 (C, 4-Nos), 129.5 (2CH, 4-Nos), 127.0 (C, C<sub>5a</sub>), 125.0 (2CH, 4-Nos), 117.0 (C, C<sub>8</sub>), 115.7 (CH, C<sub>9</sub>), 103.2 (CH, C<sub>6</sub>), 74.9 (CH, C<sub>10a</sub>), 55.8 (CH, C<sub>3</sub>), 54.4 (CH, C<sub>α</sub>-Ala), 52.9 (2CH<sub>2</sub>, pipe), 48.8 (CH<sub>2</sub>, C<sub>1</sub>), 26.2 (2CH<sub>2</sub>, pipe), 24.1 (CH<sub>2</sub>, pipe), 20.0 (CH<sub>3</sub>, 3-CH<sub>3</sub>),

13.3 (CH<sub>3</sub>, CH<sub>3</sub>-Ala); HRMS (ESI-TOF)  $m/z$  calcd for C<sub>25</sub>H<sub>30</sub>ClN<sub>6</sub>O<sub>6</sub>S [M + H]<sup>+</sup> 577.1631, found 577.1619.

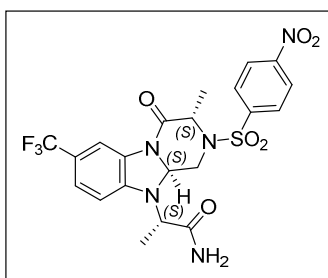
**(*R*)-2-((3*R*,10*aR*)-3-methyl-2-((4-nitrophenyl)sulfonyl)-4-oxo-7-(trifluoromethyl)-1,3,4,10*a*-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)propanamide 9(3,1,3,1) and (*R*)-2-((3*S*,10*aS*)-3-methyl-2-((4-nitrophenyl)sulfonyl)-4-oxo-7-(trifluoromethyl)-1,3,4,10*a*-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)propanamide 9(3,1,2,1)**



Yield 54 mg (57%) of amorphous solid. Purified by semi-preparative HPLC. (*R*):(*S*) ratio of the crude = 37:62. (*R*):(*S*) ratio of the purified product = 53:47. HPLC: RT =1.90 min; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) (*RRR*)-epimer (53%) 8.20 (d, *J* = 9.0 Hz, 2H, 4-Nos), 8.04 (d, *J* = 9.0 Hz, 2H, 4-Nos), 7.70 (s, 1H, NH), 7.52 (d, *J* = 1.9 Hz, 1H, 6-H), 7.38 (s, 1H, NH), 7.20 (dd, *J* = 8.3, 1.9 Hz, 1H, 8-H), 6.62 (d, *J* = 8.4 Hz, 1H, 9-H), 5.90 (dd, *J* = 7.5, 4.2 Hz, 1H, 10*a*-H), 4.30 (q, *J* = 7.2 Hz, 1H, 3-H), 4.23 (q, *J* = 7.2 Hz, 1H, α-H-Ala), 4.20 (dd, *J* = 11.6, 4.6 Hz, 1H, 1-H), 3.66 (dd, *J* = 12.0, 7.6 Hz, 1H, 1-H), 1.54 (d, *J* = 7.2 Hz, 3H, 3-CH<sub>3</sub>), 1.36 (d, *J* = 7.1 Hz, 3H, CH<sub>3</sub>-Ala) (*RSS*)-epimer (47%) 8.31 (d, *J* = 9.0 Hz, 2H, 4-Nos), 8.12 (d, *J* = 9.0 Hz, 2H, 4-Nos), 7.60 (d, *J* = 1.9 Hz, 1H, 6-H), 7.58 (bs, 1H, NH), 7.31 (bs, 1H, NH), 7.25 (d, *J* = 8.2 Hz, 1H, 8-H), 6.61 (d, *J* = 8.2 Hz, 1H, 9-H), 5.99 (dd, *J* = 8.4, 3.9 Hz, 1H, 10*a*-H), 4.30 (dd, *J* = 11.2, 3.9 Hz, 1H, 1-H), 4.29 (q, *J* = 7.2 Hz, 3-H), 4.21 (q, *J* = 7.1 Hz, 1H, α-H), 3.48 (dd, *J* = 11.2, 8.5 Hz, 1H, 1-H), 1.56 (d, *J* = 7.1 Hz, 3H, 3-CH<sub>3</sub>), 1.39 (d, *J* = 7.1 Hz, 1H, CH<sub>3</sub>-Ala); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) (*RRR*)-epimer 172.3 (C, CONH<sub>2</sub>), 164.3 (C, C<sub>4</sub>), 149.9 (C, 4-Nos), 143.4 (C, C<sub>9a</sub>), 141.5 (C, 4-Nos), 131.5 (C, C<sub>6a</sub>), 129.2 (2CH, 4-Nos), 124.6 (2CH, 4-Nos), 124.5 (q, *J* = 270.9 Hz, C, CF<sub>3</sub>), 122.8 (q, *J* = 4.3 Hz, CH, C<sub>8</sub>),

118.7 (q,  $J = 31.7$  Hz, C, C<sub>7</sub>), 110.1 (q,  $J = 3.7$  Hz, C, C<sub>6</sub>), 108.5 (CH, C<sub>9</sub>), 74.6 (CH, C<sub>10a</sub>), 55.4 (CH, C<sub>3</sub>), 53.7 (CH, C<sub>α</sub>-Ala), 48.1 (CH<sub>2</sub>, C<sub>1</sub>), 19.4 (CH<sub>3</sub>, 3-CH<sub>3</sub>), 13.0 (s, CH<sub>3</sub>, CH<sub>3</sub>-Ala); (RSS)-epimer, 172.6 (C, CONH<sub>2</sub>), 164.9 (C, C<sub>4</sub>), 150.1 (C, 4-Nos), 144.0 (C, C<sub>9a</sub>), 142.0 (C, 4-Nos), 130.8 (C, C<sub>5a</sub>), 129.4 (2CH, 4-Nos), 125.0 (q,  $J = 270.6$  Hz, C, CF<sub>3</sub>), 124.9 (2CH, 4-Nos), 123.3 (q,  $J = 4.2$  Hz, CH, C<sub>8</sub>), 118.4 (q,  $J = 32.0$  Hz, C, C<sub>7</sub>), 110.4 (d,  $J = 3.7$  Hz, C, C<sub>6</sub>), 107.0 (CH, C<sub>9</sub>), 73.6 (CH, C<sub>10a</sub>), 55.8 (s, CH, C<sub>3</sub>), 54.3 (CH, C<sub>α</sub>-Ala), 47.8 (CH<sub>2</sub>, C<sub>1</sub>), 18.5 (CH<sub>3</sub>, 3-CH<sub>3</sub>), 14.16 (s, CH<sub>3</sub>, CH<sub>3</sub>-Ala) HRMS (ESI-TOF)  $m/z$  calcd for C<sub>21</sub>H<sub>21</sub>F<sub>3</sub>N<sub>5</sub>O<sub>6</sub>S [M + H]<sup>+</sup> 528.1159, found 528.1135.

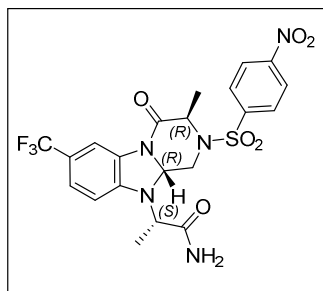
**(S)-2-((3S,10aS)-3-methyl-2-((4-nitrophenyl)sulfonyl)-4-oxo-7-(trifluoromethyl)-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-10(2H)-yl)propanamide 9(2,1,2,1)**



Yield 53.2 mg (56%) of amorphous solid. Purified by precipitation in MeOH. (*R*):(*S*) ratio of the crude = 11:89. (*R*):(*S*) ratio of the purified product = 10:90. HPLC: RT = 1.88 min; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 8.22 (d,  $J = 9.0$  Hz, 2H, 4-Nos), 8.05 (d,  $J = 9.1$  Hz, 2H, 4-Nos), 7.72 (bs, 1H, NH), 7.53 (d,  $J = 1.9$  Hz, 1H, 6-H), 7.40 (bs, 1H, NH), 7.22 (ddd,  $J = 8.3, 1.9, 0.9$  Hz, 1H, 8-H), 6.64 (d,  $J = 8.3$  Hz, 1H, 9-H), 5.91 (dd,  $J = 7.5, 4.2$  Hz, 1H, 10a-H), 4.32 (q,  $J = 7.1$  Hz, 1H, 3-H), 4.24 (q,  $J = 7.2$  Hz, 1H,  $\alpha$ -H-Ala), 4.22 (dd,  $J = 11.9, 4.2$  Hz, 1H, 1-H), 3.68 (dd,  $J = 12.0, 7.6$  Hz, 1H, 1-H), 1.55 (d,  $J = 7.2$  Hz, 3H, 3-CH<sub>3</sub>), 1.37 (d,  $J = 7.1$  Hz, 3H, CH<sub>3</sub>-Ala); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 172.6 (C, CONH<sub>2</sub>), 164.9 (C, C<sub>4</sub>), 150.1 (C, 4-Nos), 144.0 (C, C<sub>9a</sub>), 142.0 (C, 4-Nos), 130.8 (C, C<sub>5a</sub>), 129.4 (2CH, 4-Nos), 125.0 (q,  $J = 270.6$  Hz, C, CF<sub>3</sub>), 124.9 (2CH, 4-Nos), 123.3 (q,  $J = 4.2$  Hz, CH, C<sub>8</sub>), 118.4 (q,  $J = 32.0$  Hz, C, C<sub>7</sub>), 110.4 (d,  $J = 3.7$  Hz, C, C<sub>6</sub>), 107.0 (CH, C<sub>9</sub>), 73.6 (CH, C<sub>10a</sub>), 55.8 (s, CH,

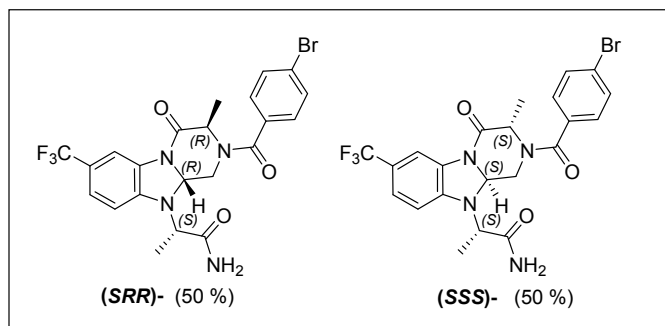
C<sub>3</sub>), 54.3 (CH, C<sub>α</sub>-Ala), 47.8 (CH<sub>2</sub>, C<sub>1</sub>), 18.5 (CH<sub>3</sub>, 3-CH<sub>3</sub>), 14.16 (s, CH<sub>3</sub>, CH<sub>3</sub>-Ala); HRMS (ESI-TOF) *m/z* calcd for C<sub>21</sub>H<sub>21</sub>F<sub>3</sub>N<sub>5</sub>O<sub>6</sub>S [M + H]<sup>+</sup> 528.1159, found 528.1133.

**(S)-2-((3*R*,10*aR*)-3-methyl-2-((4-nitrophenyl)sulfonyl)-4-oxo-7-(trifluoromethyl)-1,3,4,10*a*-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)propanamide 9(2,1,3,1)**



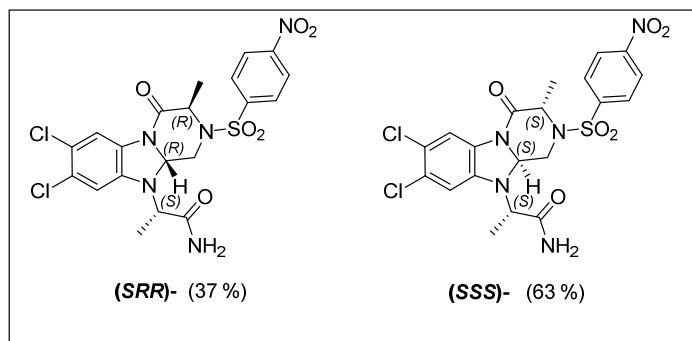
Yield 13.5 mg (39%) of amorphous solid. Purified by precipitation in MeOH. (*R*):(*S*) ratio of the crude = 77:33. (*R*):(*S*) ratio of the purified product = 93:7. HPLC: RT =1.91 min; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 8.31 (d, *J* = 9.0 Hz, 2H, 4-Nos), 8.12 (d, *J* = 9.0 Hz, 2H, 4-Nos), 7.60 (d, *J* = 1.9 Hz, 1H, 6-H), 7.58 (bs, 1H, NH), 7.31 (bs, 1H, NH), 7.25 (d, *J* = 8.2 Hz, 1H, 8-H), 6.61 (d, *J* = 8.2 Hz, 1H, 9-H), 5.99 (dd, *J* = 8.4, 3.9 Hz, 1H, 10*a*-H), 4.30 (dd, *J* = 11.2, 3.9 Hz, 1H, 1-H), 4.29 (q, *J* = 7.2 Hz, 3-H), 4.21 (q, *J* = 7.1 Hz, 1H, α-H), 3.48 (dd, *J* = 11.2, 8.5 Hz, 1H, 1-H), 1.56 (d, *J* = 7.1 Hz, 3H, 3-CH<sub>3</sub>), 1.39 (d, *J* = 7.1 Hz, 1H, CH<sub>3</sub>-Ala); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 172.3 (C, CONH<sub>2</sub>), 164.3 (C, C<sub>4</sub>), 149.9 (C, 4-Nos), 143.4 (C, C<sub>9*a*</sub>), 141.5 (C, 4-Nos), 131.5 (C, C<sub>6*a*</sub>), 129.2 (2CH, 4-Nos), 124.6 (2CH, 4-Nos), 124.5 (q, *J* = 270.9 Hz, C, CF<sub>3</sub>), 122.8 (q, *J* = 4.3 Hz, CH, C<sub>8</sub>), 118.7 (q, *J* = 31.7 Hz, C, C<sub>7</sub>), 110.1 (q, *J* = 3.7 Hz, C, C<sub>6</sub>), 108.5 (CH, C<sub>9</sub>), 74.6 (CH, C<sub>10*a*</sub>), 55.4 (CH, C<sub>3</sub>), 53.7 (CH, C<sub>α</sub>-Ala), 48.1 (CH<sub>2</sub>, C<sub>1</sub>), 19.4 (CH<sub>3</sub>, 3-CH<sub>3</sub>), 13.0 (s, CH<sub>3</sub>, CH<sub>3</sub>-Ala); HRMS (ESI-TOF) *m/z* calcd for C<sub>21</sub>H<sub>21</sub>F<sub>3</sub>N<sub>5</sub>O<sub>6</sub>S [M + H]<sup>+</sup> 528.1159, found 528.1122.

**(S)-2-((3*R*,10*aR*)-2-(4-bromobenzoyl)-3-methyl-4-oxo-7-(trifluoromethyl)-1,3,4,10*a*-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)propanamide 9(2,1,3,3) and (S)-2-((3*S*,10*aS*)-2-(4-bromobenzoyl)-3-methyl-4-oxo-7-(trifluoromethyl)-1,3,4,10*a*-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)propanamide 9(2,1,2,3)**



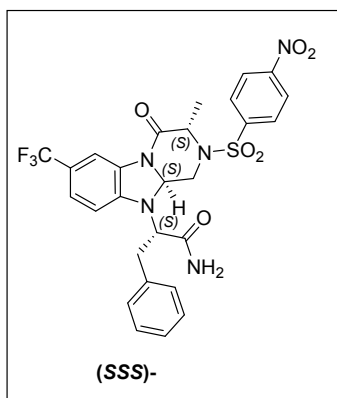
Yield 34 mg (39%) of amorphous solid. Purified by precipitation in MeOH. (*R*):(*S*) ratio of the crude = 73:27. (*R*):(*S*) ratio of the purified product = 52:48. HPLC: RT =1.82 min; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) (SRR)-epimer (50%) 7.82 (d, *J* = 2.1 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.51 (bs, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.32 – 7.27 (m, 1H), 7.24 (bs, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 6.09 (dd, *J* = 9.7, 3.3 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 1H), 4.28 – 4.03 (m, 3H), 3.60 (dd, *J* = 11.6, 10.0 Hz, 1H), 1.30 (d, *J* = 7.0 Hz, 3H) (SSS)-epimer (50%) 7.82 (d, *J* = 2.2 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.53 (bs, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.32 – 7.27 (m, 1H), 7.20 (bs, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 6.02 (dd, *J* = 9.8, 3.0 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 1H), 4.28 – 4.03 (m, 3H), 3.69 (dd, *J* = 11.5, 9.9 Hz, 1H), 1.30 (d, *J* = 7.0 Hz, 1H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) (SRR)-epimer 172.3, 169.3, 166.0, 144.7, 135.5, 131.9, 131.5, 129.5, 125.1 (d, *J* = 270.7 Hz), 123.7, 123.1 (q, *J* = 4.3 Hz), 119.3 (q, *J* = 31.9 Hz), 110.4 (q, *J* = 3.6 Hz), 107.0, 75.3, 55.3 – 54.7 (m), 54.3, 18.5, 13.8. (SSS)-epimer 172.8, 169.3, 165.9, 144.8, 135.6, 132.4, 131.9, 129.5, 125.2 (q, *J* = 270.7 Hz), 123.6, 123.3 (q, *J* = 4.2 Hz), 118.5 (q, *J* = 32.0 Hz), 110.5 (q, *J* = 3.5 Hz), 108.9, 74.5, 55.3 – 54.7 (m), 54.2, 18.4, 14.3. HRMS (ESI-TOF) *m/z* calcd for C<sub>22</sub>H<sub>21</sub>BrF<sub>3</sub>N<sub>4</sub>O<sub>3</sub> [M + H]<sup>+</sup> 525.0744, found 525.0750.

