Discovery of Benzoheterocyclic-Substituted Amide Derivatives as Apoptosis Signal-Regulating Kinase 1 (ASK1) Inhibitors

Lin Tang[a,b,c], Minxiong Li[b], Changlin Bai[b], Xuejin Feng[b], Haiyang Hu[b], Yufen Yao[d], Baiqing Li[e], Hongwei Li[f], Guohong Qin[f], Ning Xi[g,*], Genpin Lv[c,*], Lei Zhang[a,*]

a MOE International Joint Research Laboratory on Synthetic Biology and Medicines, School of Biology and Biological Engineering, South China University of Technology, Guangzhou 510006, P.R. China

b Sunshine Lake Pharmaceutical Co., Ltd., Dongguan 523871, P.R. China

c Shaoguan HEC Technology R & D Co., Ltd, Shaoguan 512000, P.R. China

d Guangdong Provincial Key Laboratory of New Drug Design and Evaluation, School of Pharmaceutical Sciences, Sun Yat-Sen University, 510006 Guangzhou, P.R. China

e Guangzhou National Laboratory, Guangzhou 510005, P.R. China

f Guangdong Yuchuang Electronics Co., Ltd., Shaoguan 512721, P.R. China

g Institute of Drug Discovery Technology, Ningbo University, Ningbo 315211, P.R. China

*Corresponding author.

E-mail: xining@nbu.edu.cn (Ning Xi); dyglee@163.com (Genpin lv); lzhangce@scut.edu.cn (Lei Zhang).

Supplementary Information

1. Synthetic procedures of the intermediates

1.1. methyl 1-(5-carbamoyl-2,4-difluorophenyl)-1H-imidazole-5-carboxylate (**4**)

To a solution of **1** (8.87 g, 51.60 mmol) in MeOH (300 mL) were added **2** (12.85 g, 62.93 mmol) and Dimethyl acetal (150 mL), the mixture was stirred at 80°C for 12 hours and then cooled to room temperature. After that, **3** (30.50 g, 156.22 mmol) and K_2CO_3 (14.40 g, 103.20 mmol) were added to the mixture, and the reaction was continued to be stirred at room temperature for 24 hours. The resulting mixture was concentrated and the residue was partitioned between DCM and water. The organic layer underwent a washing process with brine, followed by drying with anhydrous Na_2SO_4, and concentration. The resulting residue was purified by column chromatography on silica gel to give the compound **4** (6.00 g, 41.4% yield) as a yellow solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.16 (s, 1H), 7.87 (m, 2H), 7.80 (s, 1H), 7.65 (t, J = 10.1 Hz, 1H), 4.21– 4.10 (m, 1H), 3.70 (s, 3H). MS (ESI) $[M+H]^+$: 282.2.

1.2. General synthetic procedures for the synthesis of compounds (**6a** – **6g**)

To a solution of **4** (1.0 mmol, 1 eq.) in 1,4-Dioxane (15 mL) were added **5** (**5a** – **5g**) (1.2 mmol, 1.2 eq.), $Pd_2(dba)_3$ (0.12 mmol, 0.1 eq.), Xant-Phos (0.12 mmol, 0.1 eq.) and Cs_2CO_3 (2.0 mmol, 2.0 eq.), the mixture was stirred at 100°C overnight under nitrogen protection. The

solution was concentrated and the resulting residue was partitioned between DCM and water. The organic layer underwent a washing process with brine, followed by drying with anhydrous Na_2SO_4, and concentration. The resulting residue was purified by column chromatography on silica gel to give the compounds (**6a** – **6g**).

1.2.1. Methyl 1- (2,4-difluoro-5- ((6-(4-isopropyl-4H-1,2,4-triazol-3-yl) pyridin-2-yl) carbamoyl) phenyl) -1H-imidazole-5-carboxylate (**6a**).

A white solid was obtained with a yield of 50.0%. MS (ESI) $[M+H]^+$: 468.5.

1.2.2. Methyl 1- (5- ((6- (4-cyclopropyl-4H-1,2,4-triazol-3-yl) pyridin-2-yl) carbamoyl) -2,4-difluorophenyl) -1H-imidazole-5-carboxylate (**6b**).

A yellow solid was obtained with a yield of 69.5%. MS (ESI) $[M+H]^+$: 466.1.

1.2.3. Methyl 1- (5- ((6- (4-cyclopentyl-4H-1,2,4-triazol-3-yl) pyridin-2-yl) carbamoyl) -2,4-difluorophenyl) -1H-imidazole-5-carboxylate (**6c**).

A yellow solid was obtained with a yield of 72.1%. MS (ESI) $[M+H]^+$: 494.1.

1.2.4. Methyl 1- (5- ((6- (4- (cyclopropylmethyl) -4H-1,2,4-triazol-3-yl) pyridin-2-yl)carbamoyl) -2,4-difluorophenyl) -1H-imidazole-5-carboxylate (**6d**).

A yellow solid was obtained with a yield of 62.0%. MS (ESI) $[M+H]^+$: 480.2.

1.2.5. Methyl 1- (2,4-difluoro-5- ((6- (4-phenyl-4H-1,2,4-triazol-3-yl) pyridin-2-yl) carbamoyl) phenyl) -1H-imidazole-5-carboxylate (**6e**).

A yellow solid was obtained with a yield of 77.7%. MS (ESI) $[M+H]^+$: 502.0.

1.2.6. Methyl 1- (2,4-difluoro-5- ((3- (4-isopropyl-4H-1,2,4-triazol-3-yl) phenyl) carbamoyl) phenyl) -1H-imidazole-5-carboxylate (**6f**).

A yellow solid was obtained with a yield of 41.2%. MS (ESI) $[M+H]^+$: 467.2.

1.2.7. Methyl 1- (5- ((3- (4-(cyclopropylmethyl) -4H-1,2,4-triazol-3-yl) phenyl) carbamoyl) -2,4-difluorophenyl) -1H-imidazole-5-carboxylate (**6g**).

A yellow solid was obtained with a yield of 59.0%. MS (ESI) $[M+H]^+$: 479.2.

1.3. General synthetic procedures for the synthesis of compounds (**7a** – **7g**)

To a solution of **6** (**6a** – **6g**) (1.0 mmol, 1 eq.) in THF (10 mL) was added DIBAL (10.0 mmol, 10.0 eq., 1.5 mol/L in toluene) at -10°C, the mixture was stirred at -10°C for 1 hour under nitrogen protection. The resulting mixture was poured into ice water and then extracted with DCM for three times. The organic layer underwent a washing process with brine, followed by

drying with anhydrous Na_2SO_4, and concentration. The resulting residue was purified by column chromatography on silica gel to give the compounds (**7a** – **7g**).

1.3.1.2,4-difluoro-5-(5-(hydroxymethyl)-1H-imidazol-1-yl)-N-(6-(4-isopropyl-4H-1,2,4-triazol-3-yl)pyridin-2-yl)benzamide (**7a**).

A white oil was obtained with a yield of 58.7%. MS (ESI) $[M+H]^+$: 440.5.

*1.3.2.*N-*(6-(4-cyclopropyl-4H-1,2,4-triazol-3-yl)pyridin-2-yl)-2,4-difluoro-5-(5-(hydroxymethyl)-1H-imidazol-1-yl)benzamide* (**7b**).

A yellow solid was obtained with a yield of 74.3%. MS (ESI) $[M+H]^+$: 438.2.

*1.3.3.*N-*(6-(4-cyclopentyl-4H-1,2,4-triazol-3-yl)pyridin-2-yl)-2,4-difluoro-5-(5-(hydroxymethyl)-1H-imidazol-1-yl)benzamide* (**7c**).

A yellow solid was obtained with a yield of 34.7%. MS (ESI) $[M+H]^+$: 466.4.

*1.3.4.*N-*(6-(4-(cyclopropylmethyl)-4H-1,2,4-triazol-3-yl)pyridin-2-yl)-2,4-difluoro-5-(5-(hydroxymethyl)-1H-imidazol-1-yl)benzamide* (**7d**).

A white solid was obtained with a yield of 69.0% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.06 (s, 1H), 8.72 (s, 1H), 8.20 (d, J = 8.2 Hz, 1H), 8.04 (q, J = 7.7 Hz, 2H), 7.93 (d, J = 7.6 Hz, 1H), 7.90 – 7.76 (m, 2H), 7.05 (s, 1H), 5.06 (t, J = 5.3 Hz, 1H), 4.49 (d, J = 7.4 Hz, 2H), 4.37 (d, J = 5.3 Hz, 2H), 1.23 – 1.17(m, 1H), 0.50 – 0.43 (m, 2H), 0.34 (d, J = 4.2Hz, 2H). MS (ESI) $[M+H]^+$: 452.2.

1.3.5.2,4-difluoro-5-(5-(hydroxymethyl)-1H-imidazol-1-yl)-N-(6-(4-phenyl-4H-1,2,4-triazol-3-yl)pyridin-2-yl)benzamide (**7e**).

A white solid was obtained with a yield of 18.1%. MS (ESI) $[M+H]^+$: 474.1.

1.3.6.2,4-difluoro-5-(5-(hydroxymethyl)-1H-imidazol-1-yl)-N-(3-(4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzamide (**7f**).

A yellow white solid was obtained with a yield of 91.4%. MS (ESI) $[M+H]^+$: 439.1.

*1.3.7.*N-*(3-(4-(cyclopropylmethyl)-4H-1,2,4-triazol-3-yl)phenyl)-2,4-difluoro-5-(5-(hydroxymethyl)-1H-imidazol-1-yl)benzamide* (**7g**).

A white solid was obtained with a yield of 63.7%. MS (ESI) $[M+H]^+$: 451.2.

1.4. 2,4-difluoro-5-nitrobenzamide (**10**)

To a solution of **9** (4.12 g, 29.60 mmol) in H_2SO_4 (15 mL, 98%) was added KNO_3 (3.52 g, 34.80 mmol) at 0^{o}C, the mixture was stirred at 0^{o}C for 2 hours. The resulting mixture was

poured into ice water (200 mL), the formed precipitate was filtered, washed with water and dried under vacuum to give the compound **10** (4.29 g, 78.0% yield) as a white solid. MS (ESI) $[M+H]^+$: 203.1.

1.5. 5-amino-2,4-difluorobenzamide (**11**)

To a solution of **10** (3.50 g, 17.40 mmol) in MeOH (20 mL) was added 10% Pd/C (0.50 g, 0.47 mmol), the mixture was stirred at room temperature overnight under hydrogen protection. The mixture was filtered and the filtrate was concentrated. The resulting residue was purified by column chromatography on silica gel to give the compound **11** (2.30 g, 77.0% yield) as a white solid. MS (ESI) $[M+H]^+$: 173.0.

1.6. 2,4-difluoro-5-(2-hydroxyacetamido)benzamide (**13**)

11 (1.05 g, 6.10 mmol) and **12** (0.71 g, 1.50 mmol) were added into a reaction flask, the mixture was stirred at 110℃ for 4 hours. After cooling, the resulting mixture was diluted with MeOH (20 mL) and then concentrated. The resulting residue was purified by column chromatography on silica gel to give the compound **13** (1.00 g, 71.0% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.47 (s, 1H), 8.11 (t, J = 8.3 Hz, 1H), 7.69 (s, 2H), 7.45 (t, J = 10.5 Hz, 1H), 5.83 (t, J = 5.8 Hz, 1H), 4.04 (d, J = 5.7 Hz, 2H). MS (ESI) $[M+H]^+$: 231.1.

1.7. 7-fluoro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide (**14**)

To a solution of **13** (0.99 g, 4.30 mmol) in DMF (20 mL) was added NaH (0.56 g, 14.02 mmol) at 0 °C, the mixture was stirred at 60°C for 8 hours. The resulting mixture was poured into ice water (200 mL) and the pH was adjusted to 9 with citric acid. Finally, the solution was extracted with ethyl acetate three times. The organic layer underwent a washing process with brine, followed by drying with anhydrous Na_2SO_4, and concentration. The resulting residue was purified by column chromatography on silica gel to give the compound **14** (0.21 g, 23.0% yield) as a white solid. MS (ESI) $[M+H]^+$: 211.1.

1.8. methyl 2-fluoro-4-hydroxybenzoate (**19**)

To a solution of **18** (6.00 g, 38.40 mmol) in MeOH (200 mL) was added H_2SO_4 (2.09 mL, 38.40 mmol, 98%) at 0 °C, the mixture was stirred at reflux overnight. The resulting mixture was concentrated and diluted with ethyl acetate (50mL), the pH was adjusted to 7 with saturated sodium bicarbonate solution. The organic phase was separated and the aqueous phase was

extracted with ethyl acetate for two times. The organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated to give the compound **19** (6.20 g, 94.8% yield) as a yellow solid. MS (ESI) $[M+H]^+$: 171.1.

1.9. methyl 2-fluoro-4-hydroxy-5-nitrobenzoate (**20**)

To a solution of **19** (6.00 g, 35.30 mmol) in H_2SO_4 (100 mL, 98%) was added KNO_3 (4.28 g, 42.30 mmol) at 0 °C, the mixture was stirred at 0°C for 2 hours. The resulting mixture was poured into ice water (200 mL), the formed precipitate was filtered, washed with water and dried under vacuum to give the compound **20** (6.70 g, 88.3% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.47 (s, 1H), 8.45 (d, J = 7.7 Hz, 1H), 6.99 (d, J = 12.2 Hz, 1H), 3.84 (s, 3H); MS (ESI) $[M+H]^+$: 216.0.

1.10. methyl 4-((1-ethoxy-2-methyl-1-oxopropan-2-yl)oxy)-2-fluoro-5-nitrobenzoate (**22**)

To a solution of **20** (5.20 g, 24.20 mmol) in DMF (70 mL) were added **21** (14.10 g, 72.50 mmol) and K_2CO_3 (6.67 g, 48.30 mmol), the mixture was stirred at 100°C for 1 hour. The mixture was poured into water (200 mL) and the solution was extracted with ethyl acetate for three times. The organic layer underwent a washing process with brine, followed by drying with anhydrous Na_2SO_4, and concentration. The resulting residue was purified by column chromatography on silica gel to give the compound **22** (1.05 g, 13.2% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.43 (d, J = 7.6 Hz, 1H), 6.97 (d, J = 12.2 Hz, 1H), 4.21 (q, J = 7.1Hz, 2H), 3.86 (s, 3H), 1.66 (s, 6H), 1.17 (t, J = 7.1Hz, 3H).

1.11.methyl 7-fluoro-2,2-dimethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxylate (**23**)

To a solution of **22** (1.10 g, 3.34 mmol) in MeOH (50 mL) was added 10% Pd/C (0.71 g, 0.67 mmol), the mixture was stirred at 50°C overnight under hydrogen protection. The mixture was filtered and the filtrate was concentrated. The resulting residue was purified by column chromatography on silica gel to give the compound **23** (0.65 g, 77.0% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.82 (s, 1H), 7.43 (d, J = 7.2 Hz, 1H), 7.00 (d, J = 11.5 Hz, 1H), 3.82 (s, 3H), 1.44 (s, 6H); MS (ESI) $[M+H]^+$: 254.1.

1.12. 7-fluoro-2,2-dimethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide (**24**)

To an ammonia-methanol solution (25 mL, 175 mmol, 7mol/L) was added **23** (0.20 g, 0.79 mmol), the mixture was stirred at 80°C overnight. The mixture was concentrated and the

resulting residue was purified by column chromatography on silica gel to give the compound **24** (0.16 g, 85.0% yield) as a white solid. MS (ESI) $[M+H]^+$: 239.1.

1.13. methyl (E)-4-(3-ethoxy-3-oxoprop-1-en-1-yl)-2-fluorobenzoate (**29**)

To a solution of **27** (3.02 g, 13.00 mmol) in 1,4-Dioxane (15 mL) were added PPh_3 (0.34 g, 1.30 mmol), $Pd(OAc)_2$ (0.30 g, 1.30 mmol), TEA (8.56 g, 26.30 mmol) and **28** (1.55 g, 15.50 mmol), the mixture was stirred at 100°C for 8 hours under nitrogen protection. The solution was concentrated and the resulting residue was partitioned between DCM and water. The organic layer underwent a washing process with brine, followed by drying with anhydrous Na_2SO_4, and concentration. The resulting residue was purified by column chromatography on silica gel to give the compound **29** (2.94 g, 90.0% yield) as a white solid. MS (ESI) $[M+H]^+$: 253.2.

1.14. methyl (E)-4-(3-ethoxy-3-oxoprop-1-en-1-yl)-2-fluoro-5-nitrobenzoate (**30**)

Compound **30** was synthesized using the same method as described for compound **20** and obtained as a white solid in a 92.0% yield. MS (ESI) $[M+H]^+$: 298.1.

1.15. methyl 6-fluoro-2-oxo-1,2,3,4-tetrahydroquinoline-7-carboxylate (**31**)

Compound **31** was synthesized using the same method as described for compound **23** and obtained as a white solid in a 66.0% yield. MS (ESI) $[M+H]^+$: 224.1.

1.16. 6-fluoro-2-oxo-1,2,3,4-tetrahydroquinoline-7-carboxamide (**32**)

Compound **32** was synthesized using the same method as described for compound **24** and obtained as a yellow solid in a 78.0% yield. MS (ESI) $[M+H]^+$: 209.2.

1.17. methyl 6-fluoro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-7-carboxylate (**34**)

Compound **34** was synthesized using the same method as described for compounds **17a** and **17b**. It was obtained as a yellow solid with a yield of 83.0%. MS (ESI) $[M+H]^+$: 238.1.

1.18. 6-fluoro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-7-carboxamide (**35**)

Compound **35** was synthesized using the same method as described for compound **24** and obtained as a yellow solid in a 85.0% yield. MS (ESI) $[M+H]^+$: 223.1.

1.19. 3-bromo-4-fluoroaniline (**38**)

To a solution of **37** (4.02 g, 18.30 mmol) in MeOH (15 mL) were added iron powder (6.20 g, 110.0 mmol), NH_4Cl (1.95 g, 36.50 mmol) and water (10 mL), the mixture was stirred at 80°C for 8 hours. The solution was concentrated and the resulting residue was partitioned

between DCM and water. The organic layer underwent a washing process with brine, followed by drying with anhydrous Na_2SO_4, and concentration. The resulting residue was purified by column chromatography on silica gel to give the compound **38** (3.20 g, 92.0% yield) as a yellow solid. MS (ESI) $[M+H]^+$: 190.1.

1.20. N-(3-bromo-4-fluorophenyl)-3-methylbut-2-enamide (**40**)

To a solution of **38** (3.14 g, 16.50 mmol) in DCM (15 mL) were added **39** (2.00 g, 16.90 mmol) and pyridine (2.62 g, 33.00 mmol), the mixture was stirred at room temperature overnight. The mixture was poured into water (300 mL) and the pH was adjusted to 6 with citric acid. The resulting solution was extracted with ethyl acetate for three times. The organic layer underwent a washing process with brine, followed by drying with anhydrous Na_2SO_4, and concentration. The resulting residue was purified by column chromatography on silica gel to give the compound **40** (4.12 g, 91.0% yield) as a yellow solid. MS (ESI) $[M+H]^+$: 272.1.

1.21. 7-bromo-6-fluoro-4,4-dimethyl-3,4-dihydroquinolin-2(1H)-one (**41**)

To a solution of **40** (4.10 g, 15.10 mmol) in DCM (50 mL) was added $AlCl_3$ (8.11 g, 60.80 mmol), the mixture was stirred at room temperature overnight. The mixture was filtered and the filtrate was concentrated. The resulting residue was purified by column chromatography on silica gel to give the compound **41** (1.02 g, 24.9% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.24 (s, 1H), 7.26 (d, J = 9.7 Hz, IH), 7.11 (d, J = 6.3 Hz. 1H), 2.33 (s, 2H), 1.18 (s, 6H); MS (ESI) $[M+H]^+$: 272.1.

1.22. methyl 6-fluoro-4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinoline-7-carboxylate (**42**)

To a solution of **41** (0.50 g, 2.00 mmol) in MeOH (20 mL) was added $Pd(dppf)Cl_2$ (0.21 g, 0.26 mmol) and TEA (0.55 mL, 4.00 mmol), then pressurized to 2.5 MPa with carbon monoxide. The mixture was stirred at 80°C for 20 hours. The solution was concentrated and the resulting residue was partitioned between DCM and water. The organic layer underwent a washing process with brine, followed by drying with anhydrous Na_2SO_4, and concentration. The resulting residue was purified by column chromatography on silica gel to give the compound **42** (0.33 g, 70.0% yield) as a white solid. MS (ESI) $[M+H]^+$: 252.3.

1.23. 6-fluoro-4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinoline-7-carboxamide (**43**)

Compound **43** was synthesized using the same method as described for compound **24** and obtained as a yellow solid in a 98.7% yield. MS (ESI) $[M+H]^+$: 237.2.

1.24. methyl 6-fluoro-1,4,4-trimethyl-2-oxo-1,2,3,4-tetrahydroquinoline-7-carboxylate (**45**)

Compound **45** was synthesized using the same method as described for compounds **17a** and **17b**. It was obtained as a yellow solid with a yield of 79.6%. MS (ESI) $[M+H]^+$: 266.2.

1.25. 6-fluoro-1,4,4-trimethyl-2-oxo-1,2,3,4-tetrahydroquinoline-7-carboxamide (**46**)

Compound **46** was synthesized using the same method as described for compound **24** and obtained as a yellow solid in a 84.5% yield. MS (ESI) $[M+H]^+$: 251.4.

1.26. methyl (Z)-2-fluoro-4-(4-methoxy-4-oxobut-1-en-1-yl)benzoate (**49**)

Compound **49** was synthesized using the same method as described for compound **29** and obtained as a yellow oil in a 31.0% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.84 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 13.5 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 6.61 – 6.55(m, 2H), 3.84 (s, 3H), 3.64 (s, 3H), 3.34 (d, J = 5.5 Hz, 2H); MS (ESI) $[M+H]^+$: 253.2.

