Electronic Supplementary Information

Structure activity relationship of C1-C2-linker substituted 1,5-naphthyridine analogs of oxabicyclooctane-linked novel bacterial topoisomerase inhibitors as broad-spectrum antibacterial agents (Part-7)

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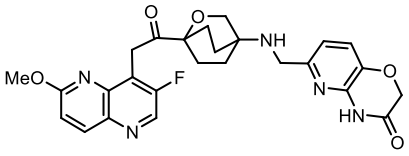
Synthesis of compound 5 (Scheme 1)



To a solution of tert-butyl 1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)-1-hydroxyethyl)-2-oxabicyclo[2.2.2]octan-4-ylcarbamate (+)-**26** (300 mg) in dichloromethane (6.7 mL) was added Dess-Martin periodinane (313 mg) at room temperature, the mixture was stirred at the same temperature for 18 h. The mixture was washed with saturated sodium hydrogen carbonate solution, saturated sodium sulfite solution and brine. The organic extracts were dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography (silica, toluene : ethyl acetate = 2:1) of the residue gave **27** (264 mg).^{1}H NMR ($CDCl_3$): δ_H 1.83–1.90 (m, 2H), 1.99–2.10 (m, 2H), 2.11–2.24 (m, 4H), 4.01 (s, 3H), 4.15 (s, 2H), 4.35 (brs, 1H), 4.54 (s, 2H), 7.05 (d, *J* = 8.6 Hz, 1H), 8.17 (d, *J* = 8.6 Hz, 1H), 8.65 (s, 1H). MS (ESI^+) *m/z*: 446 (MH^+). HRMS (ESI^+) for $C_{23}H_{29}FN_3O_5$ (MH^+): calcd, 446.20912; found, 446.20918.

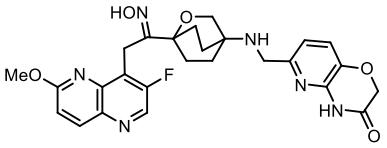
To a solution of **27** (30.0 mg) in dichloromethane (0.306 mL) was added trifluoroacetic acid (0.30 mL) at 0 ºC, the mixture was stirred at the same temperature for 1 hr and then concentrated in vacuo. After dilution of the residue with water, the mixture was adjusted to pH 11 by adding 1 N sodium hydroxide solution. The aqueous mixture was extracted with dichloromethane/methanol (10:1). The organic extracts were washed with 1 N sodium hydroxide solution and brine, dried over anhydrous sodium sulfate, filtered,

and then concentrated in vacuo to give **28** (23.2 mg). ^{1}H NMR ($CDCl_3$): δ_H 1.22 (brs, 2H), 1.66–1.84 (m, 4H), 1.98–2.18 (m, 4H), 3.81 (s, 2H), 3.99 (s, 3H), 4.55 (s, 2H), 7.05 (d, *J* = 9.2 Hz, 1H), 8.18 (d, *J* = 9.2 Hz, 1H), 8.65 (s, 1H). MS (ESI^+) *m/z*: 346 (MH^+). HRMS (ESI^+) for $C_{18}H_{21}FN_3O_3$ (MH^+): calcd, 346.15669; found, 346.15730.

A mixture of **28** (20.0 mg), **29** (10.8 mg) and acetic acid (66 uL) in dimethylformamide (0.46 mL) was stirred at room temperature for 30 minute. Sodium triacetoxyborohydride (17.2 mg) was added to the mixture at 0 ºC, the mixture was stirred at room temperature for overnight. After dilution of the mixture with sodium carbonate solution, the mixture was extracted with dichloromethane. The organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography (silica, chloroform: methanol = 10:1) of the residue gave **5** (28.3 mg). mp 183-184 ^{o}C, ^{1}H NMR (DMSO-d_6): δ_H 1.65–1.82 (m, 4H), 1.84–1.95 (m, 2H), 1.98–2.09 (m, 3H), 3.65 (d, *J* = 6.1 Hz, 2H), 3.79 (s, 2H), 3.96 (s, 3H), 4.50 (s, 2H), 4.59 (s, 2H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 9.2 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 8.29 (d, *J* = 9.2 Hz, 1H), 8.81 (s, 1H), 11.16 (s, 1H). MS (ESI^+) *m/z*: 508 (MH^+). HRMS (ESI^+) for $C_{26}H_{27}FN_5O_5$ (MH^+): calcd, 508.19962; found, 508.19896.

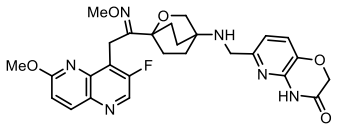
Anal. calcd for $C_{26}H_{26}FN_5O_5 \cdot 1.2H_2O$, C 59.02, H 5.41, N 13.24%. Found: C 59.15, H 5.13, N 12.91%.

Synthesis of compounds 13 and 14 (Scheme 1)



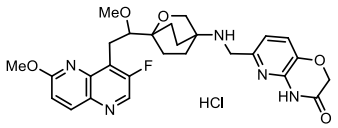
A mixture of **5** (65.0 mg) and hydroxylamine hydrochloride (35.6 mg) in pyridine (7.4 mL) was heated at 80 ºC for 51 h and then concentrated in vacuo. After dilution of the residue with dichloromethane, the mixture was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Preparative thin layer chromatography (silica, chloroform : methanol = 10:1) of the residue gave **13** (17.4 mg, 33%) and **14** (31.1 mg, 58%). **13**: mp 191 ^{o}C, ^{1}H NMR (DMSO-d_6): δ_H 1.55–2.13 (m, 7H), 2.59–2.71 (m, 2H), 3.64 (s, 2H), 3.71 (s, 2H), 3.99 (s, 3H), 4.07 (s, 2H), 4.59 (s, 2H), 7.01 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 9.2 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 8.24 (d, *J* = 8.6 Hz, 1H), 8.73 (s, 1H), 10.55 (s, 1H), 11.15 (s, 1H). MS (ESI^+) *m/z*: 523 (MH^+). HRMS (ESI^+) for $C_{26}H_{28}FN_6O_5$ (MH^+): calcd, 523.21052; found, 523.21148. Anal. calcd for $C_{26}H_{27}FN_6O_5$, C 59.76, H 5.21, N 16.08%. Found: C 59.04, H 5.19, N 15.78%. **14**: mp 248 ^{o}C, ^{1}H NMR (DMSO-d_6): δ_H 1.47–1.58 (m, 2H), 1.61–1.72 (m, 2H), 1.75–1.91 (m, 3H), 1.96–2.09 (m, 2H), 3.36 (s, 2H), 3.55 (d, *J* = 6.1 Hz, 2H), 4.03 (s, 3H), 4.18 (s, 2H), 4.57 (s, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 9.2 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 8.25 (d, *J* = 9.2 Hz, 1H), 8.66 (s, 1H), 10.75 (s, 1H), 11.12 (s, 1H). MS (ESI^+) *m/z*: 523 (MH^+). HRMS (ESI^+) for $C_{26}H_{28}FN_6O_5$ (MH^+): calcd, 523.21052; found, 523.21114. Anal. Calcd for $C_{26}H_{27}FN_6O_5$, C 59.76, H 5.21, N 16.08%. Found: C 59.20, H 5.26, N 15.70%.

Synthesis of compound 15 (Scheme 1)



A mixture of **5** (150 mg) and *O*-methylhydroxylamine hydrochloride (98.7 mg) in pyridine (7.4 mL) was heated at 80 ºC for 51 h and then concentrated in vacuo. After dilution of the residue with dichloromethane, the mixture was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Preparative thin layer chromatography (silica, chloroform: methanol = 10:1) of the residue gave **15** (65.3 mg, 52%). ^{1}H NMR (DMSO-d_6): δ_H 1.46–1.56 (m, 2H), 1.60–1.72 (m, 2H), 1.76–1.91 (m, 3H), 1.92–2.02 (m, 2H), 3.35 (s, 2H), 3.54 (d, J = 4.9 Hz, 2H), 3.63 (s, 3H), 4.02 (s, 3H), 4.16 (s, 2H), 4.57 (s, 2H), 6.95 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 8.26 (d, J = 9.2 Hz, 1H), 8.69 (d, J = 1.2 Hz, 1H), 11.13 (s, 1H). MS (ESI$^+$) *m/z*: 537 (MH$^+$). HRMS (ESI$^+$) for $C_{27}H_{30}FN_6O_5$ (MH$^+$): calcd, 537.22617; found, 537.22663. Anal. Calcd for $C_{27}H_{29}FN_6O_5$, C 60.44, H 5.45, N 15.66%. Found: C 60.29, H 5.44, N 15.73%.

Synthesis of compound (-)-6 (Scheme 2)



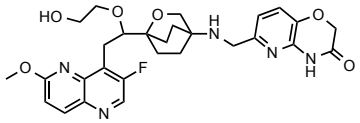
To a suspension of sodium hydride (42.9 mg, 55% in mineral oil) in *N*,*N*-dimethylformamide (3.5 mL) was added a solution of tert-butyl 1-(2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)-1-hydroxyethyl)-2-oxabicyclo[2.2.2]octan-4-ylcarbamate (-)-**26** (200 mg) in *N*,*N*-dimethylformamide (0.6 mL) at -40 ºC, the mixture was stirred at -20 ºC for 2 h. Methyl benzenesulfonate (66.7 mL) was added to the mixture. The mixture was stirred under cooling with ice for 2.5 h. After dilution of the mixture with water, the mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Preparative thin layer chromatography (silica, toluene: methanol = 7:1) of the residue gave **30** (125 mg). ^{1}H NMR ($CDCl_3$): δ_H 1.42 (s, 9H), 1.78−1.94 (m, 4H), 1.97−2.23 (m, 4H), 3.08 (s, 3H), 3.28 (dd, J = 12.7, 3.6 Hz, 1H), 3.42 (ddd, J = 12.7, 4.2, 1.8 Hz, 1H), 3.61 (dd, J = 9.1, 3.6 Hz, 1H), 3.86−3.94 (m, 2H), 4.09 (s, 3H), 4.28 (brs, 1H), 7.07 (d, J = 9.1 Hz, 1H), 8.17 (d, J = 9.1 Hz, 1H), 8.62 (s, 1H). MS (ESI$^+$) *m/z*: 462 (MH$^+$). HRMS (ESI$^+$) for $C_{24}H_{33}FN_3O_5$ (MH$^+$): calcd, 462.24042; found, 462.23972.

To a solution of **30** (80.0 mg) in dichloromethane (0.79 mL) was added trifluoroacetic acid (0.77 mL) at 0 ºC, the mixture was stirred at the same temperature for 30 minutes and then concentrated in vacuo. After dilution of the residue with water, the mixture was adjusted to pH 11 by adding 1 N sodium

hydroxide solution. The aqueous mixture was extracted with dichloromethane/methanol (10:1). The organic extracts were washed with 1 N sodium hydroxide solution and brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo to give deprotected amine (52.2 mg). ^{1}H NMR ($CDCl_3$): δ_H 1.60−1.93 (m, 6H), 1.98−2.06 (m, 1H), 2.13−2.22 (m, 1H), 3.07 (s, 3H), 3.29 (dd, *J* = 12.7, 9.1 Hz, 1H), 3.42 (ddd, *J* = 12.7, 4.2, 1.8 Hz, 1H), 3.57 (s, 2H), 3.61 (dd, *J* = 9.1, 4.2 Hz, 1H), 4.09 (s, 3H), 7.07 (d, *J* = 9.1 Hz, 1H), 8.18 (d, *J* = 9.1 Hz, 1H), 8.62 (s, 1H). MS (ESI$^+$) *m/z*: 362 (MH^+). HRMS (ESI$^+$) for $C_{19}H_{25}FN_3O_3$ (MH^+): calcd, 362.18799; found, 362.18769.

A mixture of the aforementioned amine (50.0 mg), **29** (25.9 mg) and acetic acid (158 uL) in dimethylformamide (1.1 mL) was stirred at room temperature for 30 minutes. Sodium triacetoxyborohydride (41.0 mg) was added to the mixture at 0 ºC, the mixture was stirred at room temperature for overnight. After dilution of the mixture with sodium carbonate solution, the mixture was extracted with dichloromethane. The organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography (silica, chloroform: methanol = 10:1) of the residue gave (-)-**6** (55.7 mg). mp 219-220 ^{o}C, ^{1}H NMR (DMSO-d_6): δ_H 1.55−1.92 (m, 8H), 1.95−2.07 (m, 1H), 2.94 (s, 3H), 3.15 (dd, *J* = 12.2, 9.2 Hz, 1H), 3.29−3.38 (m, 1H), 3.50 (s, 2H), 3.55 (dd, *J* = 9.2, 4.3 Hz, 1H), 3.60 (s, 2H), 4.04 (s, 3H), 4.58 (s, 2H), 6.99 (d, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 9.2 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 8.27 (d, *J* = 9.2 Hz, 1H), 8.75 (s, 1H), 11.15 (s, 1H). MS (ESI$^+$) *m/z*: 524 (MH^+). HRMS (ESI$^+$) for $C_{27}H_{31}FN_5O_5$ (MH^+): calcd, 524.23092; found, 524.23153. Anal. Calcd for $C_{27}H_{30}FN_5O_5 \cdot HCl \cdot 0.6H_2O$, C 56.81, H 5.69, N 12.27%. Found: C 56.55, H 5.50, N 12.18%.

Synthesis of compound ((±)-7) (Scheme 2)



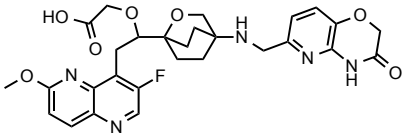
To a cooled (0 ^{o}C) solution of (±)-**26** (250 mg, 0.56 mmol, 1.0 eq) in dried THF (25 mL) was added NaH (89 mg, 60% in mineral, 2.24 mmol, 4.0 eq) portion wise. Then the mixture was stirred at the same temperature for 30 min, and ethyl bromoacetate (93 mg, 0.56 mmol, 1.0 eq) were added. The resulting mixture was stirred at room temperature overnight, and partitioned between water and EtOAc. The organic layers were washed by brine, dried over sodium sulfate and concentrated. The residue was purified by preparative TLC to give **31a** (52 mg, 17.4 %). MS (ESI)$^+$ *m/z* 534 $(M+H)^+$.

A solution of **31a** (52 mg, 0.10 mmol, 1.0 eq) in dried THF (20 mL) was added $LiBH_4$ (9 mg, 0.39 mmol, 4.0 eq), and the resulting mixture was stirred at room temperature for 30 min. The residue was concentrated under reduced pressure and partitioned between water and EtOAc. The organic layers were washed with brine, dried over sodium sulfate and concentrated to give the primary alcohol (40 mg, 83.3 %). MS (ESI)$^+$ *m/z* 492 $(M+H)^+$.

A solution of the primary alcohol (40 mg, 0.08 mmol) in dichloromethane (5 mL) was added TFA (5 mL) and the mixture was stirred at room temperature for 1h and then concentrated under reduced pressure. The residue was basified by aqueous solution of sodium carbonate (pH = 8 ~ 9) and extracted with EtOAc. The organic layers were washed by brine, dried over sodium sulfate, concentrated to give free amine (25 mg, 78.1 %). MS $(ESI)^+$ *m/z* 392 $(M+H)^+$.

A solution of the free amine (25 mg, 0.06 mmol, 1.0 eq) and aldehyde **29** (23 mg, 0.13 mmol, 2.0 eq) in DMF:AcOH = 7:1 (5 mL) was stirred at room temperature for 30 min and then $NaBH(OAc)_3$ (39 mg, 0.19 mmol, 3.0 eq) was added. The mixture was stirred at room temperature for 1h, and purified by preparative HPLC to give (±)-**7** (11 mg, 31.4 %). ^{1}H-NMR (CD_3OD, 400 MHz) δ_H 8.64 (s, 1H), 8.18 ~ 8.20 (d, *J* = 9.39 Hz, 1H), 7.33 ~ 7.35 (d, *J* = 7.83 Hz, 1H), 7.15 ~ 7.17 (d, *J* = 9.39 Hz, 1H), 7.07 ~ 7.09 (d, *J* = 7.83 Hz, 1H), 4.67 (s, 2H), 4.19 (s, 2H), 4.09 (s, 3H), 3.84 ~ 3.89 (m, 3H), 3.35 ~ 3.47 (m, 2H), 3.03 ~ 3.08 (m, 1H), 2.03 ~ 2.31 (m, 8H). MS $(ESI)^+$ *m/z* 554 $(MH)^+$.

Synthesis of compound (±)-8 (Scheme 2)



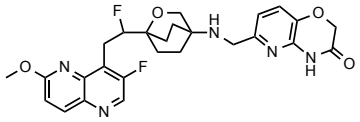
To a cooled (0 ^oC) solution of (±)-**26** (150 mg, 0.34 mmol, 1.0 eq) in dried THF (15 mL) was added NaH (54 mg, 60 % in mineral, 1.36 mmol, 4.0 eq) portion wise, and stirred at the same temperature for 30 min. Then 2-bromo-*tert*-butyl-acetate (65 mg, 0.34 mmol, 1.0 eq) was added and the resulting mixture was stirred at room temperature overnight. Partitioned between water and EtOAc, the organic layers were washed with brine, dried over sodium sulfate, concentrated, and purified by preparative TLC to give compound alkylated ester **31b** (120 mg, 63.8 %). MS $(ESI)^+$ *m/z* 562 $(MH)^+$.

A solution of the ester (120 mg, 0.21 mmol, 1.0 eq) in dichloromethane (5 mL) was added TFA (5 mL), stirred at room temperature for 30 min and concentrated. The residue was treated by saturated aqueous sodium carbonate solution to pH = 8 ~ 9, and then by diluted by aqueous HCl until pH reached 6. The reaction mixture was extracted with EtOAc, the organic layers were washed with brine, dried over sodium sulfate and concentrated to give deprotected free amine (75 mg, 86.2 %), which was used for the next step directly.

A solution of the free amine (75 mg, 0.19mmol, 1.0 eq) and aldehyde **29** (66 mg, 0.37 mmol, 2.0 eq) in DMF: AcOH = 7:1 (5 mL) was stirred at room temperature for 30 min and then $NaBH(OAc)_3$ (118 mg, 0.57 mmol, 3.0 eq) was added. The mixture was stirred at room temperature for 1h, and purified by preparative HPLC to give **(±)-8** (27 mg, 25.7 %). ^{1}H-NMR (CD_3OD, 400 MHz,) δ_H 8.61 (s, 1H), 8.18 ~ 8.20 (d, *J* = 9.39 Hz, 1H), 7.34 ~ 7.36 (d, *J* = 7.83 Hz, 1H), 7.15 ~ 7.17 (d, *J* = 8.61 Hz, 1H), 7.06 ~ 7.08 (d, *J* = 8.61 Hz, 1H), 4.68 (s, 2H), 4.19 (s, 2H), 4.09 (s, 3H), 4.00 ~ 4.06 (m, 2H), 3.84 ~ 3.89 (m, 3H), 3.33 ~

3.44 (m, 2H), 2.01 ~ 2.30 (m, 8H). MS $(ESI)^+$ *m/z* 568 $(MH)^+$.

Synthesis of compound (±)-9 (Scheme 3)

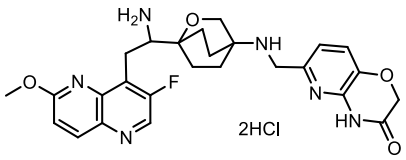


A mixture of (±)-**26** (0.1 g, 0.223 mmol) in anhydrous dichloromethane (6 mL) was added DAST (36 mg, 0.223 mmol) drop wise at -78 ^oC. The reaction was stirred overnight at room temperature and then diluted with 20 mL of dichloromethane, washed with saturated Na_2CO_3 and brine and was concentrated to dryness. The residue was purified by preparative TLC (25 % EtOAc in petroleum ether) to give pure **32** (0.06 g, yield 60 %). MS $(ESI)^+$ *m/z* 450 $(MH)^+$.

To a solution of 3**2** (0.06 g, 0.134mmol) in dichloromethane (2 mL) was added TFA (2 mL) and the mixture was stirred at room temperature for 30 min and concentrated under reduced pressure. After dilution of the residue with water, the mixture was washed with methyl tert-butbyl ether twice. The aqueous layer was adjusted to pH 13 by addition of aqueous Na_2CO_3 solution and extract twice with EtOAc. The combined EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give free amine. MS $(ESI)^+$ *m/z* 350 $(MH)^+$.

A mixture of just prepared free amine (30 mg, 0.086mmol) and the aldehyde **29** (23 mg, 0.129 mmol) in anhydrous DMF (3.5 mL) was added acetic acid (0.5 mL) and stirred at room temperature for 30 min. The resulting solution was added three times of sodium triacetoxyborohydride (36 mg, 0.172 mmol) and stirred at room temperature for overnight. The mixture was concentrated under reduced pressure. After dilution of the residue with dichloromethane, the mixture was washed with saturated sodium carbonate solution, water and brine. The organic extracts were dried over anhydrous Na_2SO_4 then concentrated under reduced pressure. The residue was purified by preparative TLC (dichloromethane/methanol = 10: 1) to give a solid. To a solution of this solid (10 mg, 0.02 mmol) in dichloromethane (2 mL) and ethanol (0.5 mL) was added a solution of hydrogen chloride (5 uL, 0.02 mmol, 4 M in dioxane) under cooling with ice, the mixture was stirred at room temperature for 2 h and concentrated under reduced pressure. Treatment of the residue with ethanol gave **(±)-9**.HCl. ^{1}H-NMR (400 MHz, CD_3OD) δ_H 8.94 (s, 1 H), 8.31 (d, J = 8.4 Hz, 1H), 7.34-7.36 (m, 2H), 7.12 (d, J = 7.2 Hz, 1H), 4.68 (s, 2 H), 4.05-4.36 (m, 8 H), 3.62-3.66 (m, 1 H), 3.44-3.51 (m, 1 H), 2.71-2.77 (m, 1 H), 2.46-2.53 (m, 1 H), 1.97-2.31 (m, 6 H). MS $(ESI)^+$ *m/z* 511$(MH)^+$.

Synthesis of (+)-10 and (-)-10 (Scheme 4)



A mixture of **27** (40.0 mg), ammonium acetate (173.0 mg) and sodium cyanoborohydride (81.75 mg) in methanol (640 mL) and dichloromethane (260 mL) was stirred at room temperature for 6 days and then concentrated in vacuo. After dilution of the residue with dichloromethane, the mixture was washed with saturated sodium hydrogencarbonate solution and brine. The organic extracts were dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Preparative thin layer chromatography (silica, dichloromethane : methanol = 10:1) of the residue gave **33** (26.0 mg, 65%). ^{1}H NMR (DMSO-d_6): δ_H 1.36 (s, 9H), 1.74–2.00 (m, 8H), 2.83–2.96 (m, 2H), 3.30 (s, 3H), 3.78 (s, 2H), 4.02 (s, 3H), 6.59 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 8.25 (d, J = 9.2 Hz, 1H), 8.73 (s, 1H), MS (ESI$^+$) *m/z* 447 (MH$^+$), HRMS (ESI$^+$) for $C_{23}H_{32}FN_4O_4$ (MH$^+$): calcd, 447.24076; found, 447.24086.

To a suspension of **33** (350 mg) in ethyl acetate (12 mL) and sodium hydrogencarbonate solution (316 mg in 3.7 mL of water) was added benzyl chloroformate (134 mL) under cooling with ice, the mixture was stirred at the same temperature for 10 minutes. After dilution of the mixture with water, the mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Treatment of the residue with hexane/ethyl acetate (2:1) gave **34** (398 mg). ^{1}H NMR ($CDCl_3$): δ_H 1.44 (s, 9H), 1.62–1.71 (m, 1H), 1.73–1.94 (m, 3H), 1.98–2.33 (m, 4H), 3.32 (t, J = 12.2 Hz, 1H), 3.40–3.53 (m, 1H), 3.90–4.03, (m, 3H), 4.07 (s, 3H), 4.23–4.39 (m, 1H), 4.70 (d, J = 12.2 Hz, 1H), 4.76 (d, J = 12.8 Hz, 1H), 4.89 (d, J = 10.4 Hz, 0.2H), 5.24 (d, J = 10.4 Hz, 0.8H), 6.72 (d, J = 7.3 Hz, 0.3H), 6.95–7.01 (m, 1.7H), 7.03 (d, J = 9.2 Hz, 1H), 7.16–7.30 (m, 3H), 8.09 (d, J = 9.2 Hz, 0.1H), 8.14 (d, J = 8.6 Hz, 0.9H), 8.53 (s, 1H). MS (ESI$^+$) *m/z* 581 (MH$^+$). HRMS (ESI$^+$) for $C_{29}H_{32}FN_4O_4$ (MH$^+$): calcd, 581.27754; found, 581.27665. Optical resolution (CHIRALPAK IA, hexane: IPA:MTBE = 85:10:5) of the racemate (380 mg) gave (+)-**34** (183 mg, $[a]^{24}_D$ +102.2 (*c* 0.3, MeOH)) and (-)-**34** (186 mg, $[a]^{27}_D$ -107.7 (*c* 0.3, MeOH)

The title compound (+)-**35** (131 mg) was prepared from (+)-**34** (170 mg) in the same manner as described for the synthesis of **28**. (+)-**35** ^{1}H NMR (DMSO-d_6): δ_H 0.94–1.08 (brs, 2H), 1.46–1.89 (m, 6H), 2.04–2.14 (m, 1H), 2.21–2.31 (m, 1H), 3.26–3.36 (m, 1H), 3.46–3.54 (m, 1H), 3.61–3.71 (m, 2H), 3.97–4.06 (m, 1H), 4.08 (s, 3H), 4.70 (d, J = 12.9 Hz, 1H), 4.76 (d, J = 12.2 Hz, 1H), 5.25 (d, J = 9.8 Hz, 1H), 6.71 (d, J = 6.7 Hz, 0.2H), 6.94–7.02 (m, 1.8H), 7.03 (d, J = 9.2 Hz, 1H), 7.16–7.33 (m, 3H), 8.09 (d, J = 9.2 Hz, 0.2H), 8.14 (d, J = 9.2 Hz, 0.8H), 8.53 (s, 1H), MS (ESI$^+$) *m/z* 481 (MH$^+$), HRMS (ESI$^+$) for $C_{26}H_{30}FN_4O_4$ (MH$^+$): calcd, 481.22511; found, 481.22500.

The title compound (-)-**35** (132 mg) was prepared in the same manner from (-)-**34** (170 mg). (-)-**35** ^{1}H NMR (DMSO-d_6): δ_H 0.93–1.13 (brs, 2H), 1.46–1.88 (m, 6H), 2.05–2.14 (m, 1H), 2.20–2.32 (m, 1H), 3.26–3.36 (m, 1H), 3.46–3.54 (m, 1H), 3.61–3.71 (m, 2H), 3.97–4.14 (m, 1H), 4.08 (s, 3H), 4.70 (d, J =

12.2 Hz, 1H), 4.76 (d, *J* = 12.2 Hz, 1H), 5.25 (d, *J* = 9.8 Hz, 1H), 6.71 (d, *J* = 6.7 Hz, 0.3H), 6.94–7.01 (m, 1.7H), 7.03 (d, *J* = 8.6 Hz, 1H), 7.16–7.33 (m, 3H), 8.09 (d, *J* = 9.2 Hz, 0.2H), 8.14 (d, *J* = 9.2 Hz, 0.8H), 8.53 (s, 1H), MS (ESI^+) *m/z* 481 (MH^+), HRMS (ESI^+) for $C_{26}H_{30}FN_4O_4$ (MH^+): calcd, 481.22511; found, 481.22522.

Compound (+)-**36** (121 mg) was prepared from (+)-**35** (100 mg) and **29** (36.9 mg) in the same manner as described for the synthesis of **5**. (+)-**36** ^1H NMR ($CDCl_3$): δ_H 1.58–1.91 (m, 6H), 2.12–2.34 (m, 2H), 3.27–3.37 (m, 1H), 3.44–3.55 (m, 1H), 3.73–3.81 (m, 4H), 3.98–4.06 (m, 1H), 4.07 (s, 3H), 4.64 (s, 2H), 4.73 (q, *J* = 12.6 Hz, 2H), 5.27 (d, *J* = 9.8 Hz, 1H), 6.71 (d, *J* = 7.3 Hz, 0.3H), 6.93–7.29 (m, 9H), 8.08–8.16 (m, 1.7H), 8.54 (s, 1H), MS (ESI^+) *m/z* 643 (MH^+), HRMS (ESI^+) for $C_{34}H_{36}FN_6O_6$ (MH^+): calcd, 643.26803; found, 643.26717.

The enantiomeric compound (-)-**36** (117 mg) was prepared in the same manner from (-)-**35** (100 mg) and **29** (36.9 mg). (-)-**36** ^1H NMR ($CDCl_3$): δ_H 1.63–1.90 (m, 6H), 2.07–2.35 (m, 2H), 3.26–3.37 (m, 1H), 3.46–3.55 (m, 1H), 3.72–3.82 (m, 4H), 3.98–4.06 (m, 1H), 4.08 (s, 3H), 4.64 (s, 2H), 4.73 (q, *J* = 12.9 Hz, 2H), 5.26 (d, *J* = 10.3 Hz, 1H), 6.71 (d, *J* = 6.1 Hz, 0.3H), 6.93–7.30 (m, 9H), 7.94–8.16 (m, 1.7H), 8.54 (s, 1H), MS (ESI^+) *m/z*: 643 (MH^+), HRMS (ESI^+) for $C_{34}H_{36}FN_6O_6$ (MH^+): calcd, 643.26803; found, 643.26728.

A suspension of (+)-**36** (100 mg) and 10% Pd–C (36.0 mg) in acetic acid (3.1 mL) was stirred at room temperature for 3 h under H_2 atmosphere (1 kg/cm^2). After the insoluble materials were filtered off, the filtrate was concentrated in vacuo to give (+)-**10** (70.0 mg). ^1H NMR (DMSO-d_6): δ_H 1.14 (brs, 2H), 1.57–1.99 (m, 9H), 2.85–2.96 (m, 2H), 3.22–3.41 (m, 1H), 3.58 (s, 2H), 3.63 (s, 2H), 4.02 (s, 3H), 4.59 (s, 2H), 7.01 (d, *J* = 8.6 Hz, 1H), 7.21 (d, *J* = 9.2 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 8.25 (d, *J* = 8.6 Hz, 1H), 8.73 (s, 1H), 11.15 (s, 1H), MS (ESI^+) *m/z* 509 (MH^+), HRMS (ESI^+) for $C_{26}H_{30}FN_6O_4$ (MH^+): calcd, 509.23126; found, 509.23213.

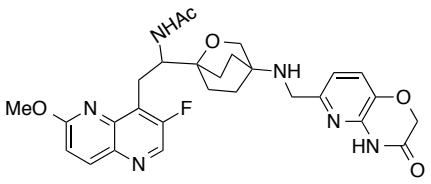
To a solution of the free base (60.0 mg) in dichloromethane (0.30 mL) and ethanol (0.59 mL) was added a solution of hydrochloric acid (0.236 mL, 1 M), the mixture was stirred at room temperature for 4 h and then concentrated in vacuo to give (+)-**10**.HCl (63.0 mg). mp 234-235 ^oC, ^1H NMR (DMSO-d_6): d 1.92–2.14 (m, 8H), 3.12–3.21 (m, 1H), 3.42–3.54 (m, 1H), 3.63–3.72 (m, 1H), 3.95–4.03 (m, 2H), 4.06 (s, 3H), 4.03–4.14 (m, 2H), 4.69 (s, 2H), 7.28 (d, *J* = 8.6 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 8.00 (brs, 3H), 8.33 (d, *J* = 9.2 Hz, 1H), 8.83 (s, 1H), 9.68 (brs, 2H), 11.32 (s, 1H). MS (ESI^+) *m/z* 509 (MH^+) (as free base). HRMS (ESI^+) for $C_{26}H_{30}FN_6O_4$ (MH^+) (as free base): calcd, 509.23126; found, 509.23204. Anal. calcd for $C_{26}H_{29}FN_6O_4 \cdot 3HCl \cdot 0.5H_2O$, C 49.81, H 5.31, N 13.40%. Found: C 50.18, H 5.41, N 13.31%.

The free base of (-)-**10** (71.5 mg) was prepared from (-)-**36** (100 mg) in the same manner as described above. ^1H NMR (DMSO-d_6): δ_H 1.56–1.99 (m, 9H), 2.85–2.98 (m, 2H), 3.27–3.36 (m, 1H), 3.59 (s, 2H), 3.63 (s, 2H), 4.02 (s, 3H), 4.59 (s, 2H), 7.01 (d, *J* = 8.6 Hz, 1H), 7.21 (d, *J* = 9.2 Hz, 1H), 7.28 (d, *J* = 7.9

Hz, 1H), 8.26 (d, J = 8.6 Hz, 1H), 8.74 (s, 1H), 11.16 (s, 1H), MS (ESI^+) *m/z*: 509 (MH^+), HRMS (ESI^+) for $C_{26}H_{30}FN_6O_4$ (MH^+): calcd, 509.23126; found, 509.23207. Anal. calcd for $C_{26}H_{29}FN_6O_4 \cdot 3HCl \cdot 1.5H_2O$, C 48.42, H 5.47, N 13.03%. Found: C 48.36, H 5.41, N 12.88%.

The hydrochloride salt (-)-**10**.HCl (57.8 mg) was prepared in the same manner from the free base (60.0 mg). ^1H NMR (DMSO-d_6): δ_H 1.93–2.25 (m, 8H), 3.12–3.21 (m, 1H), 3.48–3.56 (m, 1H), 3.63–3.71 (m, 1H), 3.96–4.04 (m, 2H), 4.06 (s, 3H), 4.05–4.14 (m, 2H), 4.69 (s, 2H), 7.28 (d, J = 9.2 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.99 (brs, 3H), 8.33 (d, J = 9.2 Hz, 1H), 8.83 (s, 1H), 9.67 (brs, 2H), 11.31 (s, 1H), MS (ESI^+) *m/z*: 509 (MH^+) (as free base), HRMS (ESI^+) for $C_{26}H_{30}FN_6O_4$ (MH^+) (as free base): calcd, 509.23126; found, 509.23115.

Synthesis of compound (±)-11 (Scheme 5)

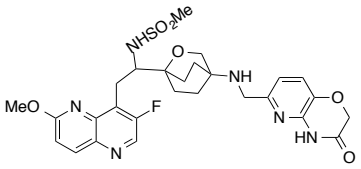


To a solution of (**±**)-**33** (105 mg crude, 0.24 mmol, 1.0 eq) in dichloromethane (10 mL) was added Et_3N (71 mg, 0.71 mmol, 3.0 eq) and DMAP (10 mg, cat.) and then Ac_2O (29 mg, 0.28 mmol, 1.2 eq), and the resulting mixture was stirred at room temperature for 2h. Partitioned between water and dichloromethane, the organic layers were washed by brine, dried over sodium sulfate and concentrated, purified by prep-TLC to give N-acetyl-**33** (48 mg, 41.7 %). ^1H-NMR ($CDCl_3$, 400 MHz): δ_H 8.58 (s, 1H), 8.18 ~ 8.20 (d, J = 9.39 Hz, 1H), 7.04 ~ 7.06 (d, J = 8.61 Hz, 1H), 5.82 ~ 5.84 (d, J = 10.17 Hz, 1H), 3.94 ~ 4.28 (m, 7H), 3.24 ~ 3.54 (m, 4H), 1.77 ~ 2.33 (m, 8H), 1.61 (s, 3H), 1.42 (s, 9H).

A solution of N-acetyl-**33** (48 mg, 0.10 mmol) in dichloromethane (5 mL) was added TFA (5 mL) was stirred at room temperature for 1h and then concentrated. The residue was basified by sodium carbonate solution until pH = 8 ~ 9, and extracted by EtOAc. The organic layers were washed with brine, dried over sodium sulfate, concentrated to give free amine (35 mg, 89.7 %). MS $(ESI)^+$ *m/z* 389 $(MH)^+$.

A solution of aforementioned free amine (35 mg, 0.09mmol, 1.0 eq) and aldehyde **29** (32 mg, 0.18 mmol, 2.0 eq) in DMF:AcOH = 7:1 (5 mL) was stirred at room temperature for 30 min and then $NaBH(OAc)_3$ (57 mg, 0.27 mmol, 3.0 eq) was added and the reaction mixture was stirred at room temperature for 1h. The mixture was purified by prep-HPLC to give **(±)-11** (19 mg, 38.0 %). ^1H-NMR (400 MHz, CD_3OD) δ_H 8.59 (s, 1H), 8.14 ~ 8.16 (d, J = 8.61 Hz, 1H), 7.34 ~ 7.36 (d, J = 7.83 Hz, 1H), 7.14 ~ 7.16 (d, J = 8.61 Hz, 1H), 7.08 ~ 7.10 (d, J = 7.83 Hz, 1H), 4.68 (s, 2H), 4.43 ~ 4.46 (m, 1H), 4.21 (s, 2H), 4.11 (s, 3H), 4.06 (s, 2H), 3.60 ~ 3.68 (m, 1H), 3.14 ~ 3.20 (m, 1H), 1.85 ~ 2.30 (m, 9H), 1.69 (s, 3H). MS $(ESI)^+$ *m/z* 550 $(MH)^+$.

Synthesis of compound (±)-12 (Scheme 5)

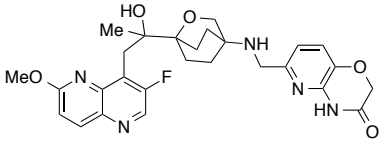


To a solution of (±)-**33** (110 mg crude, 0.25 mmol, 1.0 eq) in dichloromethane (10 mL) was added Et_3N (75 mg, 0.75 mmol, 3.0 eq) and then MsCl (35 mg, 0.30 mmol, 1.2 eq), and the resulting mixture was stirred at room temperature for 2h. Water was added and partitioned between water and dichloromethane, the organic layers were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by prep-TLC to give **33**-methane sulfonamide (72 mg, 55.8 %). MS $(ESI)^+$ *m/z* 525 $(MH)^+$.

A solution of methane sulfonamide (72 mg, 0.14 mmol) in dichloromethane (5 mL) was added TFA (5 mL) and stirred at room temperature for 1h and then concentrated. The residue was basified by sodium carbonate solution until pH = 8 ~ 9, and extracted by EtOAc. The organic layers were washed with brine, dried over sodium sulfate, and concentrated to give methane sulfonamide free amine (43 mg, 74.1 %). MS $(ESI)^+$ *m/z* 425 $(MH)^+$.

A solution of the free amine (43 mg, 0.10 mmol, 1.0 eq) and the aldehyde **29** (35 mg, 0.20 mmol, 2.0 eq) in DMF: AcOH = 7:1 (5 mL) was stirred at room temperature for 30 min then $NaBH(OAc)_3$ (64 mg, 0.30 mmol, 3.0 eq) was added. The mixture was stirred at room temperature for 1h and purified by prep-HPLC to give **(±)-12** (23 mg, 39.9 %). ^{1}H-NMR 400 MHz, CD_3OD): δ_H 8.64 (s, 1H), 8.18 ~ 8.20 (d, *J* = 8.61 Hz, 1H), 7.35 ~ 7.37 (d, *J* = 7.83 Hz, 1H), 7.16 ~ 7.18 (d, *J* = 8.61 Hz, 1H), 7.07 ~ 7.09 (d, *J* = 7.83 Hz, 1H), 4.68 (s, 2H), 4.21 (s, 2H), 4.11 (s, 3H), 4.05 ~ 4.08 (m, 1H), 3.98 (s, 2H), 3.50 ~ 3.58 (m, 1H), 3.21 ~ 3.28 (m, 2H), 2.30 (s, 3H), 2.00 ~ 2.26 (m, 8H), MS $(ESI)^+$ *m/z* 587 $(MH)^+$.

Synthesis of compound (±)-16 (Scheme 6)



A solution of **37** (383 mg, 1.5 mmol) in 5 mL of THF was added CH_3MgBr (1 mL, 3.0 M in ether, 3 mmol) at -70 ^oC. The mixture was stirred at -70 ^oC for 30 minutes then warmed to room temperature. To the reaction mixture was added saturated NH_4Cl and extracted with EtOAc twice. The organic layer was concentrated and the residue was purified by prep-TLC (PE: EtOAc= 5:1) to afford a white solid **38** (R=Me) (120 mg, yield 30 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 4.23 (s, 1H), 3.93 (s, 2 H), 3.57 (d, J = 6.4 Hz, 1 H), 1.92-2.07 (m, 4 H), 1.69-1.78 (m, 4 H), 1.36 (s, 9 H), 0.98 (d, J = 6.4 Hz, 3 H).

A suspension of **38** (R = Me) (120 mg, 0.44 mmol) and Dess-Martin periodinane (940 mg, 2.2 mmol) in 10 mL dichloromethane was stirred overnight at room temperature. Reaction was filtered and the solid

was washed with dichloromethane. The filtrate was concentrated and the residue was purified by prep-TLC (PE: EtOAc= 3:1) to afford a white solid **39** (R = Me) (54 mg, yield 45 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 4.00 (s, 2 H), 2.17 (s, 3 H), 2.04-2.11 (m, 2 H), 1.90-1.98 (m, 2 H), 1.79-1.86 (m, 2 H), 1.40 (s, 9 H).

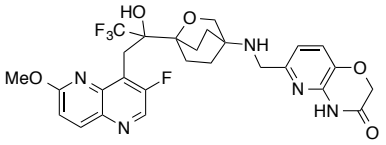
A solution of **40** (77 mg, 0.4 mmol) in 3 mL of THF was added LDA (0.2 mL, 2.0 M in THF, 0.4 mmol) drop wise to at -78 ^{o}C and stirred for 15 min. To this mixture was added drop wise a solution of **39** (R = Me) (54 mg, 0.2 mmol, in 1 mL of THF). The resulting mixture was stirred at -78 ^{o}C for 30 min then warmed to room temperature. The reaction was quenched by addition of saturated NH_4Cl and extracted with EtOAc twice. The organic layer was concentrated and the residue was purified by prep-TLC (PE: EtOAc= 3:1) to afford a white solid **41** (R = Me) (37 mg, yield 40 %). MS $(ESI)^+$ *m/z* 462 $(MH)^+$.

To a solution of **41** (R = Me) (37 mg, 0.08 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 30 min and concentrated under reduced pressure. After dilution of the residue with water, the mixture was washed with methyl *t*-butyl ether twice. The aqueous layer was adjusted to pH= 13 by addition of aqueous Na_2CO_3 solution and extracted twice with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give pure **42** (R = Me) (25 mg, yield 86 %). MS $(ESI)^+$ *m/z* 362 $(MH)^+$.

A mixture of **42** (R = Me) (25 mg, 0.07 mmol) and pyridoxazinecarbaldehyde **29** (20 mg, 0.11 mmol) in anhydrous DMF (3.5 mL) was added acetic acid (0.5 mL) was stirred at room temperature for 30 min. The resulting solution was added three times of sodium triacetoxyborohydride (42 mg, 0.2 mmol) and stirred at room temperature overnight. The mixture was concentrated under reduced pressure. After dilution of the residue with dichloromethane, the mixture was washed with saturated sodium carbonate solution, water and brine. The organic extracts were dried over anhydrous Na_2SO_4 then concentrated under reduced pressure. The residue was purified by prep-TLC (dichloromethane/methanol = 10: 1) to give **(±)-16** (R = Me) (21 mg, yield 55 %). MS $(ESI)^+$ *m/z* 524 $(MH)^+$.

To a solution of **(±)-16** (R = Me) (21 mg, 0.04 mmol) in dichloromethane (2 mL) and ethanol (0.5 mL) was added a solution of hydrogen chloride (10 uL, 0.1 mmol, 4 M in dioxane) under cooling with ice, the mixture was stirred at room temperature for 2 h and concentrated under reduced pressure. Treatment of the residue with ethanol gave **(±)-16**.HCl (R = Me). ^{1}H-NMR (400 MHz, CD_3OD) δ_H 9.05 (s, 1H), 8.37 (d, J = 7.2 Hz, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 4.68 (s, 2 H), 4.24 (s, 2 H), 4.16 (s, 3 H), 4.08 (s, 2 H), 3.80 (d, J = 12.8 Hz, 1H), 3.60 (d, J = 12.8 Hz, 1H), 2.37-2.42 (m, 2 H), 2.01-2.29 (m, 6 H), 1.02 (s, 3 H). MS $(ESI)_+$ *m/z* 524 $(MH)^+$.

Synthesis of compound (±)-17 (Scheme 6)



A solution of **37** (762 mg, 3 mol) and CF_3TMS (1.14 g, 8 mmol) in 20 mL of DMF was cooled to 0 ^oC with ice-water. To this solution was added powdered CsF (1.3 g, 8 mmol) in small batches. The mixture was stirred overnight at room temperature, diluted with 50 mL of EtOAc, washed with water and brine, condensed. The residue was purified by column chromatography (25 % EtOAc in PE) to give pure **38** (R = CF_3) (230 mg, yield 24 %). MS $(ESI)^+$ *m/z* 326 $(MH)^+$.

A suspension of **38** (R = CF_3) (230 mg, 0.71 mmol) and Dess-Martin periodinane (452 mg, 1.06 mmol) in dichloromethane was stirred overnight at room temperature. The reaction was filtered and the solid was washed with dichloromethane. The filtrate was concentrated and the residue was purified by prep-TLC (PE: EtOAc= 3:1) to afford a white solid **39** (R = CF_3) (160 mg, yield 69 %). ^1H-NMR (400 MHz, $CDCl_3$) δ_H 4.00 (s, 2 H), 1.95-2.21 (m, 6 H), 1.84-1.92 (m, 2 H), 1.76-1.83 (m, 2 H), 1.39 (s, 9 H).

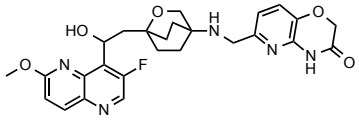
A solution of **40** (192 mg, 1.0 mmol, in 4 mL of THF) was added LDA (0.5 mL, 2.0 M in THF, 1.0 mmol) drop wise at -78 ^oC and stirred for 15 minutes. To this mixture was added drop wise a solution of **39** (R = CF_3) (160 mg, 0.49 mmol, in 1 mL of THF). The resulting mixture was stirred at -78 ^oC for 30 min then warmed to room temperature and stirred overnight. Saturated NH_4Cl was added to quench the reaction followed by extraction with EtOAc twice. The organic layer was concentrated and the residue was purified by prep-TLC (PE: EtOAc= 3:1) to afford a white solid **41** (R = CF_3) (37 mg, yield 18 %). MS $(ESI)^+$ *m/z* 516 $(MH)^+$.

To a solution of **41** (R = CF_3) (37 mg, 0.072 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 30 minutes and concentrated under reduced pressure. After dilution of the residue with water, the mixture was washed with methyl *tert*-butyl ether twice. The aqueous layer was adjusted to pH= 13 by addition of aqueous Na_2CO_3 solution and extracted twice with EtOAc. The combined EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give pure **42** (R = CF_3) (20 mg, yield 67 %). MS $(ESI)^+$ *m/z* 416 $(MH)^+$.

A mixture of **42** (R = CF_3) (20 mg, 0.048 mmol) and pyridoxazinecarbaldehyde **29** (13 mg, 0.072 mmol) in anhydrous DMF (3.5 mL) was added acetic acid (0.5 mL) was stirred at room temperature for 30 min. The resulting solution was added three times of sodium triacetoxyborohydride (21 mg, 0.1 mmol) and stirred at room temperature for overnight. The mixture was concentrated under reduced pressure. After dilution of the residue with dichloromethane, the mixture was washed with saturated sodium carbonate solution, water and brine. The organic extracts were dried over anhydrous Na_2SO_4 then concentrated under reduced pressure. The residue was purified by prep-TLC (dichloromethane/methanol = 10: 1) to give a solid. To a solution of this solid (17 mg, 0.029 mmol) in dichloromethane (2 mL) and

ethanol (0.5 mL) was added a solution of hydrogen chloride (7.3 uL, 0.029 mmol, 4 M in dioxane) under cooling with ice, the mixture was stirred at room temperature for 2 hours and concentrated in vacumm. Treatment of the residue with ethanol gave **(±)-17**.HCl (R = CF_3). ^{1}H-NMR (400 MHz, CD_3OD) δ_H ppm 8.77 (s, 1 H), 8.30 (d, J = 9.2 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 9.2 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 4.68 (s, 2 H), 4.21 (s, 2 H), 4.12 (s, 3 H), 3.95-4.01 (m, 2 H), 3.85 (d, J= 14.8 Hz, 1 H), 3.74 (d, J= 14.4 Hz, 1 H), 2.42-2.54 (m, 2 H), 2.05-2.16 (m, 6 H), MS (ESI)$^+$ *m/z* 578 $(MH)^+$.

Synthesis of compounds (+)-19 and (-)-19 (Scheme 7)



To a solution of **43** (5.78 g) in tetrahydrofuran (225 mL) was added n-butyl lithium (7.21 mL, 2.6 M in hexane) at -78 ^{o}C, the mixture was stirred at the same temperature for 30 minutes. A solution of **44** (2.02 g) was added to the mixture at -78 ^{o}C, the mixture was stirred at the same temperature for 2 h. After quenching the reaction by adding of a citric acid solution (36.0 mL, 0.5 M in water), the aqueous solution was extracted with dichloromethane followed by diluting with water. The organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography (hexane/ethyl acetate = 3:1) of the residue gave the racemate **45** (2.64 g). Optical resolution of the racemate **45** (CHIRALPAK IC, TBME : hexane : ethanol = 5 : 3 : 2) gave (+)-**45** and (-)-**45**. (+)-**45** $[\alpha]_D^{27}$ +13.7 (*c* 0.2, MeOH), IR (ATR) 3333, 1710, 1614, 1161 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.43 (s, 9H), 1.79–1.95 (m, 5H), 2.04–2.21 (m, 4H), 2.34 (dd, *J* = 14.7, 9.2 Hz, 1H), 3.91–3.99 (m, 2H), 4.06 (s, 3H), 4.28 (s, 1H), 5.51 (d, *J* = 8.6 Hz, 1H), 5.77 (ddd, *J* = 9.2, 8.6, 3.0 Hz, 1H), 7.09 (d, *J* = 9.2 Hz, 1H), 8.21 (d, *J* = 9.2 Hz, 1H), 8.62 (d, *J* = 1.2 Hz, 1H), MS (ESI$^+$) *m/z* 448 (MH^+), HRMS (ESI$^+$) for $C_{23}H_{31}FN_3O_5$(MH^+): calcd, 448.22477; found, 448.22560. (-)-**45** $[\alpha]_D^{27}$ -10.4 (*c* 0.2, MeOH), IR (ATR) 3324, 1710, 1614, 1161 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) d 1.43 (s, 9H), 1.80–1.95 (m, 5H), 2.03–2.21 (m, 4H), 2.34 (dd, *J* = 14.7, 9.2 Hz, 1H), 3.91–3.99 (m, 2H), 4.06 (s, 3H), 4.28 (s, 1H), 5.51 (d, *J* = 8.6 Hz, 1H), 5.77 (ddd, *J* = 9.2, 8.6, 3.0 Hz, 1H), 7.09 (d, *J* = 9.2 Hz, 1H), 8.21 (d, *J* = 9.2 Hz, 1H), 8.62 (d, *J* = 1.2 Hz, 1H), MS (ESI$^+$) *m/z* 448 (MH^+), HRMS (ESI$^+$) for $C_{23}H_{31}FN_3O_5$(MH^+): calcd, 448.22477; found, 448.22543.

Deprotection of (+)-**45** (125 mg) by treatment with TFA in a manner similar to the synthesis of (-)-**6** gave free amine (91.4 mg). $[\alpha]_D^{25}$ +25.2 (*c* 0.1, $CHCl_3$), IR (ATR) 3415, 1613, 1202 cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 1.38 (s, 2H), 1.62–1.95 (m, 7H), 2.04–2.19 (m, 2H), 2.35 (dd, *J* = 14.7, 9.8 Hz, 1H), 3.60–3.67 (m, 2H), 4.06 (s, 3H), 5.47–5.58 (m, 1H), 5.77–5.85 (m, 1H), 7.09 (d, *J* = 9.2 Hz, 1H), 8.21 (d, *J* = 9.2 Hz, 1H), 8.63 (d, *J* = 1.2 Hz, 1H). MS (ESI$^+$) *m/z*: 348 (MH^+). HRMS (ESI$^+$) for $C_{18}H_{23}FN_3O_3$(MH^+): calcd, 348.17234; found, 348.17286.

Reductive amination of the aldehyde **29** (41.2 mg) with the amine (76.4 mg) just prepared from (+)-45 in the same manner as described for the synthesis of (-)-**6** gave (+)-**19** (95.9 mg) as a power from ethanol. mp 125 ^{o}C, $[\alpha]_D^{27}$ +26.3 (*c* 0.1, DMF), IR (ATR) 1696, 1614, 1185 cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 1.49–1.84 (m, 8H), 1.90 (dd, *J* = 14.0, 5.5 Hz, 1H), 1.96–2.02 (m, 1H), 2.13 (dd, *J* = 14.0, 7.3 Hz, 1H), 3.36–3.48 (m, 2H), 3.57 (d, *J* = 5.5 Hz, 2H), 4.04 (s, 1H),

4.58 (s, 2H), 5.23 (d, J = 5.5 Hz, 1H), 5.90–5.99 (m, 1H), 6.97 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 9.2 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 8.27 (d, J = 9.2 Hz, 1H), 8.74 (d, J = 1.8 Hz, 1H), MS (ESI^+) *m/z* 510 (MH^+), HRMS (ESI^+) for $C_{26}H_{29}FN_5O_5$ (MH^+): calcd, 510.21527; found, 510.21575.

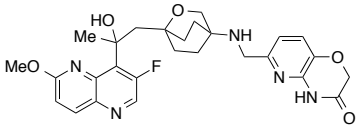
Anal. Calcd for $C_{26}H_{28}FN_5O_5 \cdot 0.8\ H_2O$, C 59.60, H 5.69, N 13.37%. Found C 59.56, H 5.50, N 13.20%.

Deprotection of (-)-**45** (125 mg) with TFA gave enantiomeric free amine (85.5 mg). $[\alpha]_D^{25}$ -25.3 (*c* 0.1, $CHCl_3$), IR (ATR) 3414, 1613, 1202 cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6) δ_H 1.61–1.95 (m, 7H), 2.04–2.19 (m, 2H), 2.35 (dd, J = 14.7, 9.2 Hz, 1H), 3.60–3.67 (m, 2H), 4.06 (s, 3H), 5.48–5.56 (m, 1H), 5.78–5.84 (m, 1H), 7.09 (d, J = 9.2 Hz, 1H), 8.21 (d, J = 9.2 Hz, 1H), 8.63 (d, J = 1.2 Hz, 1H), MS (ESI^+) *m/z*: 348 (MH^+), HRMS (ESI^+) for $C_{18}H_{23}FN_3O_3$ (MH^+): calcd, 348.17234; found, 348.17189.

A similar reductive amination of **29** (41.2 mg) with the free amine (76.4 mg) from (-)-**45** as described earlier produced enantiomer (-)-**19** (97.3 mg) as powder from ethanol. mp 125 °C, $[\alpha]_D^{24}$ -27.0 (*c* 0.1, DMF), IR (ATR) 1695, 1614, 1185 cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6) δ_H 1.49–1.84 (m, 8H), 1.90 (dd, J = 14.0, 5.5 Hz, 1H), 1.96–2.02 (m, 1H), 2.13 (dd, J = 14.0, 7.3 Hz, 1H), 3.36–3.48 (m, 2H), 3.57 (d, J = 5.5 Hz, 2H), 4.04 (s, 1H), 4.58 (s, 2H), 5.23 (d, J = 5.5 Hz, 1H), 5.90–5.99 (m, 1H), 6.97 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 9.2 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 8.27 (d, J = 9.2 Hz, 1H), 8.74 (d, J = 1.8 Hz, 1H), MS (ESI^+) *m/z* 510 (MH^+), HRMS (ESI^+) for $C_{26}H_{29}FN_5O_5$ (MH^+): calcd, 510.21527; found, 510.21576.

Anal. calcd for $C_{26}H_{28}FN_5O_5 \cdot H_2O$, C 59.19, H 5.73, N 13.28%. Found C 59.37, H 5.50, N 13.14%.

Synthesis of compound (±)-20 (Scheme 8)



A solution of **44** (810 mg, 3 mmol) in THF (10 mL) was added MeMgCl (2.1 mL, 6.3 mmol) at -78 °C under N_2 and then stirred at -78 °C for 1.5 hours. After quenching with saturated ammonium chloride solution, the mixture was extracted with EtOAc twice. The organic layers were dried and concentrated. The residue was purified by column chromatography (PE:EtOAc=4:1) to give **46** (800 mg, 93.7 %).

To a solution of **46** (800 mg, 2.8 mmol) in dichloromethane (70 mL) was added Dess-Martin (2.0 g, 4.7 mmol). The mixture was stirred at room temperature for 1.5 hours. The reaction was filered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (PE:EtOAc=4:1) to give **47** (450 mg, 56.7%).

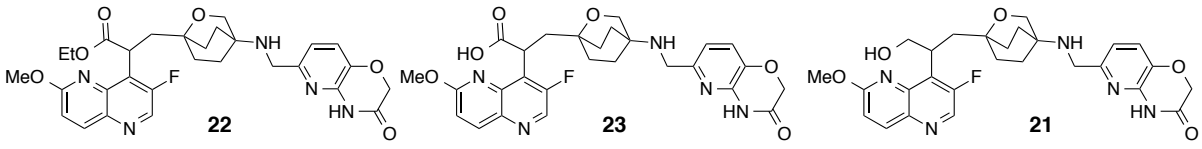
A solution of **48** (570 mg, 3.2 mmol) in THF at -78 °C was added LDA (1.75 mL, 3.5 mmol) drop wise and stirred for 20 minutes. A solution of **47** (450 mg, 1.6 mmol) in THF was added drop wise to the mixture for 15 minute at -78 °C. The mixture was stirred at 0 °C for 30 min. After quenching the reaction by addition of saturated NH_4Cl it was extracted with EtOAc twice. The organic layer was

concentrated and the residue was purified by column chromatography (PE:EtOAc=4:1) to give **49** (370 mg, 25 %). MS $(ESI)^+$ *m/z* 462 $(MH)^+$.

To a solution of **49** (370 mg, 0.8mmol) in dichloromethane (5 mL) was added TFA (15 mL). The mixture was stirred at room temperature overnight. The reaction mixture was concentrated and then the $NaHCO_3$ solution was added. The mixture was extracted with dichloromethane/MeOH (10:1). The organic extracts were dried over anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure to give the crude free amine (220 mg**,** 76.5%). MS $(ESI)^+$ *m/z* 362 $(MH)^+$.

A mixture of the free amine (30 mg, 0.08 mmol) and pyridoxazinecarbaldehyde **29** (50 mg, 0.28mmol) in anhydrous DMF (3.5 mL) was added acetic acid (0.5 mL) was stirred at room temperature for 30 min. The resulting solution was added three times of sodium triacetoxyborohydride (50 mg, 0.25 mmol) and stirred at room temperature for overnight. The mixture was concentrated under reduced pressure. After dilution of the residue with dichloromethane, the mixture was washed with saturated sodium carbonate solution, water and brine. The organic extracts were dried over anhydrous Na_2SO_4 then concentrated in vacuo. The residue was purified by prep-TLC (DCM/MeOH = 10: 1) to afford a solid **(±)-20**. ^{1}H-NMR (400 MHz, CD_3OD) δ_H 8.65 (s, 1 H), 8.25 (d, J = 8.8 Hz ,1 H), 7.45 (d, J = 9.6 Hz, 1H), 7.2 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 4.64 (s, 2 H), 4.19 (s, 3 H), 4.05 (m, 2 H), 3.65 (m, 1H), 3.45 (m, 1H), 2.61 (d, J = 8.0 Hz, 1H), 2.25 (m, 1 H), 1.75-2.1 (m, 8 H), 1.65 (s, 3 H), MS $(ESI)^+$ *m/z* 524 $(MH)^+$.

Synthesis of compound (±)-22, (±)-23 and (±)-21 (Scheme 9)



To a solution of **50** (215 mg, 0.43 mmol) in EtOAc (20 mL) was added Pd/C (100 mg, 10 %) and the mixture was stirred at 40 °C for 1.5 h. After filtration, the mixture was concentrated in vacuo to give the crude **51** (210 mg, 96.8%). MS $(ESI)^+$ *m/z* 504.5 $(MH)^+$.

To a solution of **51** (210 mg, 0.432 mmol) in dichloromethane (2 mL) was added TFA (10 mL). The mixture was stirred at room temperature overnight. The reaction solution was concentrated and then the aqueous $NaHCO_3$ solution was added. The mixture was extracted with ethyl acetate. The organic extracts were washed with water, dried over anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure to give the crude free amine (120 mg**,** 69.2%). MS $(ESI)^+$ *m/z* 404.5 $(MH)^+$.

A mixture of the aforementioned free amine (120 mg, 0.3 mmol) and pyridoxazinecarbaldehyde **29** (150 mg, 0.83 mmol) in anhydrous DMF (3.5 mL) was added acetic acid (0.5 mL) and stirred at room temperature for 30 min. The resulting solution was added to three fold excess of sodium

triacetoxyborohydride (210 mg, 1 mmol) and stirred at room temperature overnight. The mixture was concentrated under reduced pressure. After dilution of the residue with dichloromethane, the mixture was washed with saturated sodium carbonate solution, water and brine. The organic extracts were dried over anhydrous Na_2SO_4 then concentrated in vacuo. The residue was purified by prep-TLC (DCM/MeOH = 10: 1) to afford (±)-**22** as a solid. ^{1}H-NMR (400 MHz, CD_3OD) δ_H 8.65 (s, 1 H), 8.25 (d, J = 8.8 Hz, 1 H), 7.45 (d, J = 9.6 Hz, 1H), 7.2 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 5.7 (d, J = 9.6 Hz, 1H), 4.64 (s, 2 H), 4.19 (s, 3 H), 4.00 (s, 2 H), 3.85 (s, 2H), 2.25 (m, 2 H), 1.75-2.1 (m, 8 H), 1.05-1.1 (m, 2 H), MS $(ESI)^+$ *m/z* 566.5 $(MH)^+$.

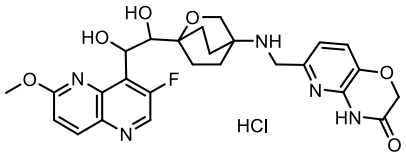
A solution of **22** (100 mg, 0.177 mmol) in 10 mL of THF/MeOH/H_2O (2:2:1) was added $LiOH.H_2O$ (84 mg, 2 mmol) at room temperature. The mixture was stirred overnight, diluted with water and washed with MTBE twice. The water layer was acidified to pH= 5 with hydrochloric acid then extracted with EtOAc twice. The EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4 and condensed. The residue was purified by prep-TLC (DCM/MeOH = 8: 1) to give (±)-**23** as a white solid. ^{1}H-NMR (400 MHz, CD_3OD) δ_H 8.65 (s, 1 H), 8.25 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 9.6 Hz, 1H), 7.2 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 4.78 (d, J = 8.0 Hz, 1H), 4.65 (s, 2H), 4.15 (s, 3 H), 3.8 (s, 2 H), 3.5 (m, 2 H), 2.65 (d, J = 9 Hz,1H), 2.25 (m, 1 H), 1.65-1.9 (m, 8 H), MS $(ESI)^+$ *m/z* 538.5 $(MH)^+$.

To a solution of **51** (150 mg, 0.3 mmol) in THF (10 mL) was added $LiAlH_4$ (20 mg, 0.53 mmol). The mixture was stirred at room temperature for 1.5 h. After quenching the reaction with saturated ammonium chloride solution, the mixture was extracted with EtOAc twice. The organic layers were dried and concentrated to give the crude **52** (50 mg, 36.2%). MS $(ESI)^+$ *m/z* 462 $(MH)^+$.

To a solution of **52** (50 mg, 0.11mmol) in dichloromethane (2 mL) was added TFA (5 mL). The mixture was stirred at room temperature for overnight. The reaction solution was concentrated and then the $NaHCO_3$ solution was added. The mixture was extracted with dichloromethane/MeOH (10:1). The organic extracts were dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo to give the crude free amine (30 mg**,** 76.5%). MS $(ESI)^+$ *m/z* 362 $(MH)^+$.

A mixture of the aforementioned free amine (30 mg, 0.08 mmol) and pyridoxazinecarbaldehyde **29** (50 mg, 0.28mmol) in anhydrous DMF (3.5 mL) was added acetic acid (0.5 mL) was stirred at room temperature for 30 min. The resulting solution was added three times of sodium triacetoxyborohydride (50 mg, 0.25 mmol) and stirred at room temperature for overnight. The mixture was concentrated under reduced pressure. After dilution with dichloromethane, the mixture was washed with saturated sodium carbonate solution, water and brine. The organic extracts were dried over anhydrous Na_2SO_4 then concentrated in vacuo. The residue was purified by prep-TLC (DCM/MeOH = 10: 1) to afford (±)-**21** as a solid. ^{1}H-NMR (400 MHz, CD_3OD) δ_H 8.65 (s, 1 H), 8.25 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 9.6 Hz, 1H), 7.2 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 4.64 (s, 2 H), 4.19 (s, 3 H), 4.00 (m, 1 H), 3.65 (s, 2H), 3.35 (s, 1H), 3.25 (s, 1H), 1.95 (m, 2 H), 1.75-2.1 (m, 8 H), MS $(ESI)^+$ *m/z* 524 $(M+1)^+$.

Synthesis of compounds (+)-24 and (-)-24 (Scheme 10)



A mixture of **53** (800 mg), osmium tetroxide solution (0.95 mL, 2.5 wt% in tert-butanol) and 4-methylmorpholine *N*-oxide solution (146 mL, 50 wt% in water) in *tert*-butanol (13.6 mL) and water (1.36 mL) was stirred at room temperature for 5 h. After dilution of the mixture with water, the mixture was added sodium hydrogen sulfite (1.12 g). The mixture was extracted with ethyl acetate. The organic extracts were dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography of the residue gave the racemate **54** (844.1 mg). ^{1}H NMR ($CDCl_3$): δ_H 1.42 (s, 9H), 1.77–2.30 (m, 8H), 3.68–3.73 (m, 2H), 3.82–3.98 (m, 2H), 4.06 (s, 3H), 4.28 (brs, 1H), 5.68 (dd, J = 8.6, 3.1 Hz, 1H), 5.78 (d, J = 7.9 Hz, 1H), 7.10 (d, J = 8.6 Hz, 1H), 8.23 (d, J = 9.2 Hz, 1H), 8.65 (d, J = 1.2 Hz, 1H), MS (ESI$^+$) *m/z*: 464 (MH^+), HRMS (ESI$^+$) for $C_{23}H_{31}FN_3O_6$ (MH^+): calcd, 464.21969; found, 464.22023.

Optical resolution of the racemate **54** with CHIRALPAK IA (hexane-ethanol = 30:70) gave (+)-**54** (473 mg, $[\alpha]^{27}_D$ +61.7 (*c* 0.3, $CHCl_3$)) and (-)-**54** (461.5 mg, $[\alpha]^{27}_D$ -47.9 (*c* 0.3, $CHCl_3$)).

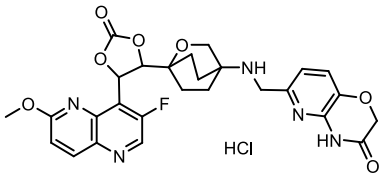
Deprotection of (+)-**54** (195 mg) in the same manner as described earlier gave free amine (140 mg). ^{1}H NMR ($CDCl_3$): δ_H 1.40–2.27 (m, 8H), 3.51–3.63 (m, 2H), 3.65–3.82 (m, 2H), 4.06 (s, 3H), 5.73 (q, J = 3.5 Hz, 1H), 5.79 (d, J = 7.9 Hz, 1H), 7.11 (d, J = 9.2 Hz, 1H), 8.23 (d, J = 9.2 Hz, 1H), 8.65 (d, J = 1.2 Hz, 1H), MS (ESI$^+$) *m/z* 364 (MH^+), HRMS (ESI$^+$) for $C_{18}H_{23}FN_3O_4$ (MH^+): calcd, 364.16726; found, 364.16631.