**(S)-2-((3*R*,10*aR*)-7,8-dichloro-3-methyl-2-((4-nitrophenyl)sulfonyl)-4-oxo-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)propanamide and 9(2,2,3,1) (S)-2-((3*S*,10*aS*)-7,8-dichloro-3-methyl-2-((4-nitrophenyl)sulfonyl)-4-oxo-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)propanamide 9(2,2,2,1)**



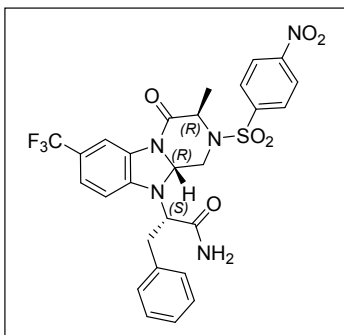
Yield 16 mg (37%) of amorphous solid. Purified by semi-preparative HPLC. (*R*):(*S*) ratio of the crude = 55:45. (*R*):(*S*) ratio of the purified product = 37:63. HPLC: RT =1.73 min; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) (SRR)-epimer (37%) 8.30 (d, *J* = 9.0 Hz, 2H, 4-Nos), 8.09 (d, *J* = 9.0 Hz, 2H, 4-Nos), 7.60 (s, 1H, NH), 7.44 (s, 1H, 9-H), 7.32 (s, 1H, NH), 6.73 (s, 1H, 6-H), 5.95 (dd, *J* = 8.0, 4.1 Hz, 1H, 10a-H), 4.30-4.20 (m, 3H, 1-H, 3-H and α-H-Ala ), 3.47 (dd, *J* = 11.7, 8.1 Hz, 1H, 1-H), 1.54 (d, *J* = 7.1 Hz, 3H, 3-CH<sub>3</sub>), 1.38 (d, *J* = 7.1 Hz, 3H, CH<sub>3</sub>-Ala); (SSS)-epimer (63%) 8.23 (d, *J* = 9.0 Hz, 2H, 4-Nos), 8.02 (d, *J* = 9.0 Hz, 2H, 4-Nos), 7.72 (s, 1H, NH), 7.42 (s, 1H, NH), 7.37 (s, 1H, 9-H), 6.75 (s, 1H, 6-H), 5.81 (dd, *J* = 7.2, 4.5 Hz, 1H, 10a-H), 4.29-4.20 (m, 2H, 3-H and α-H-Ala), 4.17 (dd, *J* = 12.5, 4.5 Hz, 1H, 1-H), 3.70 (dd, *J* = 12.4, 7.3 Hz, 1H, 1-H), 1.53 (d, *J* = 7.2 Hz, 3H, 3-CH<sub>3</sub>), 1.32 (d, *J* = 7.1 Hz, 3H, CH<sub>3</sub>-Ala); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) (SRR)-epimer 172.7 (C, CONH<sub>2</sub>-Ala), 164.8 (C, C<sub>4</sub> ), 150.3 (C, 4-Nos), 141.9 (C, 4-Nos ), 140.8 (C, C<sub>9a</sub>), 131.6 ( C, C<sub>5a</sub>), 129.6 (2CH, 4-Nos), 126.8 (CH, C<sub>8</sub>), 125.0 (2CH, 4-Nos), 120.1 (C, C<sub>7</sub>), 115.1 (CH, C<sub>9</sub>), 110.5 (CH, C<sub>6</sub>), 75.1 (CH, C<sub>10a</sub>), 55.4 (CH, C<sub>3</sub>), 54.0 (CH, α-H-Ala), 48.5 (CH<sub>2</sub>, C<sub>1</sub>), 19.3 (CH<sub>3</sub>, 3-CH<sub>3</sub>), 13.9 (CH<sub>3</sub>, CH<sub>3</sub>-Ala). (SSS)-epimer 172.2 (C, CONH<sub>2</sub>-Ala), 164.6 (C, C<sub>4</sub>), 149.6 (C, 4-Nos), 141.6 (C, 4-Nos), 140.7 (C, C<sub>9a</sub>), 129.9 (C, C<sub>5a</sub>), 128.9 (2CH, 4-Nos), 126.7 (CH, C<sub>8</sub>), 124.4 (2CH, 4-Nos), 118.8 (C, C<sub>7</sub>), 114.5 (CH, C<sub>9</sub>), 108.3 (CH, C<sub>6</sub>), 73.0 (CH, C<sub>10a</sub>), 55.3 (CH, C<sub>3</sub>), 54.2 ( CH, α-H-Ala), 47.1 (CH<sub>2</sub>, C<sub>1</sub>), 17.7 (CH<sub>3</sub>, 3-CH<sub>3</sub>), 13.4 (CH<sub>3</sub>, CH<sub>3</sub>-Ala); HRMS (ESI-TOF) *m/z* calcd for C<sub>20</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>5</sub>O<sub>6</sub>S [M + H]<sup>+</sup> 528.0506, found 528.0497.

**(S)-2-((3S,10aS)-3-methyl-2-((4-nitrophenyl)sulfonyl)-4-oxo-7-(trifluoromethyl)-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-10(2H)-yl)-3-phenylpropanamide**  
**9(6,1,2,1)**



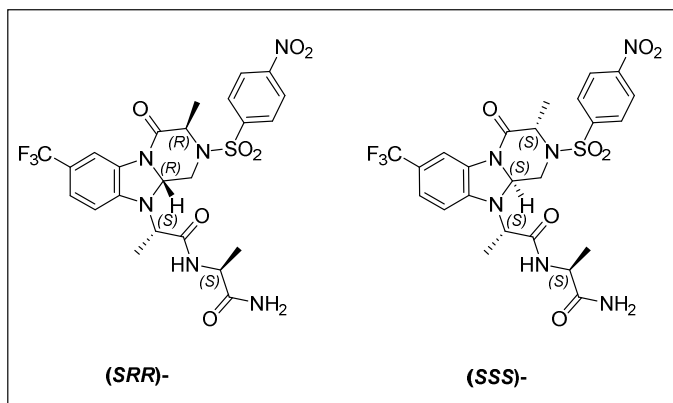
Yield 18 mg (23%) of amorphous solid. Purified by precipitation in MeOH. (*R*):(*S*) ratio of the crude = 16:84. (*R*):(*S*) ratio of the purified product = 4:96. HPLC: RT = 2.38 min; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 8.30 (d, *J* = 8.9 Hz, 2H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.63 (bs, 1H), 7.56 (d, *J* = 1.7 Hz, 1H), 7.42 (bs, 1H), 7.35 – 7.30 (m, 3H), 7.28 – 7.17 (m, 3H), 6.85 (d, *J* = 8.3 Hz, 1H), 5.90 (dd, *J* = 8.3, 3.7 Hz, 1H), 4.43 (dd, *J* = 9.5, 6.5 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 1H), 3.78 (dd, *J* = 11.3, 3.7 Hz, 1H), 3.28 (dd, *J* = 13.7, 6.4 Hz, 1H), 3.04 (dd, *J* = 13.7, 9.6 Hz, 1H), 2.57 – 2.51 (m, 1H), 1.53 (d, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (126 MHz, ) δ 170.6, 164.6, 150.5, 143.7, 141.6, 138.4, 131.1, 129.8, 129.4, 129.0, 127.2, 125.1, 125.1 (q, *J* = 270.7 Hz), 123.5 (q, *J* = 4.5 Hz), 118.5 (q, *J* = 32.3 Hz), 110.5 (q, *J* = 2.3 Hz), 108.1, 74.9, 61.0, 55.9, 47.9, 34.1, 20.0; HRMS (ESI-TOF) *m/z* calcd for C<sub>27</sub>H<sub>25</sub>F<sub>3</sub>N<sub>5</sub>O<sub>6</sub>S [M + H]<sup>+</sup> 604.1472, found 604.1454.

**(S)-2-((3R,10aR)-3-methyl-2-((4-nitrophenyl)sulfonyl)-4-oxo-7-(trifluoromethyl)-1,3,4,10a-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-10(2H)-yl)-3-phenylpropanamide**  
**9(6,1,3,1)**



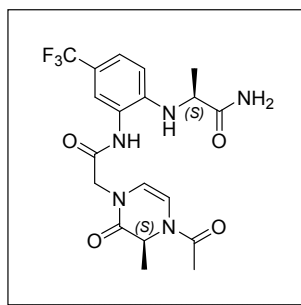
Yield 18.5 mg (24%) of amorphous solid. Purified by precipitation in MeOH. (*R*):(*S*) ratio of the crude = 76:24. (*R*):(*S*) ratio of the purified product = 92:8. HPLC: RT =2.43 min; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 8.26 (d, *J* = 8.9 Hz, 2H), 7.95 (d, *J* = 8.9 Hz, 2H), 7.58 (bs, 1H), 7.56 (d, *J* = 1.8 Hz, 1H), 7.32 (bs, 1H), 7.33 – 7.19 (m, 6H), 6.91 (d, *J* = 8.3 Hz, 1H), 5.39 (dd, *J* = 8.5, 3.6 Hz, 1H), 4.51 (dd, *J* = 8.4, 7.3 Hz, 1H), 4.29 (dd, *J* = 11.2, 3.7 Hz, 1H), 4.11 (q, *J* = 7.0 Hz, 1H), 3.33 (dd, *J* = 14.0, 7.1 Hz, 1H), 3.26 (dd, *J* = 11.1, 8.7 Hz, 1H), 3.08 (dd, *J* = 14.0, 8.7 Hz, 1H), 1.34 (d, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (126 MHz, ) δ 171.1, 164.6, 150.5, 143.6, 142.0, 137.9, 131.9, 129.7, 129.5, 128.9, 127.2, 125.1, 125.0 (q, *J* = 271.0 Hz), 123.4 (q, *J* = 3.8 Hz), 119.3 (q, *J* = 32.2 Hz), 110.65 (q, *J* = 2.9 Hz), 109.6, 75.9, 60.2, 55.9, 48.2, 33.8, 20.0. HRMS (ESI-TOF) *m/z* calcd for C<sub>27</sub>H<sub>25</sub>F<sub>3</sub>N<sub>5</sub>O<sub>6</sub>S [M + H]<sup>+</sup> 604.1472, found 604.1451.

**(*S*)-N-((*S*)-1-amino-1-oxopropan-2-yl)-2-((3*R*,10*aR*)-3-methyl-2-((4-nitrophenyl)sulfonyl)-4-oxo-7-(trifluoromethyl)-1,3,4,10*a*-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)propanamide (*SRR*)-14 and (*S*)-N-((*S*)-1-amino-1-oxopropan-2-yl)-2-((3*S*,10*aS*)-3-methyl-2-((4-nitrophenyl)sulfonyl)-4-oxo-7-(trifluoromethyl)-1,3,4,10*a*-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrazin-10(2*H*)-yl)propanamide (*SSS*)-14**



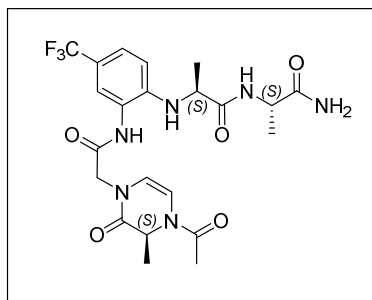
Yield 14.5 mg (34%) of amorphous solid. (*R*):(*S*) ratio of the crude = 56:44. (*R*):(*S*) ratio of the purified product = 40:60. Purified by semi-preparative HPLC. HPLC RT = 1.93 min; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) (SRR)-epimer (40%) 8.30 (d, *J* = 8.9 Hz, 2H), 8.14 (d, *J* = 7.8 Hz, 1H), 8.11 (d, *J* = 8.9 Hz, 2H), 7.58 (d, *J* = 1.8 Hz, 1H), 7.44 (s, 1H), 7.25 – 7.21 (m, 2H), 7.14 (s, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 6.02 (dd, *J* = 8.1, 4.0 Hz, 1H), 4.40 – 4.17 (m, 4H), 3.47 (dd, *J* = 11.6, 8.2 Hz, 1H), 1.57 (d, *J* = 7.2 Hz, 3H), 1.41 (d, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 7.1 Hz, 3H); (SSS)-epimer (60%) 8.57 (d, *J* = 7.7 Hz, 1H), 8.19 (d, *J* = 8.9 Hz, 2H), 8.00 (d, *J* = 8.9 Hz, 2H), 7.51 (d, *J* = 1.8 Hz, 1H), 7.48 (s, 1H), 7.25 – 7.21 (m, 2H), 7.10 (s, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 5.87 (dd, *J* = 7.0, 4.5 Hz, 1H), 4.49 (q, *J* = 7.0 Hz, 1H), 4.40 – 4.17 (m, 3H), 4.12 (dd, *J* = 12.4, 4.5 Hz, 1H), 3.70 (dd, *J* = 12.4, 7.2 Hz, 1H), 1.55 (d, *J* = 7.2 Hz, 3H), 1.31 (d, *J* = 7.1 Hz, 6H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) (SRR)-epimer 173.8, 169.8, 164.4, 149.9, 143.0, 141.3, 131.6, 129.2, 124.6, 124.5 (q, *J* = 270.7 Hz), 122.7 (q, *J* = 3.8 Hz), 118.9 (q, *J* = 32.0 Hz), 110.5 – 110.0 (m), 108.6, 74.6, 55.4, 53.9, 48.1, 47.2, 19.2, 18.4, 13.2; (SSS)-epimer 173.8, 169.8, 164.7, 149.5, 143.5, 141.7, 130.3, 128.9, 125.54 (q, *J* = 277.2 Hz), 124.4, 123.0 (q, *J* = 4.2 Hz), 118.3 (q, *J* = 32.1 Hz), 110.1 – 109.7 (m), 107.1, 72.4, 55.3, 53.9, 48.1, 48.0, 18.4, 17.6, 12.8. HRMS (ESI-TOF) *m/z* calcd for C<sub>24</sub>H<sub>26</sub>F<sub>3</sub>N<sub>6</sub>O<sub>7</sub>S [M + H]<sup>+</sup> 599.1530, found 599.1546.

**(S)-2-((2-(2-((S)-4-acetyl-3-methyl-2-oxo-3,4-dihydropyrazin-1(2H)-yl)acetamido)-4-(trifluoromethyl)phenyl)amino)propanamide 16**



Yield 29 mg (43%) of amorphous solid. Purified by semi-preparative HPLC. HPLC: RT = 0.71 min.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  (ppm) 9.66 (s, 1H), 7.54 (d,  $J$  = 1.8 Hz, 1H, ), 7.41 (s, 1H), 7.36 (dd,  $J$  = 8.6, 1.7 Hz, 1H), 7.11 (s, 1H), 6.61 (t,  $J$  = 8.3 Hz, 1H), 6.39 (dd,  $J$  = 5.9, 1.5 Hz, 1H), 6.04 (d,  $J$  = 5.9 Hz, 1H), 4.92 (qd,  $J$  = 6.7, 1.0 Hz, 1H), 4.38 (q,  $J$  = 16.3 Hz, 2H), 3.94 (dd,  $J$  = 13.4, 6.5 Hz, 2H, ), 2.12 (s, 3H), 1.41 (d,  $J$  = 6.9 Hz, 3H), 1.17 (d,  $J$  = 7.0 Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  (ppm) 175.5, 168.3, 167.2, 166.8, 144.5, 125.2 (q,  $J$  = 270.3 Hz), 124.2 (q,  $J$  = 3.4 Hz), 122.9, 122.7 (d,  $J$  = 3.6 Hz), 116.4 (q,  $J$  = 32.1 Hz), 115.3, 111.0, 108.2, 52.3, 50.6, 49.0, 21.5, 19.1, 15.7. HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{22}\text{F}_3\text{N}_5\text{O}_4$   $[\text{M} + \text{H}]^+$  442.1624, found 442.1752.

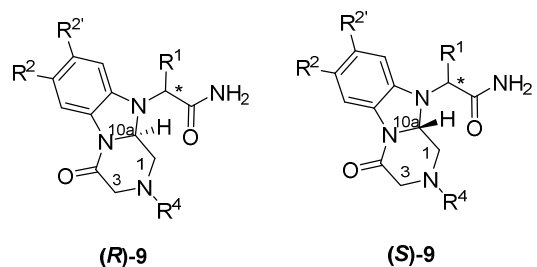
**(S)-2-((2-((S)-4-acetyl-3-methyl-2-oxo-3,4-dihydropyrazin-1(2H)-yl)acetamido)-4-(trifluoromethyl)phenyl)amino)-N-((S)-1-amino-1-oxopropan-2-yl)propanamide 17**



Yield 25 mg (35%) of amorphous solid. Purified by semi-preparative HPLC. HPLC: RT = 0.67 min;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  (ppm) 9.63 (s, 1H), 8.16 (d,  $J$  = 7.7 Hz, 1H), 7.60 (d,  $J$  = 2.1 Hz, 1H), 7.32 (dd,  $J$  = 8.6, 1.4 Hz, 1H), 7.23 (s, 1H), 6.99 (s, 1H), 6.64 (d,  $J$  = 8.7 Hz, 1H), 6.39 (dd,  $J$  = 5.9, 1.4 Hz, 1H), 6.03 (d,  $J$  = 5.9 Hz, 1H), 5.66 (d,  $J$  = 7.3 Hz, 1H), 4.91 (dd,  $J$  = 7.0, 1.3 Hz, 1H), 4.39 (dd,  $J$  = 39.7, 16.4 Hz, 2H), 4.23 (p,  $J$  = 7.1 Hz, 1H), 4.10 (p,  $J$

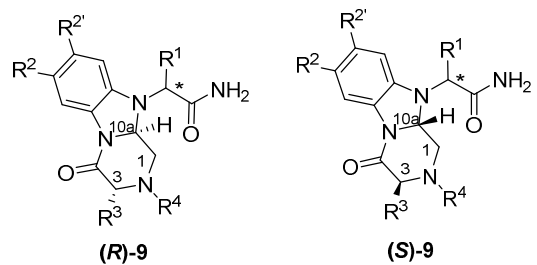
= 6.8 Hz, 1H), 2.12 (s, 3H), 1.38 (d,  $J$  = 6.8 Hz, 3H), 1.21 (d,  $J$  = 7.1 Hz, 3H), 1.17 (d,  $J$  = 7.0 Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 174.23, 172.9, 168.2, 167.0, 166.6, 144.2, 125.3 (q,  $J$  = 270.3 Hz), 123.8 (q,  $J$  = 4.1 Hz), 123.1, 122.4 (q,  $J$  = 3.5 Hz), 116.4 (q,  $J$  = 32.2 Hz), 115.3, 111.2, 108.1, 52.1, 50.6, 48.7, 48.3, 21.5, 19.1, 19.0, 15.7. HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{28}\text{F}_3\text{N}_6\text{O}_5$   $[\text{M} + \text{H}]^+$  513.2068, found 513.2076.