1.27. methyl (Z)-2-fluoro-4-(4-methoxy-4-oxobut-1-en-1-yl)-5-nitrobenzoate (**50**)

Compound **50** was synthesized using the same method as described for compound **20** and obtained as a yellow oil in a 25.5% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.44 (d, J = 6.7 Hz, 1H), 7.84 (d, J = 11.7 Hz, 1H), 6.90 (d, J = 15.7 Hz, 1H), 6.72 – 6.63 (m, 1H), 3.90 (s, 3H), 3.65 (s, 3H), 3.42 (d, J = 7.3 Hz, 2H).

1.28. methyl 5-amino-2-fluoro-4-(4-methoxy-4-oxobutyl)benzoate (**51**)

To a solution of **50** (0.40 g, 1.35 mmol) in MeOH (30 mL) was added 10% Pd/C (0.29 g, 0.27 mmol), the mixture was stirred at 50^{o}C overnight under hydrogen protection. The resulting mixture was filtered and the filtrate was concentrated under vacuum to give the compound **51** (0.36 g, 100.0% yield) as a yellow oil. MS (ESI) $[M+H]^+$: 270.2.

1.29. methyl 7-fluoro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepine-8-carboxylate (**52**)

To an acetic acid solution (20 mL) was added **51** (0.26 g, 0.97 mmol), the mixture was stirred at reflux overnight. The mixture was concentrated and the resulting residue was purified by column chromatography on silica gel to give the compound **52** (0.16 g, 70.0% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.62 (s, 1H), 7.45 (d, J = 6.7 Hz, 1H), 7.32 (d, J = 11.2 Hz, 1H), 3.85 (s, 3H), 2.74 (t, J = 6.6 Hz, 2H), 2.19 – 2.08 (m, 4H); MS (ESI) $[M+H]^+$: 238.2.

1.30. 7-fluoro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepine-8-carboxamide (**53**)

Compound **53** was synthesized using the same method as described for compound **24** and

obtained as a yellow solid in a 87.0% yield. MS (ESI) $[M+H]^+$: 223.2.

1.31. methyl 7-fluoro-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepine-8-carboxylate (**55**)

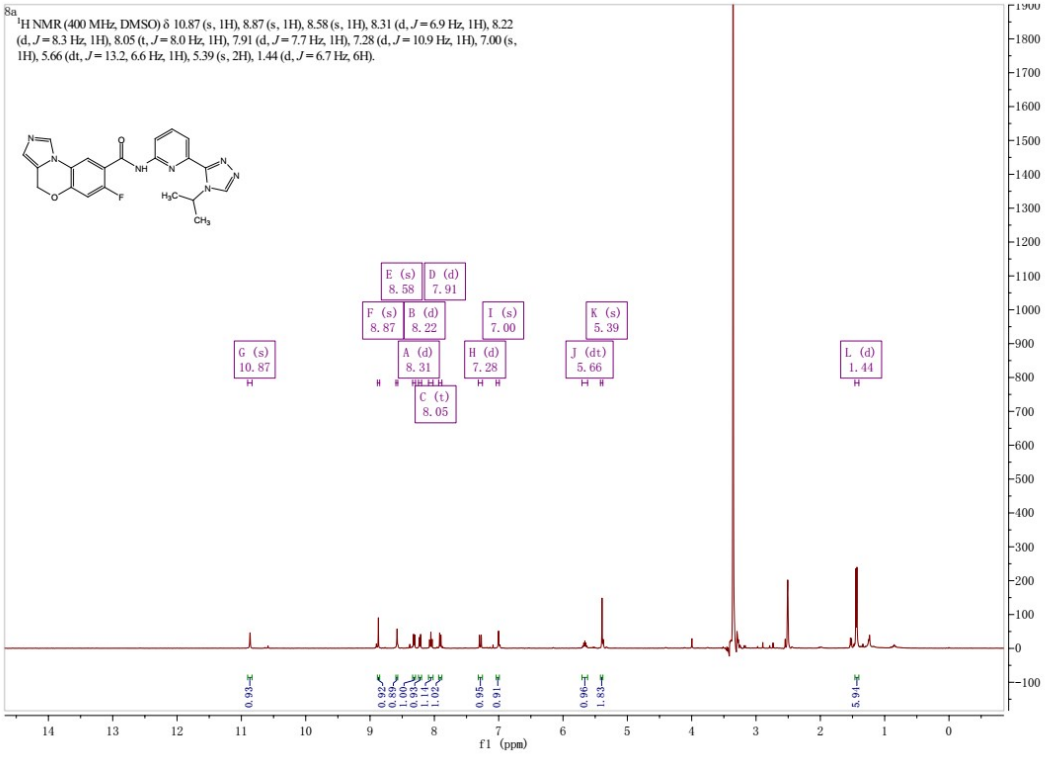
Compound **55** was synthesized using the same method as described for compounds **17a** and **17b**. It was obtained as a white solid with a yield of 65.0%. MS (ESI) $[M+H]^+$: 252.2.

1.32. 7-fluoro-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepine-8-carboxamide (**56**)

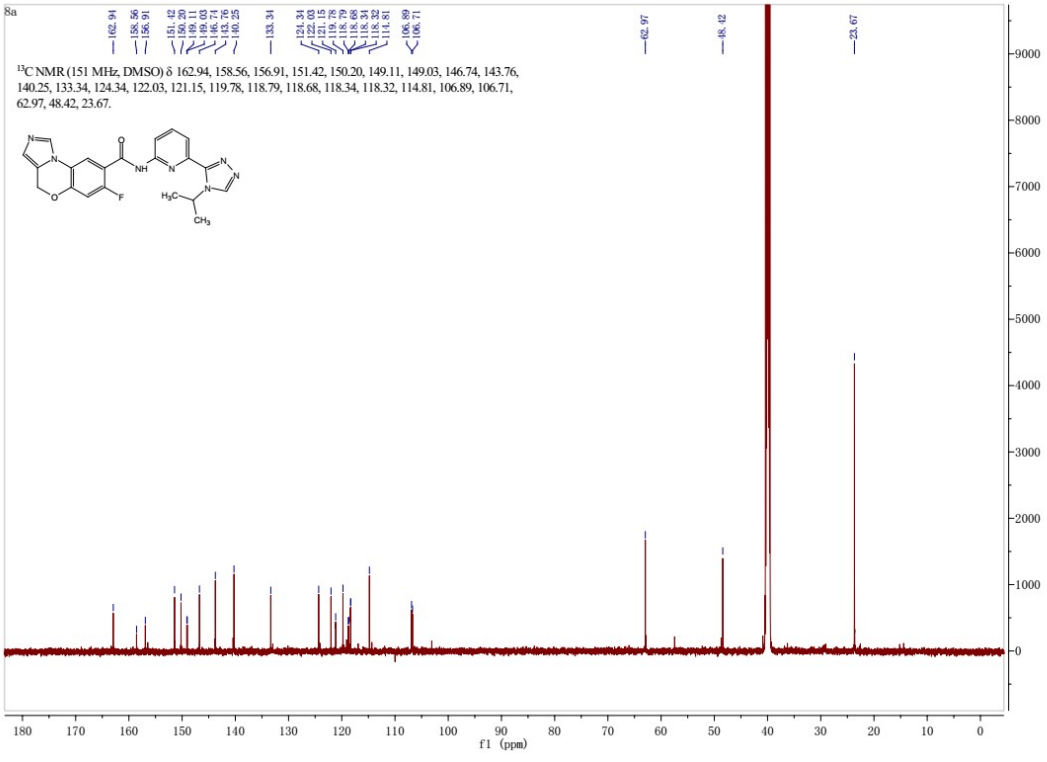
Compound **56** was synthesized using the same method as described for compound **24** and obtained as a white solid in a 92.0% yield. MS (ESI) $[M+H]^+$: 237.2.

2. Copies of ^{1}H-NMR and ^{13}C-NMR for target compounds（8a~8g, 15a~15e, 17a, 17b, 25, 26, 33a~33c, 36, 44, 47, 54a~54d, 57a~57d）

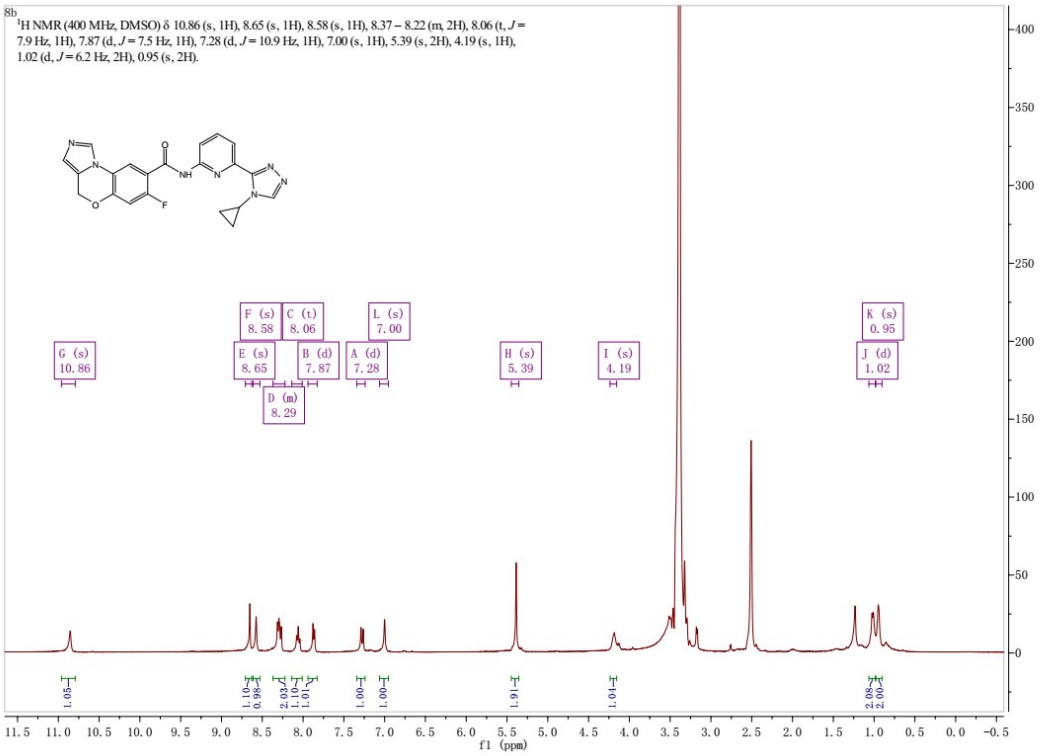
^{1}H-NMR of Compound 8a:



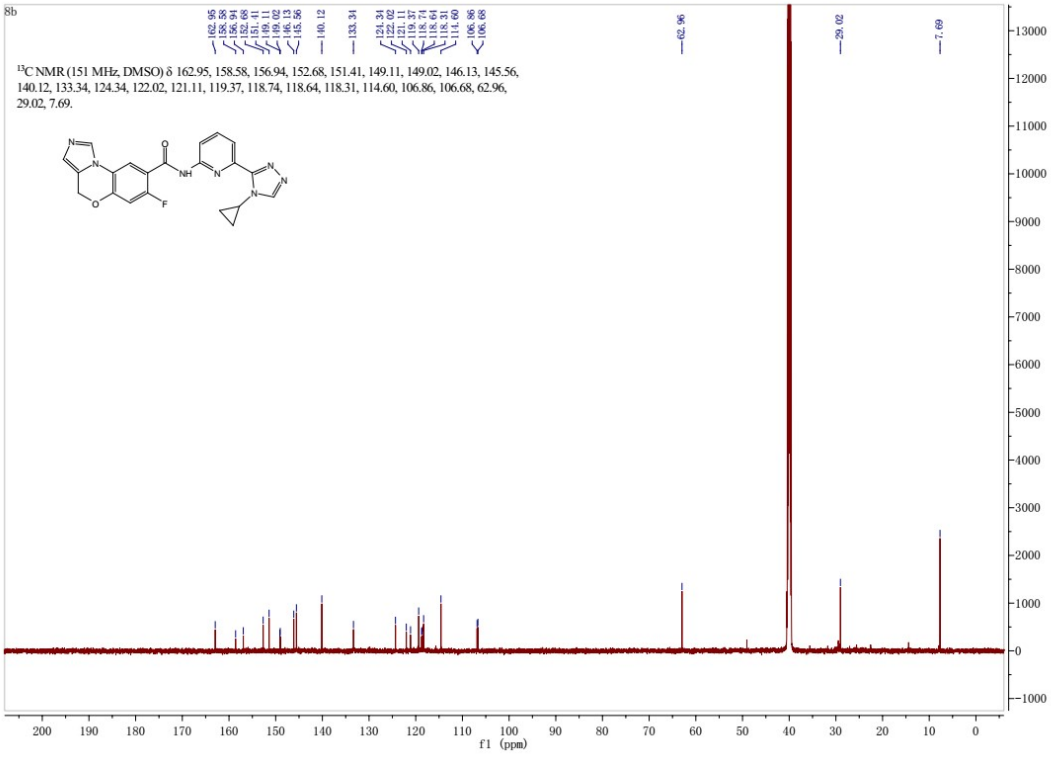
^{13}C-NMR of Compound 8a:



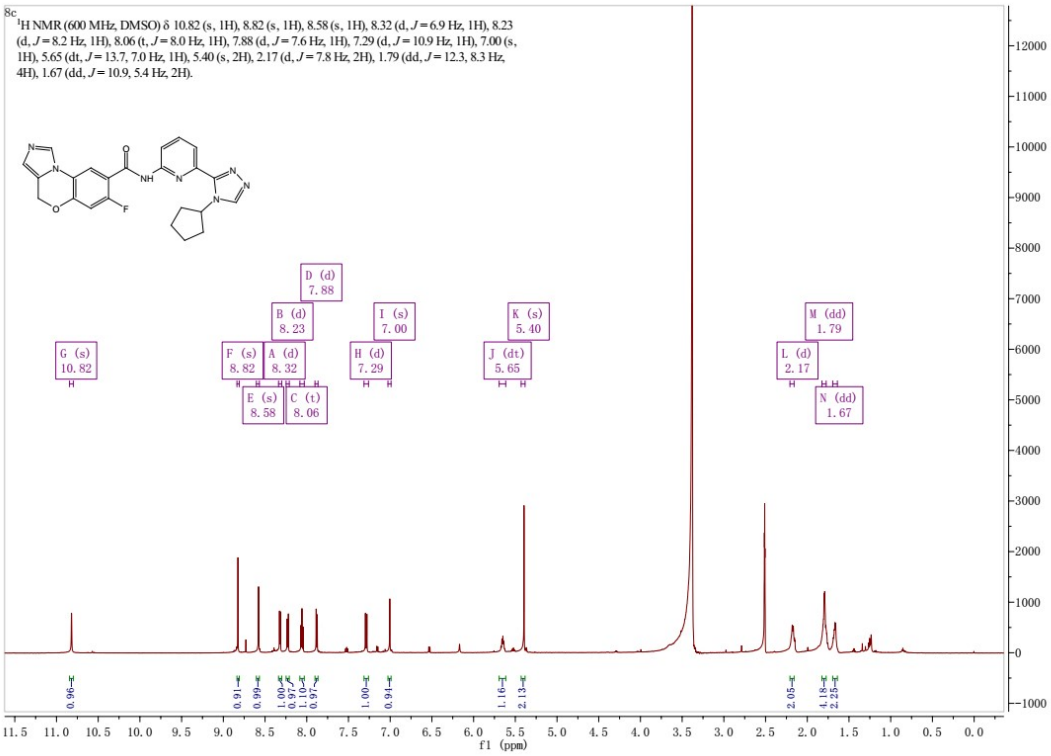
^{1}H-NMR of Compound 8b:



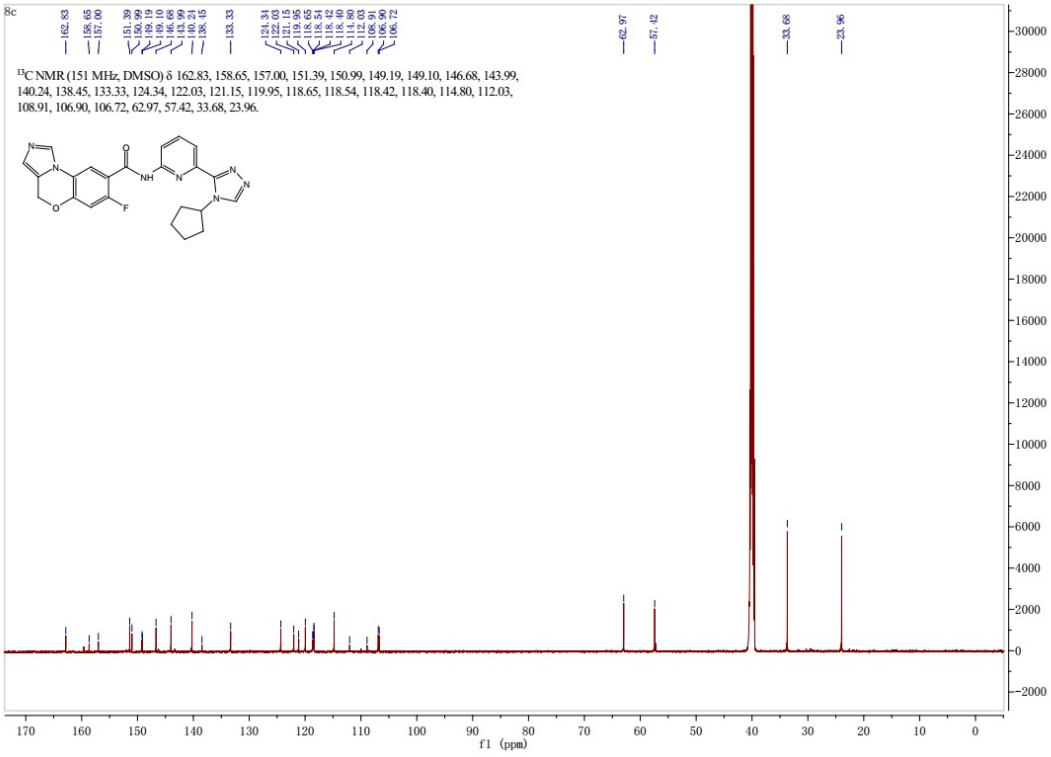
^{13}C-NMR of Compound 8b:



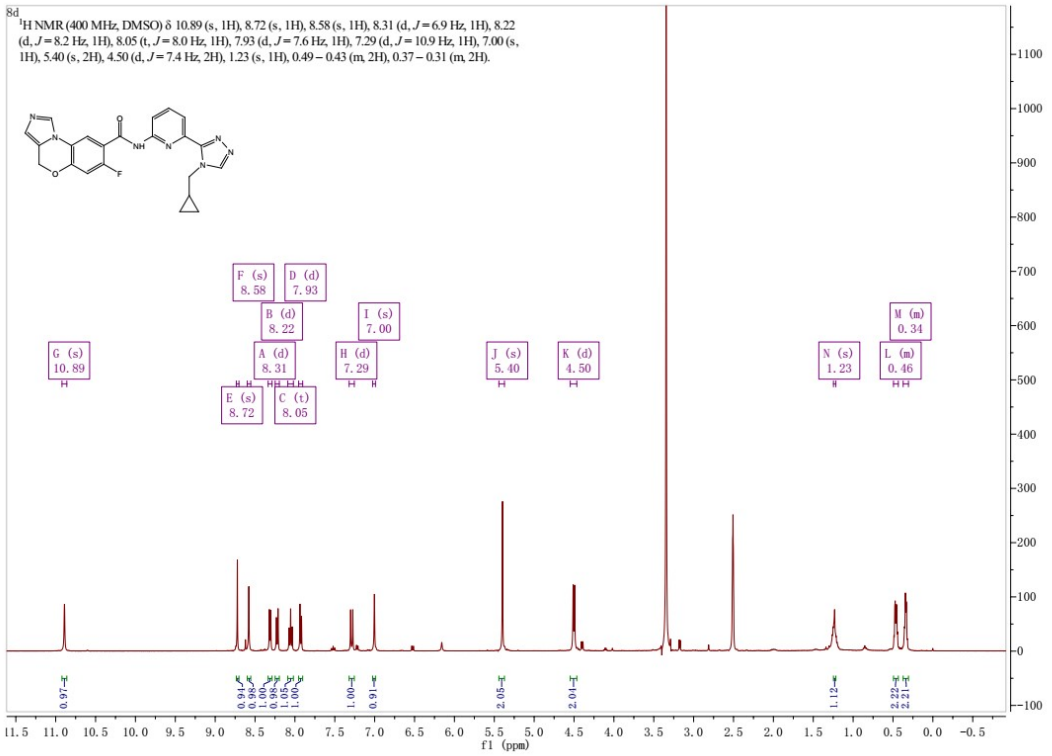
^{1}H-NMR of Compound 8c:



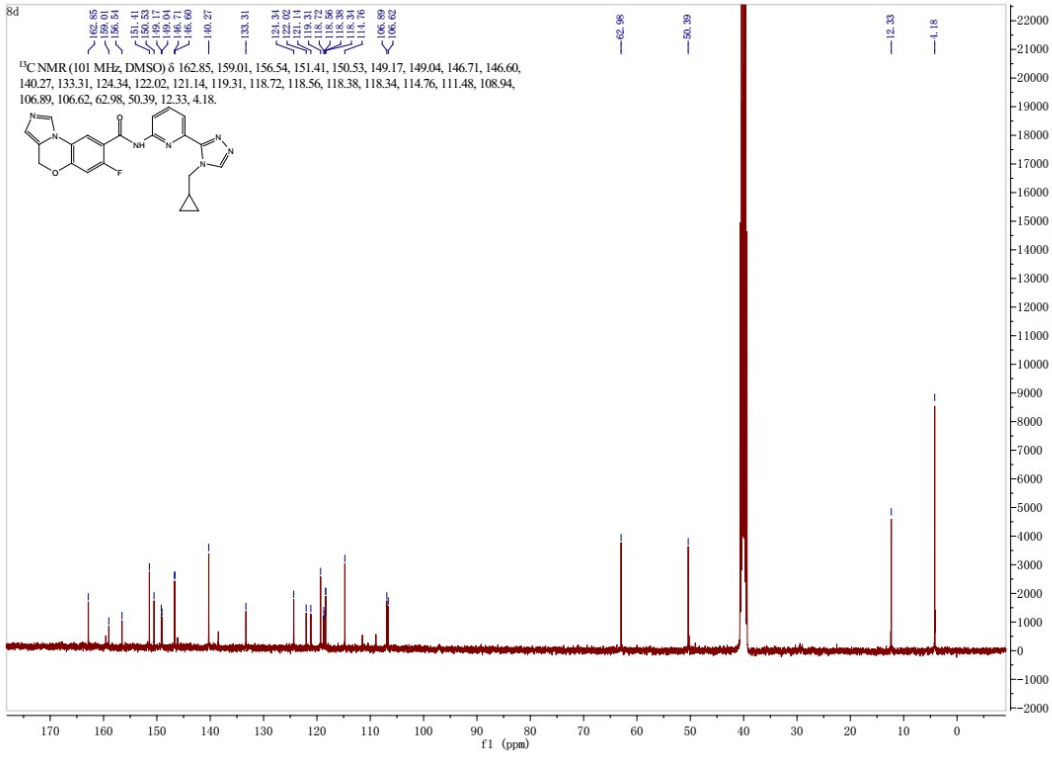
^{13}C-NMR of Compound 8c:



