# Supporting Information

## Discovery of BMS-846372, a Potent and Orally Active Human CGRP Receptor Antagonist for the Treatment of Migraine.

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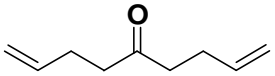
## Experimental section

**Chemistry**. **General Details**. All commercially available reagents and solvents were used without further purification unless otherwise stated. All reactions were carried out under an inert atmosphere of dry nitrogen in oven-dried glassware unless otherwise stated. Flash column chromatography was performed using 40-60 μm Silica Gel 60 (EMD Chemicals, Inc.) as the stationary phase, or pre-packed columns from ISCO Inco., Biotage, or Thomson Instrument Co. $^{1}$H NMR spectra were recorded on a Bruker 400 or 500 MHz machine with tetramethylsilane or residual protiated solvent used as a reference. $^{13}$C NMR were recorded on a Bruker DRX-500 instrument operating at 125 MHz with residual $^{12}$C solvent used as a reference. Low resolution mass spectra were recorded using a Waters Micromass ZQ with electrospray ionization. High resolution mass spectra were recorded using a Waters Micromass LCT time of flight mass spectrometer with electrospray ionization.

### Synthesis and characterization of intermediates

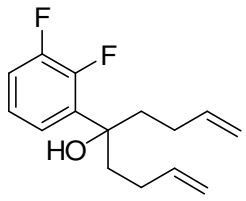
Intermediate 6




**Nona-1,8-dien-5-one**. In an oven-dried 500 mL round-bottomed flask was added 4-pentenoyl chloride (6.04 mL, 54.7 mmol) in THF (80 mL) to give a tan solution. After cooling to -78ºC, 3-butenylmagnesium bromide (115 mL, 57.5 mmol) was added via syringe over 90 min. After warming to room temperature for 3 hours, the reaction was quenched with saturated $NH_4Cl$ solution. THF was stripped off and the remaining was extracted with EtOAc. The organic layer was washed with brine, dried with $Na_2SO_4$, and concentrated to a slightly yellow oil. Purification (two batches) by FCC up to

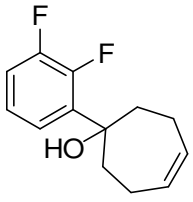
40% $Et_2O$/hexane afforded the product as a colorless oil: (5.13g, 68%). $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.84 – 5.68 (m, 2H), 5.05 – 4.90 (m, 4H), 2.49 (t, J = 7.4 Hz, 4H), 2.35 – 2.20 (m, 4H).

Intermediate 7



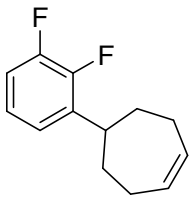

**5-(2,3-Difluorophenyl)nona-1,8-dien-5-ol**. In an oven-dried 250 mL round-bottomed flask was added 1-bromo-2,3-difluorobenzene (2.304 mL, 20.58 mmol) in THF (60 mL) to give a colorless solution. After cooling to -78ºC, BuLi (8.23 mL, 20.58 mmol) was added dropwise via syringe. The mixture was stirred at -78ºC for 20 minutes, and nona-1,8-dien-5-one (2.37 g, 17.15 mmol) (azeotroped with dry benzene) was added dropwise via canuula (plus 6ml THF rinse). The mixture was warmed up to room temperature over 1 hour. Quenched with water and the THF solvent was stripped off. The remaining mixture was extracted with EtOAc. The layers were separated and the organic layer was washed with brine, dried with $Na_2SO_4$, and concentrated to a yellow oil. The residue was purified by FCC up to 35% $Et_2O$/hexane. The desired fractions were pooled and concentrated to the product as a colorless oil (2.39g, 55.3%). $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.30 - 7.22 (m, 1H), 7.10 - 7.03 (m, 2H), 5.82 – 5.70 (m, 2H), 4.97 – 4.85 (m, 4H), 2.20 – 2.00 (m, 4H), 2.00 – 1.75 (m, 4H).

Intermediate 8



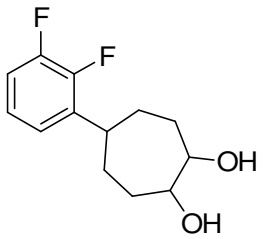
**(Z)-1-(2,3-Difluorophenyl)cyclohept-4-enol**. In a 1 L round-bottomed flask was added 5-(2,3-difluorophenyl)nona-1,8-dien-5-ol (1.76 g, 6.98 mmol) in $CH_2Cl_2$ (600 mL) to give a colorless solution. Grubbs I (0.175 g, 0.209 mmol) was added, and the mixture was heated at 40ºC for 2 hours. TLC showed clean conversion to a more polar spot (some impurities from starting material remained). The mixture was concentrated to dryness and the residue was subject to purification up to 50% $Et_2O$/hexane (twice). The major peak was pooled and concentrated to the product as a light green oil (1.40g, 89.2%): $^1$H NMR (400 MHz, $CDCl_3$) δ 7.34 - 7.25 (m, 1H), 7.08 - 7.00 (m, 2H), 5.90 – 5.80 (m, 2H), 2.60 – 2.48 (m, 2H), 2.21 (t, J = 7.0 Hz, 2H), 2.10 – 1.98 (m, 2H), 1.90 – 1.75 (m, 2H).

Intermediate 9



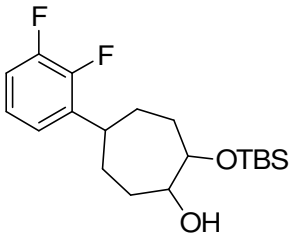

**(Z)-5-(2,3-Difluorophenyl)cyclohept-1-ene**. In a 250 mL round-bottomed flask was added (Z)-1-(2,3-difluorophenyl)cyclohept-4-enol (2.05 g, 9.14 mmol) in $CH_2Cl_2$ (40 mL) to give a colorless solution. Triethylsilane (7.30 mL, 45.7 mmol) was added, followed by TFA (20 mL). The mixture was stirred at room temperature for 3 hours. TLC showed a complete conversion (Rf = 0.42 by pure hexane). It was concentrated down to a bi-layer oil (the lower layer wasn't hexane-soluble). Purification by FCC using only hexane afforded the desired product as a colorless oil (1.684g, 88%): $^1$H NMR (400 MHz, $CDCl_3$) δ 7.00 – 6.90 (m, 3H), 5.90 – 5.82 (m, 2H), 3.20 – 3.05 (m, 1H), 2.40 – 2.15 (m, 4H), 1.90 – 1.78 (m, 2H), 1.60 – 1.40 (m, 2H).

Intermediate 10




**5-(2,3-Difluorophenyl)cycloheptane-1,2-diol**. See: D. A. Spiegel et al. Tetrahedron 2002, 58, 6545-6554. In a 250 mL round-bottomed flask was added (Z)-5-(2,3-difluorophenyl)cyclohept-1-ene (1.249 g, 6.00 mmol) and NMO (1.546 g, 13.19 mmol) in Acetone (9 mL) and Water (0.18 mL) to give a white suspension. Osmium tetroxide (0.301 mL, 0.024 mmol) (2.5 wt% solution in 2-methyl-2-propanol) was added. The mixture was stirred at room temperature. NMO gradually dissolved within 30 minutes to become a yellow solution. 1h: TLC showed complete conversion to a much polar spot. Sodium bisulfite (200mg) was added and stirring continued for 30 minutes. Acetone was stripped off and the residue was extracted with EtOAc three times. The combined organic layers were washed with brine, dried and concentrated to a white solid (crude weight: 1.7g). It was directly carried onto next reaction.

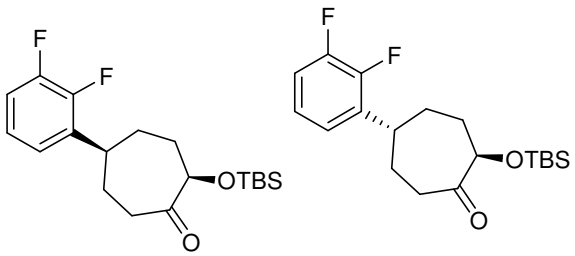
Intermediate 11




**2-(tert-Butyldimethylsilyloxy)-5-(2,3-difluorophenyl)cycloheptanol**. In a 250 mL round-bottomed flask was added 5-(2,3-difluorophenyl)cycloheptane-1,2-diol (1.454 g, 6.0 mmol) (crude material, azeotroped with dry benzene) in DMF (20 mL) to give a colorless solution. TBS-Cl (0.995 g, 6.60 mmol) and imidazole (0.980 g, 14.40 mmol) were added, and the mixture was stirred at room temperature for 5 hours. TLC (2/1 hexane/EtOAc) indicated complete conversion to two main spots. It

was diluted with water and extracted with EtOAc twice. The combined organic layers were washed with brine, dried with $Na_2SO_4$ and concentrated to a colorless oil. Purification by FCC up to 30% EtOAc/hexane afforded the desired mono-protected product as a broad peak. The product fractions were pooled and concentrated to a colorless oil (1.79g, 84% for two steps): $^1$H NMR (400 MHz, $CDCl_3$) δ 7.02 – 6.85 (m, 3H), 3.98 – 3.70 (m, 2H), 3.18 – 3.02 (m, 1H), 2.15 – 1.82 (m, 4H), 1.80 – 1.45 (m, 4H), 0.91 (s, 9H), 0.90 (2s, 6H).

Intermediate 12/13



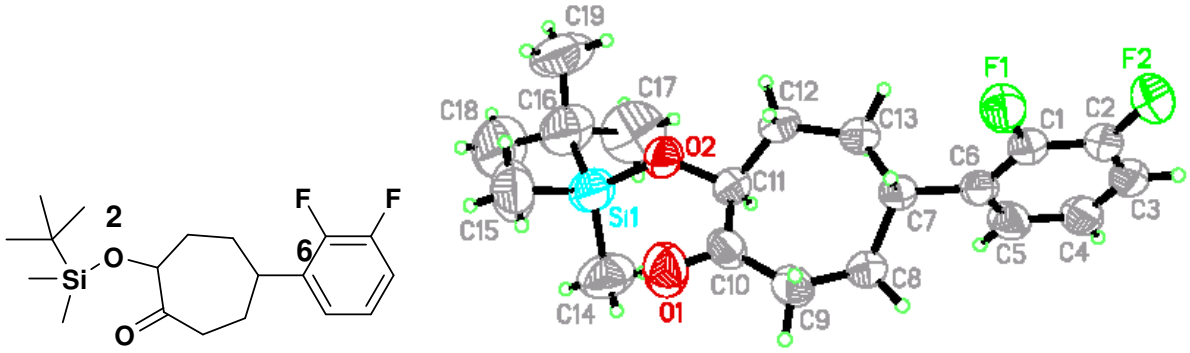

**12** **13**

**(±)-(2R,5R)-2-(tert-Butyldimethylsilyloxy)-5-(2,3-difluorophenyl)cycloheptanone**. In a 250 mL round-bottomed flask was added 2-(tert-butyldimethylsilyloxy)-5-(2,3-difluorophenyl)cycloheptanol (1.73 g, 4.85 mmol) in $CH_2Cl_2$ (50 mL) to give a colorless solution. Dess-Martin Periodinane (2.264 g, 5.34 mmol) was added in one portion, and the mixture was stirred at room temperature overnight for 17h. TLC showed complete conversion. It was diluted with $Et_2O$ and treated with 40 ml saturated $Na_2S_2O_3$ and $Na_2HCO_3$ solution (1/1 mixture) until the milky solution became clear (10min). The layers were separated and the aqueous layer was extracted with $Et_2O$. The combined organic layers were washed with brine, dried with $Na_2SO_4$, and concentrated to a colorless oil (with some solids insoluble in hexane). Purification by FCC up to 40% $Et_2O$ in hexane afforded two peaks. They were individually pooled and concentrated. The less polar major one (978 mg, 55%) was a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.02 – 6.90 (m, 3H), 4.34 (d, J = 4.6 Hz, 1H), 2.82 – 2.75 (m, 2H), 2.54 – 2.46 (m, 1H), 2.45 – 2.32 (m, 1H), 2.17 – 1.98 (m, 2H), 1.90 - 1.68 (m, 3H), 0.94 (s, 9H), 0.08 (s, 6H); $^{13}$C NMR (125

MHz, $CDCl_3$) δ 213.4, 150.7 (dd, J = 247.6 and 13.4 Hz), 147.8 (dd, J = 245.7 and 13.4 Hz), 137.5 (d, J = 11.5 Hz), 127.7, 122.2, 114.7 (d, J = 17.3 Hz), 79.0, 40.0, 39.2, 33.2, 30.7, 29.4, 25.8, 18.2, -5.0. The more polar minor one solidified upon standing to a white solid (698 mg, 39%). It was re-crystallized from hexane and X-ray analysis verified the anti-stereochemistry relation. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.10 – 6.97 (m, 2H), 6.97 – 6.90 (m, 1H), 4.34 (dd, J = 3.0 and 9.7 Hz, 1H), 3.04 – 2.94 (m, 1H), 2.80 – 2.70 (m, 1H), 2.62 – 2.50 (m, 1H), 2.18 – 1.72 (m, 6H), 0.90 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 211.0, 150.8 (dd, J = 248.6 and 13.5 Hz), 148.1 (dd, J = 246.7 and 12.5 Hz), 136.4 (d, J = 11.5 Hz), 124.2, 122.3, 115.1 (d, J = 17.3 Hz), 78.4, 40.3, 39.4, 34.3, 33.0, 30.4, 25.9, 18.5, -4.5, -5.1.