Usual reductive amination of aldehyde **29** (66.9 mg) with the amine (130 mg) prepared above afforded (+)-**24** as a powder. $[\alpha]_D^{25}$ +16.0 (*c* 0.2, MeOH), ^{1}H NMR (DMSO-d_6): δ_H 1.36–2.00 (m, 8H), 2.14 (brs, 1H), 2.88–3.25 (m, 2H), 3.51 (brs, 2H), 3.64 (t, J = 5.8 Hz, 1H), 4.03 (s, 3H), 4.57 (s, 2H), 5.00 (d, J = 5.5 Hz, 1H), 5.39 (d, J = 6.7 Hz, 1H), 5.78 (d, J = 6.1 Hz, 1H), 6.93 (d, J = 8.6 Hz, 1H), 7.22 (d, J = 9.2 Hz, 1H), 7.23 (d, J = 9.2 Hz, 1H), 8.26 (d, J = 9.2 Hz, 1H), 8.70 (d, J = 1.8 Hz, 1H), 11.11 (s, 1H), MS (ESI+) *m/z*: 526 (MH+), HRMS (ESI+) for $C_{26}H_{29}FN_5O_6$ (MH+): calcd, 526.21019; found, 526.21096. Anal. calcd for $C_{26}H_{28}FN_5O_6 \cdot HCl \cdot 0.7H_2O$, C 54.35, H 5.33, N 12.19%. Found C 54.57, H 5.44, N 11.85%.

Similar TFA deprotection of (-)-**54** (195 mg) gave the enantiomeric free amine (142 mg). ^{1}H NMR ($CDCl_3$): δ_H 1.40–2.27 (m, 8H), 3.51–3.63 (m, 2H), 3.65–3.82 (m, 2H), 4.06 (s, 3H), 5.73 (q, J = 3.5 Hz, 1H), 5.79 (d, J = 7.9 Hz, 1H), 7.11 (d, J = 9.2 Hz, 1H), 8.23 (d, J = 9.2 Hz, 1H), 8.65 (d, J = 1.2 Hz, 1H), MS (ESI$^+$) *m/z*: 364 (MH^+), HRMS (ESI$^+$) for $C_{18}H_{23}FN_3O_4$ (MH^+): calcd, 364.16726; found, 364.16759.

(-)-**24** (138 mg) was prepared in the similar manner from the enatiomeric free amine (130 mg) by reductive amination. $[\alpha]_D^{25}$ -22.3 (*c* 0.2, MeOH), ^{1}H NMR (DMSO-d_6): δ_H 1.36–2.00 (m, 8H), 2.14 (brs, 1H), 2.95–3.26 (m, 2H), 3.51 (s, 2H), 3.64 (t, *J* = 5.5 Hz, 1H), 4.03 (s, 3H), 4.57 (s, 2H), 5.01 (d, *J* = 6.1 Hz, 1H), 5.39 (d, *J* = 6.7 Hz, 1H), 5.78 (t, *J* = 6.1 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 9.2 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 8.26 (d, *J* = 9.2 Hz, 1H), 8.70 (d, *J* = 1.8 Hz, 1H), 11.11 (s, 1H), MS (ESI$^+$) *m/z*: 526 (MH^+), HRMS (ESI$^+$) for $C_{26}H_{29}FN_5O_6$ (MH^+): calcd, 526.21019; found, 526.20961. Anal. calcd for $C_{26}H_{28}FN_5O_6 \cdot HCl \cdot 0.5H_2O$, C 54.69, H 5.30, N 12.27%. Found C 54.80, H 5.33, N 12.11%.

Synthesis of compound (+)-25 and (-)-25 (Scheme 10)



To a solution of (+)-**54** (270 mg) in dichloromethane (3.0 mL) was added triethylamine (146 mL) and triphosgene (176 mg) under cooling with ice, the mixture was stirred at the same temperature for 3 h, and then concentrated in vacuo. Flash chromatography (silica, hexane : ethyl acetate = 1:1) of the residue gave (+)-**55** (222 mg). ^{1}H NMR ($CDCl_3$): δ_H 1.43 (s, 9H), 1.48–2.34 (m, 8H), 3.96–4.08 (m, 2H), 4.10 (s, 3H), 4.32 (brs, 1H), 4.73 (d, *J* = 6.1 Hz, 1H), 6.39 (d, *J* = 5.5 Hz, 1H), 7.13 (d, *J* = 9.2 Hz, 1H), 8.23 (d, *J* = 9.2 Hz, 1H), 8.71 (s, 1H), MS (ESI$^+$) *m/z*: 490 (MH^+), HRMS (ESI$^+$) for $C_{24}H_{29}FN_3O_7$ (MH^+): calcd, 490.19895; found, 490.19921.

Usual Boc deprotection of (+)-**55** (110 mg) with TFA gave the free amine (84.5 mg). ^{1}H NMR ($CDCl_3$): δ_H 1.35–2.33 (m, 8H), 3.64–3.75 (m, 2H), 4.10 (s, 3H), 4.73 (d, *J* = 5.5 Hz, 1H), 6.40 (d, *J* = 5.5 Hz, 1H), 7.13 (d, *J* = 9.2 Hz, 1H), 8.22 (d, *J* = 9.2 Hz, 1H), 8.71 (s, 1H), MS (ESI$^+$) *m/z*: 390 (MH^+), HRMS (ESI$^+$) for $C_{19}H_{21}FN_3O_5$ (MH^+): calcd, 390.14652; found, 390.14627.

The free amine (80 mg) was reductively aminated with aldehyde **29** (38.4 mg) following usual protocol to give **(+)-25** (103 mg) as a powder. $[\alpha]_D^{23}$ +102 (*c* 0.2, MeOH), ^{1}H NMR (DMSO-d_6): δ_H 1.44–1.81 (m, 6H), 1.98–2.10 (m, 2H), 3.62 (brs, 2H), 3.70 (s, 2H), 4.03 (s, 3H), 4.59 (s, 2H), 4.97 (d, *J* = 5.5 Hz, 1H), 6.45 (d, *J* = 5.5 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 9.2 Hz, 1H), 8.37 (d, *J* = 9.2 Hz, 1H), 8.96 (s, 1H), 11.15 (s, 1H), MS (ESI$^+$) *m/z*: 552 (MH^+), HRMS (ESI$^+$) for $C_{27}H_{27}FN_5O_7$ (MH^+): calcd, 552.18945; found, 552.18865. Anal. calcd for $C_{27}H_{26}FN_5O_7 \cdot HCl$, C 55.15, H 4.63, N 11.91%. Found C 55.01, H 4.64, N 11.83%.

The enantiomer (-)-**55** (164 mg) was prepared in the similar manner from (-)-**54** (260 mg). ^{1}H NMR ($CDCl_3$): δ_H 1.43 (s, 9H), 1.58–1.99 (m, 6H), 2.08–2.35 (m, 2H), 3.96–4.10 (m, 2H), 4.10 (s, 3H), 4.32 (brs, 1H), 4.73 (d, *J* = 6.1 Hz, 1H), 6.39 (d, *J* = 5.5 Hz, 1H), 7.13 (d, *J* = 9.2 Hz, 1H), 8.22 (d, *J* = 9.2 Hz,

1H), 8.71 (s, 1H), MS (ESI^+) *m/z* 490 (MH^+), HRMS (ESI^+) for $C_{24}H_{29}FN_3O_7$ (MH^+): calcd, 490.19895; found, 490.19983.

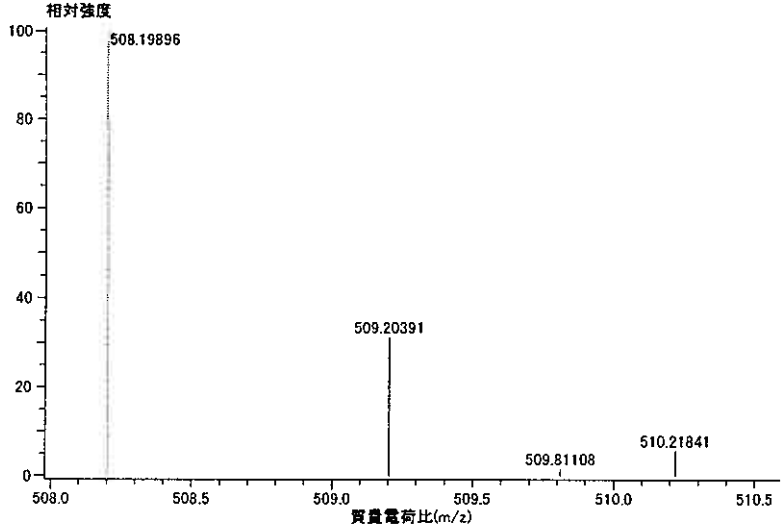
TFA catalyzed deprotection of (-)-**55** (150 mg) produced the free amine (119 mg). ^1H NMR ($CDCl_3$): δ_H 1.38–2.31 (m, 8H), 3.64–3.76 (m, 2H), 4.10 (s, 3H), 4.73 (d, *J* = 6.1 Hz, 1H), 6.40 (d, *J* = 6.1 Hz, 1H), 7.13 (d, *J* = 9.2 Hz, 1H), 8.22 (d, *J* = 9.2 Hz, 1H), 8.71 (s, 1H), MS (ESI^+) *m/z* 390 (MH^+), HRMS (ESI^+) for $C_{19}H_{21}FN_3O_5$ (MH^+): calcd, 390.14652; found, 390.14601.

The aforementioned free amine (110 mg) was reacted with aldehyde **29** (52.8 mg) in a standard manner to yield (-)-**25** (159 mg) as a powder. mp 211 ^oC, $[\alpha]_D^{24}$ -88 (*c* 0.2, MeOH), ^1H NMR (DMSO-d_6): δ_H 1.42–1.81 (m, 6H), 1.98–2.10 (m, 2H), 3.63 (d, *J* = 5.5 Hz, 1H), 3.70 (brs, 2H), 4.03 (s, 3H), 4.59 (s, 2H), 4.97 (d, *J* = 5.5 Hz, 1H), 6.45 (d, *J* = 5.5 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 9.2 Hz, 1H), 8.37 (d, *J* = 9.2 Hz, 1H), 8.96 (s, 1H), 11.15 (s, 1H), MS (ESI^+) *m/z* 552 (MH^+), HRMS (ESI^+) for $C_{27}H_{27}FN_5O_7$ (MH^+): calcd, 552.18945; found, 552.18940. Anal. calcd for $C_{27}H_{26}FN_5O_7 \cdot HCl$, C 55.15, H 4.63, N 11.91%. Found C 54.89, H 4.35, N 11.76%.

測定データ名: 136-07-062
試料名(分子量): 136-07-062(mw=507)
イオン化モード: デュアルESI+
オリフィス1電圧: 45V　　リングレンズ電圧: 10[V]
測定日時: 2010/03/29 13:25:45

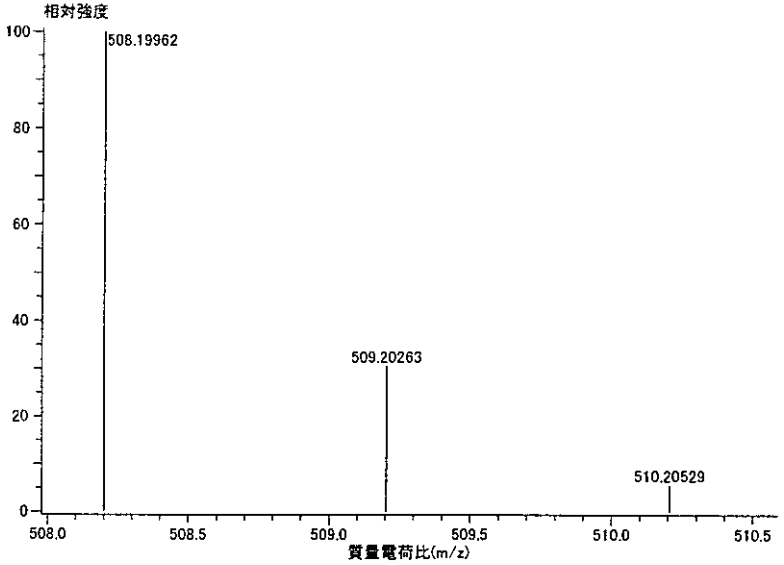
装置構成: JMS-T100LP

質量電荷比範囲: 100.00..1000.00
イオンガイドピーク間電圧: 2500V



組成式: $C_{28}H_{27}FN_5O_5$
モノアイソトピック質量: 508.19962　　平均質量: 508.52168
説明:

作成日時: 2010/03/29 14:03:34
整数質量: 508
作成者: Administrator



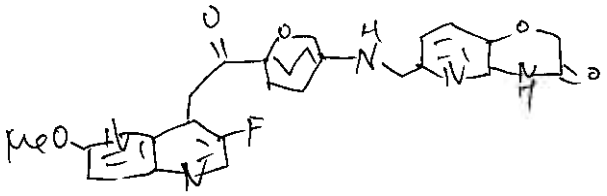
Compound 5

データ: 136-07-062
試料名: 136-07-062(mw=507)
説明:
イオン化モード: デュアルESI+
処理履歴: m/z軸決定[ピーク検出[重心,40,面積];ベース補正[10.0%];平滑化[5...

測定日時: 2010/03/29 13:25:45
測定者: Administrator
質量校正データ: HCOONa-Pos
作成日時: 2010/03/29 14:03:33
作成者: Administrator

電荷数: 1　　許容誤差: 5.00(mmu)　　不飽和数: -1.5 .. 20.0 (端数: 両方)
元素: ^{12}C:0 .. 28, ^{1}H:0 .. 27, ^{19}F:0 .. 1, ^{14}N:0 .. 5, ^{16}O:0 .. 5

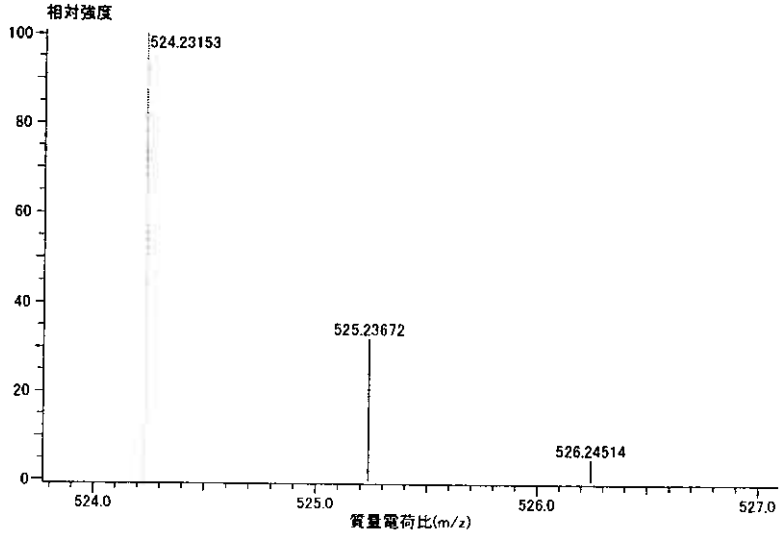
質量	強度	計算質量	質量差 mmu	推定組成式	不飽和数
508.19896	283570.18	508.19962	-0.66	$^{12}C_{28}{}^{1}H_{27}{}^{19}F_{1}{}^{14}N_{5}{}^{16}O_{5}$	15.5



測定データ名: 136-08-024
試料名(分子量): 136-08-024(mw=523 free)
イオン化モード: デュアルESI+
オリフィス1電圧: 45V　　リングレンズ電圧: 10[V]
測定日時: 2010/06/10 12:11:40

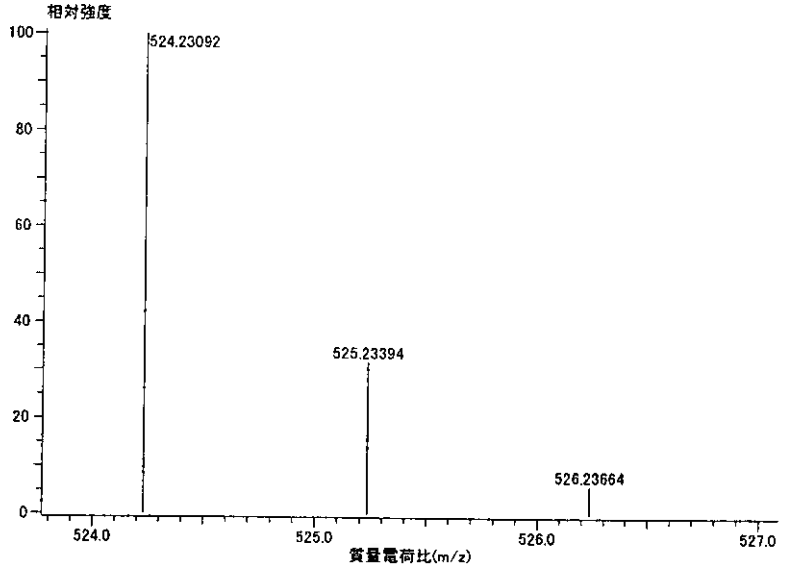
装置構成: JMS-T100LP

質量電荷比範囲: 100.00..1000.00
イオンガイドピーク間電圧: 2500V



組成式: $C_{27}H_{31}FN_5O_5$
モノアイソトピック質量: 524.23092　　平均質量: 524.56414
説明:

作成日時: 2010/06/10 13:51:52
整数質量: 524
作成者: Administrator



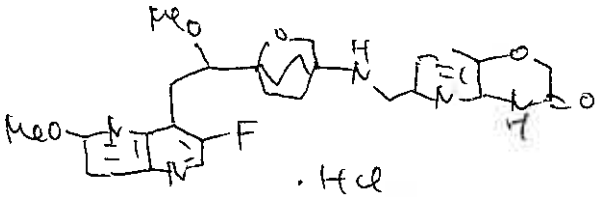
Compound (-)-6

データ: 136-08-024
試料名: 136-08-024(mw=523 free)
説明:
イオン化モード: デュアルESI+
処理履歴: m/z軸決定[ピーク検出[重心,35,面積];ベース補正[10.0%];平滑化[5...

測定日時: 2010/06/10 12:11:40
測定者: Administrator
質量校正データ: HCOONa-Pos
作成日時: 2010/06/10 13:51:51
作成者: Administrator

電荷数: 1　　許容誤差: 5.00(mmu)　　不飽和数: -1.5 .. 20.0 (端数: 両方)
元素: ^{12}C:0 .. 27, ^{1}H:0 .. 31, ^{19}F:0 .. 1, ^{14}N:0 .. 5, ^{16}O:0 .. 5

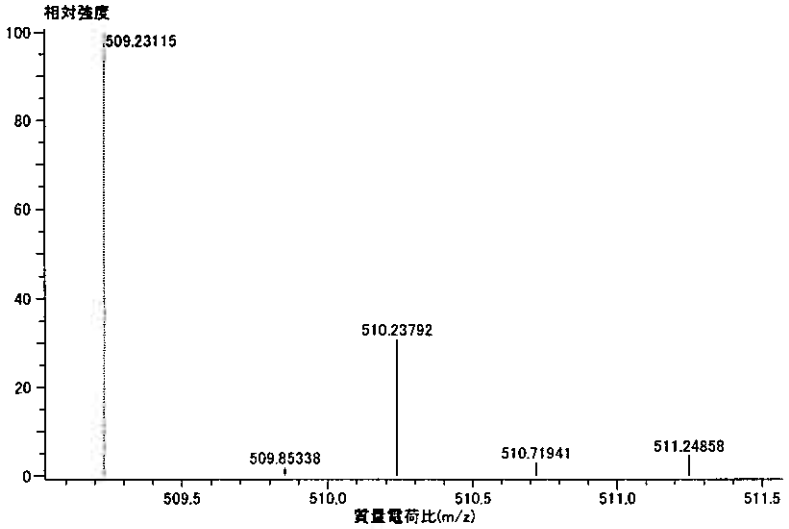
質量	強度	計算質量	質量差 mmu	推定組成式	不飽和数
524.23151	395288.56	524.23092	0.61	$^{12}C_{27}{}^{1}H_{31}{}^{19}F_{1}{}^{14}N_{5}{}^{16}O_{5}$	14.5



測定データ名: 136-08-013
試料名(分子量): 136-08-013(mw=508 free)
イオン化モード: デュアルESI+
オリフィス1電圧: 45V　　リングレンズ電圧: 10[V]
測定日時: 2010/05/27 14:39:51

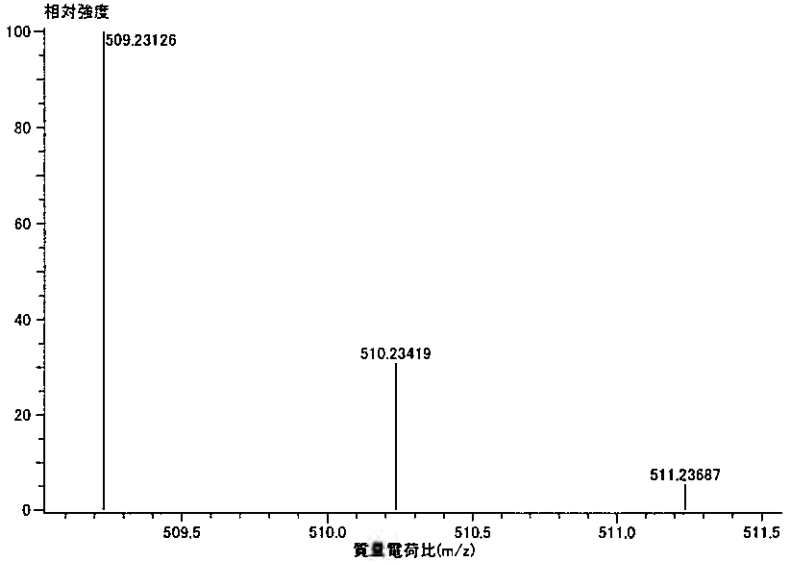
装置構成: JMS-T100LP

質量電荷比範囲: 100.00..1000.00
イオンガイドピーク間電圧: 2500V



組成式: $C_{26}H_{30}FN_6O_4$
モノアイソトピック質量: 509.23126　　平均質量: 509.55284
説明:

作成日時: 2010/05/27 15:59:51
整数質量: 509
作成者: Administrator



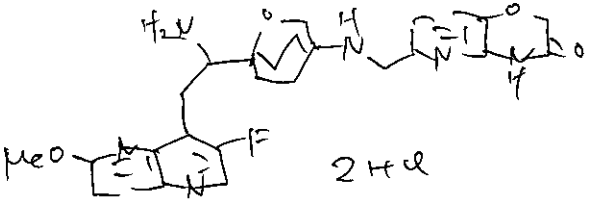
Compound (-)-10

データ: 136-08-013
試料名: 136-08-013(mw=508 free)
説明:
イオン化モード: デュアルESI+
処理履歴: m/z軸決定[ピーク検出[重心,50,面積];ベース補正[10.0%];平滑化[3...

測定日時: 2010/05/27 14:39:51
測定者: Administrator
質量校正データ: HCOONa-Pos
作成日時: 2010/05/27 15:59:50
作成者: Administrator

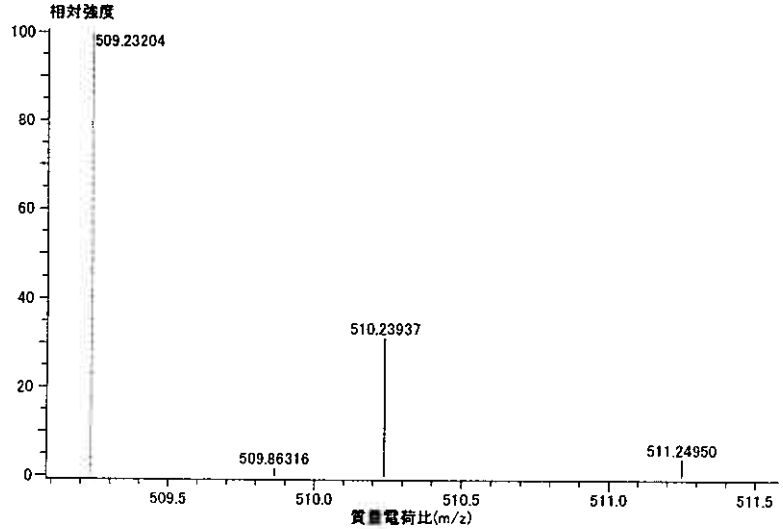
電荷数: 1　　許容誤差: 5.00(mmu)　　不飽和数: -1.5 .. 20.0 (端数: 両方)
元素: ^{12}C:0 .. 26, ^{1}H:0 .. 30, ^{19}F:0 .. 1, ^{14}N:0 .. 6, ^{16}O:0 .. 4

質量	強度	計算質量	質量差 mmu	推定組成式	不飽和数
509.23115	233117.25	509.23126	-0.11	$^{12}C_{26}{}^{1}H_{30}{}^{19}F_{1}{}^{14}N_{6}{}^{16}O_{4}$	14.5



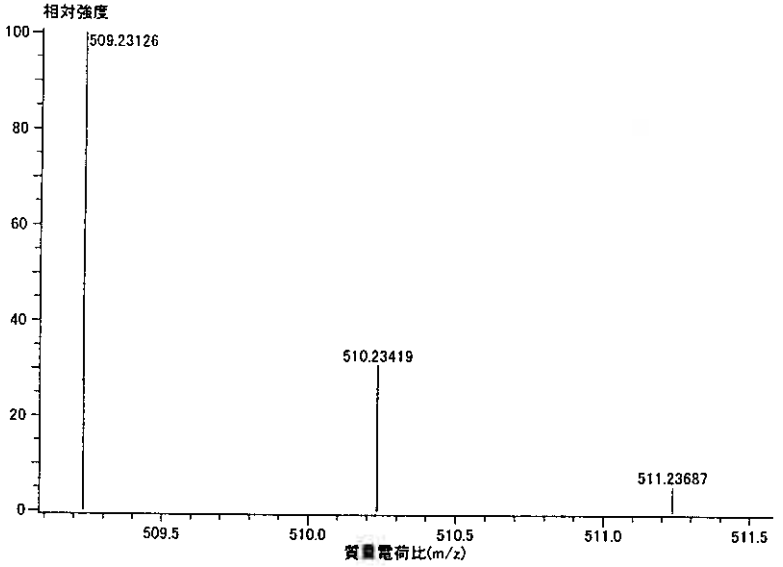
測定データ名: 136-08-012
試料名(分子量): 136-08-012(mw=508 free)
イオン化モード: デュアルESI+
オリフィス1電圧: 45V　　リングレンズ電圧: 10[V]
測定日時: 2010/05/25 13:20:13

装置構成: JMS-T100LP
質量電荷比範囲: 100.00_1000.00
イオンガイドピーク間電圧: 2500V



組成式: $C_{28}H_{30}FN_6O_4$
モノアイソトピック質量: 509.23126　　平均質量: 509.55284
説明:

作成日時: 2010/05/25 13:57:41
整数質量: 509
作成者: Administrator



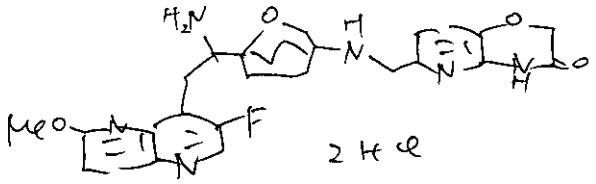
Compound (+)-10

データ: 136-08-012
試料名: 136-08-012(mw=508 free)
説明:
イオン化モード: デュアルESI+
処理履歴: m/z軸決定[ピーク検出[重心,45,面積]:ベース補正[10.0%];平滑化[5...

測定日時: 2010/05/25 13:20:13
測定者: Administrator
質量校正データ: HCOONa-Pos
作成日時: 2010/05/25 13:57:41
作成者: Administrator

電荷数: 1　　許容誤差: 5.00(mmu)　　不飽和数: -1.5 _ 20.0 (端数: 両方)
元素: ^{12}C:0 _ 26, ^{1}H:0 _ 30, ^{19}F:0 _ 1, ^{14}N:0 _ 6, ^{16}O:0 _ 4

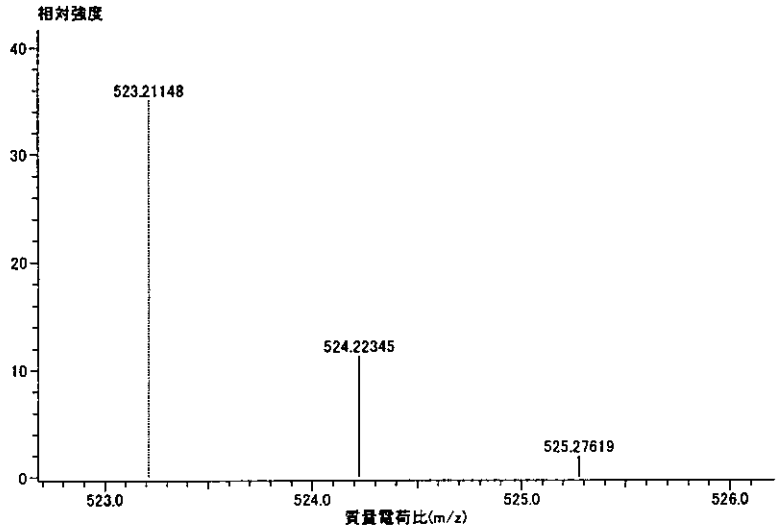
質量	強度	計算質量	質量差 mmu	推定組成式	不飽和数
509.23204	194356.24	509.23126	0.79	$^{12}C_{28}{}^{1}H_{30}{}^{19}F_{1}{}^{14}N_{6}{}^{16}O_{4}$	14.5



測定データ名: 136-07-069-1
試料名(分子量): 136-07-069-1(mw=522)
イオン化モード: デュアルESI+
オリフィス1電圧: 45V　　リングレンズ電圧: 10[V]
測定日時: 2010/04/09 14:12:11

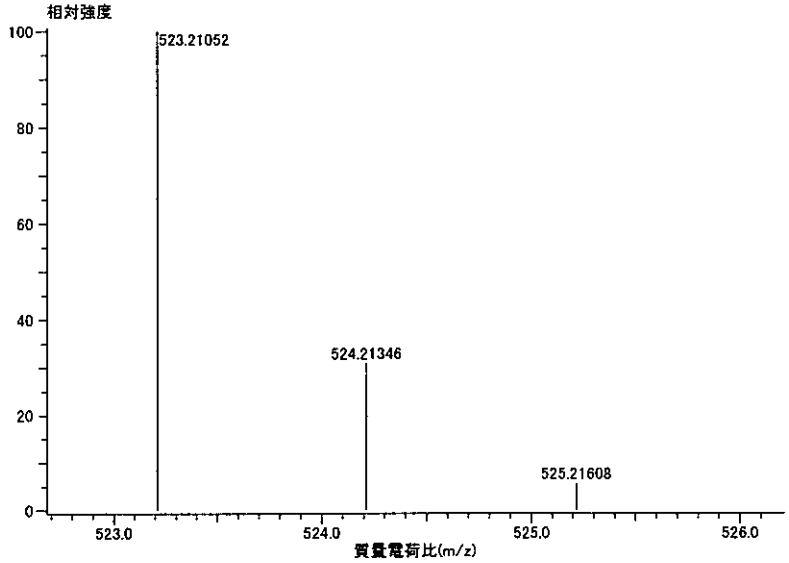
装置構成: JMS-T100LP

質量電荷比範囲: 100.00..1000.00
イオンガイドピーク間電圧: 2500V



組成式: $C_{26}H_{28}FN_6O_5$
モノアイソトピック質量: 523.21052　　平均質量: 523.53636
説明:

作成日時: 2010/04/09 15:11:06
整数質量: 523
作成者: Administrator



Compound 13

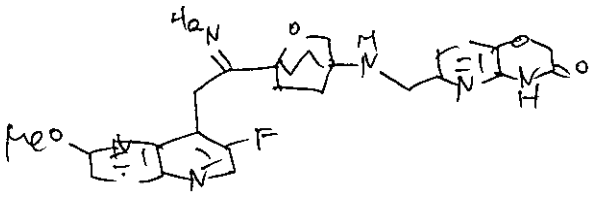
データ: 136-07-069-1
試料名: 136-07-069-1(mw=522)
説明:
イオン化モード: デュアルESI+
処理履歴: m/z軸決定[ピーク検出[重心,40,面積];ベース補正[10.0%];平滑化[5...