**Table 1.** NMR spectral data of diagnostic protons and carbons of compounds **9(R<sup>1</sup>,R<sup>2</sup>,1,R<sup>4</sup>)**



| Comp.             | Configuration       |   |     | <sup>1</sup> H NMR |                    |                     |                 |            | <sup>13</sup> C NMR |                |                |
|-------------------|---------------------|---|-----|--------------------|--------------------|---------------------|-----------------|------------|---------------------|----------------|----------------|
|                   | α (R <sup>1</sup> ) | 3 | 10a | 10a-H              | J <sub>10a-1</sub> | J <sub>10a-1'</sub> | 1-H             | 3-H        | C <sub>10a</sub>    | C <sub>1</sub> | C <sub>3</sub> |
| <b>9(1,1,1,1)</b> | S                   | - | RS  | 5.55               | 9.4                | 3.7                 | 3.22, 4.46      | 3.72, 4.30 | 77.0                | 45.9           | 46.6           |
| <b>9(2,1,1,1)</b> | S                   | - | R   | 5.70               | 9.4                | 3.6                 | 3.43-3.28, 4.46 | 3.73, 4.32 | 75.9                | 47.0           | 47.8           |
|                   | S                   | - | S   | 5.59               | 9.2                | 3.6                 | 3.30-3.41, 4.36 | 3.80, 4.29 | 74.8                | 46.9           | 47.8           |
| <b>9(2,1,1,2)</b> | S                   | - | R   | 5.65               | 9.5                | 3.6                 | 3.15, 4.41      | 3.54, 4.24 | 76.1                | 46.7           | 48.0           |
|                   | S                   | - | S   | 5.57               | 9.5                | 3.5                 | 3.15, 4.26-4.31 | 3.63, 4.22 | 74.9                | 46.9           | 47.8           |
| <b>9(2,2,1,1)</b> | S                   | - | R   | 5.68               | 9.3                | 3.6                 | 3.29, 4.40      | 3.73, 4.29 | 76.6                | 47.5           | 48.2           |
| <b>9(2,3,1,2)</b> | S                   | - | R   | 5.49               | 9.5                | 3.7                 | 3.04, 4.36      | 4.18, 3.49 | 76.0                | 46.9           | 47.9           |
|                   | S                   | - | S   | 5.36               | 9.5                | 3.5                 | 3.01, 4.30-4.22 | 3.56, 4.16 | 74.4                | 47.2           | 47.7           |
| <b>9(3,1,1,1)</b> | R                   | - | R   | 5.67               | 9.4                | 3.6                 | 3.30, 4.43      | 3.70, 4.29 | 74.8                | 46.9           | 47.8           |
|                   | R                   | - | S   | 5.60               | 9.2                | 3.6                 | 3.37, 4.36      | 3.80, 4.32 | 75.9                | 47.0           | 47.8           |
| <b>9(4,1,1,1)</b> | S                   | - | R   | 5.57               | 9.4                | 3.4                 | 3.32-3.40, 4.65 | 3.79, 4.28 | 76.8                | 47.0           | 48.0           |
|                   | S                   | - | S   | 5.52               | 9.4                | 3.4                 | 3.21, 4.65      | 3.79, 4.29 | 75.3                | 47.4           | 48.3           |
| <b>9(5,1,1,1)</b> | S                   | - | R   | 5.84               | 9.3                | 3.5                 | 3.41, 4.58      | 3.75, 4.33 | 77.0                | 46.6           | 47.8           |
| <b>9(6,1,1,1)</b> | S                   | - | S   | 5.67               | 9.2                | 3.5                 | 3.33, 4.46      | 3.82, 4.32 | 75.2                | 47.0           | 47.8           |
|                   | S                   | - | R   | 5.27               | 9.2                | 3.4                 | 3.20, 4.48      | 3.66, 4.22 | 76.0                | 46.7           | 48.1           |
|                   | S                   | - | S   | 5.59               | 9.2                | 3.5                 | 3.23-3.34, 4.04 | 3.61, 4.17 | 76.9                | 46.8           | 48.1           |

**Table 2.** NMR spectral data of diagnostic protons and carbons of compounds **9(R<sup>1</sup>,R<sup>2</sup>,2,R<sup>4</sup>)** and **9(R<sup>1</sup>,R<sup>2</sup>,3,R<sup>4</sup>)**

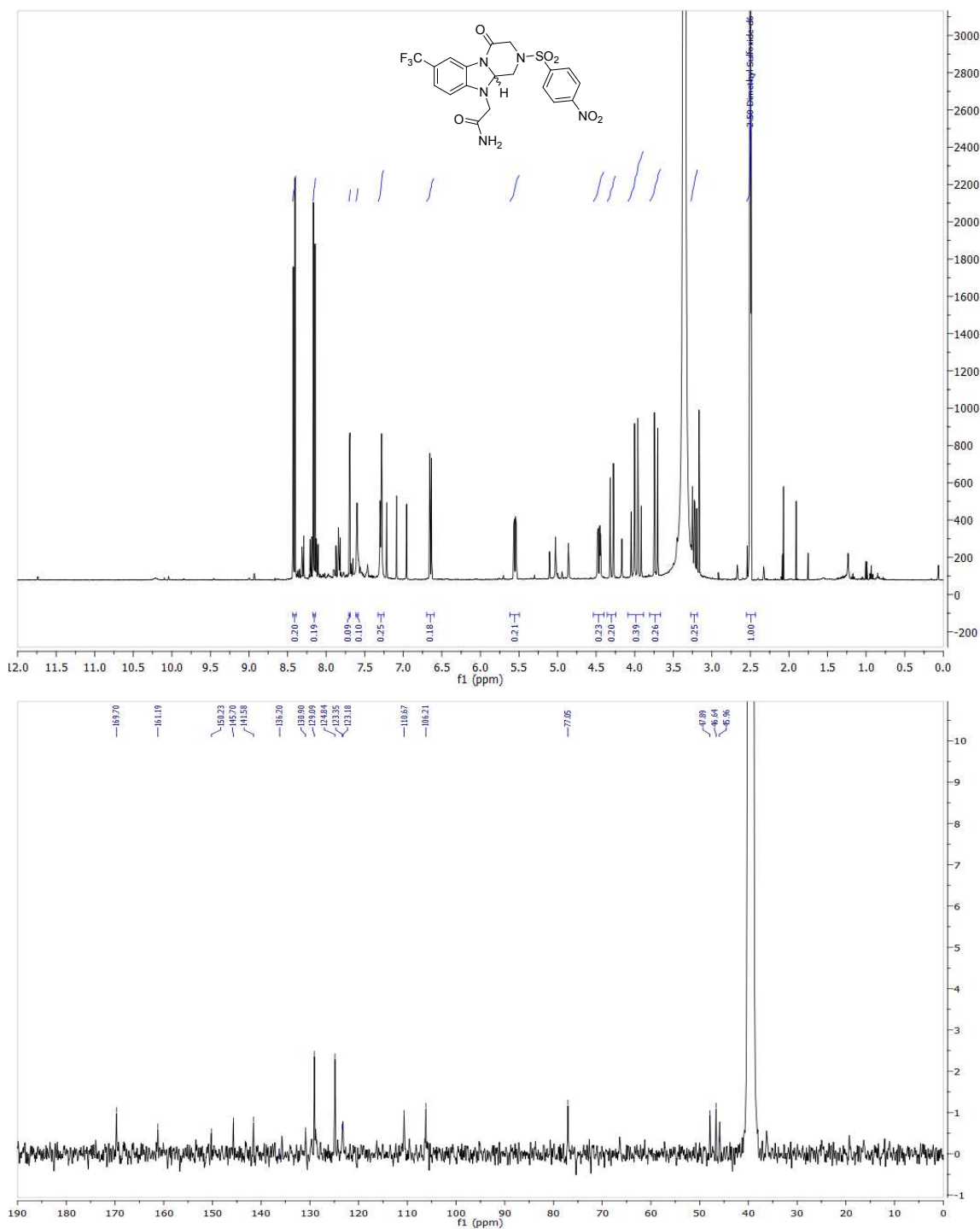


| Comp.             | Configuration       |   |     | <sup>1</sup> H NMR |                    |                     |             |           | <sup>13</sup> C NMR |                |                |
|-------------------|---------------------|---|-----|--------------------|--------------------|---------------------|-------------|-----------|---------------------|----------------|----------------|
|                   | α (R <sup>1</sup> ) | 3 | 10a | 10a-H              | J <sub>10a-1</sub> | J <sub>10a-1'</sub> | 1-H         | 3-H       | C <sub>10a</sub>    | C <sub>1</sub> | C <sub>3</sub> |
| <b>9(1,1,2,1)</b> | -                   | S | S   | 5.79               | 7.8                | 4.0                 | 3.48, 4.29  | 4.22      | 76.1                | 47.1           | 55.8           |
| <b>9(1,1,3,1)</b> | -                   | R | R   | 5.79               | 7.8                | 4.0                 | 3.48, 4.29  | 4.21      | 76.1                | 47.1           | 55.8           |
| <b>9(2,1,2,1)</b> | S                   | S | S   | 5.91               | 7.5                | 4.2                 | 3.68, 4.22  | 4.32      | 73.6                | 47.9           | 55.8           |
| <b>9(2,1,3,1)</b> | S                   | R | R   | 5.99               | 8.5                | 3.9                 | 3.48, 4.30  | 4.29      | 74.6                | 48.1           | 55.4           |
| <b>9(2,1,2,2)</b> | S                   | R | R   | 5.95               | 9.0                | 3.5                 | 3.26, 4.25  | 4.04      | 75.4                | 48.9           | 55.6           |
|                   | S                   | S | S   | 5.92               | 8.6                | 3.6                 | 3.24, 4.17  | 4.06      | 74.0                | 48.9           | 55.8           |
|                   | S                   | R | R   | 6.12               | 9.6                | 3.5                 | 3.75, 4.12- | 4.59      | 75.4                | 50.6           | 55.1           |
| <b>9(2,1,2,4)</b> | S                   | S | S   | 6.04               | 9.9                | 3.6                 | 4.28        | 4.55      | 74.6                | 50.6           | 55.2           |
|                   |                     |   |     |                    |                    |                     | 3.65, 4.21  |           |                     |                |                |
| <b>9(2,1,2,3)</b> | S                   | R | R   | 6.09               | 9.7                | 3.3                 | 3.60, 4.03- | 4.23      | 75.3                | 54.7-          | 54.3           |
|                   | S                   | S | S   | 6.61               | 9.8                | 3.0                 | 4.28        | 4.19      | 74.5                | 55.3           | 54.2           |
|                   |                     |   |     |                    |                    |                     | 3.69, 4.03- |           |                     | 54.7-          |                |
| <b>9(2,2,2,1)</b> |                     |   |     |                    |                    |                     | 4.28        |           |                     | 55.3           |                |
|                   | S                   | R | R   | 5.95               | 8.0                | 4.1                 | 3.47, 4.30- | 4.30-4.20 | 75.1                | 48.5           | 55.4           |
|                   | S                   | S | S   | 5.81               | 7.2                | 4.5                 | 4.20        | 4.30-4.20 | 73.0                | 47.5           | 55.3           |
| <b>9(2,3,2,1)</b> |                     |   |     |                    |                    |                     | 3.70, 4.17  |           |                     |                |                |
|                   | S                   | R | R   | 5.89               | 8.4                | 3.9                 | 3.34-3.40,  | 4.10-4.30 | 74.9                | 48.8           | 55.8           |
|                   | S                   | S | S   | 5.37               | 7.6                | 4.2                 | 4.10-4.30   | 4.10-4.30 | 73.1                | 48.3           | 55.7           |
| <b>9(3,1,2,1)</b> |                     |   |     |                    |                    |                     | 3.48, 4.10- |           |                     |                |                |
|                   | R                   | R | R   | 5.90               | 7.5                | 4.2                 | 4.30        |           | 74.6                | 48.1           | 55.4           |
|                   | R                   | S | S   | 6.00               | 8.4                | 3.8                 | 3.68, 4.22  | 4.32      | 73.6                | 47.9           | 55.8           |
| <b>9(6,1,3,1)</b> | S                   | R | R   | 5.42               | 8.4                | 3.6                 | 3.48, 4.30  | 4.29      | 75.9                | 48.2           | 55.9           |
| <b>9(6,1,2,1)</b> | S                   | S | S   | 5.88               | 8.2                | 3.6                 | 3.26, 4.29  | 4.11      | 74.9                | 47.9           | 55.9           |
|                   |                     |   |     |                    |                    |                     | 3.78, 4.43  | 4.11      |                     |                |                |

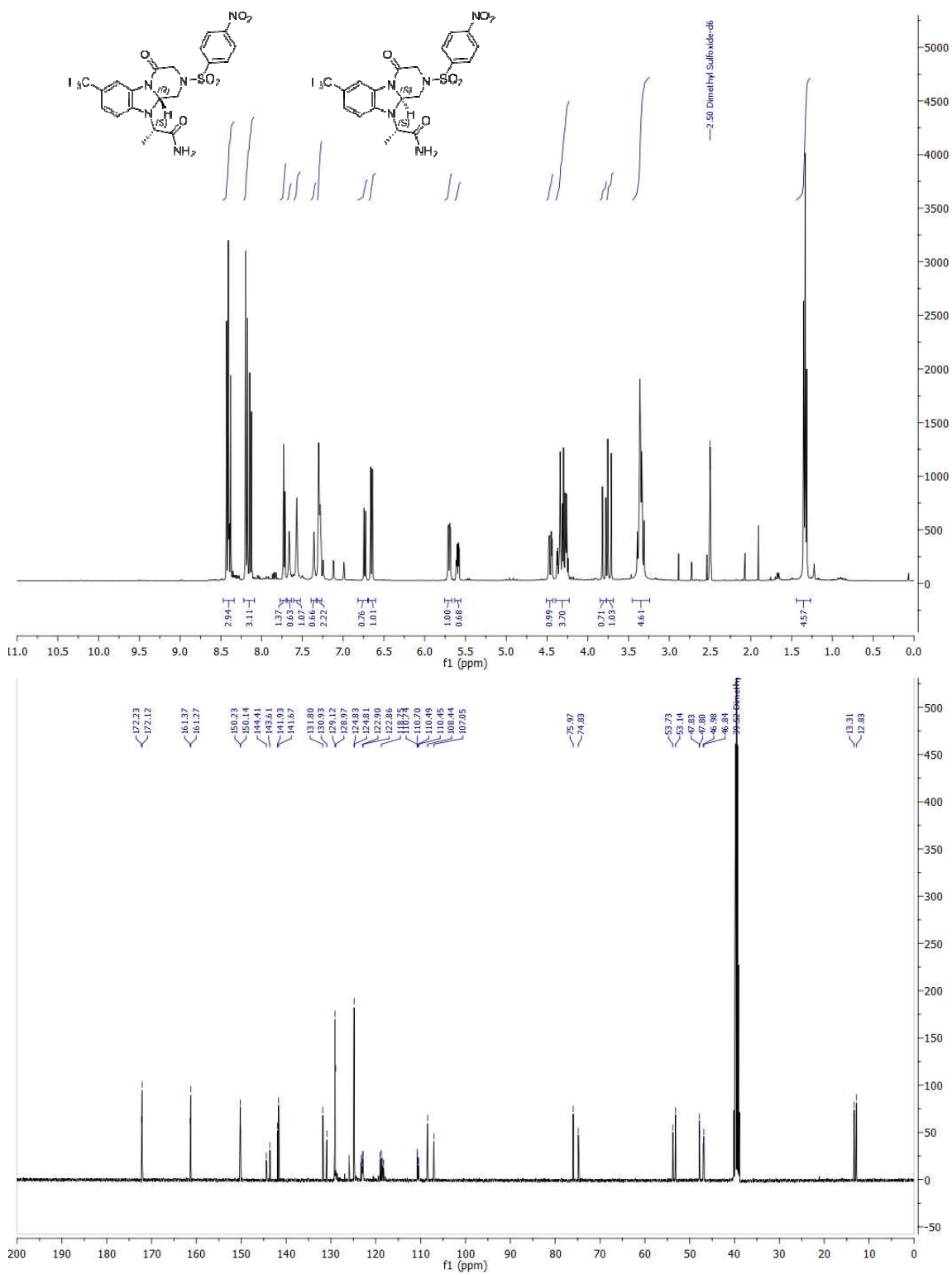


## NMR spectra of compounds

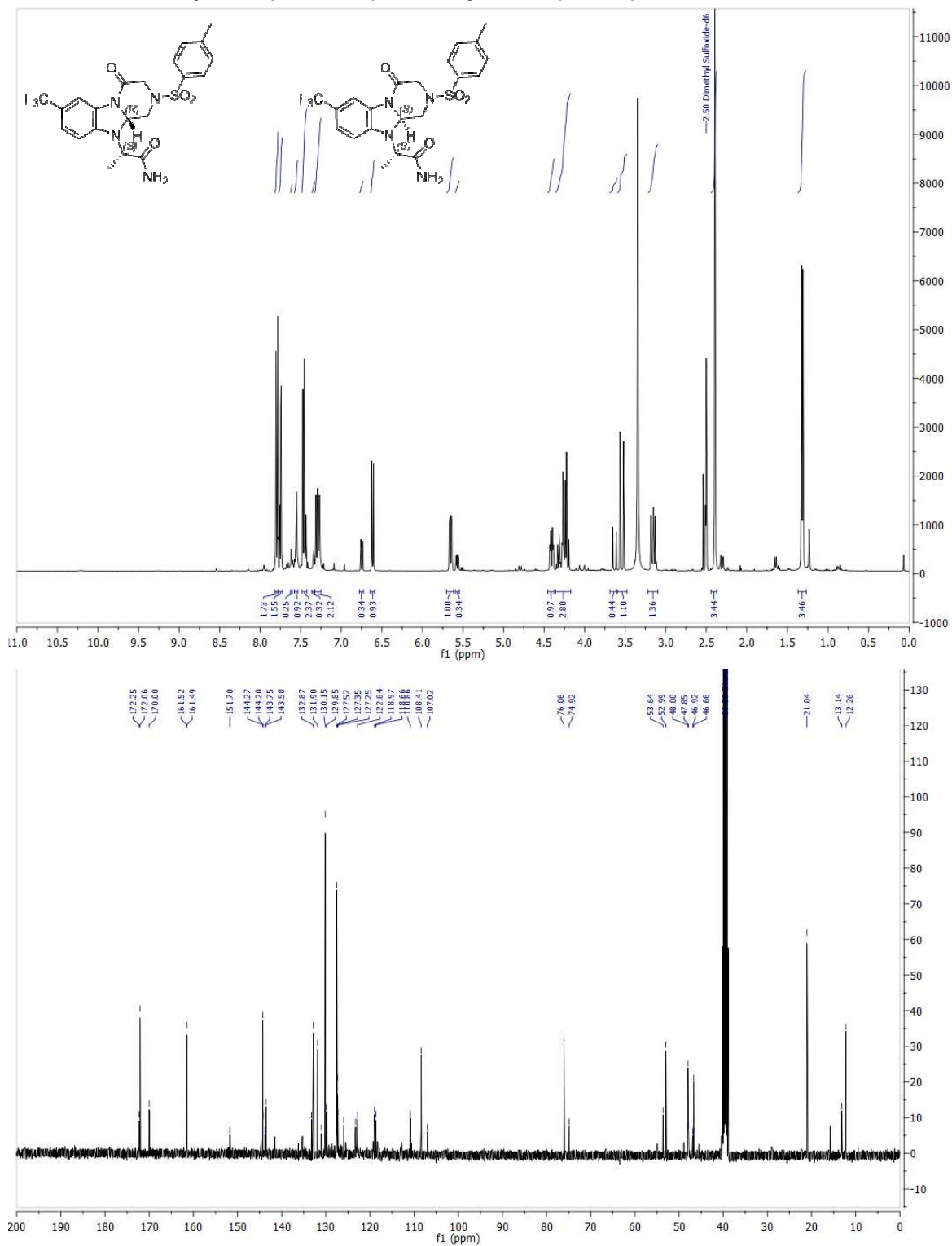
$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $d_6$ -DMSO) for compound 9(1,1,1,1)



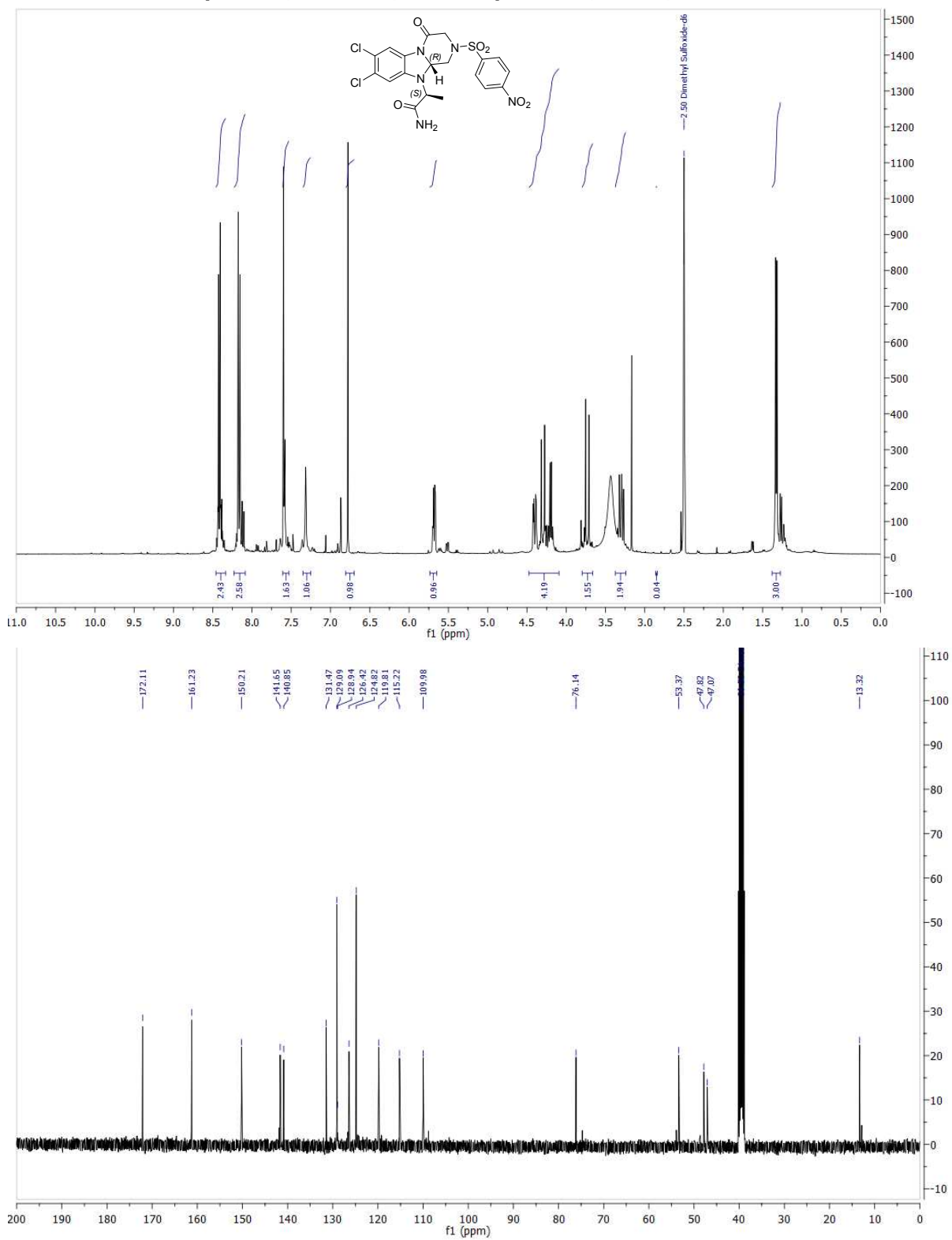
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $d_6$ -DMSO) for compound 9(2,1,1,1)**



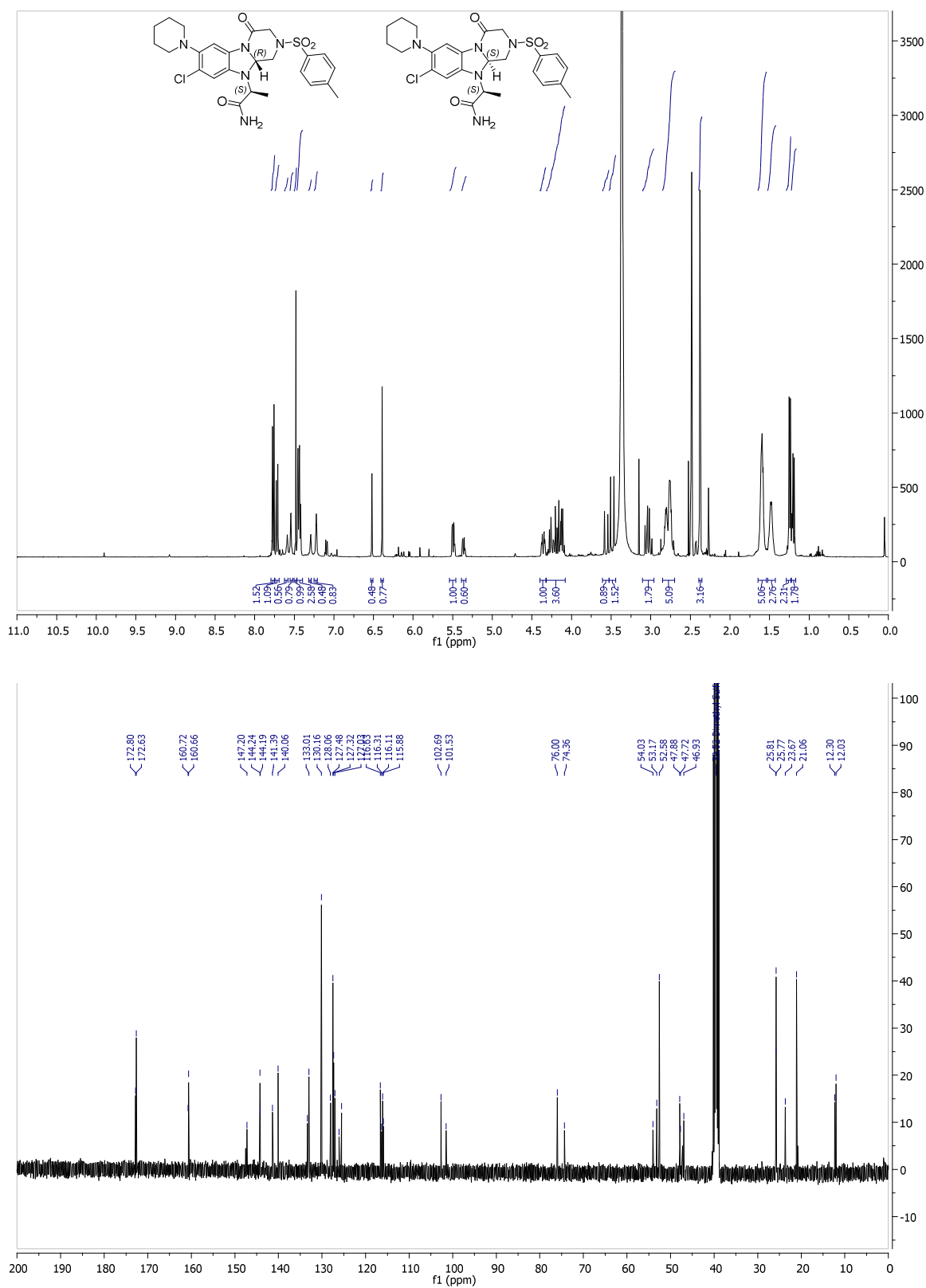
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(2,1,1,2)**



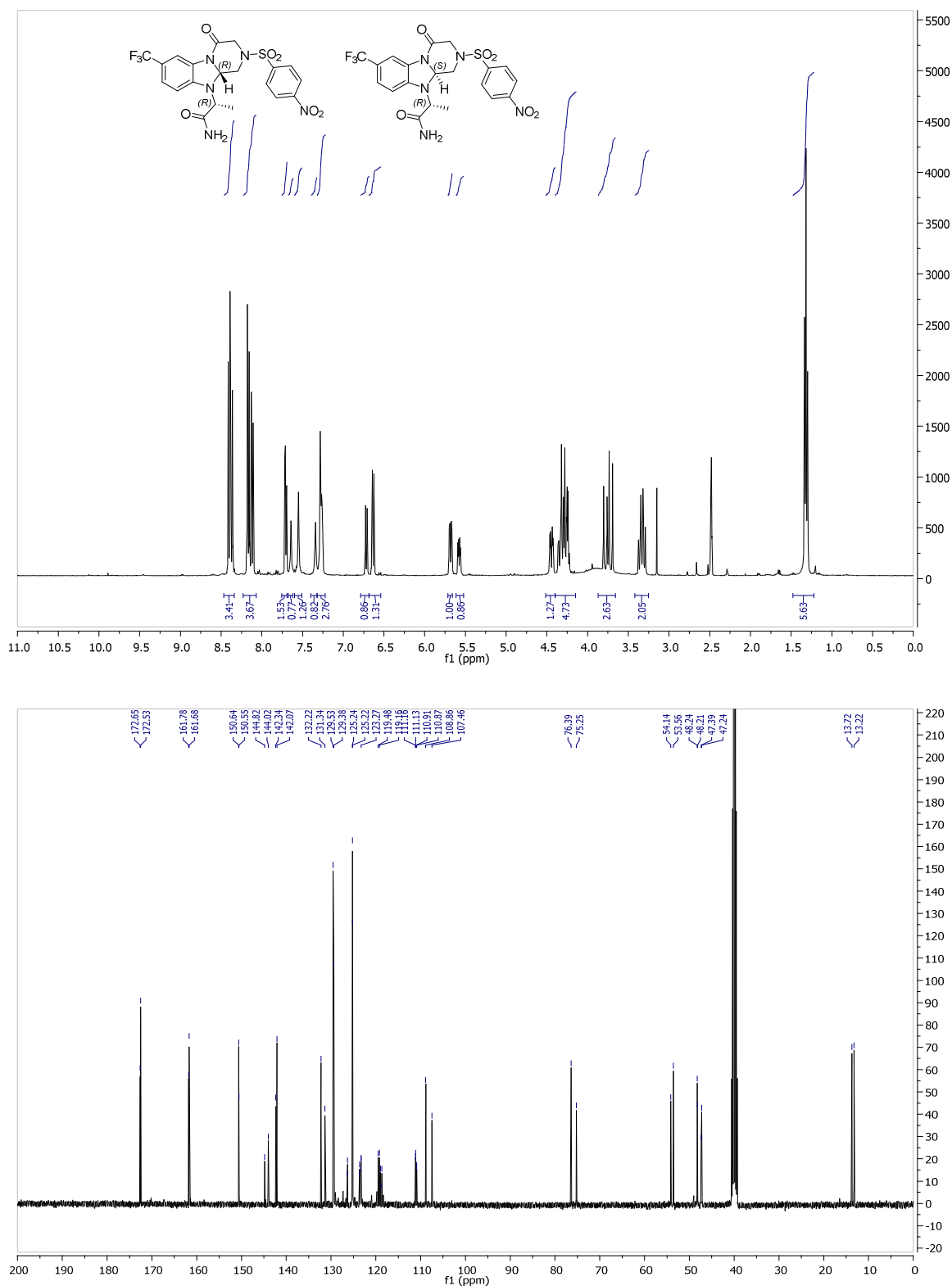
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(2,2,1,1)**



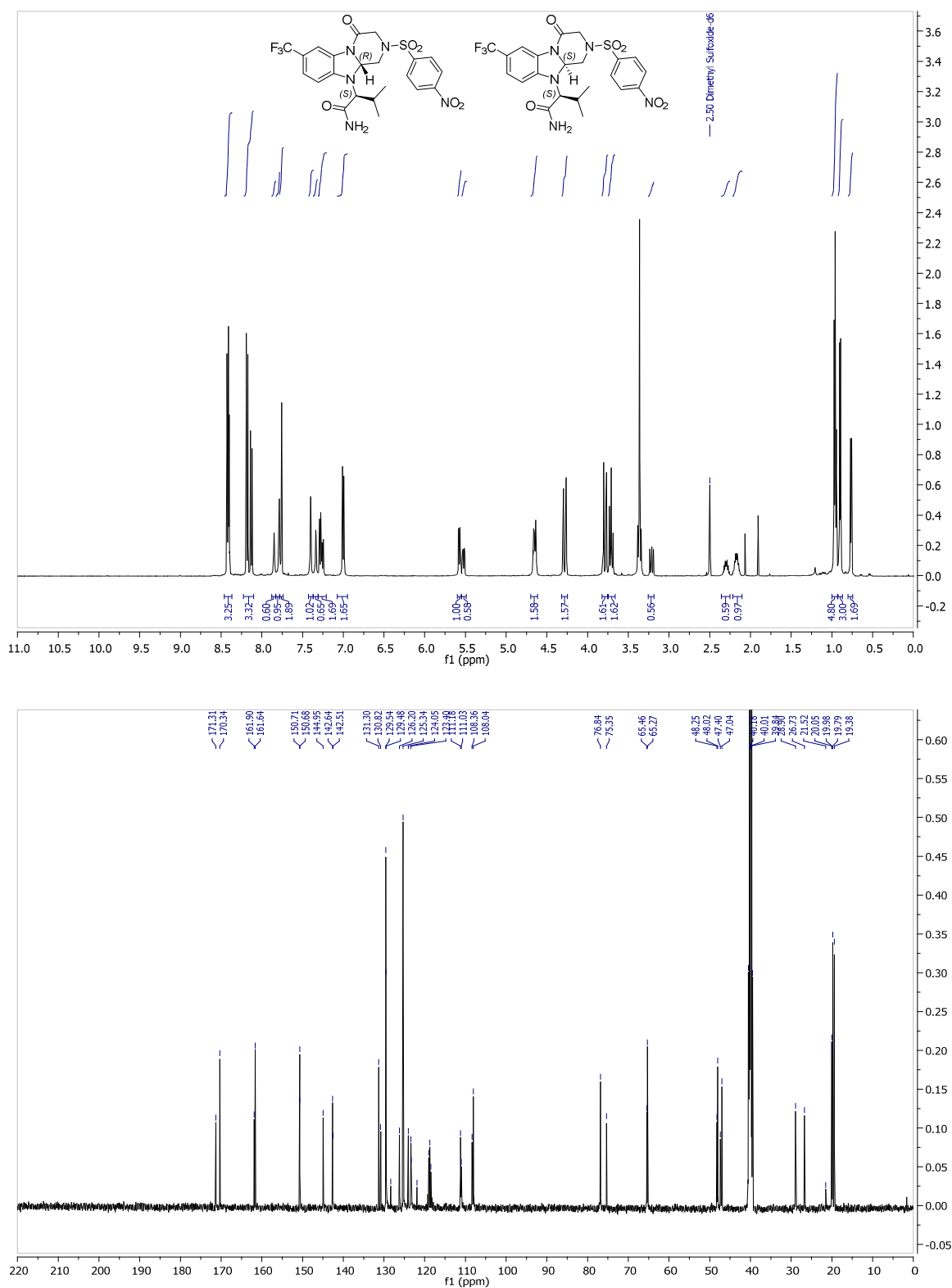
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(2,3,1,2)**