X-ray structure of 13:

**Structures:**




**Crystal Data:**

Chemical formula: $C_{19}H_{28}O_2SiF_2$ $Fw = 354.50$

Crystal system: Monoclinic

Space Group: $P2_1/c$

$a =$ 21.5216(8) Å $\alpha = 90°$

$b =$ 7.3268(2) Å $\beta = 103.228(2)°$

$c =$ 13.4188(4) Å $\gamma = 90°$

$V = 2059.79(11)$ Å$^3$

No. of molecules/cell: $Z = 4$

Calculated crystal density: $d_x = 1.143$ g cm$^{-3}$

Absorption coefficient: $\mu =$ 0.139 mm$^{-1}$

$\theta$ range for lattice parameters (°): 2.95-26.78

**Experimental:**

*Crystallization*

Crystal source: DCM

Crystal description: Colorless block

Crystal size (mm): 0.51 x 0.38 x 0.20

*Data Collection*

Temperature (K): 298

$\theta_{max}$ (°): 26.78 (Mo Kα)

No. of reflections measured: 7768

No. of independent reflections: 4335 ($R_{int} = 0.0259$)

No. of observed reflections ($I \geq 2\sigma$): 2572

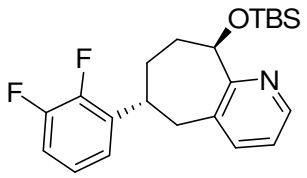
**Refinement:**

No. of parameters refined: 218 No. of reflections used: 2572 $-0.801 \leq \Delta\rho \leq 1.132$ e/Å$^3$

$R(F) = 0.1407$ $wR(F^2) = 0.3550$ $S = 2.281$ $w = 1/[\sigma^2 (Fo^2) + (0.1)^2 + 0.0000\ P]$ $P = (Fo^2 + 2\ Fc^2)/3$

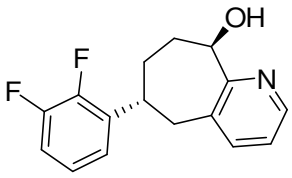
*Treatment of Hydrogen Atoms*: All hydrogen atoms were located from difference maps and refined isotropically.

Intermediate 14




**(±)-(6, 9-anti)-9-(tert-Butyldimethylsilyloxy)-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine**. In a 25 mL flask was added (±)-2-(tert-butyldimethylsilyloxy)-5-(2,3-difluorophenyl)cycloheptanone (279 mg, 0.787 mmol) in Ethanol (4 mL) to give a colorless solution. Sodium tetrachloroaurate(III) dihydrate (9.39 mg, 0.024 mmol) and Propargylamine (0.101 mL, 1.574 mmol) were added. The reaction was heated at 80ºC for 5 hours. After the tan mixture was cooled to room temperature, it was diluted with EtOAc, filtered through a plug of cotton, and concentrated to a tan oil. FCC up to 20% EtOAc/hexane afforded the desired product as a major peak (60.3mg, 20%) as well as a little recovered starting material: $^1$H NMR (400 MHz, $CDCl_3$) δ 8.45 – 8.40 (m, 1H), 7.32 – 7.29 (m, 1H), 7.08 – 7.04 (m, 1H), 7.04 – 6.92 (m, 2H), 6.92 – 6.80 (m, 1H), 5.13 – 5.07 (m, 1H), 3.30 – 3.00 (m, 3H), 2.32 – 2.10 (m, 2H), 2.10 – 1.90 (m, 2H), 0.91 (s, 9H), 0.074 (s, 3H), 0.042 (s, 3H).

Intermediate 15



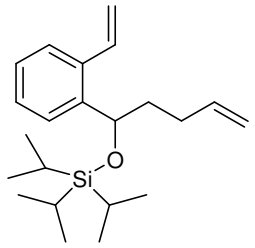
**(6, 9-anti)-6-(2,3-Difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol**. In a 50 mL round-bottomed flask was added **(±)-(**6R,9R)-9-(tert-butyldimethylsilyloxy)-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (60.3 mg, 0.155 mmol) in THF (3 mL) to give a colorless solution. TBAF (0.310 mL, 0.310 mmol) was added, and the mixture was stirred at room temperature overnight for 19h. LCMS and TLC showed complete conversion. THF was stripped off and the residue was diluted with EtOAc, washed with water, brine, dried with $Na_2SO_4$, and concentrated to a tan oil. FCC up to 30% EtOAc/hexane afforded one peak, which was pooled and concentrated to a white solid (35.7mg, 84%): LCMS: [M + H] = 276; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.42 – 8.40 (m, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.16 (dd, J = 7.2 and 5.0 Hz, 1H), 7.15 – 7.00 (m, 3H), 5.97 (br., 1H), 4.88 (dd, J = 11.6 and 1.6 Hz, 1H), 3.19 (t, J = 12.8 Hz, 1H), 2.99 – 2.83 (m, 1H), 2.80 (d, J = 14.4 Hz, 1H), 2.38 – 2.23 (m, 1H), 2.23 – 2.05 (m, 2H), 1.69 – 1.50 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 160.7, 150.8 (d, J = 247.4 Hz), 148.1 (d, J = 261.2 Hz), 145.1, 137.8, 136.5 (d, J = 12.3 Hz), 133.6, 124.2, 122.4, 122.1, 115.1 (d, J = 16.9 Hz), 71.8, 40.5, 37.6, 36.2, 35.8.

Intermediate 18


**2-Bromo-3-vinylpyridine.** See Spivey, A.C.; Shukla, L.; Hayler, J.F. *Org. Lett.* **2007**, *9*, 891-894. Butyllithium (22.75 mL, 59.1 mmol) was added to the THF (450 mL) suspension of methyltriphenylphosphonium bromide (21.13 g, 59.1 mmol) at 0 °C. The solution turned to orange and the reaction was lift to room temperature for 30 min before cooled it back to 0 °C. 2-bromonicotinaldehyde (10 g, 53.8 mmol) in 50 mL THF was added through canula to the reaction solution. The precipitate was formed and the reaction was lift to room temperature. The color of the reaction turned to green, gray. After a while, the color of te reaction became orange again. The reaction

was stirred at room temperature over weekend. The solvent was removed mostly via vacuum and the crude was partitioned between water and diethyl ether. The organic layer was separated and the aqueous layer was extract twice with diethyl ether. The diethyl ether layer was combined, dried (Na2SO4), filtered and concentrated. The product was obtained by flash column eluted with ethyl acetate in hexane (10%) as yellow oil (8.78g, 89%). MS(ESI)[M+H$^+$] = 184.04; 1H NMR δ ppm (400 MHz, CHLOROFORM-*d*) 8.21 - 8.29 (m, 1 H) 7.78 (dd, *J*=7.68, 1.89 Hz, 1 H) 7.20 - 7.28 (m, 1 H) 6.96 (dd, *J*=17.37, 11.08 Hz, 1 H) 5.72 (d, *J*=17.37 Hz, 1 H) 5.46 (d, *J*=11.08 Hz, 1 H).

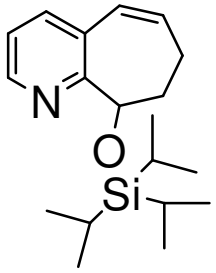
Intermediate 19




**Triisopropyl(1-(2-vinylphenyl)pent-4-enyloxy)silane.** 1-Bromo-2-vinylbenzene (2.8146 g, 15.38 mmol) was azeotropped by dry benzene twice before taken up in THF (50ml). The solution was cooled to -78 °C. BuLi (6.77 ml, 16.91 mmol) was added to the reaction mixture at -78 °C and stirred for 20 min at this temperature. pent-4-enal (1.670 ml, 16.91 mmol) was added to the reaction mixture and stirred for 4 hours while the bath temperature gradually warmed up. Chlorotriisopropylsilane (3.58 ml, 16.91 mmol) was added to the reaction mixture and the reaction was stirred overnight while the reaction was warmed up to room temperature. The solvent was mostly removed via vacuum and the crude was partitioned between ethyl acetate and water. The ethyl acetate layer was separated, dried (Na2SO4), filtered and concentrated. The product was obtained by flash column eluted with ether in hexane from 0 to 30% as clear yellow oil (3.9g, 74% yield). MS(ESI)[M+H$^+$] = 346.46; 1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.41 (dd, *J*=4.58, 1.53 Hz, 1 H) 7.81 (dd, *J*=7.78, 1.07 Hz, 1 H) 7.51 (dd,

*J*=17.70, 10.99 Hz, 1 H) 7.15 (dd, *J*=7.78, 4.73 Hz, 1 H) 5.76 (dddd, *J*=16.94, 10.38, 6.41, 6.26 Hz, 1 H) 5.61 (d, *J*=17.40 Hz, 1 H) 5.33 (d, *J*=10.99 Hz, 1 H) 5.04 (t, *J*=7.02 Hz, 1 H) 4.95 (dd, *J*=17.09, 1.83 Hz, 1 H) 4.89 (dd, *J*=10.22, 1.07 Hz, 1 H) 2.04 - 2.14 (m, 1 H) 1.95 - 2.04 (m, 2 H) 1.81 - 1.92 (m, 1 H) 1.01 - 1.11 (m, 3 H) 0.96 - 1.01 (m, 9 H) 0.91 (d, *J*=7.32 Hz, 9 H).

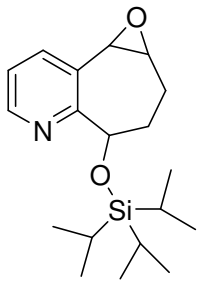
Intermediate 20




**(Z)-9-(Triisopropylsilyloxy)-8,9-dihydro-7H-cyclohepta[b]pyridine.** 2-(1-(triisopropylsilyloxy)pent-4-enyl)-3-vinylpyridine (7.07 g, 20.46 mmol) was dissolved in Dichloromethane (1.5 L). 2.0M Hydrogen chloride in ether (10.6 mL, 21.20 mmol) was added to the mixture. Reaction stirred at room temperature for 10 minutes. Nitrogen was then bubbled through the mixture for 15 minutes. GrubbsII (250 mg, 0.294 mmol) was added to the mixture. Reaction vessel was flushed with nitrogen and then fitted with a condenser. Reaction was warmed to a gentle reflux and held for 4 hours. Mixture was slowly cooled to room temperature and held overnight. Mixture was concentrate by roto-vap. The residue was purified via Biotage (Silica; Thomson 160 g; 100% Hexanes to 30% EtOAc-Hex over 1350 mL). Major peak was isolated. Fractions were concentrated to dryness. 2.05 g of clear brown oil was obtained. It was realized that the material was not free based prior to the chromatography. 5-10 mL of triethylamine was added to the column. Column was then flushed with 30% EtOAc-Hex. Major peak was isolated. Fractions were combined with the previous material. Mixture was concentrated to dryness. (Z)-9-(triisopropylsilyloxy)-8,9-dihydro-7H-cyclohepta[b]pyridine (5.60 g, 17.64 mmol, 86 % yield) was obtained as clear brown oil: 1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.27 (dd,

*J*=4.73, 1.68 Hz, 1 H) 7.46 (dd, *J*=7.78, 1.37 Hz, 1 H) 7.12 (dd, *J*=7.63, 4.88 Hz, 1 H) 6.23 (ddd, *J*=12.36, 2.75, 1.37 Hz, 1 H) 5.88 - 6.07 (m, 1 H) 5.25 (d, *J*=7.63 Hz, 1 H) 2.69 - 2.95 (m, 1 H) 2.31 - 2.46 (m, 1 H) 2.16 - 2.33 (m, 1 H) 1.89 (td, *J*=13.58, 4.58 Hz, 1 H) 1.02 - 1.15 (m, 3 H) 0.95 - 1.01 (m, 9 H) 0.87 (d, *J*=7.32 Hz, 9 H); LCMS: (M+H)+= 318.1.