測定日時: 2010/04/09 14:12:11
測定者: Administrator
質量校正データ: HCOONa-Pos
作成日時: 2010/04/09 15:11:05
作成者: Administrator

電荷数: 1　　許容誤差: 5.00(mmu)
元素: ^{12}C:0 .. 26, ^{1}H:0 .. 28, ^{19}F:0 .. 1, ^{14}N:0 .. 6, ^{16}O:0 .. 5

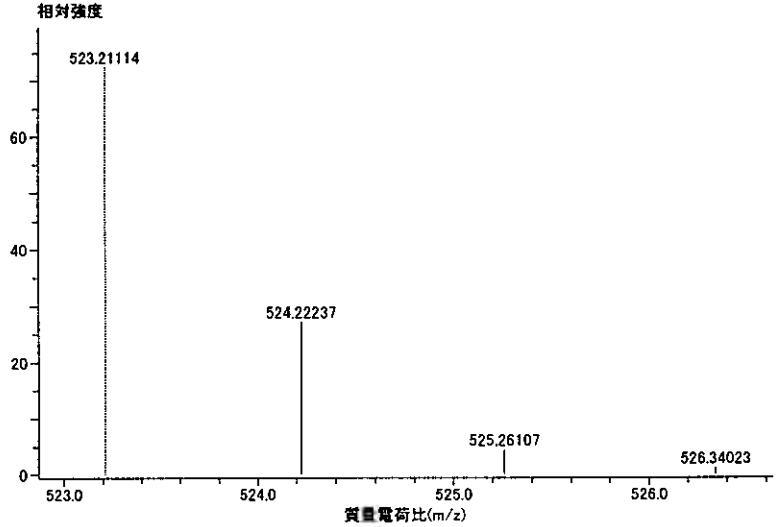
不飽和数: -1.5 .. 20.0 (端数: 両方)

質量	強度	計算質量	質量差 mmu	推定組成式	不飽和数
523.21148	59929.99	523.21052	0.96	$^{12}C_{26}{}^{1}H_{28}{}^{19}F_{1}{}^{14}N_{6}{}^{16}O_{5}$	15.5



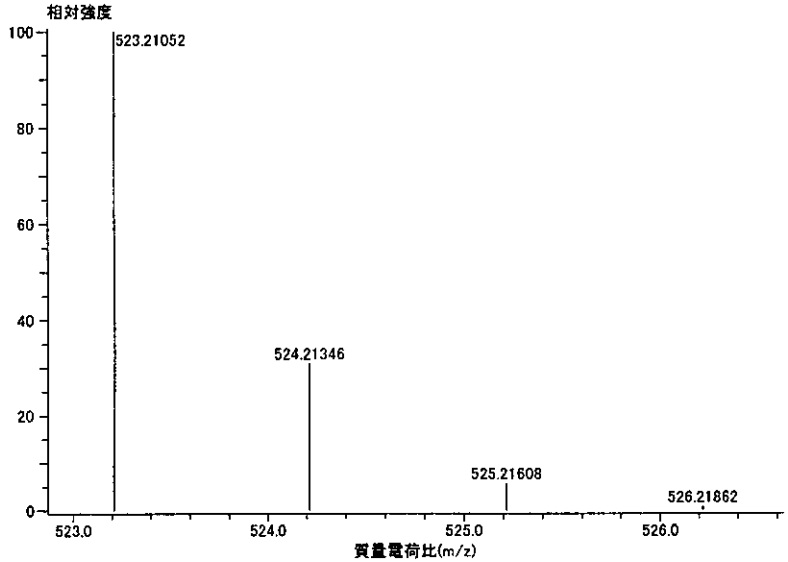
測定データ名: 136-07-069-2
試料名(分子量): 136-07-069-2(mw=522)
イオン化モード: デュアルESI+
オリフィス1電圧: 45V　　リングレンズ電圧: 10[V]
測定日時: 2010/04/16 15:01:29

装置構成: JMS-T100LP
質量電荷比範囲: 100.00..1000.00
イオンガイドピーク間電圧: 2500V



組成式: $C_{26}H_{28}FN_5O_5$
モノアイソトピック質量: 523.21052　　平均質量: 523.53636
説明:

作成日時: 2010/04/16 15:15:09
整数質量: 523
作成者: Administrator



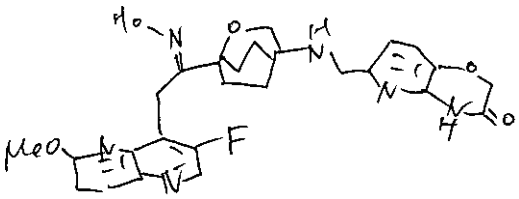
Compound 14

データ: 136-07-069-2
試料名: 136-07-069-2(mw=522)
説明:
イオン化モード: デュアルESI+
処理履歴: m/z軸決定[ピーク検出[重心,40,面積];ベース補正[10.0%];平滑化[5...

測定日時: 2010/04/16 15:01:29
測定者: Administrator
質量校正データ: HCOONa-Pos
作成日時: 2010/04/16 15:15:08
作成者: Administrator

電荷数: 1　　許容誤差: 5.00(mmu)　　不飽和数: -1.5 .. 20.0 (端数: 両方)
元素: ^{12}C:0 .. 26, ^{1}H:0 .. 28, ^{19}F:0 .. 1, ^{14}N:0 .. 6, ^{16}O:0 .. 5

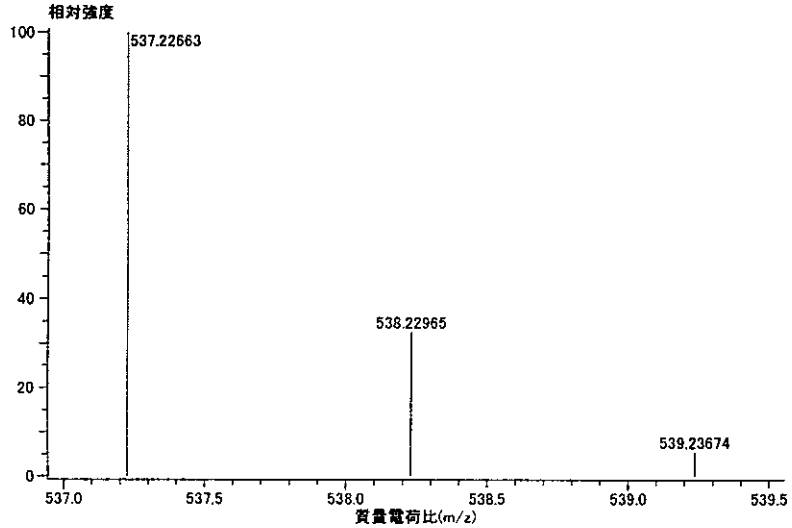
質量	強度	計算質量	質量差 mmu	推定組成式	不飽和数
523.21114	58618.55	523.21052	0.62	$^{12}C_{26}{}^{1}H_{28}{}^{19}F_{1}{}^{14}N_{5}{}^{16}O_{5}$	15.5



測定データ名: 136-08-005
試料名(分子量): 136-08-005(mw=536 free)
イオン化モード: デュアルESI+
オリフィス1電圧: 45V　　リングレンズ電圧: 10[V]
測定日時: 2010/05/27 14:52:07

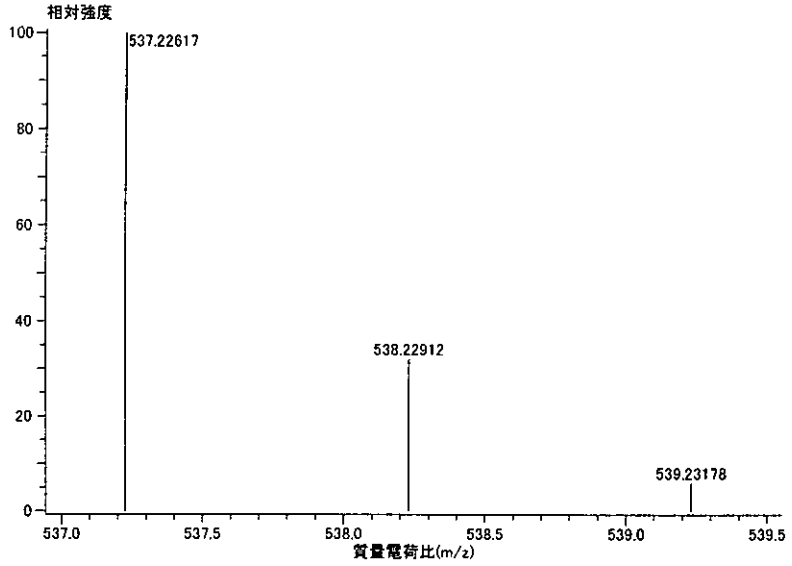
装置構成: JMS-T100LP

質量電荷比範囲: 100.00..1000.00
イオンガイドピーク間電圧: 2500V



組成式: $C_{27}H_{30}FN_6O_5$
モノアイソトピック質量: 537.22617　　平均質量: 537.56294
説明:

作成日時: 2010/05/27 16:08:07
整数質量: 537
作成者: Administrator



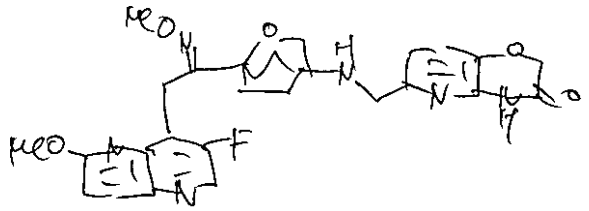
Compound 15

データ: 136-08-005
試料名: 136-08-005(mw=536 free)
説明:
イオン化モード: デュアルESI+
処理履歴: m/z軸決定[ピーク検出[重心,50,面積];ベース補正[10.0%];平滑化[5...

測定日時: 2010/05/27 14:52:07
測定者: Administrator
質量校正データ: HCOONa-Pos
作成日時: 2010/05/27 16:08:06
作成者: Administrator

電荷数: 1　　許容誤差: 5.00(mmu)　　不飽和数: -1.5 .. 20.0 (端数: 両方)
元素: ^{12}C: 0 .. 27, ^{1}H: 0 .. 30, ^{19}F: 0 .. 1, ^{14}N: 0 .. 6, ^{16}O: 0 .. 5

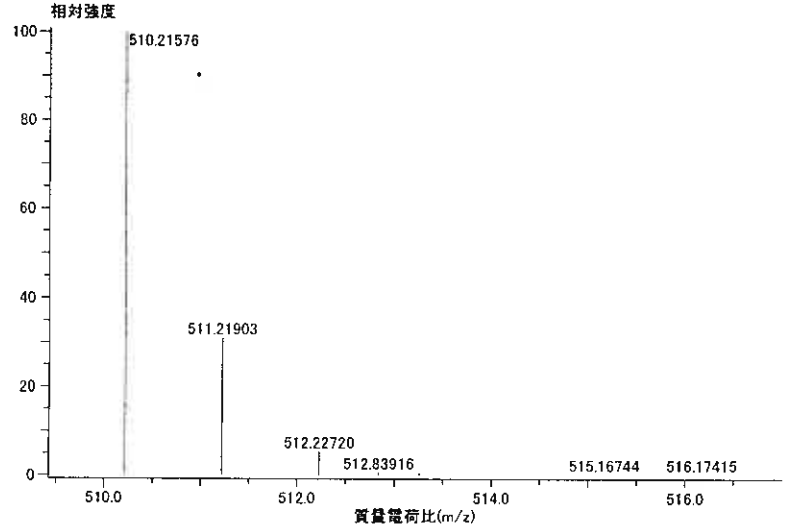
質量	強度	計算質量	質量差 mmu	推定組成式	不飽和数
537.22663	1704703.87	537.22617	0.46	$^{12}C_{27}{}^{1}H_{30}{}^{19}F_{1}{}^{14}N_{6}{}^{16}O_{5}$	15.5



測定データ名: 136-09-063
試料名(分子量): 136-09-063(mw=509)
イオン化モード: デュアルESI+
オリフィス1電圧: 45V　　リングレンズ電圧: 10[V]
測定日時: 2010/11/24 11:01:56

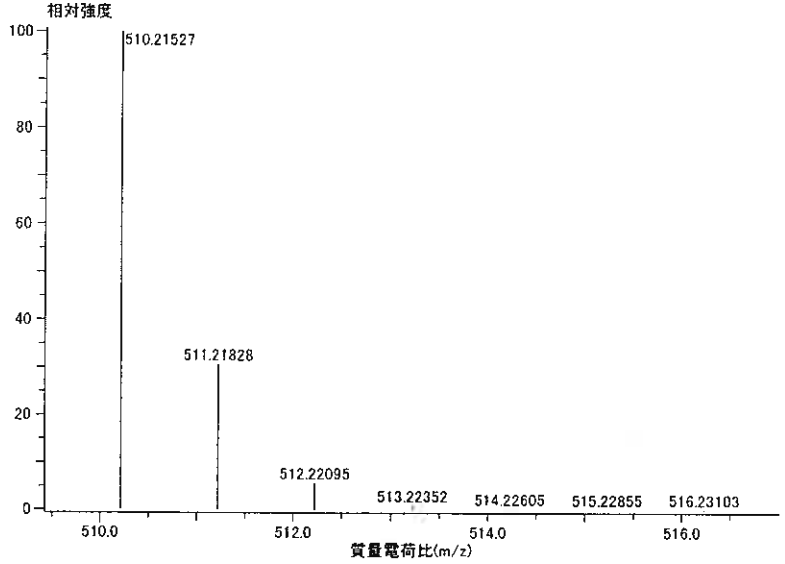
装置構成: JMS-T100LP

質量電荷比範囲: 100.00..1000.00
イオンガイドピーク間電圧: 2500V



組成式: $C_{26}H_{29}FN_5O_5$
モノアイソトピック質量: 510.21527　　平均質量: 510.53756
説明

作成日時: 2010/11/24 11:16:59
整数質量: 510
作成者: Administrator



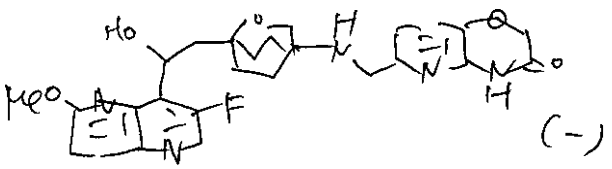
Compound (-)-19

データ: 136-09-063
試料名: 136-09-063(mw=509)
説明:
イオン化モード: デュアルESI+
処理履歴: m/z軸決定[ピーク検出[重心,40,面積];ベース補正[20.0%];平滑化[5...

測定日時: 2010/11/24 11:01:56
測定者: Administrator
質量校正データ: HCOONa-Pos
作成日時: 2010/11/24 11:16:59
作成者: Administrator

電荷数: 1　　許容誤差: 5.00(mmu)　　不飽和数: -1.5 .. 20.0 (端数: 両方)
元素: ^{12}C:0 .. 26, ^{1}H:0 .. 29, ^{19}F:0 .. 1, ^{14}N:0 .. 5, ^{16}O:0 .. 5

質量	強度	計算質量	質量差 mmu	推定組成式	不飽和数
510.21576	914834.20	510.21527	0.49	$^{12}C_{26}{}^{1}H_{29}{}^{19}F_{1}{}^{14}N_{5}{}^{16}O_{5}$	14.5

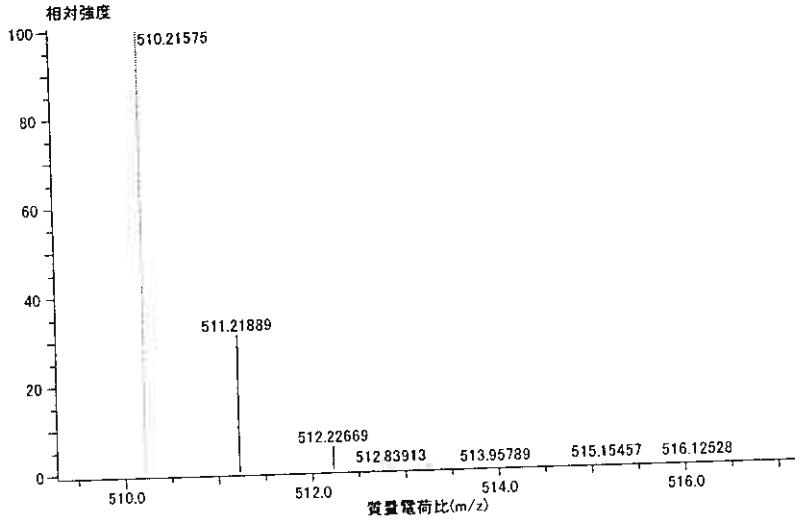


測定データ名: 136-09-062
試料名(分子量): 136-09-062(mw=509)
イオン化モード: デュアルESI+
オリフィス1電圧: 45V
測定日時: 2010/11/24 10:49:41

装置構成: JMS-T100LP

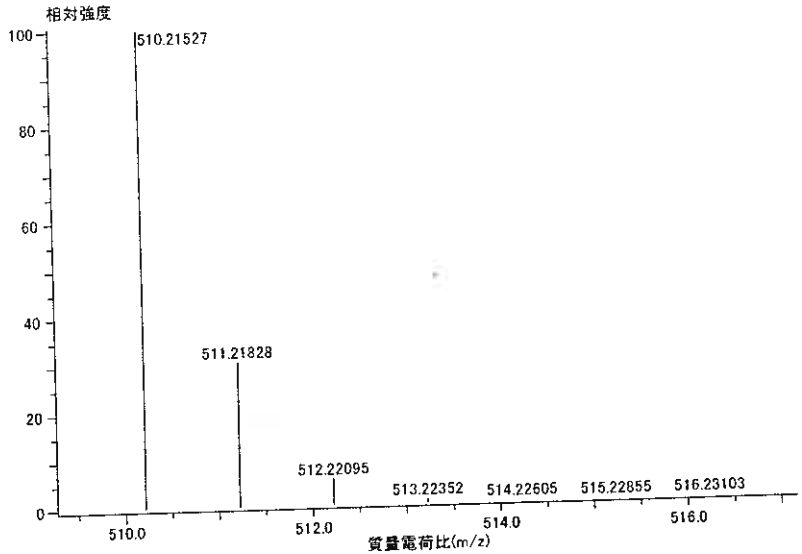
リングレンズ電圧: 10[V]

質量電荷比範囲: 100.00..1000.00
イオンガイドピーク間電圧: 2500V



組成式: $C_{26}H_{29}FN_3O_5$
モノアイソトピック質量: 510.21527
平均質量: 510.53756
説明:

作成日時: 2010/11/24 11:15:13
整数質量: 510
作成者: Administrator



Compound (+)-19

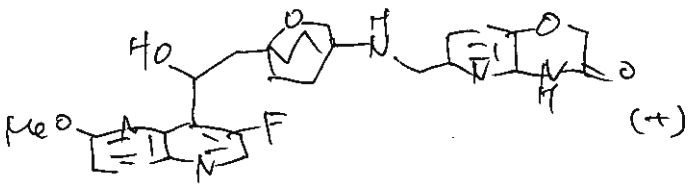
データ: 136-09-062
試料名: 136-09-062(mw=509)
説明:
イオン化モード: デュアルESI+
処理履歴: m/z軸決定{ピーク検出[重心,40,面積];ベース補正[20.0%];平滑化[5...

測定日時: 2010/11/24 10:49:41
測定者: Administrator
質量校正データ: HCOONa-Pos
作成日時: 2010/11/24 11:15:13
作成者: Administrator

不飽和数: -1.5 .. 20.0 (端数: 両方)

電荷数: 1
許容誤差: 5.00(mmu)
元素: ^{12}C:0 .. 26, ^{1}H:0 .. 29, ^{19}F:0 .. 1, ^{14}N:0 .. 5, ^{16}O:0 .. 5

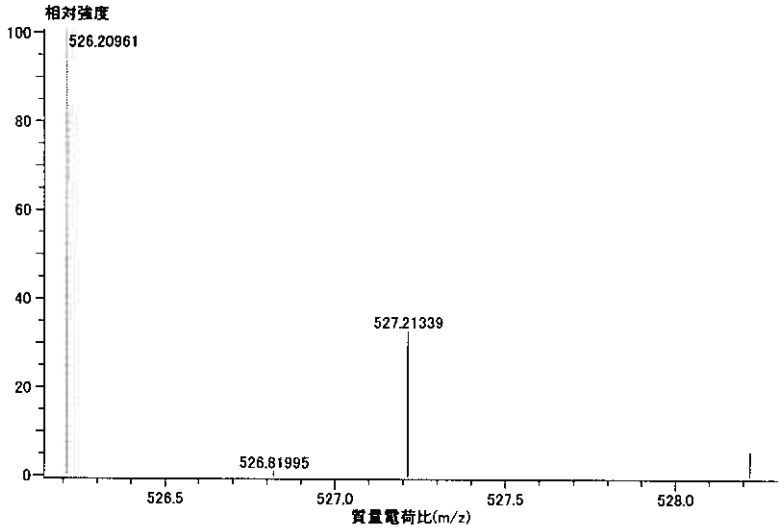
質量	強度	計算質量	質量差 mmu	推定組成式	不飽和数
510.21575	978440.52	510.21527	0.48	$^{12}C_{26}{}^{1}H_{29}{}^{19}F_{1}{}^{14}N_{3}{}^{16}O_{5}$	14.5



測定データ名: 144-3-025
試料名(分子量): 144-3-025(mw=525 free)
イオン化モード: デュアルESI+
オリフィス1電圧: 45V　　リングレンズ電圧: 10[V]
測定日時: 2009/12/07 12:28:12

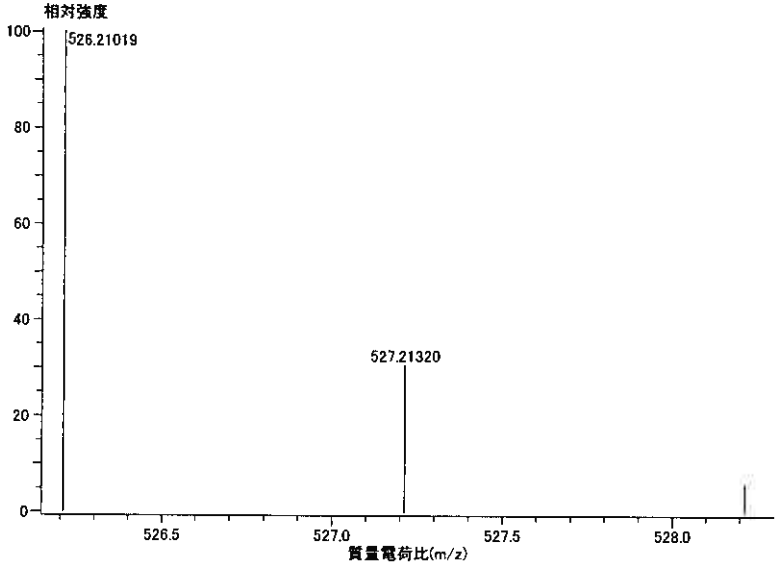
装置構成: JMS-T100LP

質量電荷比範囲: 100.00..1000.00
イオンガイドピーク間電圧: 2500V



組成式: $C_{26}H_{29}FN_5O_6$
モノアイソトピック質量: 526.21019　　平均質量: 526.53696
説明:

作成日時: 2009/12/07 13:21:24
整数質量: 526
作成者: Administrator



Compound (-)-24

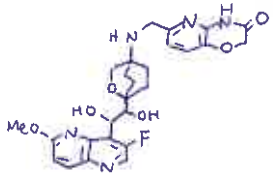
データ: 144-3-025
試料名: 144-3-025(mw=525 free)
説明:
イオン化モード: デュアルESI+
処理履歴: m/z軸決定[ピーク検出[重心,10,面積]:ベース補正[10.0%]:平滑化[...

測定日時: 2009/12/07 12:28:12
測定者: Administrator
質量校正データ: TFANa_ESI+_1000
作成日時: 2009/12/07 13:21:24
作成者: Administrator

電荷数: 1　　許容誤差: 5.00(mmu)
元素: ^{12}C:0 .. 28, ^{1}H:0 .. 29, ^{19}F:0 .. 1, ^{14}N:0 .. 5, ^{16}O:0 .. 6

不飽和数: -1.5 .. 20.0 (端数: 両方)

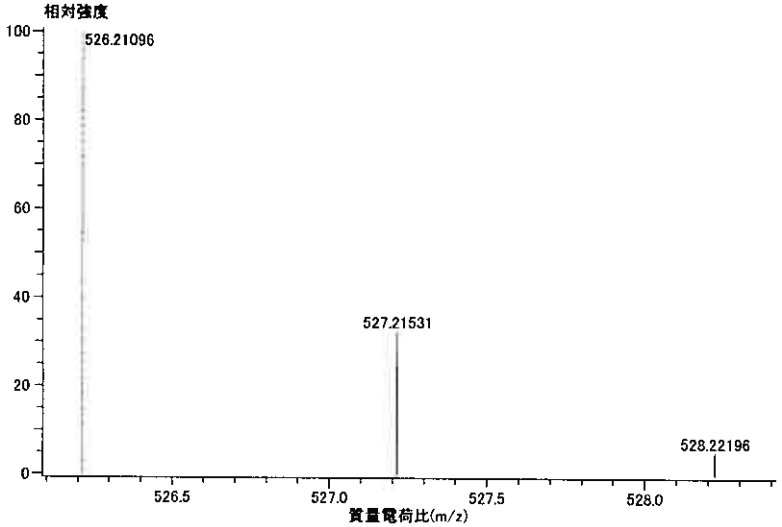
質量	強度	計算質量	質量差 mmu	推定組成式	不飽和数
526.20961	741794.41	526.21019	-0.58	$^{12}C_{26}{}^{1}H_{29}{}^{19}F_{1}{}^{14}N_{5}{}^{16}O_{6}$	14.5



測定データ名: 144-3-026
試料名(分子量): 144-3-026(mw=525 free)
イオン化モード: デュアルESI+
オリフィス1電圧: 45V　　リングレンズ電圧: 10[V]
測定日時: 2009/12/07 12:15:55

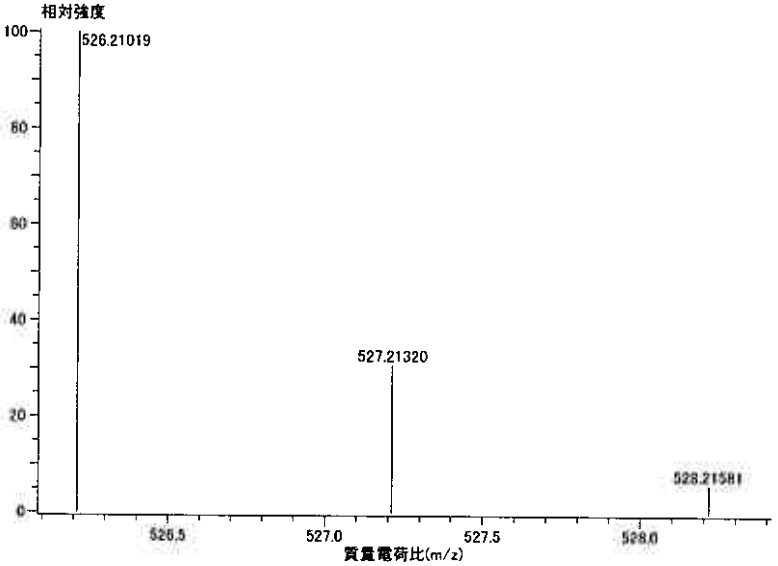
装置構成: JMS-T100LP

質量電荷比範囲: 100.00, 1000.00
イオンガイドピーク間電圧: 2500V



組成式: $C_{28}H_{29}FN_5O_5$
モノアイソトピック質量: 526.21019　　平均質量: 526.53696
説明:

作成日時: 2009/12/07 13:18:40
整数質量: 526
作成者: Administrator



Compound (+)-24

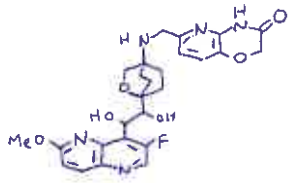
データ: 144-3-026
試料名: 144-3-026(mw=525 free)
説明:
イオン化モード: デュアルESI+
処理履歴: m/z軸決定[ピーク検出[重心,20,面積];ベース補正[10.0%];平滑化[...

測定日時: 2009/12/07 12:15:55
測定者: Administrator
質量校正データ: TFANa_ESI+_1000
作成日時: 2009/12/07 13:18:39
作成者: Administrator

電荷数: 1　　許容誤差: 5.00(mmu)
元素: ^{12}C:0 .. 26, ^{1}H:0 .. 29, ^{19}F:0 .. 1, ^{14}N:0 .. 5, ^{16}O:0 .. 6

不飽和数: -1.5 .. 20.0 (端数: 両方)

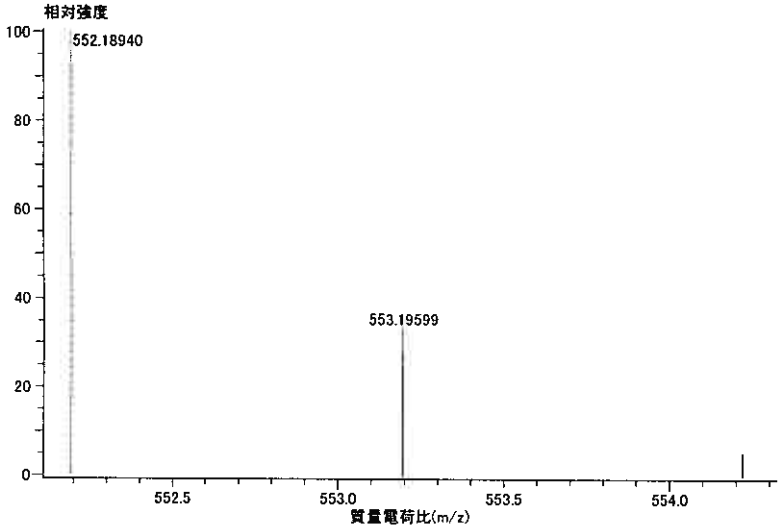
質量	強度	計算質量	質量差 mmu	推定組成式	不飽和数
526.21096	493057.65	526.21019	0.77	$^{12}C_{28}{}^{1}H_{29}{}^{19}F_{1}{}^{14}N_{5}{}^{16}O_{5}$	14.5



測定データ名: 144-3-036
試料名(分子量): 144-3-036(mw=551 free)
イオン化モード: デュアルESI+
オリフィス1電圧: 45V　　リングレンズ電圧: 10[V]
測定日時: 2009/12/18 14:47:23

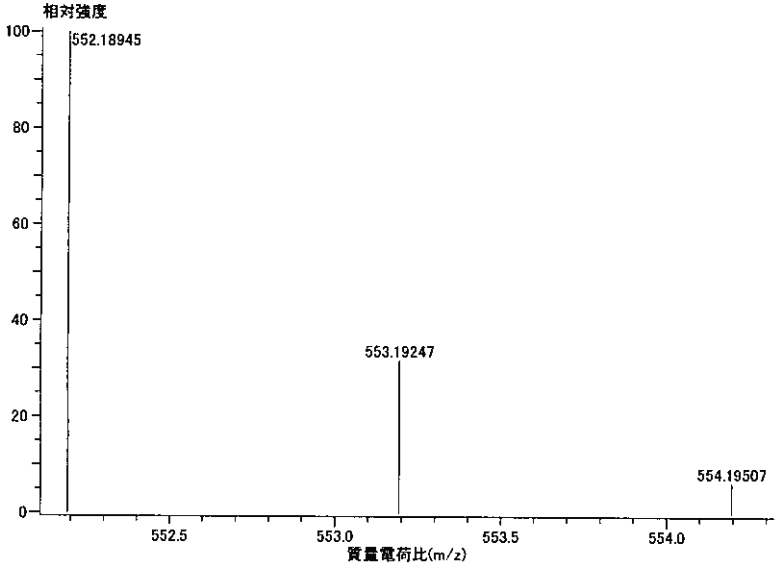
装置構成: JMS-T100LP

質量電荷比範囲: 100.00 ,1000.00
イオンガイドピーク間電圧: 2500V



組成式: $C_{27}H_{27}FN_3O_7$
モノアイソトピック質量: 552.18945　　平均質量: 552.53118
説明:

作成日時: 2009/12/18 15:09:28
整数質量: 552
作成者: Administrator



Compound (-)-25

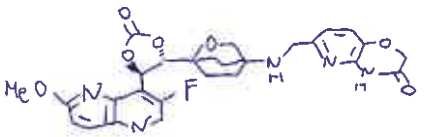
データ: 144-3-036
試料名: 144-3-036(mw=551 free)
説明:
イオン化モード: デュアルESI+
処理履歴: m/z軸決定[ピーク検出[重心,35,面積],ベース補正[10.0%]:平滑化[...

測定日時: 2009/12/18 14:47:23
測定者: Administrator
質量校正データ: TFANa_ESI+_1000
作成日時: 2009/12/18 15:09:27
作成者: Administrator

電荷数: 1　　許容誤差: 5.00(mmu)
元素: ^{12}C:0 .. 27, ^{1}H:0 .. 27, ^{19}F:0 .. 1, ^{14}N:0 .. 5, ^{16}O:0 .. 7

不飽和数: -1.5 .. 20.0 (端数: 両方)

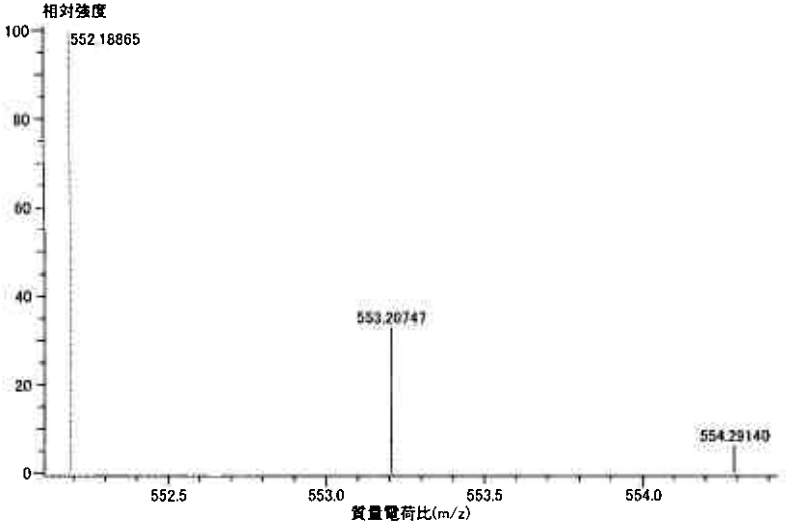
質量	強度	計算質量	質量差 mmu	推定組成式	不飽和数
552.18940	647251.26	552.18945	-0.05	$^{12}C_{27}{}^{1}H_{27}{}^{19}F_{1}{}^{14}N_{3}{}^{16}O_{7}$	16.5



測定データ名: 144-3-040
試料名(分子量): 144-3-040(mw=551 free)
イオン化モード: デュアルESI+
オリフィス1電圧: 45V　　リングレンズ電圧: 10[V]
測定日時: 2009/12/28 13:16:05

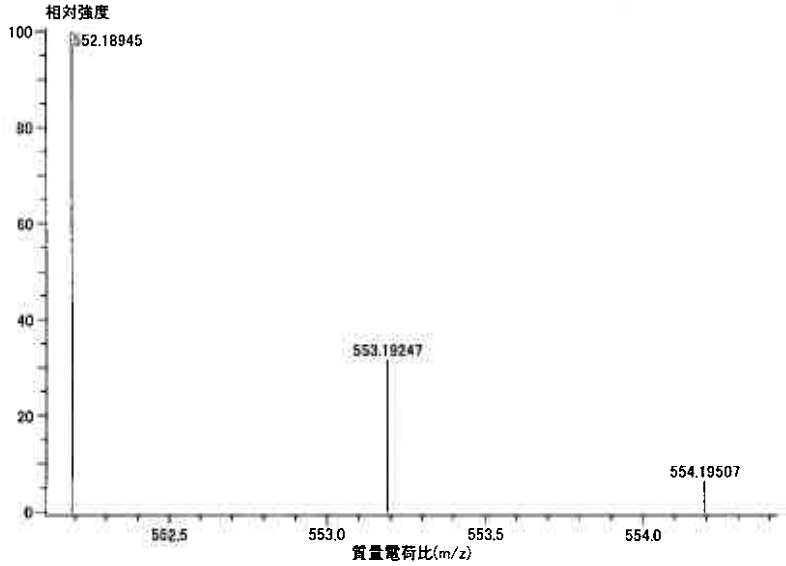
装置構成: JMS-T100LP

質量電荷比範囲: 100.00_1000.00
イオンガイドピーク間電圧: 2500V



組成式: $C_{27}H_{27}FN_5O_7$
モノアイソトピック質量: 552.18945　　平均質量: 552.53118
説明:

作成日時: 2009/12/28 14:19:37
整数質量: 552
作成者: Administrator



Compound (+)-25

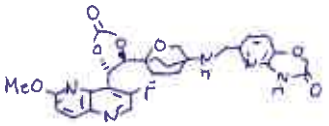
データ: 144-3-040
試料名: 144-3-040(mw=551 free)
説明:
イオン化モード: デュアルESI+
処理履歴: m/z軸決定[ピーク検出[重心,45,面積];ベース補正[10.0%];平滑化[...

測定日時: 2009/12/28 13:16:05
測定者: Administrator
質量校正データ: TFANa_ESI+_1000
作成日時: 2009/12/28 14:19:37
作成者: Administrator

電荷数: 1　　許容誤差: 5.00(mmu)
元素: ^{12}C:0 .. 27, ^{1}H:0 .. 27, ^{19}F:0 .. 1, ^{14}N:0 .. 5, ^{16}O:0 .. 7

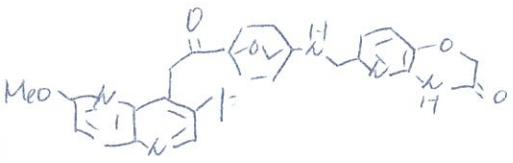
不飽和数: -1.5 .. 20.0 (端数: 両方)

質量	強度	計算質量	質量差 mmu	推定組成式	不飽和数
552.18865	102787.06	552.18945	-0.80	$^{12}C_{27}{}^{1}H_{27}{}^{19}F_{1}{}^{14}N_{5}{}^{16}O_{7}$	16.5



Compound 5

元 素 分 析 報 告 書

氏 名	坪田 成 殿	申込日付	2010 年 3 月 29 日
物質名	136-07-062		
分子式	$C_{26}H_{26}FN_5O_5$	KCL No.	
構造式（又ハ，分子式・含有元素名）		M. P. : 183-184 °C B. P. : 昇華性 : 吸湿性 :	

	C	H	N	O	S	X	M·W
calcd (%)	61.53	5.16	13.80				507.51
found (%)	59.15	5.13	12.91				

分析後の所見. 分析日付 3/29 H. Ohashi	Note No. 分析番号 : 445

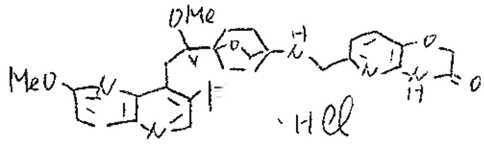
杏林製薬㈱ 創薬研究所

Compound (-)-6

元素分析報告書

氏名	柴田 成 殿	申込日付	2010 年 6月10日
物質名	136-08-024		
分子式	$C_{27}H_{30}FN_5O_5$ HCl	KCL No.	

構造式（又ハ，分子式・含有元素名）



0.6H2O 56.81 5.69 12.27

M. P.: 219-220°C (decomp)

B. P.:

昇華性:

吸湿性:

	C	H	N	O	S	X	M·W
calcd (%)	57.91	5.58	12.51				560.02
found (%)	56.55	5.50	12.18				570.83

分析後の所見，分析日付

6/10 0.6 EtOH 付加物で一致する H Ohashi

Note No.

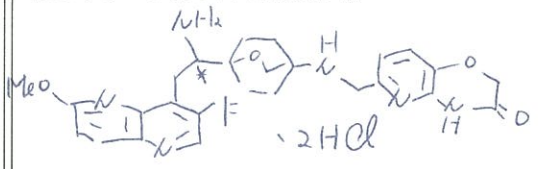
分析番号: 1075

(5.71 5.3)
574.0 0.4 6 0.512

杏林製薬(株) 創薬研究所

Compound (-)-10

元 素 分 析 報 告 書

氏 名	柴田 誠 殿	申込日付	2010 年 5月27日
物質名	136-08-013		
分子式	$C_{26}H_{29}FN_6O_4 \cdot 2HCl$	KCL No.	
構造式（又ハ，分子式・含有元素名）		M. P.：	
		B. P.：	
		昇華性：	
		吸湿性：	

	C	H	N	O	S	X	M·W
calcd(%)	53.71	5.37	14.45				581.47
found(%)	48.36	5.41	12.88				

分析後の所見. 分析日付	Note No.
5/27 H.Ohashi	分析番号： 910

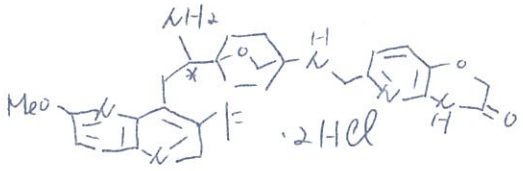
杏林製薬㈱ 創薬研究所

Compound (+)-10

元 素 分 析 報 告 書

氏 名	柴田 成 殿	申込日付	2010 年 5 月 25 日
物質名	136-08-012		
分子式	$C_{26}H_{29}FN_6O_4 \cdot 2HCl$	KCL No.	

構造式（又ハ，分子式・含有元素名）



M. P. : 234-235 °C, (decomp.).
B. P. :
昇 華 性 :
吸 湿 性 :

	C	H	N	O	S	X	M·W
calcd (%)	53.71	5.37	14.45				581.47
found (%)	50.18	5.41	13.31				

分析後の所見. 分析日付

5/25 H. Ohashi

Note No.

分析番号 : 872

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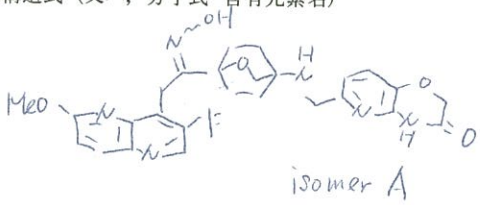
Compound 13

元 素 分 析 報 告 書

氏 名	柴田 成 殿	申込日付	2010 年 4 月 9 日
物質名	136-07-069-1		
分子式	$C_{26}H_{27}FN_6O_5$	KCL No.	
構造式（又ハ，分子式・含有元素名）	 isomer A	M. P. :	191℃
		B. P. :	
		昇華性 :	
		吸湿性 :	

	C	H	N	O	S	X	M·W
calcd (%)	59.76	5.21	16.08				522.53
found (%)	59.04	5.19	15.78				

分析後の所見. 分析日付	Note No.
4/9 H Ohashi	分析番号 : 554

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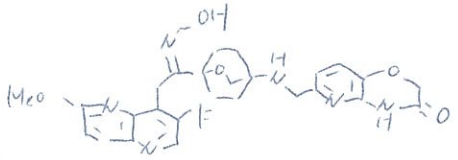
Compound 14

元 素 分 析 報 告 書

氏 名	柴田 誠殿	申込日付	2010 年 4月 9 日
物質名	136-07-069-2		
分子式	$C_{26}H_{27}FN_6O_5$	KCL No.	2010 00637
構造式（又ハ，分子式・含有元素名）	 isomer B	M. P. :	258 °C
		B. P. :	
		昇華性 :	
		吸湿性 :	

	C	H	N	O	S	X	M·W
calcd (%)	59.76	5.21	16.08				522.53
found (%)	59.20	5.26	15.70				

分析後の所見. 分析日付 AM-1207 4/13 H.Ohashi	Note No.
	分析番号 : 575

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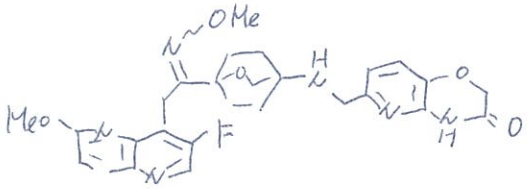
Compound 15

元 素 分 析 報 告 書

氏 名	柴田 哉 殿	申込日付	2010 年 5 月 27 日
物質名	136-08-005		
分子式	$C_{27}H_{19}FN_6O_5$	KCL No.	
構造式（又ハ，分子式・含有元素名）		M. P. :	
		B. P. :	
		昇華性 :	
		吸湿性 :	

	C	H	N	O	S	X	M·W
calcd (%)	60.44	5.45	15.66				536.55
found (%)	60.29	5.44	15.73				

分析後の所見. 分析日付	Note No.
5/27 H Ohashi	分析番号 : 909

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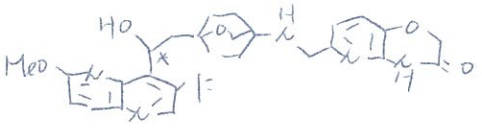
Compound (-)-19

元 素 分 析 報 告 書

氏 名	柴田 成 殿	申込日付	2010 年 11月 24日
物質名	136-09-063		
分子式	$C_{26}H_{28}FNO_5$	KCL No.	
構造式（又ハ，分子式・含有元素名）		M. P. : 125°C (from EtOH) B. P. : 昇華性 : 吸湿性 :	

	C	H	N	O	S	X	M·W
calcd (%)	61.29	5.54	13.74				509.53
found (%)	59.37	5.50	13.14				

分析後の所見. 分析日付 11/24

0.3 5 EtOH 4mg

59.41, 5.37, 13.32

H. Ohashi

Note No.

分析番号 : 1922

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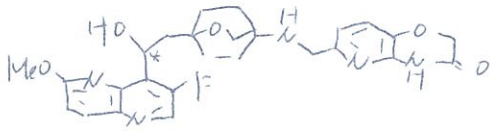
Compound (+)-19

元 素 分 析 報 告 書

氏 名	柴田 誠 殿	申込日付	2010 年 11 月 24 日
物質名	136-09-062		
分子式	$C_{26}H_{28}FN_5O_5$	KCL No.	
構造式（又ハ，分子式・含有元素名）		M. P. :	125°C (from EtOH)
		B. P. :	
		昇華性 :	
		吸湿性 :	

	C	H	N	O	S	X	M·W
calcd (%)	61.29	5.54	13.74				509.53
found (%)	59.56	5.50	13.20				

分析後の所見. 分析日付

0.35 Ethanol 和物 59.41, 5.37, 13.32

11/24 H. Ohashi

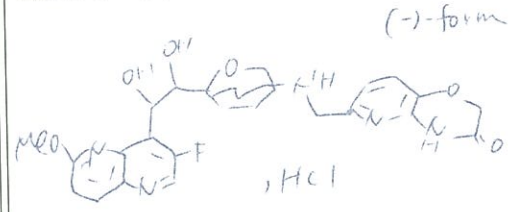
Note No.

分析番号 : 1921

杏林製薬㈱ 創薬研究所

Compound (-)-24

元 素 分 析 報 告 書

氏 名	竹内智子 殿	申込日付	09 年 12月 7日
物質名	144-3-026		
分子式	$C_{26}H_{28}FN_5O_6 \cdot HCl$	KCL No.	
構造式（又ハ，分子式・含有元素名）	(-)-form  ·HCl	M. P.：	
		B. P.：	
		昇華性：	
		吸湿性：	

	C	H	N	O	S	X	M·W
calcd (%)	55.57	5.20	12.46				561.99
found (%)	55.80	5.33	12.11				

分析後の所見. 分析日付

C.F.for 0.1 55.11 5.16 12.36

12/7 H Okushi

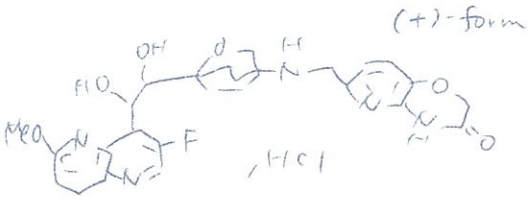
Note No.

分析番号： 1529

杏林製薬㈱ 創薬研究所

Compound (+)-24

元 素 分 析 報 告 書

氏 名	竹内智子 殿	申込日付	09 年12月7日
物質名	144-3-025		
分子式	$C_{26}H_{28}FN_5O_6 \cdot HCl$	KCL No.	
構造式（又ハ，分子式・含有元素名）	 (+)-form	M. P. :	
		B. P. :	
		昇華性 :	
		吸湿性 :	

	C	H	N	O	S	X	M·W
calcd (%)	55.57	5.20	12.46				561.99
found (%)	54.57	5.44	11.85				

分析後の所見. 分析日付

0.3EtOH 54.23 5.08 12.16

12/7 H. Ohashi

Note No.

分析番号 : 1528

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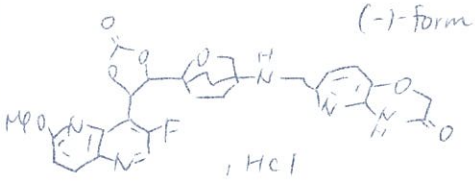
Compound (-)-25

元 素 分 析 報 告 書

氏 名	竹内智子 殿	申込日付	09 年 12 月 18 日
物質名	144-3-036		
分子式	$C_{27}H_{26}FN_5O_7 \cdot HCl$	KCL No.	
構造式（又ハ，分子式・含有元素名）	 (-)-form	M. P. : 211°C	
		B. P. :	
		昇華性 :	
		吸湿性 :	

	C	H	N	O	S	X	M·W
calcd (%)	55.15	4.63	11.91				587.98
found (%)	54.89	4.35	11.76				

分析後の所見，分析日付 12/18 H Ohashi	Note No. 分析番号 : 1605

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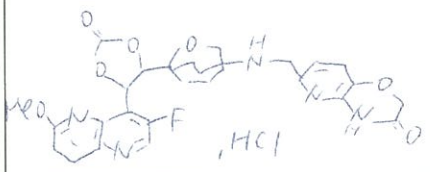
Compound (+)-25

元 素 分 析 報 告 書

氏 名	竹内智子 殿	申込日付	09 年 12 月 28 日
物質名	144-3-040		
分子式	$C_{27}H_{26}FN_5O_7 \cdot HCl$	KCL No.	
構造式（又ハ，分子式・含有元素名）	(+)-form 	M. P. :	
		B. P. :	
		昇華性 :	
		吸湿性 :	

	C	H	N	O	S	X	M·W
calcd (%)	55.15	4.63	11.91				587.98
found (%)	55.01	4.64	11.83				

分析後の所見. 分析日付	Note No.
12/28 H. Tsuruta	分析番号 : 1636

杏林製薬㈱ 創薬研究所

(±)-7 LC Chart

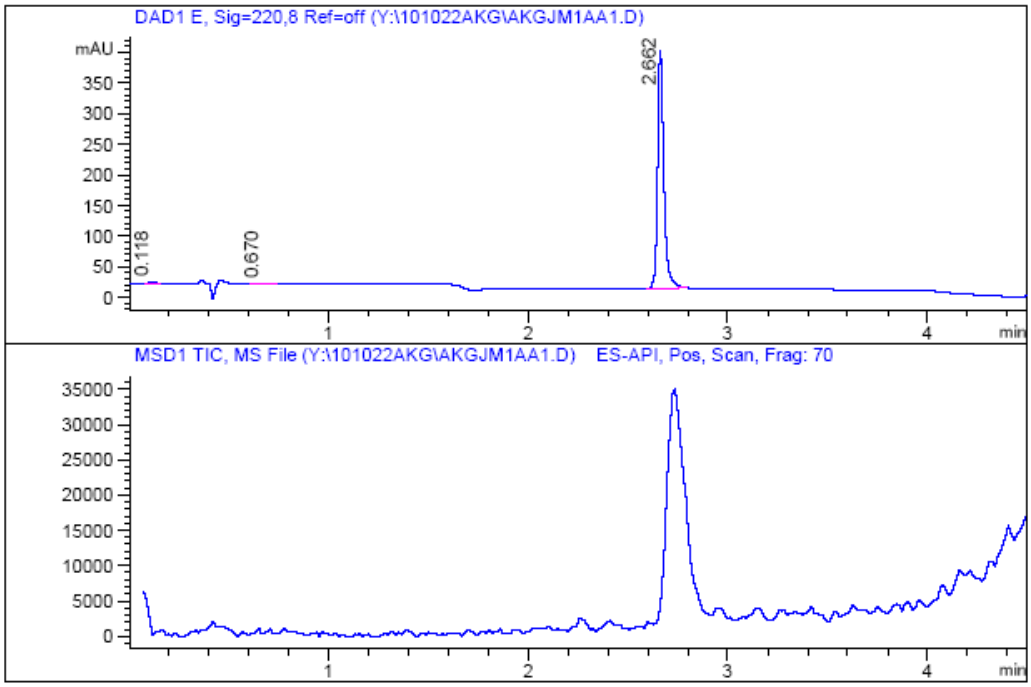
Mobile phase: A: 0.04% TFA in water. B: 0.02% TFA in acetonitrile.

Gradient: 0% B to 100% B in 3.4 minutes and holding at 100% B for 0.6 minutes, then drop back to 0% B in 0.01 min and keep for 0.49 minutes.

Column: Agilent TC-C18, 2.1*50mm, 5μm.

Flow rate: 0.6 ml/min

Temperature: 40 ℃



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Report

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Signal 1 : DAD1 E, Sig=220,8 Ref=off

Peak #	RT [min]	Area	Height	Height %	Width [min]	Area %
1	0.118	7.335	2.782	0.707	0.044	0.843
2	0.670	5.269	1.066	0.271	0.082	0.605
3	2.662	857.609	389.742	99.022	0.033	98.552

(±)-8 LC Chart

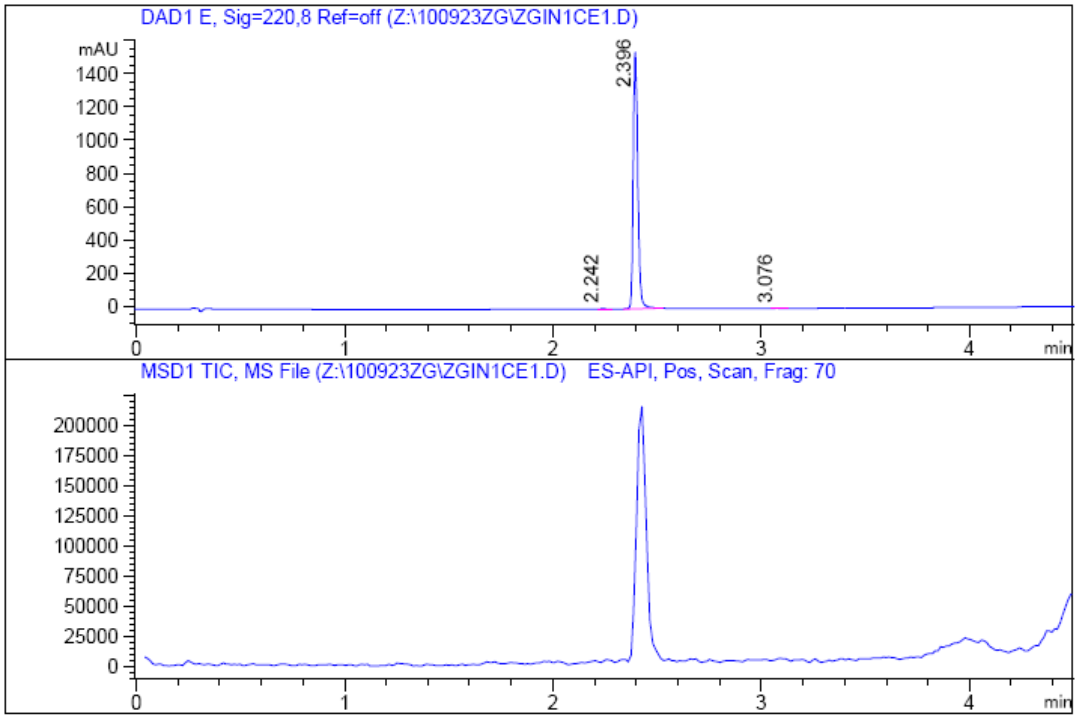
Mobile phase: A: 0.04% TFA in water. B: 0.02% TFA in acetonitrile.

Gradient: 1% B to 100% B in 3.4 minutes and holding at 100% B for 0.6 minutes, then drop back to 1% B in 0.01 min and keep for 0.49 minutes.

Column: Agilent TC-C18, 2.1*50 mm, 5 μm.

Flow rate: 0.8 ml/min

Temperature: 50 ℃



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Report

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Signal 1 : DAD1 E, Sig=220,8 Ref=off

Peak #	RT [min]	Area	Height	Height %	Width [min]	Area %
1	2.242	3.070	2.524	0.163	0.019	0.130
2	2.396	2359.612	1545.041	99.732	0.024	99.745
3	3.076	2.951	1.629	0.105	0.028	0.125

(±)-9 LC Chart

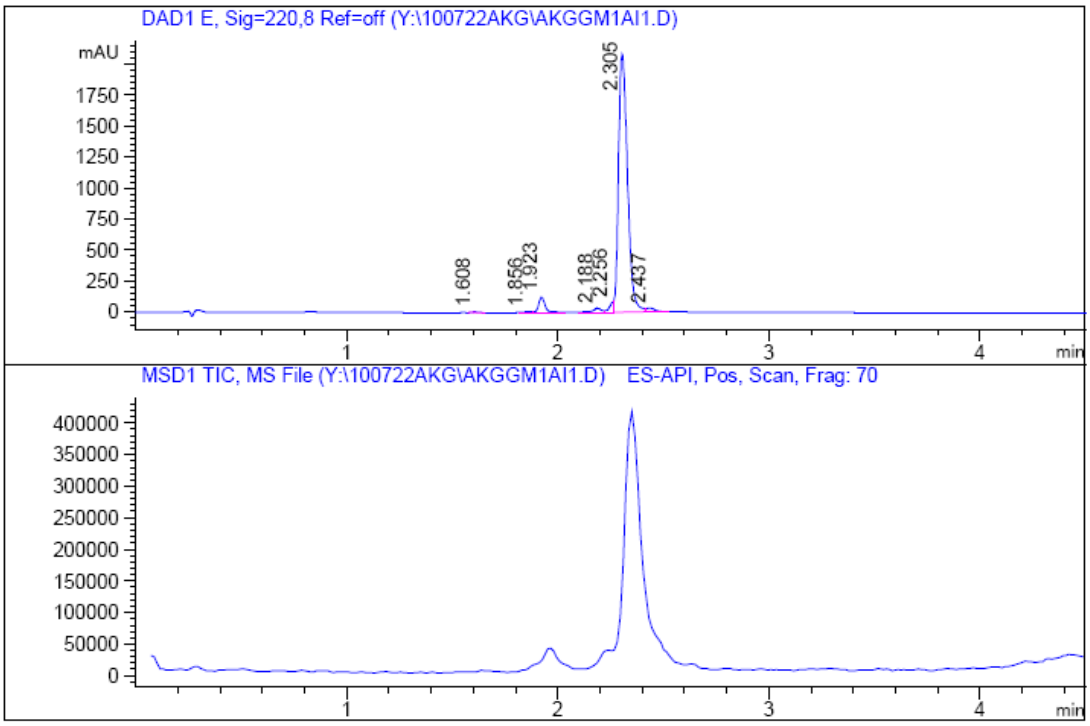
Mobile phase: A: 0.04% TFA in water. B: 0.02% TFA in acetonitrile.

Gradient: 1% B to 100% B in 3.4 minutes and holding at 100% B for 0.6 minutes, then drop back to 1% B in 0.01 min and keep for 0.49 minutes.

Column: Agilent TC-C18, 2.1*50 mm, 5 μm.

Flow rate: 0.8 ml/min

Temperature: 50 ℃



Report

Signal 1 : DAD1 E, Sig=220,8 Ref=off

Peak #	RT [min]	Area	Height	Height %	Width [min]	Area %
1	1.608	10.600	5.903	0.251	0.028	0.157
2	1.856	13.402	5.788	0.247	0.033	0.199
3	1.923	259.164	122.277	5.209	0.033	3.846
4	2.188	83.333	30.881	1.316	0.040	1.237
5	2.256	103.418	71.108	3.029	0.021	1.535
6	2.305	6180.133	2080.675	88.637	0.047	91.704
7	2.437	89.180	30.776	1.311	0.043	1.323

(±)-11 LC Chart

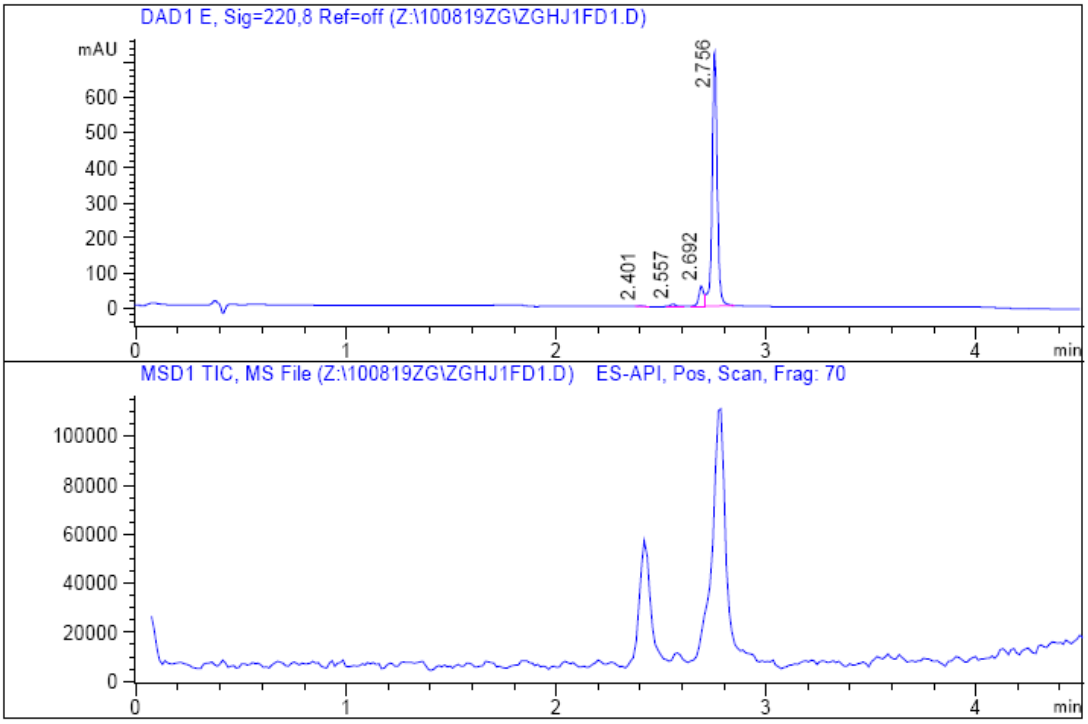
Mobile phase: A: 0.04% TFA in water. B: 0.02% TFA in acetonitrile.

Gradient: 0% B to 100% B in 3.4 minutes and holding at 100% B for 0.6 minutes, then drop back to 0% B in 0.01min and keep for 0.49 minutes.

Column: Agilent TC-C18, 2.1*50 mm, 5 μm.

Flow rate: 0.6 ml/min

Temperature: 40 ℃



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Report

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Signal 1 : DAD1 E, Sig=220,8 Ref=off

Peak #	RT [min]	Area	Height	Height %	Width [min]	Area %
1	2.401	2.694	1.909	0.242	0.022	0.202
2	2.557	11.141	6.229	0.789	0.028	0.835
3	2.692	93.302	56.485	7.158	0.024	6.989
4	2.756	1227.837	724.536	91.811	0.026	91.975

(±)-12 LC Chart

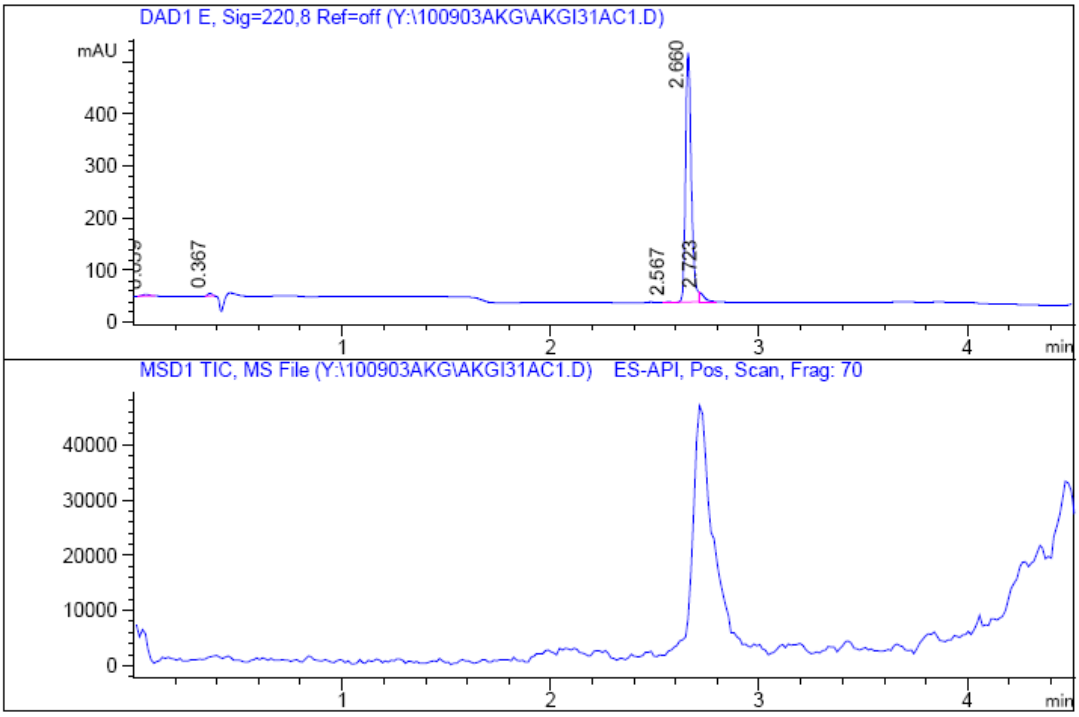
Mobile phase: A: 0.04% TFA in water. B: 0.02% TFA in acetonitrile.

Gradient: 0% B to 100% B in 3.4 minutes and holding at 100% B for 0.6 minutes, then drop back to 0% B in 0.01min and keep for 0.49 minutes.

Column: Agilent TC-C18, 2.1*50 mm, 5 μm.

Flow rate: 0.6 ml/min

Temperature: 40 ℃



Report

Signal 1 : DAD1 E, Sig=220,8 Ref=off

Peak #	RT [min]	Area	Height	Height %	Width [min]	Area %
1	0.059	6.466	2.621	0.519	0.041	0.664
2	0.367	7.511	5.693	1.127	0.022	0.772
3	2.567	2.012	1.250	0.248	0.026	0.207
4	2.660	925.911	478.863	94.816	0.030	95.137
5	2.723	31.339	16.615	3.290	0.028	3.220

(±)-16 LC Chart

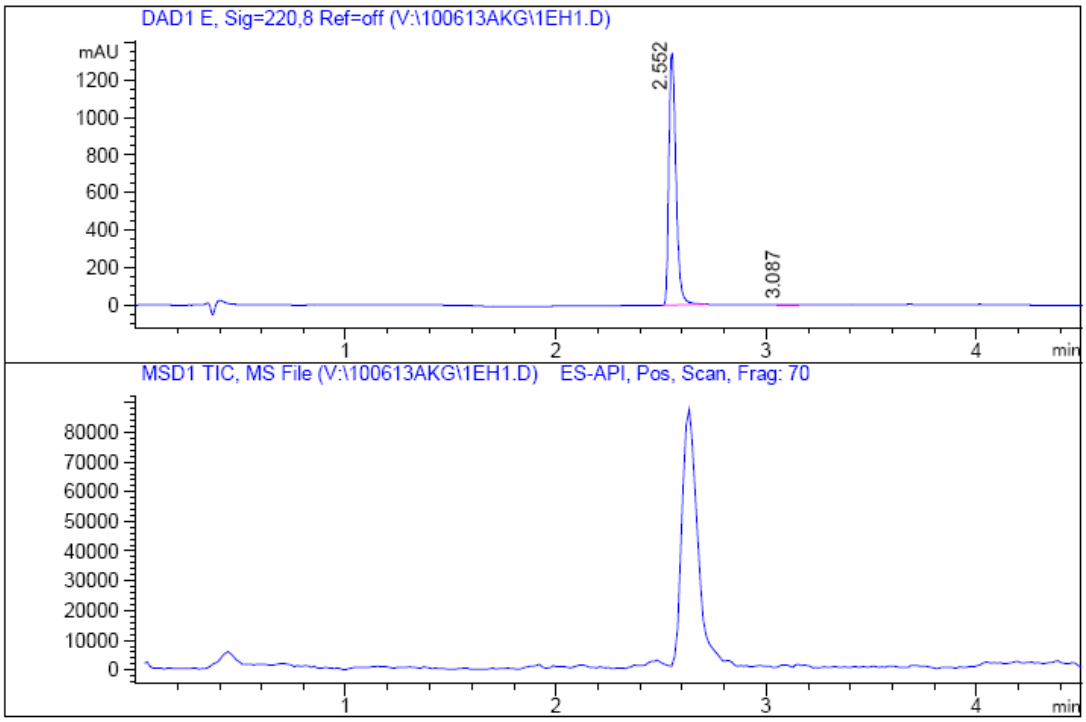
Mobile phase: A: 0.04% TFA in water. B: 0.02% TFA in acetonitrile.

Gradient: 0% B to 100% B in 3.4 minutes and holding at 100% B for 0.6 minutes, then drop back to 0% B in 0.01 min and keep for 0.49 minutes.

Column: Agilent TC-C18, 2.1*50 mm, 5 μm.