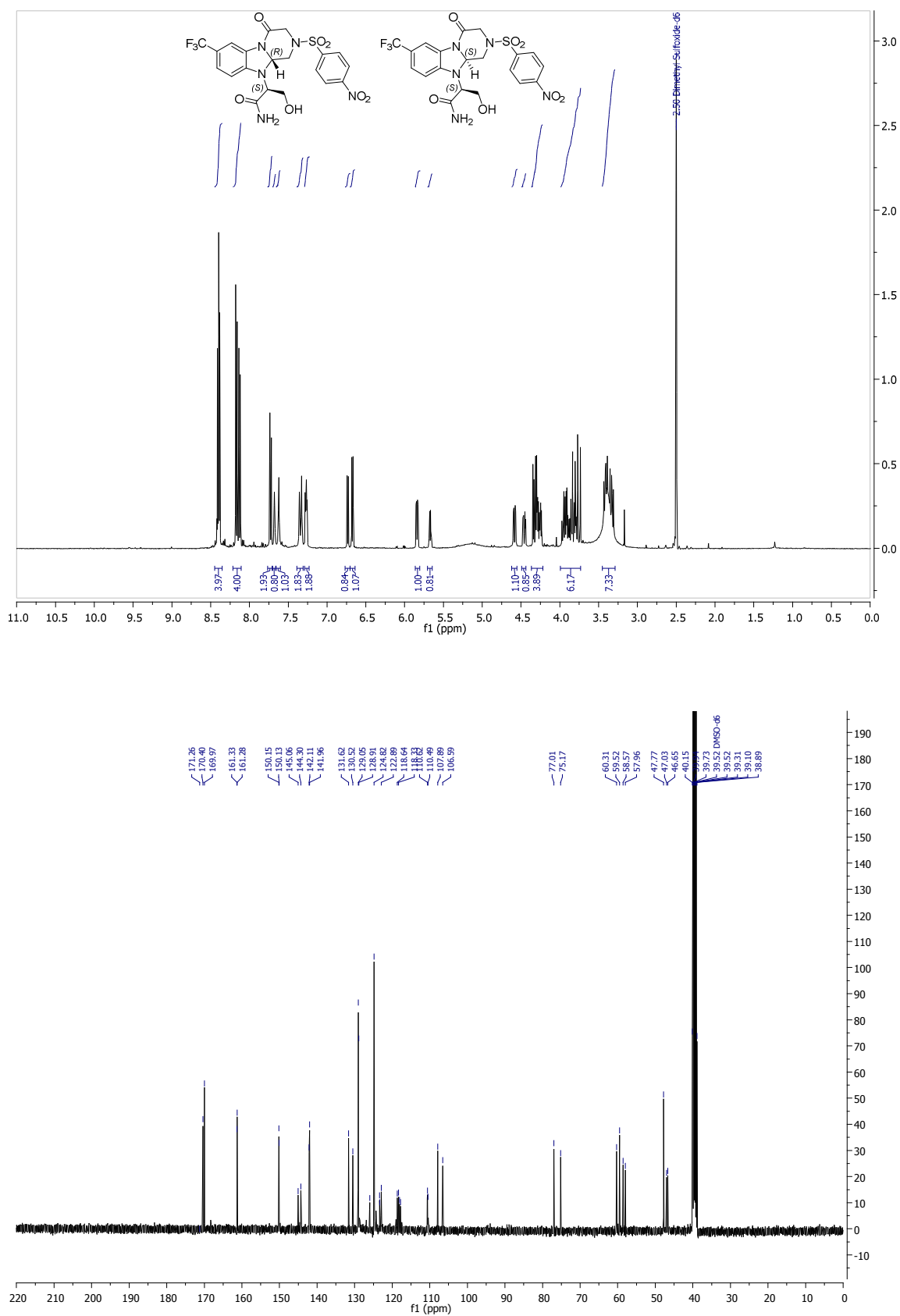
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(3,1,1,1)**



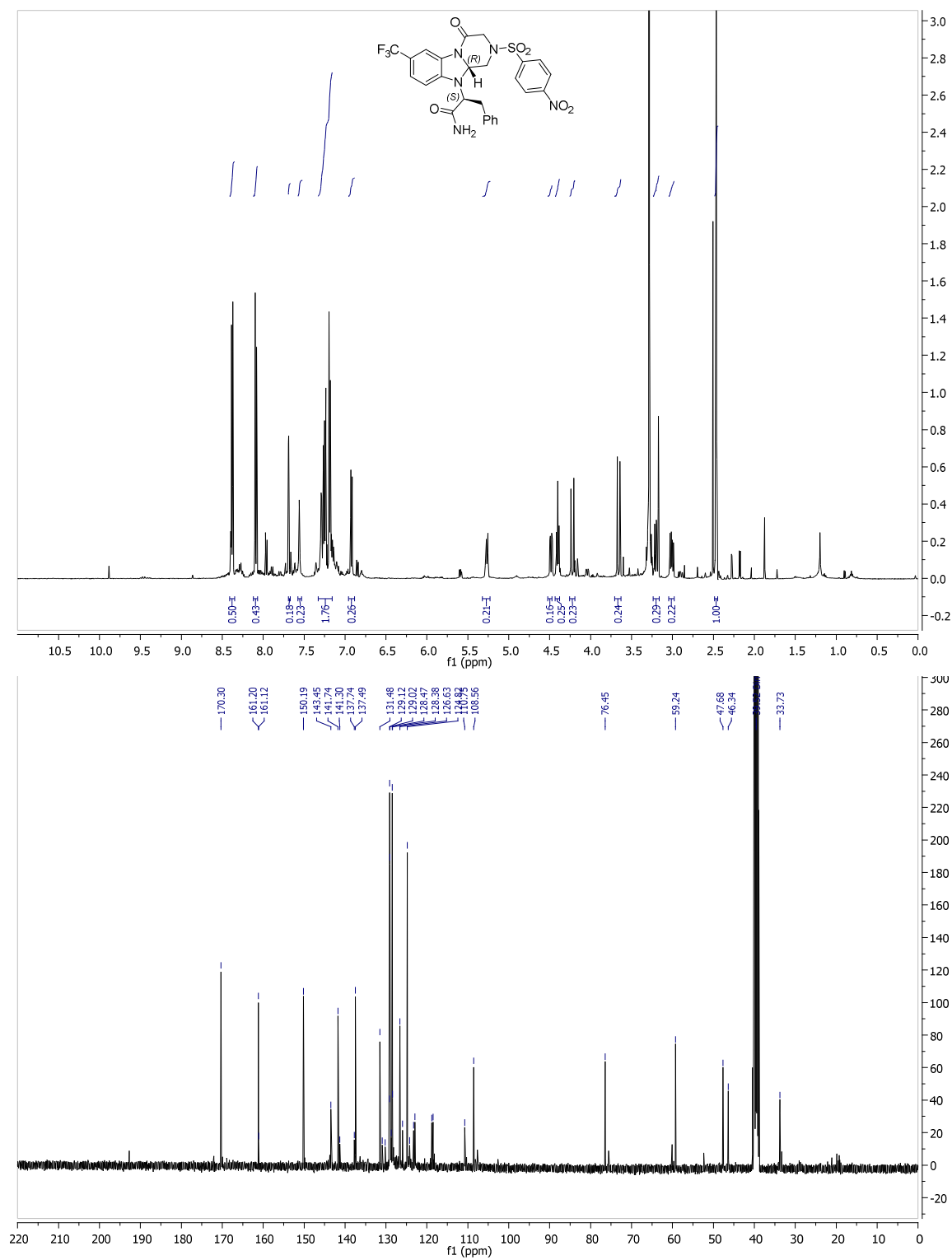
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(4,1,1,1)**



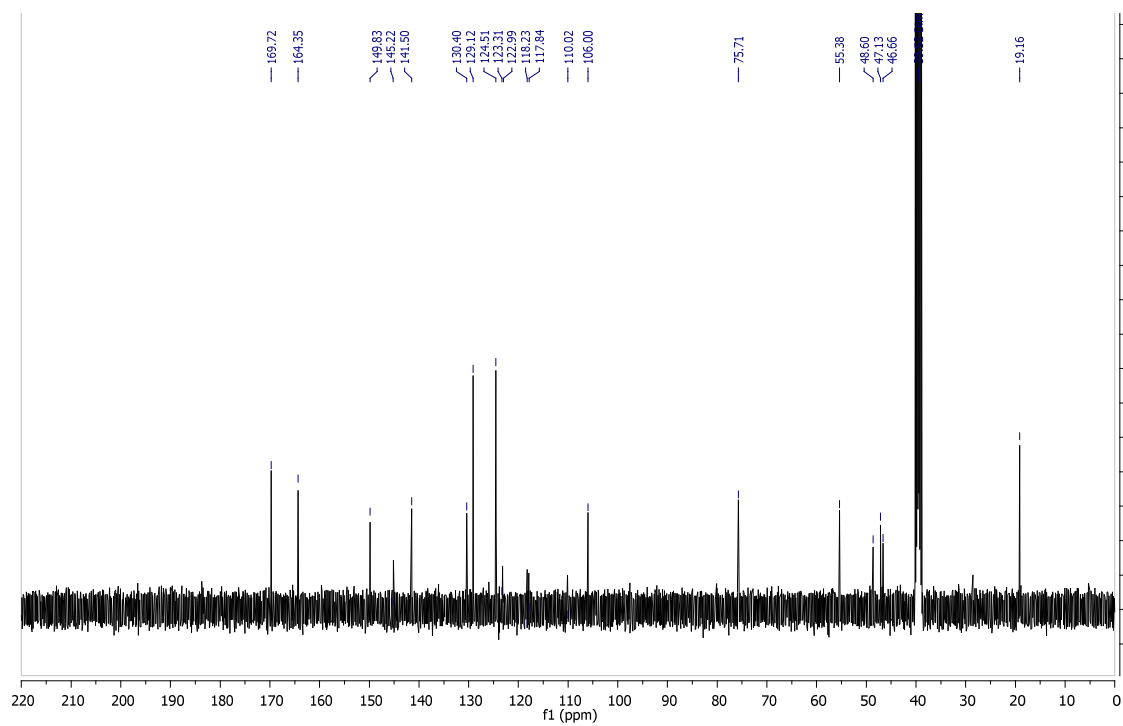
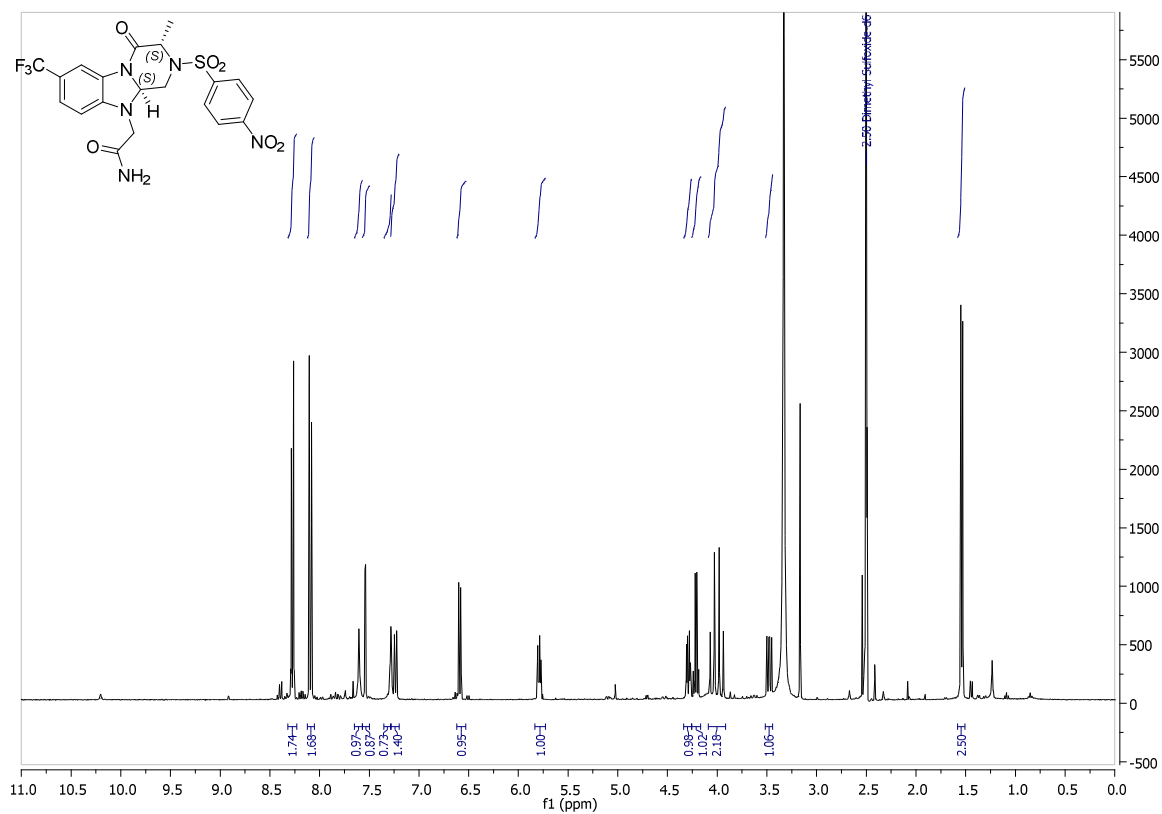
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(5,1,1,1)**



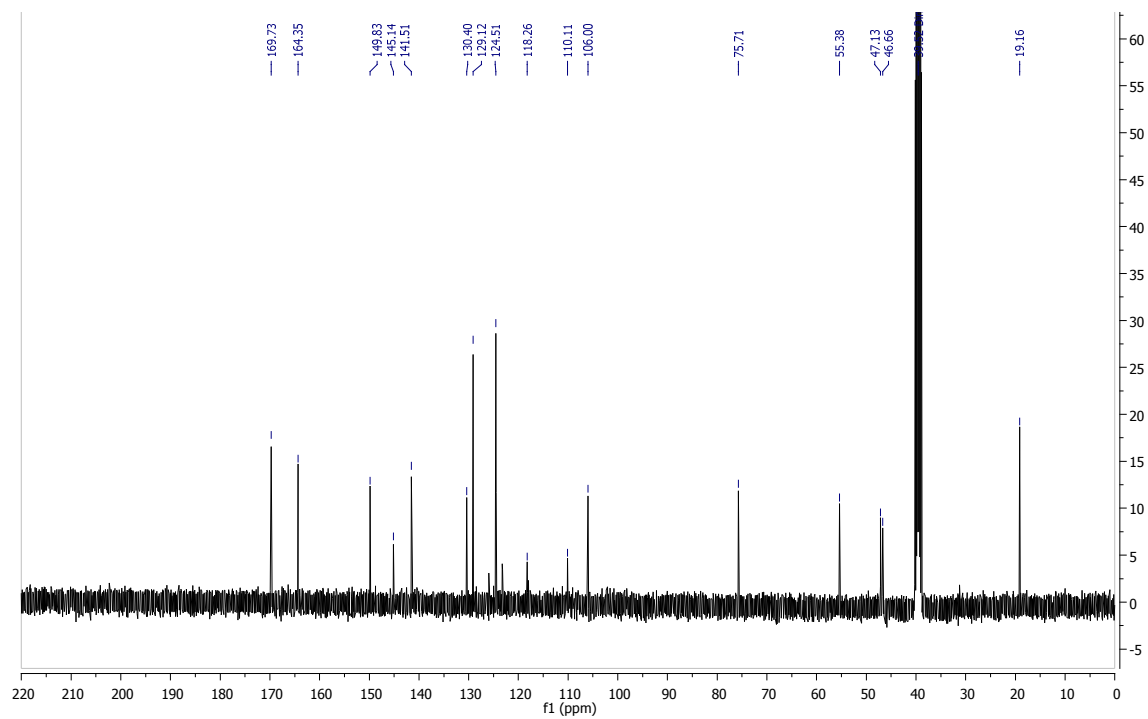
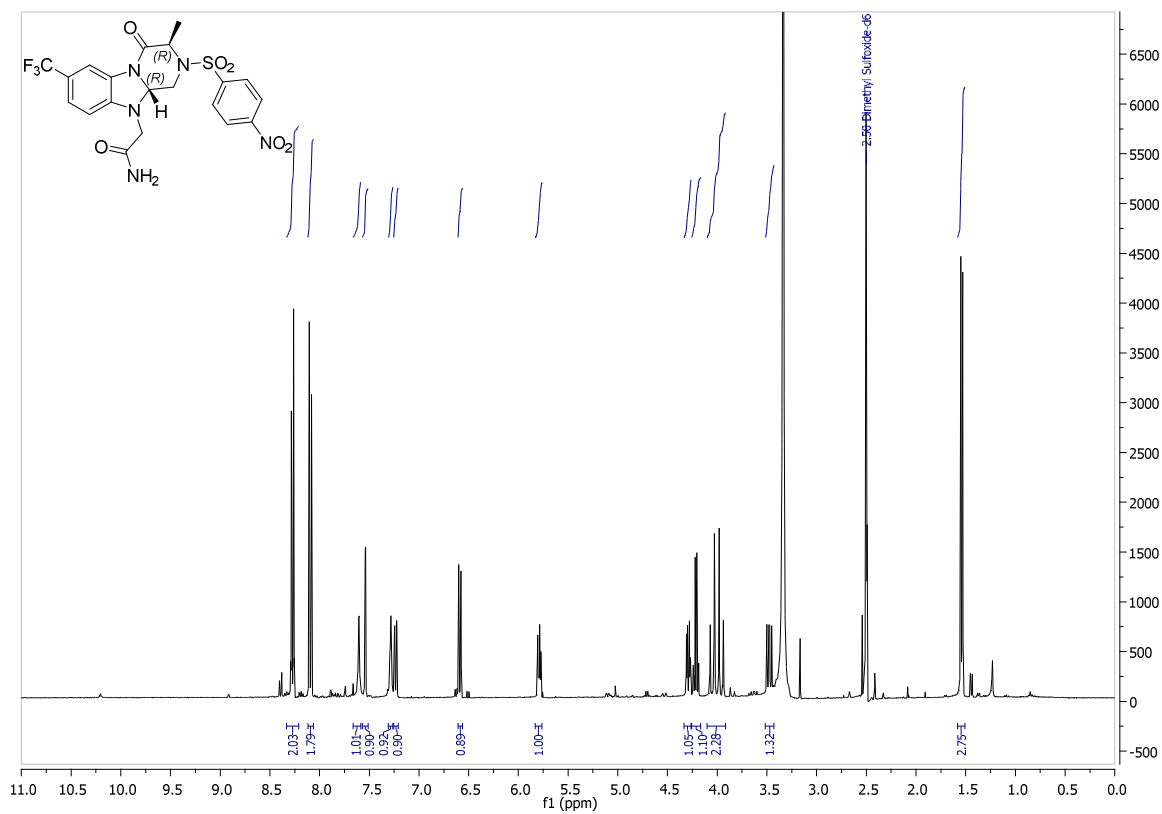
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(6,1,1,1)**



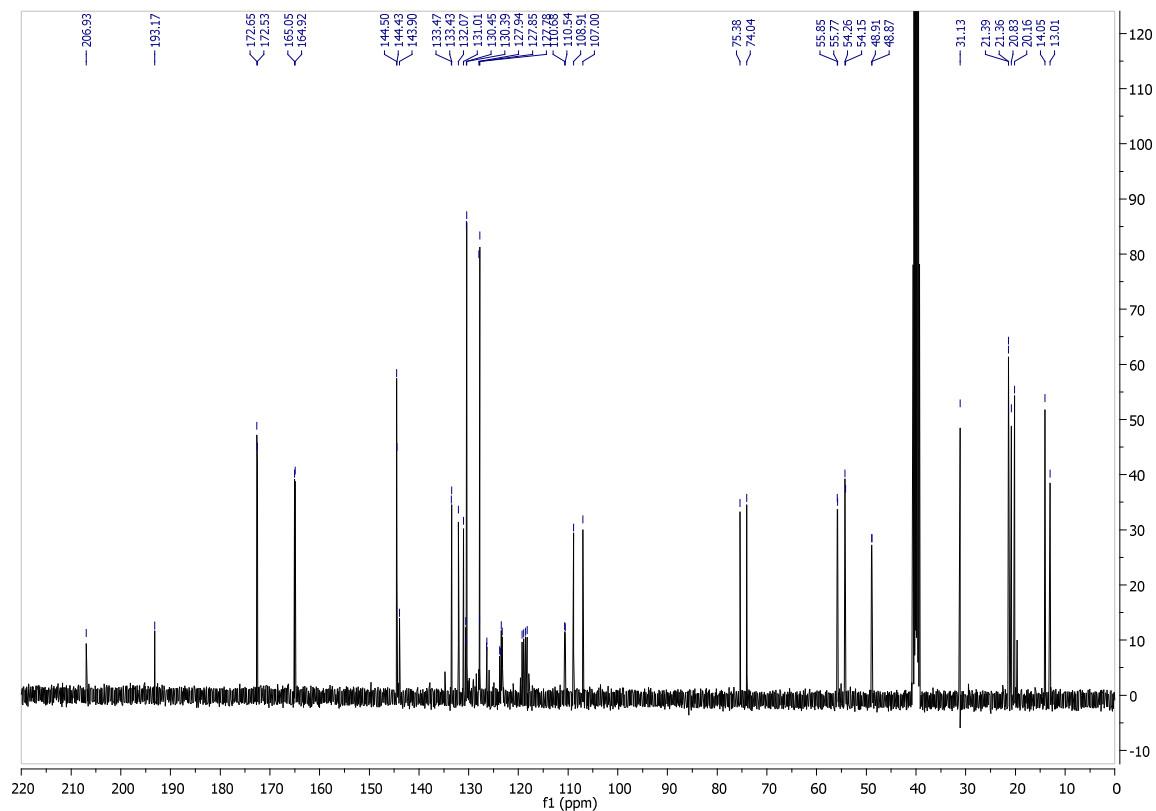
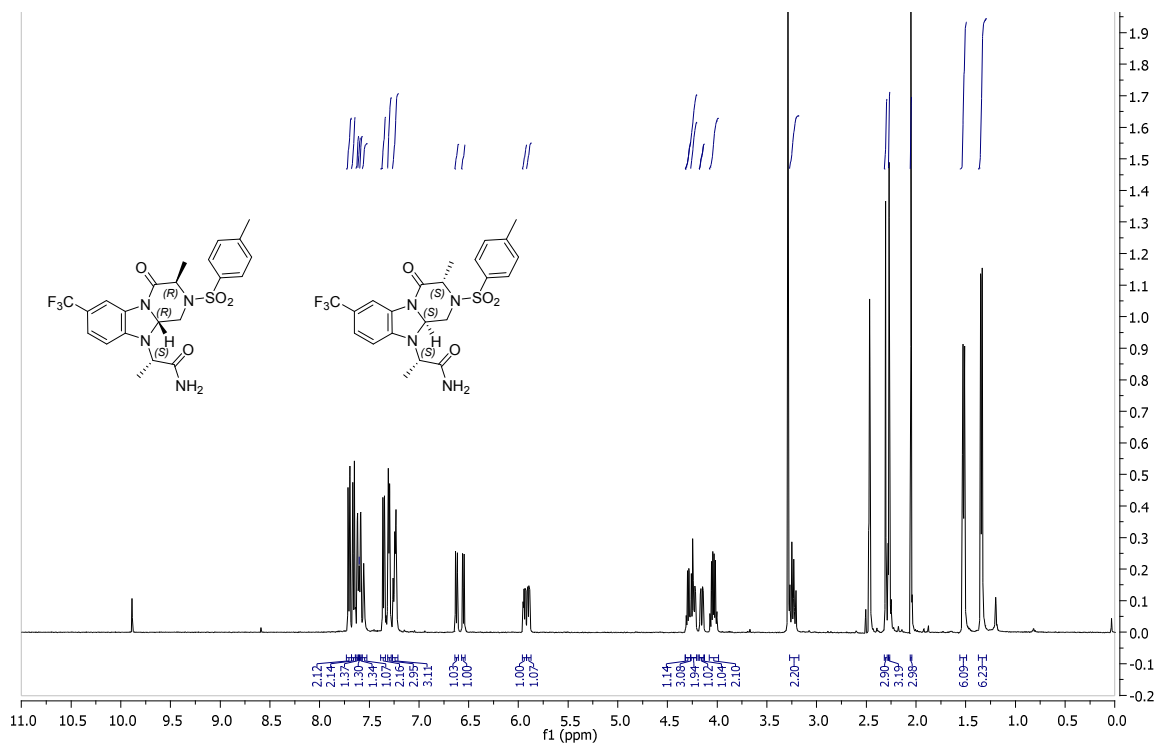
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(1,1,2,1)**



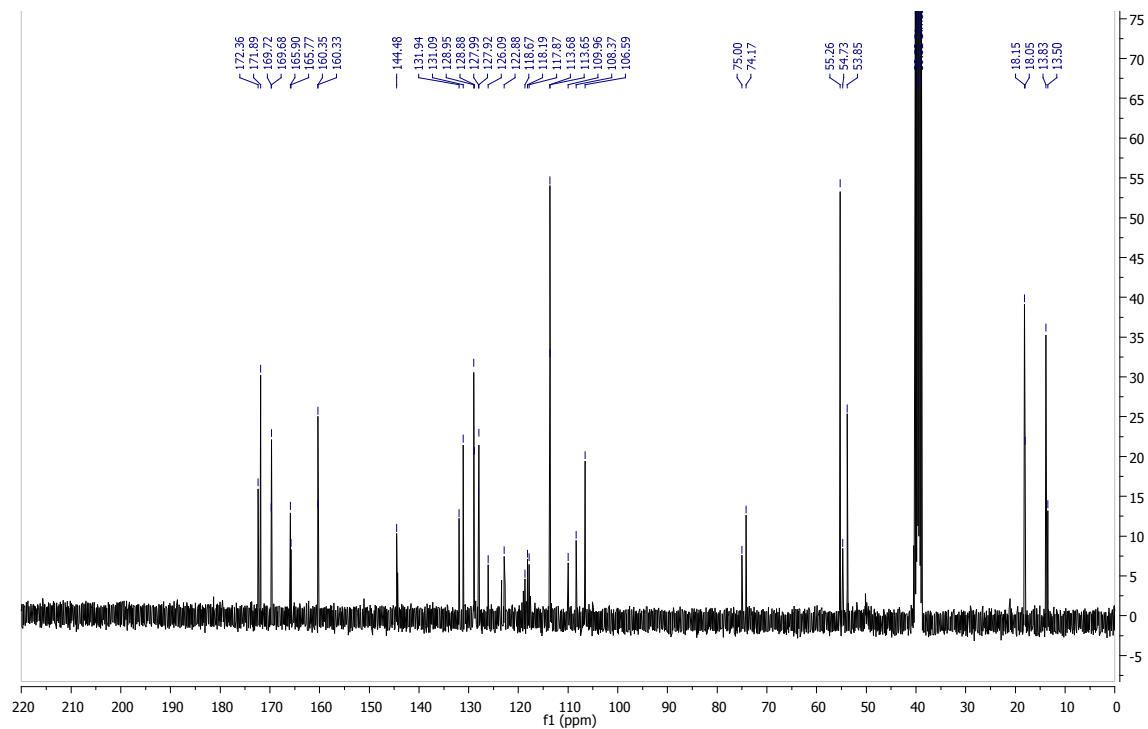
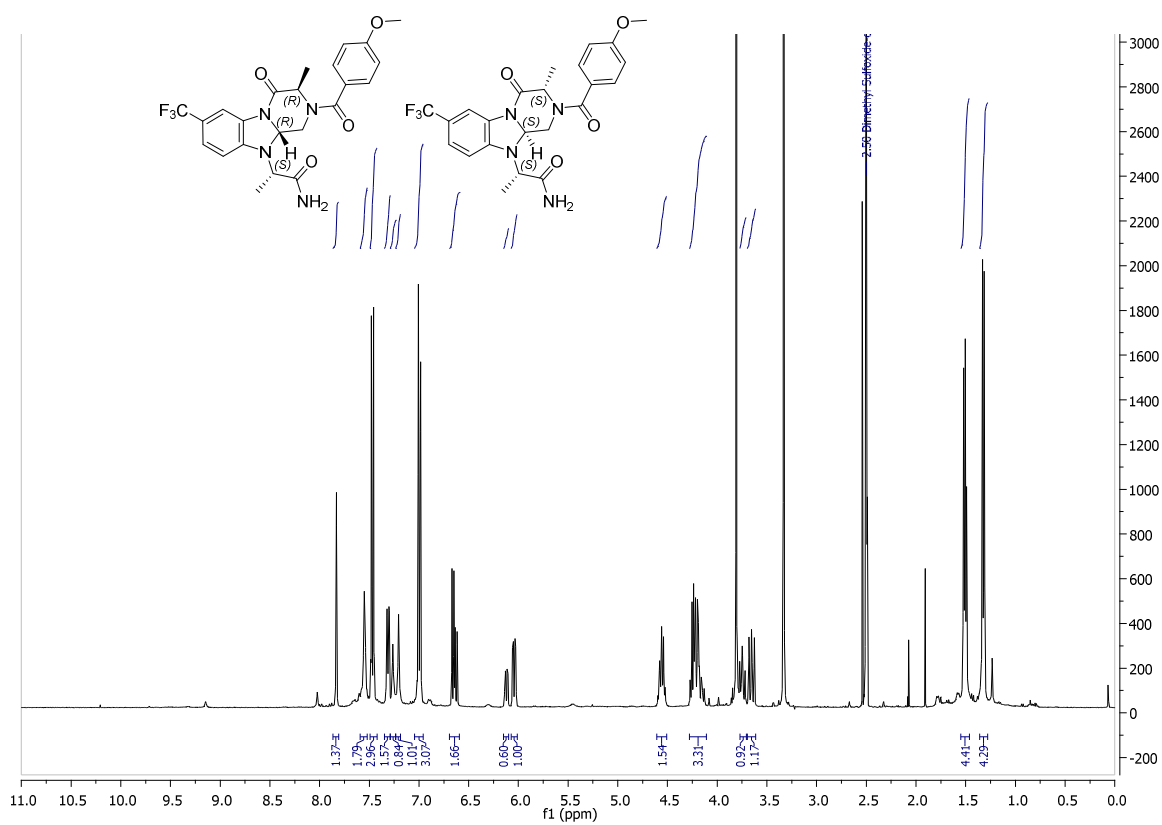
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(1,1,3,1)**



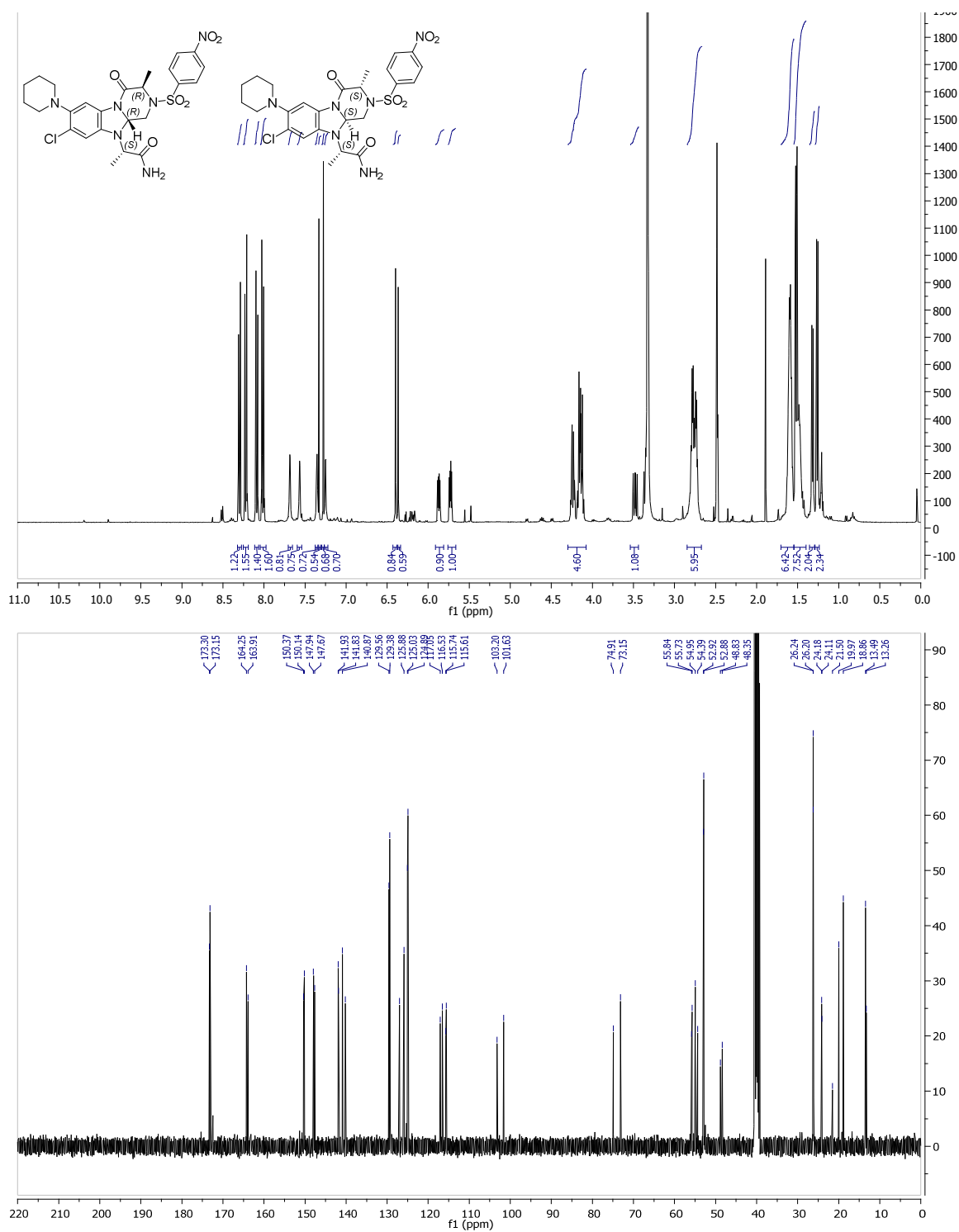
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(2,1,3,2) and 9(2,1,2,2)**



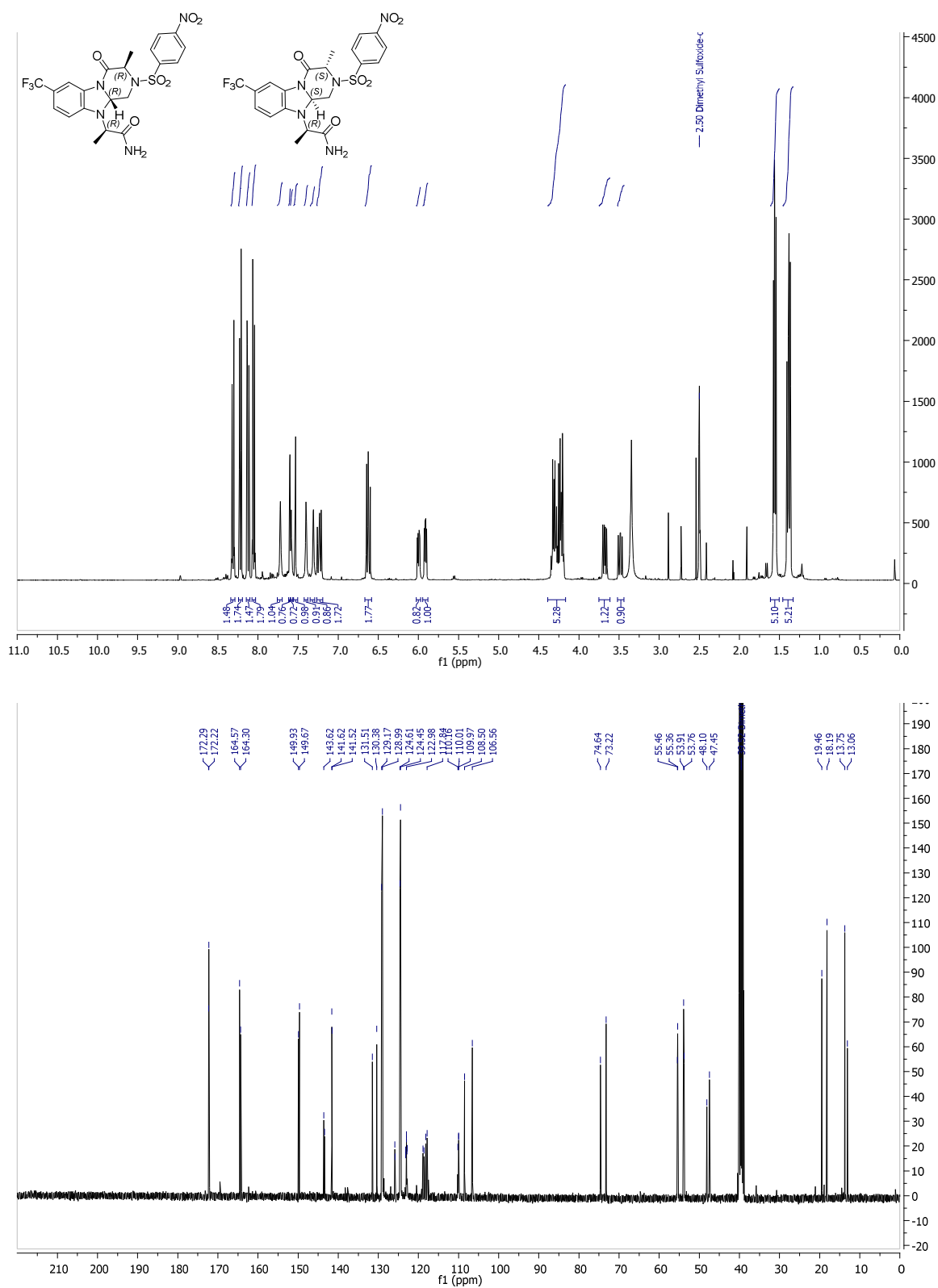
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(2,1,3,4) and 9(2,1,2,4)**



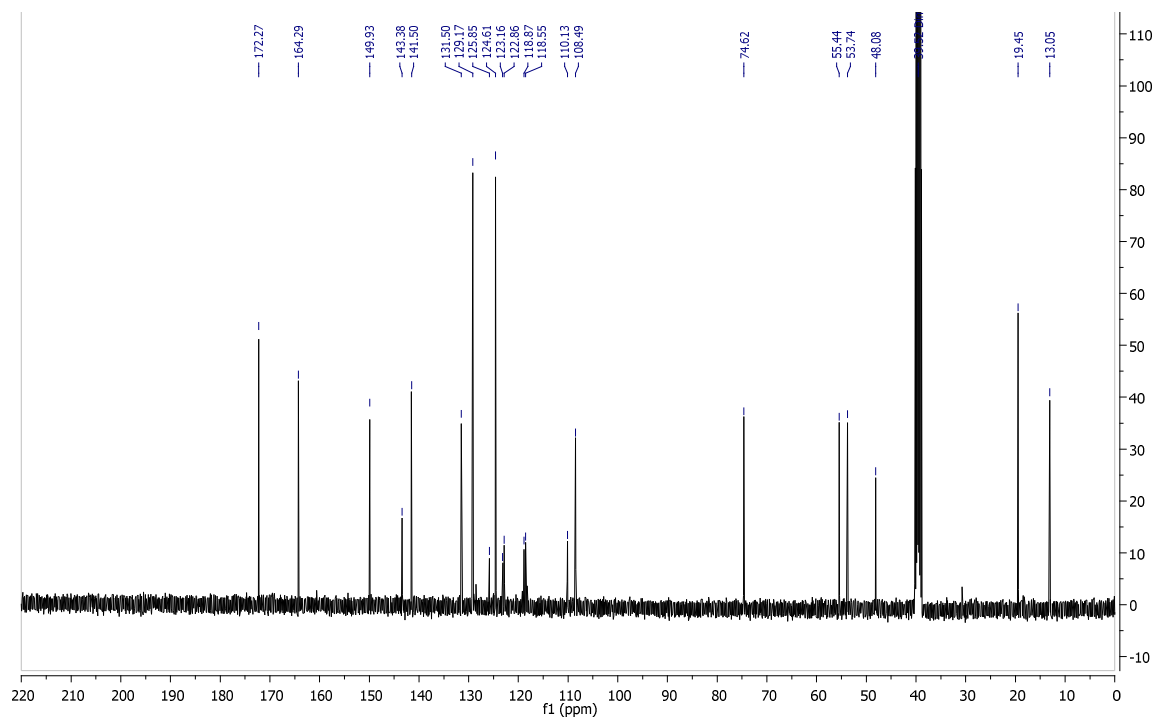
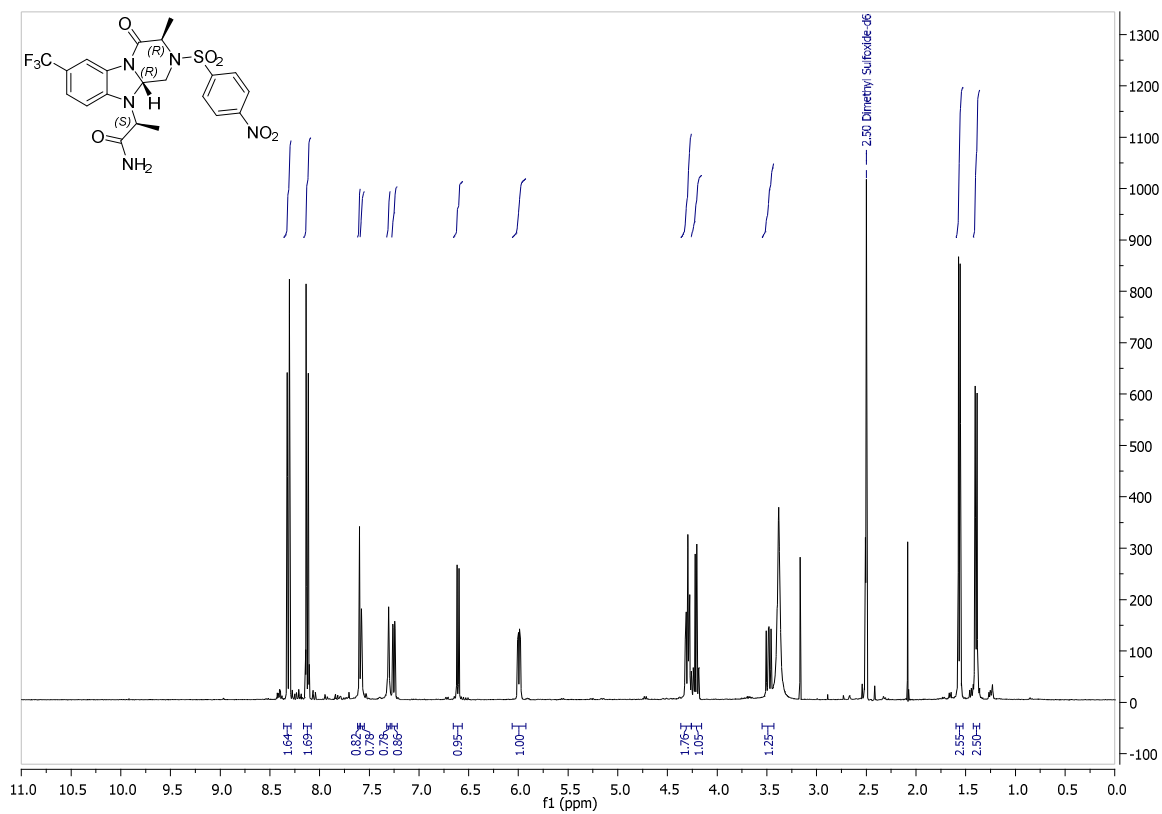
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(2,3,3,1) and 9(2,3,2,1)**



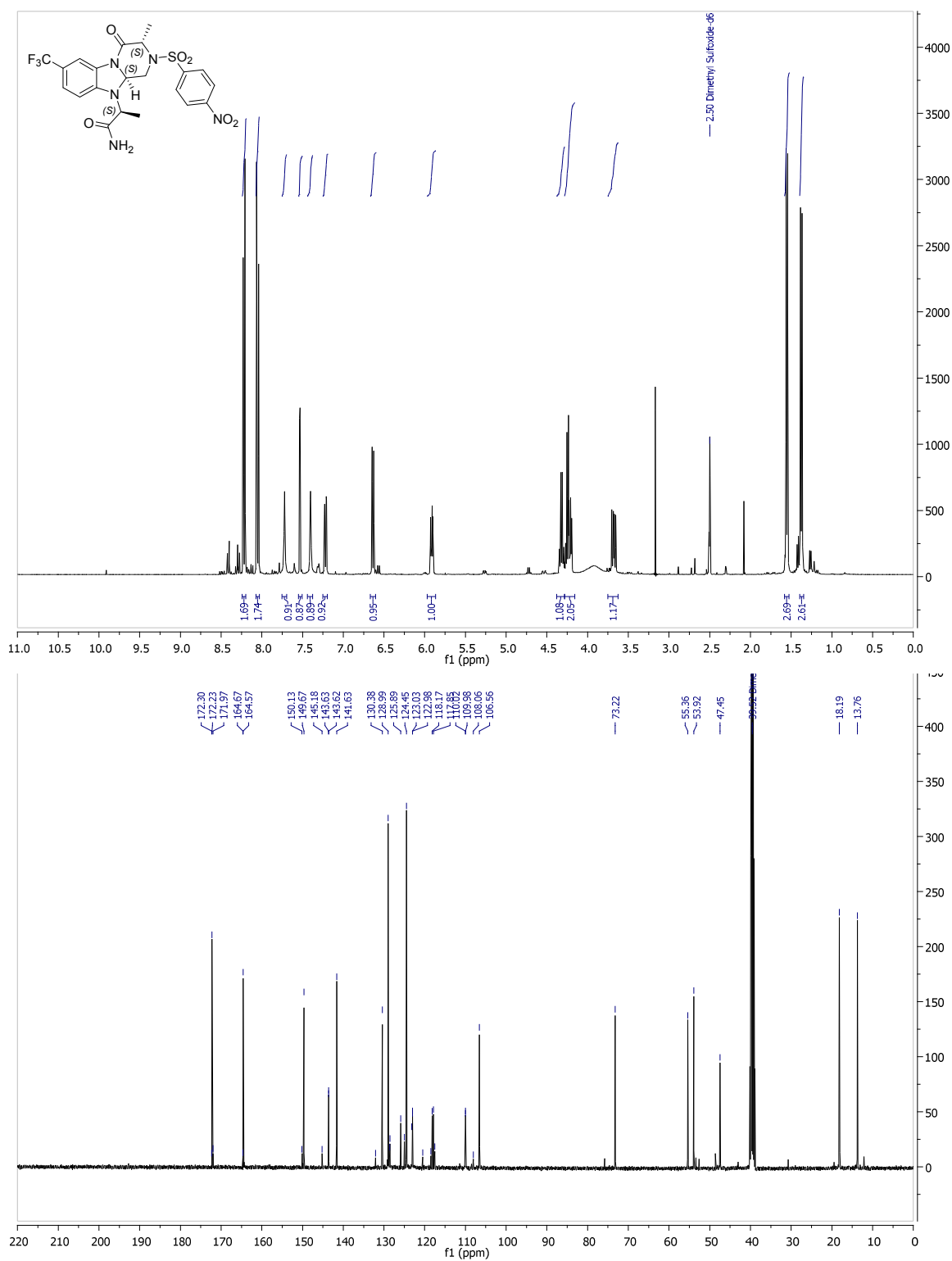
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(3,1,2,1) and 9(3,1,3,1)**



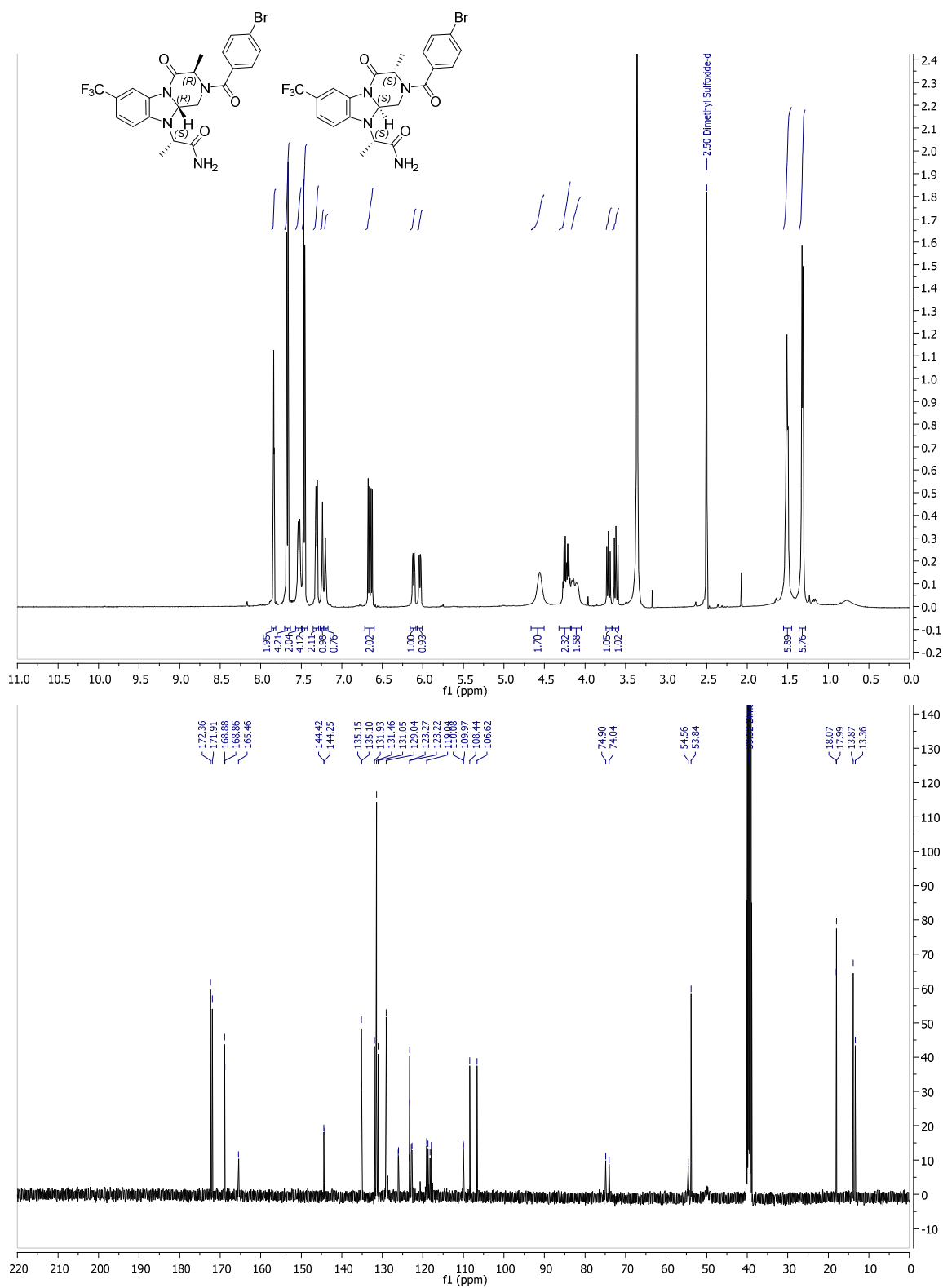
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(2,1,3,1)**



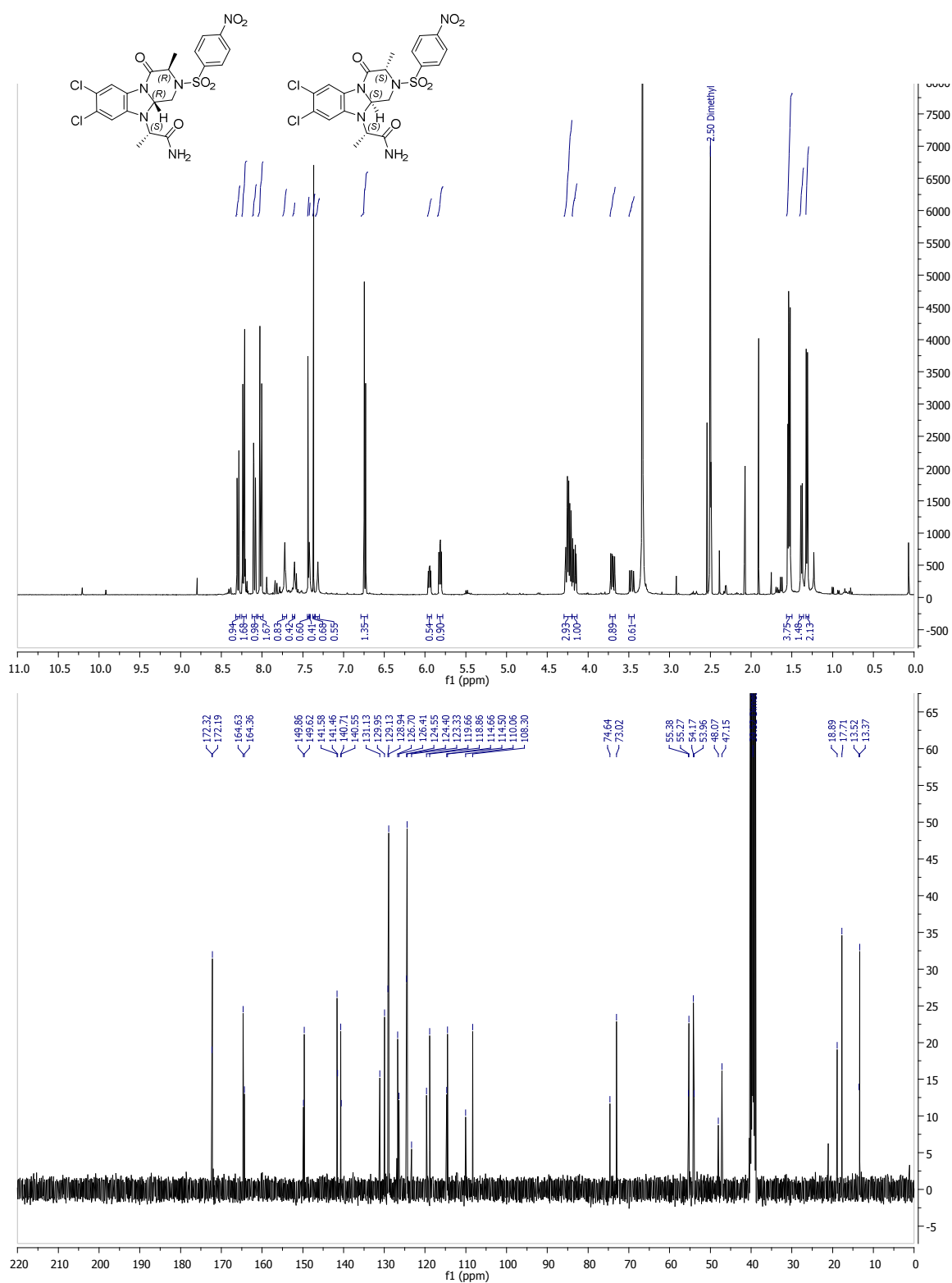
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(2,1,2,1)**



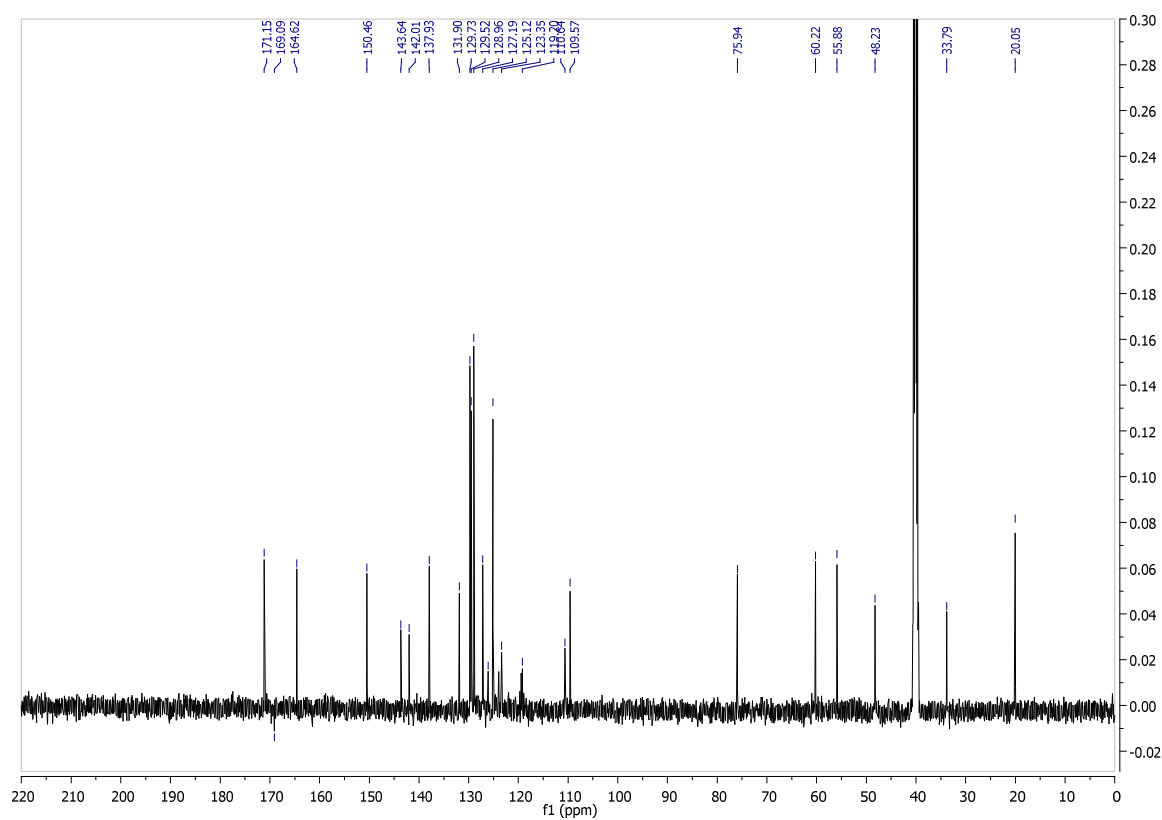
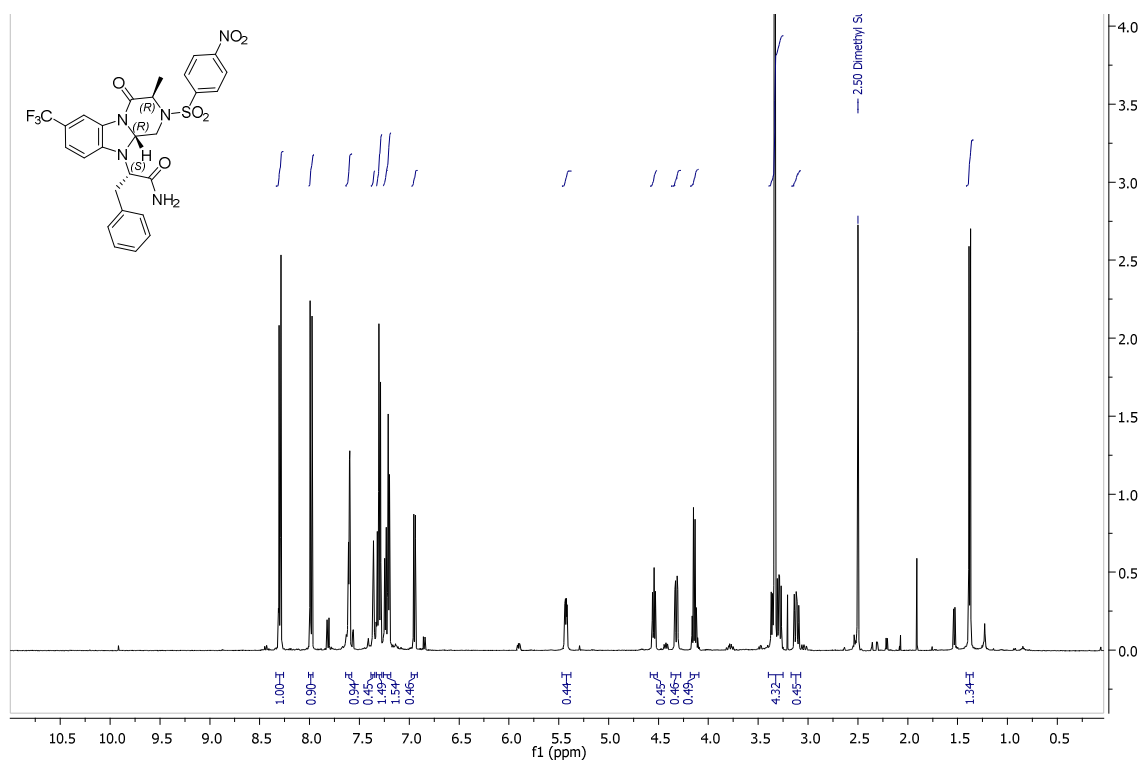
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(2,1,3,3) and 9(2,1,2,3)**



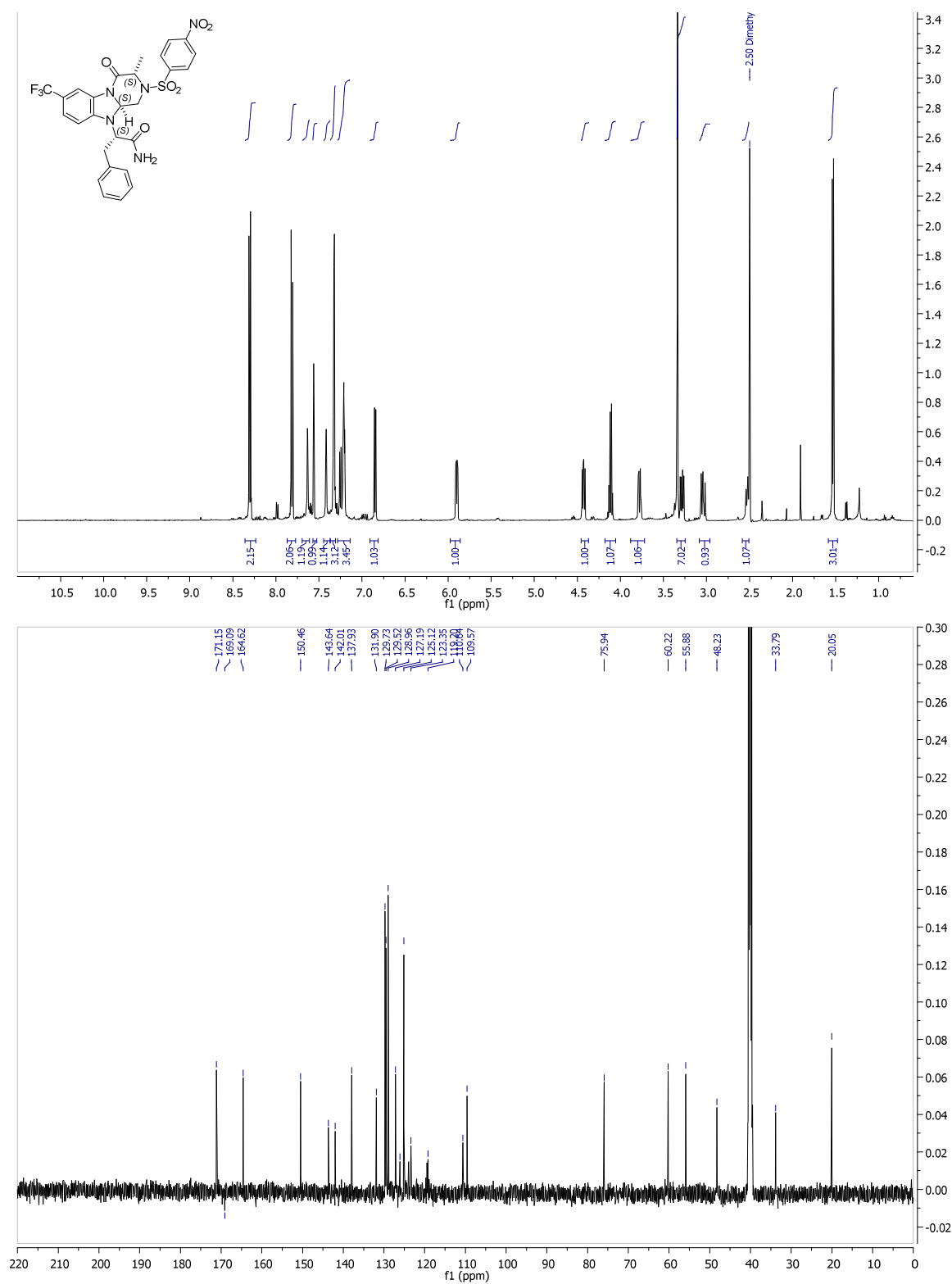
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(2,2,3,1) and 9(2,2,2,1)**



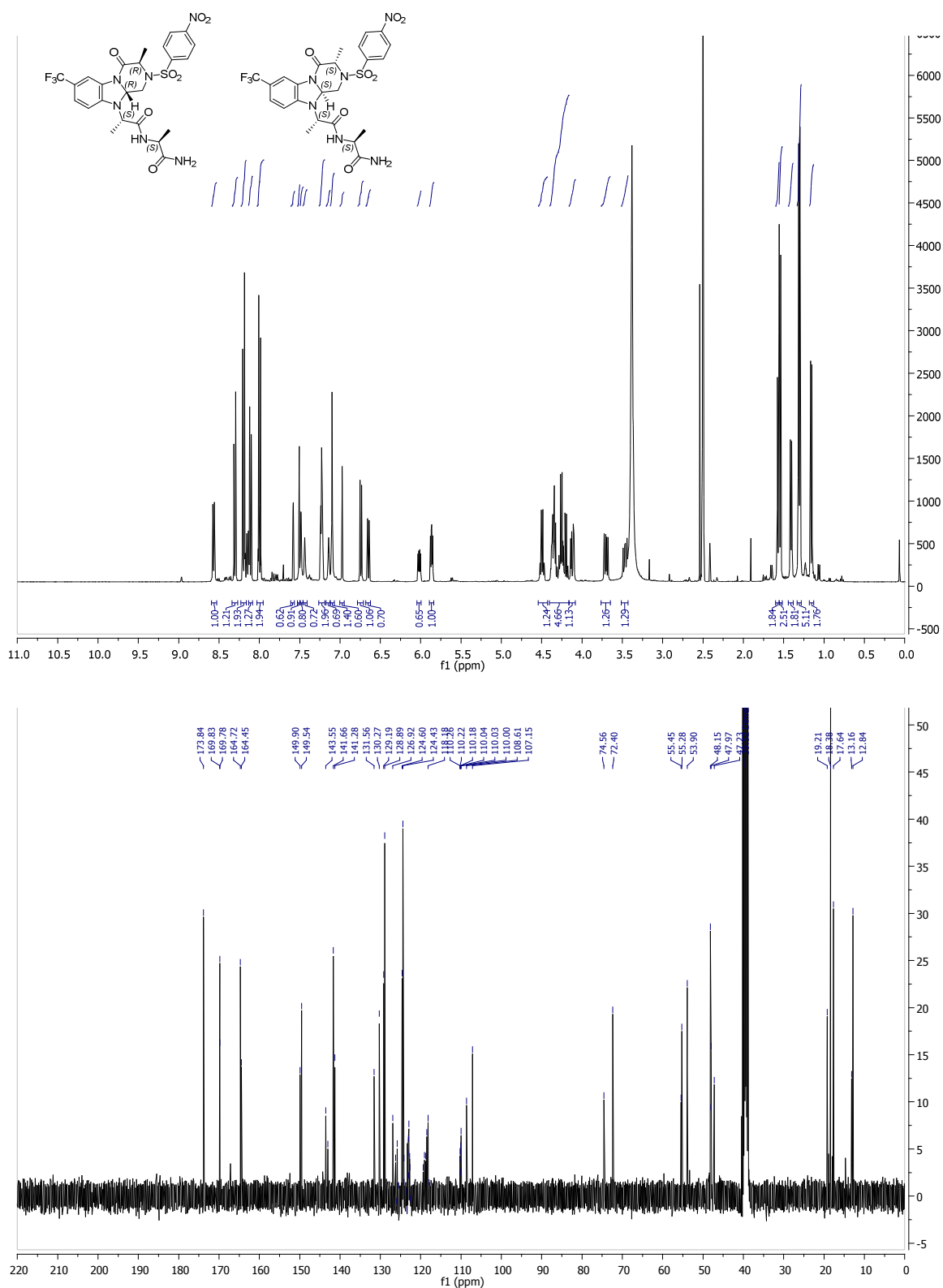
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(6,1,3,1)**



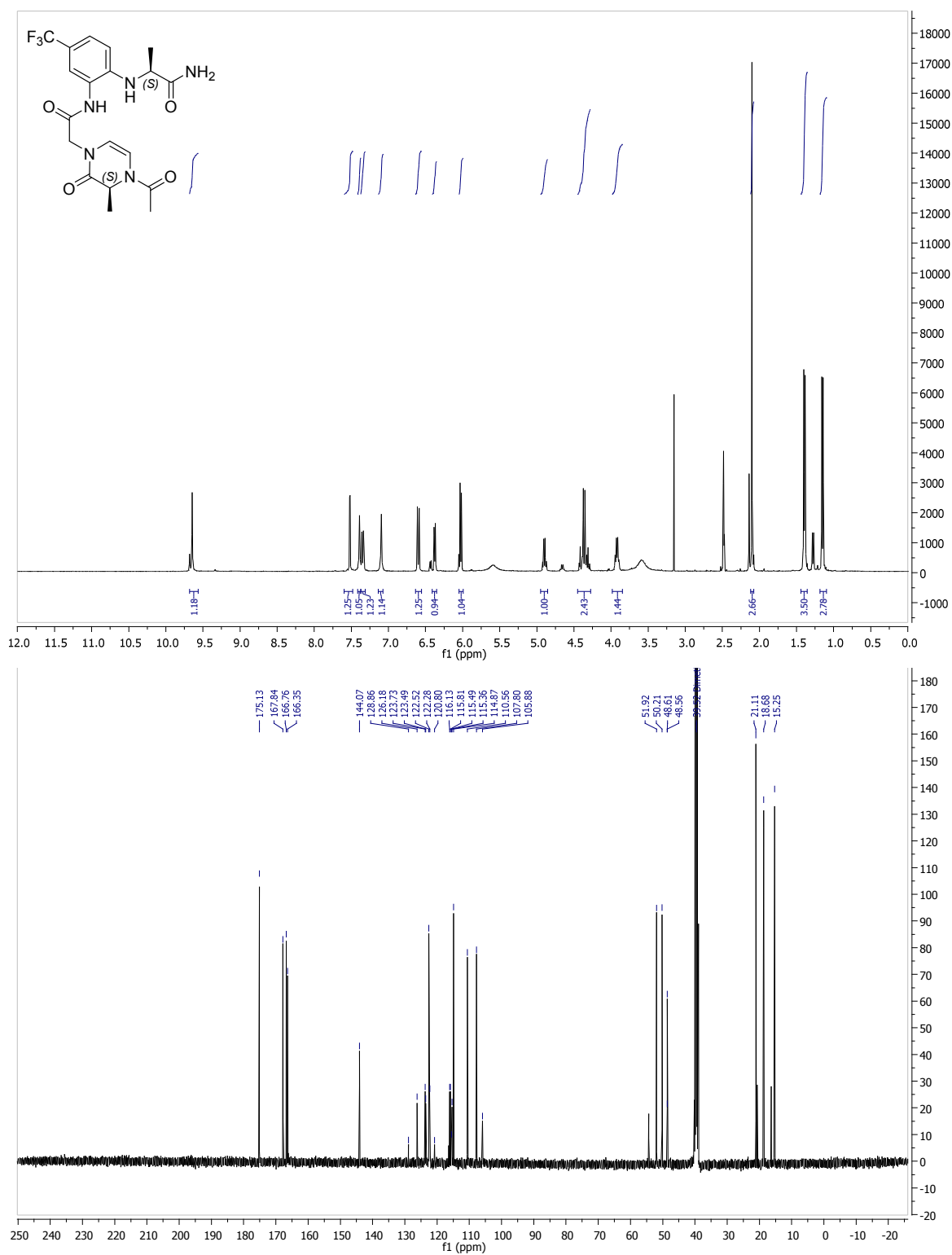
**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 9(6,1,2,1)**



**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound (*SRR*)-14 and (*SSS*)-14**



**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 16**



**$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\text{d}_6\text{-DMSO}$ ) for compound 17**