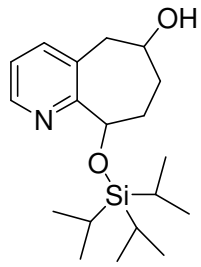
Intermediate 21




**6-Bromo-9-(triisopropylsilyloxy)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-5-yl acetate epoxide.** Reference: Morel, A.F.; Larghi, E.L.; *Tetrahedron Asymmetry*, **2004**, 15(1), 9-10; Jacobson, E.N.; Zhang, W.; Muci, A.R.; Ecker, J.R.; Deng, L.; *J. Am. Chem. Soc.*; **1991**, 113(18), 7063-7064. Sodium phosphate, dibasic (2.8 g, 19.72 mmol) was dissolved in Sodium hypochlorite (650 mL, 567 mmol). Mixture was cooled to 0°C. A mixture of (Z)-9-(triisopropylsilyloxy)-8,9-dihydro-7H-cyclohepta[b]pyridine (5.60 g, 17.64 mmol), (1S,2S)-(+)-[1,2-Cyclohexanediamino-N,N'-bis(3,5-di-t-butylsalicylidene)]manganese (III) chloride (650 mg, 1.023 mmol) and (R,R)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamino-Mn-Cl (650 mg, 1.023 mmol) in Dichloromethane (125 mL) was added to the aqueous mixture drop-wise over 1 hour. Reaction was allowed to slowly warm to room temperature. Reaction stirred at room temperature overnight. Reaction mixture was treated with celite to form a slurry. Mixture was filtered over ceilte. Solids were washed with dichloromethane. Filtrate layers were partitioned. Aqueous layer was back extracted with dichloromethane. Combined

organics were washed with brine. Organics were dried MgSO4, filtered and then concentrated to dryness. The residue was purified via Biotage (Silica; Thomson 160 g; 100% Hexanes to 30% EtOAc-Hex over 1350 mL). Major peak was isolated. Fractions were concentrated to dryness. The desired product (4.12 g, 12.35 mmol, 70.0 % yield) was obtained as clear brown oil: MS(ESI)[M+H$^+$] = 334.30; $^1$H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.42 (dd, *J*=4.88, 1.53 Hz, 1 H) 7.89 (d, *J*=7.63 Hz, 1 H) 7.23 (dd, *J*=7.63, 4.88 Hz, 1 H) 5.12 (t, *J*=3.36 Hz, 1 H) 4.05 (d, *J*=4.58 Hz, 1 H) 3.43 - 3.51 (m, 1 H) 2.36 (dq, *J*=14.11, 4.55 Hz, 1 H) 1.99 - 2.15 (m, 2 H) 1.11 - 1.17 (m, 1 H) 0.99 - 1.10 (m, 3 H) 0.94 - 0.99 (m, 9 H) 0.90 (d, *J*=7.32 Hz, 9 H).

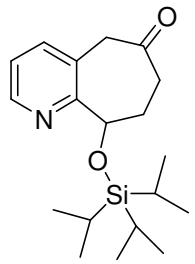
Intermediate 22




**9-(Triisopropylsilyloxy)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-6-ol.** . 10% Palladium on carbon (50% wet) (740 mg, 0.348 mmol) was added to the solution of the epoxide (4.12g, 12.35 mmol) in ethanol (40 ml). Reaction vessel was placed on a Parr apparatus and charged with 25 psi of hydrogen gas. Reaction shook at room temperature for 4 hours. Reaction was removed from the apparatus and the mixture was filtered over Celite. Filtrate was concentrated to dryness. 9-(triisopropylsilyloxy)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-6-ol (4.10 g, 12.22 mmol, 99 % yield) was obtained as brown oil. MS(ESI)[M+H$^+$] = 336.37; 1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.32 (d, *J*=4.58 Hz, 1 H) 7.46 (d, *J*=7.32 Hz, 1 H) 7.10 (dd, *J*=7.32, 4.88 Hz, 1 H) 5.14 (br. s., 1 H) 4.28 (d, *J*=1.53 Hz, 1 H) 3.75 (d, *J*=14.04 Hz, 1 H) 2.80 (dd, *J*=14.19, 6.56 Hz, 1 H) 2.53 (dddd, *J*=14.38, 8.43, 8.32, 2.44 Hz,

1 H) 1.99 (td, *J*=6.26, 3.66 Hz, 2 H) 1.82 - 1.93 (m, 1 H) 1.20 (d, *J*=4.88 Hz, 1 H) 1.10 (dq, *J*=14.69, 7.41 Hz, 3 H) 0.99 (d, *J*=7.32 Hz, 9 H) 0.91 (d, *J*=7.32 Hz, 9 H).

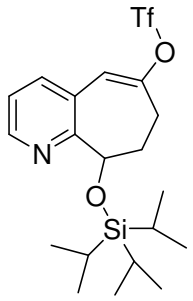
Intermediate 23




**9-(Triisopropylsilyloxy)-8,9-dihydro-5H-cyclohepta[b]pyridin-6(7H)-one.** Oxalyl chloride (2.7 mL, 30.8 mmol) was dissolved in Dichloromethane (60 mL). Mixture was cooled to -75°C. A solution of DMSO (2.2 mL, 31.0 mmol) in Dichloromethane (15 mL) was added to the mixture drop-wise over 35 minutes. Reaction stirred at -78°C for 45 minutes. A solution of 9-(triisopropylsilyloxy)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-6-ol (4.55 g, 13.56 mmol) in Dichloromethane (30 mL) was added to the mixture drop-wise over 45 minutes. Reaction stirred at -78°C for 45 minutes. Triethylamine (8.0 mL, 57.4 mmol) was added to the mixture drop-wise over 10 minutes. Reaction stirred at -78°C for 45 minutes. Dry ice bath was removed and the mixture was allowed to warm to room temperature. Reaction mixture was washed twice with water. Material was washed with brine. Organics were dried MgSO4, filtered and then concentrated to dryness. The residue was purified via Biotage (Silica; Thomson 90 g; 100% Hexanes to 30% EtOAc-Hex over 1350 mL). Major peak was isolated. Fractions

were concentrated to dryness. 9-(triisopropylsilyloxy)-8,9-dihydro-5H-cyclohepta[b]pyridin-6(7H)-one (3.69 g, 11.06 mmol, 82 % yield) was obtained as clear yellow oil: MS(ESI)[M+H$^+$] = 334.30; 1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.37 (dd, *J*=4.88, 0.61 Hz, 1 H) 7.47 (d, *J*=7.32 Hz, 1 H) 7.17 (dd, *J*=7.63, 4.88 Hz, 1 H) 5.24 (dd, *J*=4.88, 2.14 Hz, 1 H) 4.68 (d, *J*=14.34 Hz, 1 H) 3.27 (dd, *J*=14.34, 0.92 Hz, 1 H) 3.01 (ddd, *J*=12.13, 8.93, 6.10 Hz, 1 H) 2.49 (ddd, *J*=12.05, 6.26, 6.10 Hz, 1 H) 2.31 - 2.43 (m, 1 H) 2.06 - 2.19 (m, 1 H) 1.11 (dq, *J*=14.80, 7.38 Hz, 3 H) 0.99 (d, *J*=7.63 Hz, 9 H) 0.93 (d, *J*=7.32 Hz, 9 H).

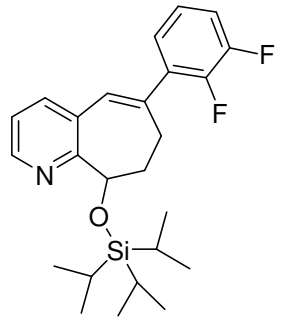
Intermediate 24




**(E)-9-(Triisopropylsilyloxy)-8,9-dihydro-7H-cyclohepta[b]pyridin-6-yl trifluoromethanesulfonate.** LDA (3.73 mL, 7.45 mmol) was added to the THF (25 mL) solution of DMPU (2.073 mL, 17.20 mmol) and 9-(triisopropylsilyloxy)-8,9-dihydro-5H-cyclohepta[b]pyridin-6(7H)-one (1.9119 g, 5.73 mmol) at -78 °C. The reaction was stirred at this temperature for 2 hours before addition of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (2.66 g, 7.45 mmol). The reaction was stirred for overnight while it was gradually warmed up to room temperature. The solvent was removed via vacuum and the crude was loaded on the flash column, eluted with ethyl acetate in hexane from 0 to 15% to 25% to afford the desired product (2.3g, 86%). MS(ESI)[M+H$^+$] = 466.33; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.37 (dd, *J*=4.78, 1.51 Hz, 1 H) 7.47 - 7.54 (m, 1 H) 7.20 (dd, *J*=7.81, 4.78 Hz, 1 H) 6.43 (d, *J*=2.01 Hz, 1 H) 5.26 (d, *J*=7.55 Hz, 1 H) 3.16 - 3.32 (m, 1 H) 2.58 - 2.69 (m, 1 H)

2.29 - 2.39 (m, 1 H) 1.85 - 1.98 (m, 1 H) 1.01 - 1.09 (m, 3 H) 0.93 - 1.00 (m, 9 H) 0.85 (d, *J*=7.05 Hz, 9 H).

Intermediate 25

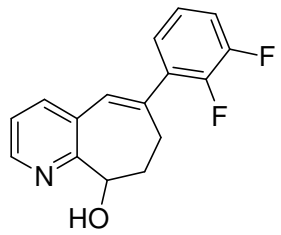



**(E)-6-(2,3-difluorophenyl)-9-(triisopropylsilyloxy)-8,9-dihydro-7H-cyclohepta[b]pyridine.**

(E)-9-(triisopropylsilyloxy)-8,9-dihydro-7H-cyclohepta[b]pyridin-6-yl trifluoromethanesulfonate (4.70 g, 10.09 mmol) was dissolved in Toluene (75 mL). 2M Sodium carbonate (12 mL, 24.00 mmol) was added to the mixture followed by 2,3-Difluorophenylboronic acid (1.60 g, 10.13 mmol). Nitrogen gas was bubbled through the mixture for 10 minutes. Reaction vessel was flushed with nitrogen. Tetrakis(triphenylphosphine)palladium(0) (190 mg, 0.164 mmol) was added to the mixture. Reaction was warmed to 110°C and held with stirring for 1.5 hours. Mixture was slowly cooled to room temperature. Mixture was diluted with water. Material was extracted twice with ethyl acetate. Organics were dried MgSO4, filtered and then concentrated to dryness. The residue was purified via Biotage (Silica; Thomson 90 g; 100% Hexanes to 20% EtOAc-Hex over 1350 mL). Biotage error

caused effluent to be dumped into the test tube rack tray. What material that could be recovered was combined and concentrated by roto-vap. Biotage purification was repeated on the residue. Major peak was isolated. Fractions were concentrated to dryness. (E)-6-(2,3-difluorophenyl)-9-(triisopropylsilyloxy)-8,9-dihydro-7H-cyclohepta[b]pyridine (2.82 g, 6.56 mmol, 65.0 % yield) was obtained as clear pale amber oil. MS(ESI)[M+H$^+$] = 430.43; 1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.33 (d, *J*=4.58 Hz, 1 H) 7.50 (d, *J*=7.63 Hz, 1 H) 7.17 (dd, *J*=7.63, 4.88 Hz, 1 H) 6.96 - 7.13 (m, 3 H) 6.41 (s, 1 H) 5.28 (d, *J*=7.02 Hz, 1 H) 3.13 (ddd, *J*=17.93, 13.05, 4.73 Hz, 1 H) 2.63 (dt, *J*=18.31, 4.12 Hz, 1 H) 2.33 - 2.45 (m, 1 H) 2.14 (td, *J*=13.35, 4.43 Hz, 1 H) 1.03 - 1.13 (m, 3 H) 0.97 - 1.04 (m, 9 H) 0.89 (d, *J*=7.02 Hz, 9 H).

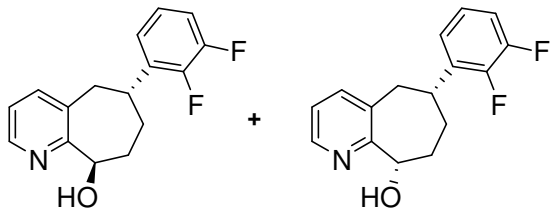
Intermediate 26




**(E)-6-(2,3-difluorophenyl)-8,9-dihydro-7H-cyclohepta[b]pyridin-9-ol.** The mixture of (E)-6-(2,3-difluorophenyl)-9-(triisopropylsilyloxy)-8,9-dihydro-7H-cyclohepta[b]pyridine (1.6072 g, 3.74 mmol) and TBAF (7.48 mL, 7.48 mmol) in THF (10 mL) was stirred at room temperature for 1 hour. LCMS showed no more starting material and conversion of the desired product. The solvent was removed via vacuum. The reaction was purified by flash column eluted with ethyl acetate in hexane from 0 to 35% to 50% to afford the desired product as a white solid (0.825g, 81%): MS(ESI)[M+H$^+$] = 274.19; 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.36 (dd, *J*=4.78, 1.51 Hz, 1 H) 7.50 (dd, *J*=7.81, 1.26 Hz, 1 H) 7.20 (dd, *J*=7.68, 4.91 Hz, 1 H) 6.96 - 7.11 (m, 3 H) 6.44 (s, 1 H) 5.63 (br., 1 H) 4.77 (dd, *J*=10.45, 2.64 Hz, 1 H) 2.78 - 2.95 (m, 1 H) 2.64 - 2.77 (m, 1 H) 2.44 - 2.62 (m, *J*=13.60, 5.48, 5.48, 2.64 Hz, 1 H) 1.92 - 2.15 (m, 1 H); 13C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 158.49 (s, 1 C) 149.39 -

152.62 (m, 1 C) 146.03 - 149.25 (m, 1 C) 145.24 (s, 1 C) 143.70 (s, 1 C) 139.94 (s, 1 C) 138.79 (s, 1 C) 134.46 (d, *J*=10.79 Hz, 1 C) 128.51 (d, *J*=11.56 Hz, 1 C) 124.37 (br. s., 1 C) 123.81 - 124.14 (m, 1 C) 122.44 (s, 1 C) 116.24 (d, *J*=16.95 Hz, 1 C) 71.49 (s, 1 C) 34.88 (s, 1 C) 32.74 (d, *J*=3.08 Hz, 1 C).

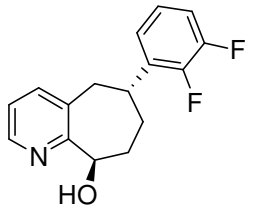
Intermediates 15 and 27




**15** **27**

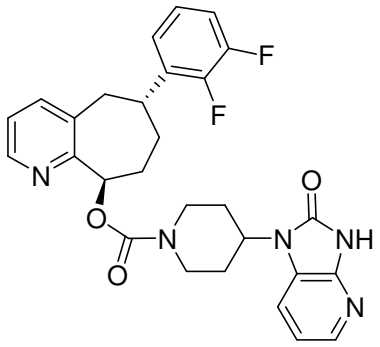
**Racemic trans-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol and cis-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol**. In a 500 mL round-bottomed flask was (E)-6-(2,3-difluorophenyl)-8,9-dihydro-7H-cyclohepta[b]pyridin-9-ol (660 mg, 2.415 mmol) in MeOH (20 mL) to give a colorless solution. Pd/C (257 mg, 0.242 mmol) was added, and the mixture was stirred under hydrogen balloon for 4h. LCMS showed complete conversion. Filtered and concentrated to a colorless oil. The cis-alcohol was much more polar that the trans-alcohol (Rf = 0.16 for cis and 0.77 for trans in 50% EtOAc/hexanes). Purification by FCC up to 80% EtOAc/hexane afforded two products: trans-alcohol (104.3mg, 16%), and cis-alcohol (492.8mg, 74%), both as white solids. Analytical data of **15** matched that of previously described. **27**: 1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.26 (d, *J*=4.58 Hz, 1 H) 7.30 (d, *J*=7.63 Hz, 1 H) 7.04 (dd, *J*=7.32, 4.88 Hz, 1 H) 6.85 - 6.98 (m, 2 H) 6.79 (t, *J*=6.87 Hz, 1 H) 5.37 (br. s., 1 H) 5.01 (dd, *J*=7.17, 3.81 Hz, 1 H) 3.28 - 3.52 (m, 2 H) 2.93 (d, *J*=13.73 Hz, 1 H) 2.17 - 2.33 (m, 1 H) 1.89 - 2.15 (m, 3 H).

Conversion of intermediate 27 to intermediate 15




**Racemic (6,9-trans-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol.** In a 100 mL round-bottomed flask was (6,9-cis)-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ol (489 mg, 1.776 mmol) (azeotroped with dry benzene) in THF (15 mL) to give a colorless solution. 4-Nitrobenzoic acid (594 mg, 3.55 mmol) and Ph3P (932 mg, 3.55 mmol) were added, and the mixture was cooled to 0°C. Diisopropyl azodicarboxylate (0.699 mL, 3.55 mmol) was added dropwise. The mixture was allowed to warm up to rt and stirred for 5h. LCMS indicated complete conversion to the desired intermediate and a little dehydrated product. It was left stirring overnight and LCMS showed no change. LiOH (8.88 mL, 8.88 mmol) was added, and the mixture was stirred at rt for 3 h. LCMS indicated complete conversion of the intermediate to product. THF was stripped off and the residue was partitioned between EtOAc and 0.2N NaOH. The layers were separated and the organic was washed with brine, dried, and concentrated to a slightly tan oil. FCC up to 50% EtOAc/hexane afforded the desired product (378 mg, 77%) as a white solid. The analytical data matched that of previously described.

**Synthesis of analytical data of BMS-846372**



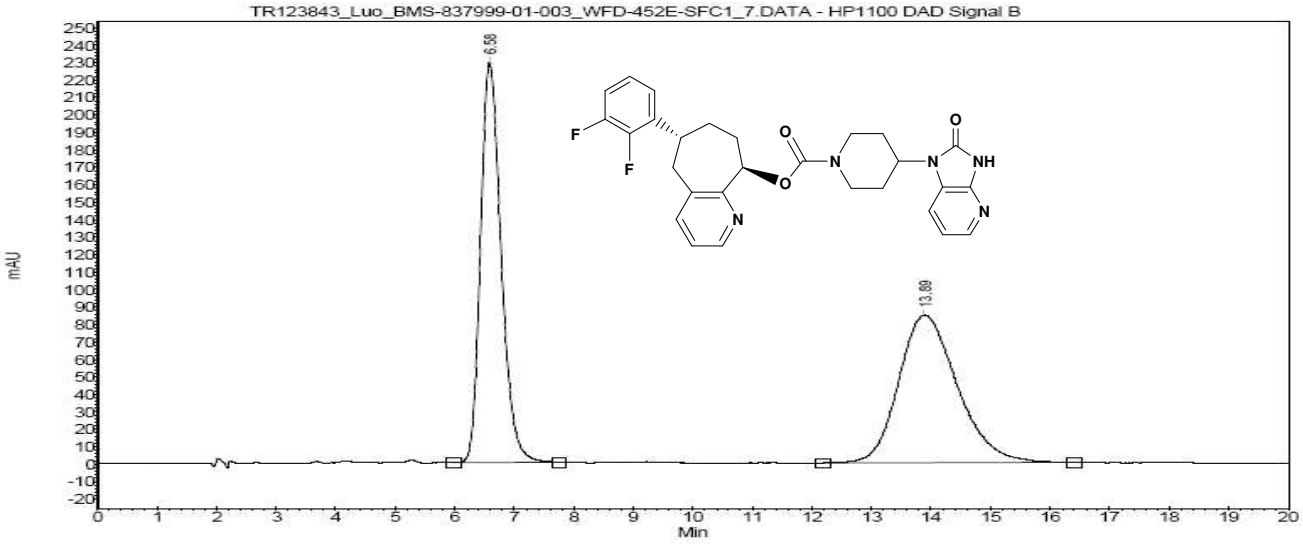

**(6*R*,9*R*)-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridin-9-yl-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (5)** and **(6*S*,9*S*)-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridin-9-yl-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (18).** In a 500 mL round-bottomed flask was added (±)-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridin-9-ol (1.8 g, 3.27 mmol) (azeotroped with dry benzene) and 4-nitrophenyl 4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (3.9 g, 4.9 mmol, 1.5 equiv.) in THF (100 mL) to give a tan suspension. After cooling to 0°C under nitrogen, sodium hydride (1.24 g, 49 mmol, 15 equiv.) was added in portions (caution: heat generation). The mixture was stirred under nitrogen at room temperature overnight for 18h. LCMS showed complete conversion. The reaction was slowly quenched with water (gas evolution) and extracted with ethyl acetate. The layers were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried with $Na_2SO_4$, and concentrated. Purification by FCC up to 8% MeOH/$CH_2Cl_2$ afforded the racemic product (1.55 g, 46%) as a white solid (LCMS and NMRs were the same as reported below). The racemic product was subjected to chral column separation to afford the enantiomerically pure **5** (BMS-846372): $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm: 11.60 (s, 1 H); 8.44 (broad-s, 1 H); 7.93 (d, *J* = 4.38 Hz, 1 H); 7.63 (d, *J* = 7.05 Hz, 1 H); 7.55 (broad, 1 H); 7.33 (m, 1 H); 7.30 (m, 1 H); 7.24 (m, 1 H); 7.22 (m, 1 H); 7.04 (s, 1 H); 5.94 (d, *J* = 11.01 Hz, 1 H); 4.46 (m, 1 H); 4.38 (m, 1 H); 4.14 (m, 1 H); 3.41 (dd, *J* = 13.63, 11.92 Hz, 1 H); 3.11 (m, 1 H); 2.94 (m, 1 H); 2.90 (t, *J* = 11.92 Hz, 1 H); 2.84 (d, *J* = 14.34 Hz, 1 H); 2.63 (m,

1 H); 2.25 (m, 1 H); 2.22 (m, 1 H); 2.20 (m, 1 H); 2.05 (d, *J* = 13.84 Hz, 1 H); 1.84 (m, 1 H); 1.79 (m, 2 H); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ ppm: 159.0; 154.1; 153.0; 149.6 (dd, *J* = 244.9, 12.0 Hz); 146.9 (dd, *J* = 244.9, 12.0 Hz); 146.3; 143.4; 139.6; 137.4; 136.2 (d, *J* = 11.1 Hz); 132.8; 124.8 (m); 123.2; 123.0 (m); 122.1; 116.2; 114.9 (d, *J* = 16.6 Hz); 114.2; 75.1; 50.0; 43.0 (2C); 38.7; 36.6; 34.5; 32.0; 28.6 (2C); $^{19}$F NMR (471 MHz, DMSO-$d_6$) δ ppm: -139.5 (d, *J* = 22.2 Hz); -145.6 (d, *J* = 22.2 Hz); CHN calcd for $C_{28}H_{27}F_2N_5O_3$: C63.32, H5.53, N13.14, found C63.72, H5.45, N12.93; HRMS calcd for $C_{28}H_{27}F_2N_5O_3$ [M+H]: 520.2160; found 520.2161. $[\alpha]_D$ = -60.22 (c = 3.43 mg/ml, $CHCl_3$); mp 248 °C (crystals); X-ray structure was obtained.

**Chiral Separation of BMS-846372**

**Analytical Report Summary: *BMS-837999-01-003***

**~90mg of BMS-837999-01-003 was submitted for chiral SFC method development and purification. Due to a lack of sufficient solubility in MeOH or MeOH/MeCN, alternative solvents were required to solubilize this compound. Following evaporation of the MeOH/MeCN mixture to a dry white solid, 5mL of chloroform was added whereupon the solid dissolved to form a clear solution. 5mL of MeOH was added to dilute the chloroform solution to a 50:50 MeOH:chloroform mixture (~9mg/mL solution). No precipitation of the compound was observed. A 50uL aliquot was then removed for analytical chiral method development. The following method provided exceptional enantiomeric resolution and should be suitable for preparative scale-up.**




| Index | Name | Time | Area | Area |
|---|---|---|---|---|
| | | [Min] | [µV.Min] | [%] |
| 1 | UNKNOWN | 6.58 | 91.6 | 48.860 |
| 2 | UNKNOWN | 13.89 | 95.9 | 51.140 |
| | | | | |
| Total | | | 187.5 | 100.000 |

**Method details:**

**Chiralpak AD-H analytical column, 4.6 x 250mm, 5µm**

**Mobile Phase: 50% MeOH in CO2**

**Temp: 35°C**

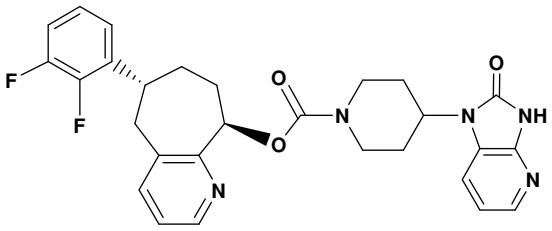
**Flow rate: 2.0 mL/min. for 20 min.**

**UV monitored @ 292nm**

**Injection: 5uL of ~1.0mg/mL solution in 50%MeOH/50%$CHCl_3$**

## Full characterization of BMS-846372

Structure:




**Chemical Formula: $C_{28}H_{27}F_2N_5O_3$**
**MW=519.5**

***Sample Purity:***

**HPLC Purity = 99.6% (@290nm)**

**Purity for Tox. Dosage calculation = 99.0%**

**= %HPLC Purity - (%Moisture + %Solvents + %EI + %Salt )**

**= 99.6% (@ 290nm) - ( 0.11 + 0.54 + 0 + 0 ) = 99.0%**

## LC-UV Purity

***Experimental Details:***

**The sample was dissolved in Methanol at a concentration of 0.33mg/ml; 2ul was injected.**

Method details:
Instrument: Waters Acquity HPLC with Waters PDA UV-Vis detection and Waters ZQ MS (ESCI probe)
Column: Waters Acquity BEH C18; 1.7um ; 150 X 2.1 mm ID; (at 35C)
Mobile phase A: 30mM ammonium carbonate in water pH9.5
Mobile phase B: : Acetonitrile
Flow: 0.35 ml/min
10-98 gradient

Hold 10%B 0-1min

10-98%B 0-32 min

Hold 98%B 32-35 min

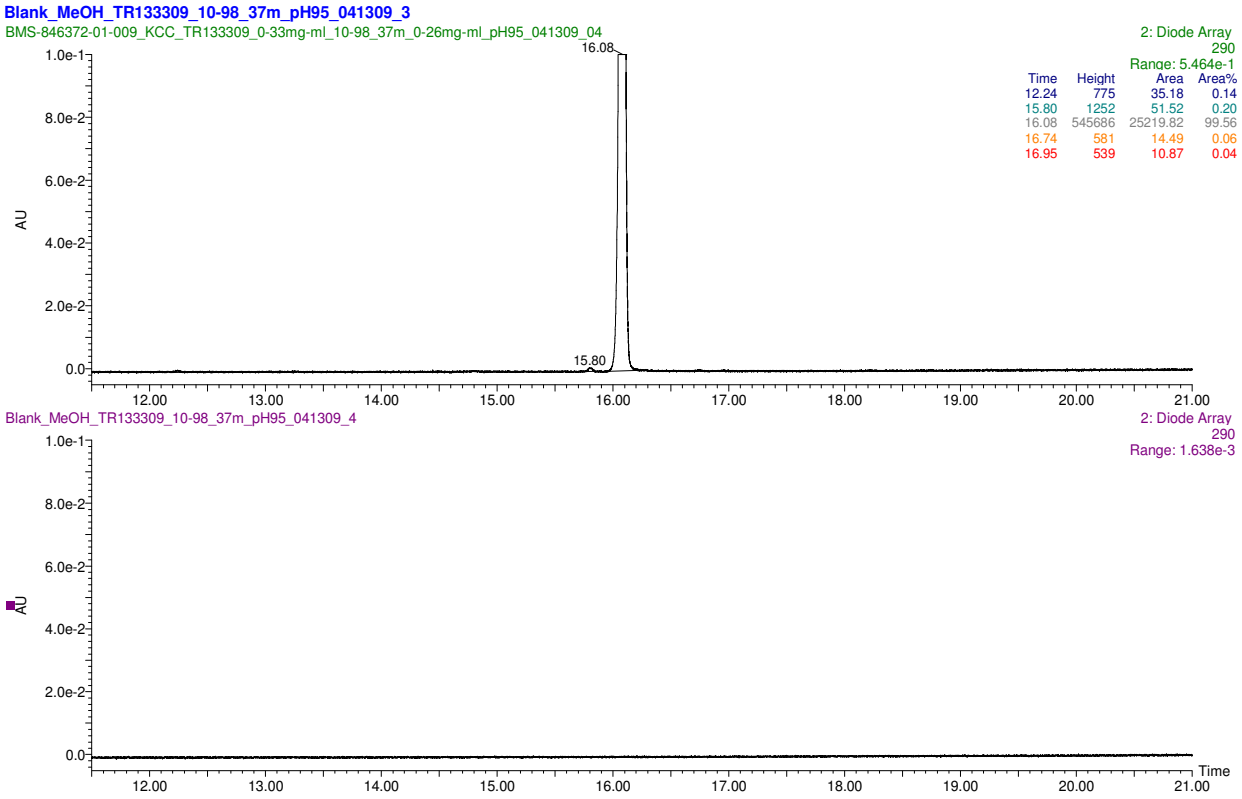
98-10%B 35.0-35.3 min

hold 10%B 35.3-40 min

UV detection:
**UV@ 290nm (220 was also checked)**
UV Sampling: 20 Hz

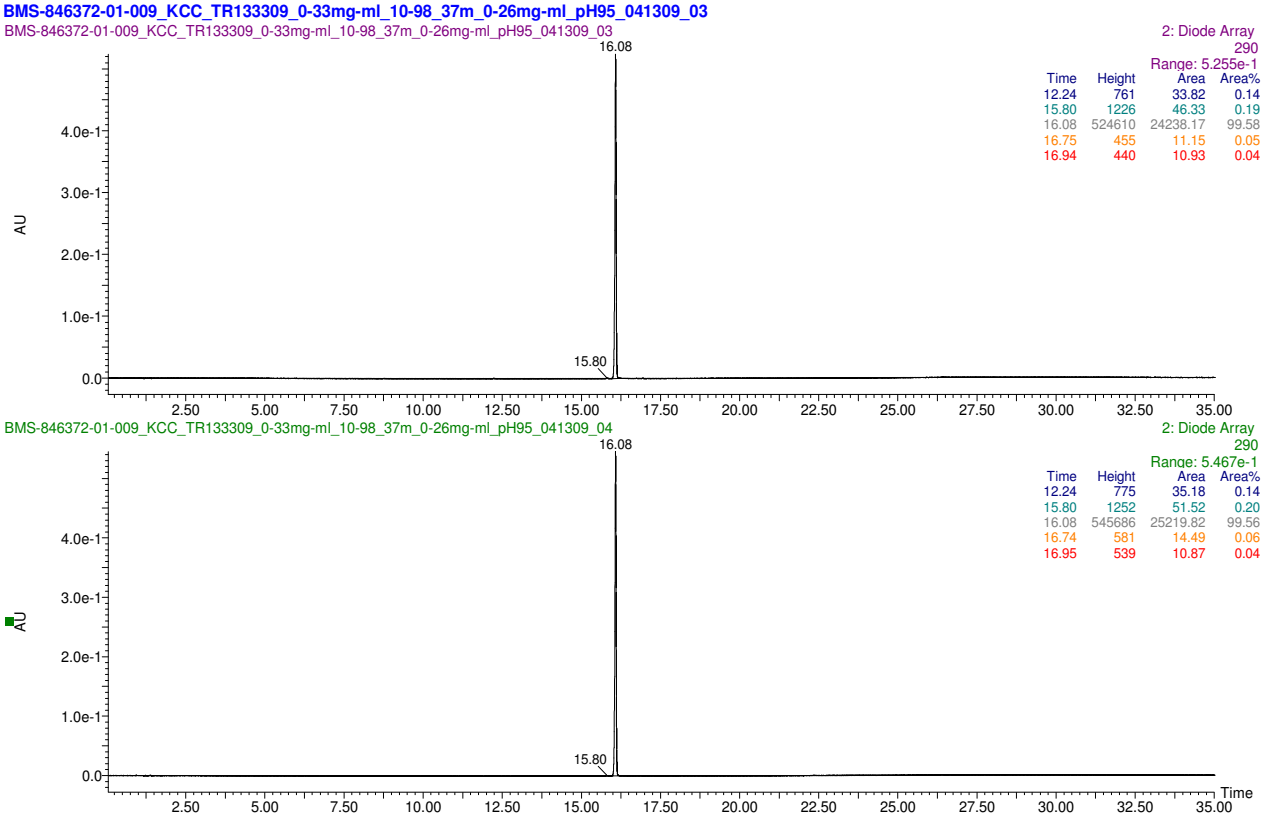
**Result Details are shown below**

**Expanded X and Y view: BMS-846372; TR133309;(top) and Methanol blank (bottom); pH9.5; UV=290nm**

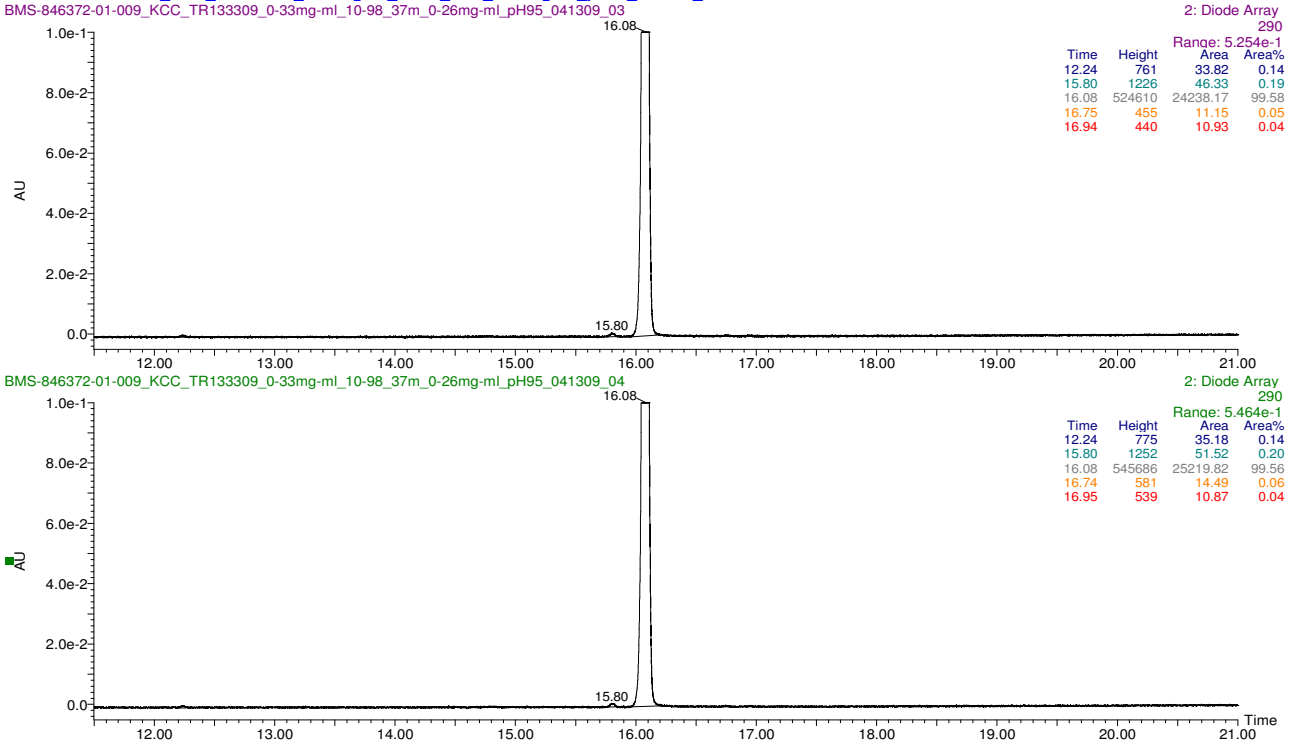



**Full scale view – BMS-846372; TR133309; 79265-047: UV at 290nm – pH9.5**

## duplicate injections




## Expanded X and Y view – BMS-846372; TR133309; 79265-047; UV at 290nm – pH9.5



## Orthogonal Method

**The sample was dissolved in Methanol at a concentration of 0.33mg/ml; 2ul was injected.**

Method details:
Instrument: Waters Acquity HPLC with Waters PDA UV-Vis detection and Waters SQ MS (ESCI probe)
Column: Waters Acquity BEH C18; 1.7um; 150 X 2.1 mm ID; (at 35C)
Mobile phase A: Water with 0.05% TFA
Mobile phase B: Acetonitrile with 0.05% TFA
Flow: 0.35 ml/min
10-40-98 gradient

Hold 10%B 0-1min

10-40%B 1-20 min

40-98%B 20-35 min

Hold 98%B 35-36 min

98-10%B 36.0-36.5 min

hold 10%B 36.5-40 min

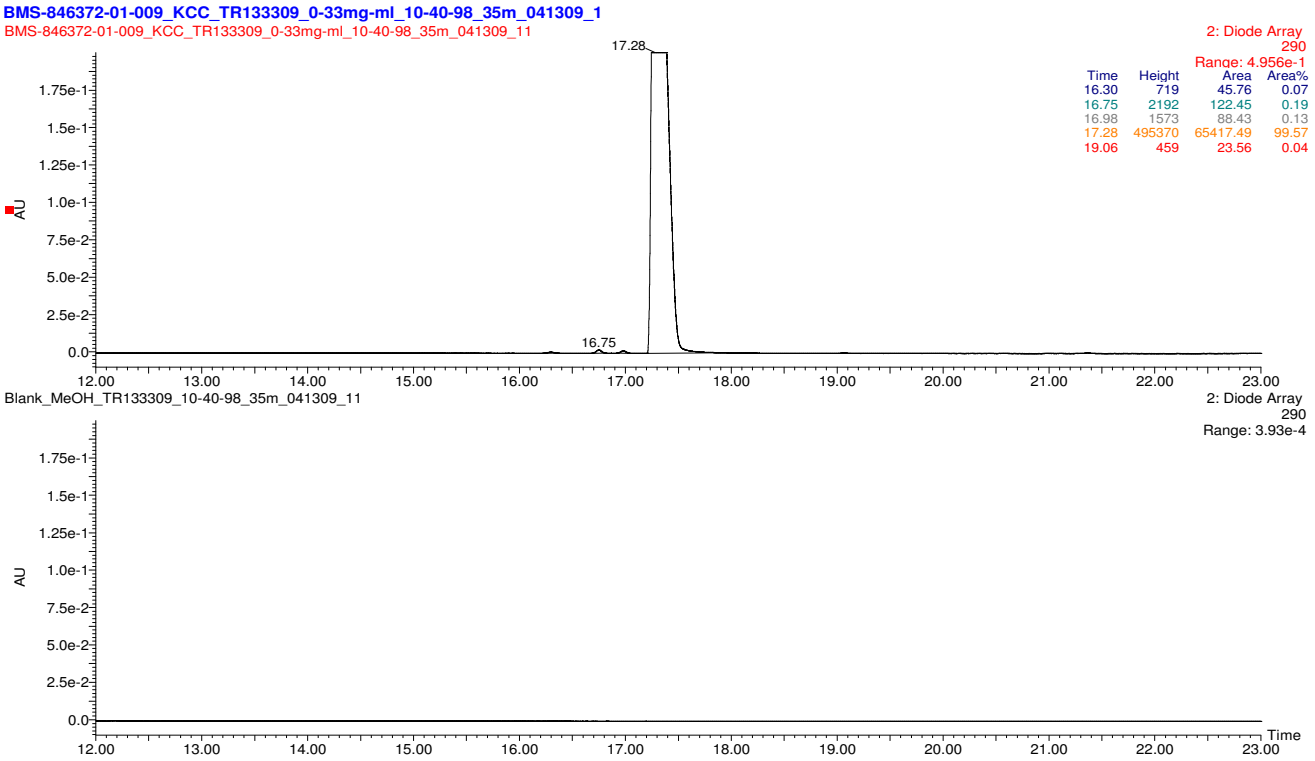
UV detection:
**UV@ 290nm**
**UV Sampling: 20 Hz**

## Tabulated Results using the Orthogonal Method

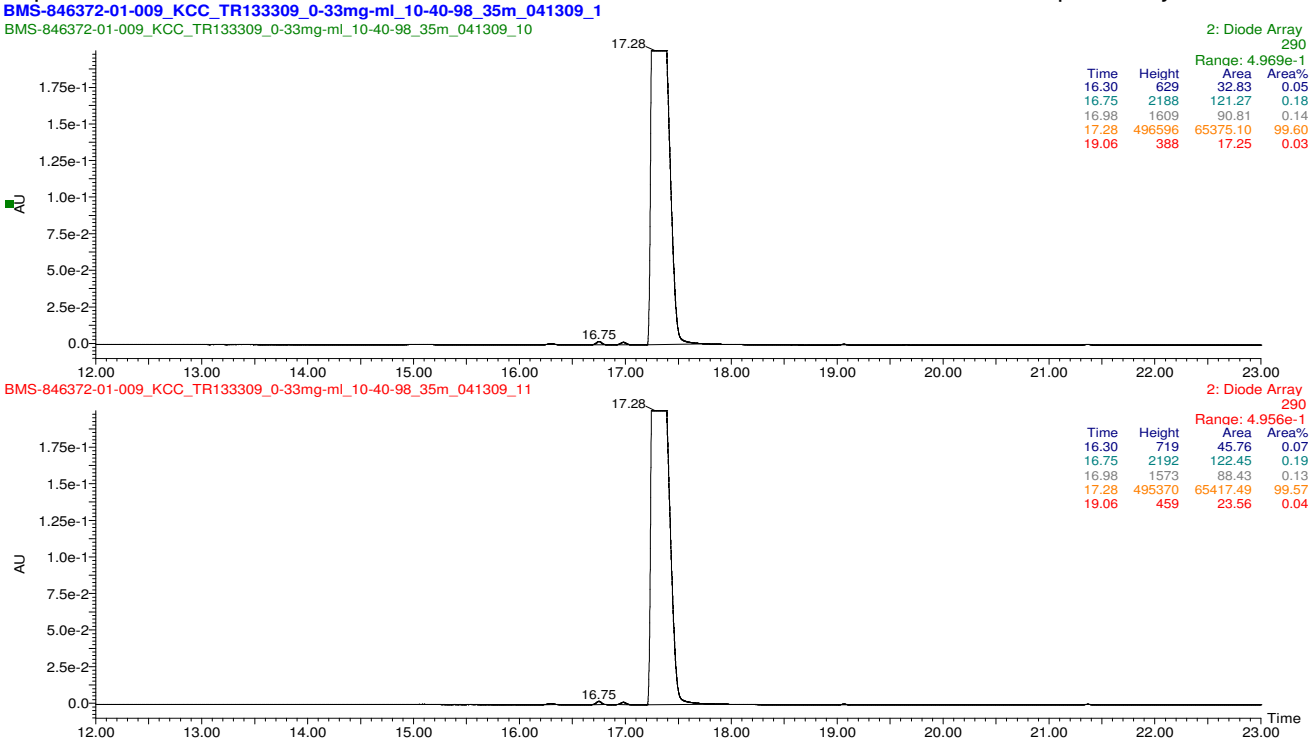
| BMS-846372-01-009; TR133309; 79265-047 10-40-98; 37m; TFA; KCC CGRP: 041409 | | | | | | |
|---|---|---|---|---|---|---|
| | Retention (min) | Area, run 1 | %, run 1 | Area, run 2 | %, run 2 | %, average of 2 |
| **Parent** | 17.3 | 65375 | 99.60% | 65417 | 99.57% | 99.59% |
| **Impurity 1** | 16.3 | 33 | 0.05% | 46 | 0.07% | 0.06% |
| **Impurity 2** | 16.8 | 121 | 0.18% | 122 | 0.19% | 0.19% |
| **Impurity 3** | 17.0 | 91 | 0.14% | 88 | 0.13% | 0.14% |
| **Impurity 4** | 19.1 | 17 | 0.03% | 24 | 0.04% | 0.03% |
| **total** | | 65,637 | 100.00% | 65,697 | 100.00% | 100.00% |

## Orthogonal Method

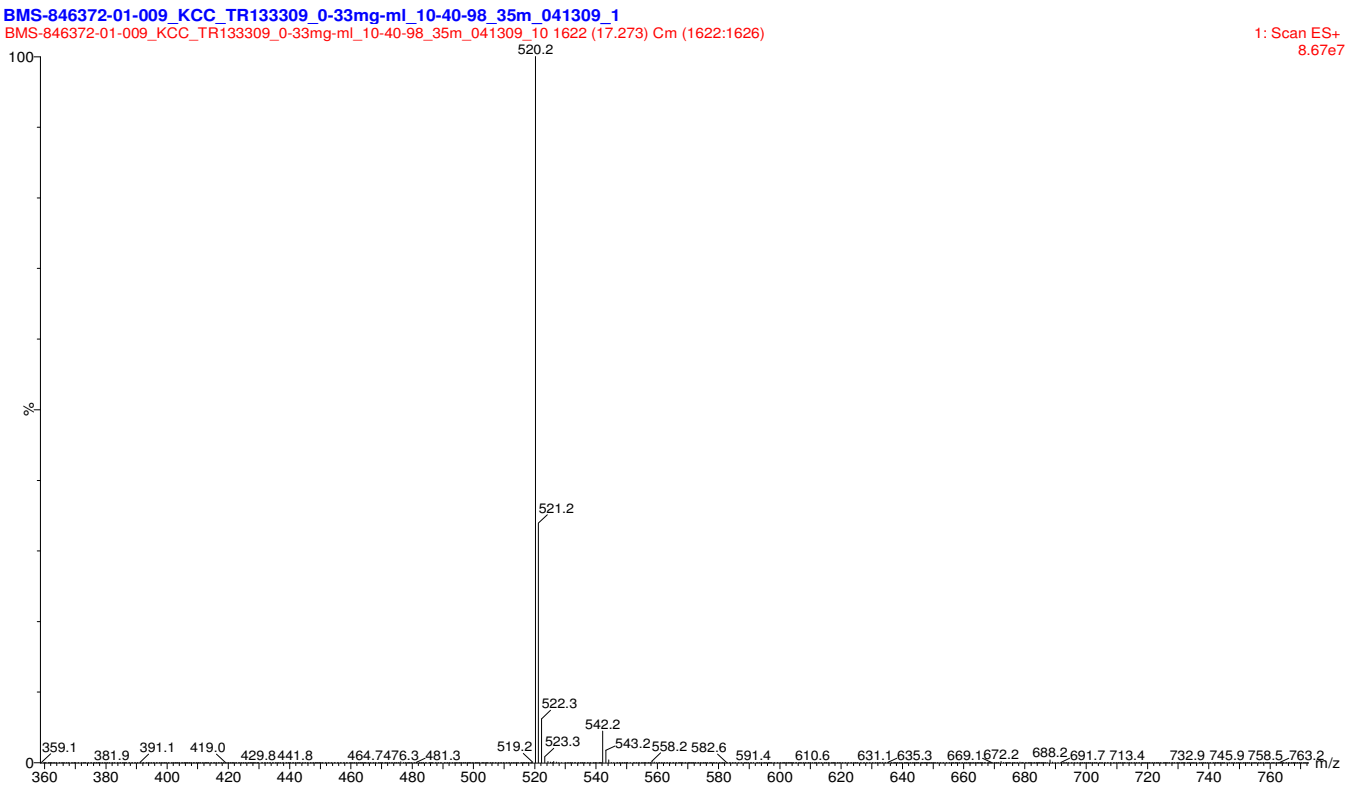
Expanded X and Y view: BMS-846372-01-009; TR133309 (top) and Methanol blank (bottom); UV=290nm




Expanded X and Y view: BMS-846372-01-009; TR133309; 79265-047; UV @290nm – duplicate injections

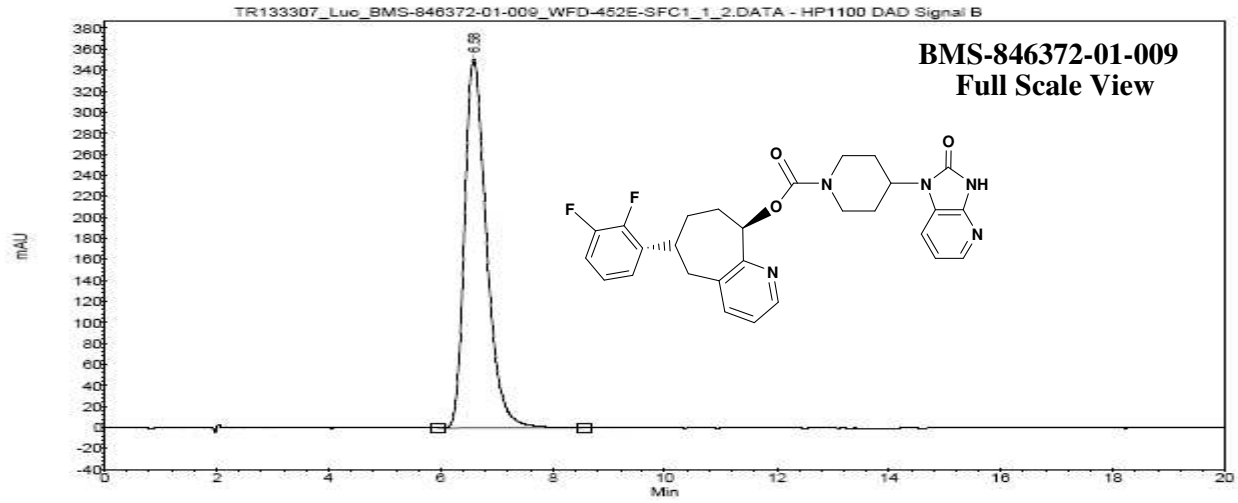


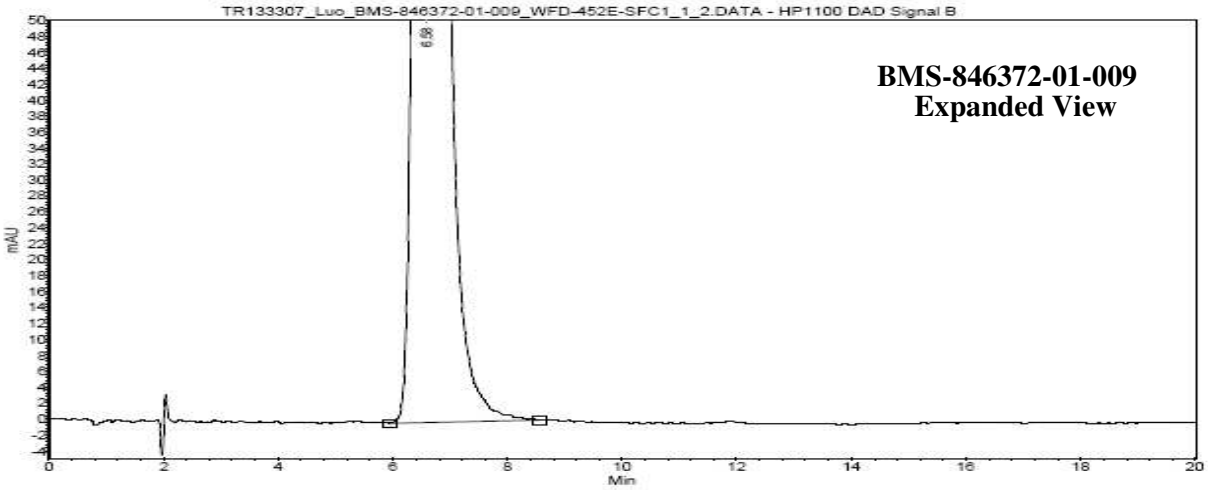

**BMS-846372-01-009; TR133309; 79265-047;**
**ES positive mass spectrum of parent peak eluting at 17.3min; (MW=519)**
**Scan Range 120-1200**




## Chiral Purity

*Analytical Report Summary*: **BMS-846372-01-009 (ee=100.0%, chiral purity=100.0%)**




| Index | Name | Time | Area | Area |
|---|---|---|---|---|
| | | [Min] | [µV.Min] | [%] |
| 1 | UNKNOWN | 6.58 | 159.0 | 100.000 |
| | | | | |
| Total | | | 159.0 | 100.000 |

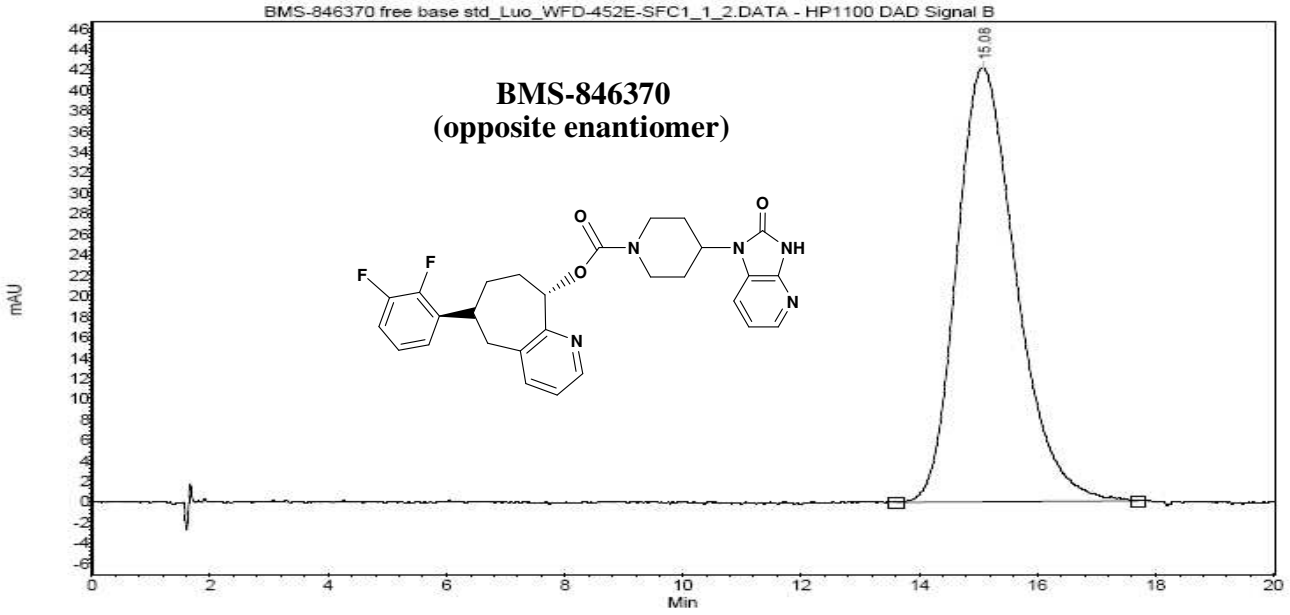
*Analytical Report Summary*: **BMS-846372-01-009 (cont.)**

**Method details:**
**Chiralpak AD-H column, 4.6 x 250mm, 5µm**
**Mobile Phase: 50% MeOH in CO2**
**Temp: 35$^0$C**
**Flow rate: 2.0 mL/min. for 20 min.**
**UV monitored @ 292 nm**
**Injection: 5uL of ~3.0mg/mL in MeOH**

**EE & Chiral Purity Calculations:**
**Enantiomer #1 (RT~ 6.6 min) area %: 100.0**
**Enantiomer #2 (RT~ 15.1 min) area %: 0.0**
**total area %: 100.0**

**EE = 100.0%**
**Chiral Purity = 100.0%**

*Analytical Report Summary*: **BMS-846370 (opposite enantiomer)**




| Index | Name | Time | Area | Area |
|---|---|---|---|---|
| | | [Min] | [µV.Min] | [%] |
| 1 | UNKNOWN | 15.08 | 49.0 | 100.000 |
| | | | | |
| Total | | | 49.0 | 100.000 |

**Method details:**
**Chiralpak AD-H column, 4.6 x 250mm, 5µm**
**Mobile Phase: 50% MeOH in CO2**
**Temp: 35$^0$C**
**Flow rate: 2.0 mL/min. for 20 min.**
**UV monitored @ 292 nm**
**Injection: 5uL of ~3.0mg/mL in MeOH**

# NMR Analysis

***Summary*:**

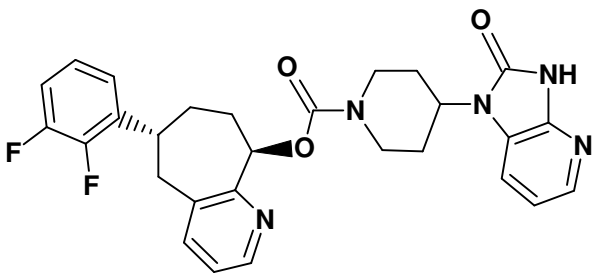
The proton, carbon, and fluorine ($^{1}H$, $^{13}C$, $^{19}F$) spectra of BMS-846372-01-009 were acquired at 300K in DMSO-$d_6$ to confirm the structure. The observed $^{1}H$, $^{13}C$, and $^{19}F$ data were consistent with the reported structure and the previous lot, BMS-846372-01-003 (TR127401, 06/16/08).

There were about 3.3 mol% (or, 0.4 wt%) of isopropanol observed in proton spectrum.

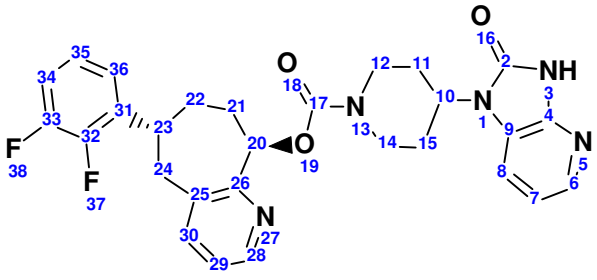
There was no detectable impurity in this sample.

The absolute stereochemistry of this molecule was not determined in this NMR analysis.

***Structure:***




***ACD-NMR numbering:***




***Experimental conditions*:**

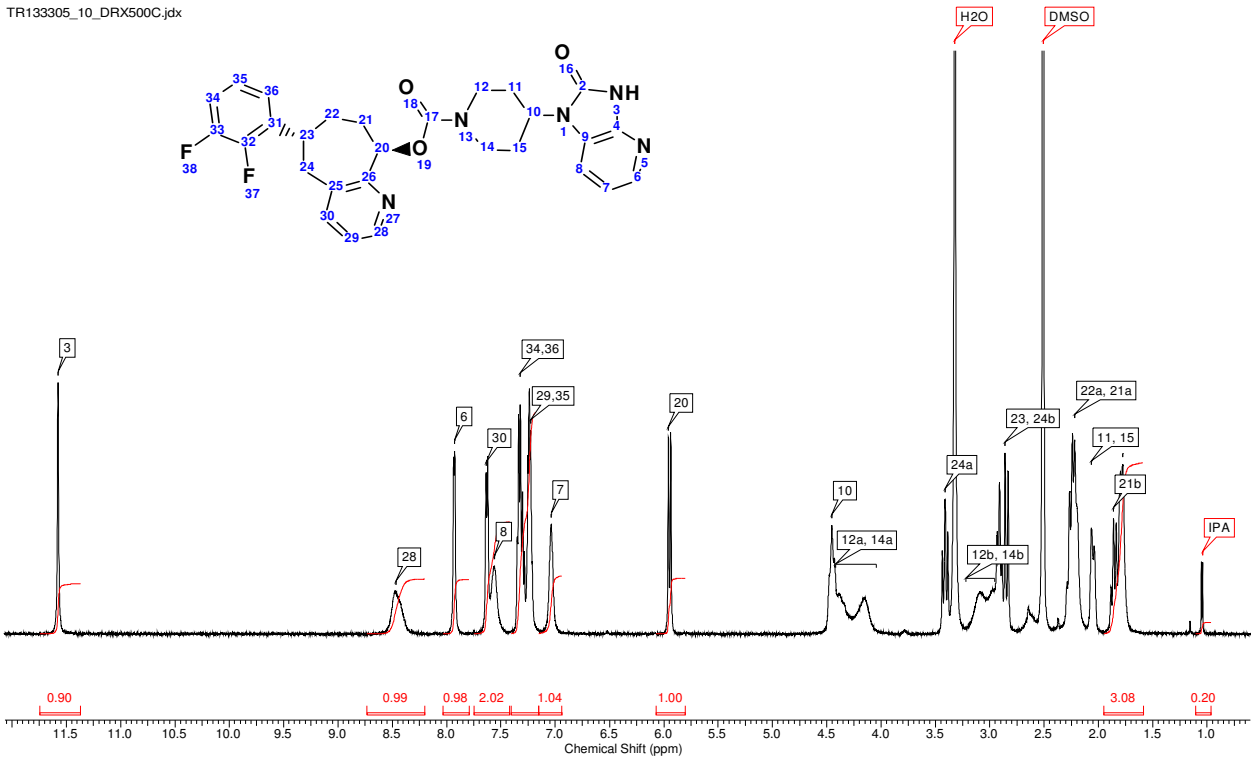
Spectrometer(s): a500, d500c

Experiments: 1D $^{1}H$, $^{13}C$, $^{19}F$; .

***Solvents:*** *DMSO-$d_6$*

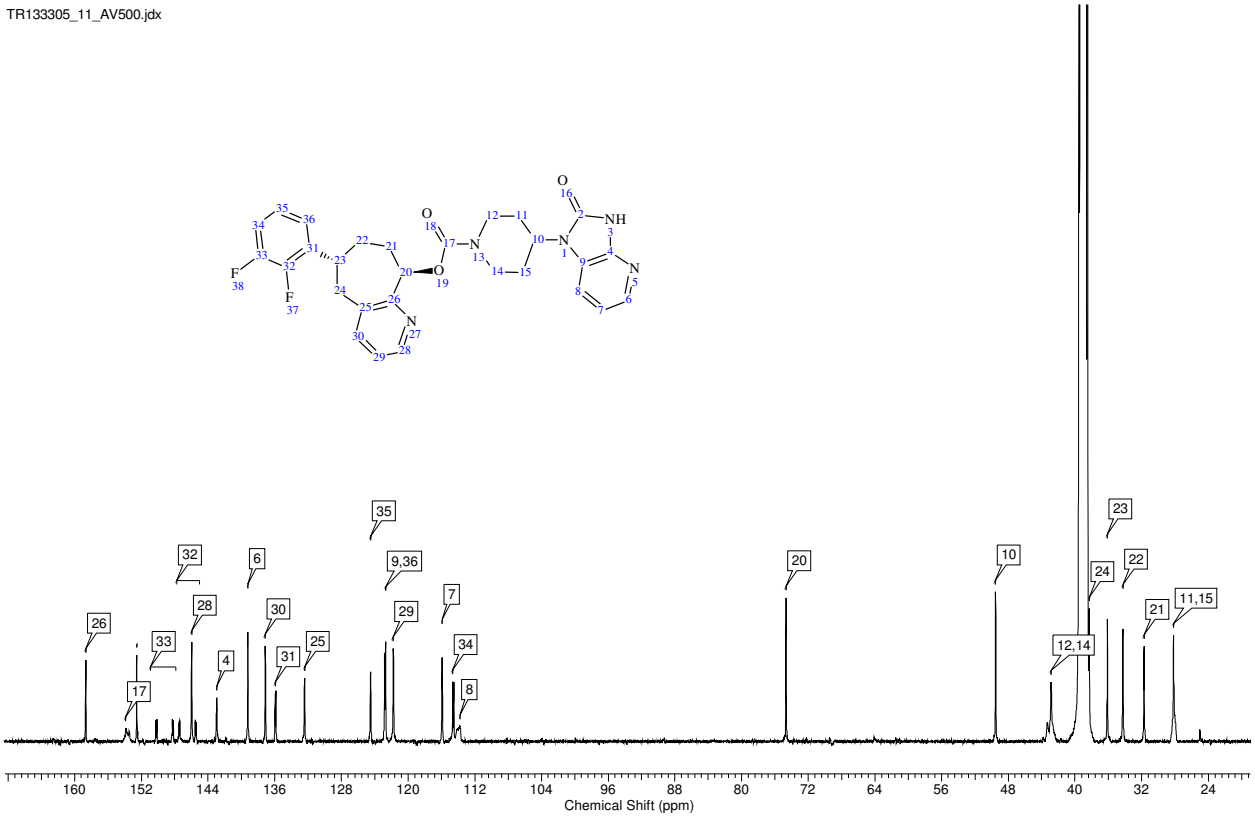
***Sample Amount:*** 4.5 mg/650 µl; 5 mm NMR tube

## Proton Spectrum of BMS-846372-01-009 (TR133305) in DMSO-$d_6$:



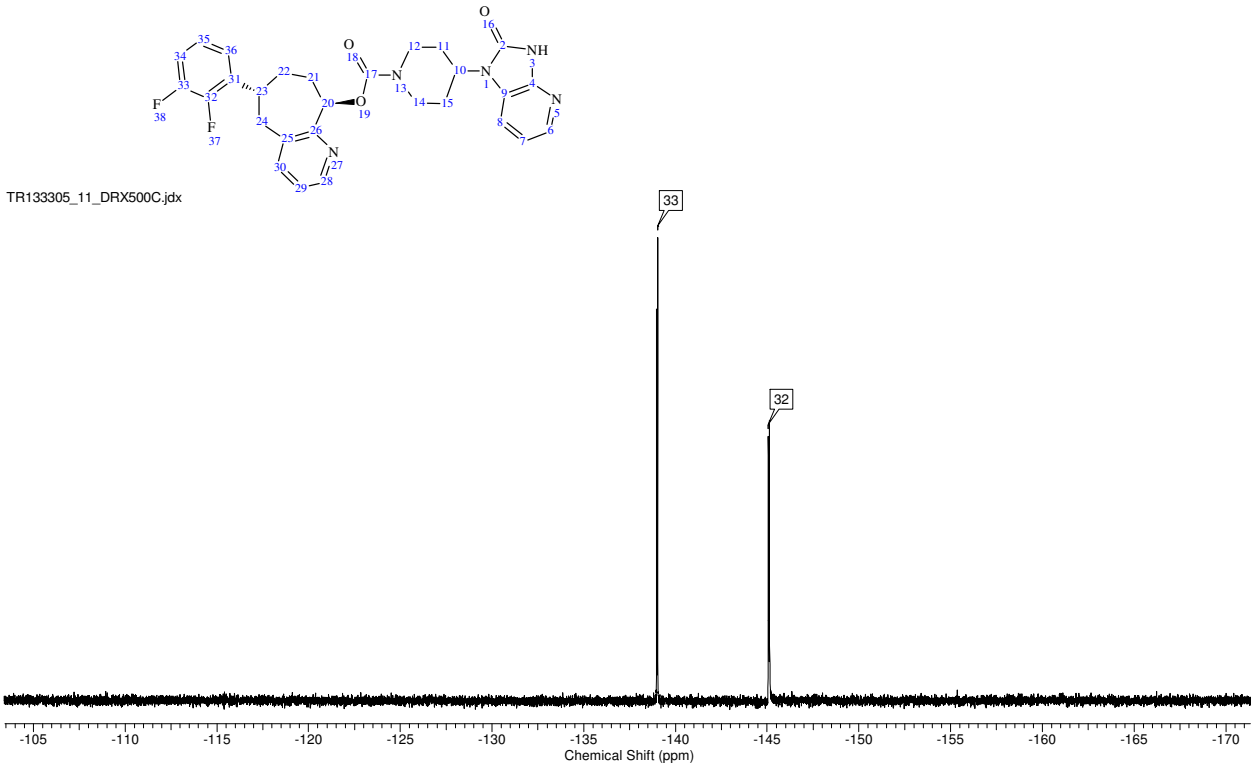

Experimental: 4.5 mg sample dissolved in 650 μl DMSO-$d_6$, 500 MHz, 4 scans with cryo probe, 1 sec of relaxation delay time, 32K points at 300K. The $^1$H chemical shift was referenced to TMS at 0.0 ppm.

## Carbon Spectrum of BMS-846372-01-009 (TR133305) in DMSO-$d_6$:




Experimental: 4.5 mg sample dissolved in 650 µl DMSO-$d_6$, 500MHz NMR. Carbon resonance frequency 125.73 MHz, 10k scans, 32K points at 300K. The $^{13}C$ chemical shift was referenced to TMS at 0.0 ppm.

## Fluorine Spectrum of BMS-846372-01-009 (TR133305) in *DMSO-$d_6$*:



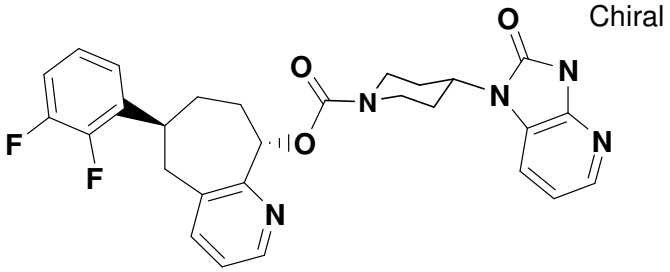

Experimental: 4.5 mg sample dissolved in 650 µl *DMSO-$d_6$*, 500 MHz NMR. Fluorine resonance frequency 470.5 MHz, 256 scans, 64K points at 300K, protons were coupled. The $^{19}F$ chemical shift was referenced to $CFCl_3$ at 0.0 ppm.

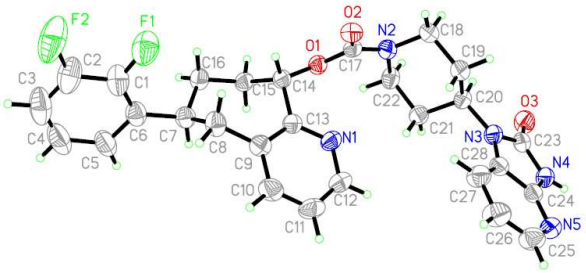
## X-ray structure of BMS-846372


**Summary:**

The submitted sample of BMS-846372 was crystallized from methanol and the crystal structure is determined by single crystal X-ray analysis (74016-057). It is a neat form. The inter-molecular hydrogen bond between amide group (N4) and carbonyl group (O2) connects the API molecules into a 1D motif. The relative stereochemistry is confirmed. The crystal does not contain a reference chiral center or heave atoms, thus the absolute configuration is not determined.


**Structures:**




**Crystal Data:**

Chemical formula: $C_{28}H_{27}O_3N_5F_2$

*Fw* = 519.55

Crystal system: Orthorhombic

Space Group : $P2_12_12_1$

$a$ = 7.5941(1) Å $\alpha = 90°$

$b$ = 13.8789(2) Å $\beta = 90°$

$c$ = 24.7319(3) Å $\gamma = 90°$

$V$ = 2606.69(6) Å$^3$

$Z = 4$ $d_x = 1.324$ g cm$^{-3}$ $\mu = 0.098$ mm$^{-1}$

$\theta$ range for lattice parameters (°): 1.65 to 27.48

**Experimental:**

*Crystallization*

Crystal source: MeOH

Crystal description: colorless block

Crystal size (mm): 0.45 x 0.33 x 0.30

*Data Collection*

Temperature (K): 298

$\theta_{max}$ (°): 27.48 (Mo Kα)

No. of reflections measured: 5956

No. of independent reflections: 5956 ($R_{int}$ = 0.000)

No. of observed reflections ($I \geq 2\sigma$): 3923

**Refinement:**

No. of parameters refined: 345 No. of reflections used: 3923 $-0.827 \leq \Delta\rho \leq 0.836$ e/Å$^3$

*R1* = 0.0759 *wR2* = 0.1541 *S* = 1.114 $w = 1/[\sigma^2 (Fo^2) + (0.1244P)^2 + 0.0000P]$ $P = (Fo^2 + 2 Fc^2)/3$

*Treatment of Hydrogen Atoms*:

All hydrogen atoms were visible on the Fourie difference maps and calculated using idealized geometry with standard bond lengths and angles during structure refinement. They had been assigned isotropic temperature factors and were included in structure factor calculations with fixed parameters.