Flow rate: 0.6 ml/min

Temperature: 40 ℃



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Report

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Signal 1 : DAD1 E, Sig=220,8 Ref=off

Peak #	RT [min]	Area	Height	Height %	Width [min]	Area %
1	2.552	3158.110	1342.000	99.855	0.036	99.839
2	3.087	5.102	1.954	0.145	0.040	0.161

(±)-17 LC Chart

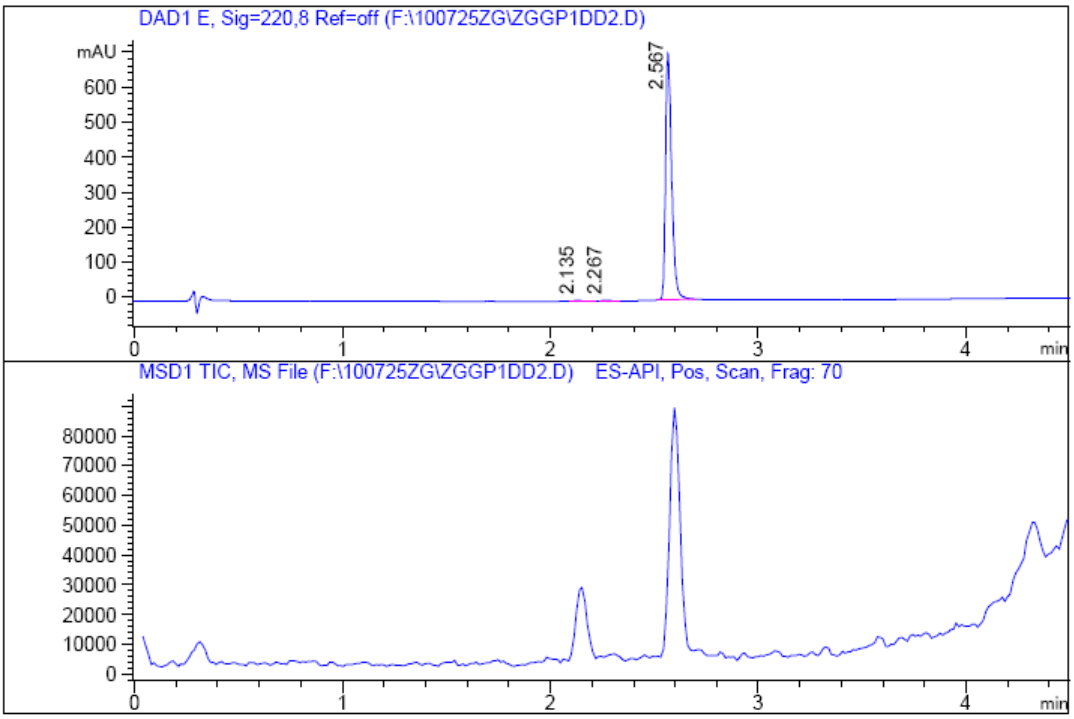
Mobile phase: A: 0.04% TFA in water. B: 0.02% TFA in acetonitrile.

Gradient: 1% B to 100% B in 3.4 minutes and holding at 100% B for 0.6 minutes, then drop back to 1% B in 0.01 min and keep for 0.49 minutes.

Column: Agilent TC-C18, 2.1*50 mm, 5 μm.

Flow rate: 0.8 ml/min

Temperature: 50 ℃



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Report

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Signal 1 : DAD1 E, Sig=220,8 Ref=off

Peak #	RT [min]	Area	Height	Height %	Width [min]	Area %
1	2.135	2.853	1.547	0.219	0.034	0.196
2	2.267	3.013	1.458	0.206	0.033	0.207
3	2.567	1452.940	704.014	99.575	0.031	99.598

18 LC Chart

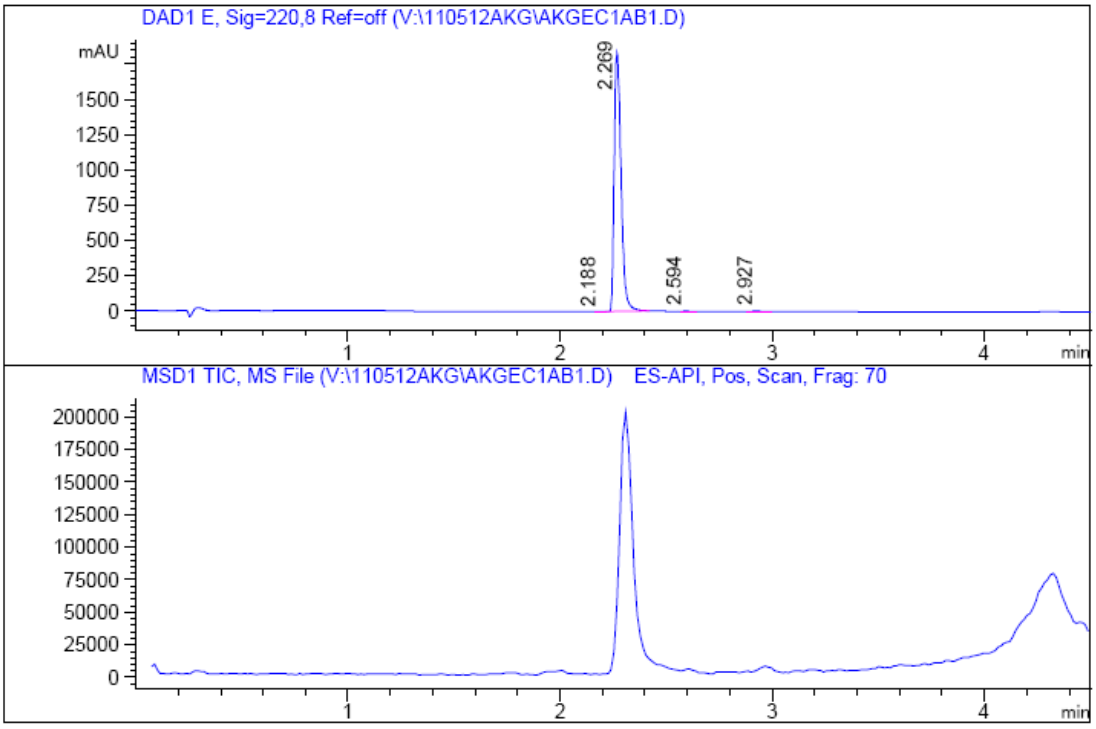
Mobile phase: A: 0.04% TFA in water. B: 0.02% TFA in acetonitrile.

Gradient: 1% B to 100% B in 3.4 minutes and holding at 100% B for 0.6 minutes, then drop back to 1% B in 0.01 min and keep for 0.49 minutes.

Column: Agilent TC-C18, 2.1*50 mm, 5 μm.

Flow rate: 0.8 ml/min

Temperature: 50 ℃



Report

Signal 1 : DAD1 E, Sig=220,8 Ref=off

Peak #	RT [min]	Area	Height	Height %	Width [min]	Area %
1	2.188	2.133	1.368	0.075	0.025	0.051
2	2.269	4131.760	1827.202	99.552	0.036	99.556
3	2.594	3.250	1.807	0.098	0.028	0.078
4	2.927	13.065	5.041	0.275	0.039	0.315

(±)-20 LC Chart

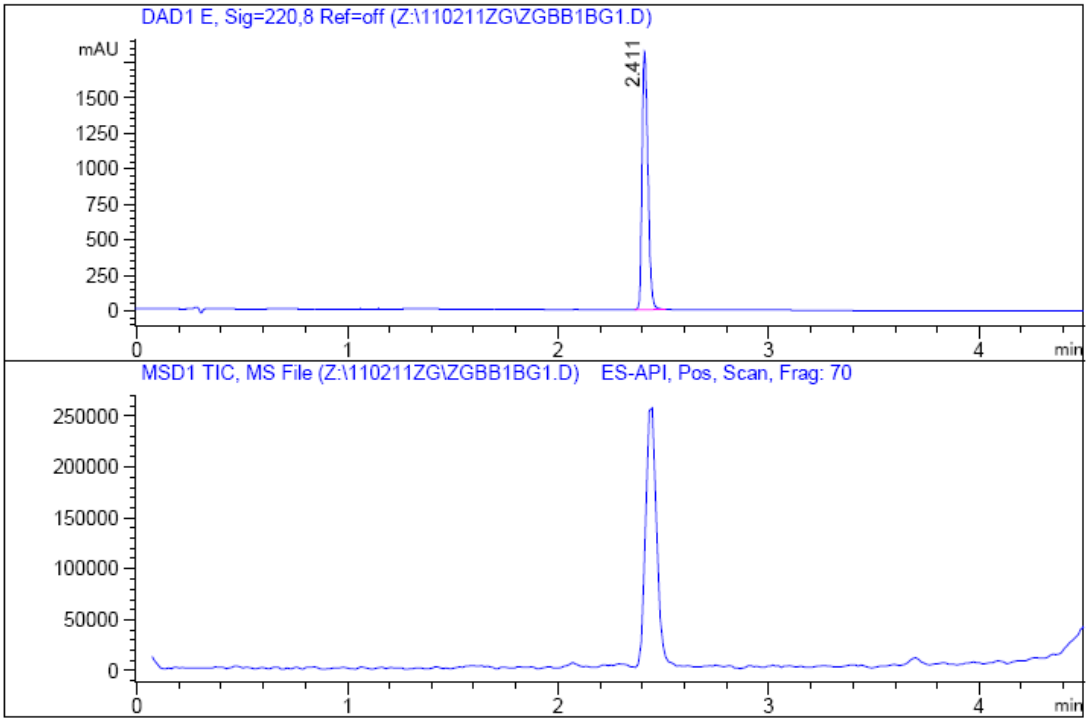
Mobile phase: A: 0.04% TFA in water. B: 0.02% TFA in acetonitrile.

Gradient: 1% B to 100% B in 3.4 minutes and holding at 100% B for 0.6 minutes, then drop back to 1% B in 0.01 min and keep for 0.49 minutes.

Column: Agilent TC-C18, 2.1*50 mm, 5 μm.

Flow rate: 0.8 ml/min

Temperature: 50℃



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Report

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Signal 1 : DAD1 E, Sig=220,8 Ref=off

Peak #	RT [min]	Area	Height	Height %	Width [min]	Area %
1	2.411	3523.996	1821.404	100.000	0.031	100.000

(±)-21 LC Chart

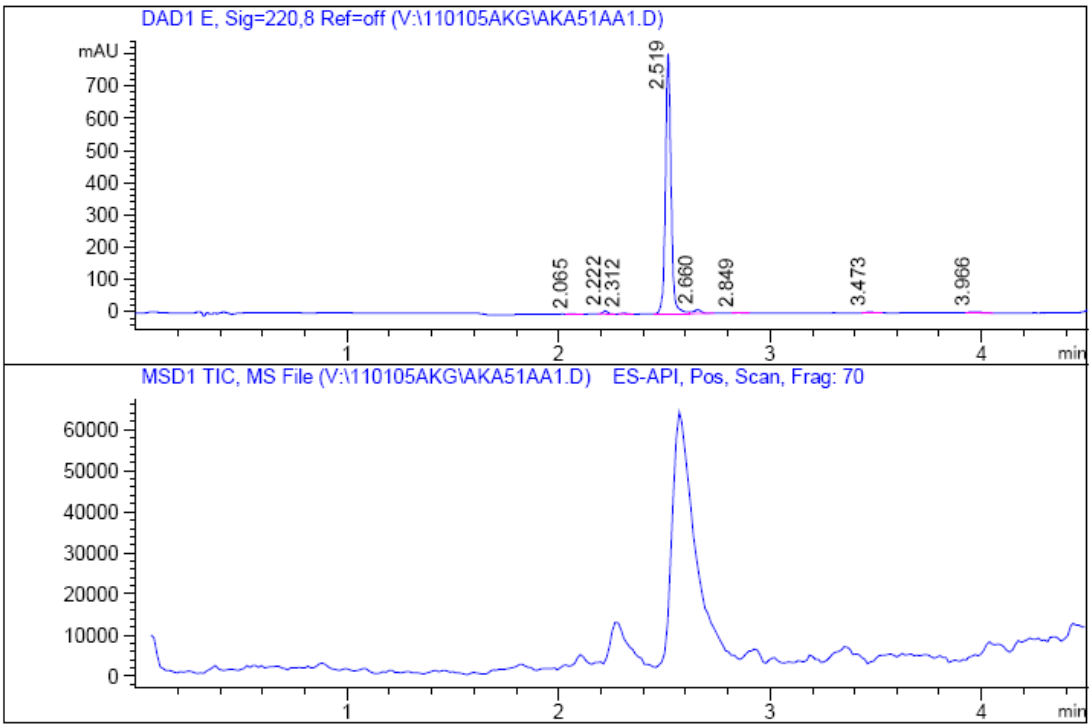
Mobile phase: A: 0.04% TFA in water. B: 0.02% TFA in acetonitrile.

Gradient: 0% B to 100% B in 3.4 minutes and holding at 100% B for 0.6 minutes, then drop back to 0% B in 0.01 min and keep for 0.49 minutes.

Column: Agilent TC-C18, 2.1*50 mm, 5 μm.

Flow rate: 0.6 ml/min

Temperature: 40 ℃



Report

Signal 1 : DAD1 E, Sig=220,8 Ref=off

Peak #	RT [min]	Area	Height	Height %	Width [min]	Area %
1	2.065	2.466	1.655	0.197	0.024	0.159
2	2.222	16.119	9.514	1.132	0.026	1.040
3	2.312	4.887	3.143	0.374	0.024	0.315
4	2.519	1475.009	806.922	96.007	0.028	95.189
5	2.660	30.664	11.786	1.402	0.037	1.979
6	2.849	3.602	1.699	0.202	0.032	0.232
7	3.473	5.322	2.716	0.323	0.031	0.343
8	3.966	11.489	3.043	0.362	0.057	0.741

(±)-22 LC Chart

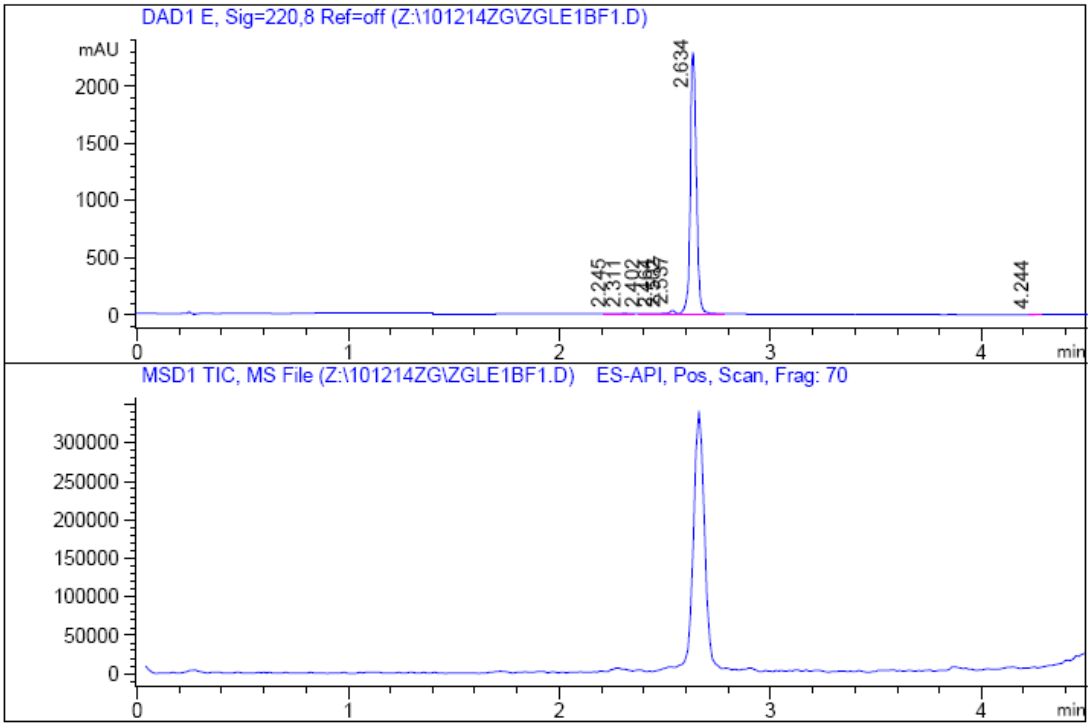
Mobile phase: A: 0.04% TFA in water. B: 0.02% TFA in acetonitrile.

Gradient: 1% B to 100% B in 3.4 minutes and holding at 100% B for 0.6 minutes, then drop back to 1% B in 0.01min and keep for 0.49 minutes.

Column: Agilent TC-C18, 2.1*50 mm, 5 μm.

Flow rate: 0.8 ml/min

Temperature: 50 ℃



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Report

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Signal 1 : DAD1 E, Sig=220,8 Ref=off

Peak #	RT [min]	Area	Height	Height %	Width [min]	Area %
1	2.245	4.653	2.725	0.116	0.025	0.100
2	2.311	12.877	8.375	0.357	0.023	0.278
3	2.402	3.341	2.226	0.095	0.023	0.072
4	2.464	5.544	4.068	0.173	0.021	0.120
5	2.502	12.869	8.857	0.378	0.022	0.277
6	2.537	49.215	30.122	1.284	0.025	1.061
7	2.634	4548.890	2288.327	97.552	0.031	98.064
8	4.244	1.314	1.054	0.045	0.020	0.028

(±)-23 LC Chart

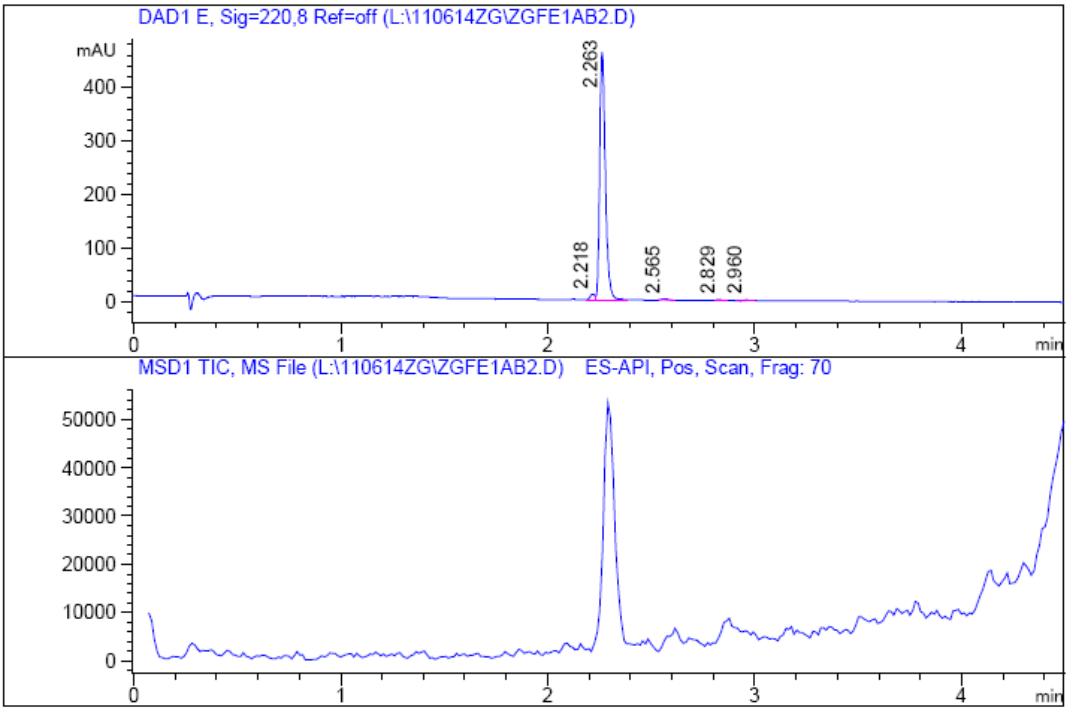
Mobile phase: A: 0.04% TFA in water. B: 0.02% TFA in acetonitrile.

Gradient: 1% B to 100% B in 3.4 minutes and holding at 100% B for 0.6 minutes, then drop back to 1% B in 0.01min and keep for 0.49 minutes.

Column: Agilent TC-C18, 2.1*50 mm, 5 μm.

Flow rate: 0.8 ml/min

Temperature: 50 ℃



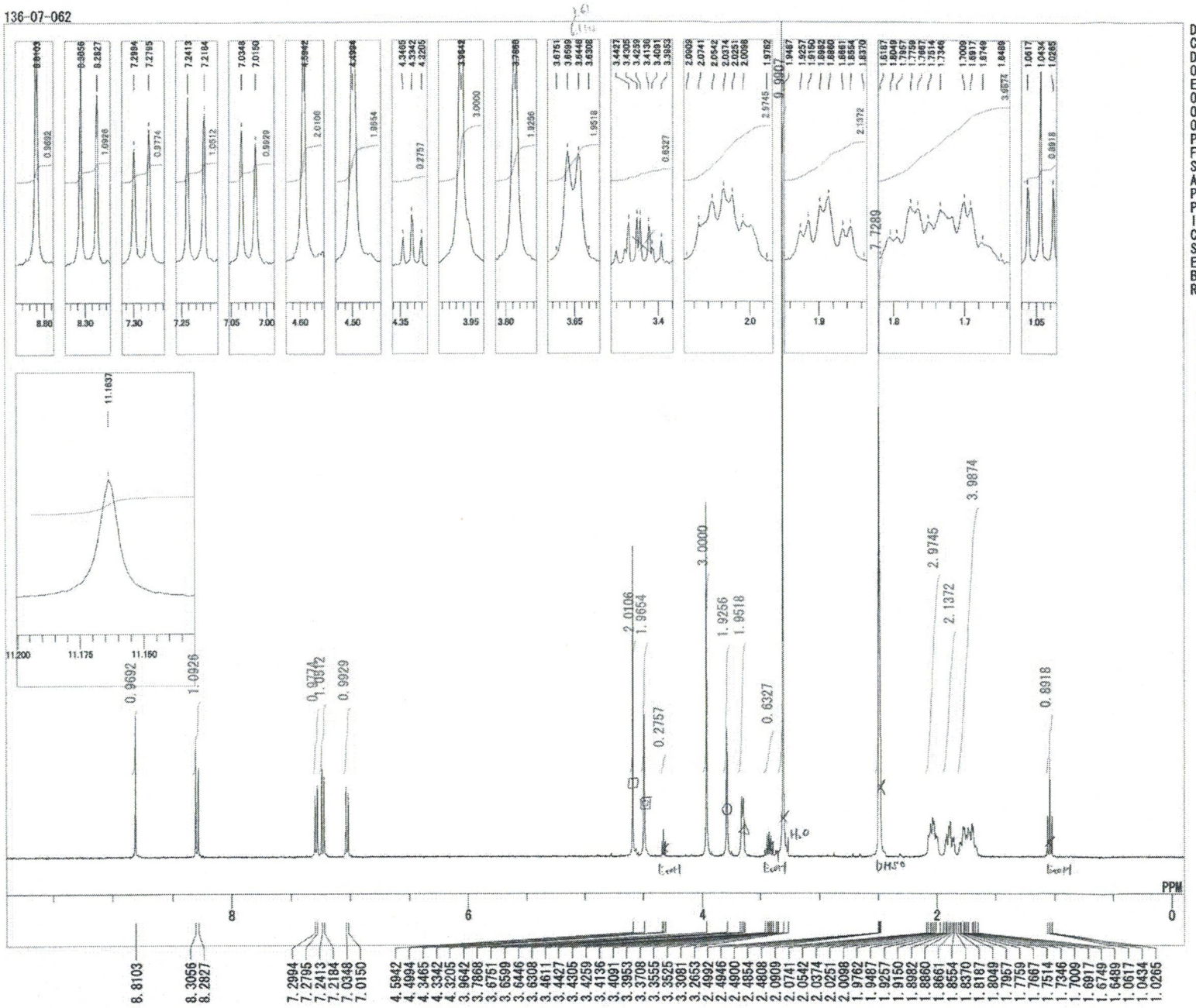
Report

Signal 1 : DAD1 E, Sig=220,8 Ref=off

Peak #	RT [min]	Area	Height	Height %	Width [min]	Area %
1	2.218	15.724	10.513	2.200	0.025	1.758
2	2.263	870.000	462.619	96.811	0.031	97.291
3	2.565	3.864	2.222	0.465	0.028	0.432
4	2.829	1.903	1.255	0.263	0.025	0.213
5	2.960	2.738	1.249	0.261	0.037	0.306

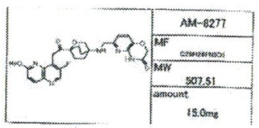
Compound 5

136-07-062



```
DFILE   F:¥ONMRチャート¥柴田¥shibata¥
COMNT   136-07-062
DATIM   29-03-2010 09:27:35
OBNUC   1H
EXMOD   single_pulse.ex2
OBFRQ         399.78 MHz
OBSET           4.19 KHz
OBFIN           7.29 Hz
POINT          20970
FREQU       12820.12 Hz
SCANS             32
ACQTM          1.6358 sec
PD             5.0000 sec
PW1            6.13 usec
IRNUC   1H
CTEMP          23.7 c
SLVNT   DMSO
EXREF          2.49 ppm
BF             0.12 Hz
RGAIN            40
```

1H-NMR (DMSO-d6) δ:
8.81 (1H, s),
8.29 (1H, d, J = 9.2 Hz),
7.29 (1H, d, J = 7.9 Hz),
7.23 (1H, d, J = 9.2 Hz),
7.02 (1H, d, J = 7.9 Hz),
4.59 (2H, s),
4.50 (2H, s),
4.33 (0H, t, J = 5.2 Hz),
3.96 (3H, s),
3.79 (2H, s),
3.65 (2H, q, J = 5.9 Hz),
3.46-3.40 (1H, m),
3.31 (10H, s),
2.50-2.48 (8H, m),
2.09-1.98 (3H, m),
1.89 (2H, ddd, J = 24.3, 12.1, 7.8
1.82-1.65 (4H, m),
1.04 (1H, t, J = 7.0 Hz).

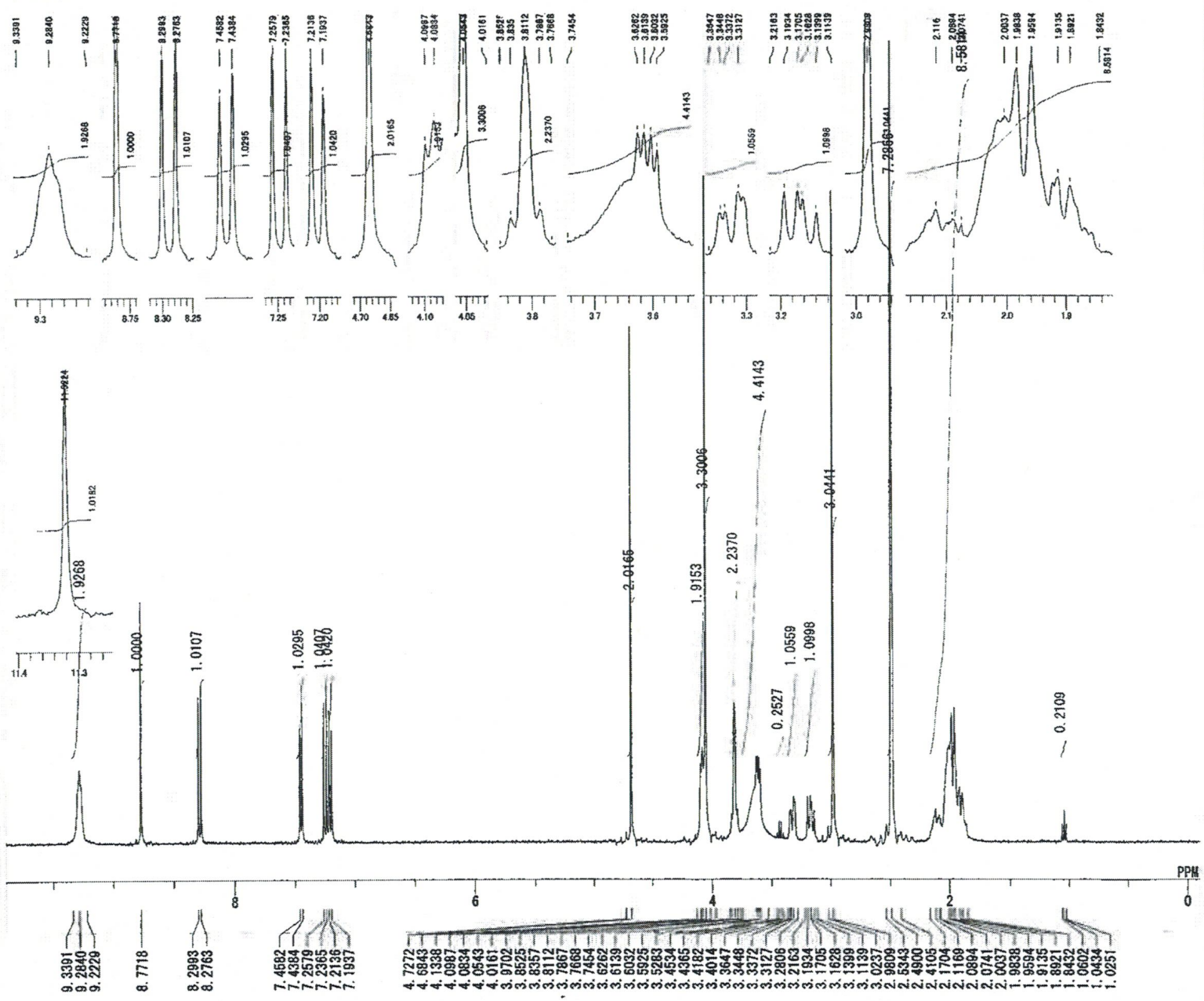


EtOH: 0.5 (three)

10.03.29

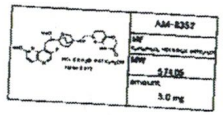
Compound (−)-6

136-08-024



```
DFILE  F:¥ONMRチャート¥柴田¥shibata¥
COMNT  136-08-024
DATIM  08-06-2010 15:52:50
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        399.78 MHz
OBSET          4.19 KHz
OBFIN          7.29 Hz
POINT         26213
FREQU      16025.40 Hz
SCANS            32
ACQTM          1.6358 sec
PD             5.0000 sec
PW1              3.00 usec
IRNUC  1H
GTEMP           22.2 c
SLVNT  DMSO
EXREF          2.49 ppm
BF             0.12 Hz
RGAIN            64
```

1H-NMR (DMSO-d6) δ:
9.28 (2H, t, J = 23.2 Hz),
8.77 (1H, s),
8.29 (1H, d, J = 9.2 Hz),
7.45 (1H, d, J = 7.9 Hz),
7.25 (1H, d, J = 8.6 Hz),
7.20 (1H, d, J = 7.9 Hz),
4.68 (2H, s),
4.09 (2H, d, J = 6.1 Hz),
4.04 (3H, d, J = 15.3 Hz),
3.85-3.77 (2H, m),
3.75-3.59 (4H, m),
3.43 (0H, q, J = 6.9 Hz),
3.34 (1H, dd, J = 11.9, 8.9 Hz),
3.17 (1H, dt, J = 21.8, 9.5 Hz),
2.98 (3H, s),
2.49 (7H, s),
1.98 (9H, tt, J = 39.4, 10.5 Hz),
1.04 (0H, t, J = 7.0 Hz).



10, 06, 08
柴田 誠

Compound (±)-7

(±)-7 ^{1}H-NMR Chart

Compound (±)-8

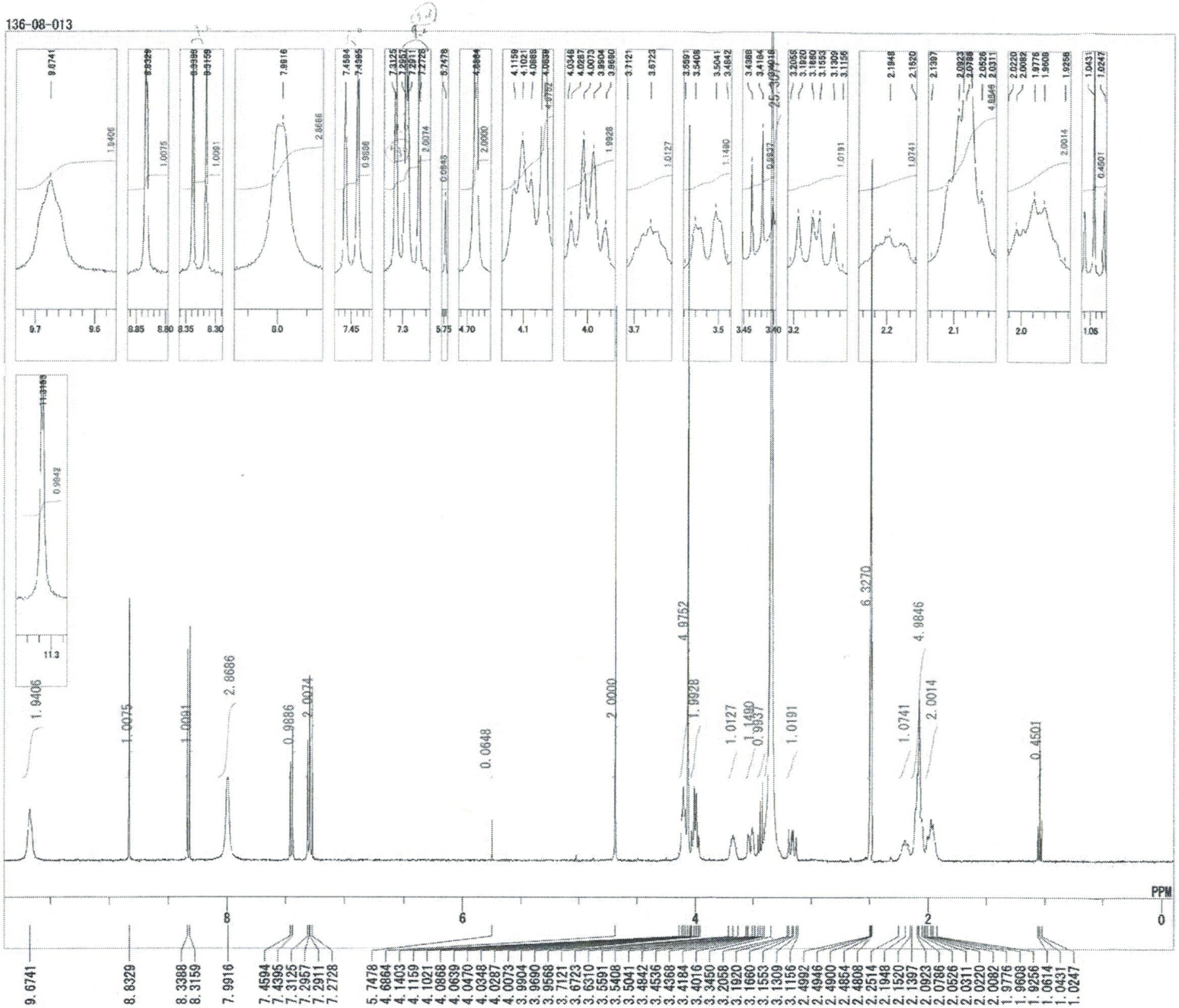
(±)-**8** ^{1}H-NMR Chart

Compound (±)-9

(±)-9 ^{1}H-NMR Chart

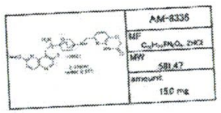
Compound (−)-10

136-08-013



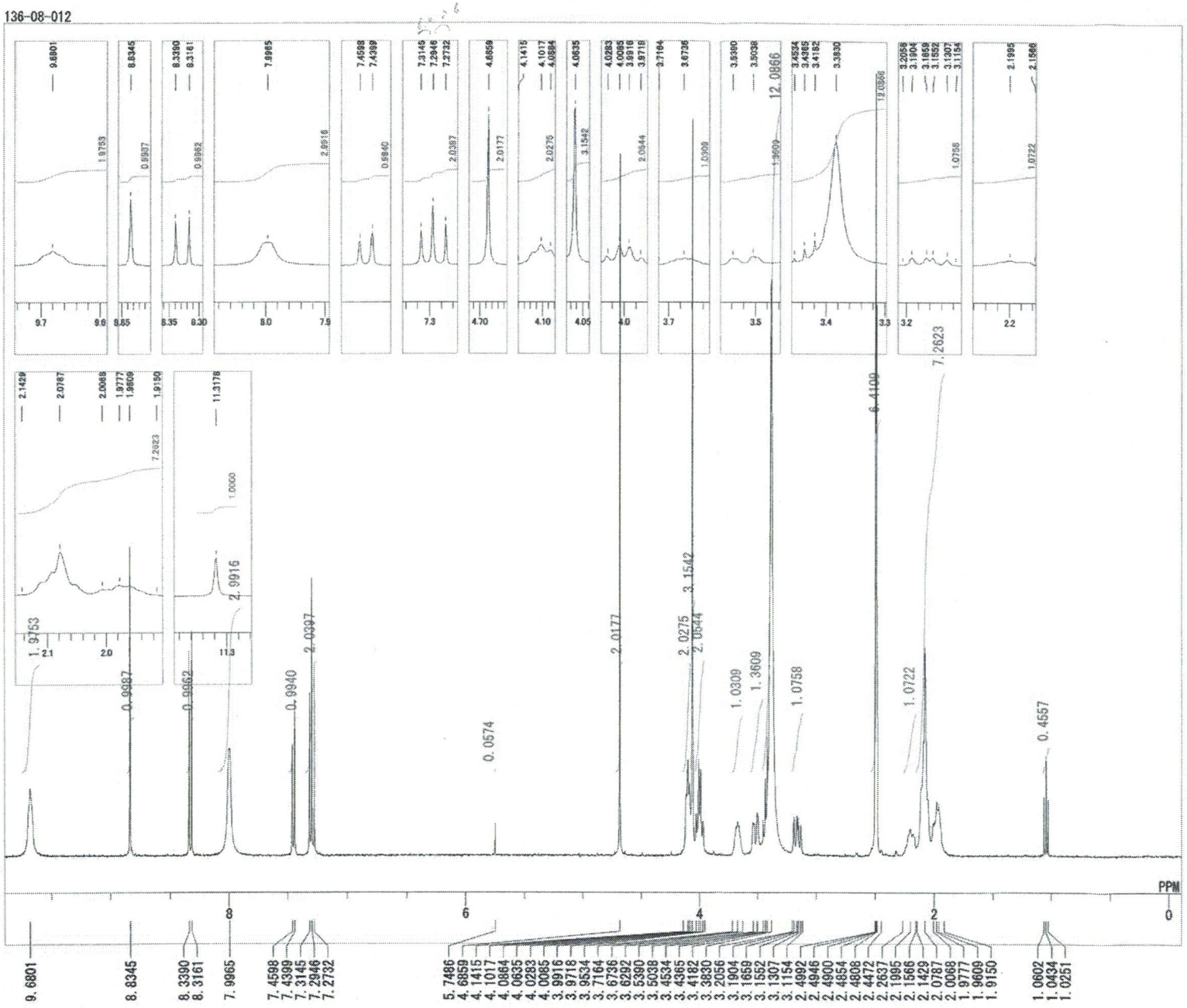
```
DFILE  F:¥ONMRチャート¥柴田¥shibata¥
COMNT  136-08-013
DATIM  27-05-2010 12:53:11
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        395.88 MHz
OBSET          6.28 KHz
OBFIN          0.87 Hz
POINT         26213
FREQU      15872.77 Hz
SCANS            16
ACQTM        1.6515 sec
PD           5.0000 sec
PW1            5.10 usec
IRNUC  1H
CTEMP         22.4 c
SLVNT  DMSO
EXREF         2.49 ppm
BF             0.12 Hz
RGAIN            38
```

1H-NMR (DMSO-d6) δ:
9.67 (2H, s),
8.83 (1H, s),
8.33 (1H, d, J = 9.1 Hz),
7.99 (3H, s),
7.45 (1H, d, J = 7.9 Hz),
7.29 (2H, dd, J = 8.8, 7.0 Hz),
5.75 (OH, s),
4.69 (2H, s),
4.09 (5H, q, J = 6.9 Hz),
4.00 (2H, dt, J = 20.4, 6.1 Hz),
3.69 (1H, d, J = 15.7 Hz),
3.52 (1H, dd, J = 22.1, 7.6 Hz),
3.43 (1H, q, J = 6.9 Hz),
3.34 (25H, s),
3.16 (1H, td, J = 15.0, 5.2 Hz),
2.50-2.48 (6H, m),
2.17 (1H, d, J = 17.0 Hz),
2.14-2.03 (5H, m),
2.02-1.93 (2H, m),
1.04 (OH, t, J = 7.3 Hz).



'10, 05, 28
柴田 成

Compound (+)-10

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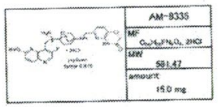
DFILE   F:¥ONMRチャート¥柴田¥shibata¥
COMNT   136-08-012
DATIM   24-05-2010 18:47:39
OBNUC   1H
EXMOD   single_pulse.ex2
OBFRQ         399.78 MHz
OBSET           4.19 KHz
OBFIN           7.29 Hz
POINT          20969
FREQU       12820.12 Hz
SCANS             32
ACQTM           1.6358 sec
PD              5.0000 sec
PW1             6.13 usec
IRNUC   1H
CTEMP          22.0 c
SLVNT   DMSO
EXREF           2.49 ppm
BF              0.12 Hz
RGAIN             40
```

1H-NMR (DMSO-d6) δ:
9.68 (2H, s),
8.83 (1H, s),
8.33 (1H, d, J = 9.2 Hz),
8.00 (3H, s),
7.45 (1H, d, J = 7.9 Hz),
7.29 (2H, t, J = 8.3 Hz),
5.75 (OH, s),
4.69 (2H, s),
4.11 (2H, t, J = 11.0 Hz),
4.06 (3H, s),
4.00 (2H, q, J = 7.5 Hz),
3.67 (1H, t, J = 17.4 Hz),
3.52 (1H, d, J = 14.1 Hz),
3.42 (12H, q, J = 9.4 Hz),
3.16 (1H, td, J = 15.0, 5.5 Hz),
2.47 (6H, td, J = 6.6, 5.7 Hz),
2.18 (1H, d, J = 17.1 Hz),
2.03 (7H, dt, J = 49.9, 19.9 Hz),
1.04 (OH, t, J = 7.0 Hz).

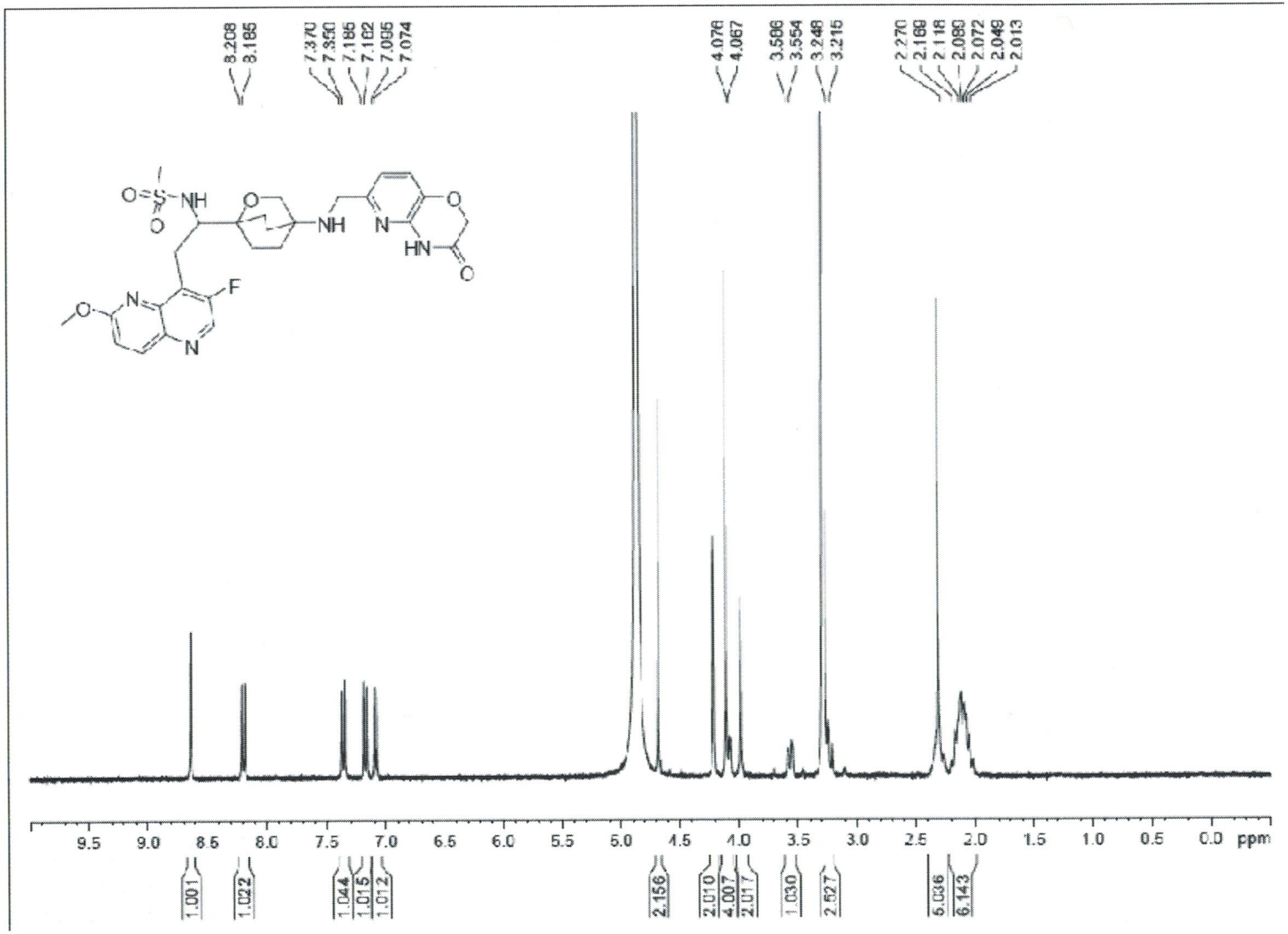


'10, 05, 24
柴田 隆

Compound (±)-11

(±)-11 ^{1}H-NMR Chart

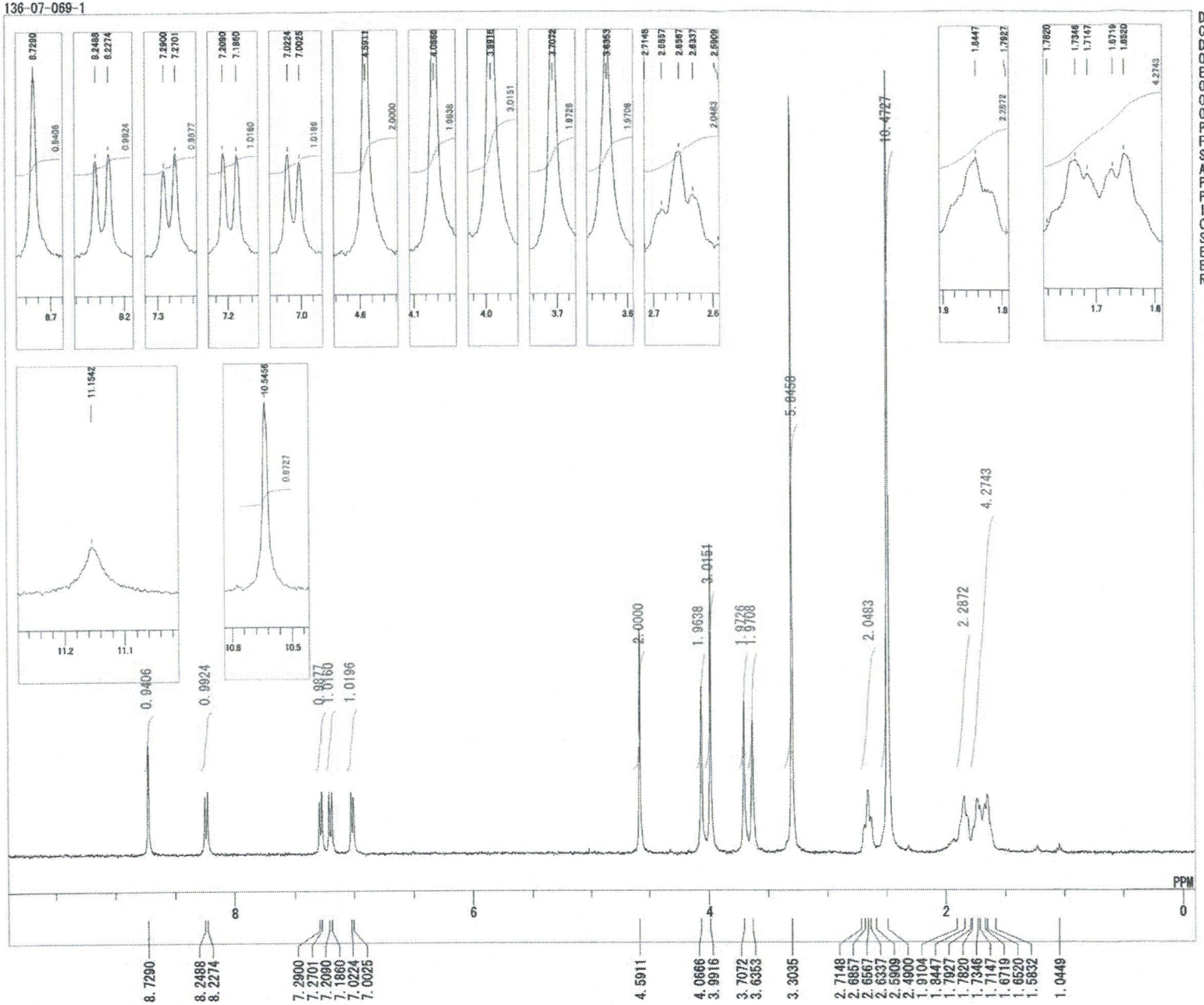
Compound (±)-12



(±)-**12** ^{1}H-NMR Chart

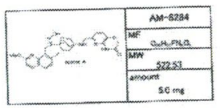
Compound 13

136-07-069-1



DFILE F:¥ONMRチャート¥柴田¥shibata¥:
COMNT 136-07-069-1
DATIM 09-04-2010 11:46:13
OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 399.78 MHz
OBSET 4.19 KHz
OBFIN 7.29 Hz
POINT 26213
FREQU 16025.40 Hz
SCANS 32
ACQTM 1.6358 sec
PD 5.0000 sec
PW1 6.13 usec
IRNUC 1H
CTEMP 24.7 c
SLVNT DMSO
EXREF 2.49 ppm
BF 0.52 Hz
RGAIN 40

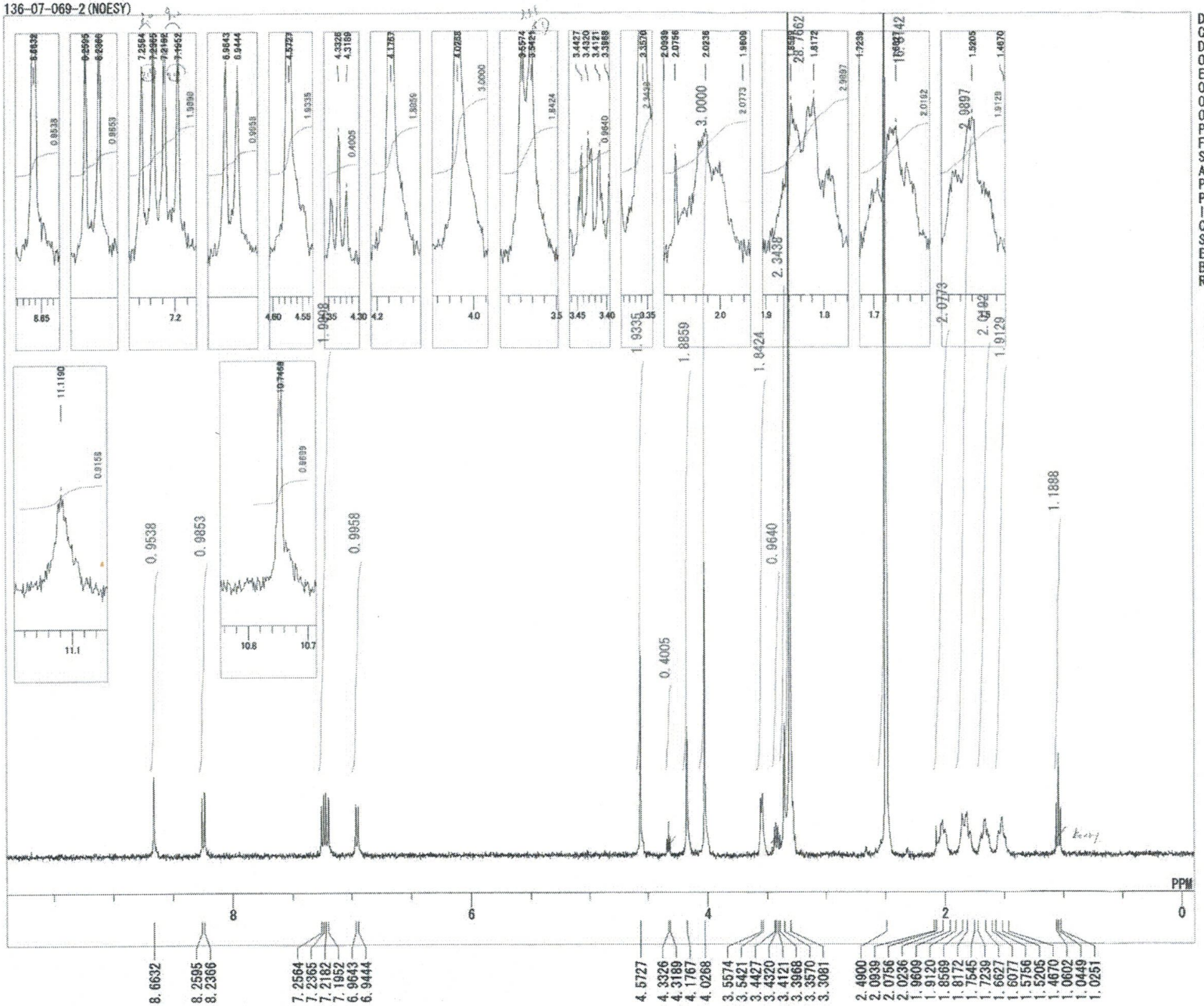
1H-NMR (DMSO-d6) δ:
8.73 (1H, s),
8.24 (1H, d, J = 8.6 Hz),
7.28 (1H, d, J = 7.9 Hz),
7.20 (1H, d, J = 9.2 Hz),
7.01 (1H, d, J = 7.9 Hz),
4.59 (2H, s),
4.07 (2H, s),
3.99 (3H, s),
3.71 (2H, s),
3.64 (2H, s),
3.30 (6H, s),
2.71-2.59 (2H, m),
2.49 (10H, s),
1.82 (2H, d, J = 20.8 Hz),
1.78-1.65 (4H, m).



10.04.09

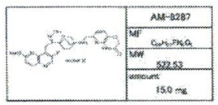
柴田 成

Compound 14




```
DFILE  F:¥ONMRチャート¥柴田¥shibata¥
COMNT  136-07-069-2(NOESY)
DATIM  10-04-2010 18:55:19
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        399.78 MHz
OBSET          4.19 KHz
OBFIN          7.29 Hz
POINT         26213
FREQU      16025.40 Hz
SCANS            16
ACQTM          1.6358 sec
PD             5.0000 sec
PW1            6.13 usec
IRNUC  1H
CTEMP         24.0 c
SLVNT  DMSO
EXREF          2.49 ppm
BF             0.12 Hz
RGAIN            40
```

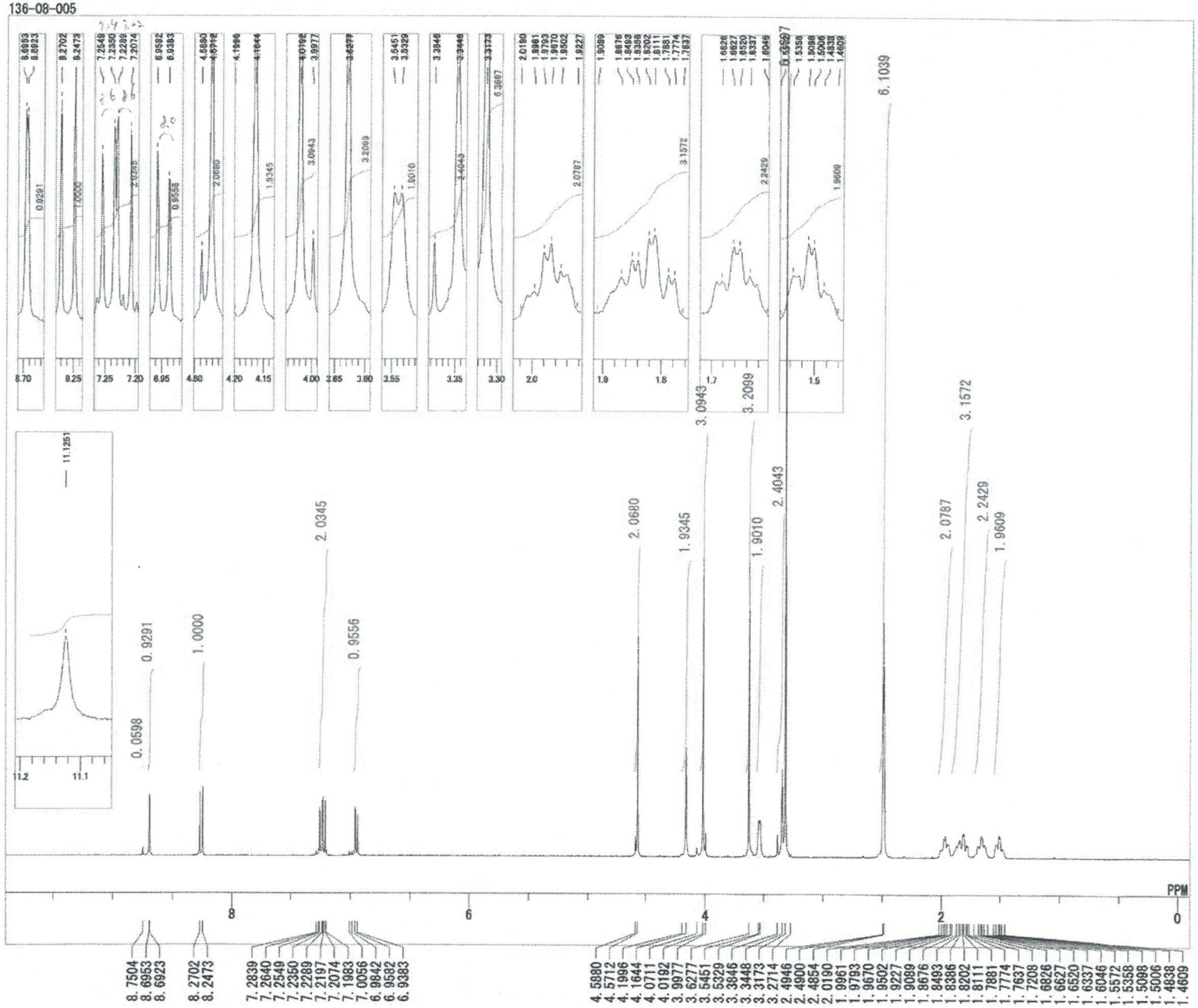
1H-NMR (DMSO-d6) δ:
8.66 (1H, s),
8.25 (1H, d, J = 9.2 Hz),
7.23 (2H, q, J = 8.2 Hz),
6.95 (1H, d, J = 7.9 Hz),
4.57 (2H, s),
4.33 (OH, d, J = 5.5 Hz),
4.18 (2H, s),
4.03 (3H, s),
3.55 (2H, d, J = 6.1 Hz),
3.42 (1H, dd, J = 13.1, 5.2 Hz),
3.36 (2H, s),
3.31 (29H, s),
2.49 (17H, s),
2.03 (2H, dd, J = 37.0, 16.2 Hz),
1.84 (3H, d, J = 15.9 Hz),
1.67 (2H, t, J = 23.2 Hz),
1.49 (2H, d, J = 21.4 Hz),
1.04 (1H, t, J = 7.0 Hz).



10,04.10

Compound 15

136-08-005



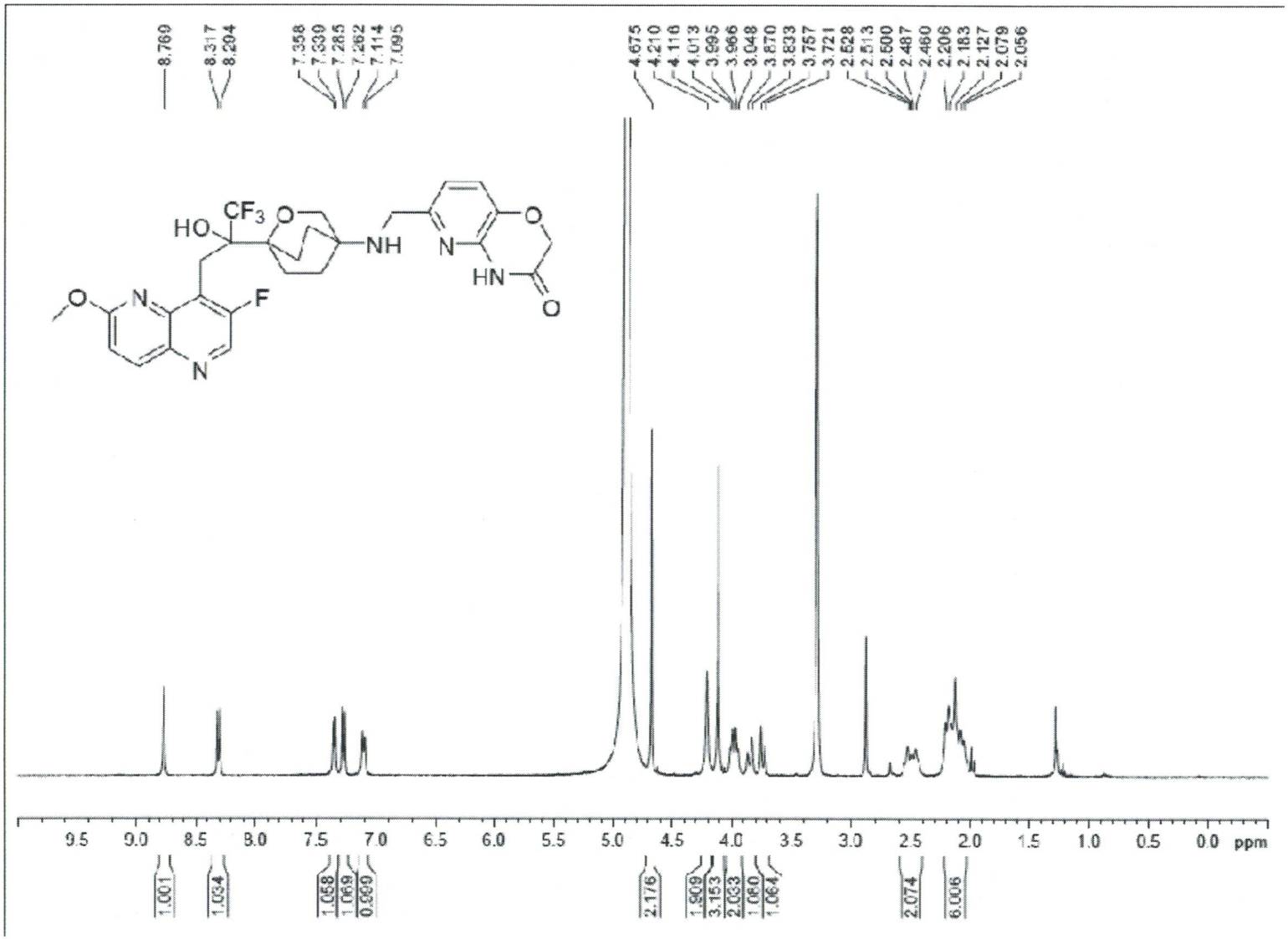
'10, 05, 25

柴田 成

Compound (±)-16

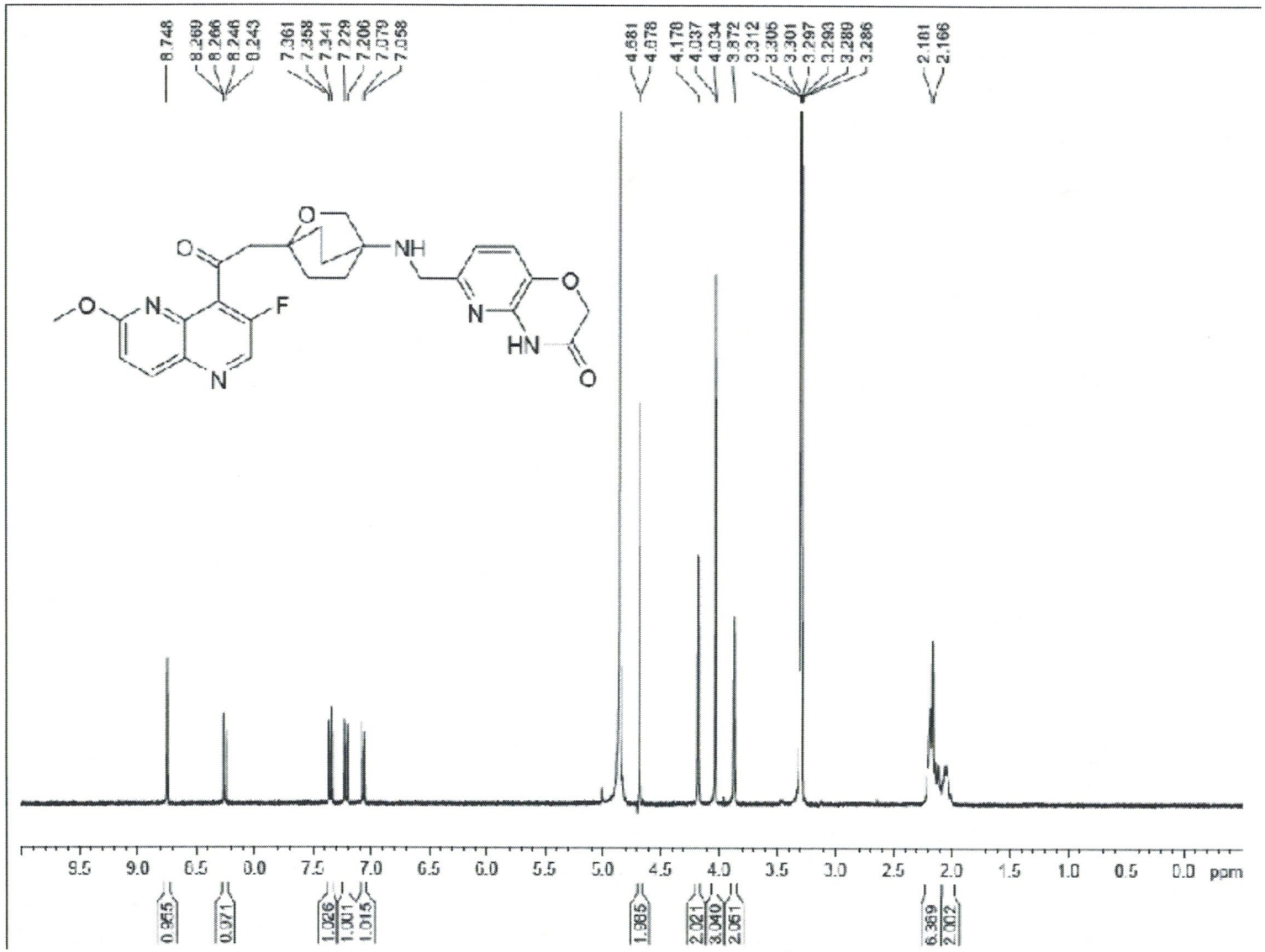
(±)-**16** ^{1}H-NMR Chart

Compound (±)-17



(±)-**17** ^{1}H-NMR Chart

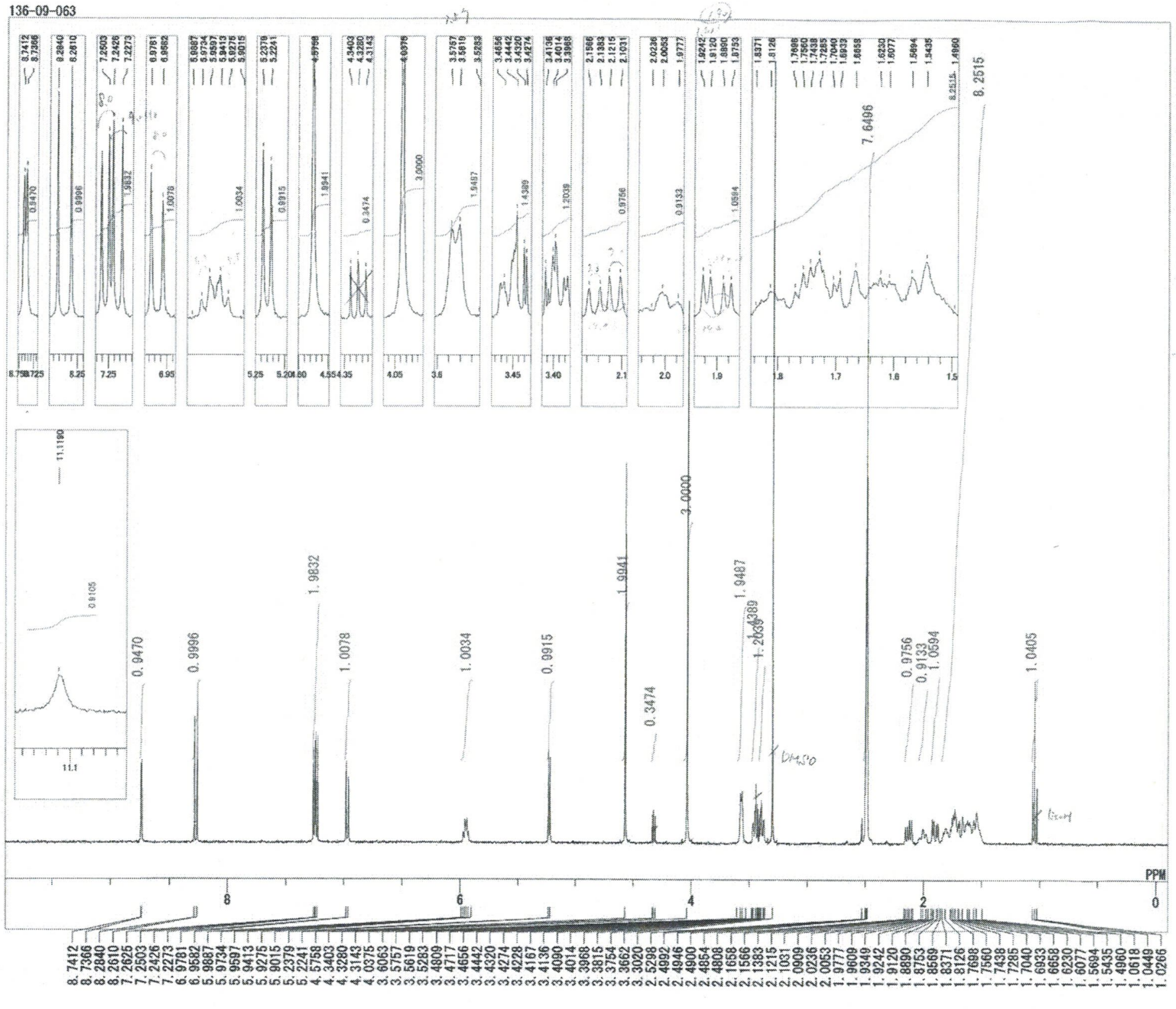
Compound 18



18 ^{1}H-NMR Chart

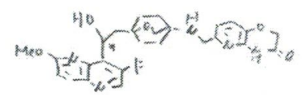
Compound (−)-19

136-09-063



```
DFILE  C:¥ALICE¥DATA¥shibata136-09-0
COMNT  136-09-063
DATIM  18-11-2010 18:44:28
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        399.78 MHz
OBSET          4.19 KHz
OBFIN          7.29 Hz
POINT         32768
FREQU      20032.05 Hz
SCANS            16
ACQTM        1.6358 sec
PD           5.0000 sec
PW1             5.62 usec
IRNUC  1H
CTEMP         24.9 c
SLVNT  DMSO
EXREF          2.49 ppm
BF             0.12 Hz
RGAIN            40
```

1H-NMR (DMSO-D6) δ:
8.74 (1H, d, J = 1.8 Hz),
8.27 (1H, d, J = 9.2 Hz),
~~7.24 (2H, q, J = 4.7 Hz),~~
6.97 (1H, d, J = 7.9 Hz),
5.95 (1H, td, J = 13.3, 7.9 Hz),
5.23 (1H, d, J = 5.5 Hz),
4.58 (2H, s),
4.33 (OH, t, J = 5.2 Hz),
4.04 (3H, s),
3.55 (2H, t, J = 9.5 Hz),
3.48-3.42 (1H, m),
3.42-3.38 (1H, m),
2.50-2.48 (8H, m),
2.13 (1H, dt, J = 19.4, 5.8 Hz),
2.00 (1H, t, J = 9.2 Hz),
1.93-1.88 (1H, m),
1.84-1.50 (8H, m),
1.04 (1H, t, J = 7.0 Hz).



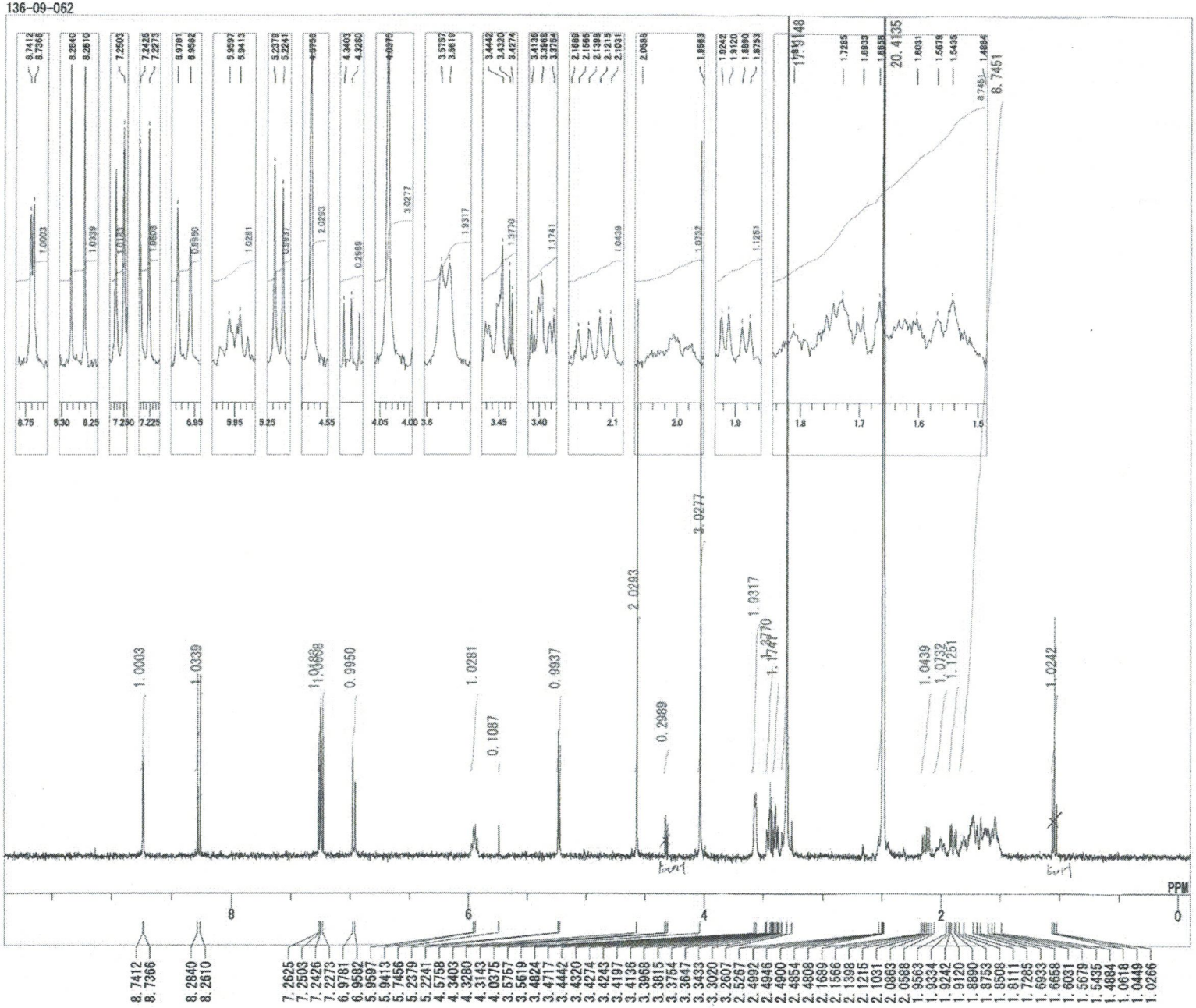
(−)-form

Exam: 0.13 (Exact)

10, 11, 18

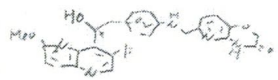
Compound (+)-19

136-09-062



```
DFILE  F:¥ONMRチャート¥柴田¥shibata¥
COMNT  136-09-062
DATIM  18-11-2010 18:35:59
OBNUC  1H
EXMOD  single_pulse.ex2
OBFRQ        399.78 MHz
OBSET          4.19 KHz
OBFIN          7.29 Hz
POINT         32768
FREQU      20032.05 Hz
SCANS            16
ACQTM        1.6358 sec
PD           5.0000 sec
PW1             5.62 usec
IRNUC  1H
CTEMP          24.9 c
SLVNT  DMSO
EXREF          2.49 ppm
BF             0.12 Hz
RGAIN            40
```

1H-NMR (DMSO-D6) δ:
8.74 (1H, d, J = 1.8 Hz),
8.27 (1H, d, J = 9.2 Hz),
7.26 (1H, d, J = 4.9 Hz),
7.23 (1H, d, J = 6.1 Hz),
6.97 (1H, d, J = 7.9 Hz),
5.95 (1H, d, J = 7.3 Hz),
5.75 (OH, s),
5.23 (1H, d, J = 5.5 Hz),
4.58 (2H, s),
4.33 (OH, t, J = 5.2 Hz),
4.04 (3H, s),
3.57 (2H, d, J = 5.5 Hz),
3.45 (1H, dt, J = 10.2, 4.7 Hz),
3.42-3.38 (1H, m),
3.32 (18H, d, J = 16.5 Hz),
2.50 (20H, dt, J = 8.6, 4.1 Hz),
2.13 (1H, dt, J = 20.6, 6.4 Hz),
2.01 (1H, d, J = 41.0 Hz),
1.93-1.88 (1H, m),
1.65 (9H, ddd, J = 69.5, 31.9, 20.0
1.04 (1H, t, J = 7.0 Hz).



(+)-form

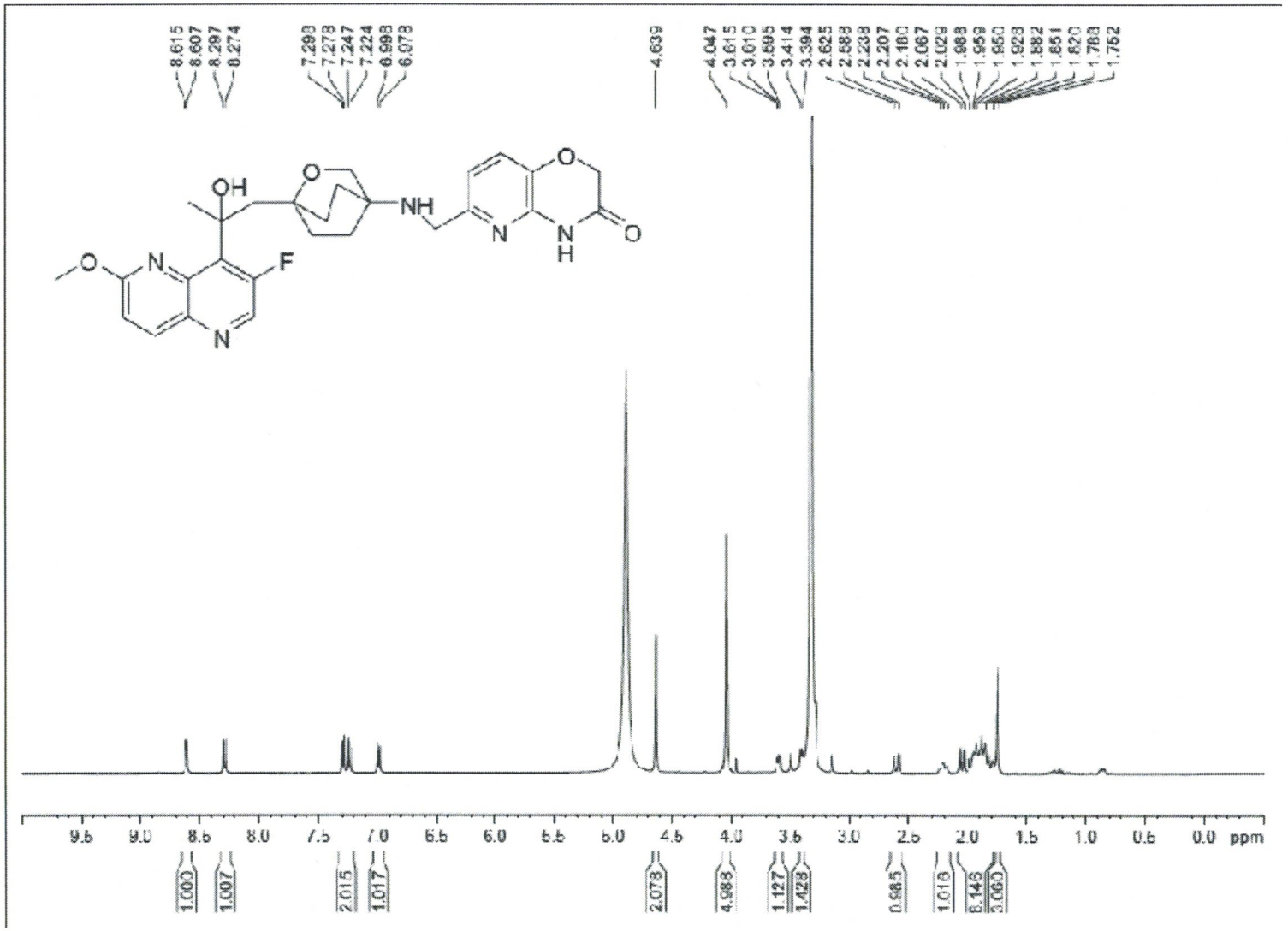
from

0.1% (three)

10, 11, 18

等の 峰

Compound (±)-20



(±)-**20** ^{1}H-NMR Chart

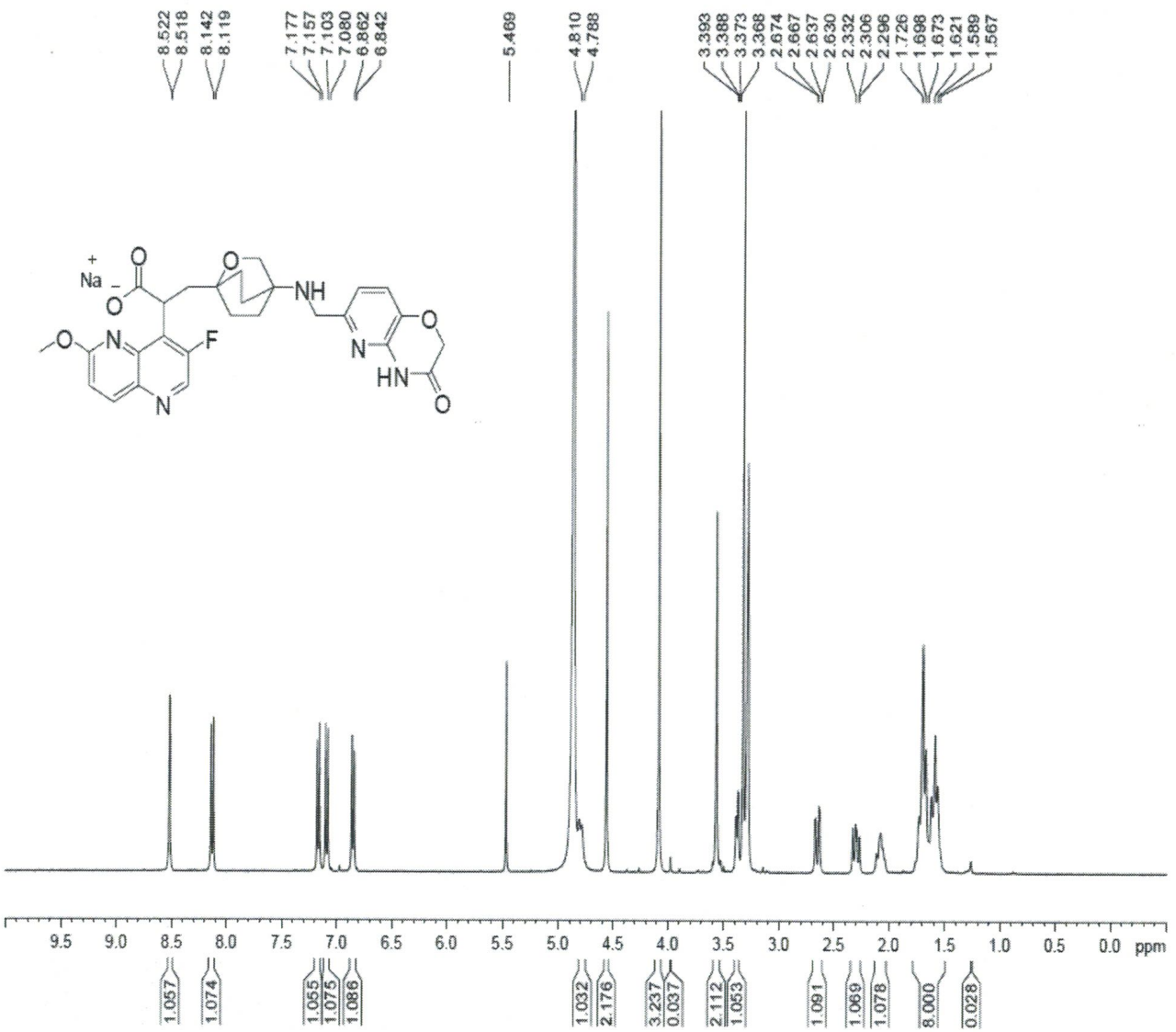
Compound (±)-21

(±)-21 ^{1}H-NMR Chart

Compound (±)-22

(±)-22 ^{1}H-NMR Chart

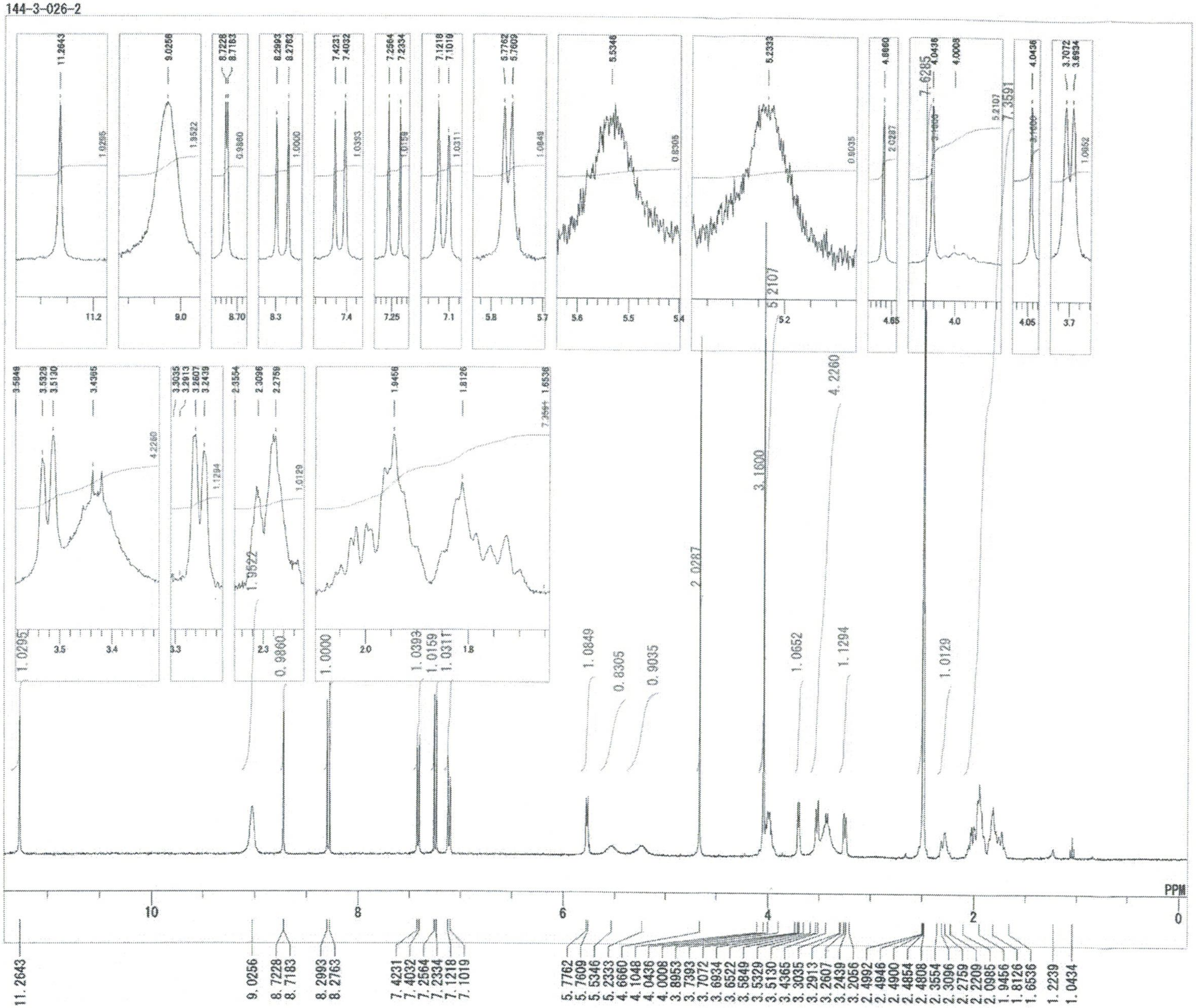
Compound (±)-23



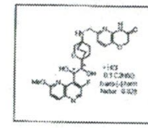
(±)-23 ^{1}H-NMR Chart

Compound (-)-24

144-3-026-2



DFILE	F:¥0NMRチャート¥竹内¥takeuchi.
COMNT	144-3-026-2
DATIM	07-12-2009 06:47:03
OBNUC	1H
EXMOD	single_pulse.ex2
OBFRQ	399.78 MHz
OBSET	4.19 KHz
OBFIN	7.29 Hz
POINT	26214
FREQU	16025.40 Hz
SCANS	64
ACQTM	1.6358 sec
PD	5.0000 sec
PW1	6.13 usec
IRNUC	1H
CTEMP	24.5 c
SLVNT	DMSO
EXREF	2.49 ppm
BF	0.12 Hz
RGAIN	40



AM-8202

MF

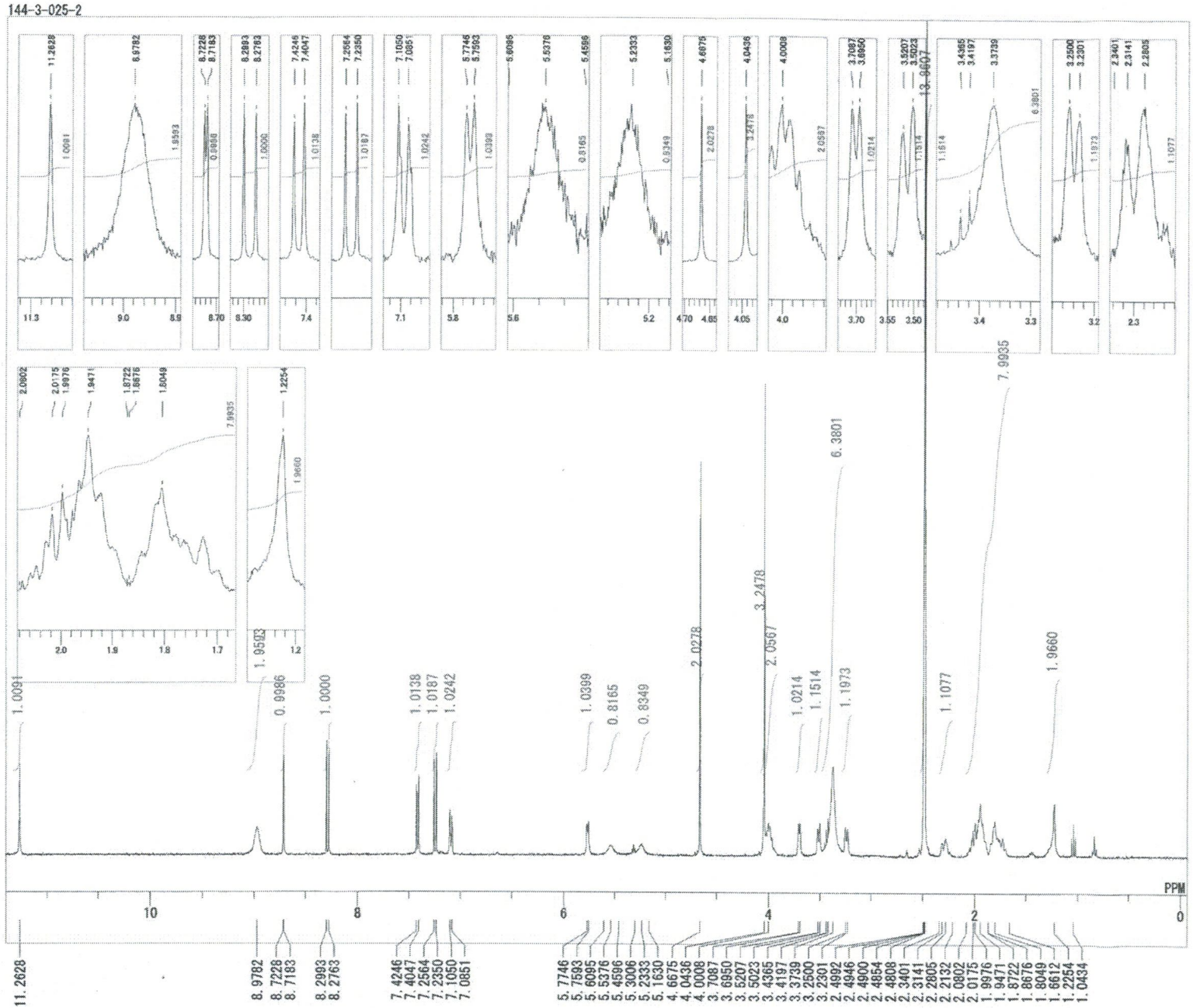
MW 566.60

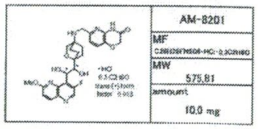
amount 10.0 mg

09/12/07

竹内[illegible]

Compound (+)-24

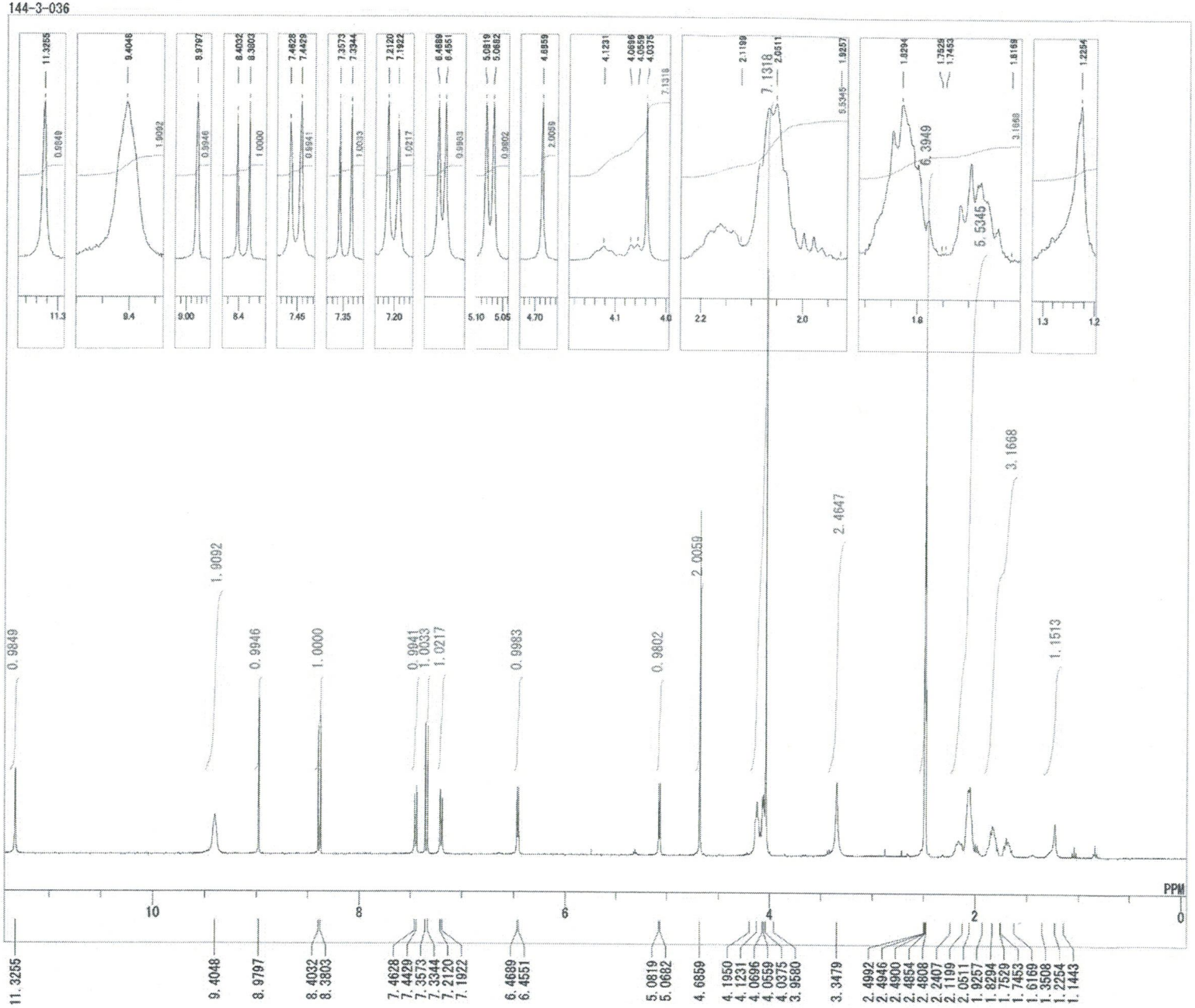




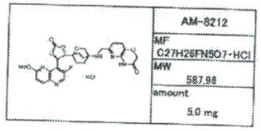
09/12/07
竹内智子

Compound (→)-25

144-3-036

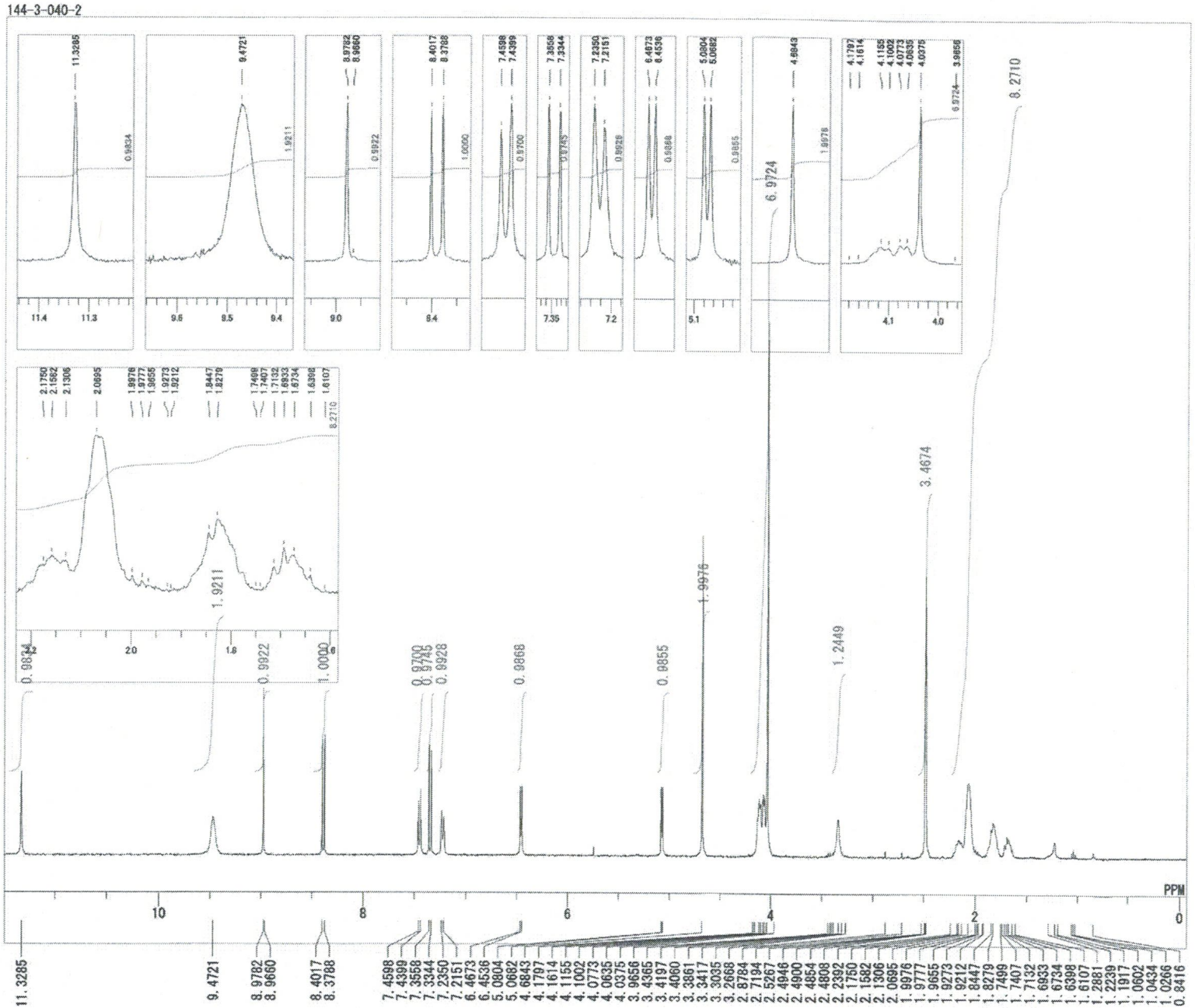


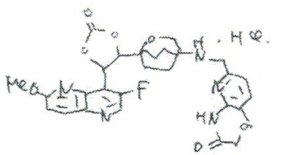
DFILE F:¥ONMRチャート¥竹内¥takeuchi
COMNT 144-3-036
DATIM 15-12-2009 10:05:27
OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 399.78 MHz
OBSET 4.19 KHz
OBFIN 7.29 Hz
POINT 26214
FREQU 16025.40 Hz
SCANS 64
ACQTM 1.6358 sec
PD 5.0000 sec
PW1 6.13 usec
IRNUC 1H
CTEMP 24.7 c
SLVNT DMSO
EXREF 2.49 ppm
BF 0.12 Hz
RGAIN 40



09112115
竹内智子

Compound (+)-25





(+)-form

09/12/24
竹内宏子