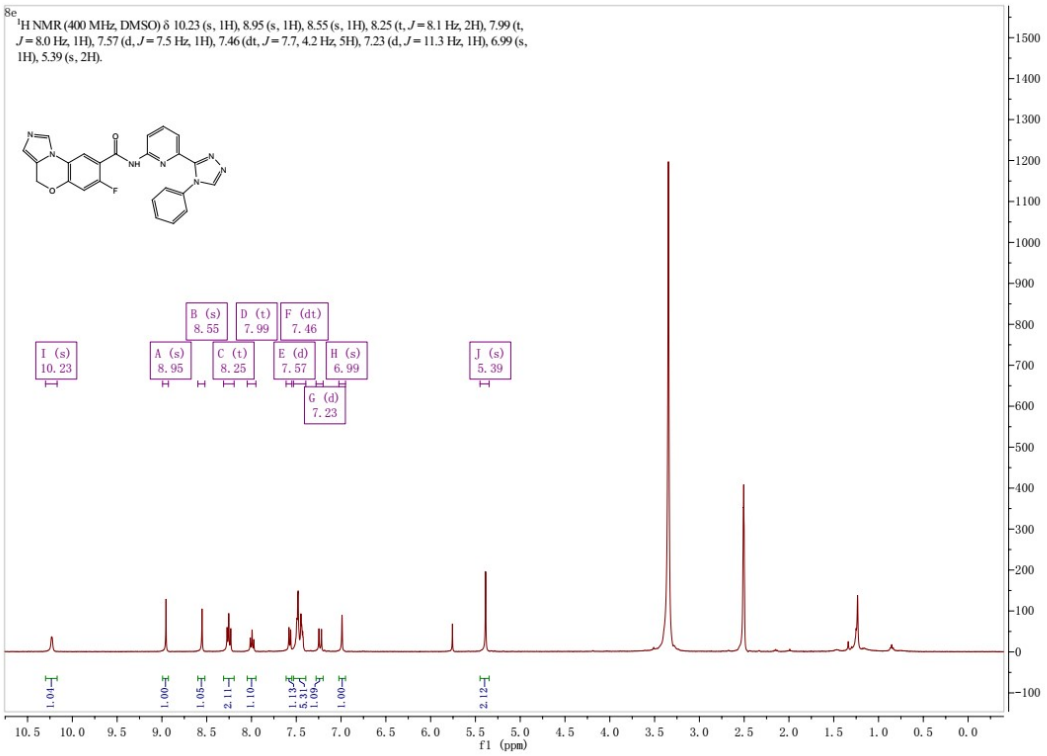
[1]H-NMR of Compound 8d:



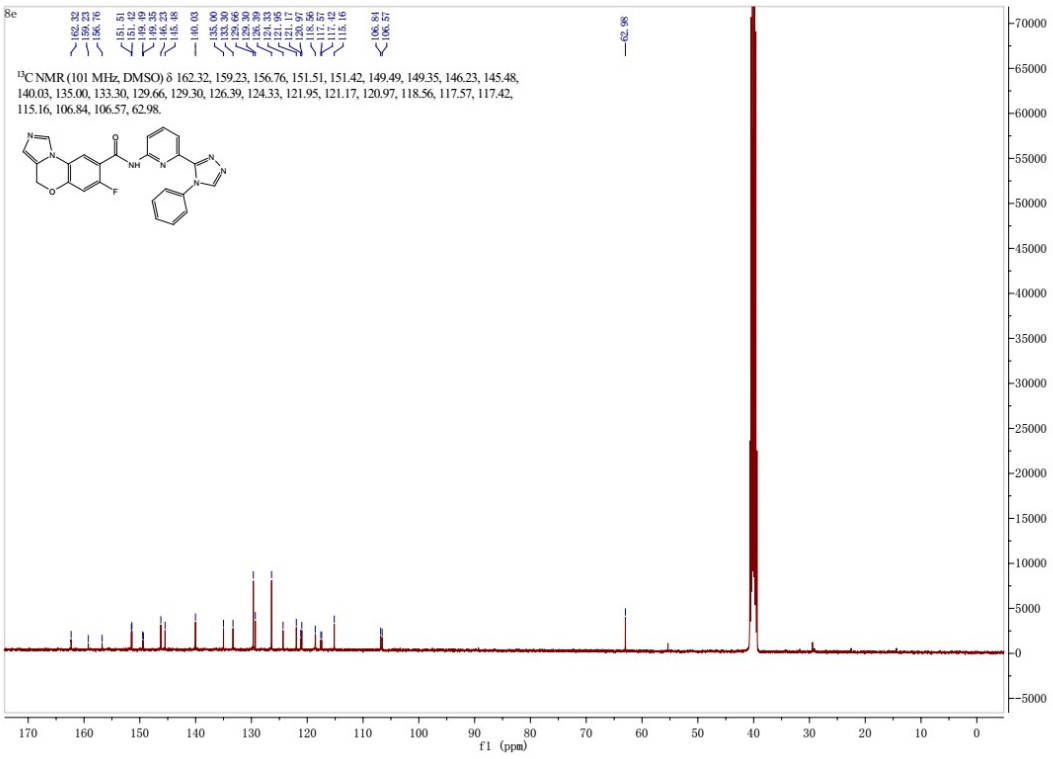
[13]C-NMR of Compound 8d:



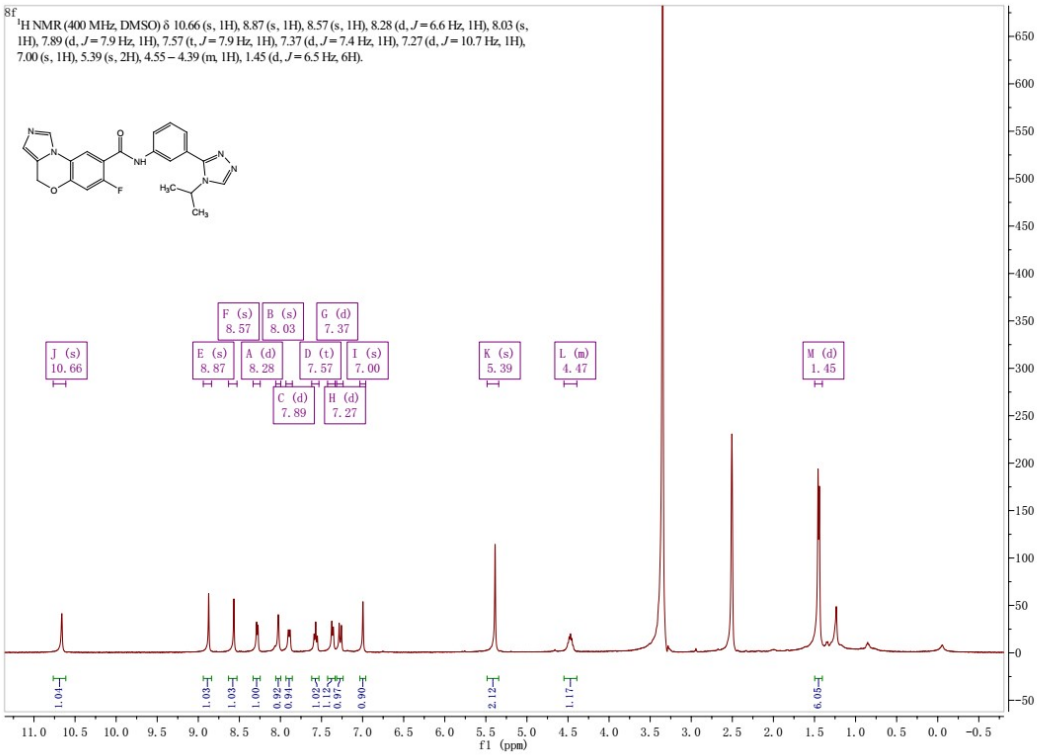
[1]H-NMR of Compound 8e:



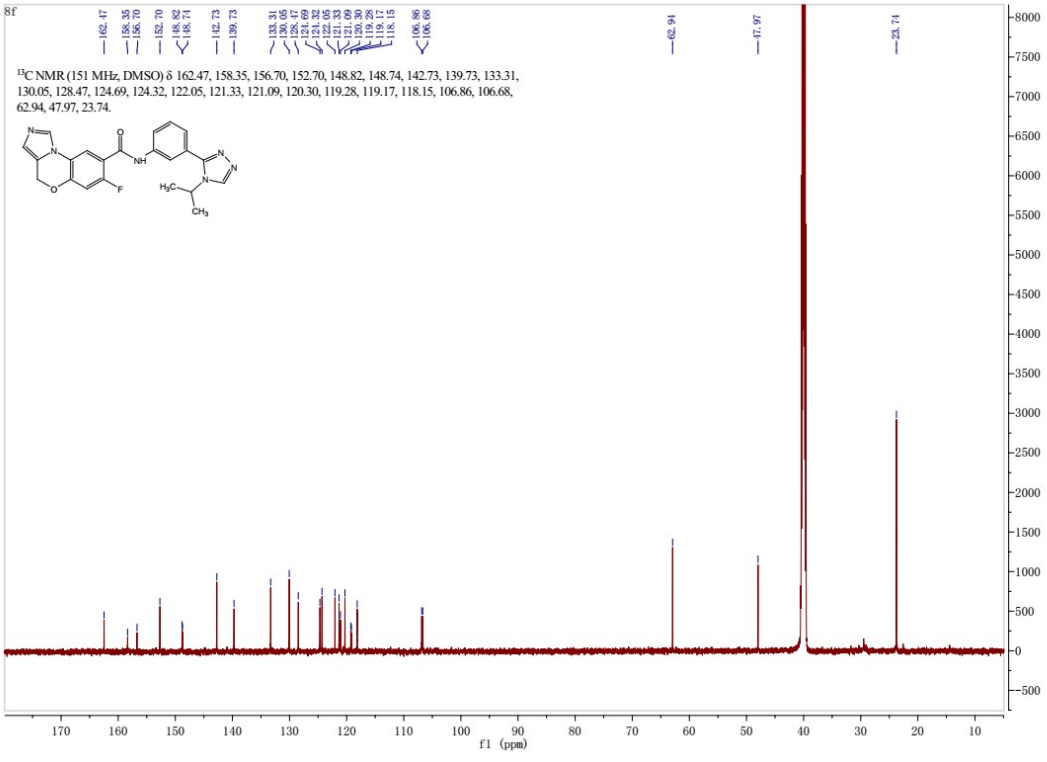
[13]C-NMR of Compound 8e:



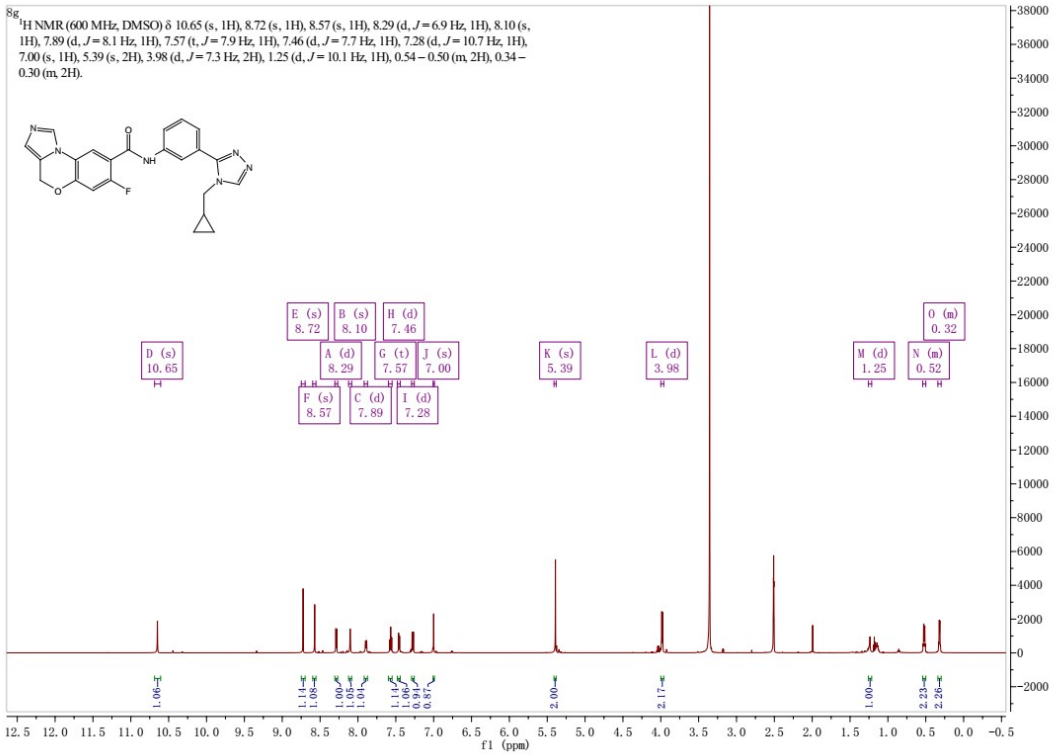
^{1}H-NMR of Compound 8f:



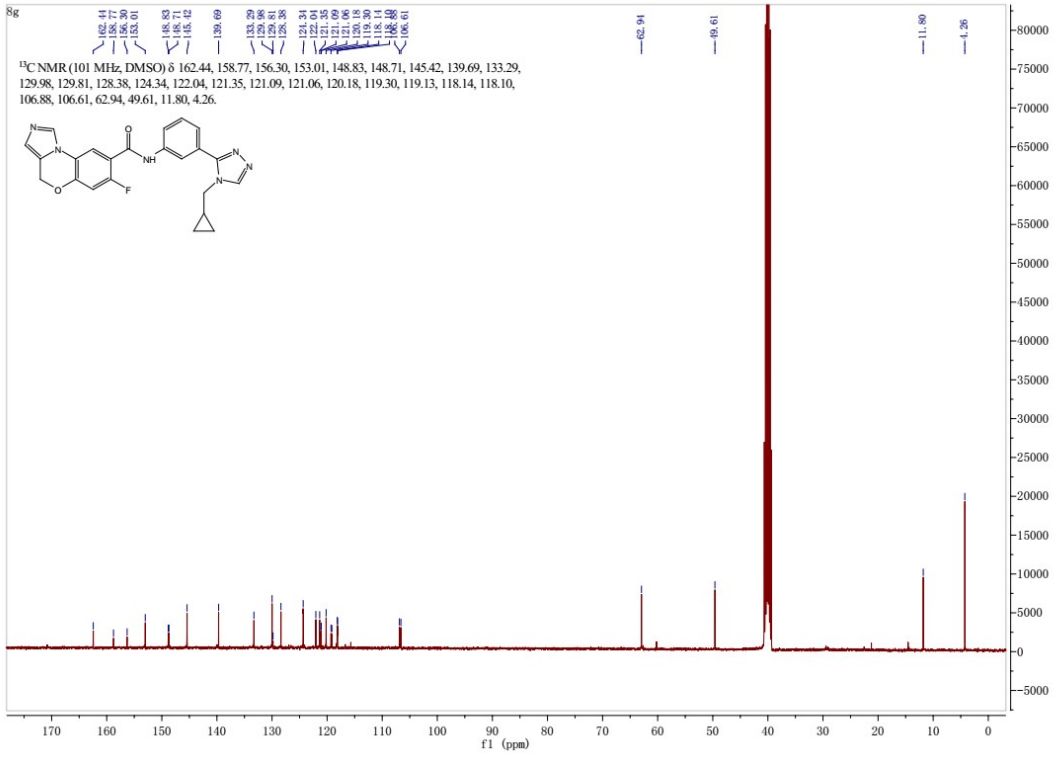
^{13}C-NMR of Compound 8f:



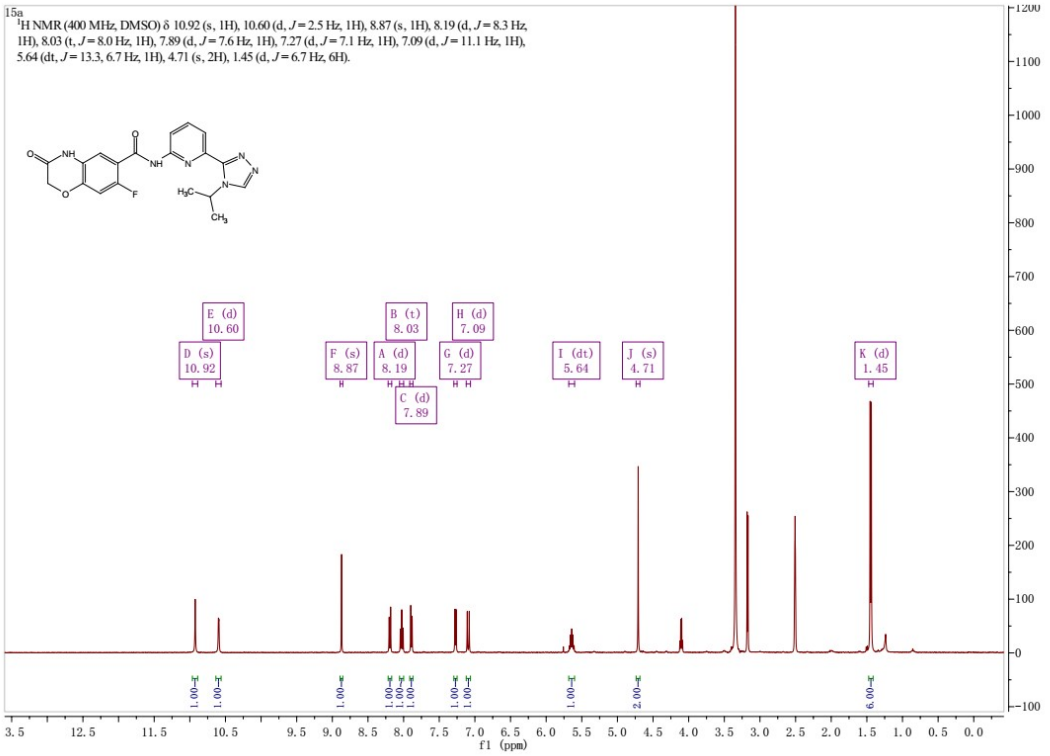
^{1}H-NMR of Compound 8g:



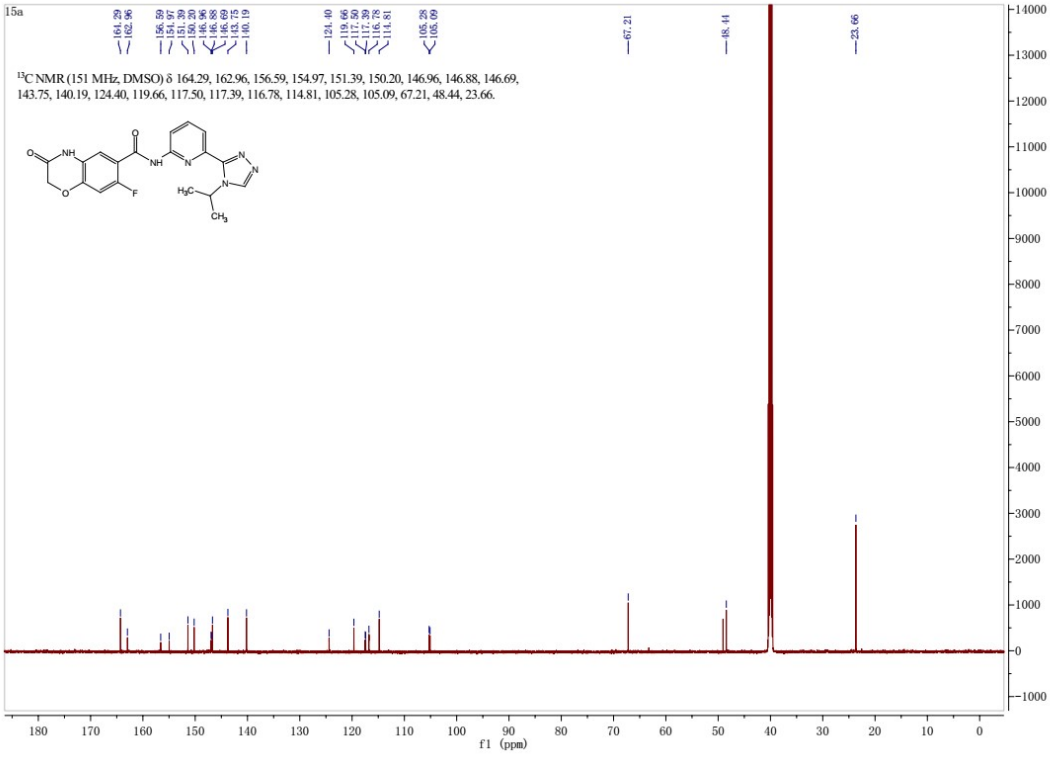
^{13}C-NMR of Compound 8g:



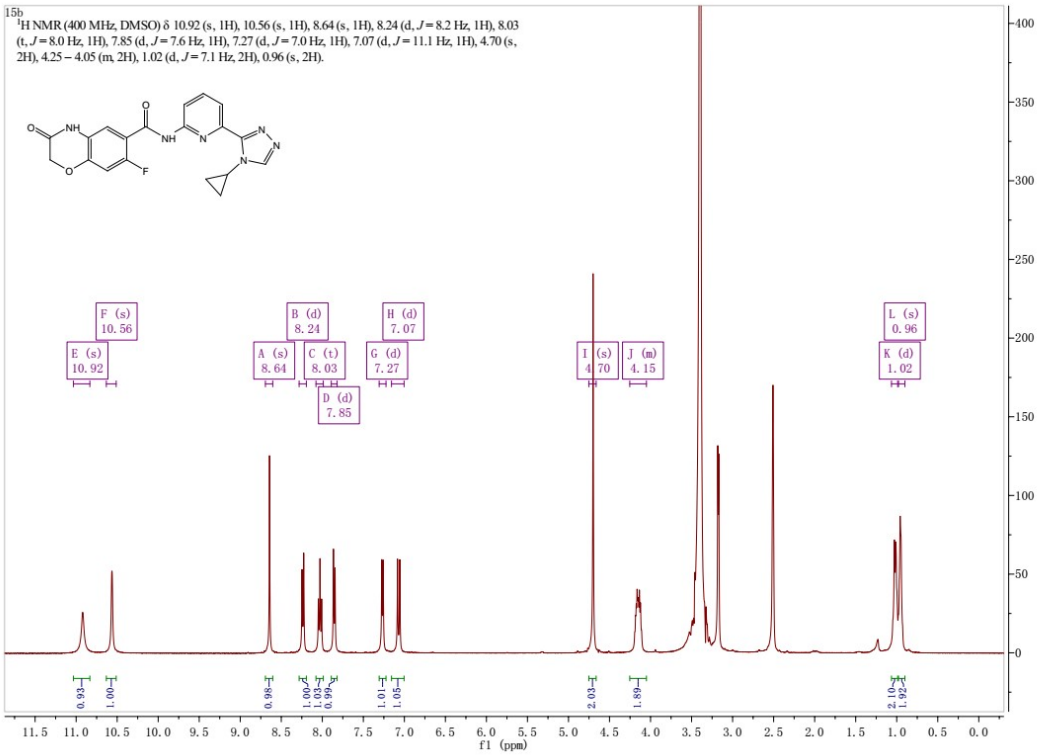
[1]H-NMR of Compound 15a:



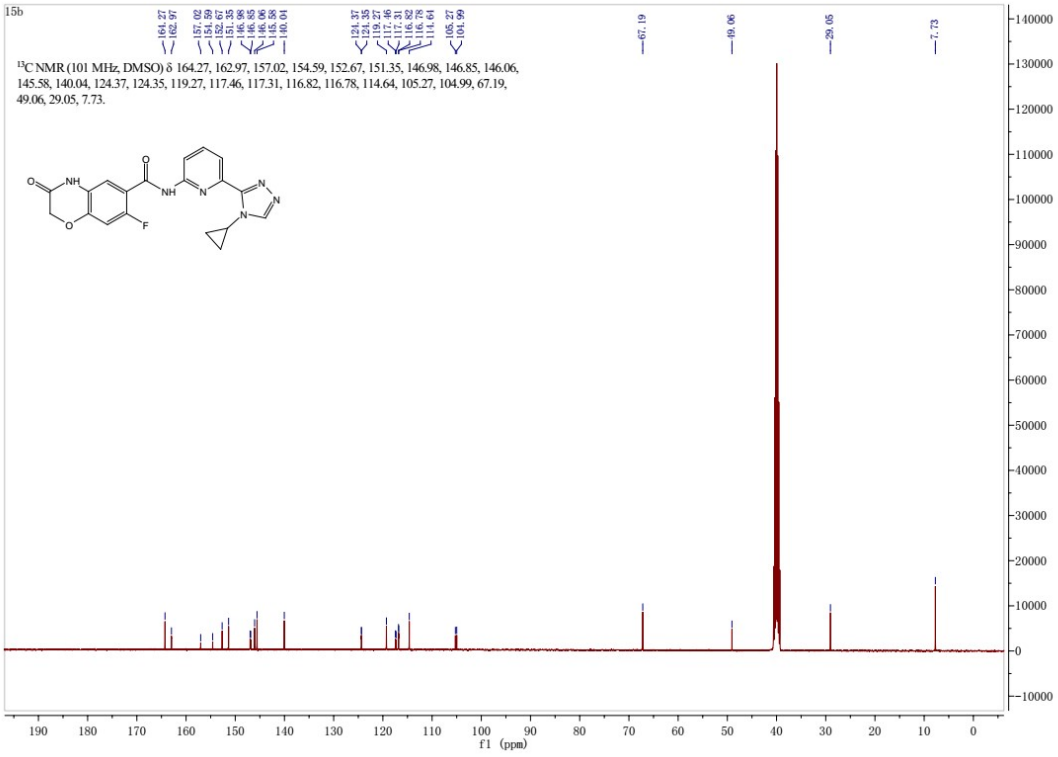
[13]C-NMR of Compound 15a:



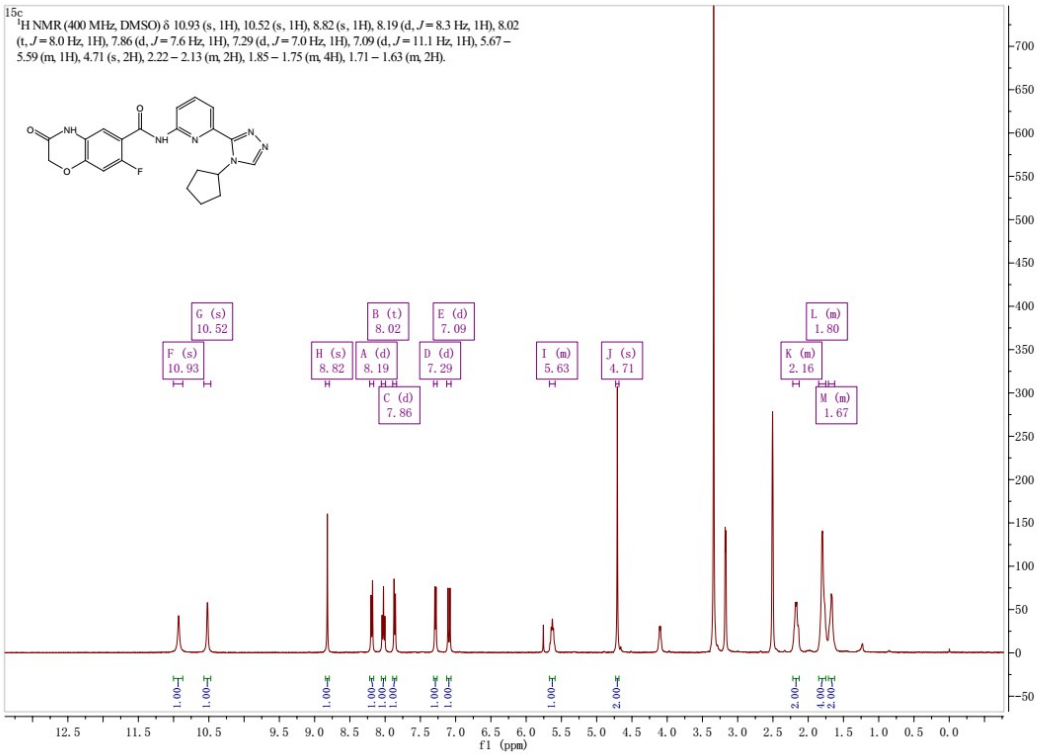
^{1}H-NMR of Compound 15b:



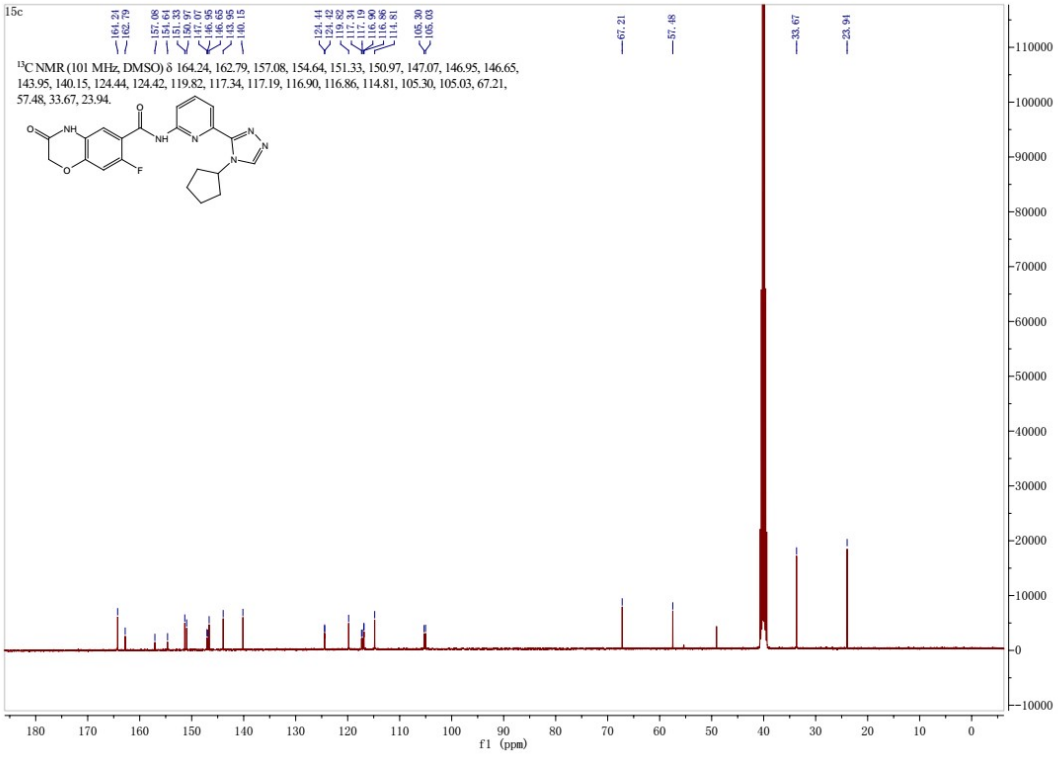
^{13}C-NMR of Compound 15b:



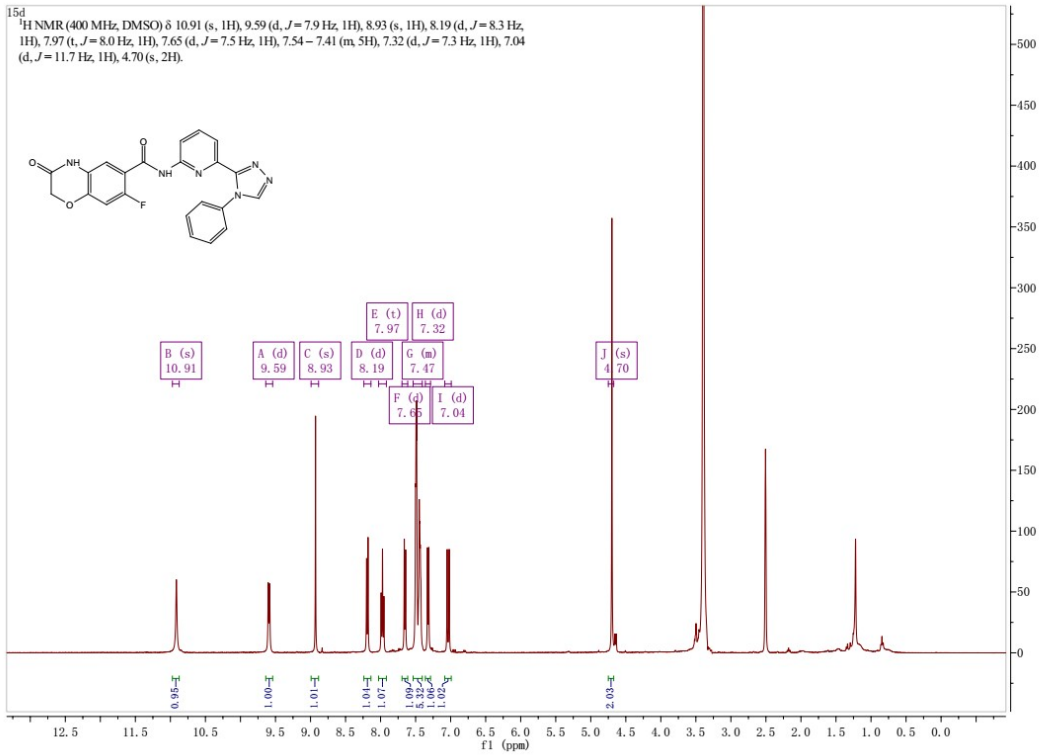
^{1}H-NMR of Compound 15c:



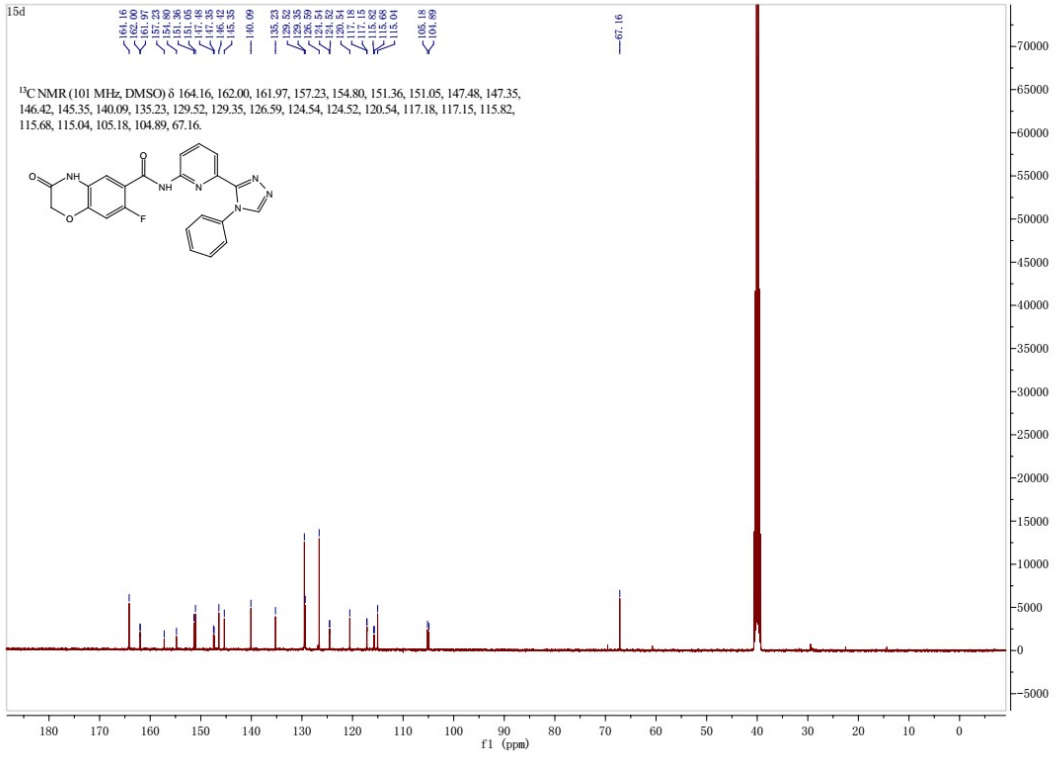
^{13}C-NMR of Compound 15c:



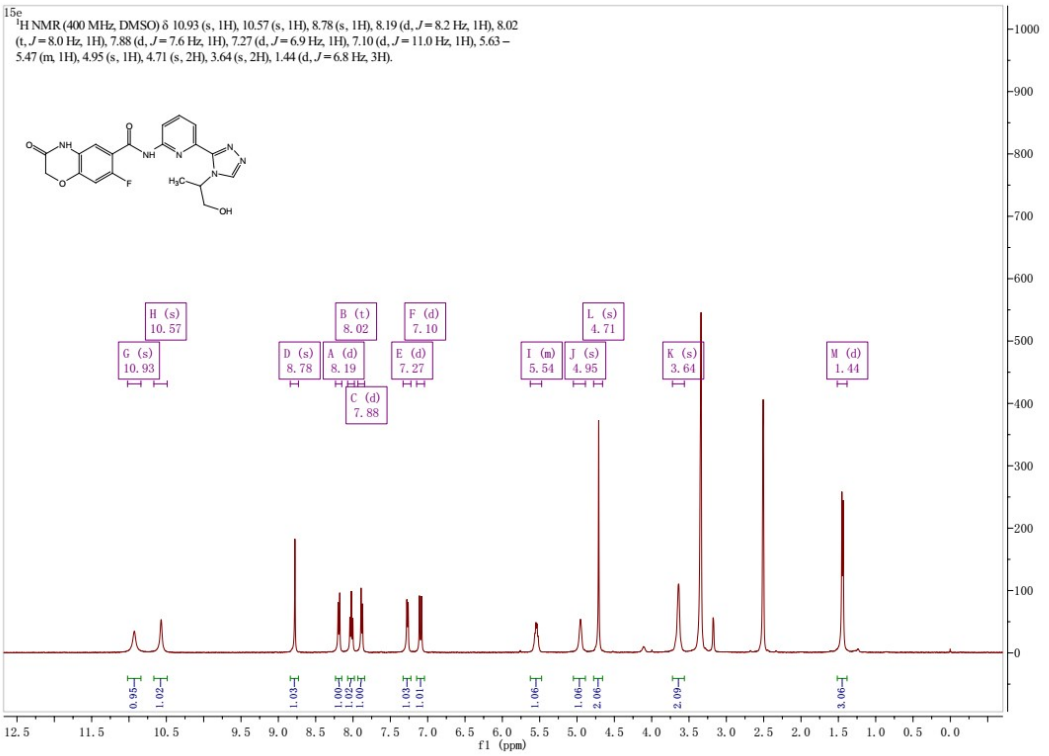
[1]H-NMR of Compound 15d:



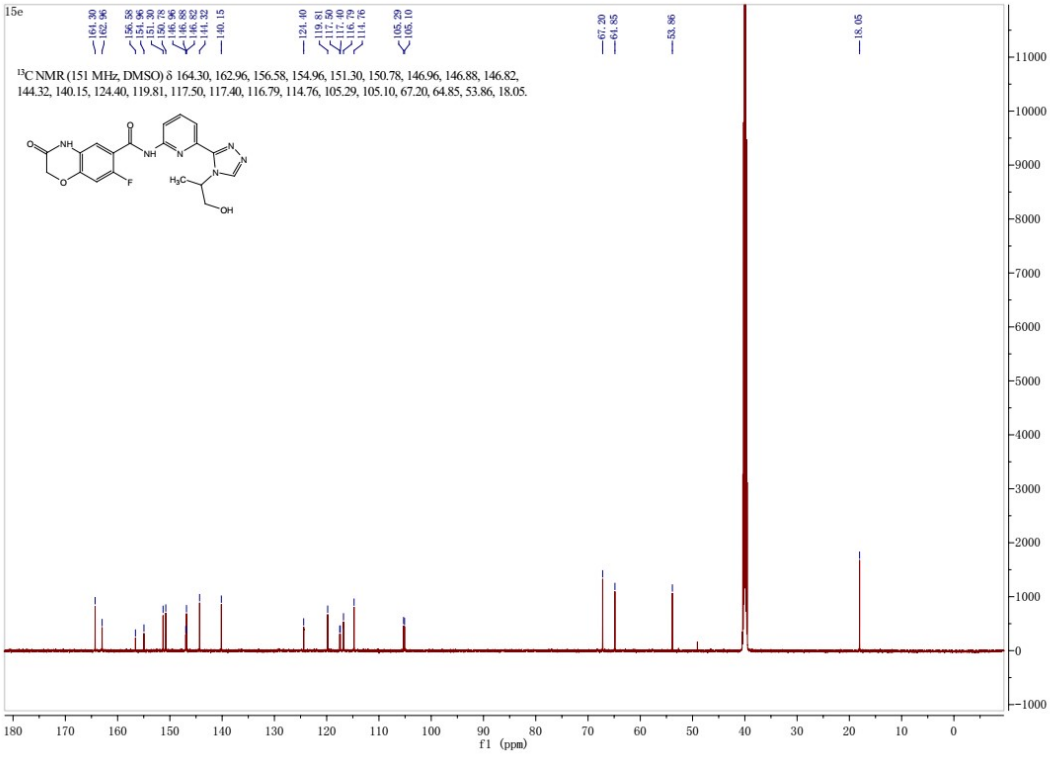
[13]C-NMR of Compound 15d:



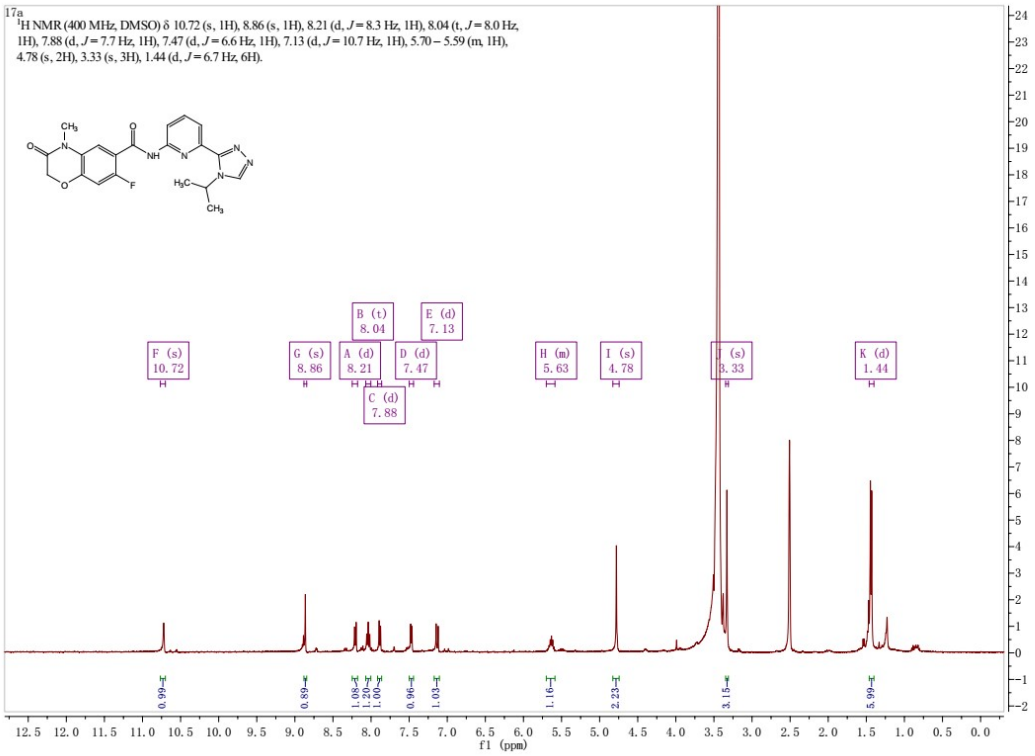
^{1}H-NMR of Compound 15e:



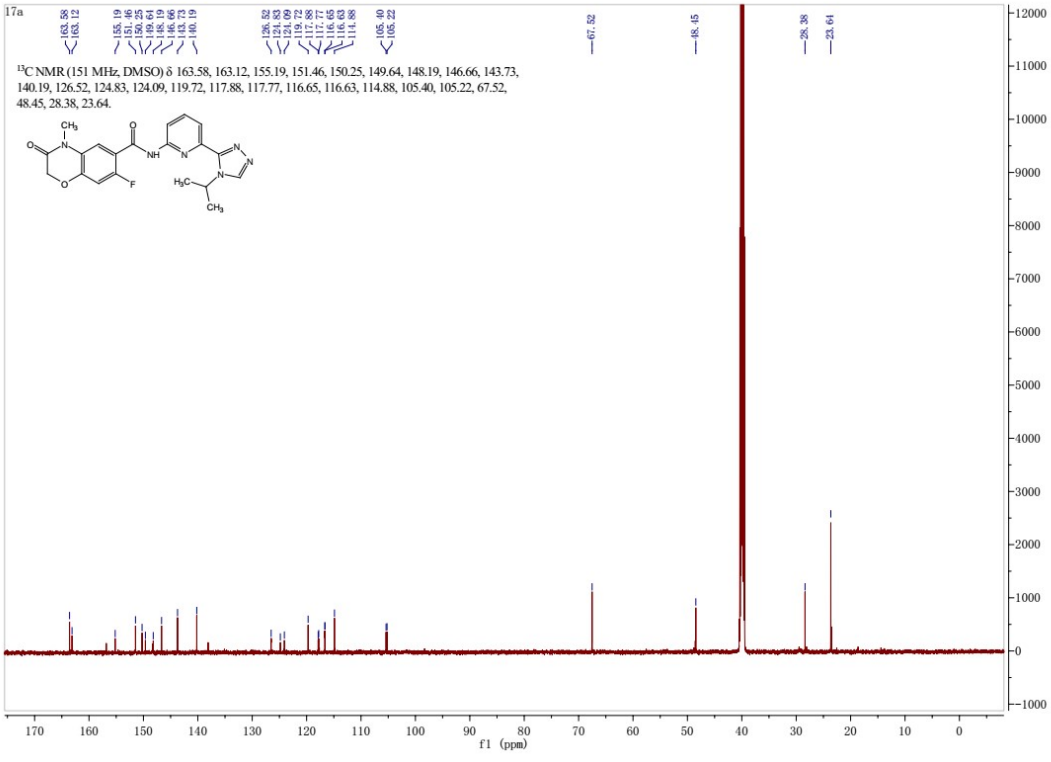
^{13}C-NMR of Compound 15e:



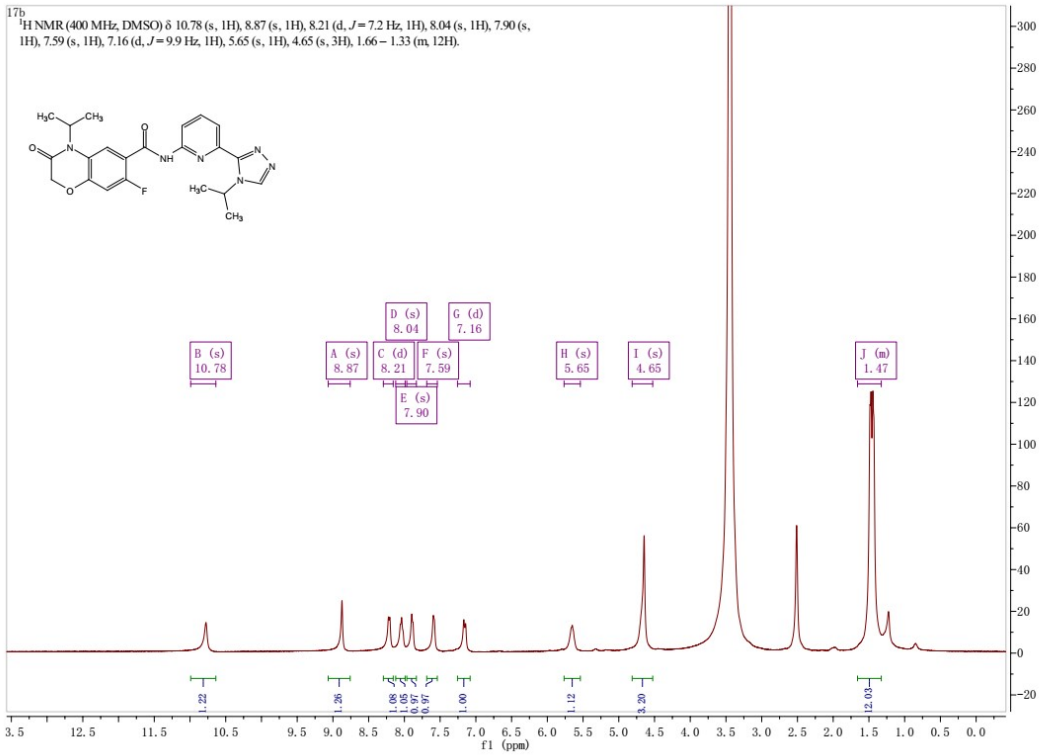
[1]H-NMR of Compound 17a:



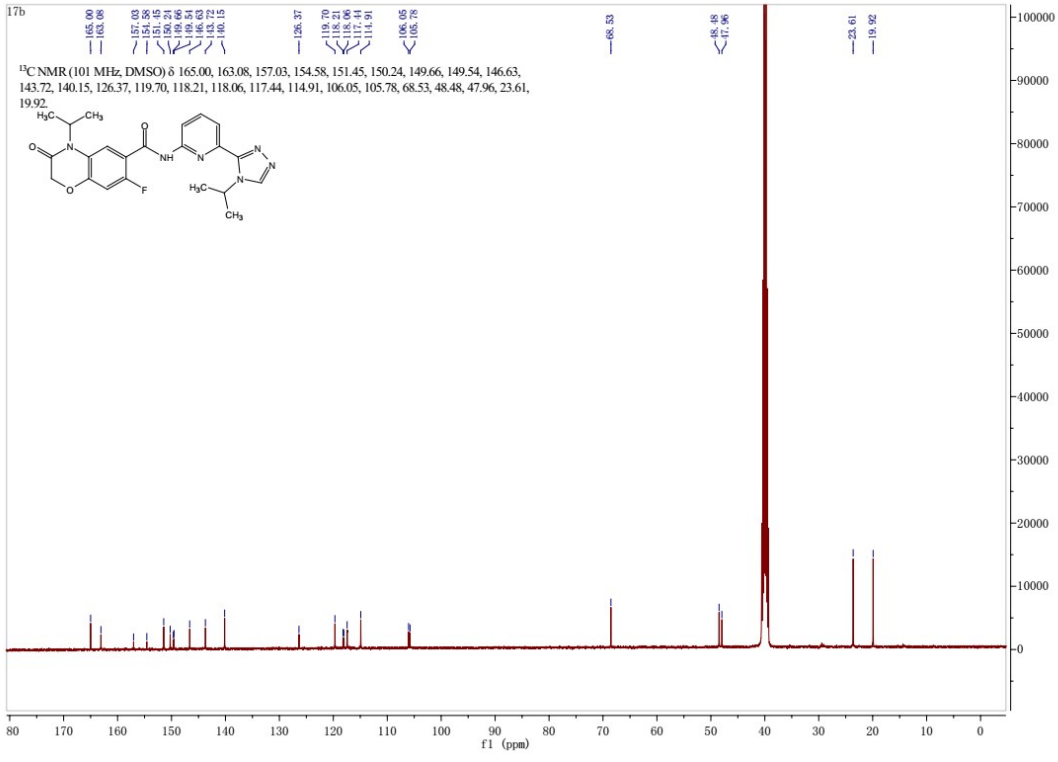
[13]C-NMR of Compound 17a:



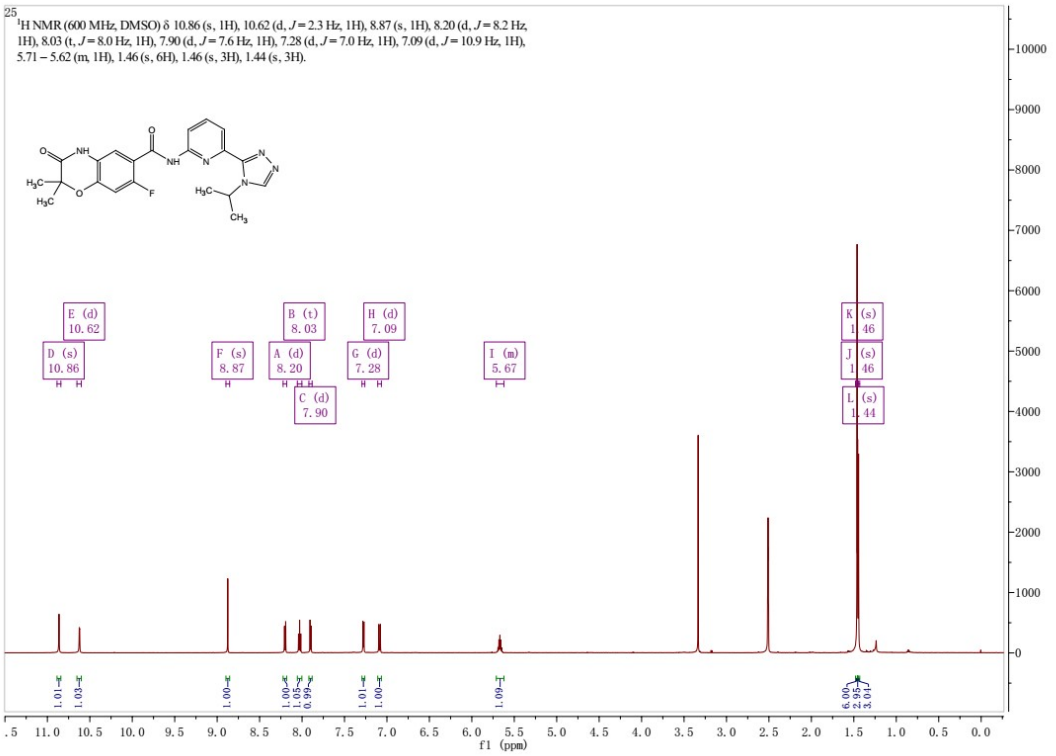
[1]H-NMR of Compound 17b:



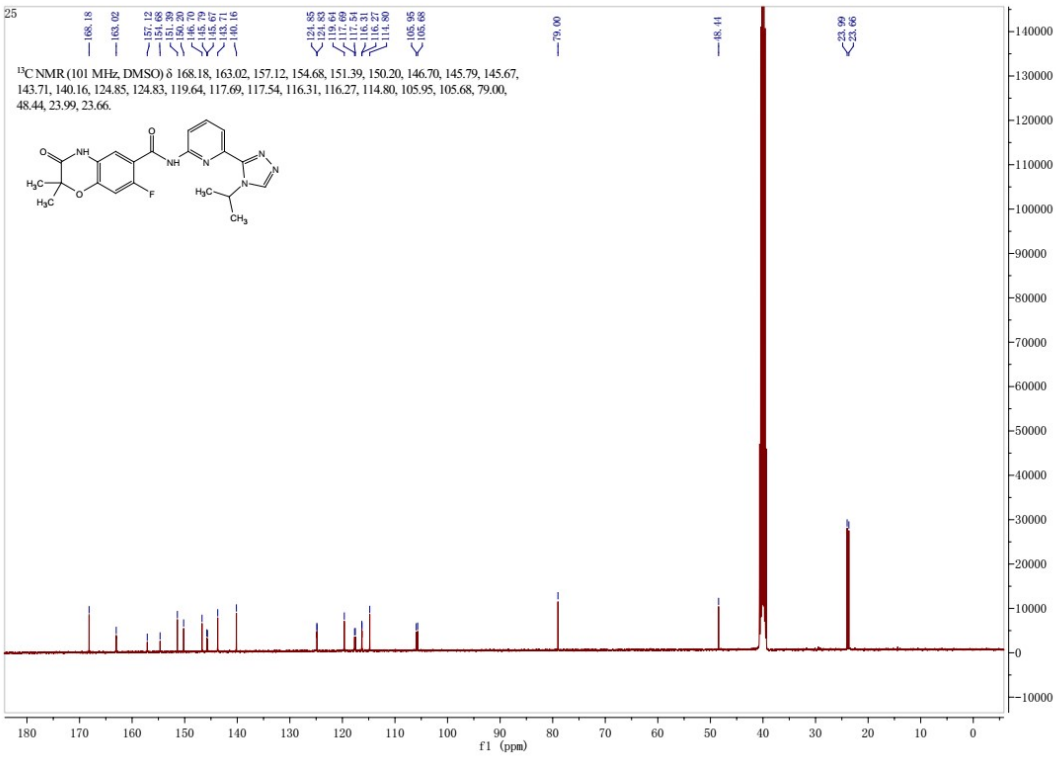
[13]C-NMR of Compound 17b:



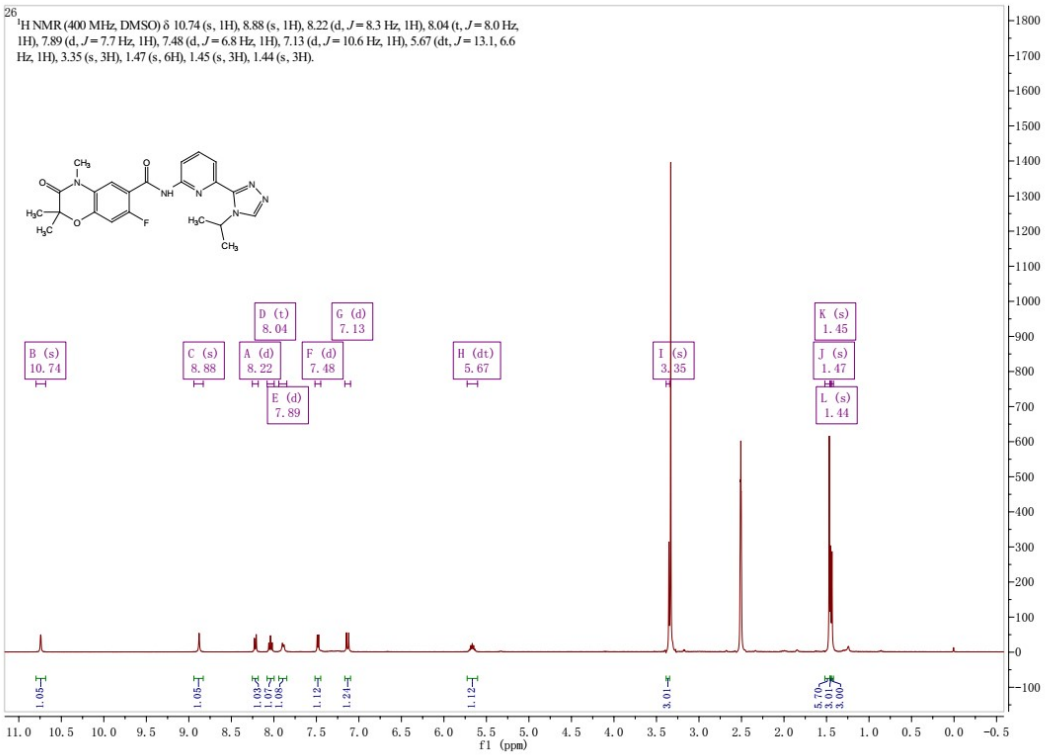
^{1}H-NMR of Compound 25:



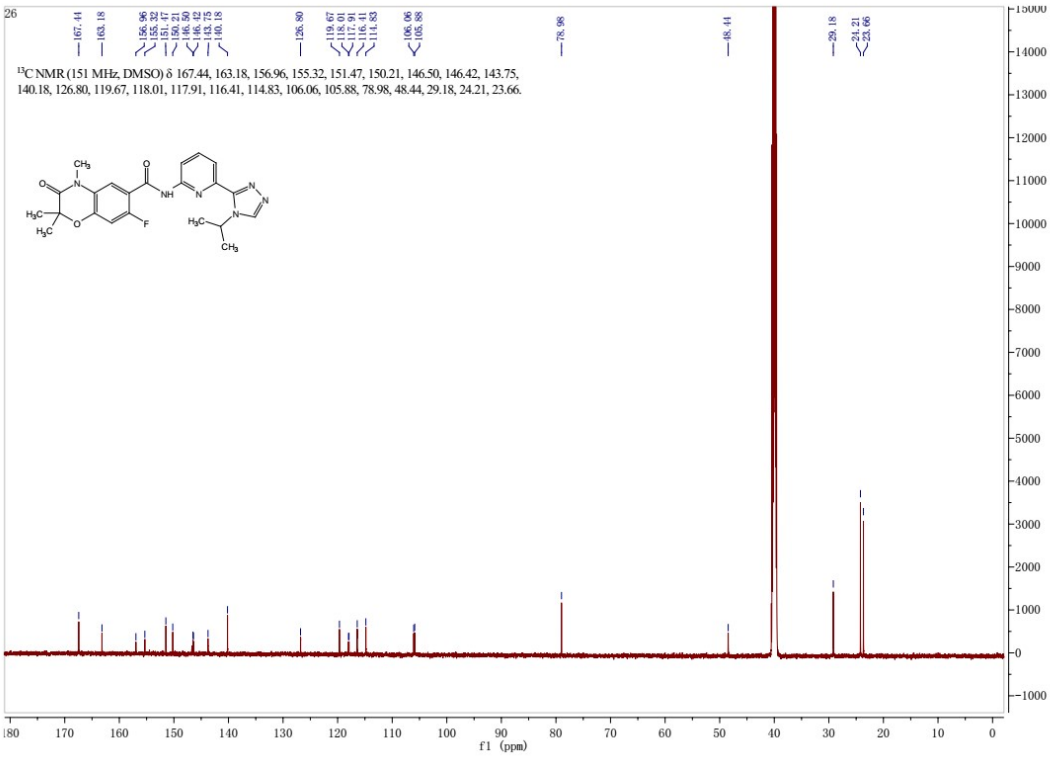
^{13}C-NMR of Compound 25:



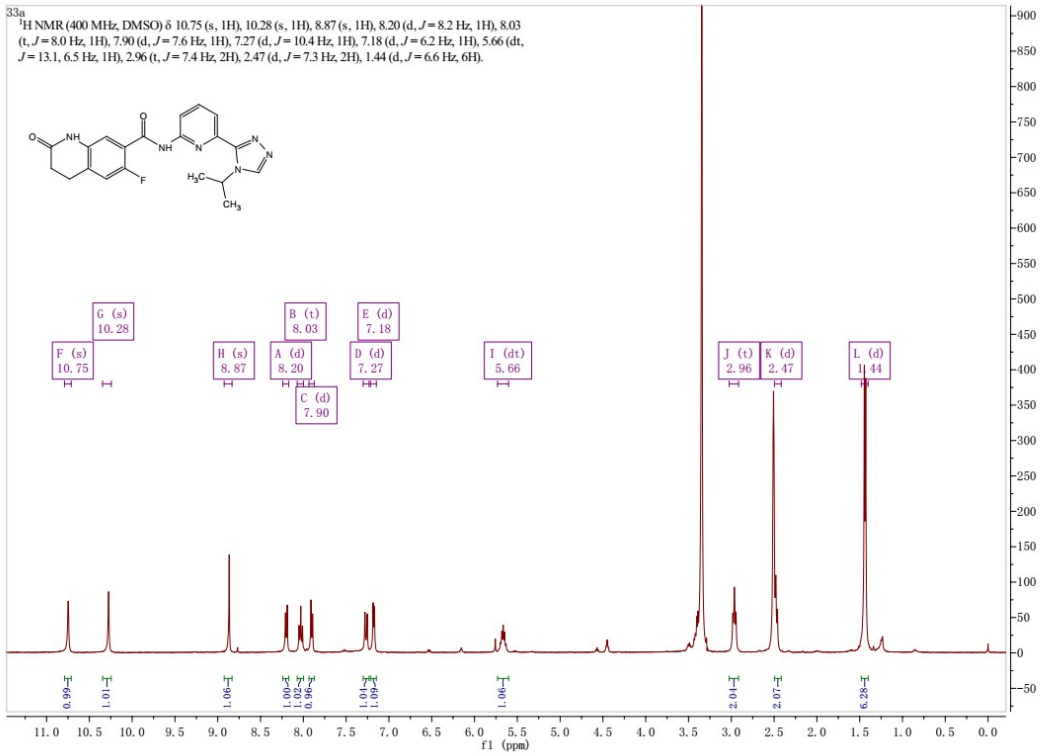
[1]H-NMR of Compound 26:



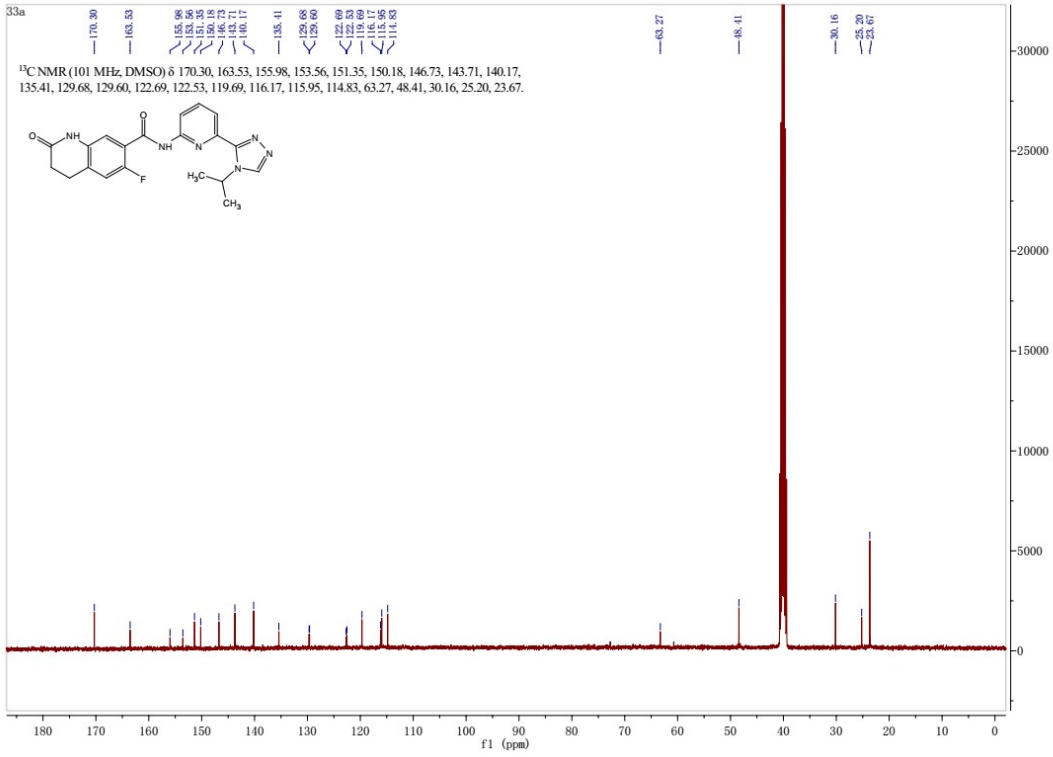
[13]C-NMR of Compound 26:



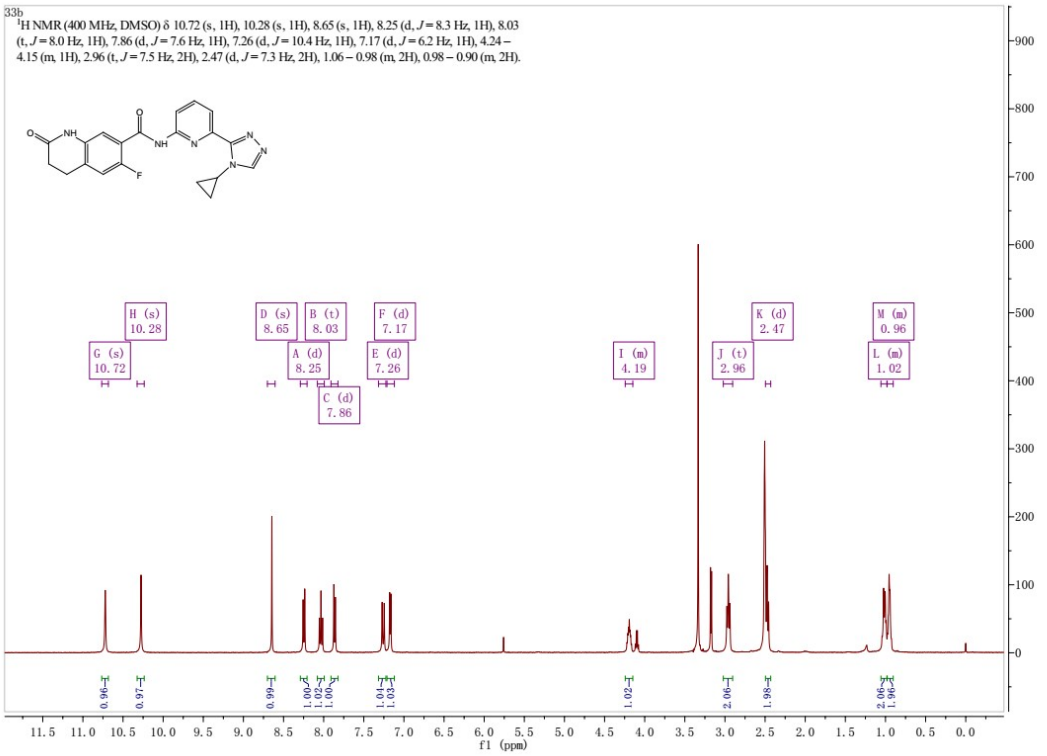
^{1}H-NMR of Compound 33a:



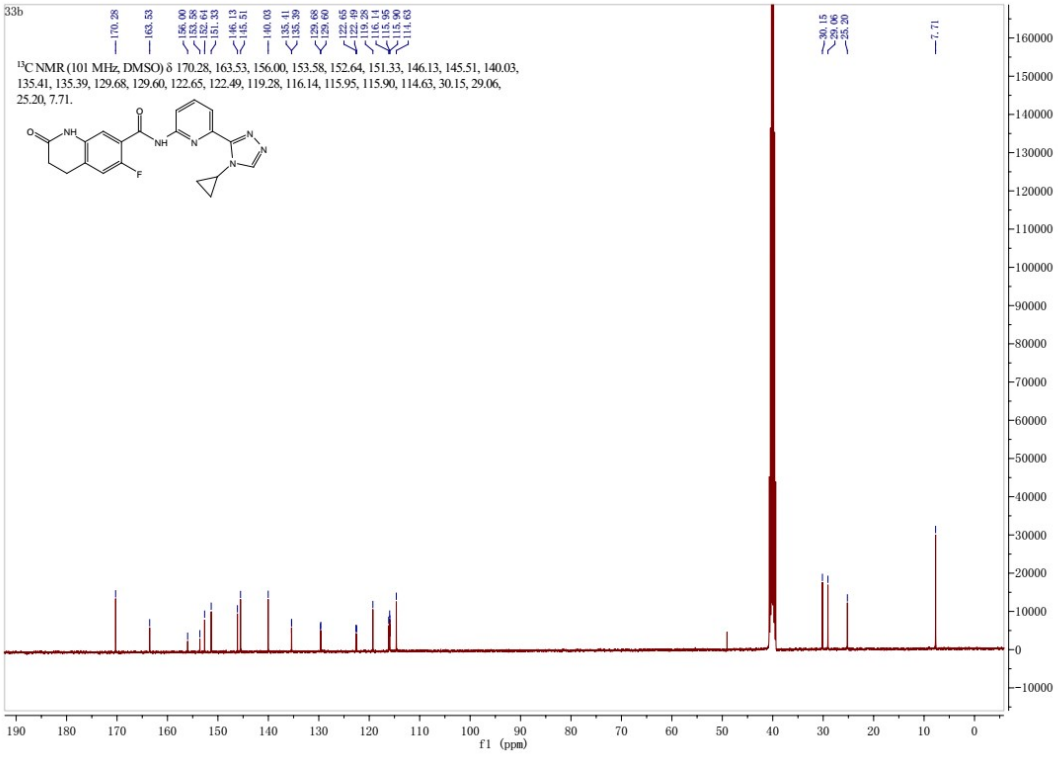
^{13}C-NMR of Compound 33a:



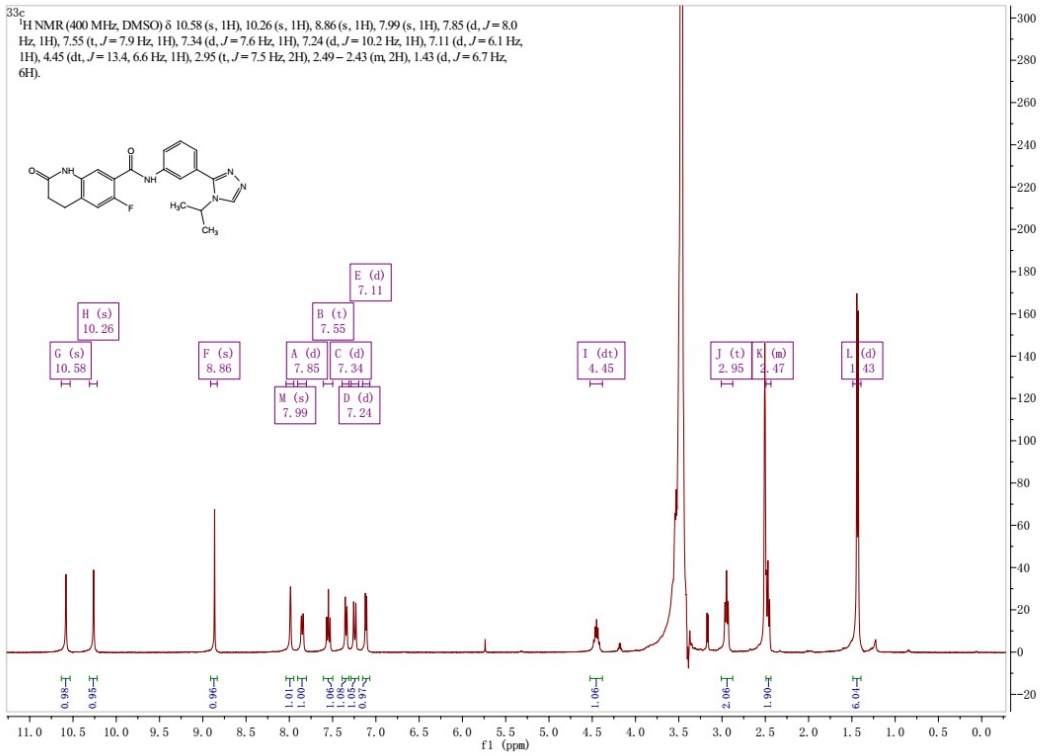
^{1}H-NMR of Compound 33b:



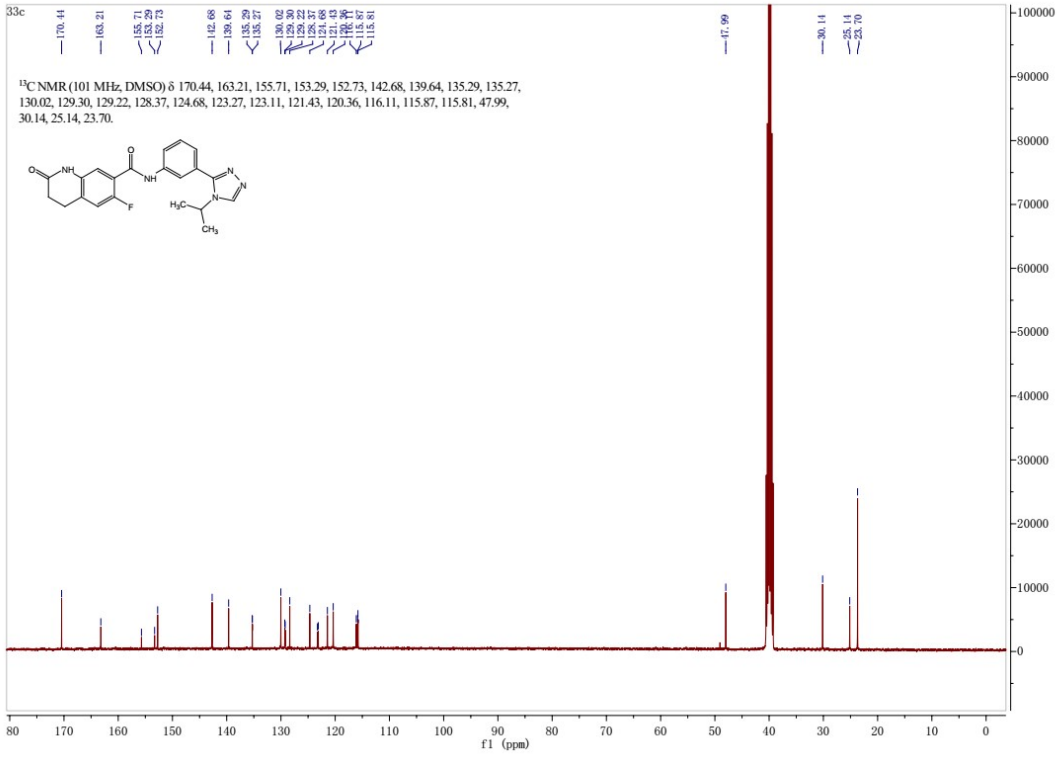
^{13}C-NMR of Compound 33b:



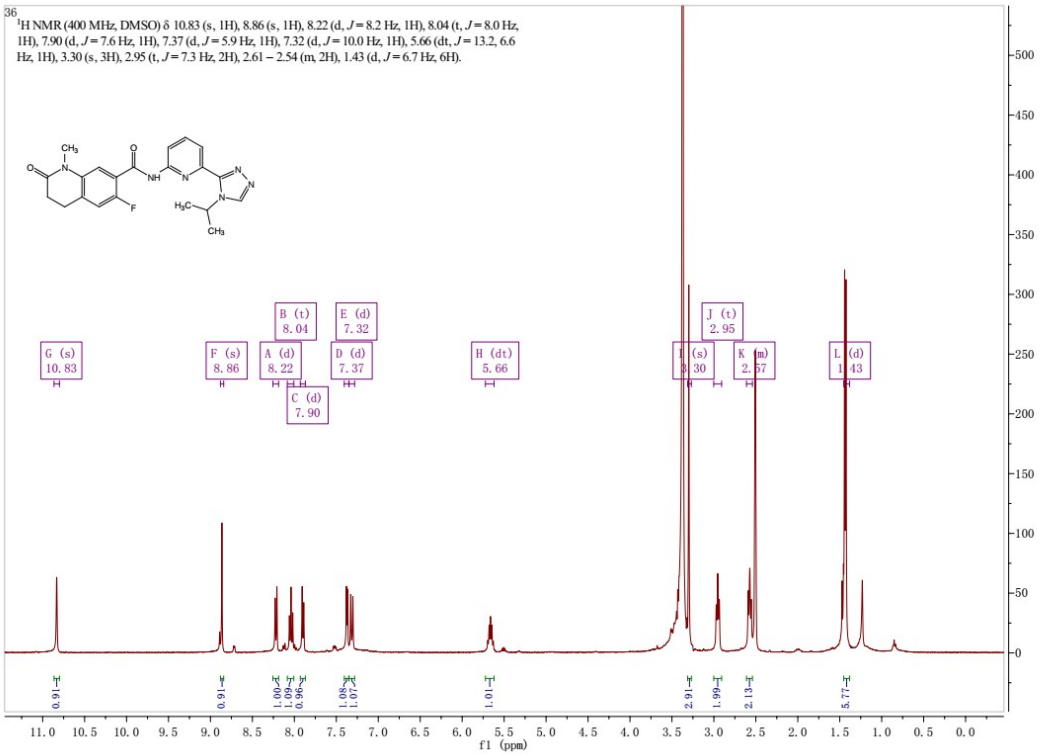
^{1}H-NMR of Compound 33c:



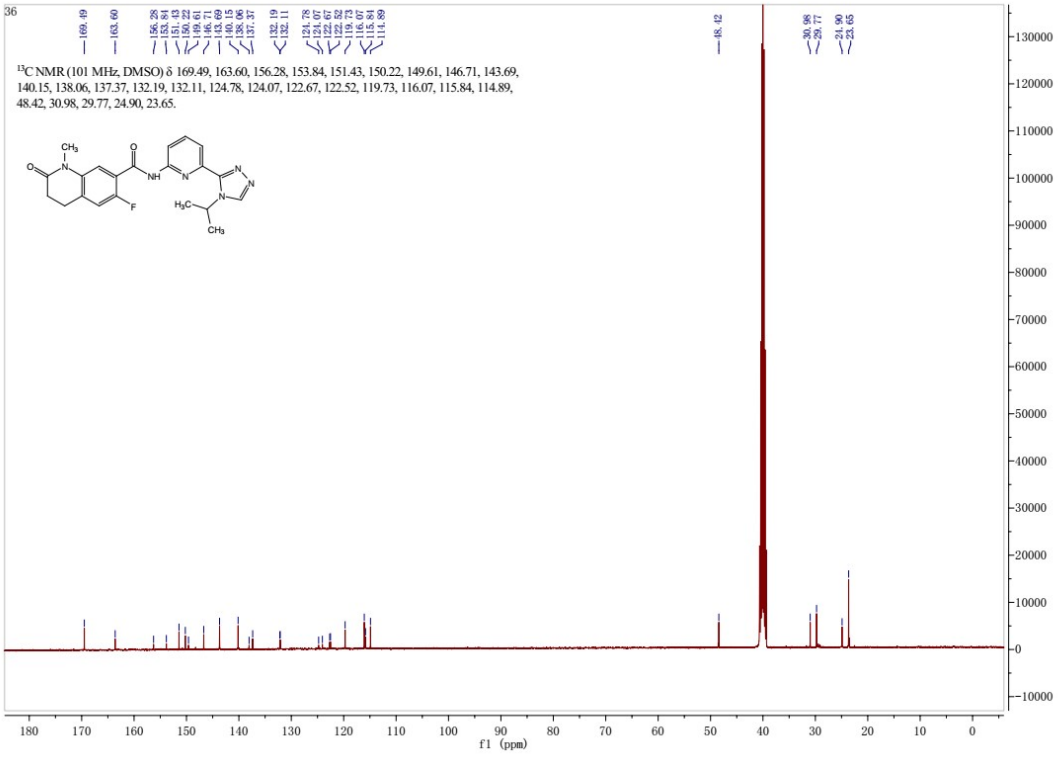
^{13}C-NMR of Compound 33c:



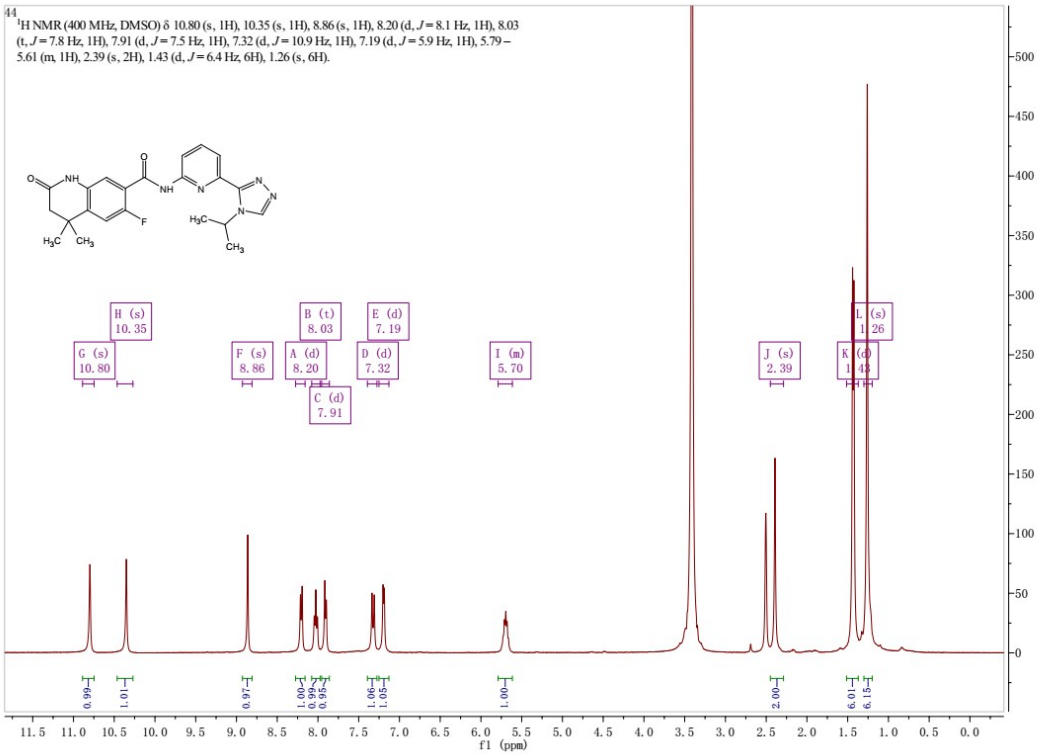
^{1}H-NMR of Compound 36:



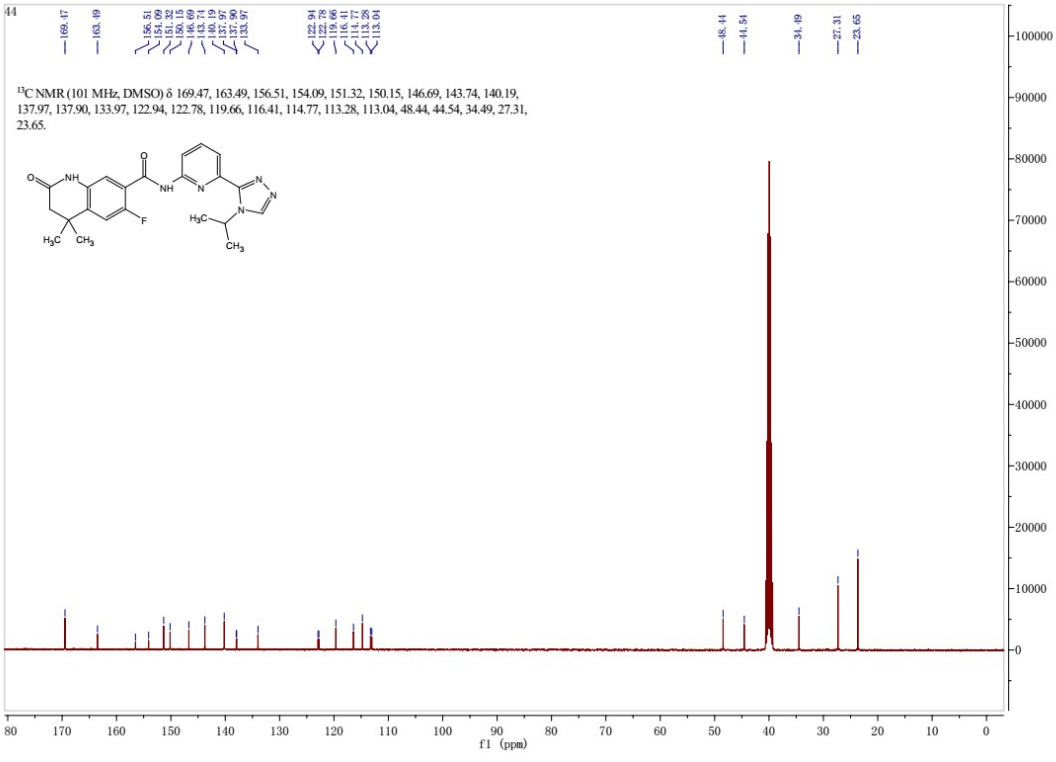
^{13}C-NMR of Compound 36:



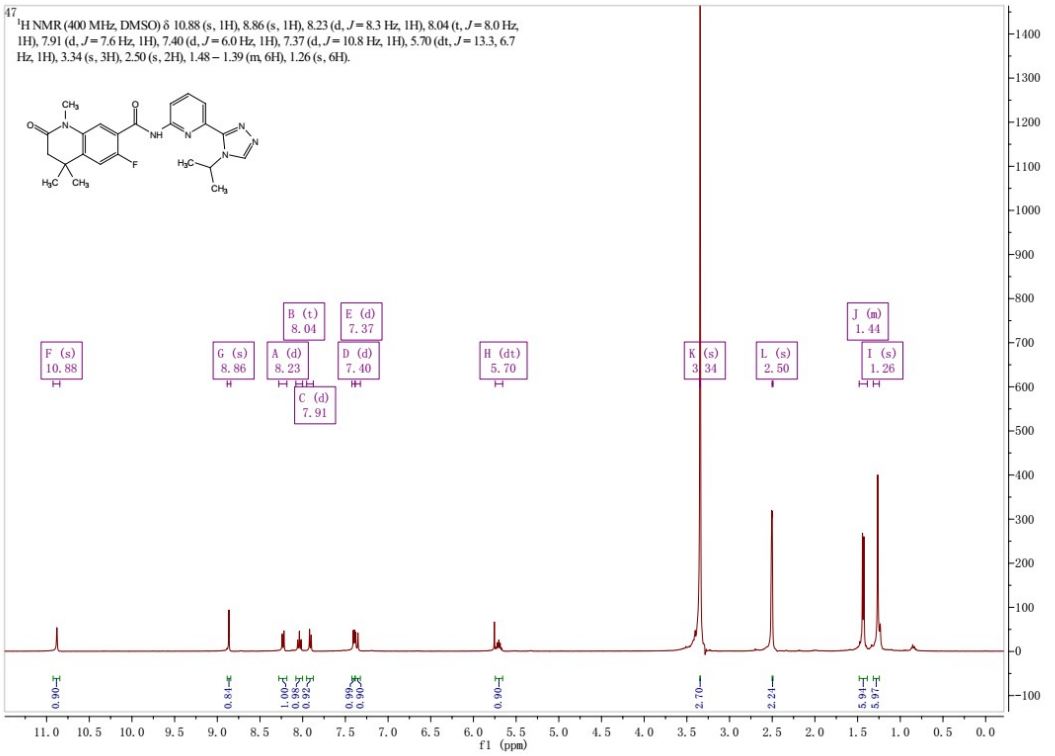
^{1}H-NMR of Compound 44:



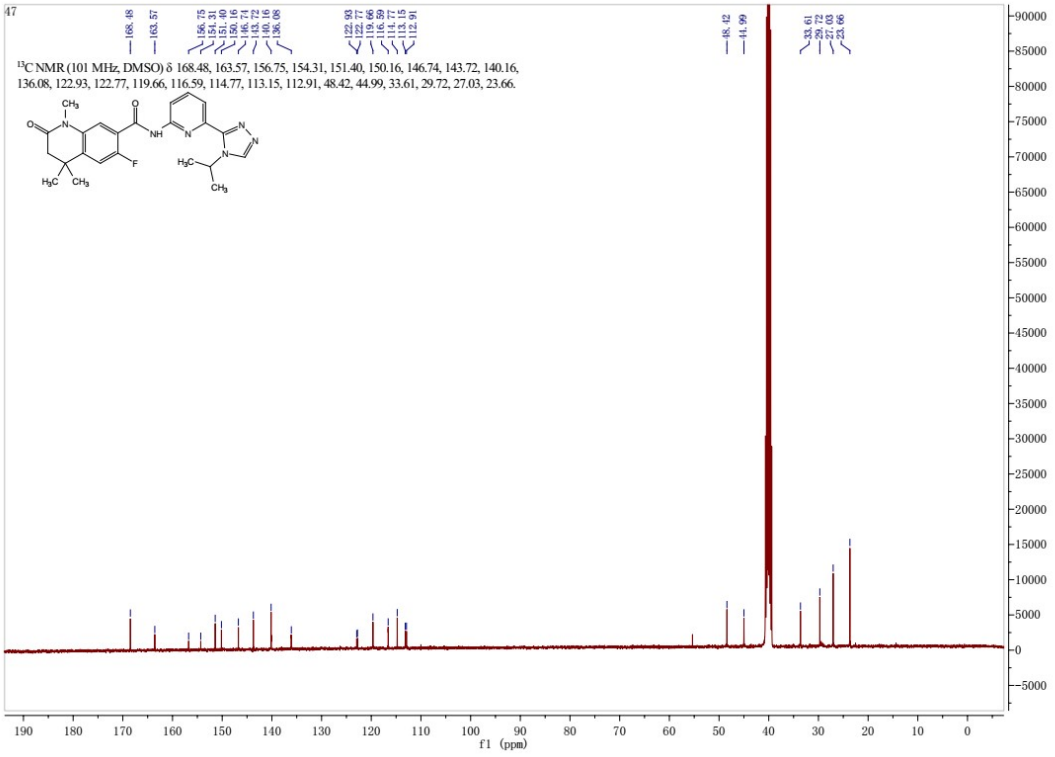
^{13}C-NMR of Compound 44:



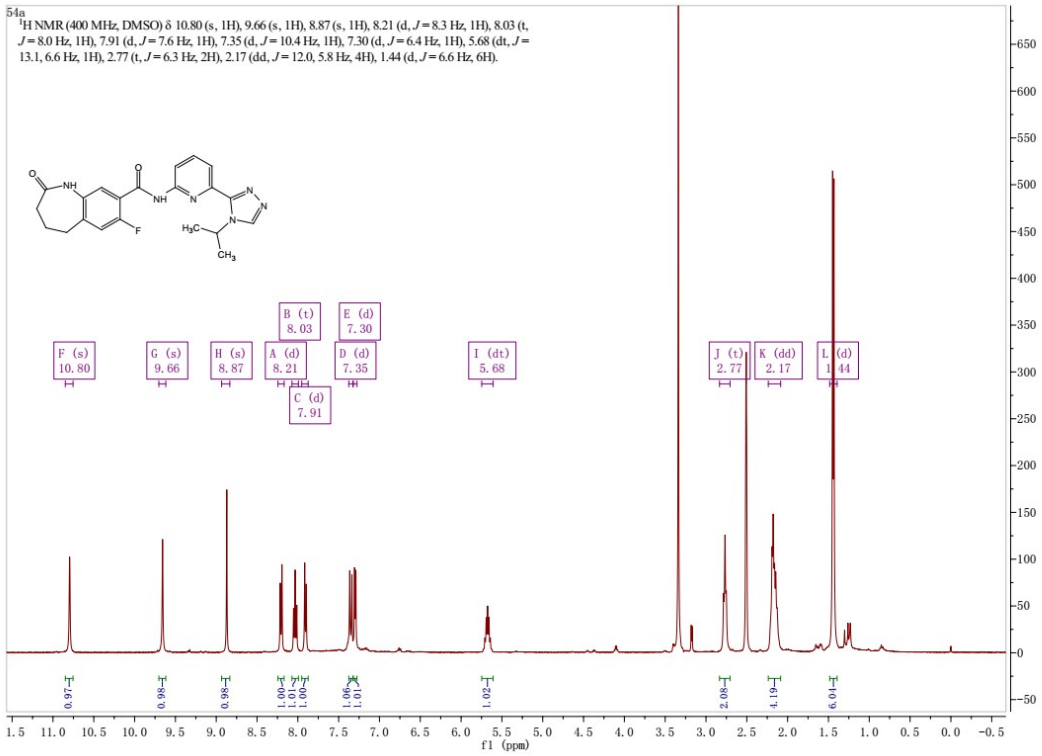
^{1}H-NMR of Compound 47:



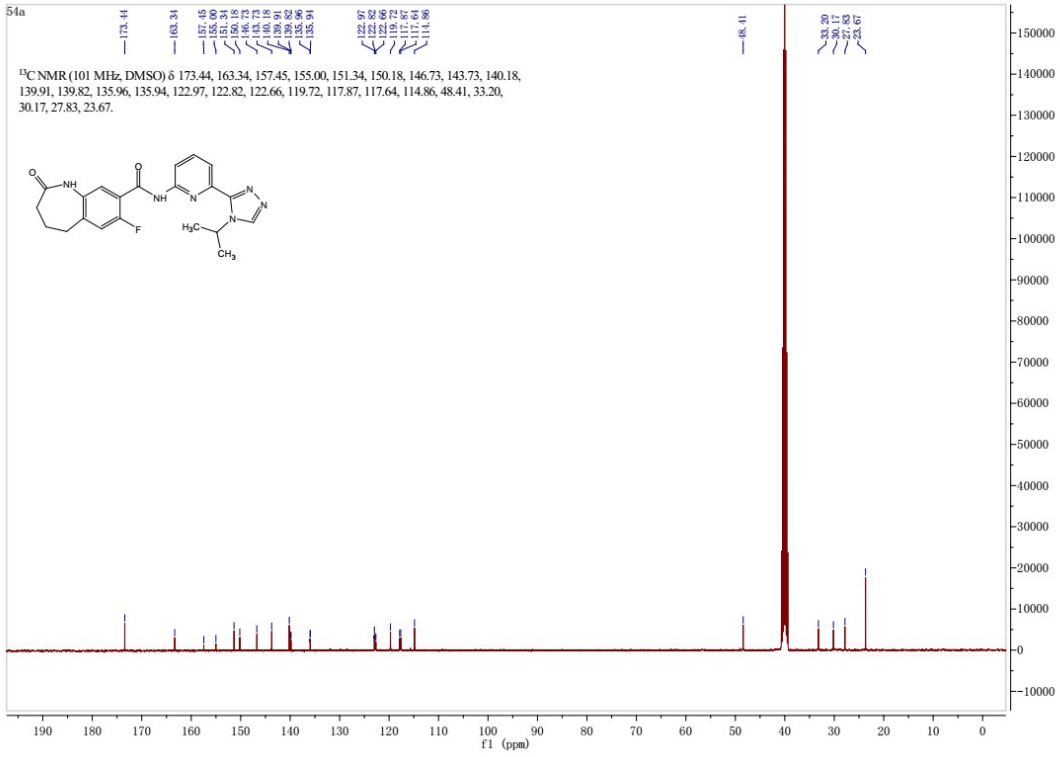
^{13}C-NMR of Compound 47:



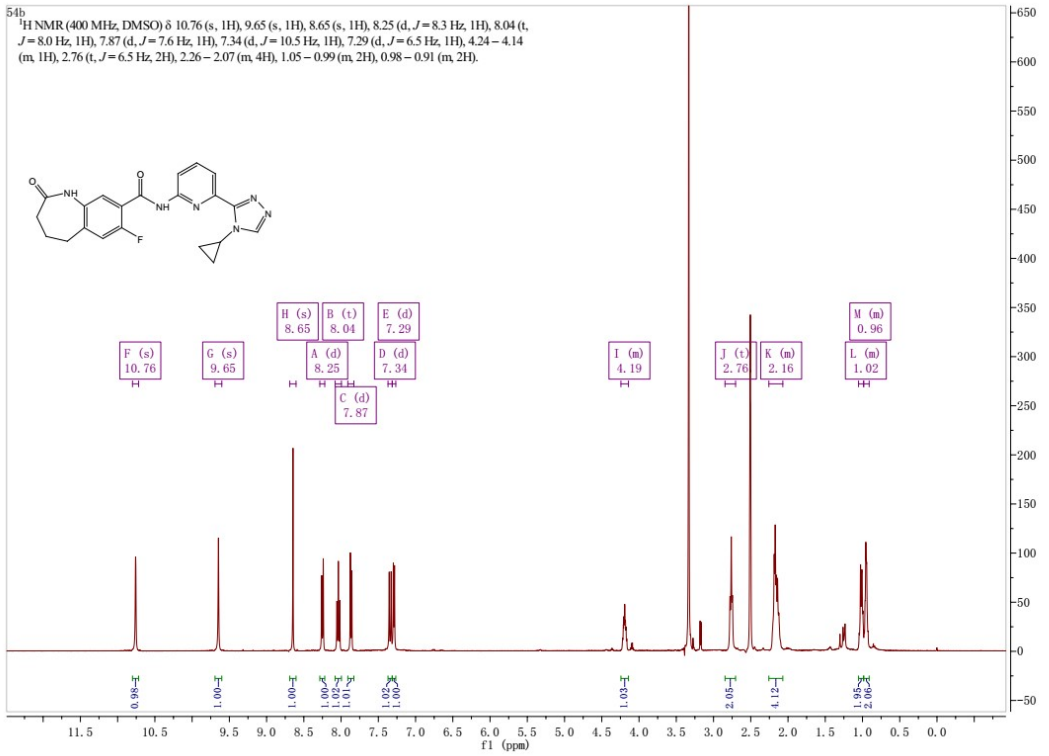
^{1}H-NMR of Compound 54a:



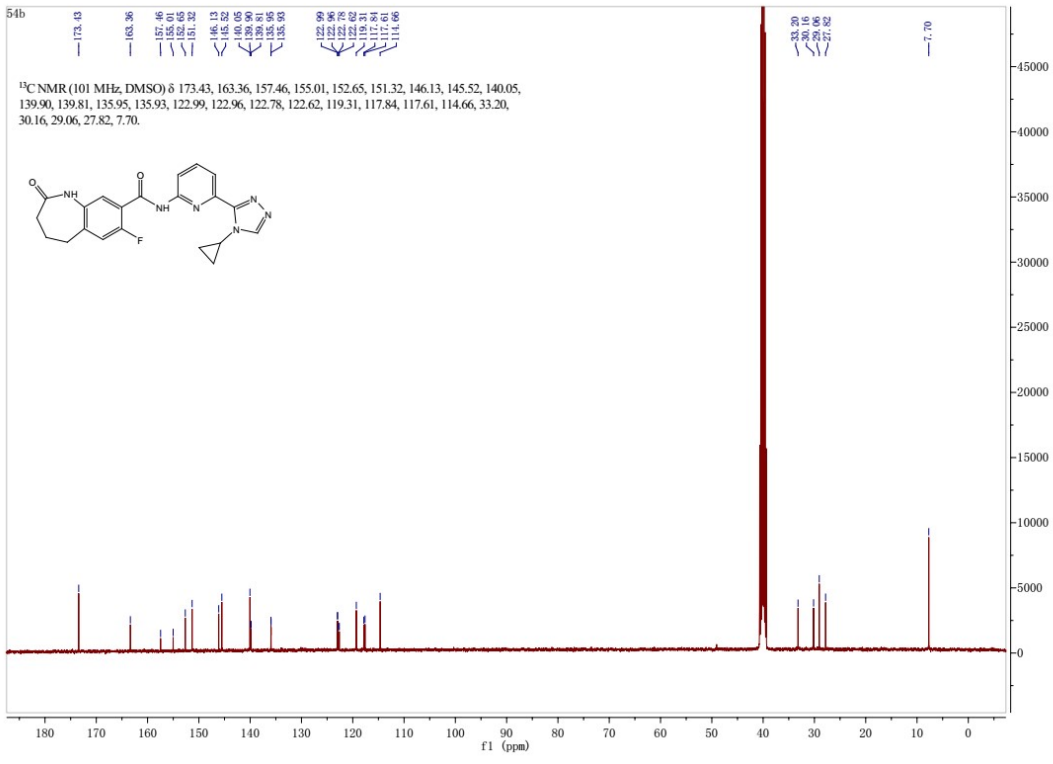
^{13}C-NMR of Compound 54a:



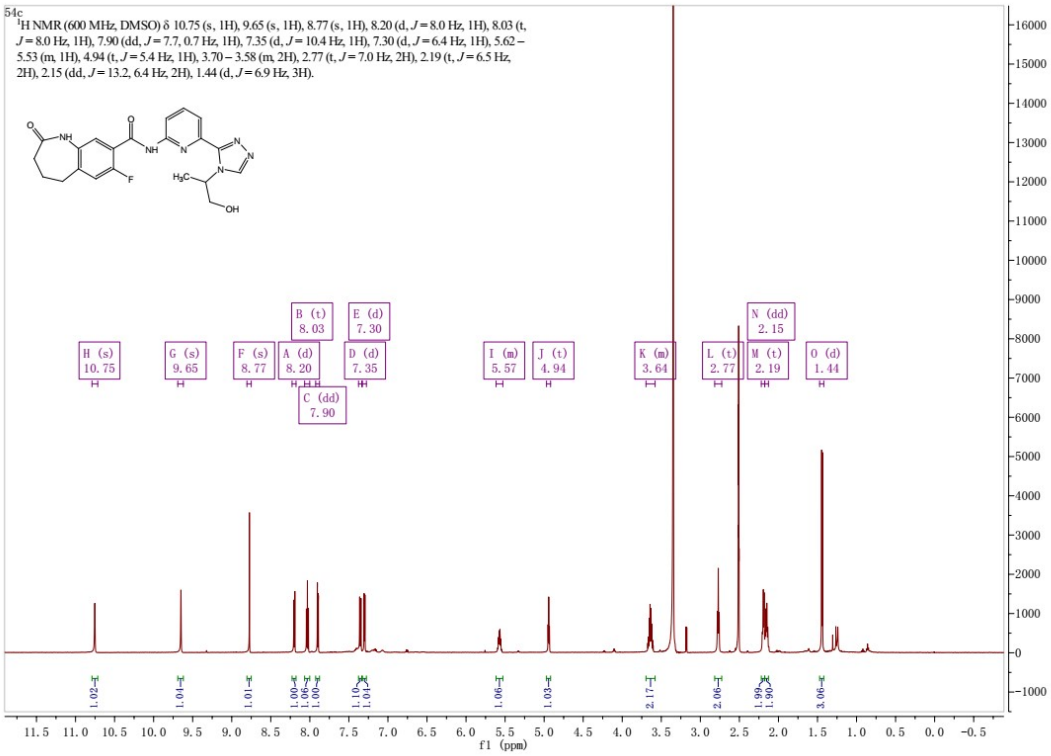
^{1}H-NMR of Compound 54b:



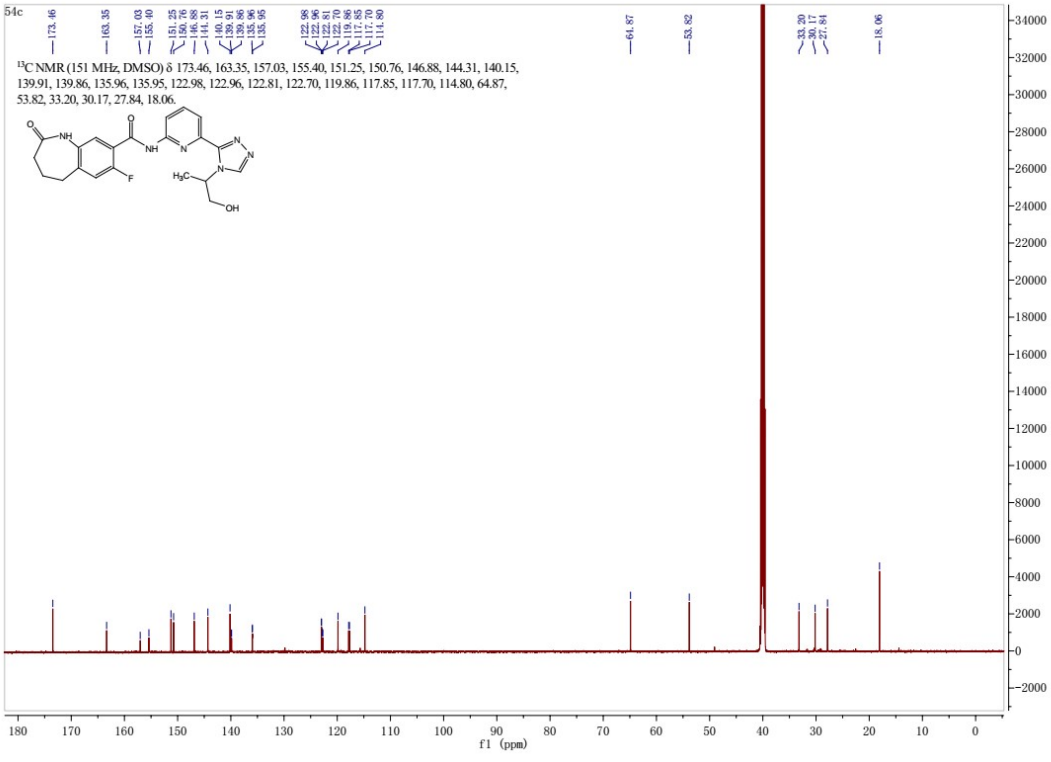
^{13}C-NMR of Compound 54b:



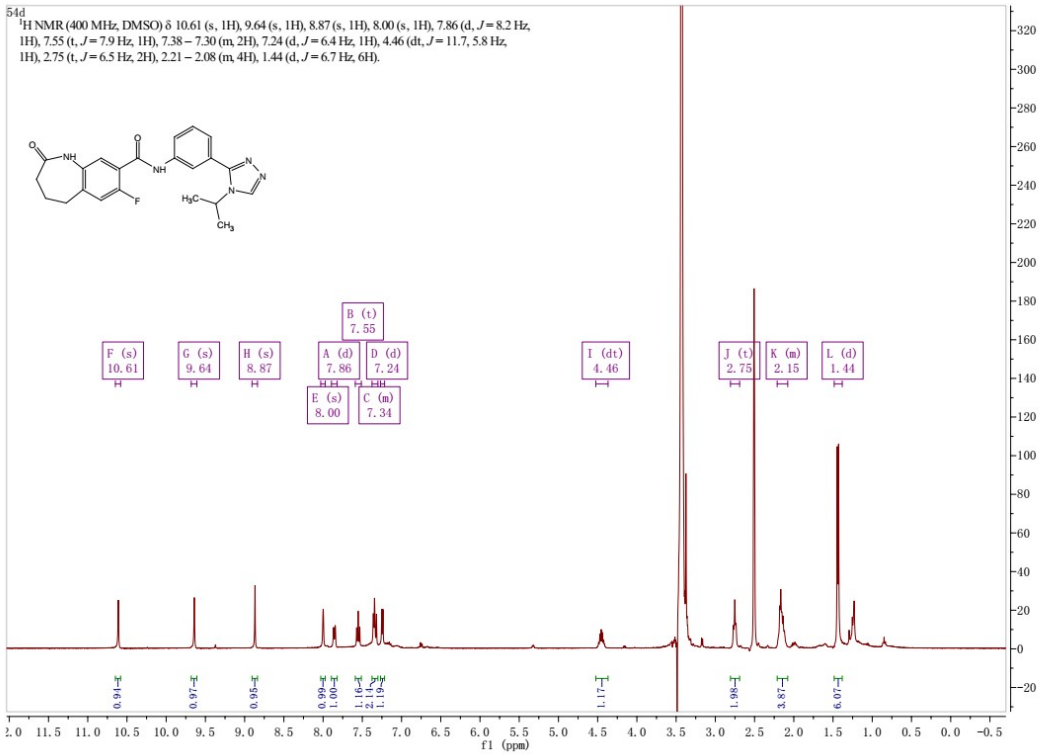
[1]H-NMR of Compound 54c:



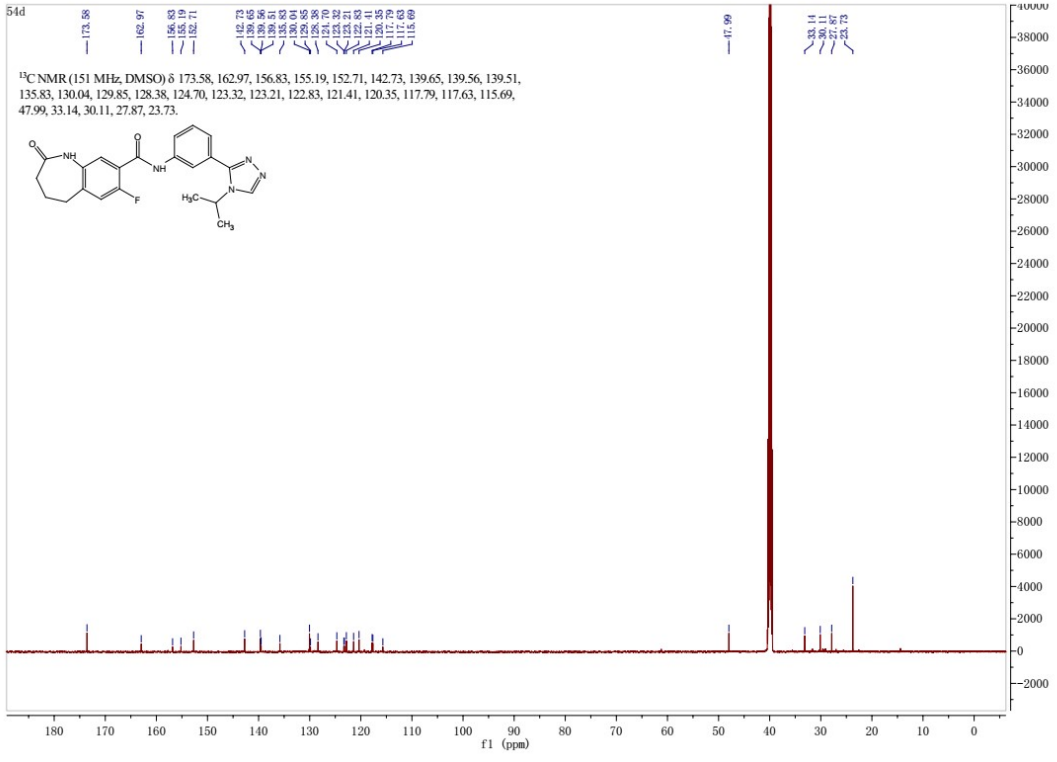
[13]C-NMR of Compound 54c:



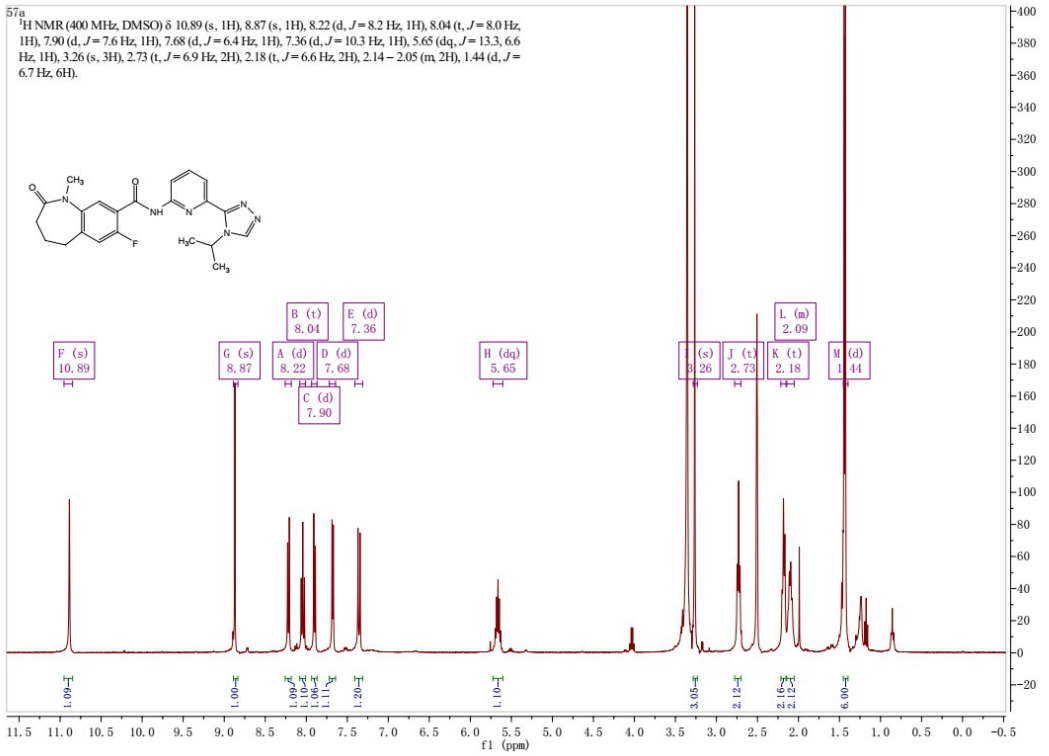
^{1}H-NMR of Compound 54d:



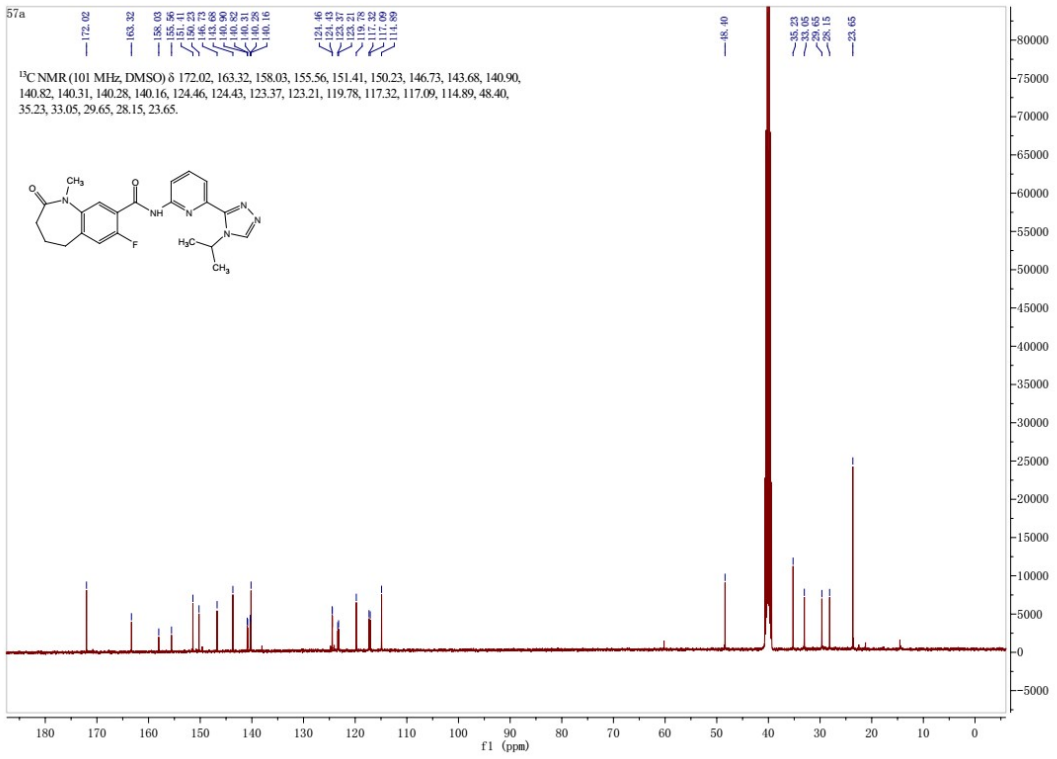
^{13}C-NMR of Compound 54d:



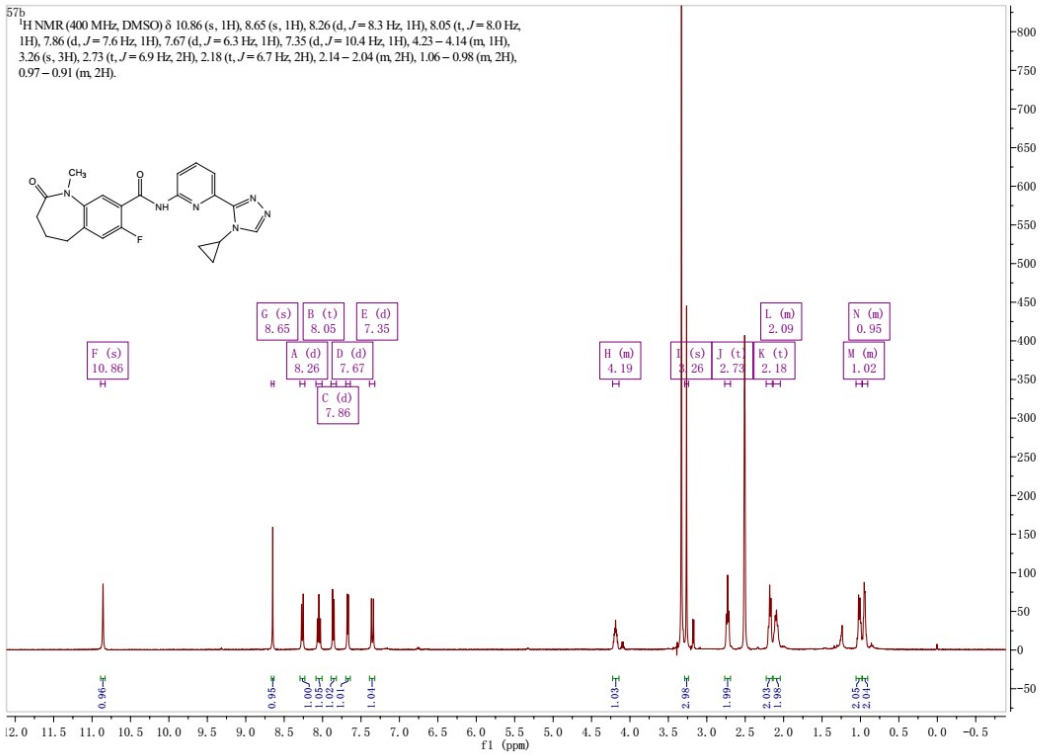
^{1}H-NMR of Compound 57a:



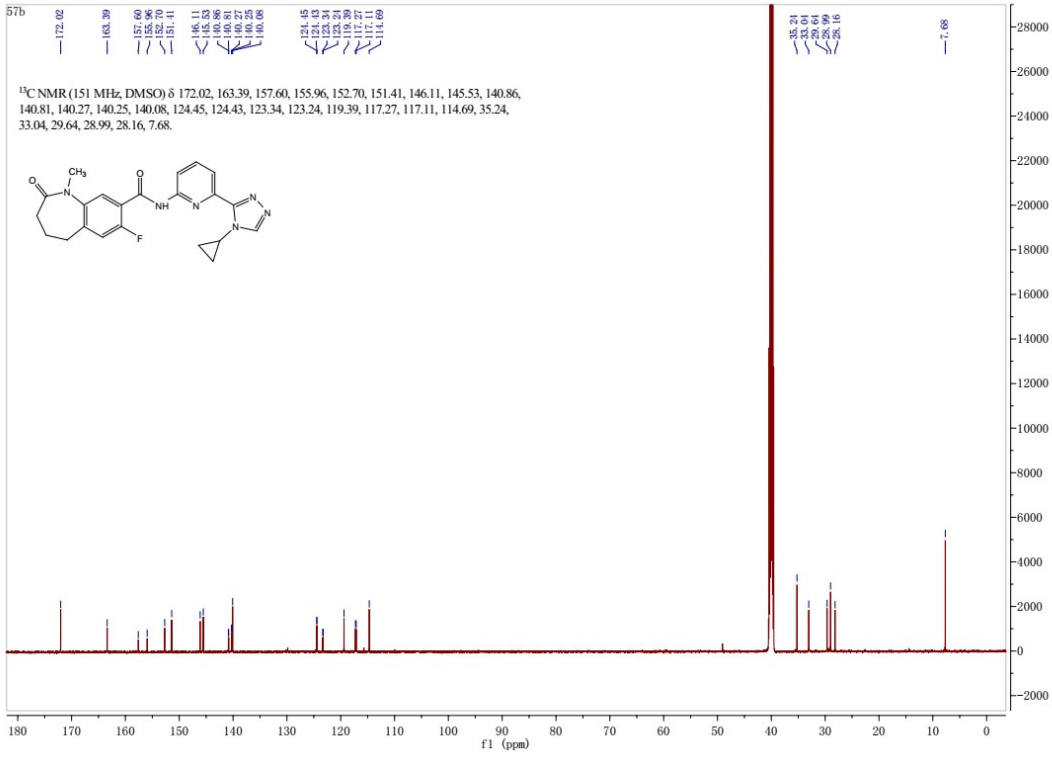
^{13}C-NMR of Compound 57a:



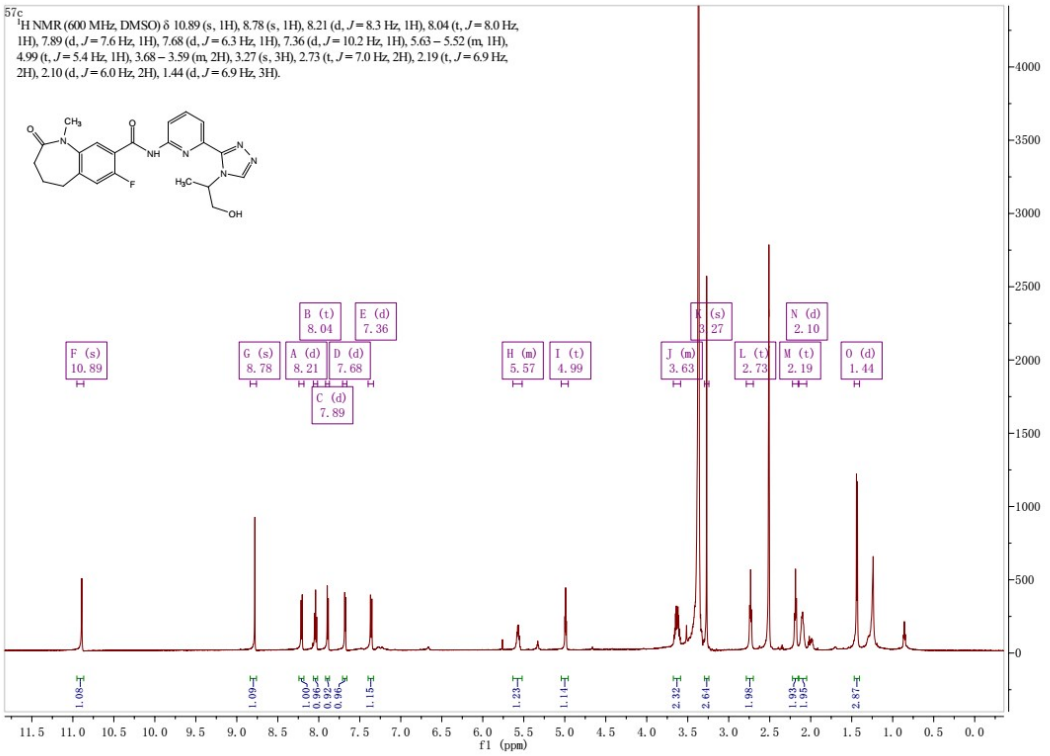
^{1}H-NMR of Compound 57b:



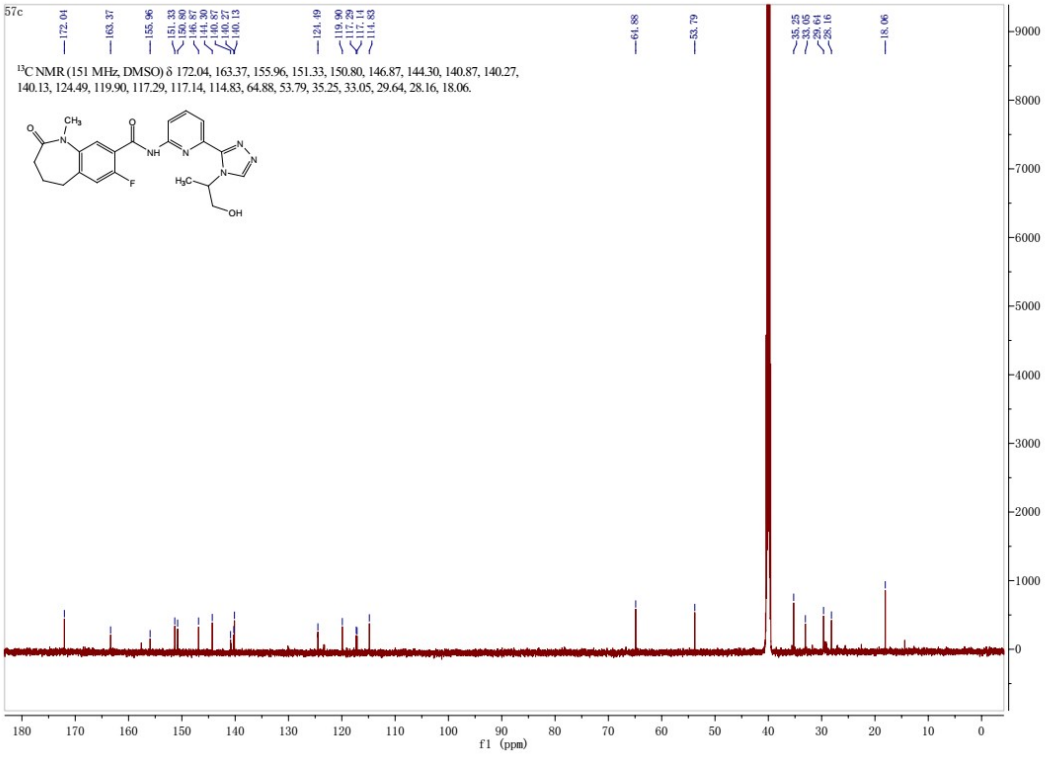
^{13}C-NMR of Compound 57b:



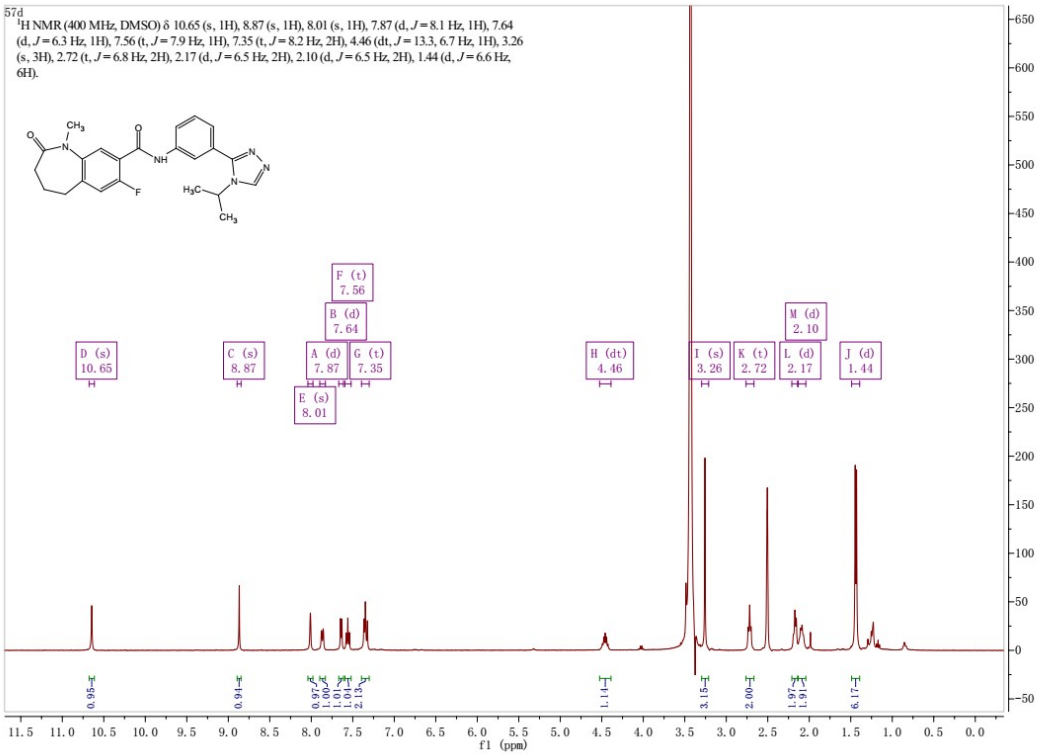
[1]H-NMR of Compound 57c:



[13]C-NMR of Compound 57c:



^{1}H-NMR of Compound 57d:



^{13}C-NMR of Compound 57d: