

Supporting Information

Content:

1. General Procedure for the synthesis of diethyl 2-(iodomethyl)cyclopropane-1,1-dicarboxylate (Step-1):..... S1
2. General Procedure for the synthesis of diethyl 2-methylenecyclopropane-1,1-dicarboxylate(Step-2):..... S2
3. General Procedure for the synthesis of (2-methylenecyclopropane-1,1-diyl)dimethanol (Step-3): S3
4. General Procedure for the synthesis of (2-methylenecyclopropane-1,1-diyl)bis(methylene) diacetate (Step-4):S4
5. General Procedure for the synthesis of (2-bromo-2-(bromomethyl)cyclopropane-1,1-diyl)bis(methylene) diacetate (Step-5):.... S5
6. Copies of ¹HNMR FT-IR, Ms and ¹³CNMR.....
7. **Tables:**
8. **Table 1.**Design, Physico-chemical and pharmacokinetic properties of pyrimidine-based carbocyclic nucleoside derivatives.
Table 2: Docking and Amino Acid interactions of the synthesized compounds
Table 3: *In vitro* studies of the synthesized compounds
9. **Figures:**
10. **Figure 1:** Zone of inhibition (A) against *Bacillus cereus* at 25µl, 50 µl, 75 µl and 100 µl (B) against *Aspergillus niger* was not observed
11. **Figure 2:** Ciprofloxacin control against the test organisms showing Zone of Inhibition
12. **IC50 graphs**

Experimental section

Materials and Methods

All chemicals (reagent grade) used were purchased from Combi-Blocks (USA), Johnson Matthey Co., Ltd. (USA) and EnamineLtd. (Ukraine). All the solvents used for the reaction are LR grade. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60F₂₅₄ plates, and visualisation on TLC was achieved by UV light. Flash column chromatography was undertaken on silica gel (100–200 mesh). ¹H NMR was recorded on 400 or 500 MHz, and chemical shifts were quoted in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane.

The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q =quartet, m = multiplet, dd = doublet of doublet. Coupling constants, *J*, were reported in the hertz unit (Hz). ESI mass spectra were obtained on Agilent and Waters instruments. All the final compounds were purified on GRACE flash chromatography by using C18 reverse-phase columns. The mobile phase was a mixture of water (0.1% formic acid) and acetonitrile. Melting points were recorded on the Buchi M-560 instrument.

Experimental procedure for Intermediate-6:

Synthesis of diethyl 2-(iodomethyl)cyclopropane-1,1-dicarboxylate(Step-1): NaH(60% suspension) (359.5 g, 5.99 moles) and tetrahydrofuron (10 L) were charged in to a 100 L GLR reactor under argon atmosphere at 25 – 30 °C and cooled to -5 °C to 0 °C (internal temperature). A solution of diethyl 2-allylmalonate (**1**) (1.5 Kg, 4.99 moles) in tetrahydrofuron (2 L) was added drop wise at -5 °C to 10 °C (Internal temperature) over 1 h. After completion of addition, reaction mixture was allowed to warm to 25 °C to 30 °C and stirred for 1 h. To this reaction mixture iodine (1.521 Kg, 5.99 moles) in tetrahydrofuron (8 L) was added drop wise at -5 °C to 10 °C over 1.5 h. After completion of addition, reaction mixture was allowed to warm to 25 °C to 30 °C and stirred for 16 h under argon atmosphere. The progress of the reaction was monitored by TLC.

Reaction mixture was poured into ice water (15 L), ethyl acetate (10 L) was added and stirred for 15 min and separated both the layers. The aqueous layer was extracted with ethyl acetate (5 L). The combined organic layer was washed with sat. Sodium thiosulfate solution (10 L)

and brine solution (5 L). The organic layer was dried over anhydrous Na₂SO₄, filter and concentrated under reduced pressure to obtain crude compound. The crude compound was purified by column chromatography on silica gel (100-200 mesh) with 0-10% ethyl acetate in pet ether. The pure fractions were collected and concentrated to afford 1.07 kg (66%) of compound-2 as pale yellow liquid.

¹H-NMR (CDCl₃) δ(ppm): 4.28-4.15 (m, 4H), 3.27-3.08 (m, 2H), 2.47-2.04 (m, 1H), 1.59-1.33 (m, 2H), 1.31-1.24 (m, 6H); MS: m/z: 327.3 [M+H]⁺. Data matches with literature values.

Synthesis of diethyl 2-methylenecyclopropane-1,1-dicarboxylate (Step-2): Potassium tert-butoxide (189.21 g, 1.68 moles) and tetrahydrofuron (6.5 L) were charged in to a 20 L, 4N RBF 25 – 30 °C under argon atmosphere. The reaction mixture was cooled to -40 °C (internal temperature). A solution of compound (2) (500 g, 1.53 moles) in tetrahydrofuron (1.5 L) was added drop wise at -40 °C to -30 °C under argon atmosphere. After completion of addition, reaction mixture was allowed to warm to 25 °C to 30 °C and stirred for 16 h. The progress of the reaction was monitored by TLC.

Reaction mixture was poured into ice water, ethyl acetate (5 L) was added and stirred for 10 min and separated both the layers. The aqueous layer was extracted with ethyl acetate (2.5 L). The combined organic layer was washed with sat. brine solution (2.5 L). The organic layer was dried over anhydrous Na₂SO₄, filter and concentrated under reduced pressure to obtain crude compound. The crude compound was purified by column chromatography on silica gel (230-400 mesh) with 0-10% ethyl acetate in pet ether. The pure fractions were collected and concentrated to afford 90 g (30%) of compound-3 as pale yellow liquid.

¹H-NMR (CDCl₃) δ(ppm): 5.64-5.54 (m, 2H), 4.25-4.17 (m, 4H), 2.47-2.04 (m, 1H), 1.59-1.33 (m, 2H), 1.31-1.24 (m, 6H); MS: m/z: 199.2 [M+H]⁺. Data matches with literature values.

Synthesis of (2-methylenecyclopropane-1,1-diyl)dimethanol (Step-3): Compound-3 (250 g, 1.26 moles) and tetrahydrofuron (1.5 L) were charged in to a 10 L, 4N RBF 25 – 30 °C under argon atmosphere. To this solution LiAlH₄ (1.513 L, 1.51 moles, 1.0 M in THF) was added drop wise at 0 °C to -10 °C under argon atmosphere. After completion of addition, reaction mixture was stirred at 0 °C for 3 h. The progress of the reaction was monitored by TLC and HPLC.

Reaction mixture was cooled to 0 °C and quenched with 5% H₂O in EtOAc (2.5 L). The resulting reaction mixture was allowed to warm 25 -30 °C and stirred for 30 min. The

reaction mass was filtered on celite pad and washed the celite pad with 50%ethyl acetate in CH₂Cl₂ (50 V). The filtrate was dried over anhydrous Na₂SO₄, filter and concentrated under reduced pressure to obtain 144 g (Crude) of compound-4 as pale yellow liquid. Crude proceeded to next step without any further purification.

Synthesis of (2-methylenecyclopropane-1,1-diyl)bis(methylene) diacetate (Step-4):Compound-4 (144 g, 1.26 moles) in pyridine (2.3 V) was charged in to a 3 L, 4N RBF 25 – 30 °C under argon atmosphere. To this solution acetic anhydride (705.6 mL, 4.9 V) was added drop wise at 0 °C to 10 °C under argon atmosphere. After completion of addition, reaction mixture was stirred at 25 °C – 30 °C for 12 h. The progress of the reaction was monitored by TLC.

Reaction mixture was distilled off under reduced pressure and dissolved in ethyl acetate (1.5 L). The organic layer was washed with 1N HCl solution (1 L), sat.NaHCO₃ solution (1L) and sat. Brine solution (1 L). The organic layer was dried over anhydrous Na₂SO₄, filter and concentrated under reduced pressure to obtain crude compound. The crude compound was purified by column chromatography on silica gel (100-200 mesh) with 0-10% ethyl acetate in pet ether. The pure fractions were collected and concentrated to afford 133 g (53% on over 2 steps) of compound-5 as pale yellow liquid.

¹H-NMR (CDCl₃) δ(ppm): 5.64-5.54 (m, 2H), 4.25–4.17 (m, 4H), 2.05 (s, 6H), 1.59-1.33 (m, 2H); MS: m/z: 199.3 [M+H]⁺.Data matches with literature values.

Synthesis of (2-bromo-2-(bromomethyl)cyclopropane-1,1-diyl)bis(methylene) diacetate (Step-5):Compound-5 in carbon tetrachloride (1.33 L) was charged in to a 5 L, 4N RBF under argon atmosphere at 25 – 30 °C. To this stirred solution bromine (41.50 mL, 0.805 moles) was added drop wise at 0 °C to 10 °C under argon atmosphere. After completion of addition, reaction mixture was stirred at same temperature for 2 h. The progress of the reaction was monitored by TLC.

Reaction mixture was cooled to 0 °C and quenched with sat. Sodium thiosulfate solution (1.33 L), stirred for 15 min and separated both the layers. The aqueous layer was extracted with ethyl acetate (5 L). The combined organic layer was washed with sat. Sodium thiosulfate solution (700 mL) and brine solution (700 mL). The organic layer was dried over anhydrous Na₂SO₄, filter and concentrated under reduced pressure to obtain crude compound. The crude compound was purified by column chromatography on silica gel (230-400 mesh) with 10-20% ethyl acetate in pet ether. The pure fractions were collected and concentrated. The

residue was triturated with n-pentane (2V), the solid compound was filtered and dried to afford 141 g (59%) of **Di bromo intermediate** as pale yellow liquid.

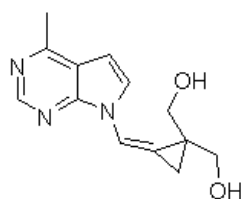
$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 4.51-4.49 (d, $J = 8.0\text{Hz}$, 2H), 4.33–4.20 (m, 4H), 3.98-3.74 (m, 2H), 2.11 (s, 3H), 2.09 (s, 3H), 1.48-1.33 (m, 2H); MS: m/z : 356.92 $[\text{M}+\text{H}]^+$. Data matches with literature values.

Compound-8a(peak-1)

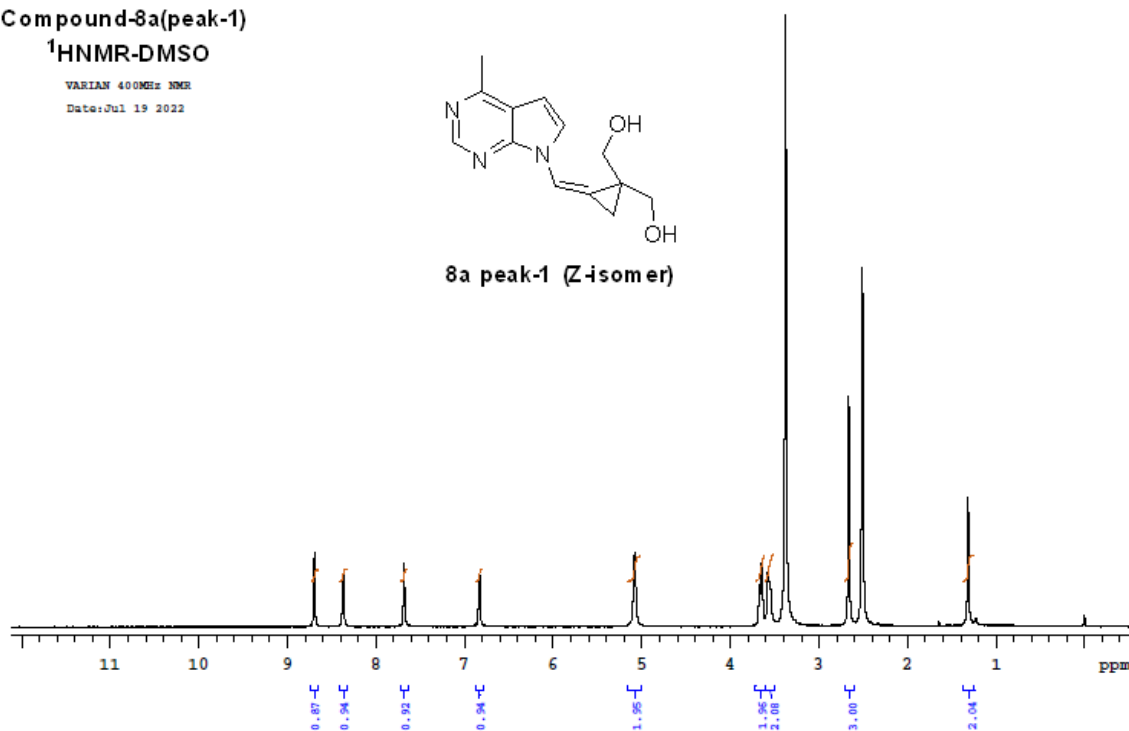
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VARIAN 400MHz NMR

Date:Jul 19 2022

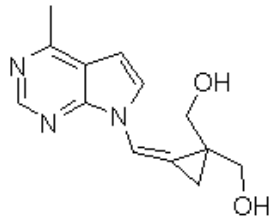


8a peak-1 (Z-isomer)

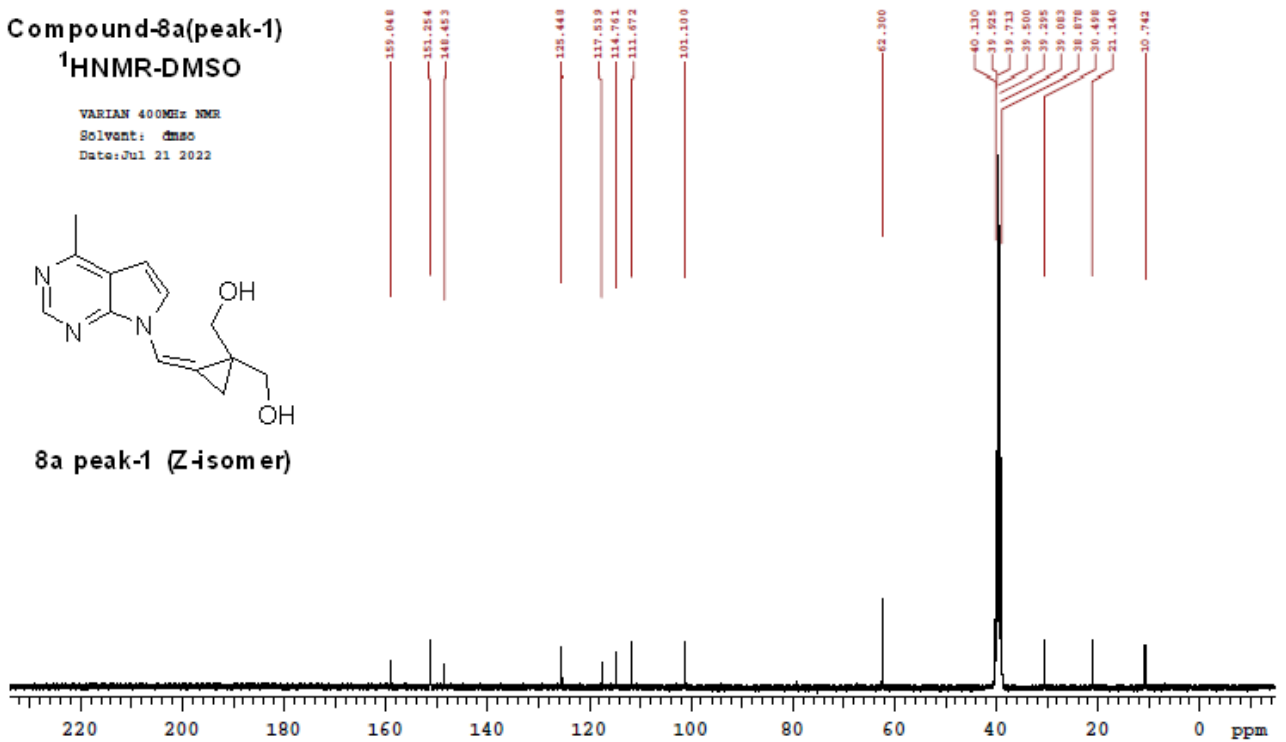


Compound-8a(peak-1)
¹HNMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsc
Date: Jul 21 2022

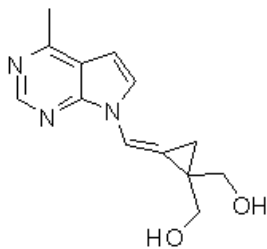


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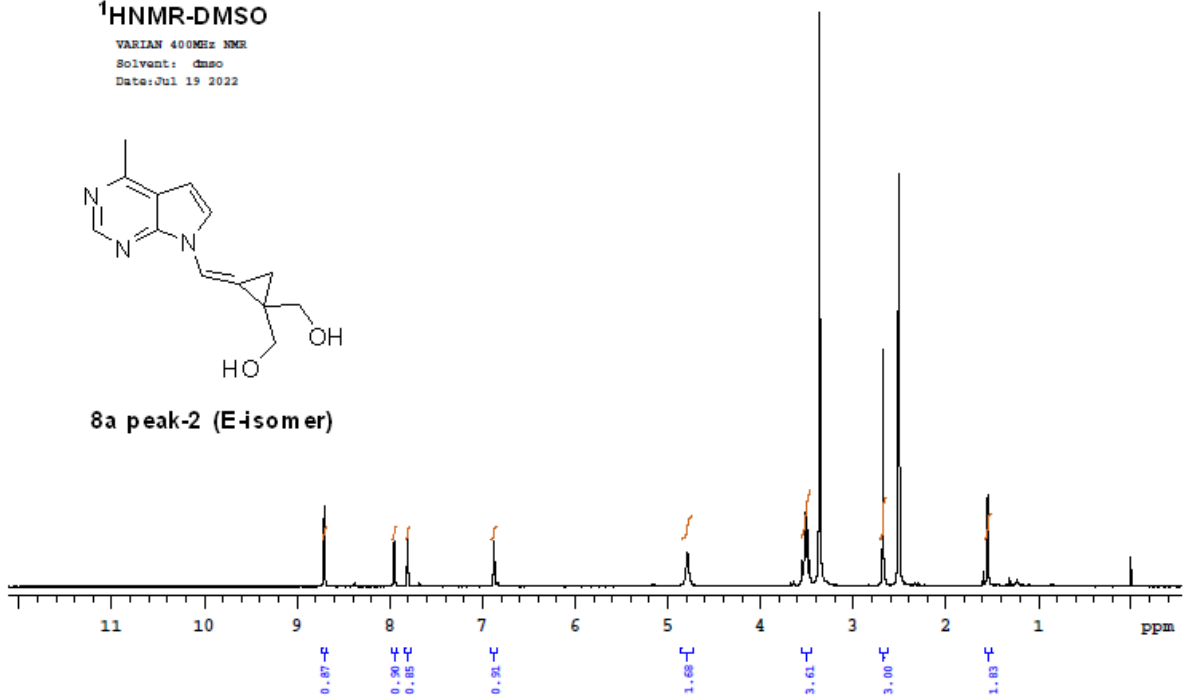


Compound-8a(peak-2)
¹HNMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsc
Date: Jul 19 2022



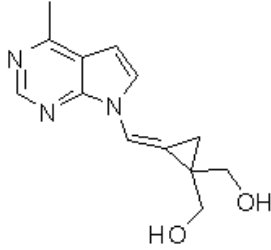
8a peak-2 (E-isomer)



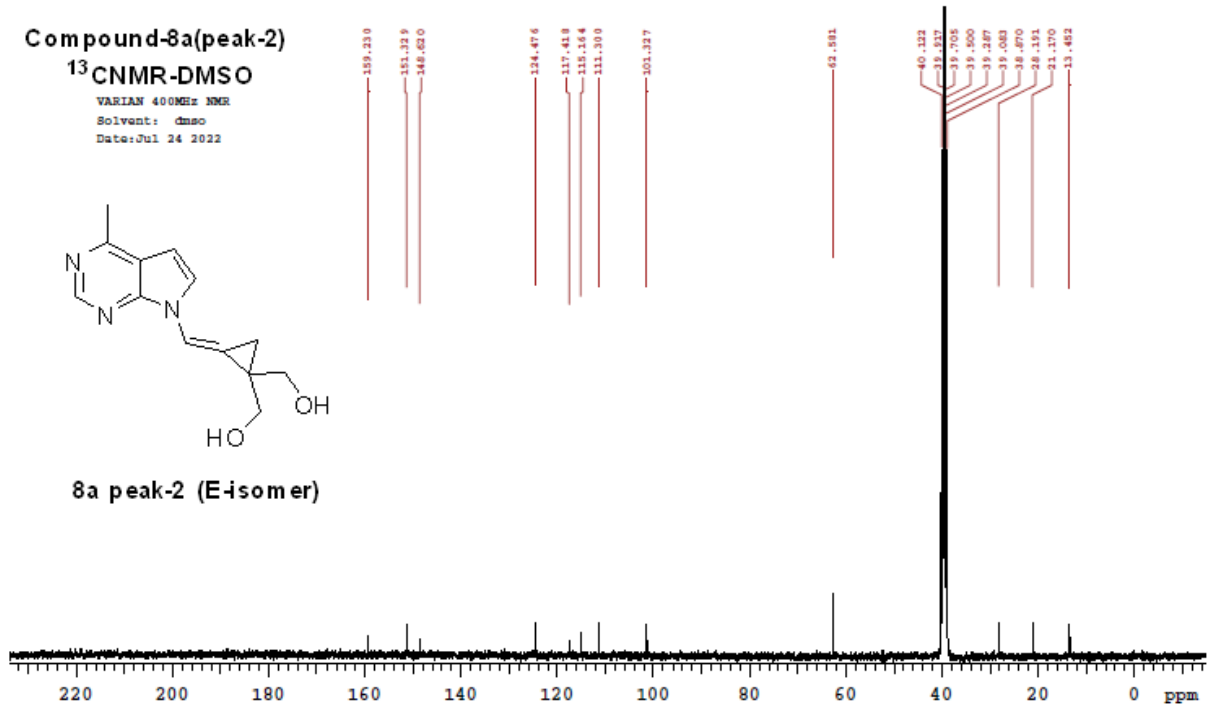
Compound-8a(peak-2)

¹³CNMR-DMSO

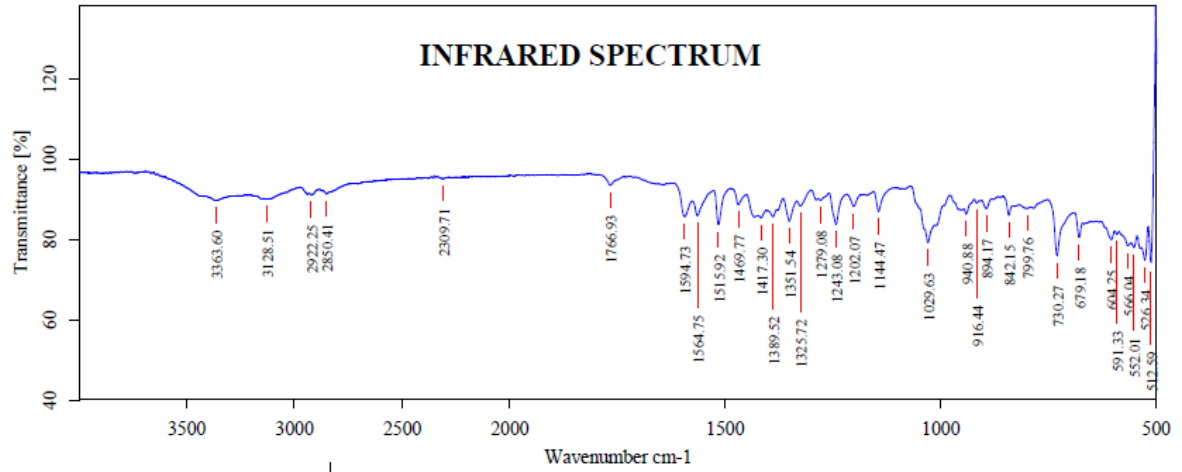
VARIAN 400MHz NMR
Solvent: dmsd
Date: Jul 24 2022



8a peak-2 (E-isomer)

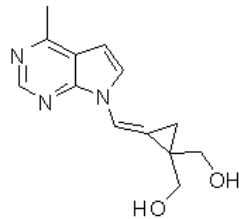


INFRARED SPECTRUM



Compound-8a(peak-2)

Lot No./Batch No:
Date & Time: 20-07-2022, 17:55:24
Operator Name: Accu Chemist

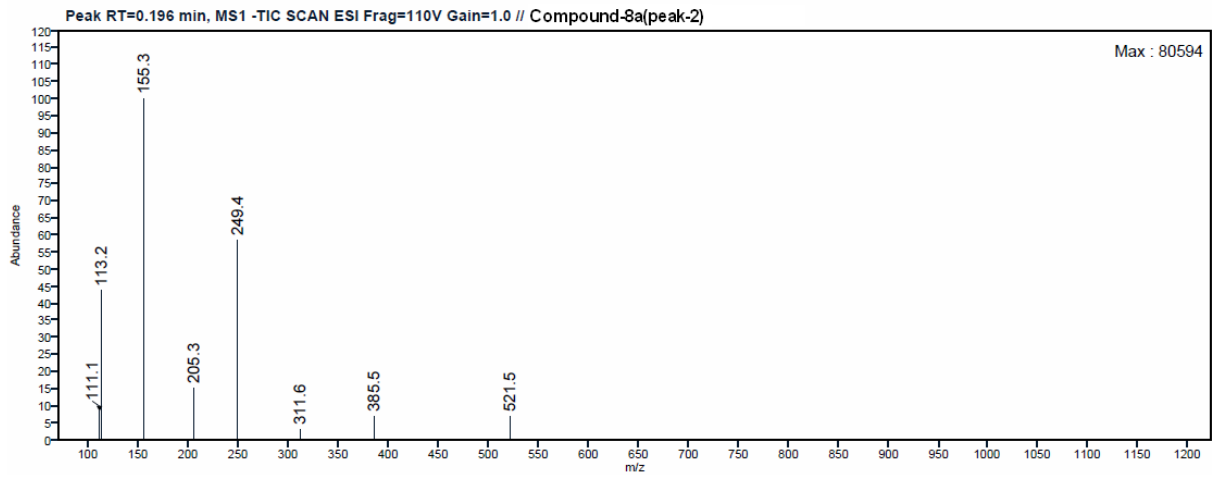
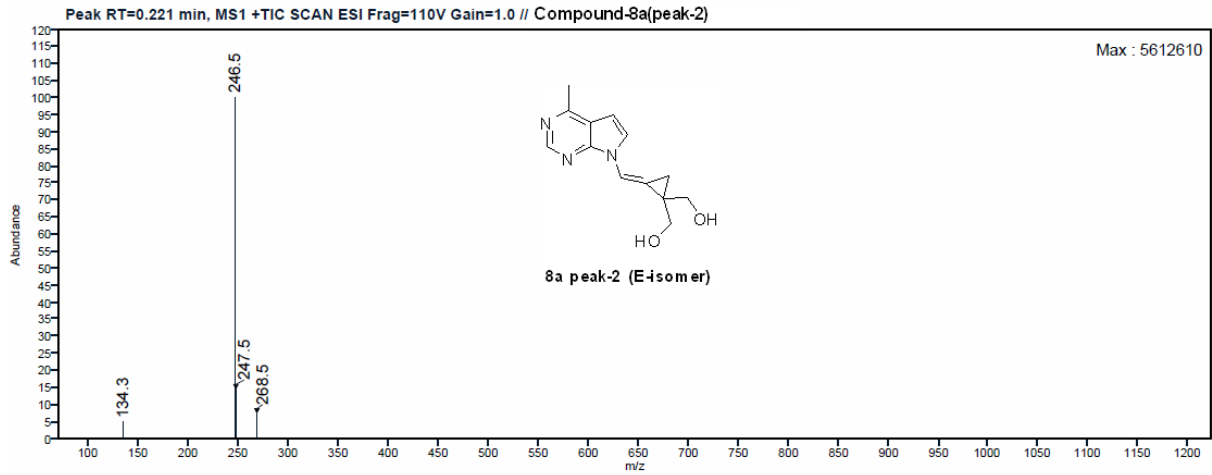


8a peak-2 (E-isomer)

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Sample Scans: 16
Frequency Range: 4000 to 500

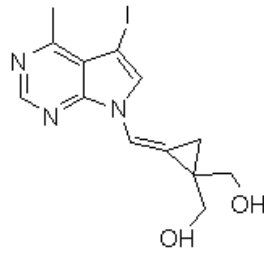
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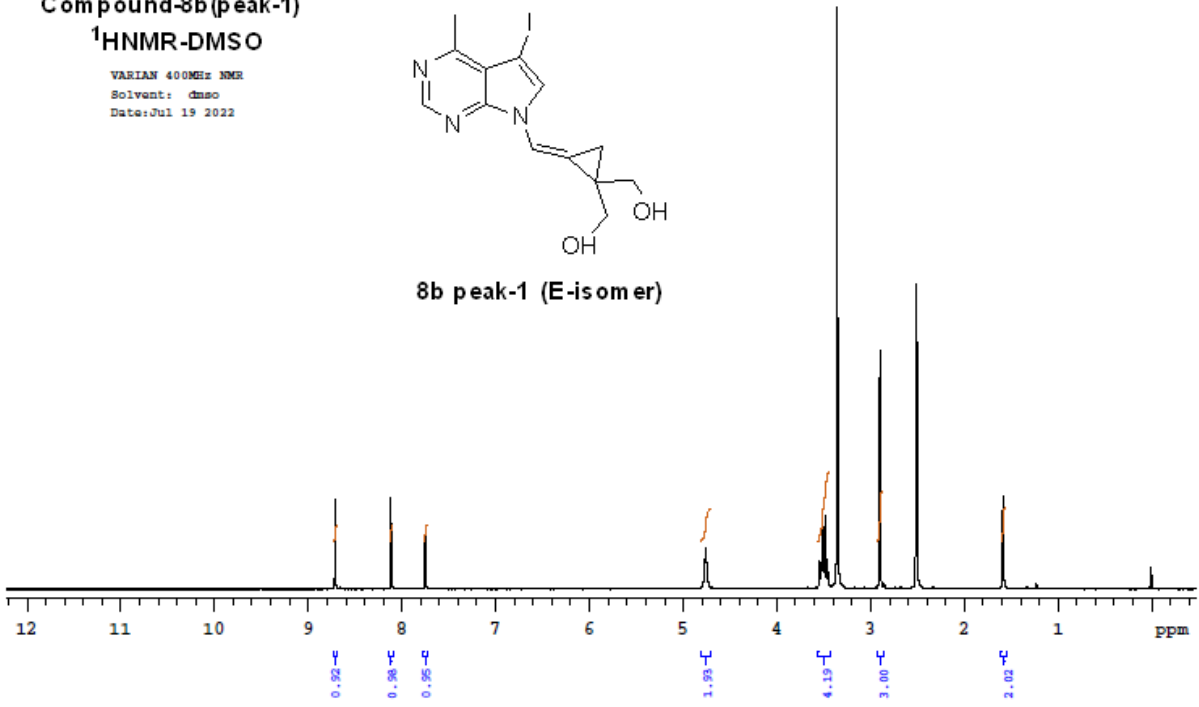
Compound-8b(peak-1)

¹HNMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsc
Date:Jul 19 2022



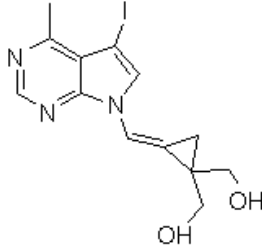
8b peak-1 (E-isomer)



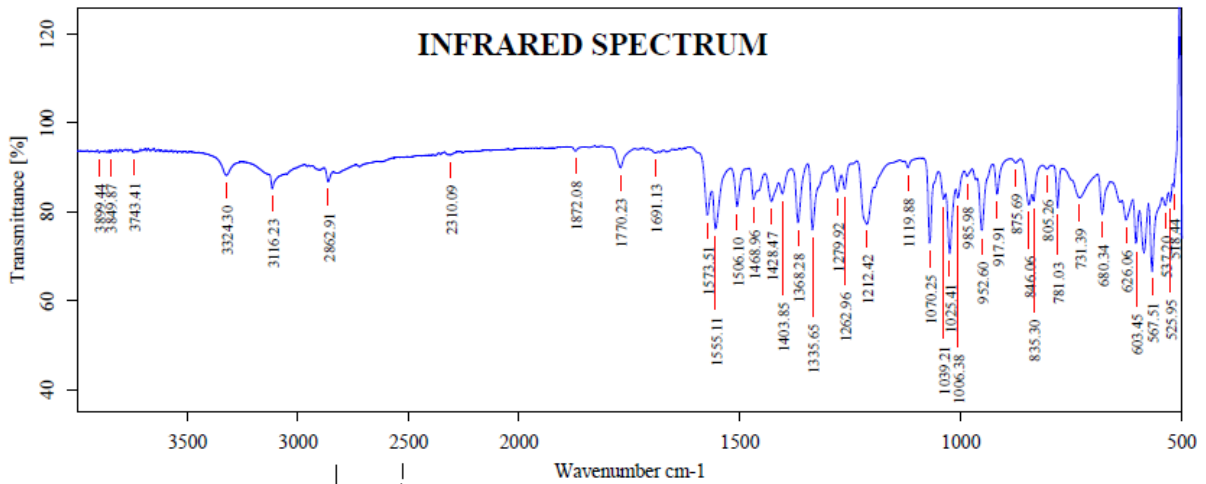
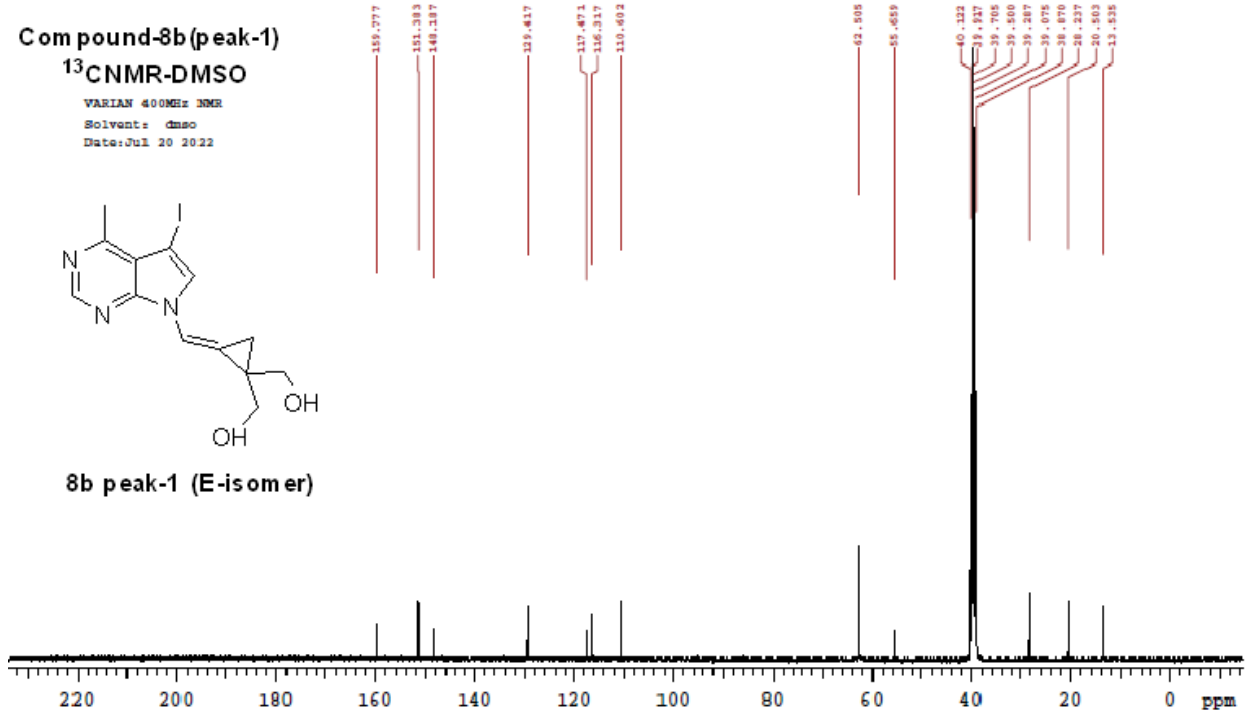
Compound-8b(peak-1)

¹³CNMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsd
Date: Jul 20 2022



8b peak-1 (E-isomer)

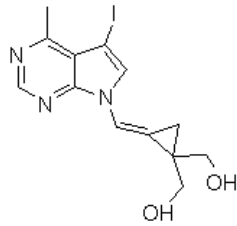


Compound-8b(peak-1)

Lot No./Batch No:

Date & Time: 20-07-2022, 18:03:45

Operator Name: Accu Chemist



8b peak-1 (E-isomer)

Instrument ID No: AA-ID-002

Experiment: ACCU87.spm

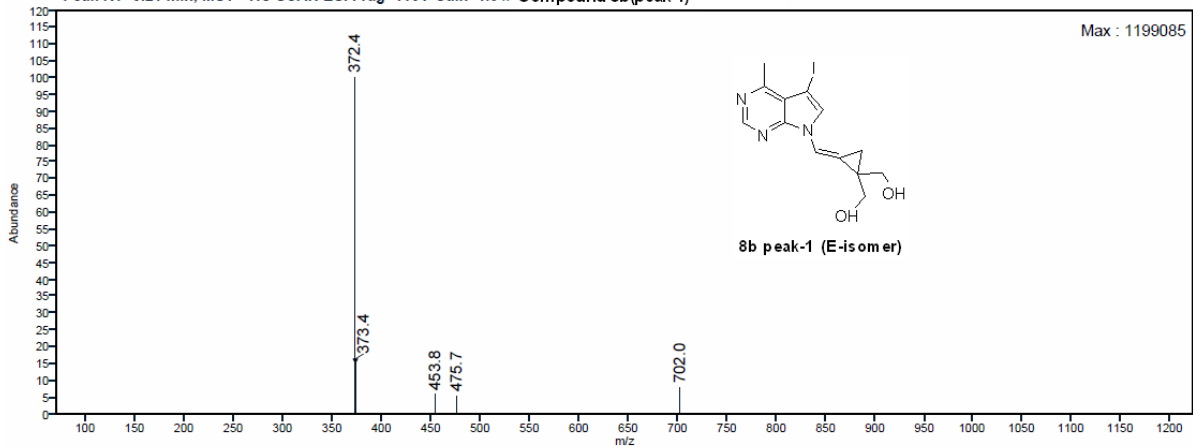
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Sample Scans: 16

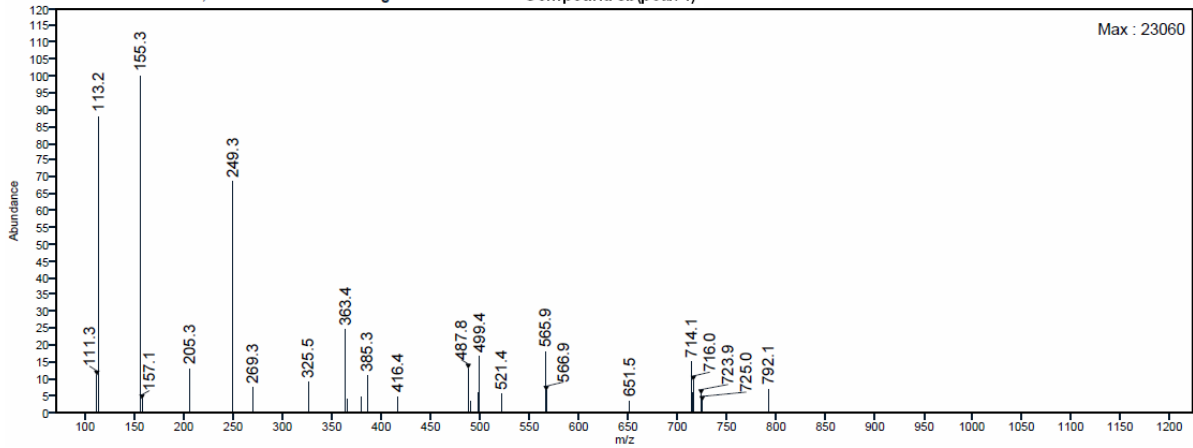
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MS Spectrum

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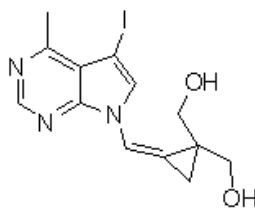
Compound-8b(peak-2)

¹H NMR-DMSO

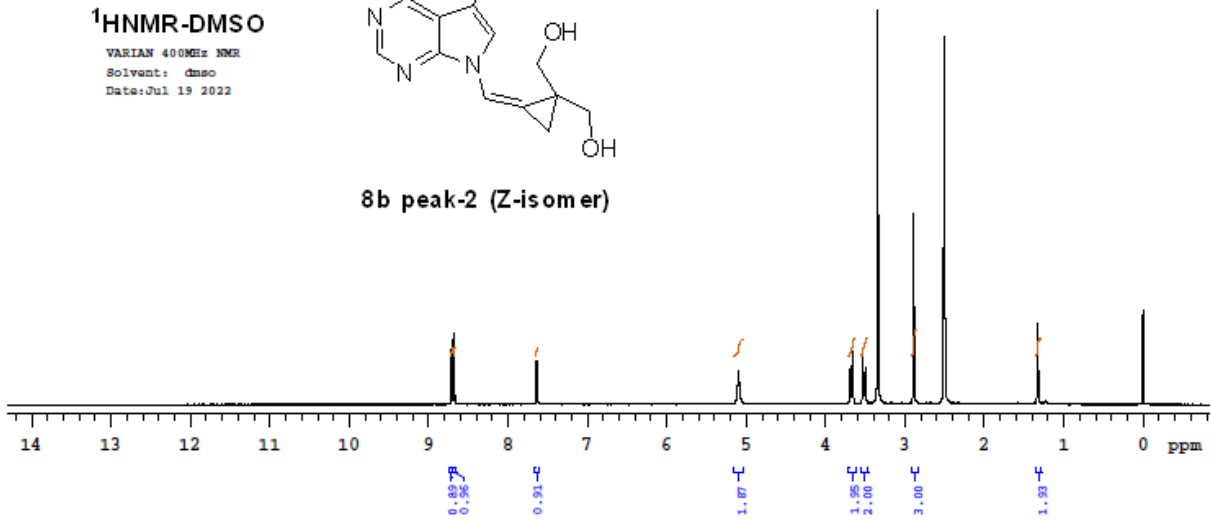
VARIAN 400MHz NMR

Solvent: dmsc

Date: Jul 19 2022



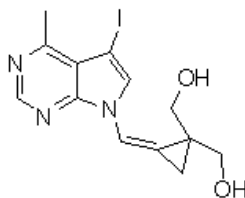
8b peak-2 (Z-isomer)



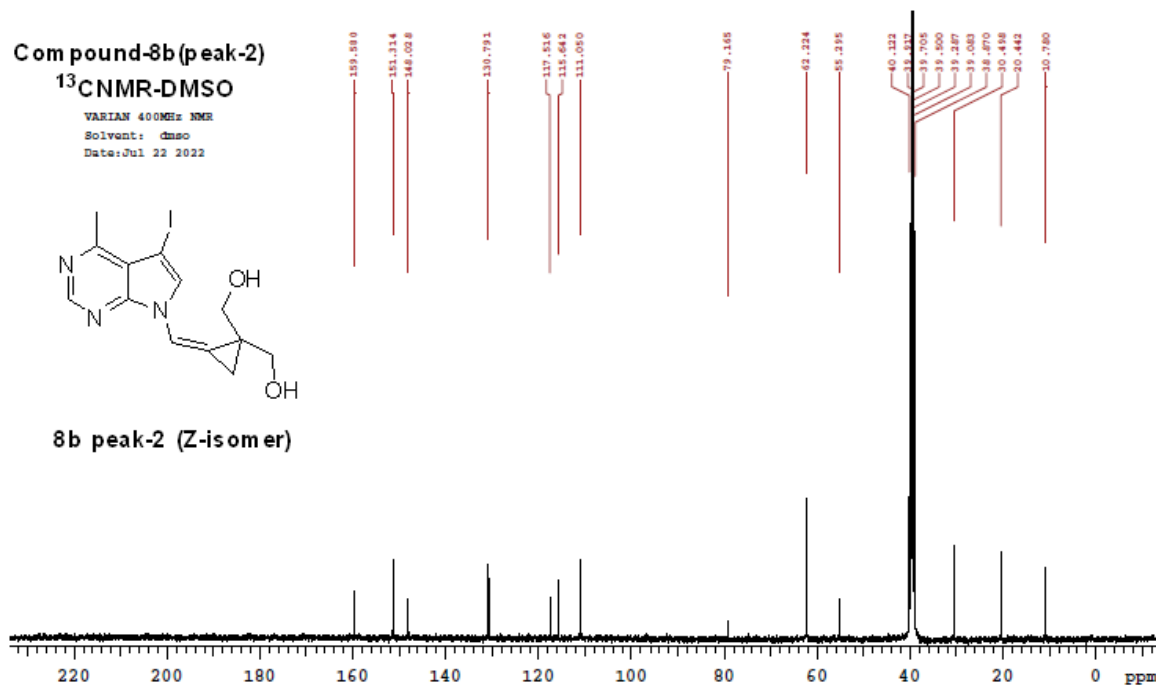
Compound-8b(peak-2)

¹³CNMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsc
Date:Jul 22 2022



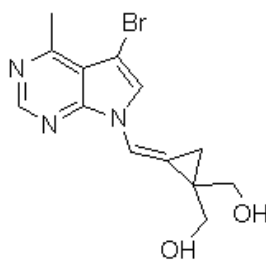
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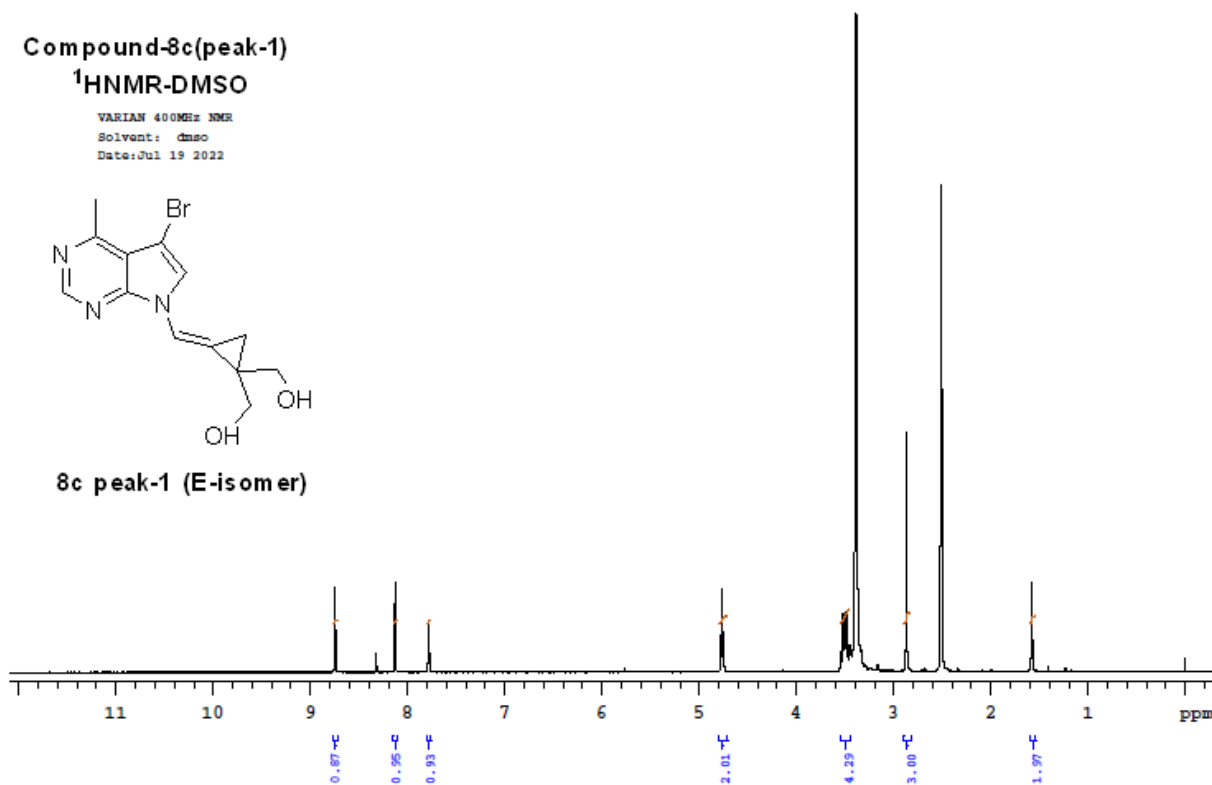
Compound-8c(peak-1)

¹HNMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsc
Date:Jul 19 2022



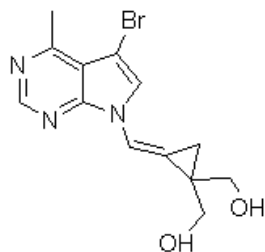
8c peak-1 (E-isomer)



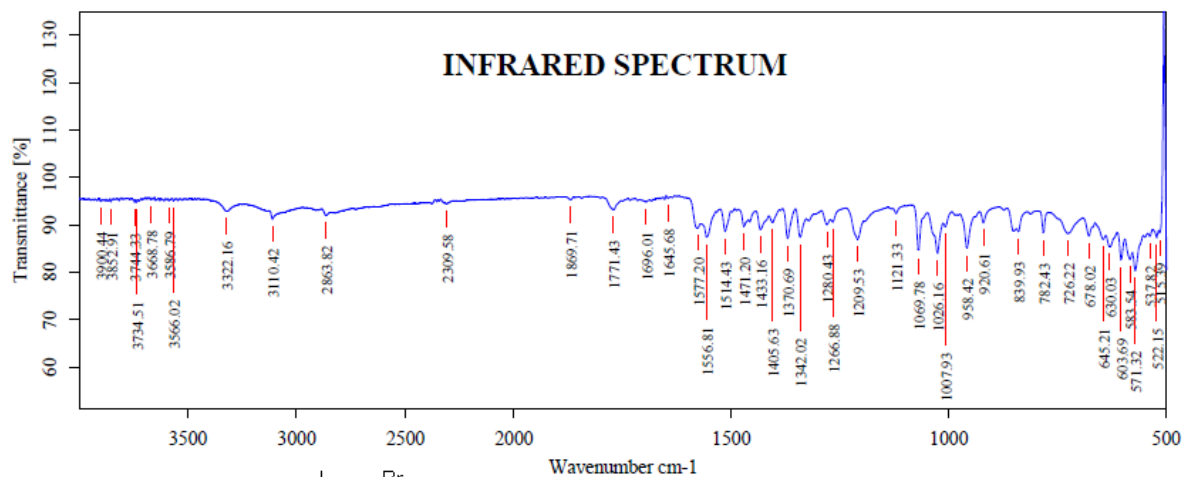
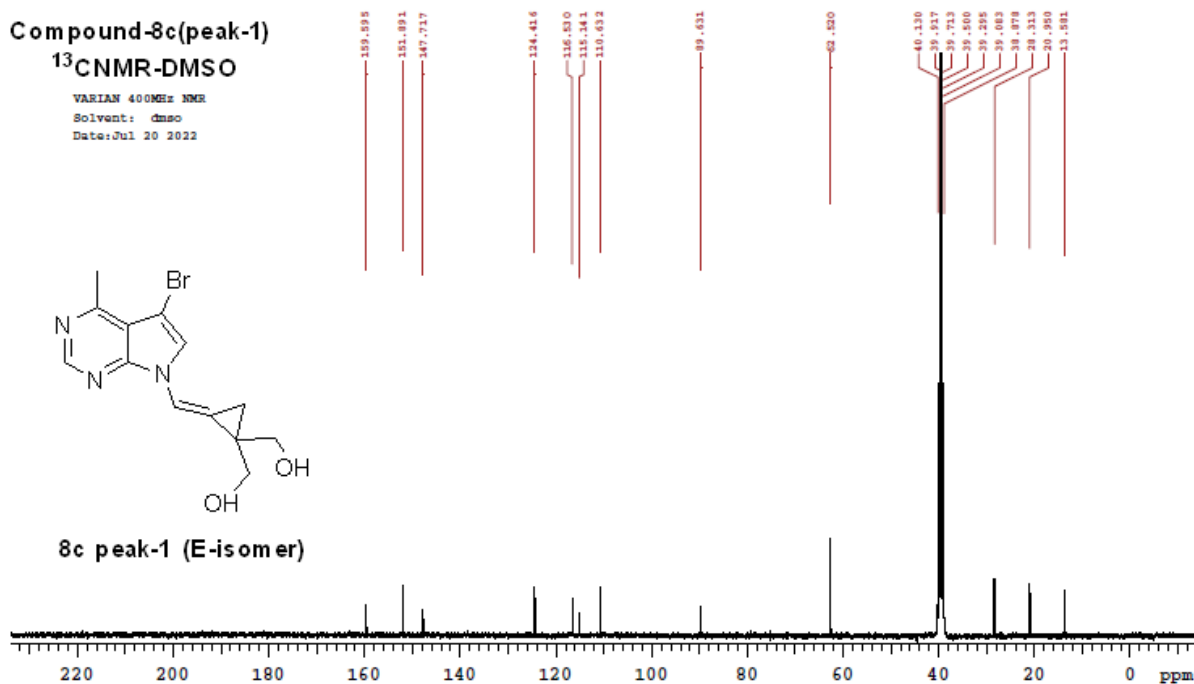
Compound-8c(peak-1)

¹³CNMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsd
Date: Jul 20 2022



8c peak-1 (E-isomer)

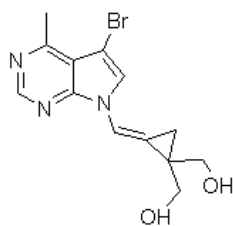


Compound-8c(peak-1)

LotNo./BatchNo:

Date & Time: 20-07-2022, 18:12:39

Operator Name: Accu Chemist



8c peak-1 (E-isomer)

Instrument ID No: AA-ID-002

Experiment: ACCU87.qm

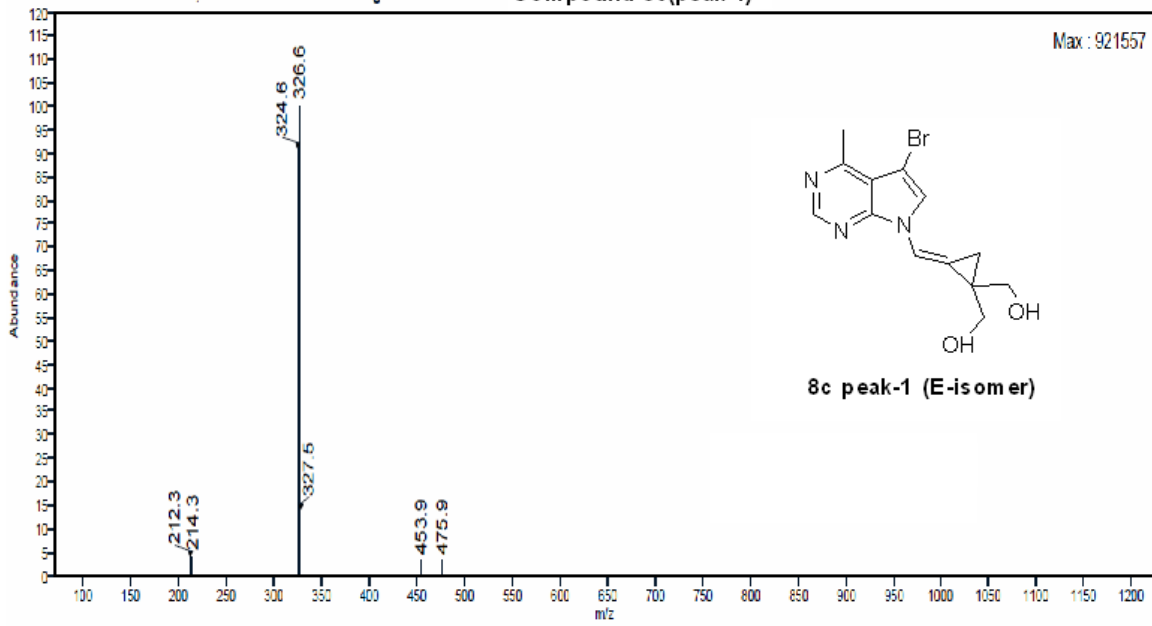
Resolution: 4

Sample Scans: 16

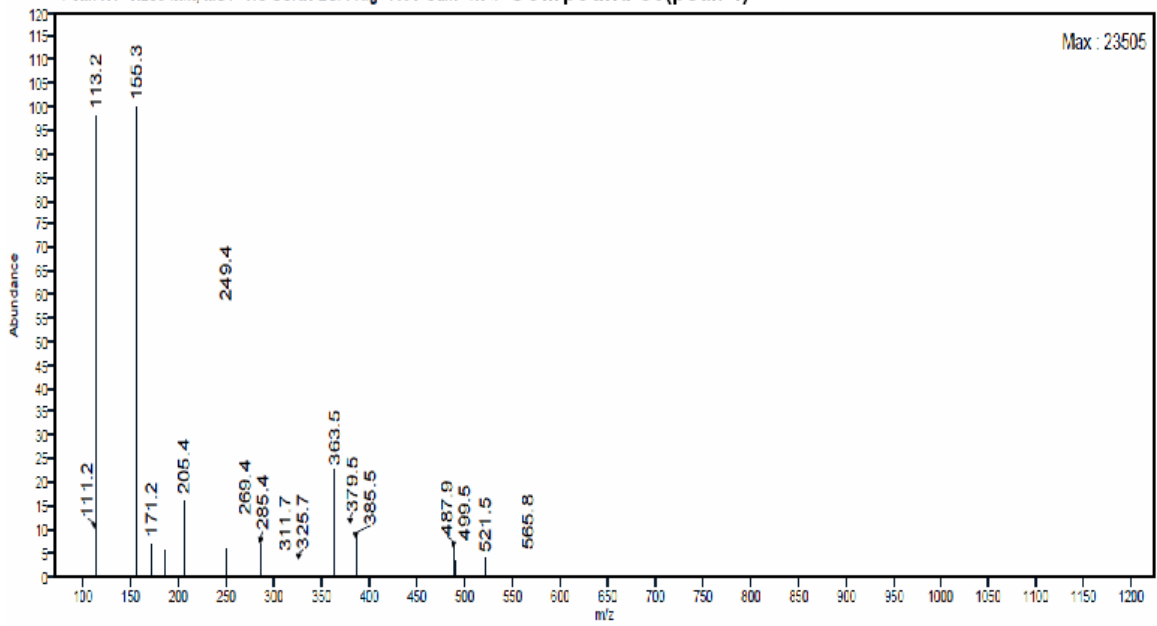
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MS Spectrum

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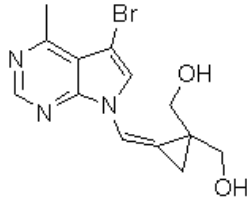
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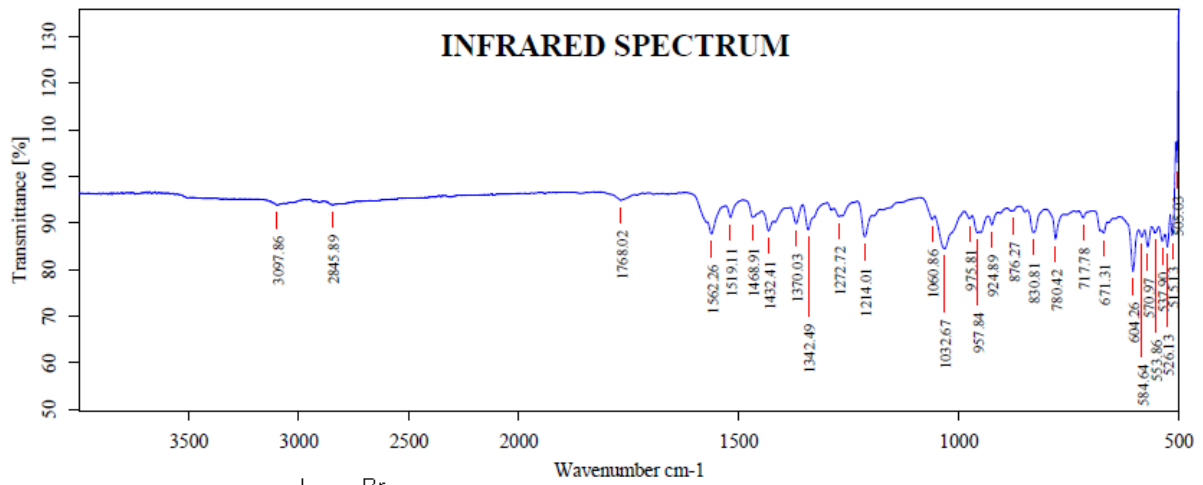
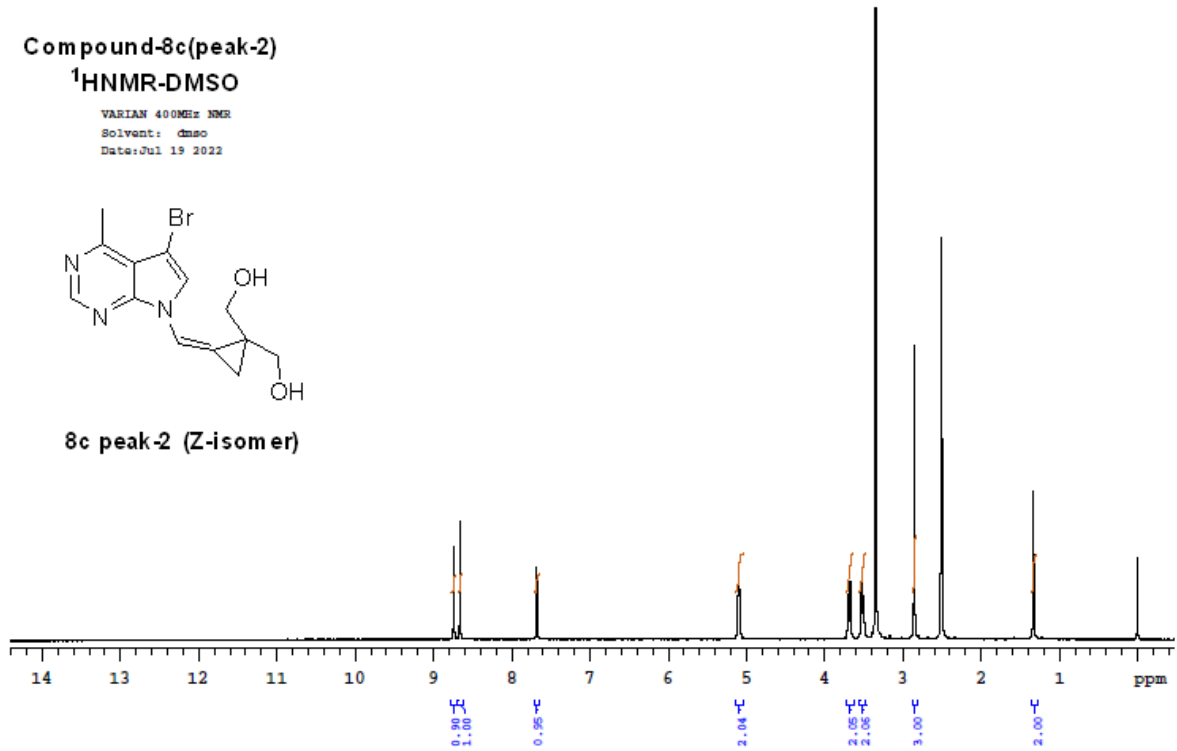
Compound-8c(peak-2)

¹H NMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsc
Date: Jul 19 2022



8c peak-2 (Z-isomer)

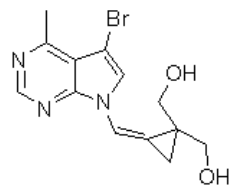


Compound-8c(peak-2)

Lot No./Batch No:

Date & Time: 20-07-2022, 17:48:33

Operator Name: Accu Chemist



8c peak-2 (Z-isomer)

Instrument ID No: AA-ID-002

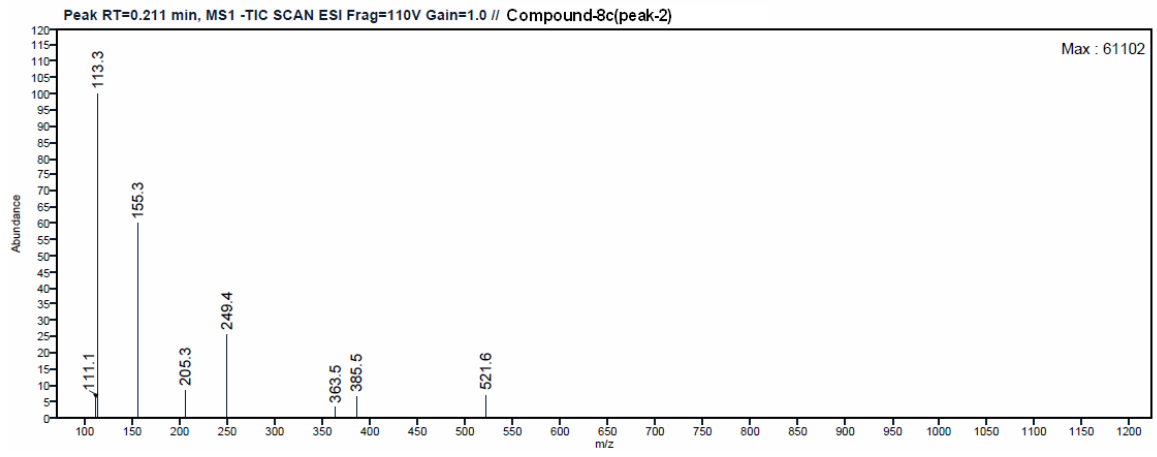
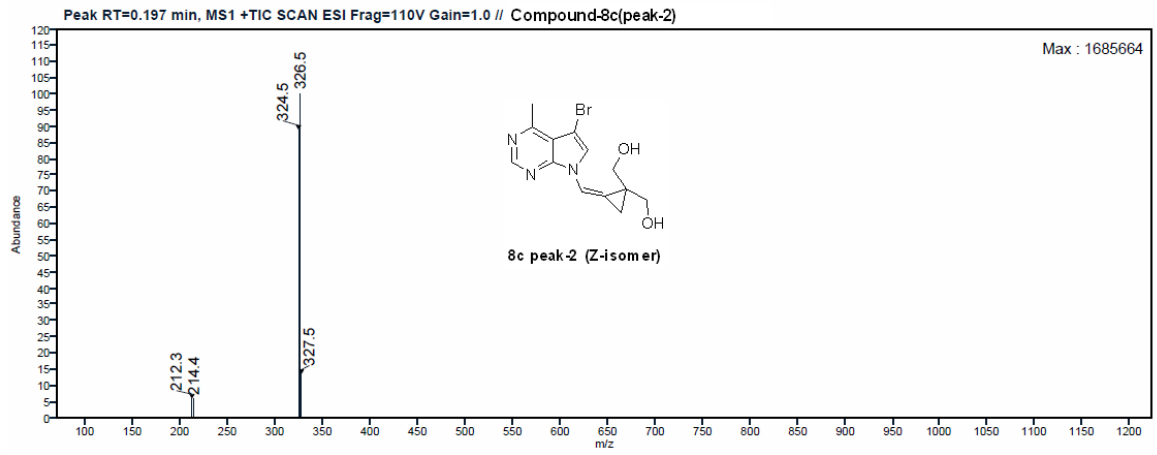
Experiment: ACCU87.spm

Resolution: 4

Sample Scans: 16

Frequency Range: 4000 to 500

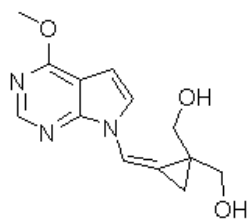
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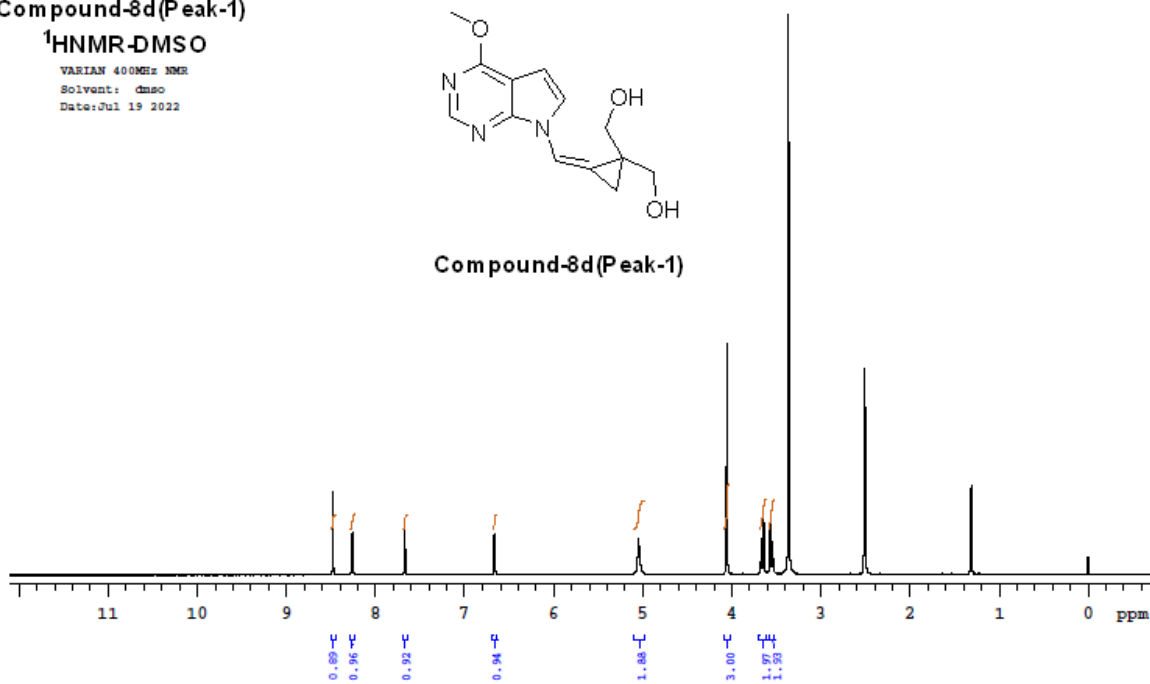
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¹HNMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsd
Date: Jul 19 2022



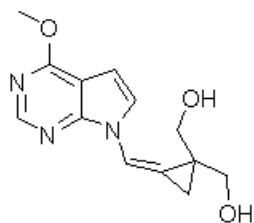
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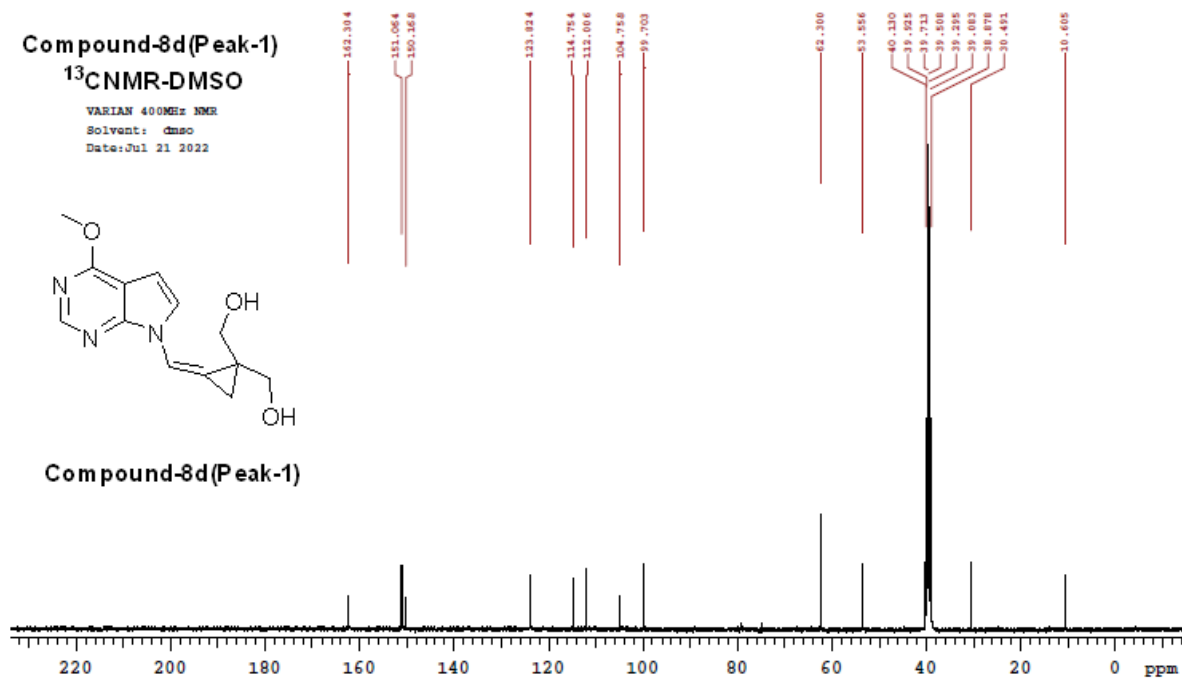
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¹³CNMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsc
Date:Jul 21 2022



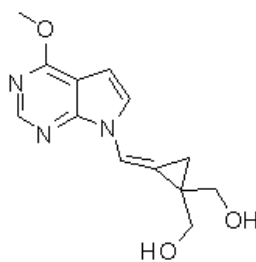
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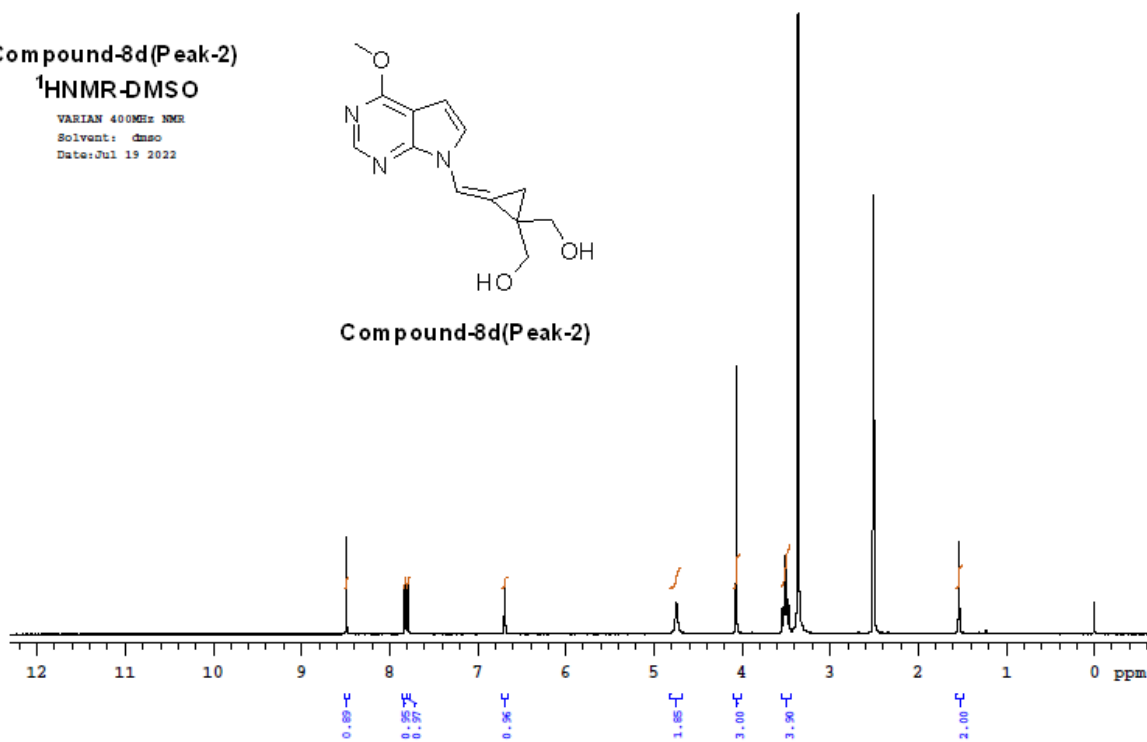
Compound-8d(Peak-2)

¹HNMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsc
Date:Jul 19 2022

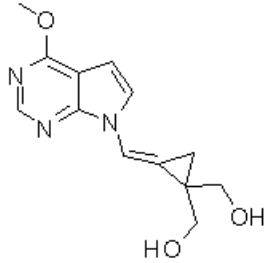


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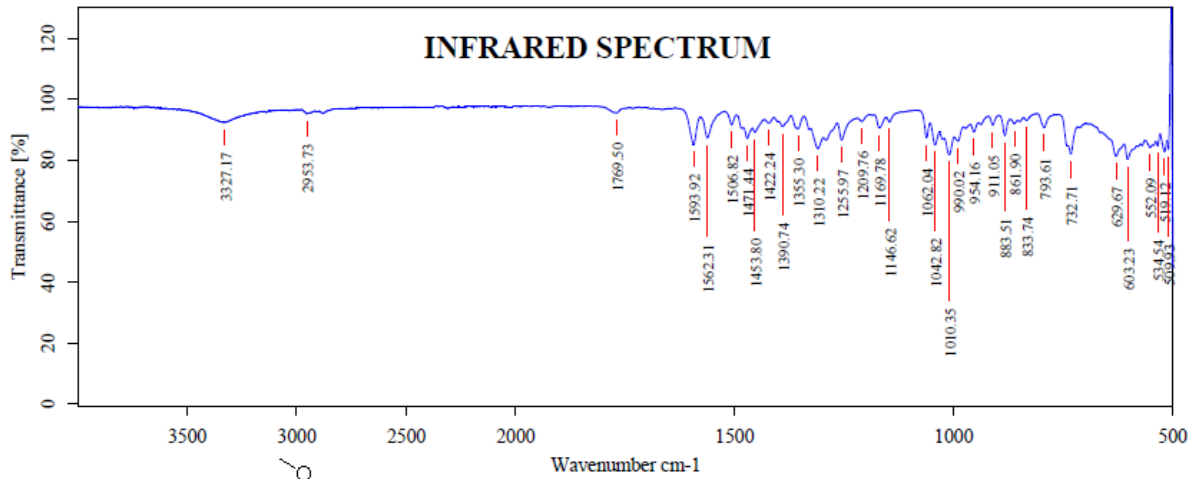
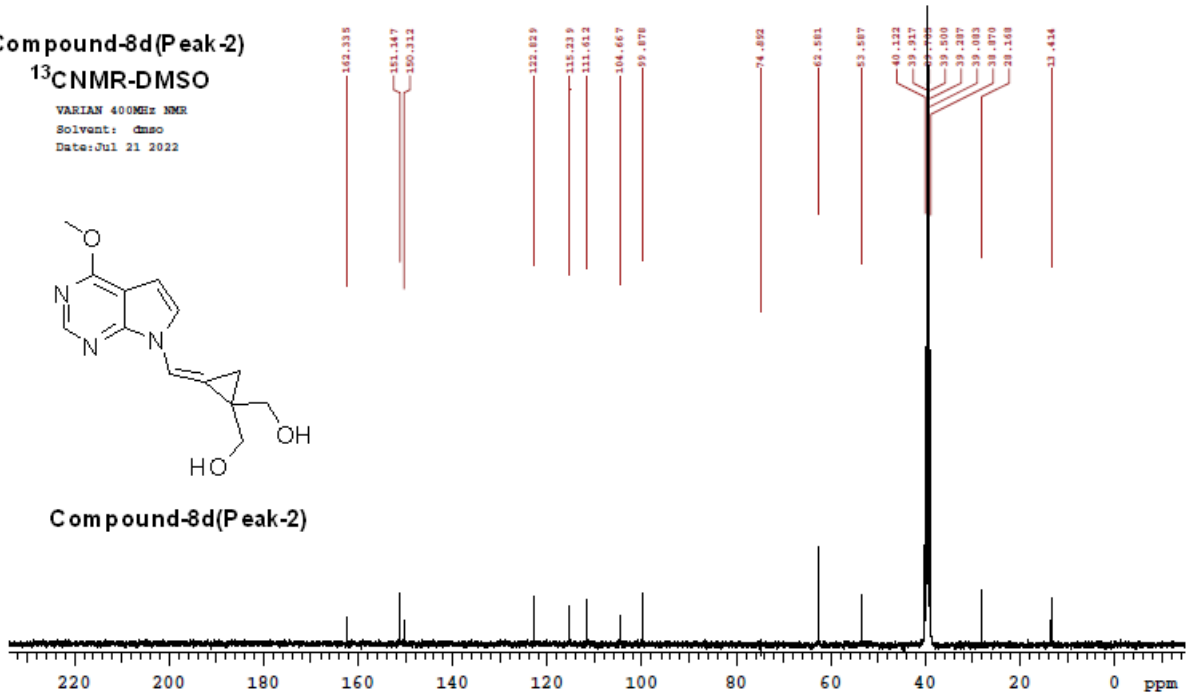


Compound-8d(Peak-2)
¹³CNMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsc
Date: Jul 21 2022



Compound-8d(Peak-2)

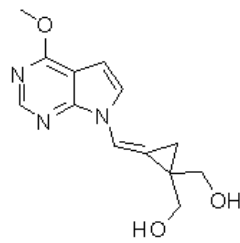


Compound-8d(Peak-2)

Lot No./Batch No:

Date & Time: 20-07-2022, 18:00:43

Operator Name: Accu Chemist



Compound-8d(Peak-2)

Instrument ID No: AA-ID-002

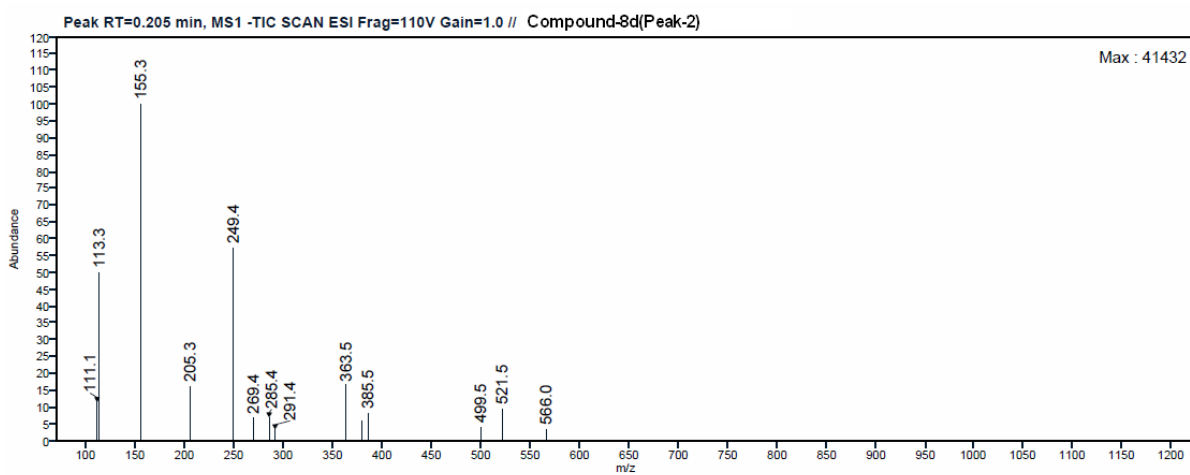
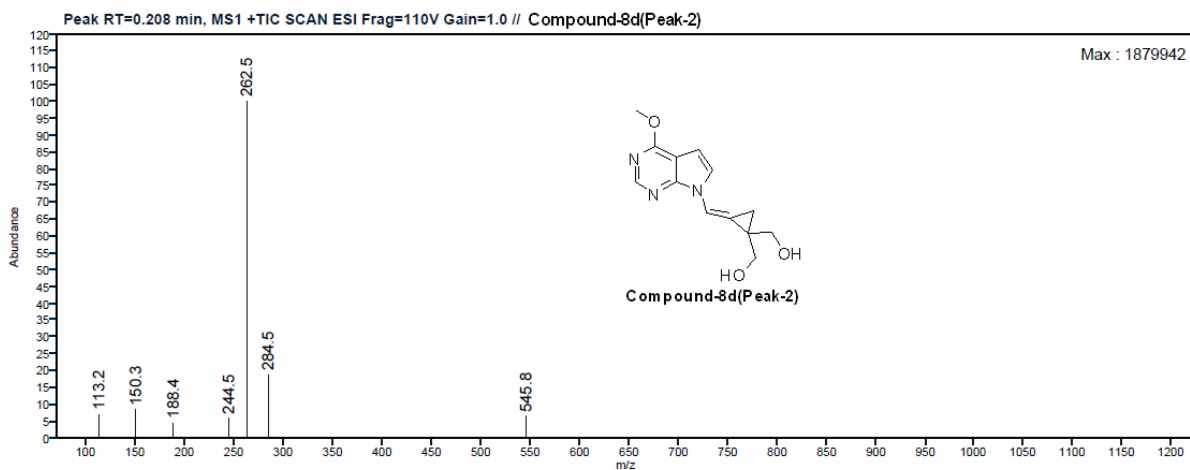
Experiment: ACCU87.spm

Resolution: 4

Sample Scans: 16

Frequency Range: 4000 to 500

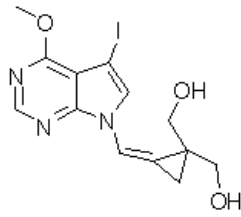
MS Spectrum



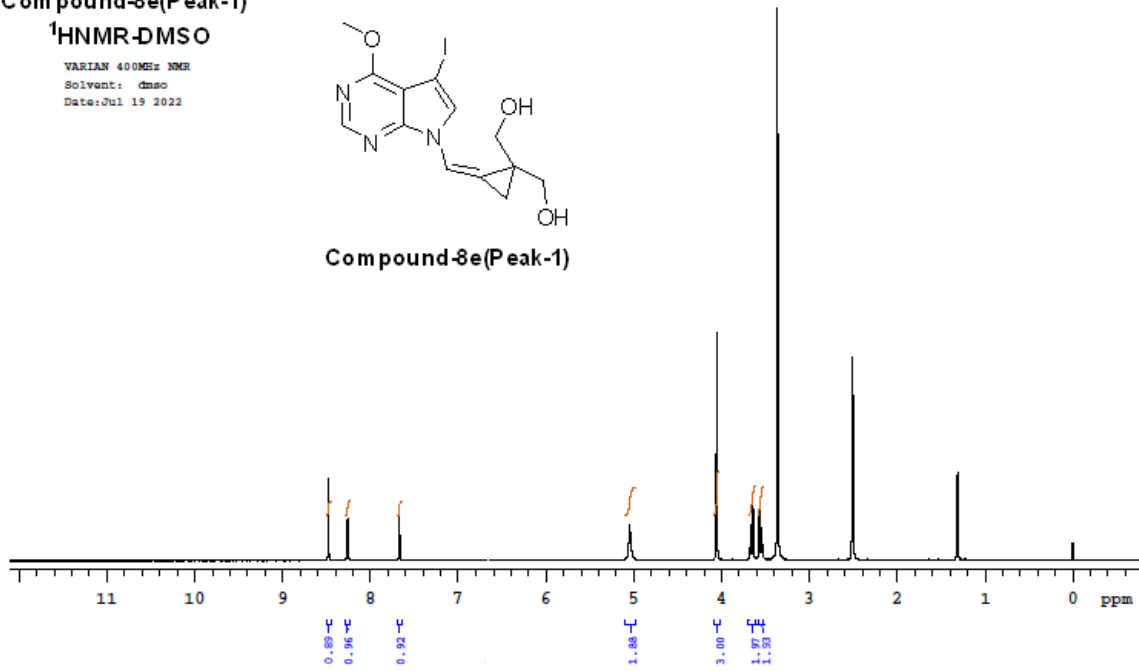
Compound-8e(Peak-1)

¹H NMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsc
Date: Jul 19 2022



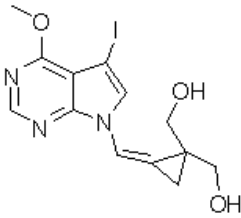
Compound-8e(Peak-1)



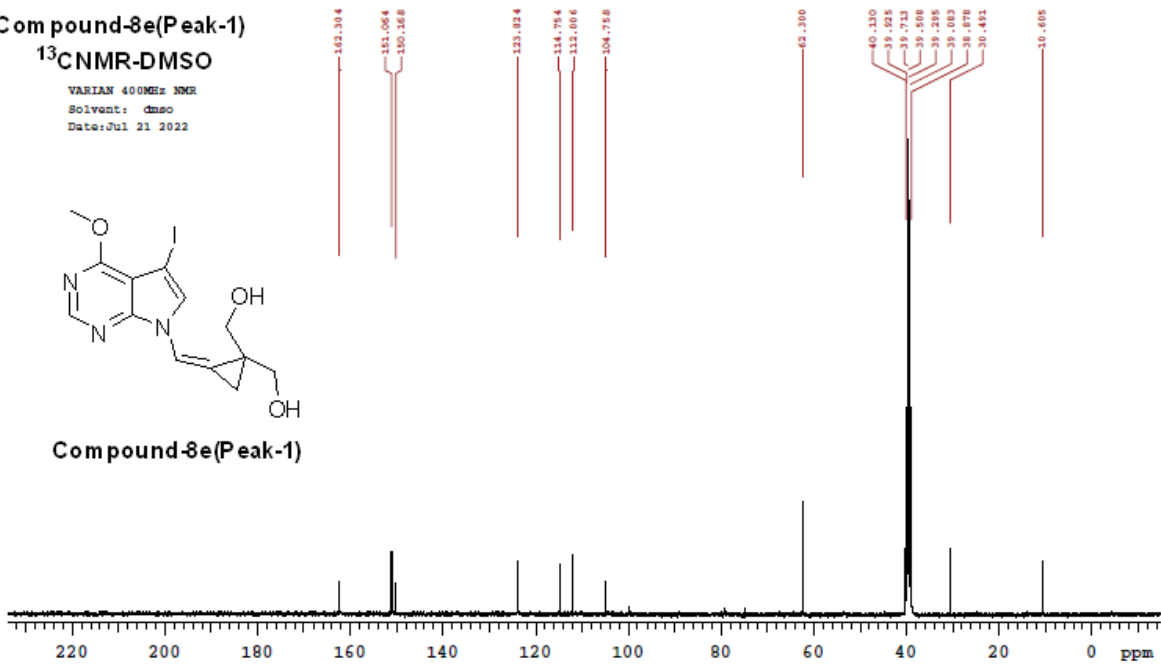
Compound-8e(Peak-1)

¹³C NMR-DMSO

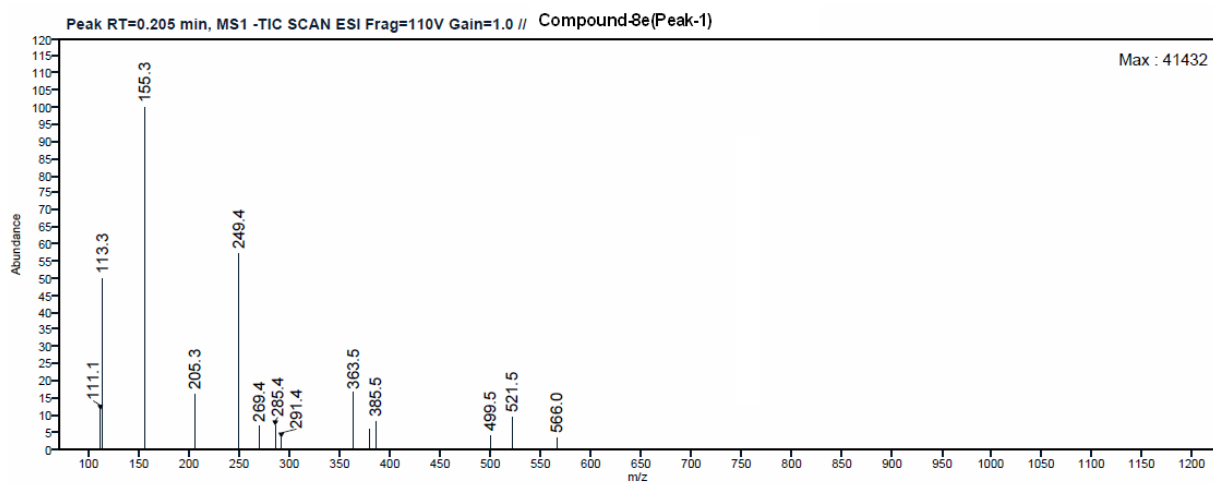
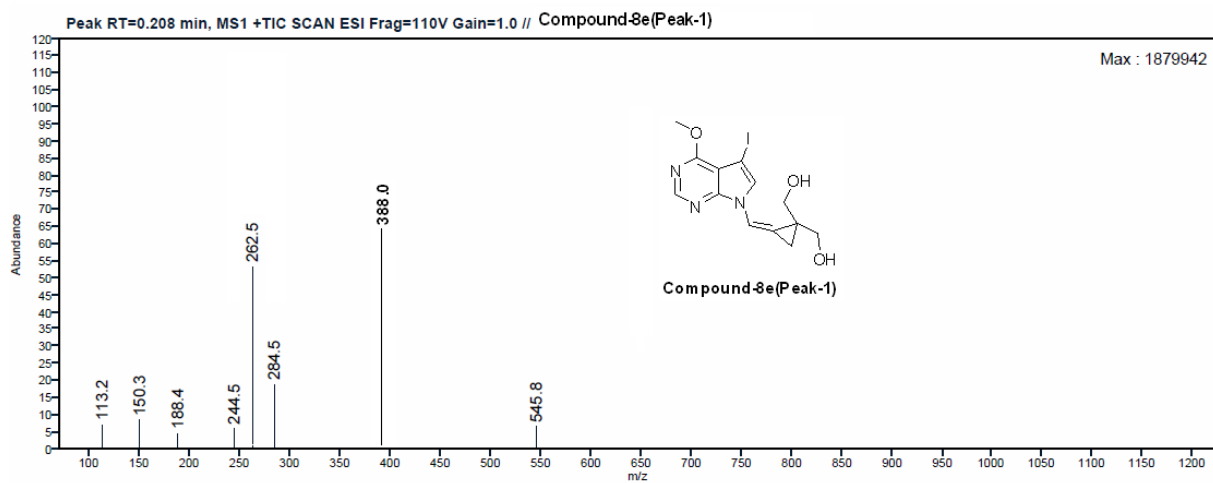
VARIAN 400MHz NMR
Solvent: dmsc
Date: Jul 21 2022



Compound-8e(Peak-1)



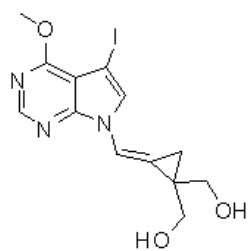
MS Spectrum



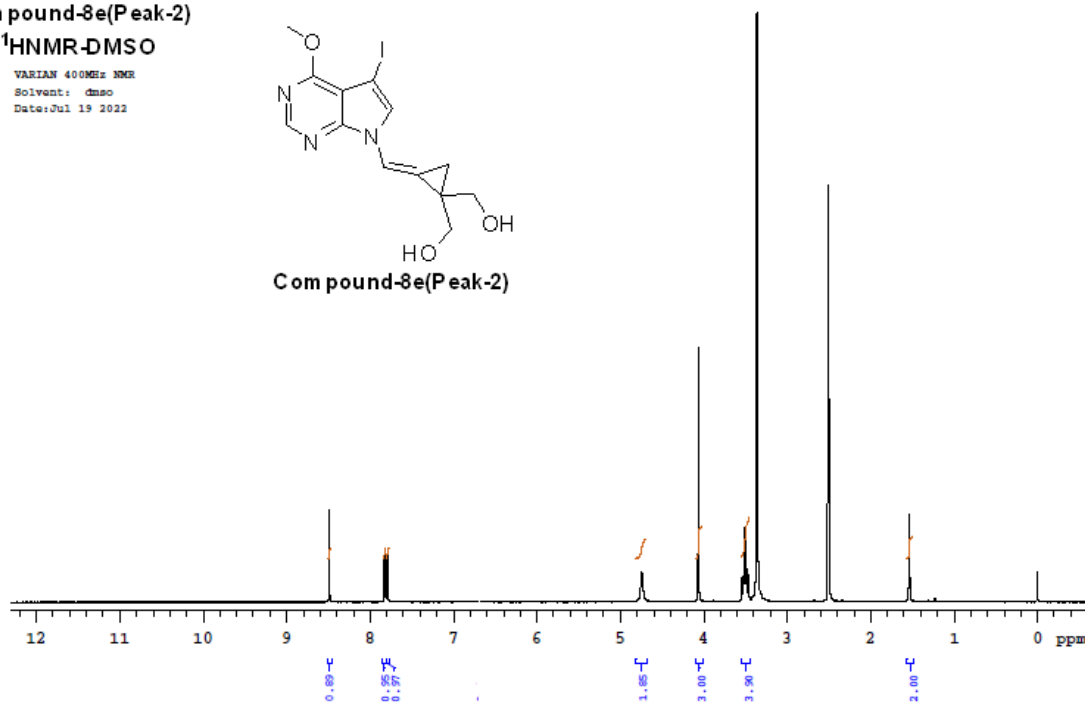
Compound-8e(Peak-2)

¹H NMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsd
Date: Jul 19 2022



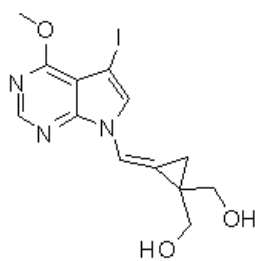
Compound-8e(Peak-2)



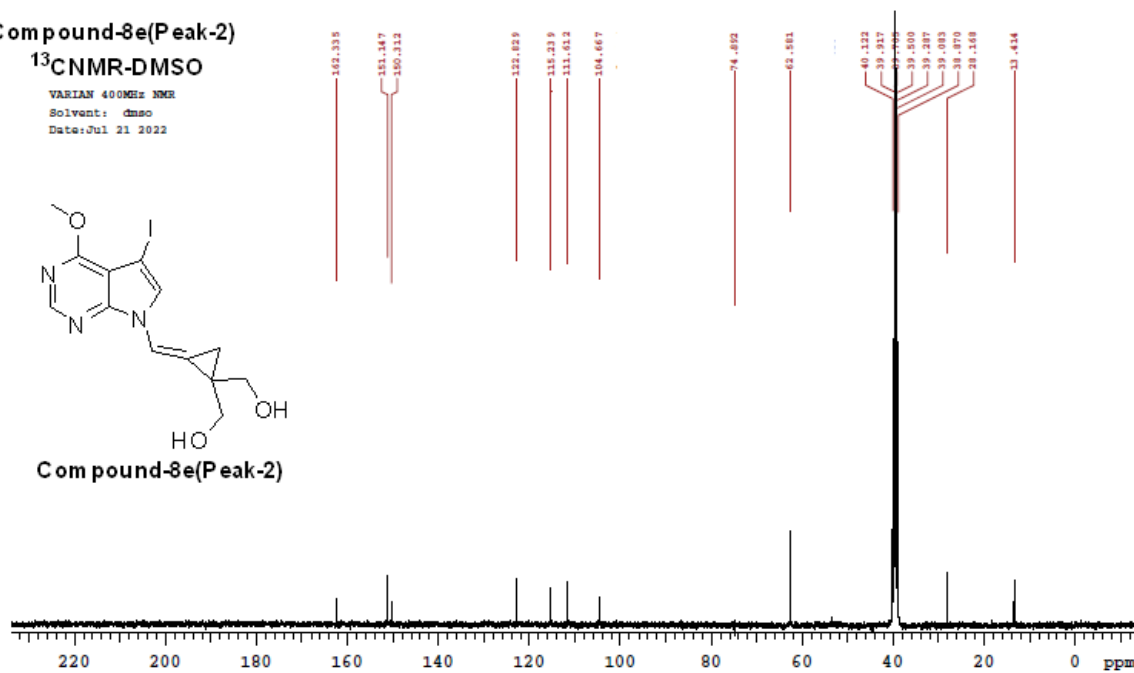
Compound-8e(Peak-2)

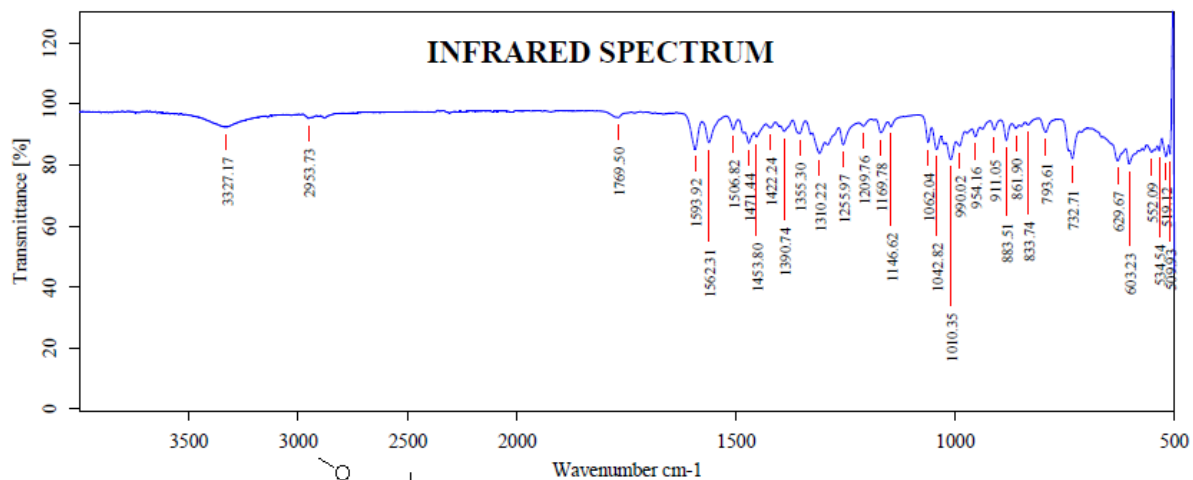
¹³C NMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsd
Date: Jul 21 2022



Compound-8e(Peak-2)



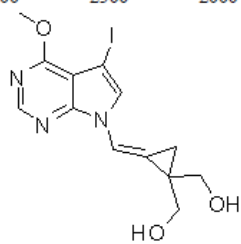


Compound-8e(Peak-2)

Lot No./Batch No:

Date & Time:20-07-2022,18:00:43

Operator Name:Accu Chemist



Compound-8e(Peak-2)

Instrument ID No: AA-ID-002

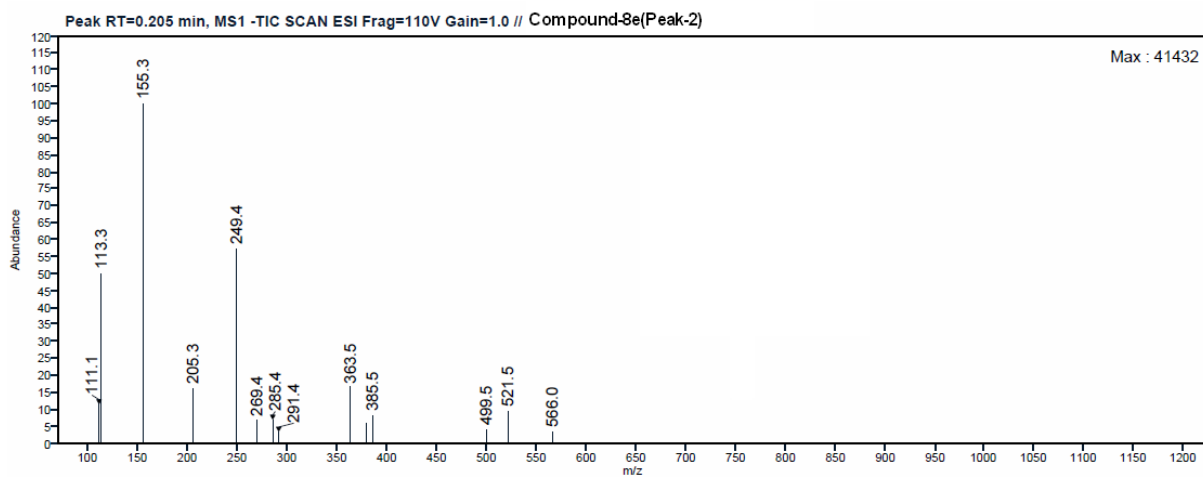
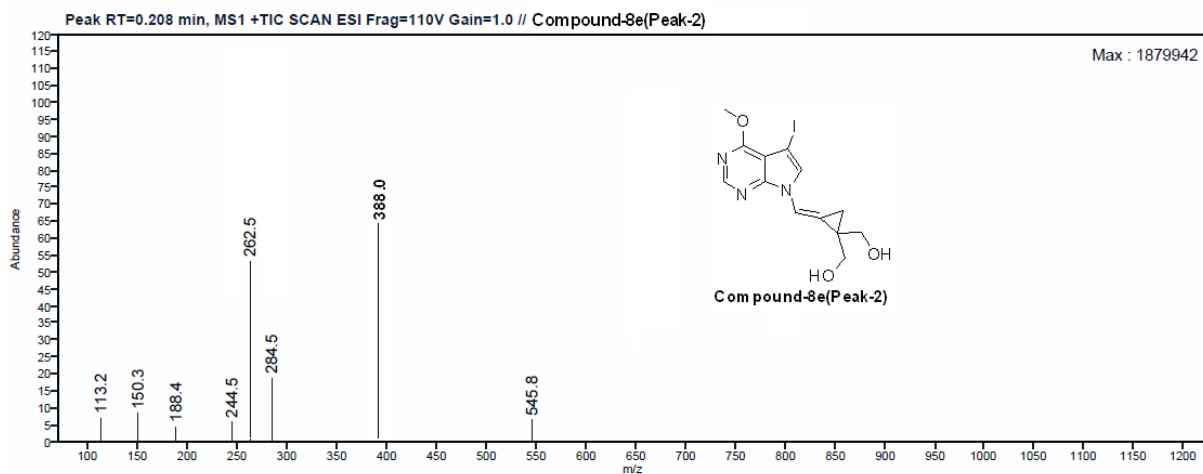
Experiment:ACCUS7.spx

Resolution:4

Sample Scans:16

Frequency Range:4000 to 500

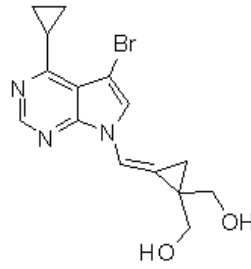
MS Spectrum



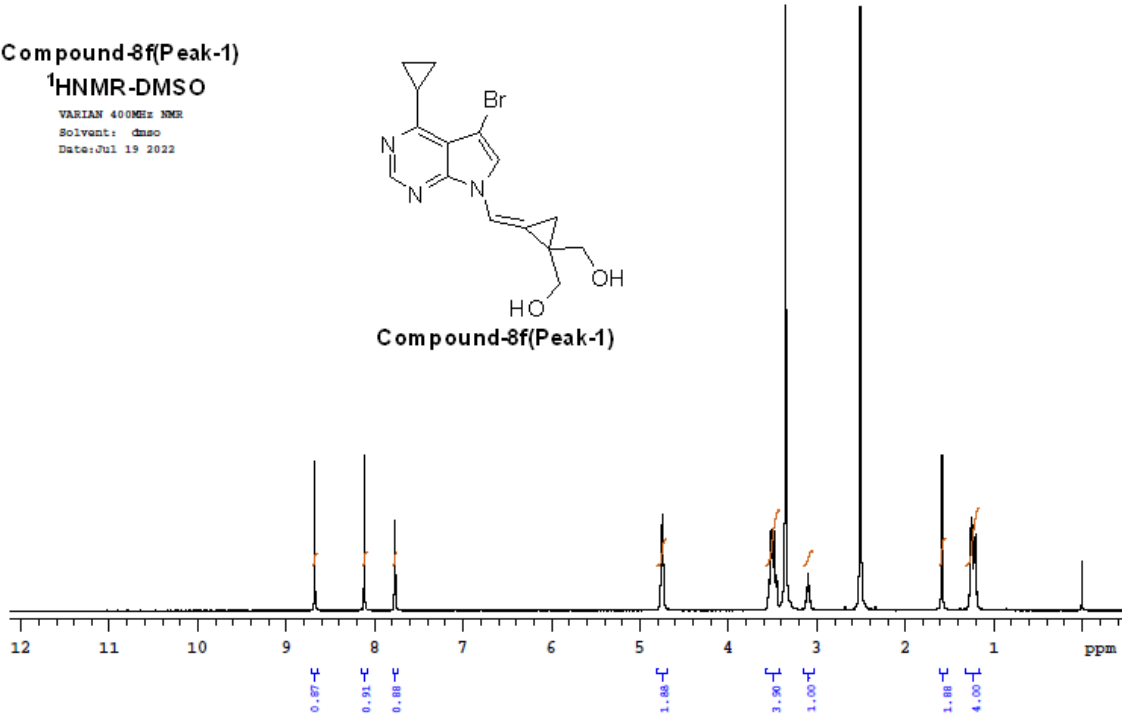
Compound-8f(Peak-1)

¹H NMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsO
Date: Jul 19 2022



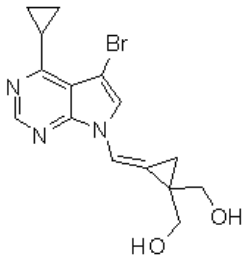
Compound-8f(Peak-1)



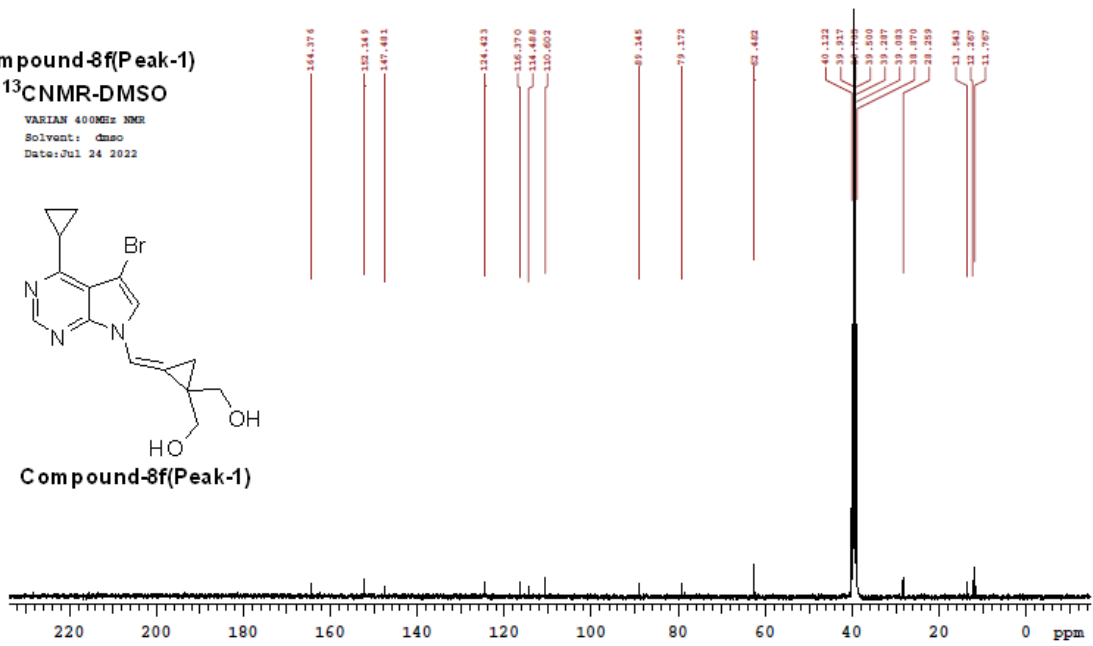
Compound-8f(Peak-1)

¹³C NMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsO
Date: Jul 24 2022



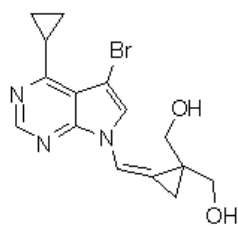
Compound-8f(Peak-1)



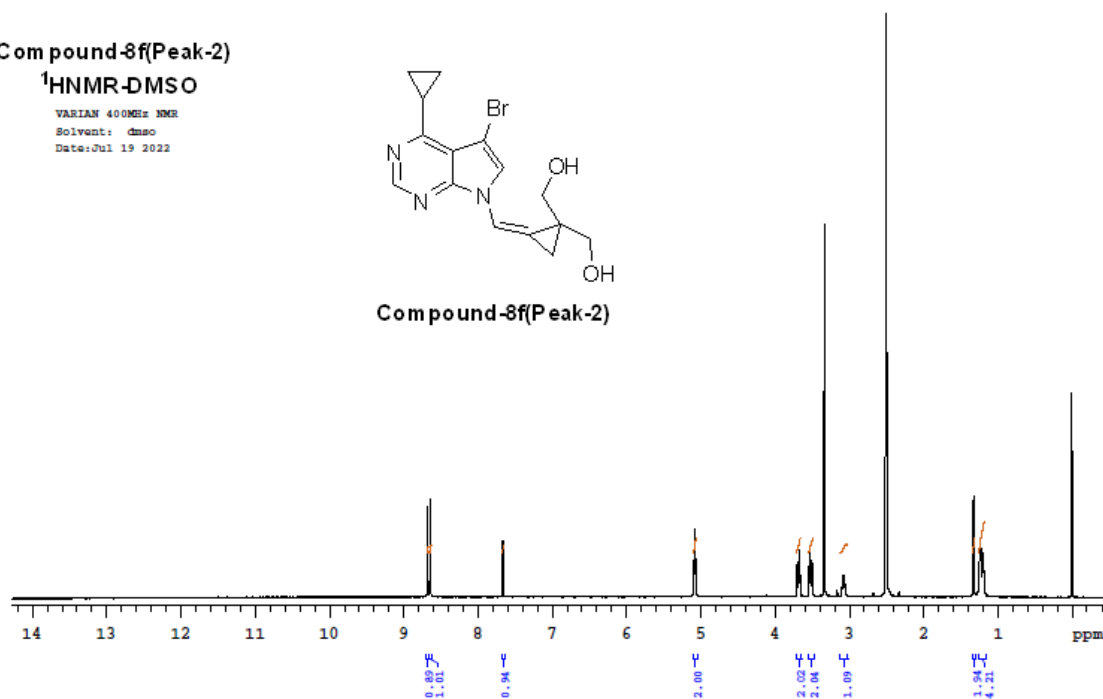
Compound-8f(Peak-2)

¹H NMR-DMSO

VARIAN 400MHz NMR
Solvent: dms0
Date: Jul 19 2022



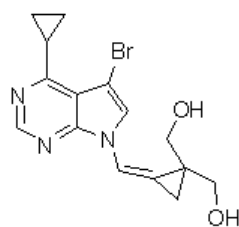
Compound-8f(Peak-2)



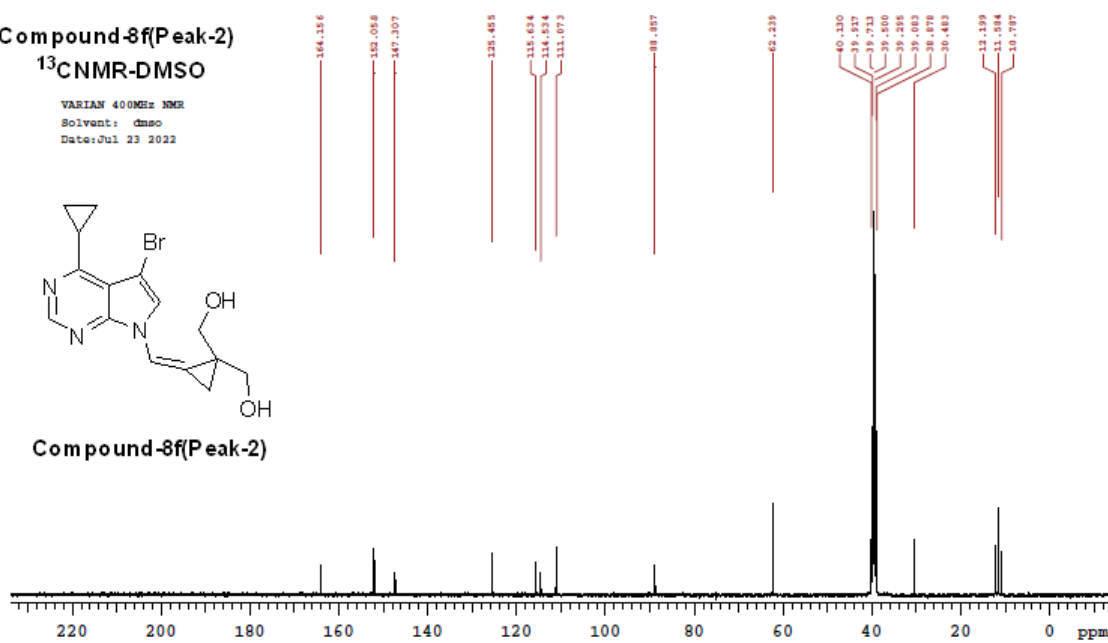
Compound-8f(Peak-2)

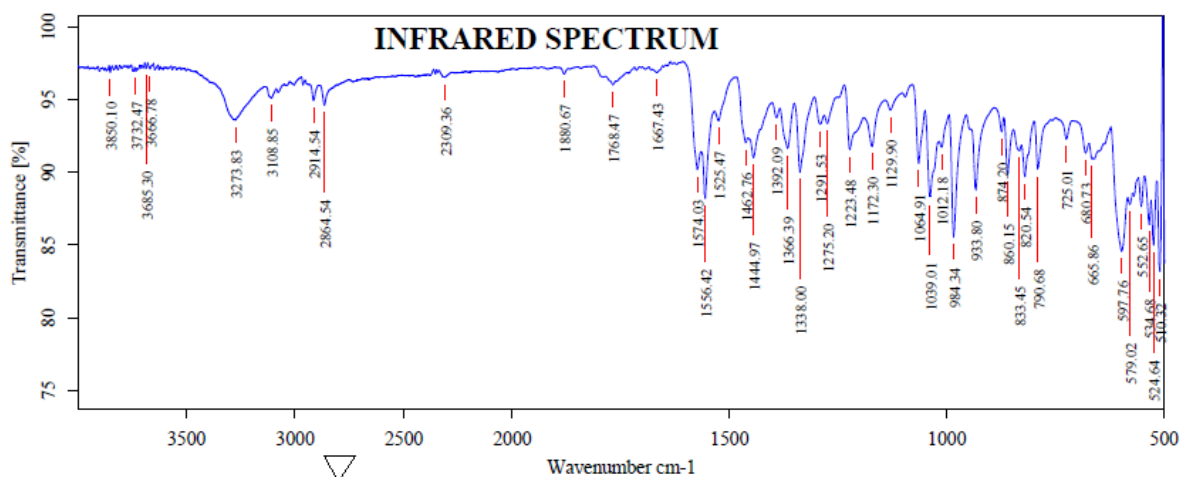
¹³C NMR-DMSO

VARIAN 400MHz NMR
Solvent: dms0
Date: Jul 23 2022



Compound-8f(Peak-2)



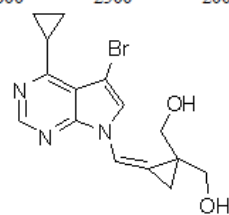


Compound-8f(Peak-2)

Lot No./Batch No:

Date & Time: 20-07-2022, 17:51:41

Operator Name: Accu Chemist



Compound-8f(Peak-2)

Instrument ID No: AA-ID-002

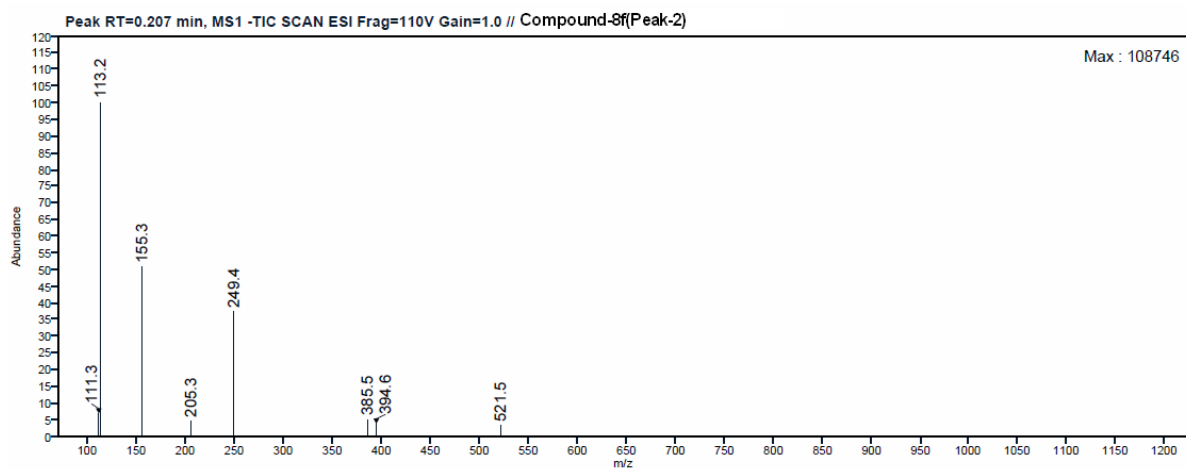
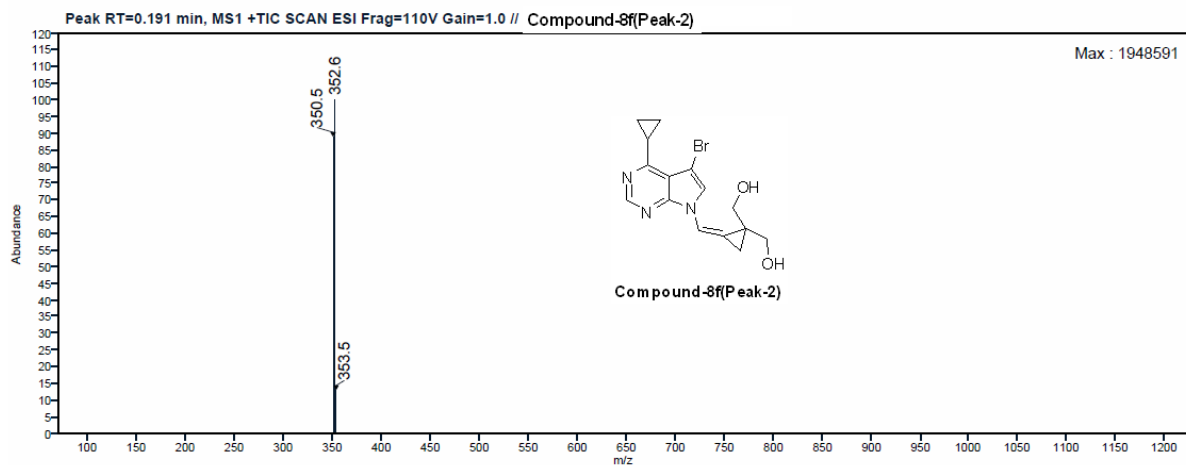
Experiment: ACCU87.spm

Resolution: 4

Sample Scans: 16

Frequency Range: 4000 to 500

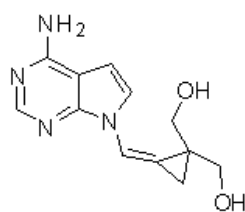
-----MS Spectrum-----



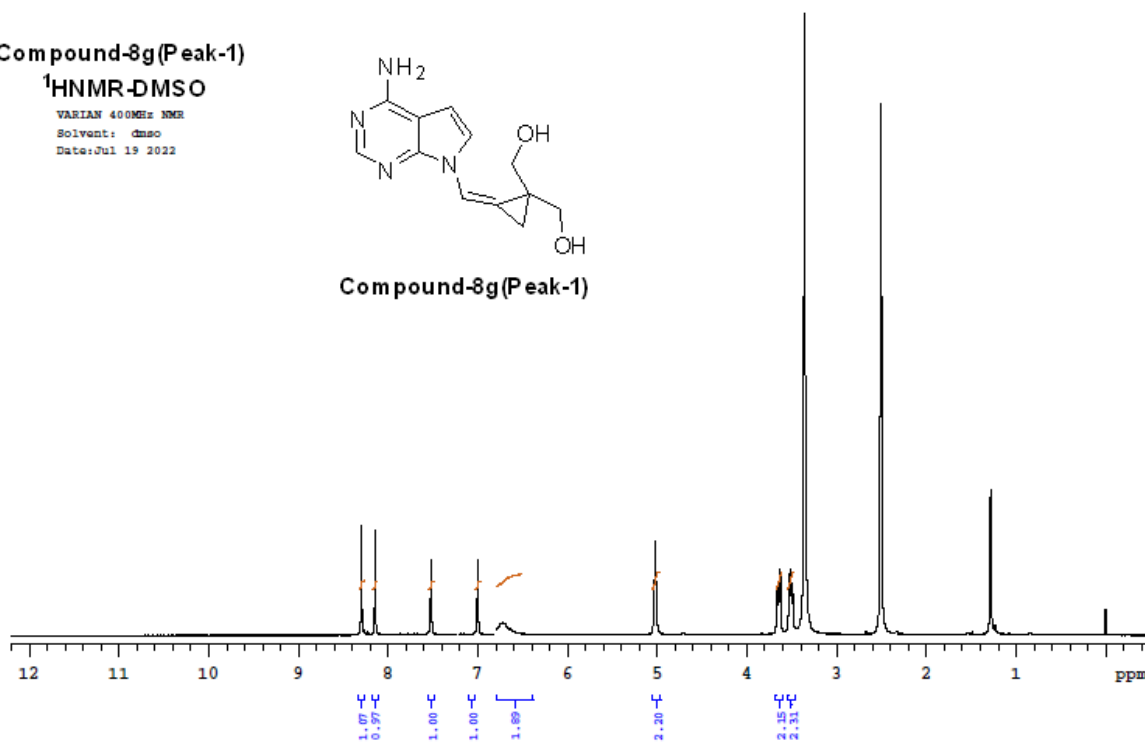
Compound-8g(Peak-1)

¹HNMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsd
Date:Jul 19 2022



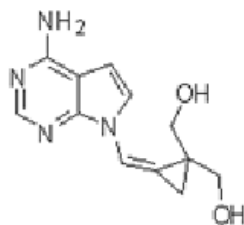
Compound-8g(Peak-1)



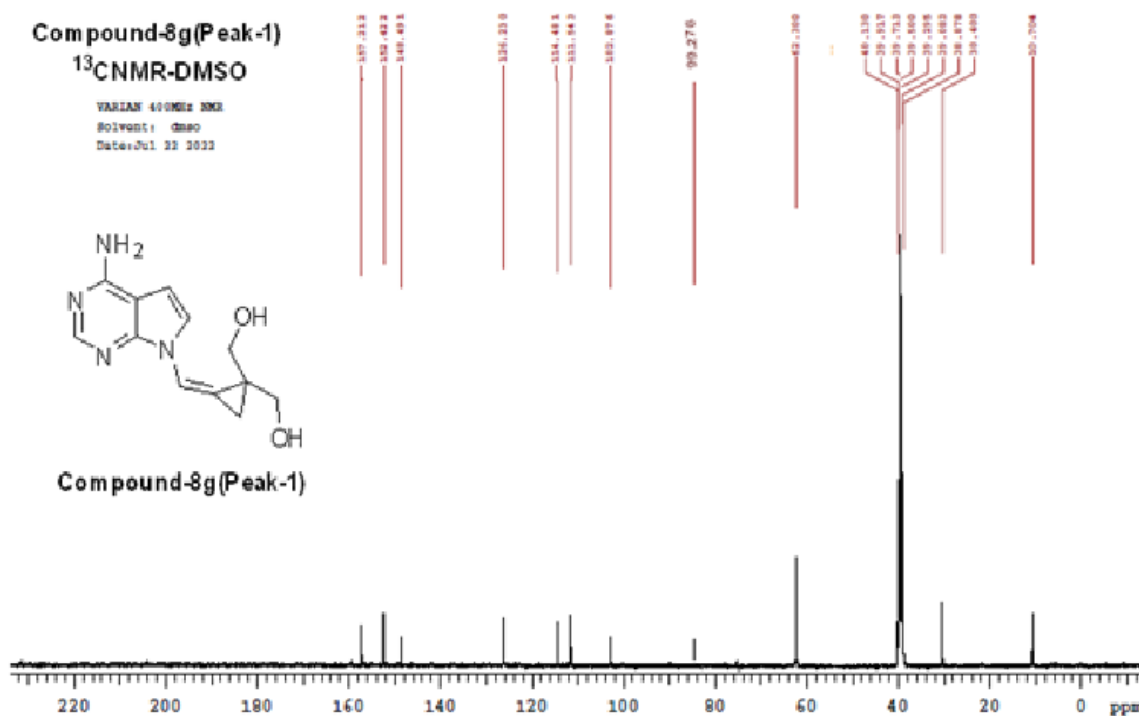
Compound-8g(Peak-1)

¹³CNMR-DMSO

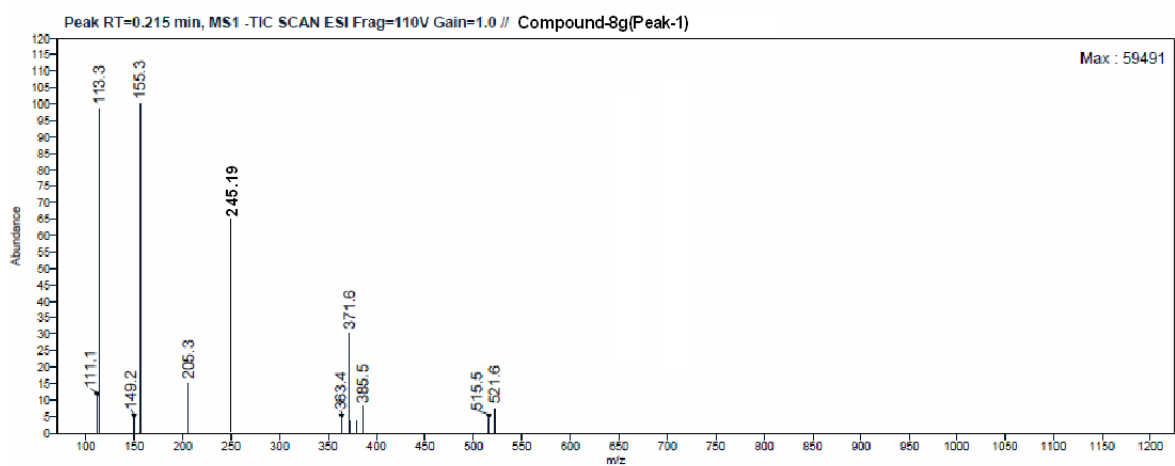
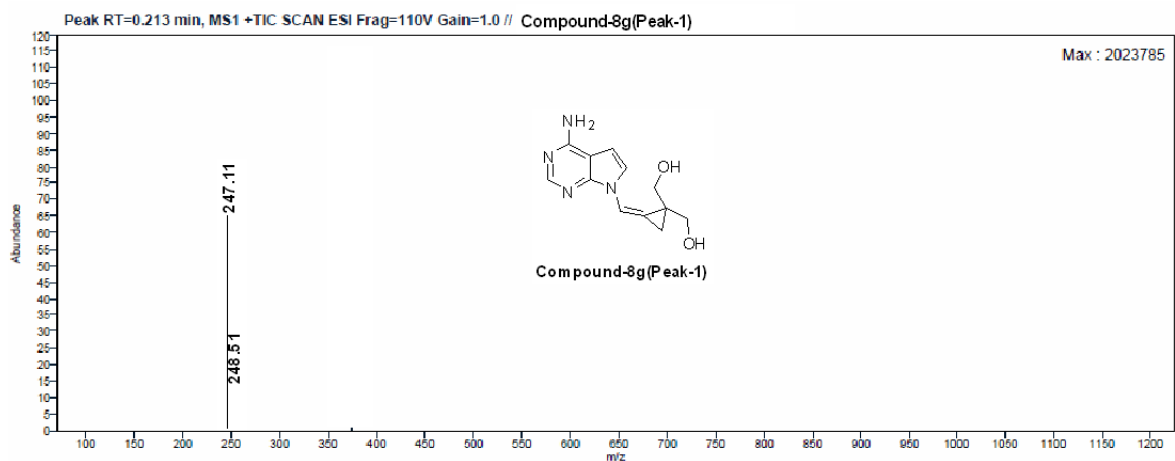
VARIAN 400MHz NMR
Solvent: dmsd
Date:Jul 23 2022



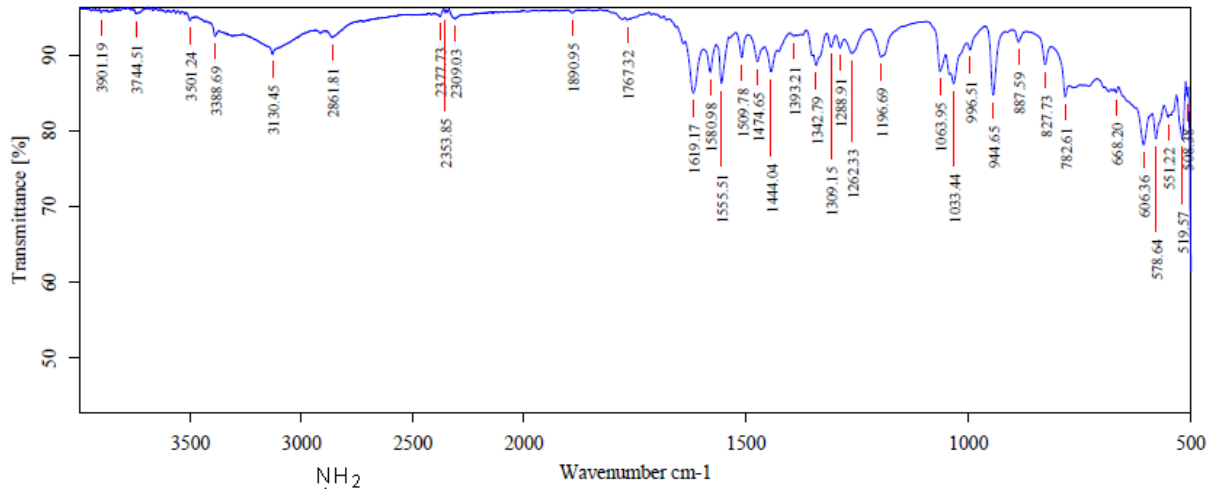
Compound-8g(Peak-1)



MS Spectrum

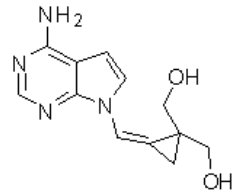


INFRARED SPECTRUM



Compound-8g(Peak-1)

Lot No./Batch No:
Date & Time: 20-07-2022, 18:15:21
Operator Name: Accru Chemist



Compound-8g(Peak-1)

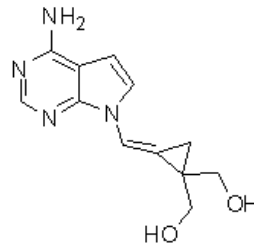
Instrument ID No: AA-ID-002

Experiment: ACCU87.spm
Resolution: 4
Sample Scans: 16
Frequency Range: 4000 to 500

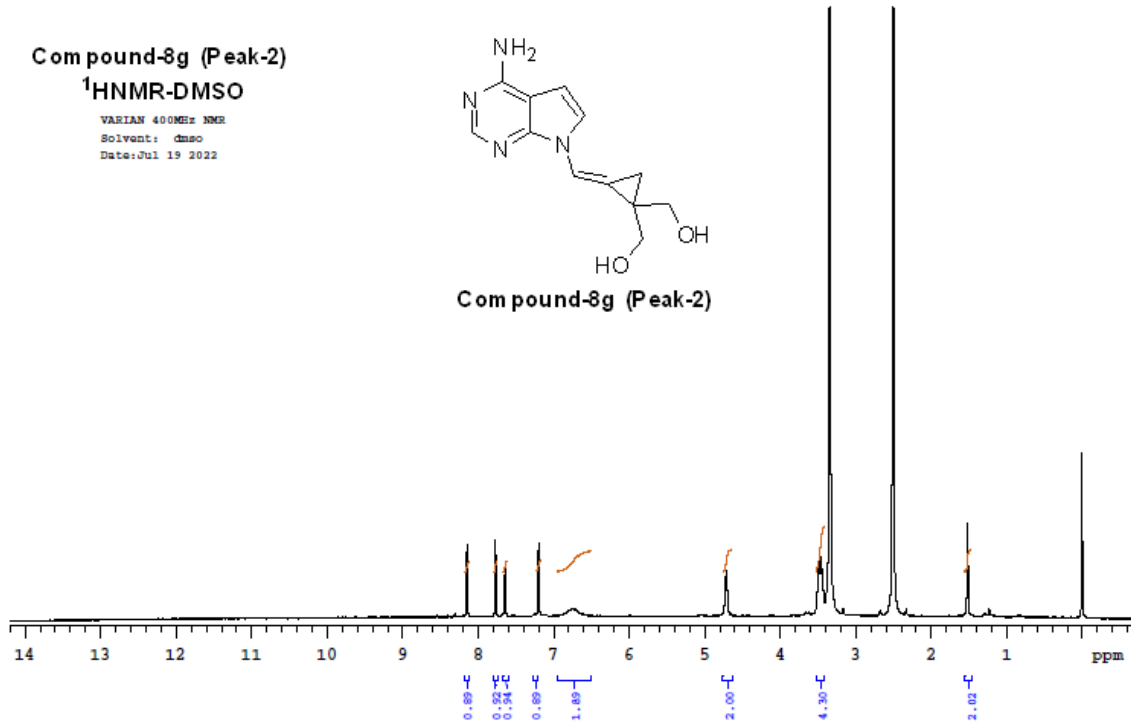
Compound-8g (Peak-2)

¹HNMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsd
Date: Jul 19 2022



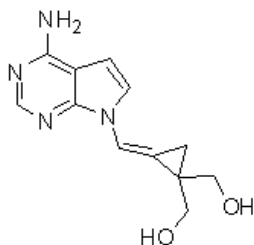
Compound-8g (Peak-2)



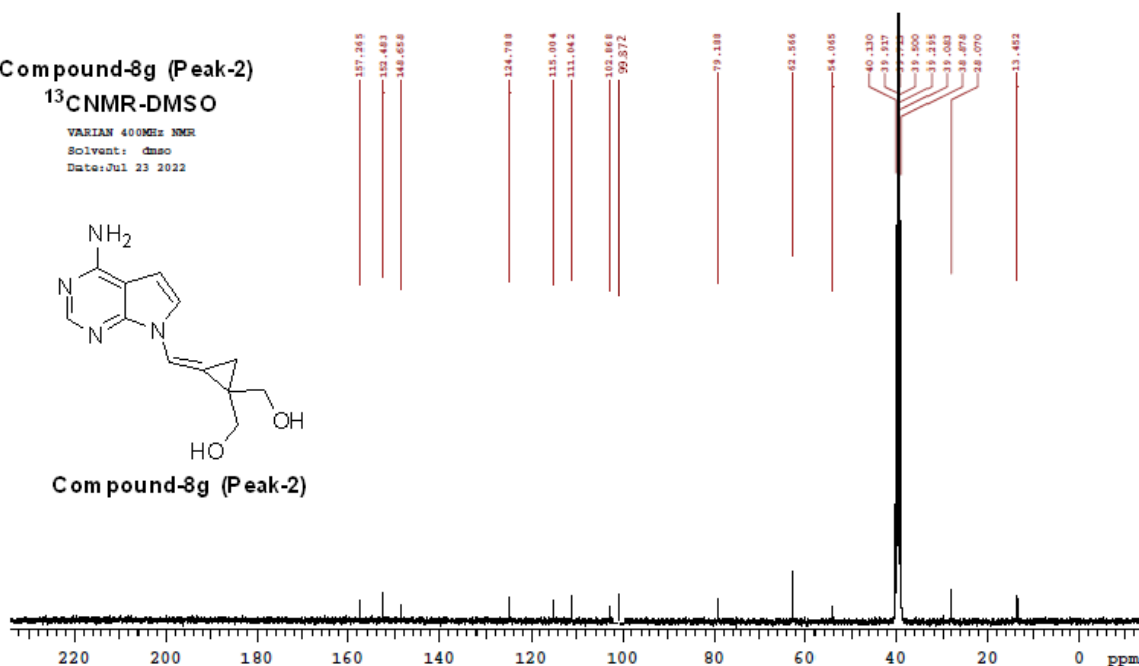
Compound-8g (Peak-2)

¹³C NMR-DMSO

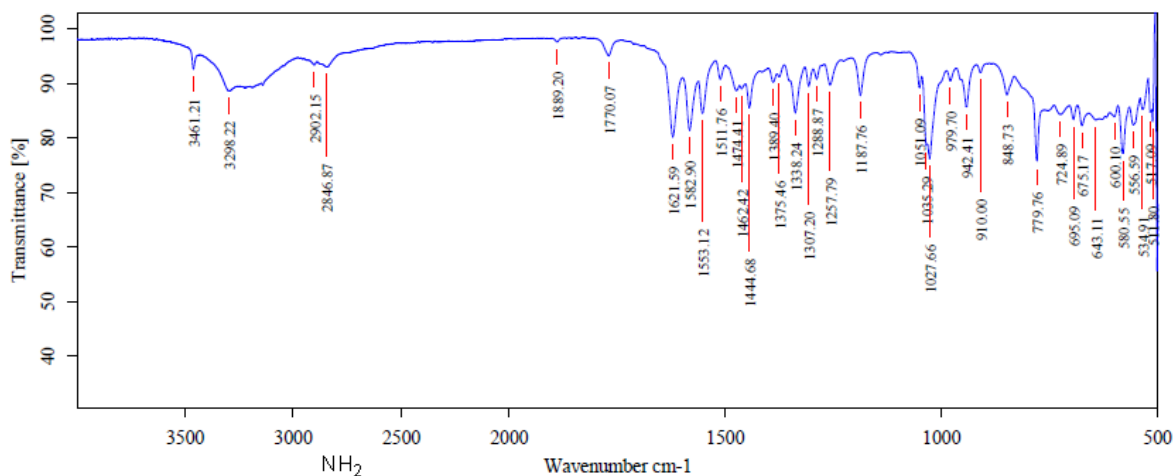
VARIAN 400MHz NMR
Solvent: dms
Date: Jul 23 2022



Compound-8g (Peak-2)



INFRARED SPECTRUM

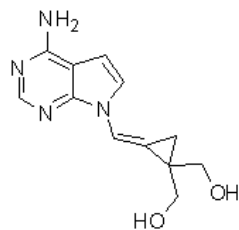


Compound-8g (Peak-2)

Lot No./Batch No:

Date & Time: 20-07-2022, 17:35:56

Operator Name: Accu Chemist



Compound-8g (Peak-2)

Instrument ID No: AA-ID-002

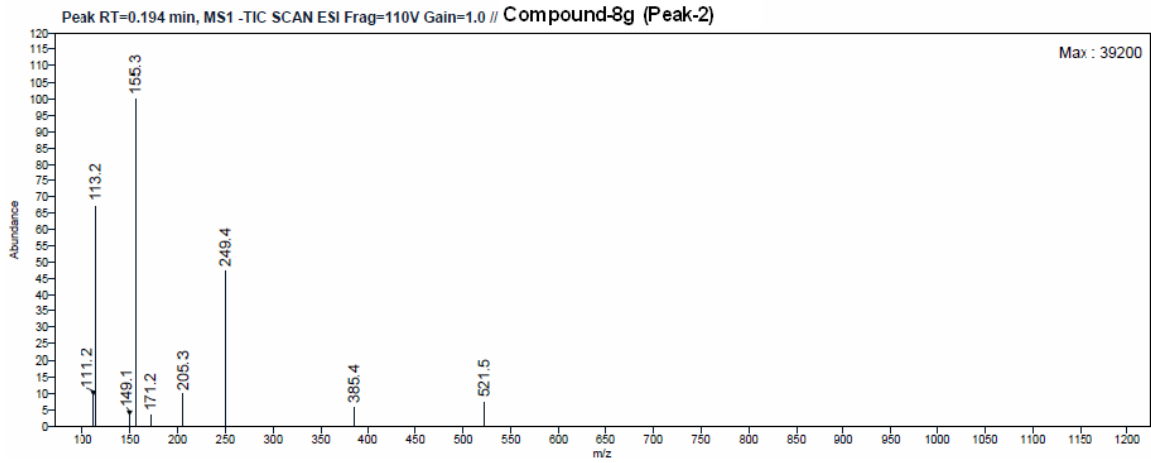
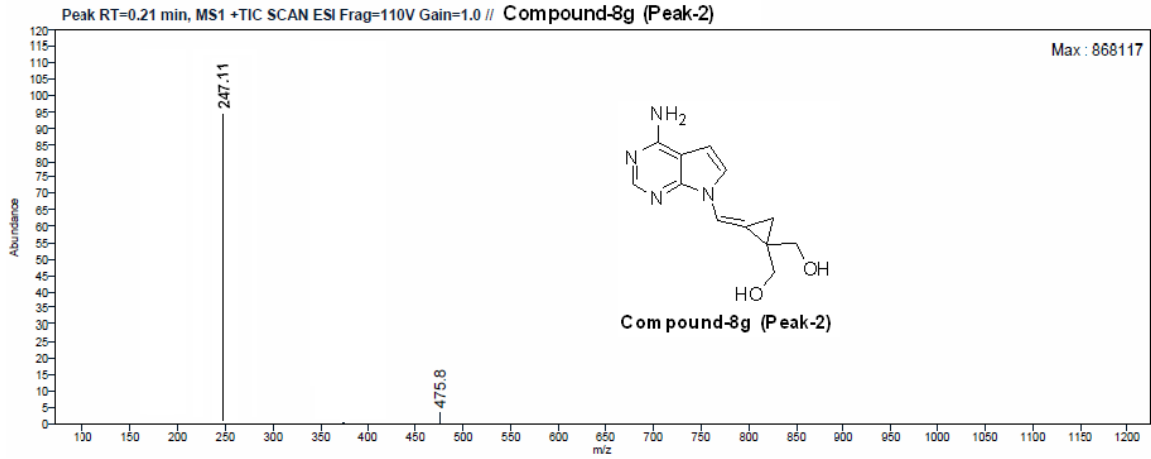
Experiment: ACCU87.spm

Resolution: 4

Sample Scans: 16

Frequency Range: 4000 to 500

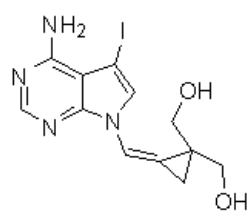
MS Spectrum



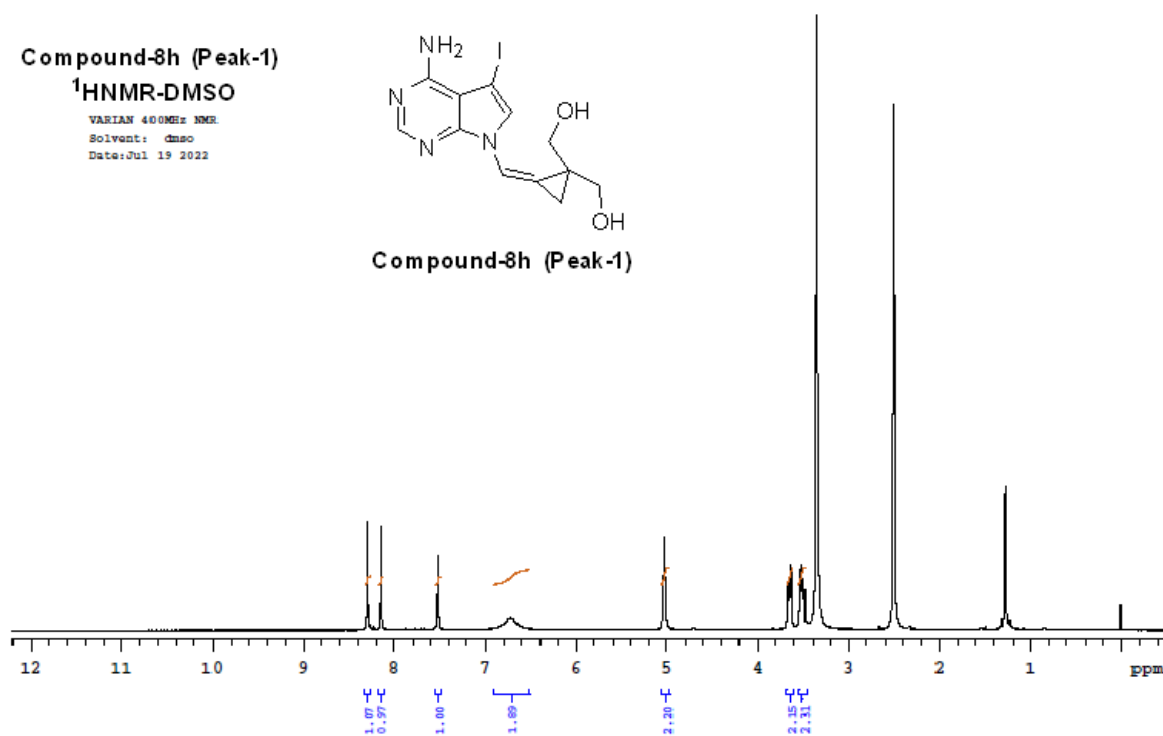
Compound-8h (Peak-1)

¹H NMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsc
Date: Jul 19 2022



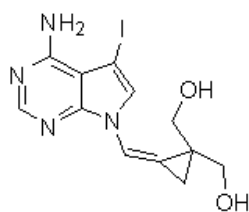
Compound-8h (Peak-1)



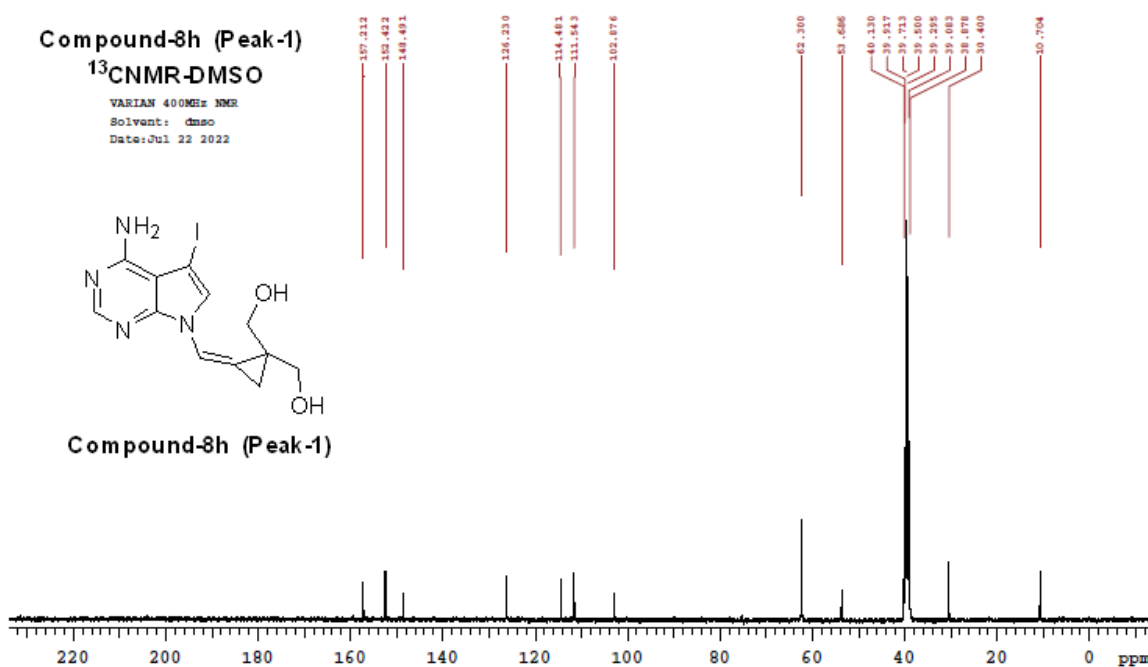
Compound-8h (Peak-1)

¹³C NMR-DMSO

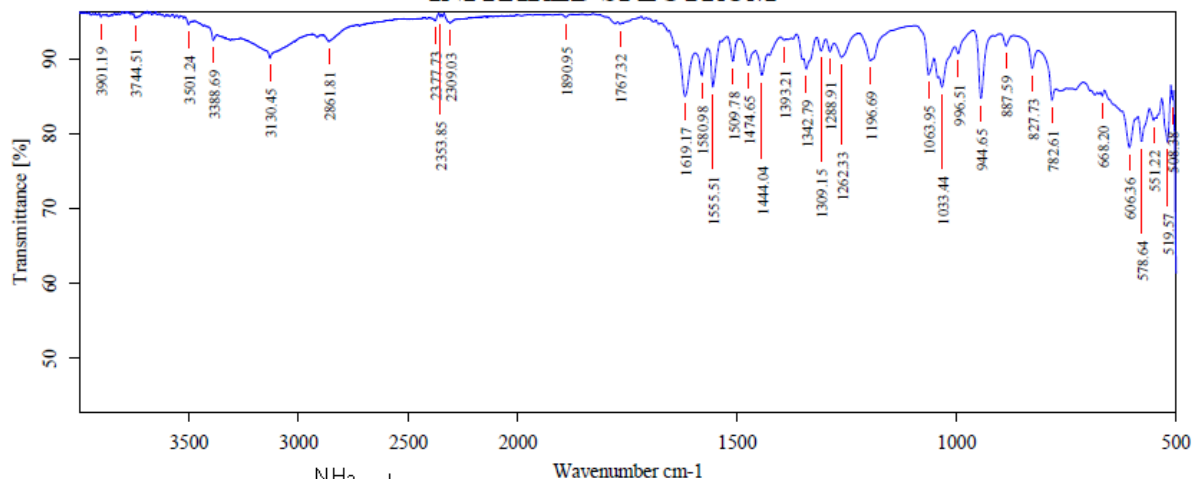
VARIAN 400MHz NMR
Solvent: dmsc
Date: Jul 22 2022



Compound-8h (Peak-1)



INFRARED SPECTRUM

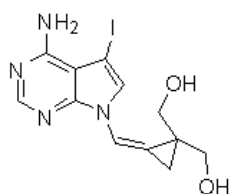


Compound-8h (Peak-1)

Lot No./Batch No:

Date & Time: 20-07-2022, 18:15:21

Operator Name: Accu Chemist



Compound-8h (Peak-1)

Instrument ID No: AA-ID-002

Experiment: ACCU87.spm

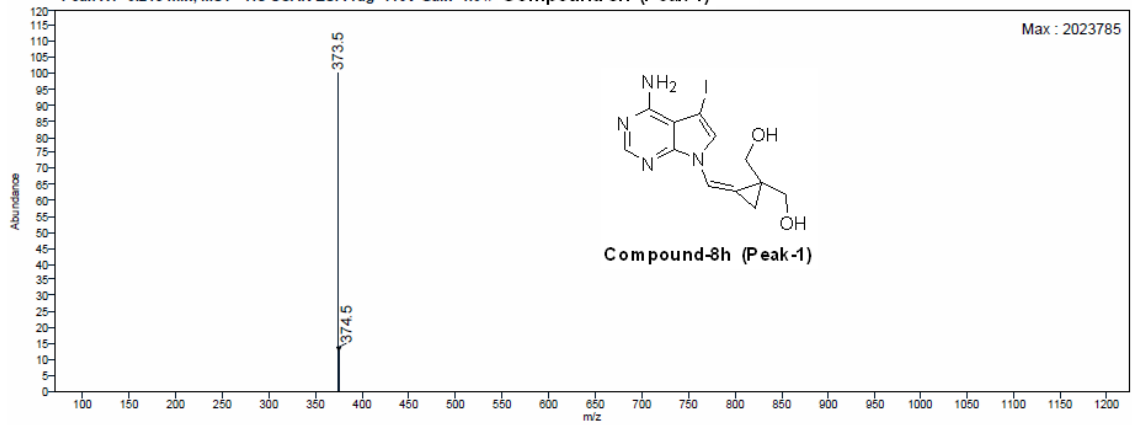
Resolution: 4

Sample Scans: 16

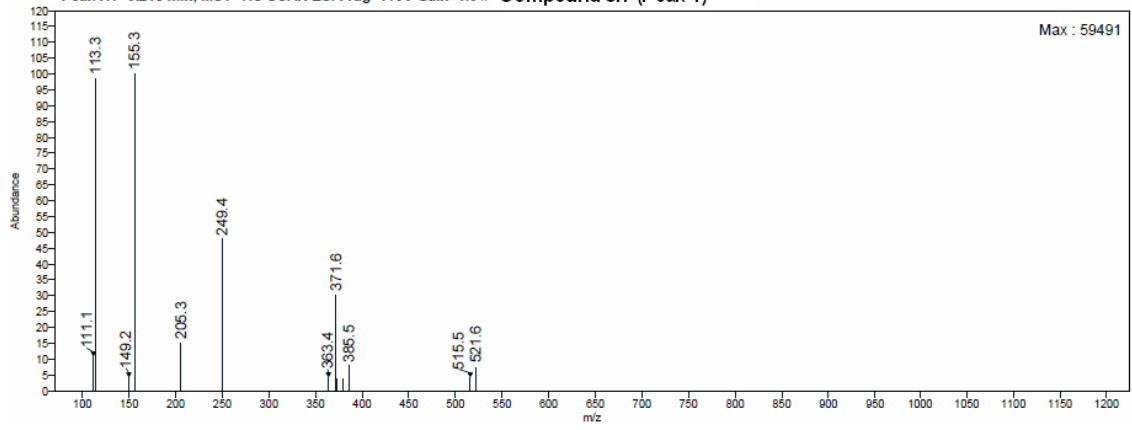
Frequency Range: 4000 to 500

MS Spectrum

Peak RT=0.213 min, MS1 +TIC SCAN ESI Frag=110V Gain=1.0 // Compound-8h (Peak-1)



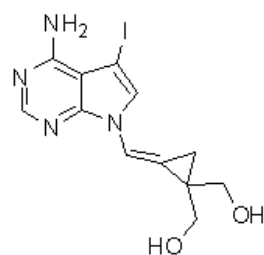
Peak RT=0.215 min, MS1 -TIC SCAN ESI Frag=110V Gain=1.0 // Compound-8h (Peak-1)



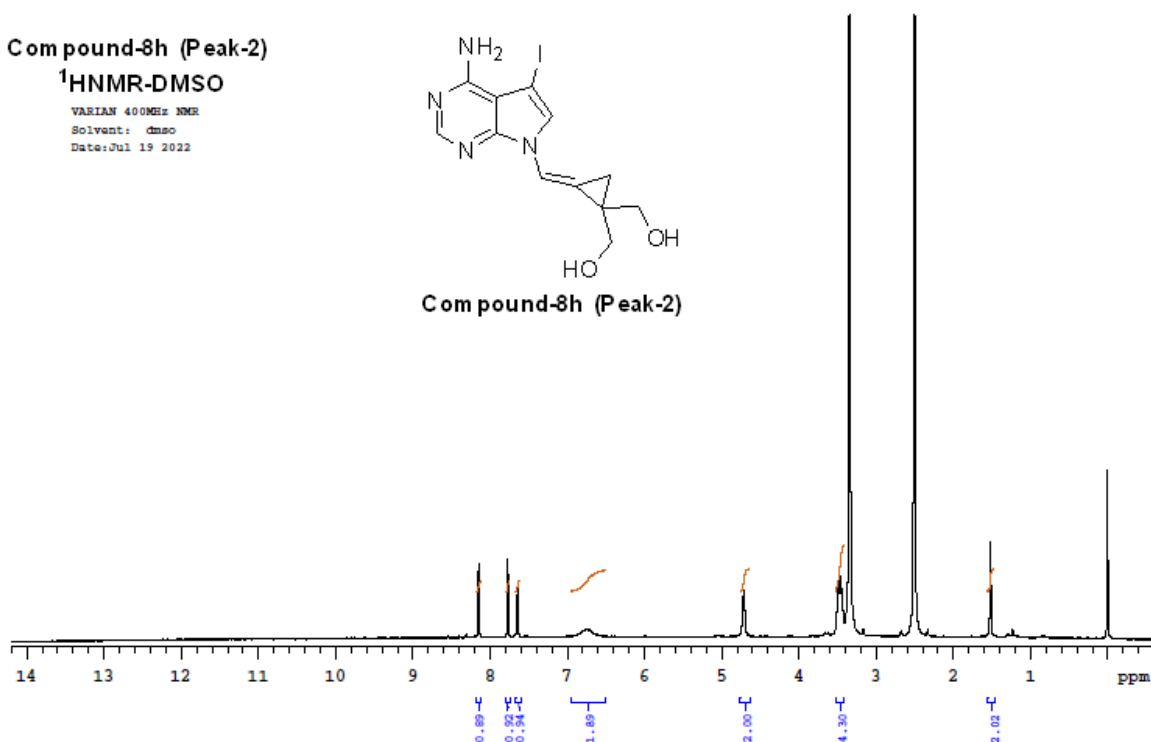
Compound-8h (Peak-2)

¹H NMR-DMSO

VARIAN 400MHz NMR
Solvent: dms
Date: Jul 19 2022



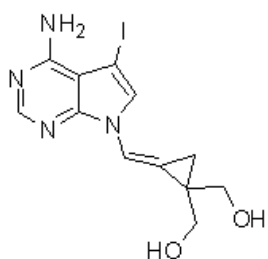
Compound-8h (Peak-2)



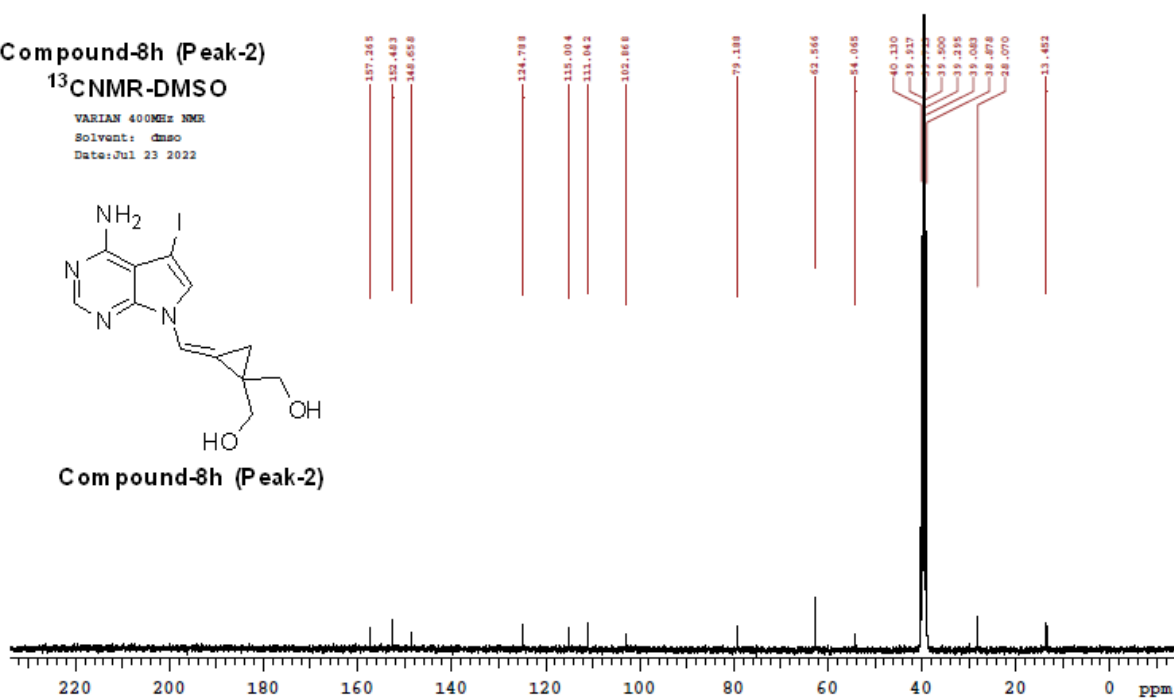
Compound-8h (Peak-2)

¹³C NMR-DMSO

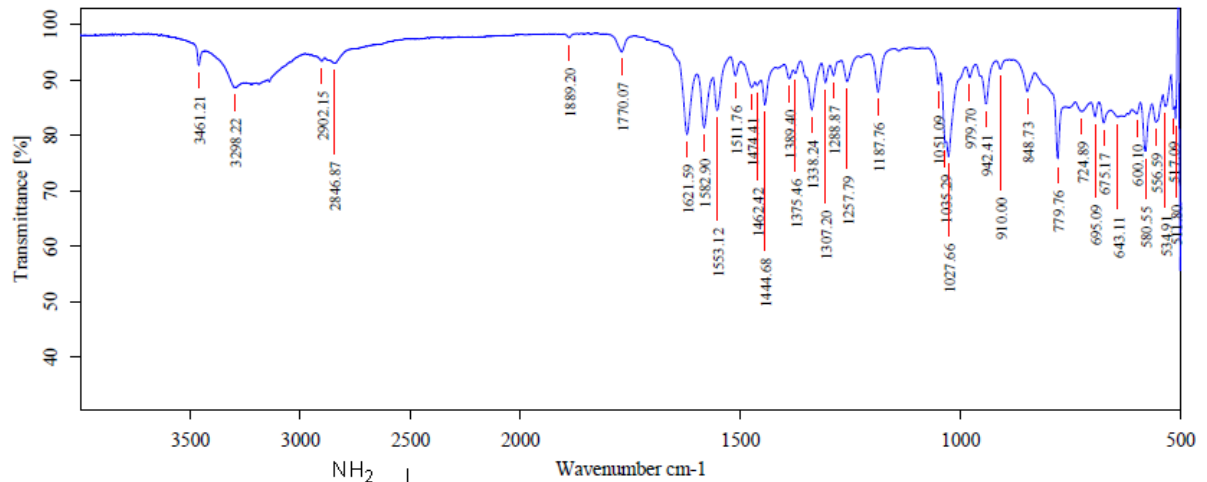
VARIAN 400MHz NMR
Solvent: dms
Date: Jul 23 2022



Compound-8h (Peak-2)



INFRARED SPECTRUM

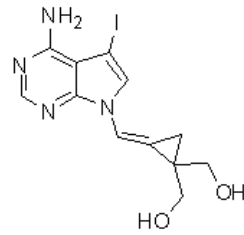


Compound-8h (Peak-2)

Lot No./Batch No:

Date & Time: 20-07-2022, 17:35:56

Operator Name: Accu Chemist



Compound-8h (Peak-2)

Instrument ID No: AA-ID-002

Experiment: ACCU87.spn

Resolution: 4

Sample Scans: 16

Frequency Range: 4000 to 500

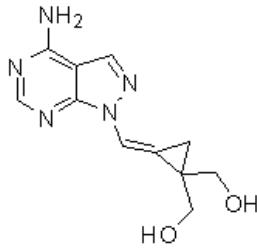
Compound 10a (Peak-1)

¹H NMR - DMSO

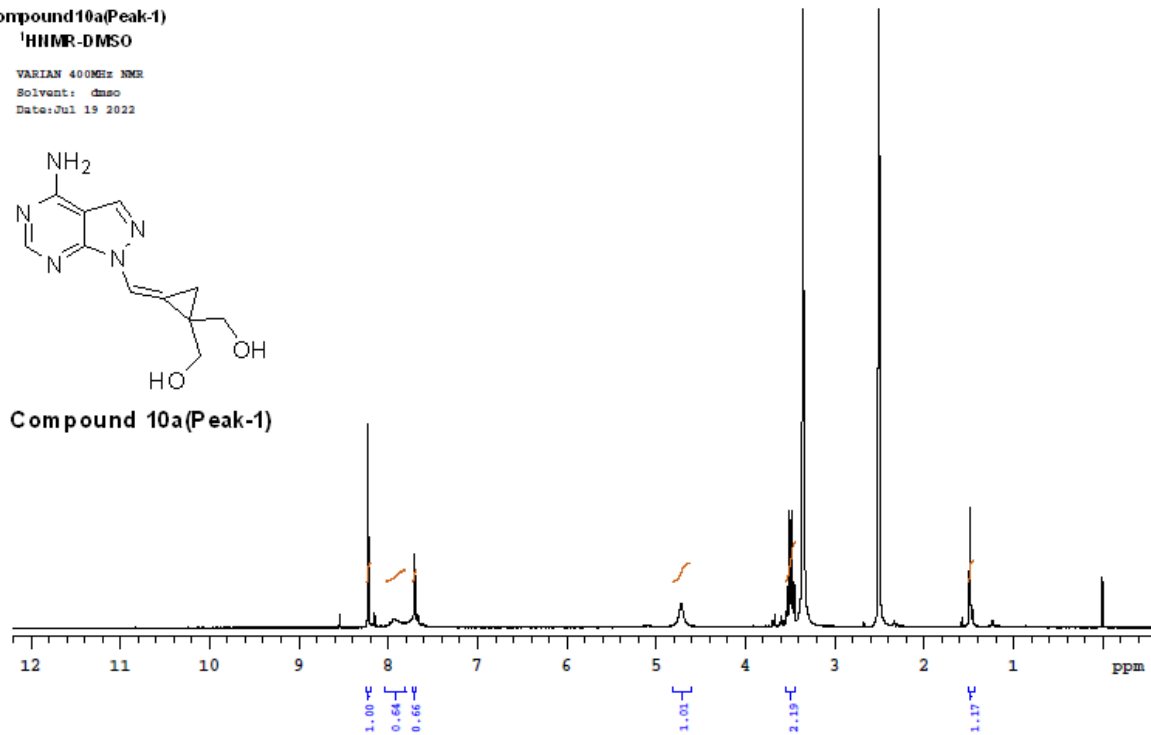
VARIAN 400MHz NMR

Solvent: dmsd

Date: Jul 19 2022



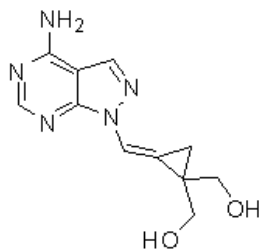
Compound 10a (Peak-1)



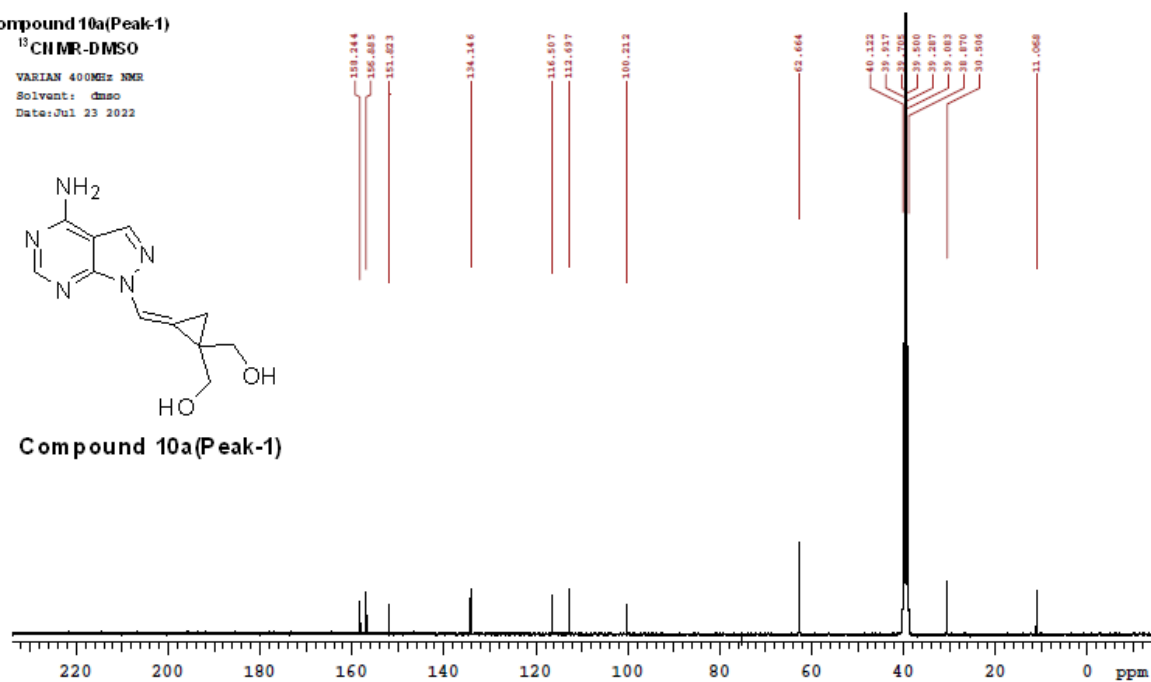
Compound 10a(Peak-1)

¹³C NMR-DMSO

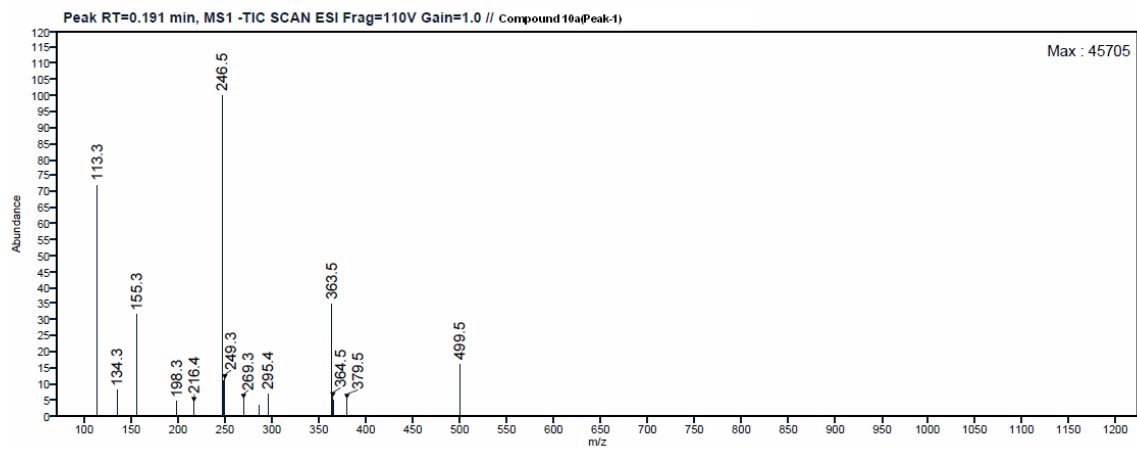
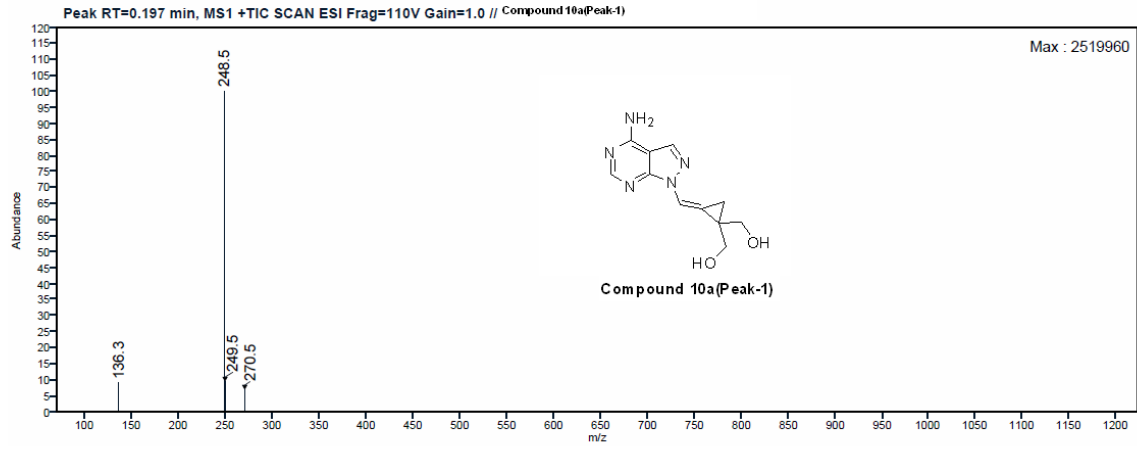
VARIAN 400MHz NMR
Solvent: dmsco
Date: Jul 23 2022



Compound 10a(Peak-1)



MS Spectrum



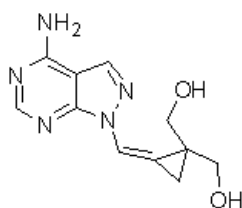
Compound 10a(Peak-2)

¹HMR-DMSO

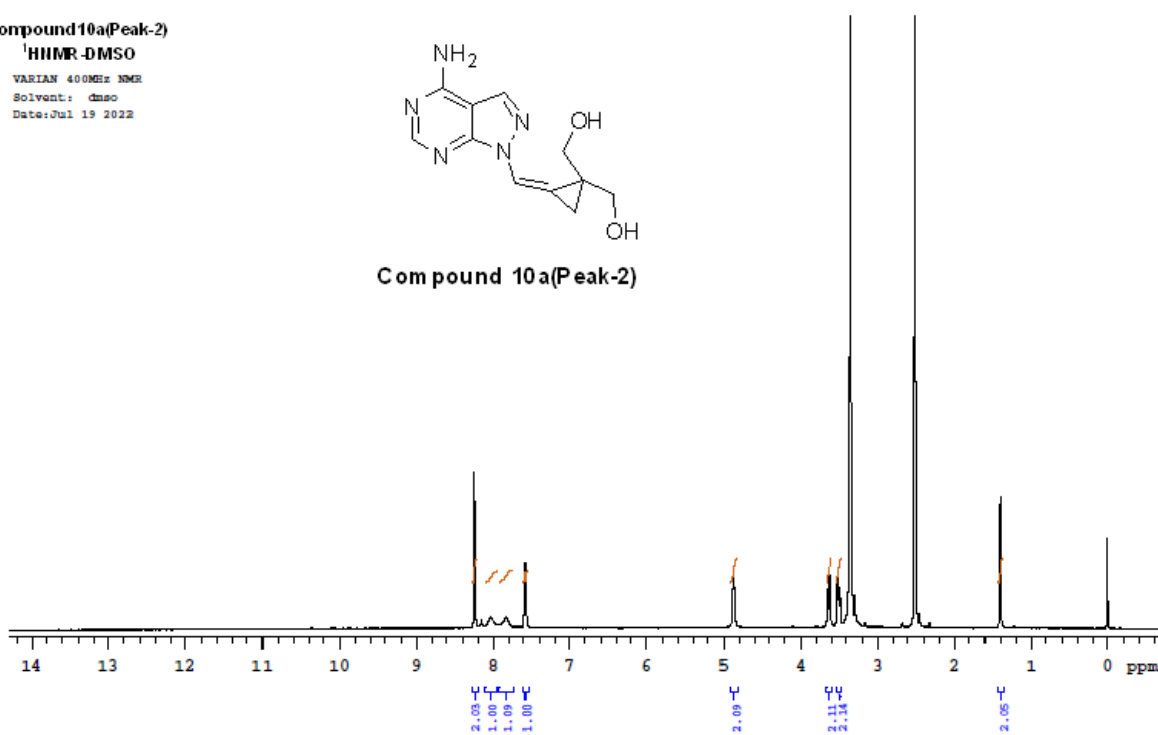
VARIAN 400MHz NMR

Solvent: dmsO

Date:Jul 19 2022



Compound 10a(Peak-2)



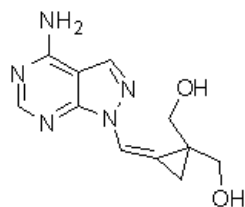
Compound 10a(Peak-2)

¹³CHMR-DMSO

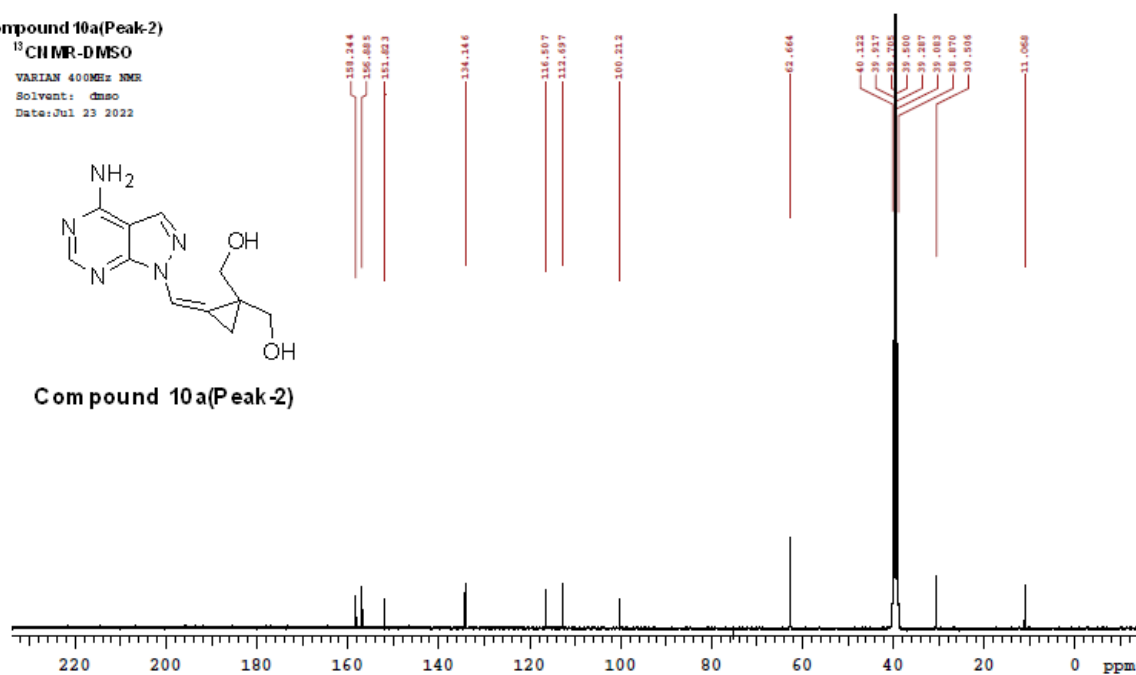
VARIAN 400MHz NMR

Solvent: dmsO

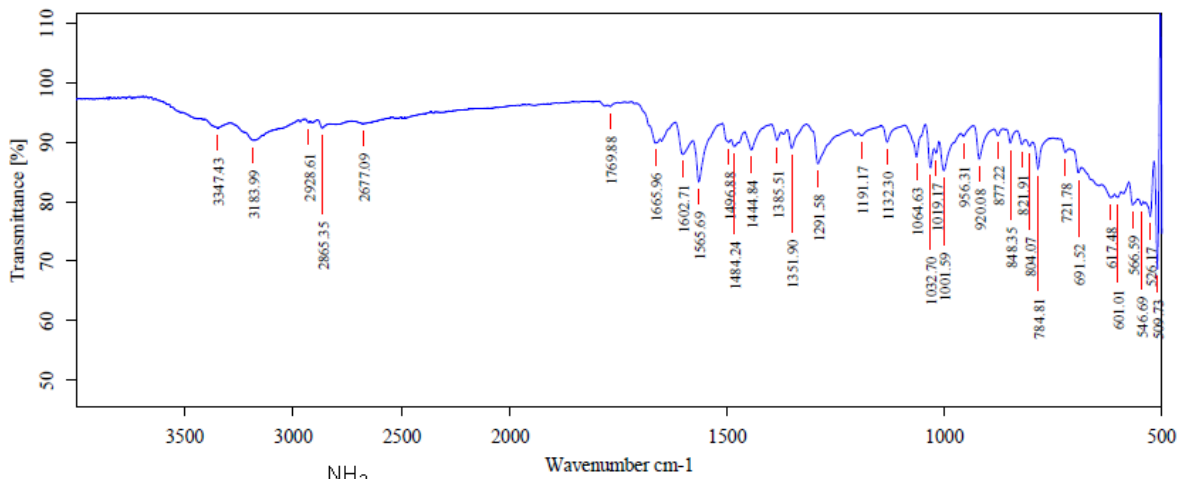
Date:Jul 23 2022



Compound 10a(Peak-2)



INFRARED SPECTRUM

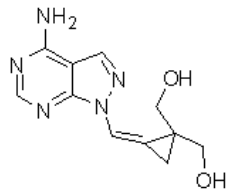


Compound 10a(Peak-2)

Lot No./Batch No:

Date & Time: 20-07-2022, 17:39:25

Operator Name: Accu Chemist



Compound 10a(Peak-2)

Instrument ID No: AA-ID-002

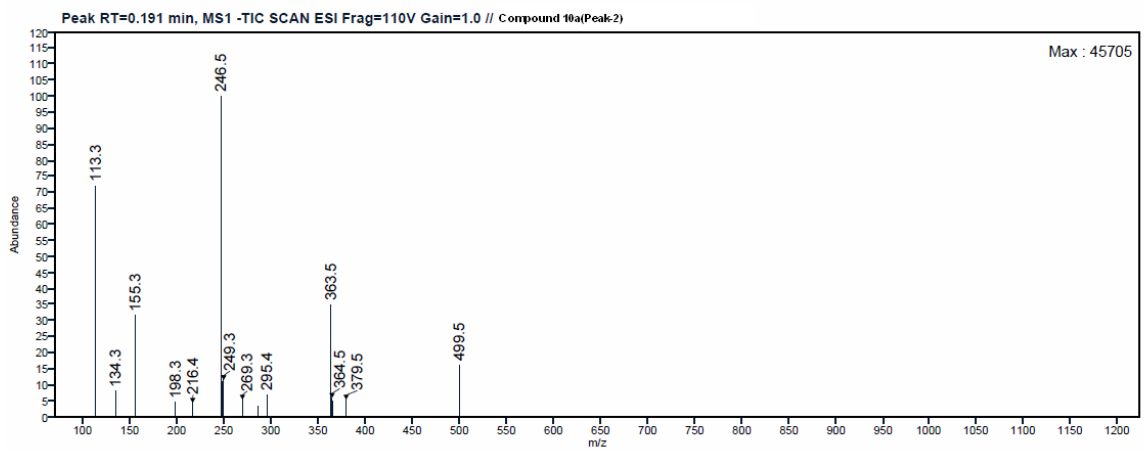
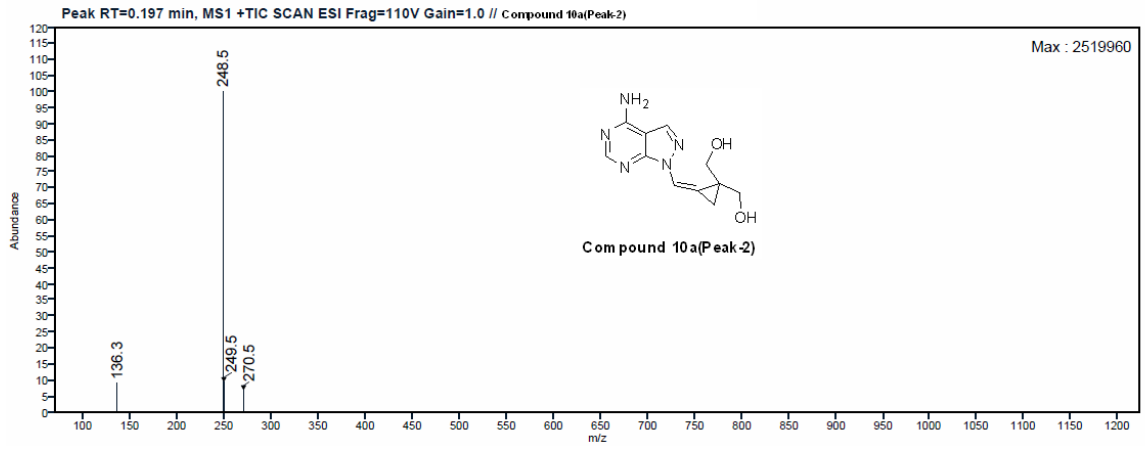
Experiment: ACCU87.spm

Resolution: 4

Sample Scans: 16

Frequency Range: 4000 to 500

-----MS Spectrum-----



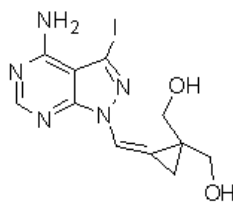
Compound 10b(Peak-1)

¹H NMR-DMSO

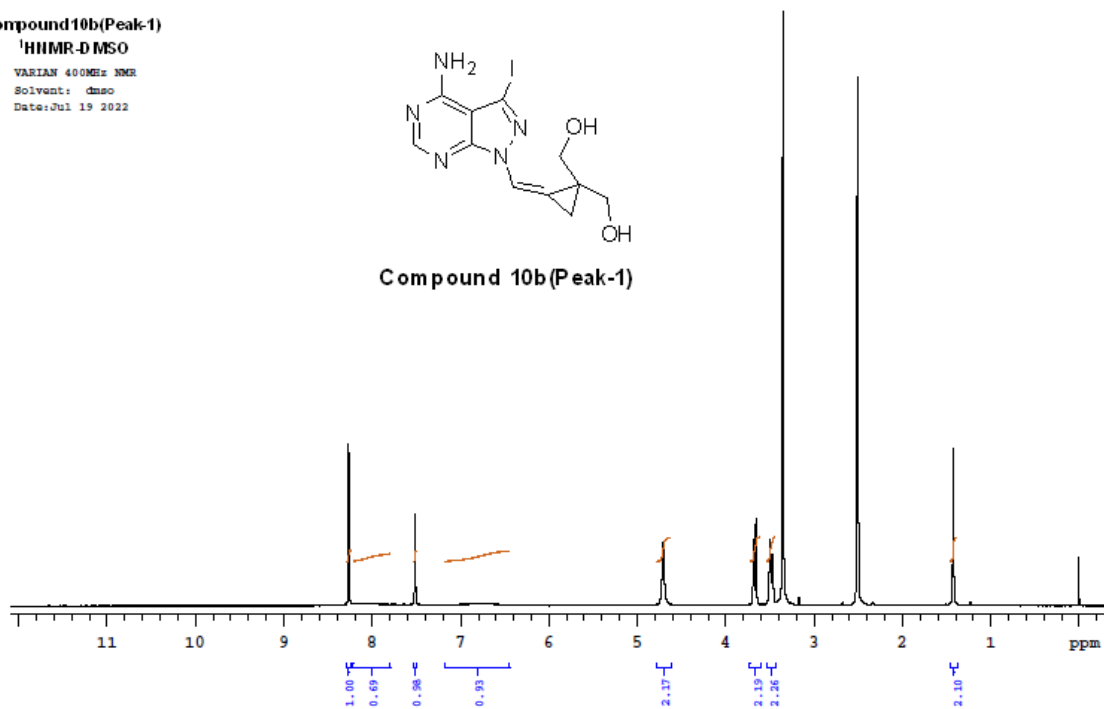
VARIAN 400MHz NMR

Solvent: dmsc

Date: Jul 19 2022



Compound 10b(Peak-1)



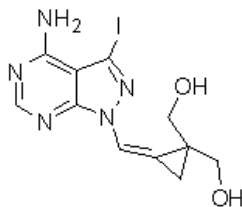
Compound 10b(Peak-1)

¹³C NMR-DMSO

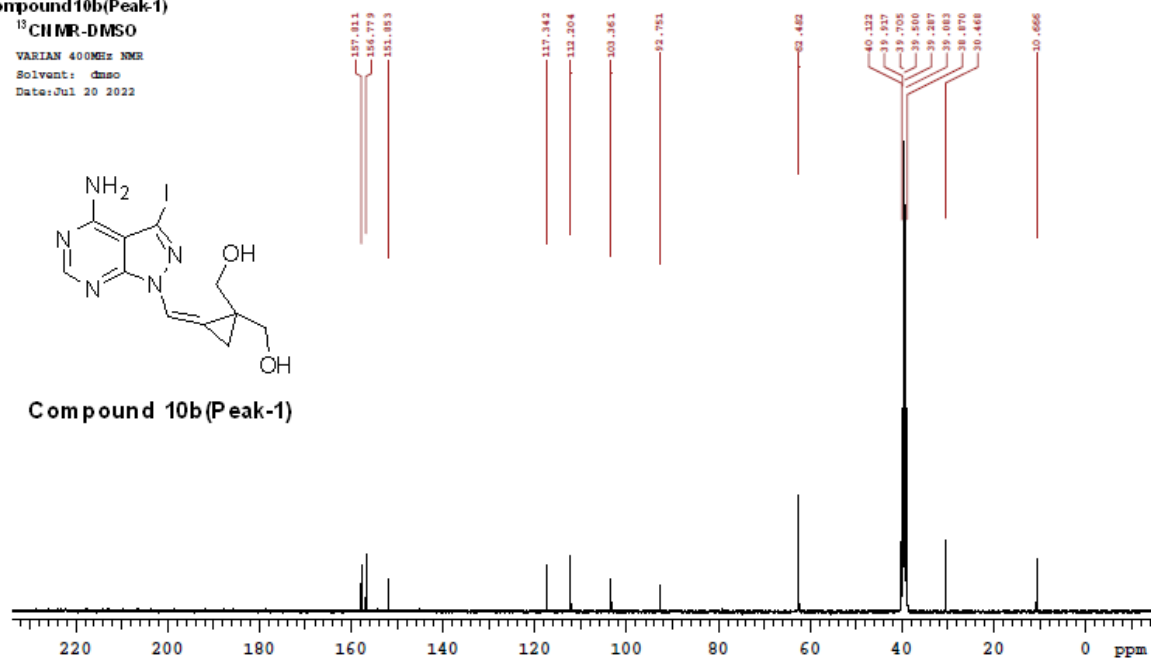
VARIAN 400MHz NMR

Solvent: dmsc

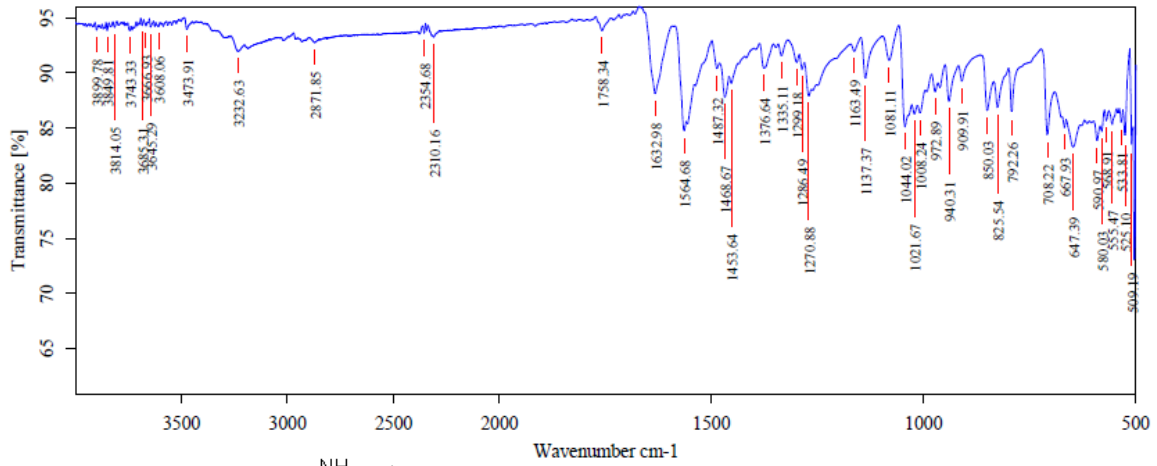
Date: Jul 20 2022



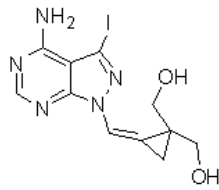
Compound 10b(Peak-1)



INFRARED SPECTRUM



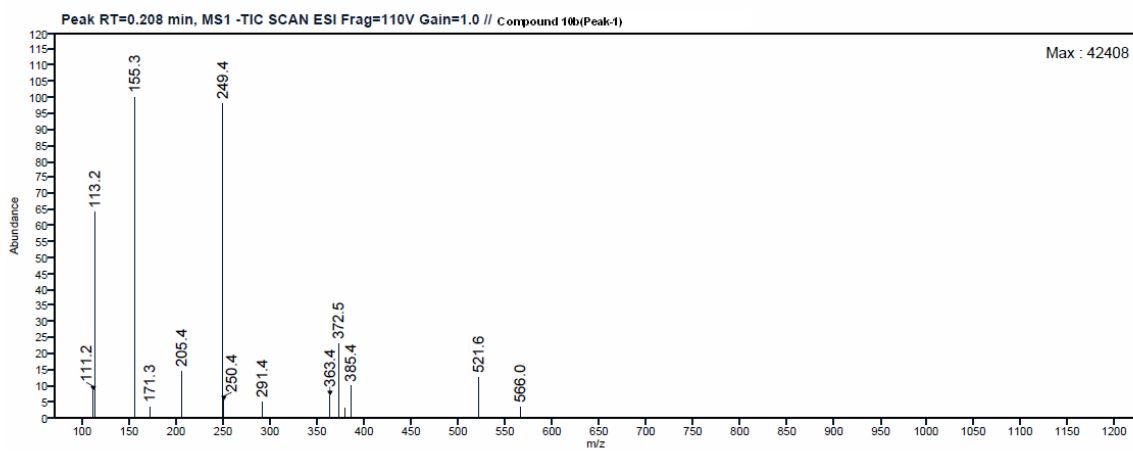
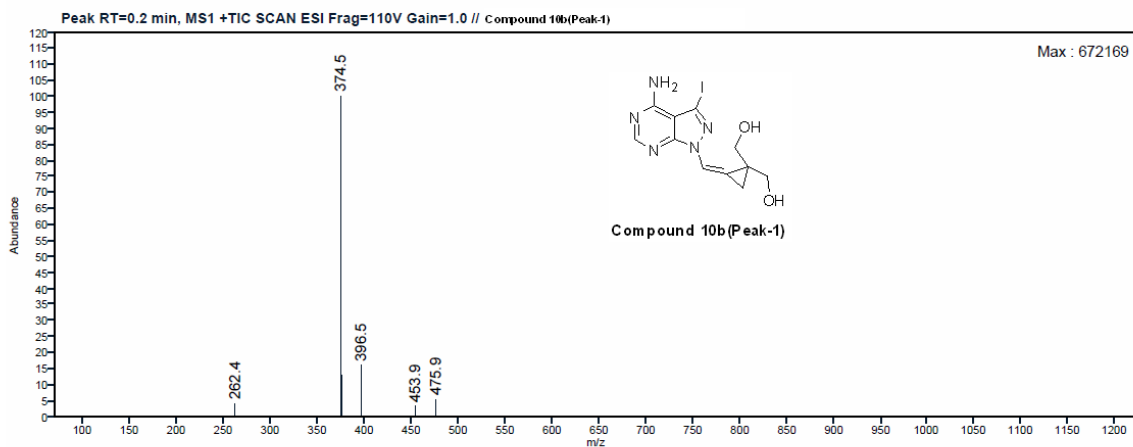
Compound 10b(Peak-1)
Lot No./Batch No:
Date & Time: 20-07-2022, 18:09:17
Operator Name: Accu Chemist



Compound 10b(Peak-1)

Instrument ID No: AA-ID-002
Experiment: ACCU87.xpm
Resolution: 4
Sample Scans: 16
Frequency Range: 4000 to 500

MS Spectrum



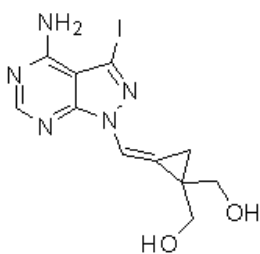
Compound 10b(Peak-2)

¹³C NMR-DMSO

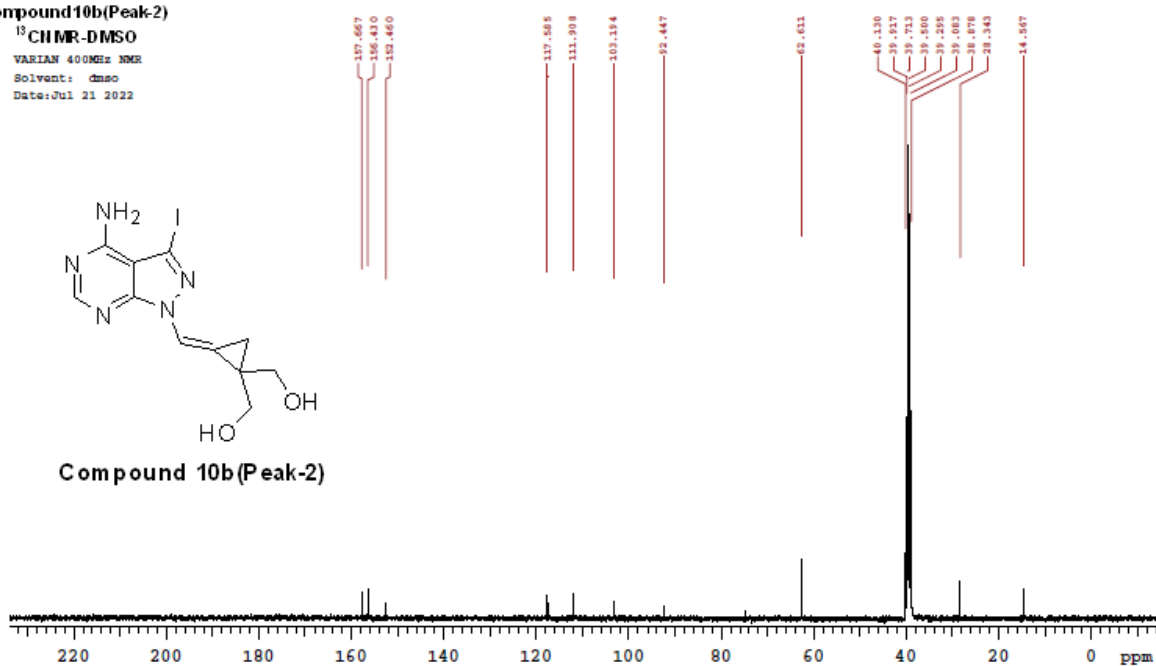
VARIAN 400MHz NMR

Solvent: dmsc

Date: Jul 21 2022



Compound 10b(Peak-2)



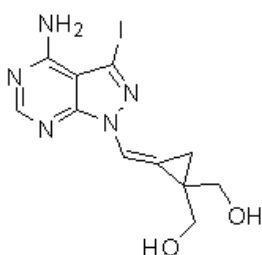
Compound 10b(Peak-2)

¹H NMR-DMSO

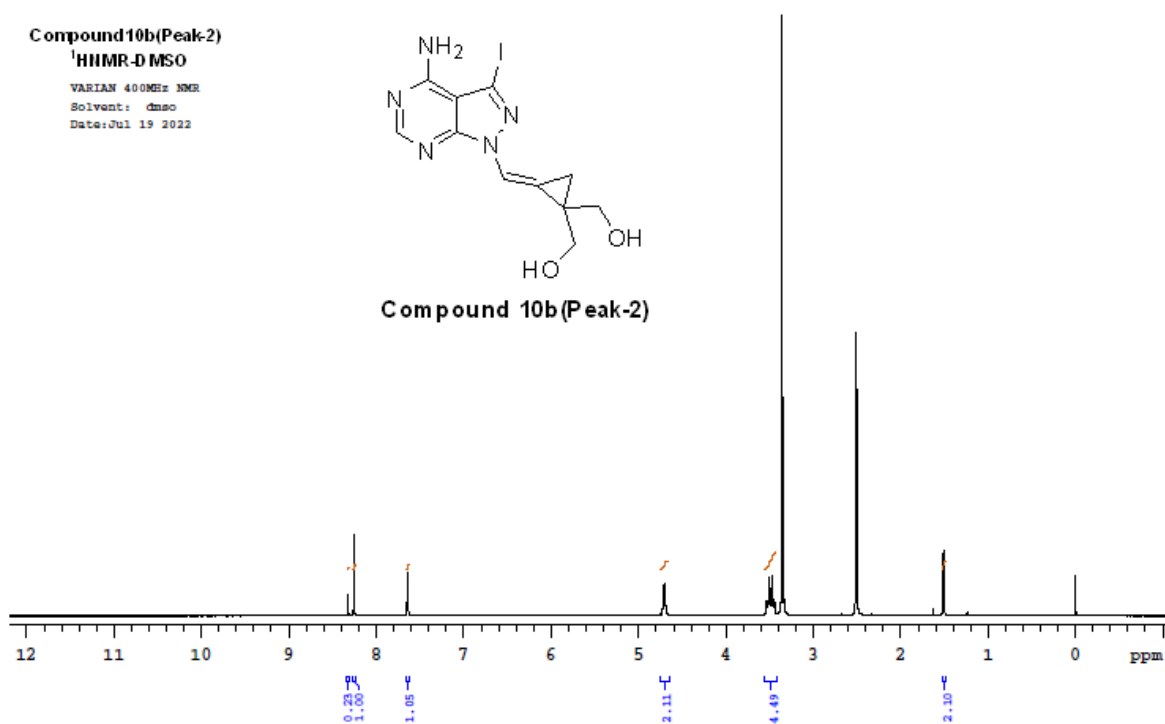
VARIAN 400MHz NMR

Solvent: dmsc

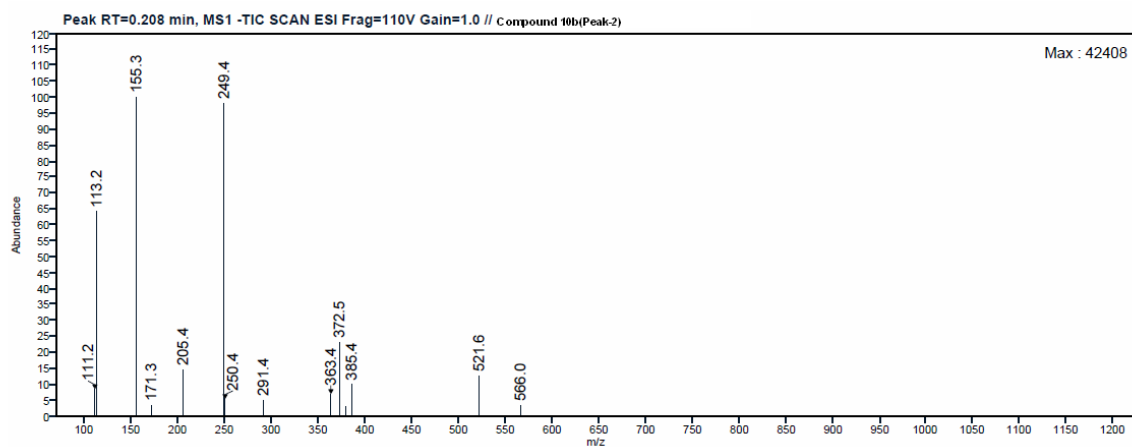
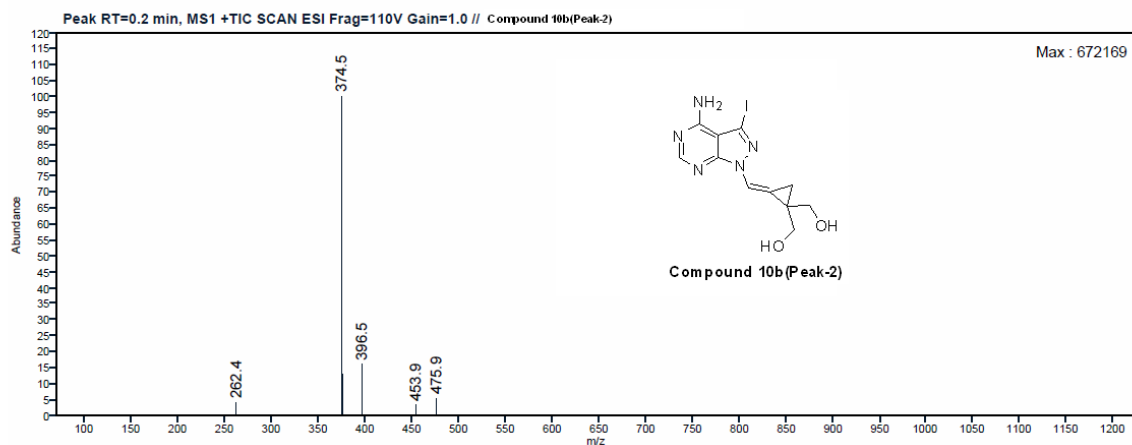
Date: Jul 19 2022



Compound 10b(Peak-2)

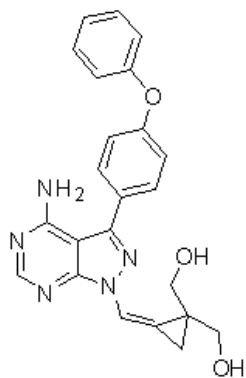


-----MS Spectrum-----

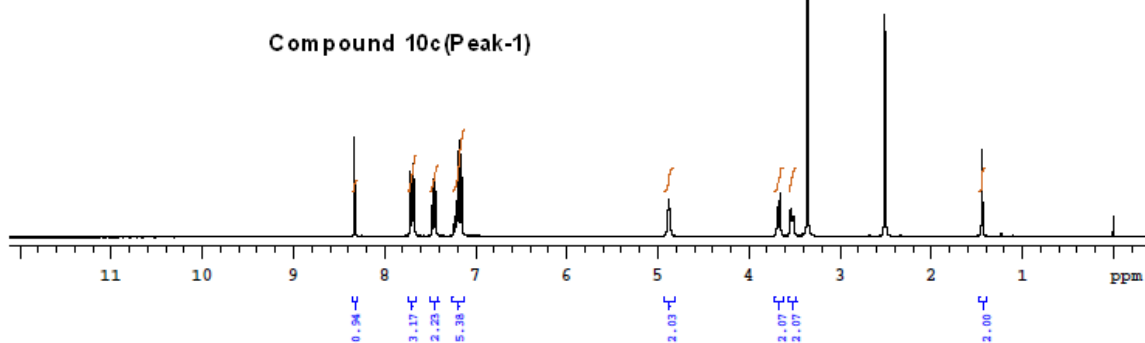


Compound 10c(Peak-1)

¹H NMR-DMSO
VARIAN 400MHz NMR
Solvent: dmsc
Date: Jul 19 2022

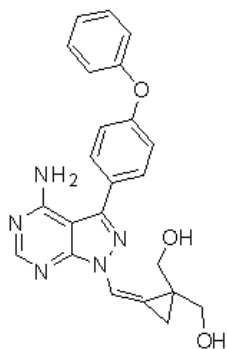


Compound 10c(Peak-1)

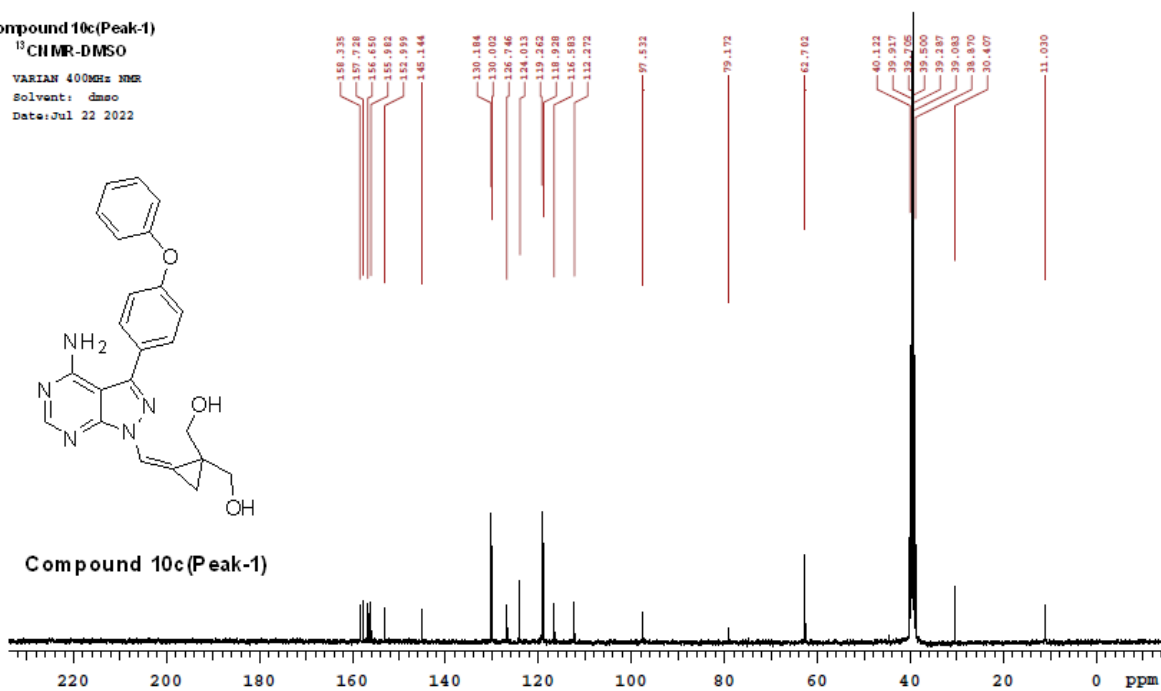


Compound 10c(Peak-1)

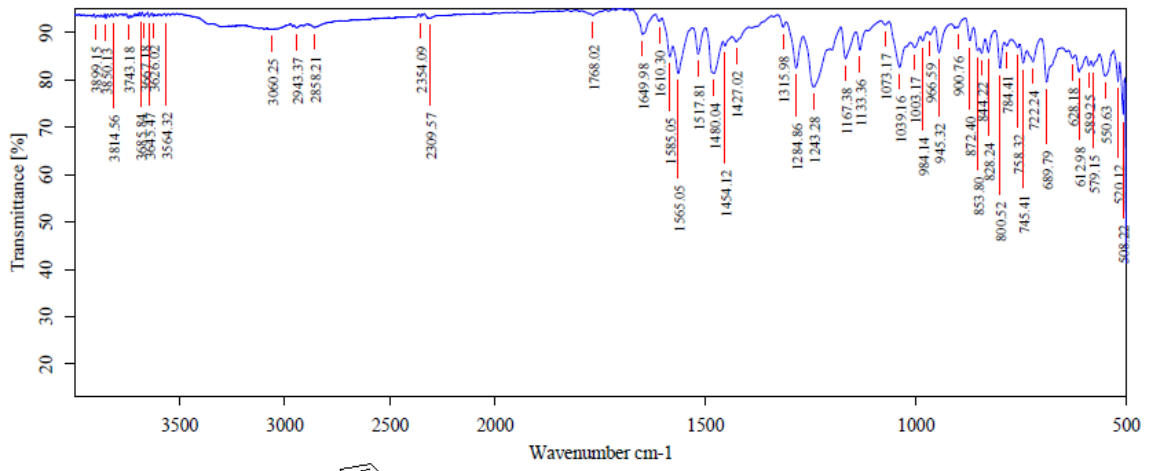
¹³C NMR-DMSO
VARIAN 400MHz NMR
Solvent: dmsc
Date: Jul 22 2022



Compound 10c(Peak-1)



INFRARED SPECTRUM

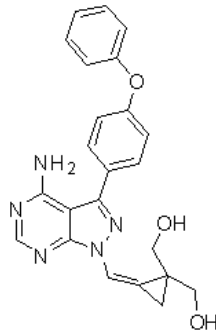


Compound 10c(Peak-1)

Lot No./Batch No:

Date & Time: 20-07-2022, 18:06:23

Operator Name: Accu Chemist



Compound 10c(Peak-1)

Instrument ID No: AA-ID-002

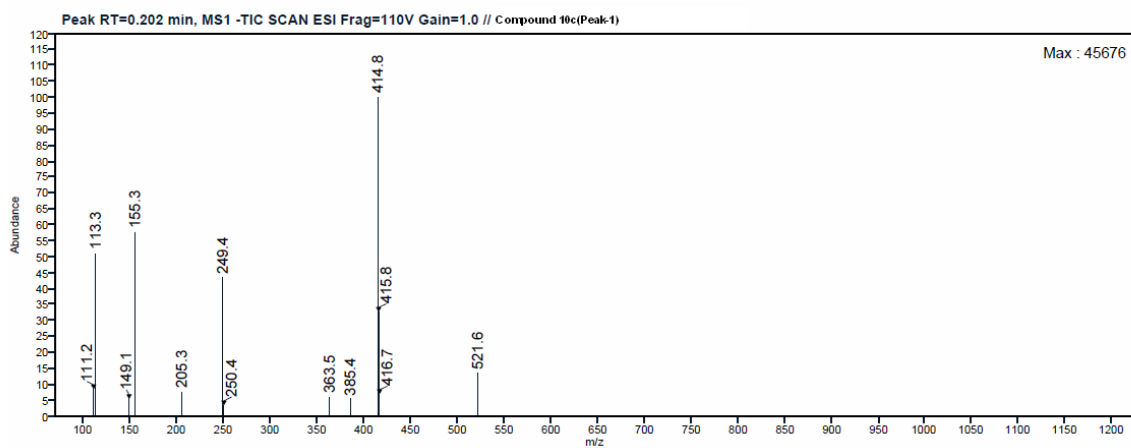
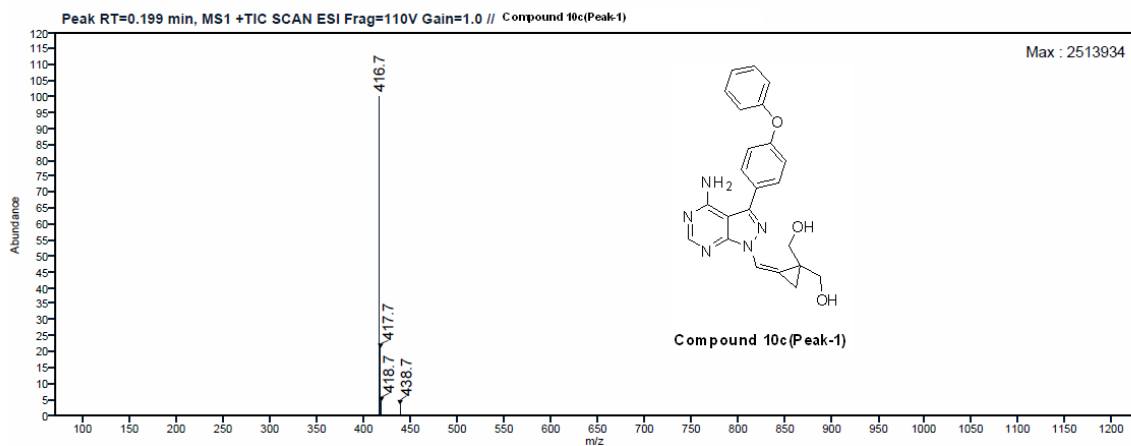
Experiment: ACCU87.spm

Resolution: 4

Sample Scans: 16

Frequency Range: 4000 to 500

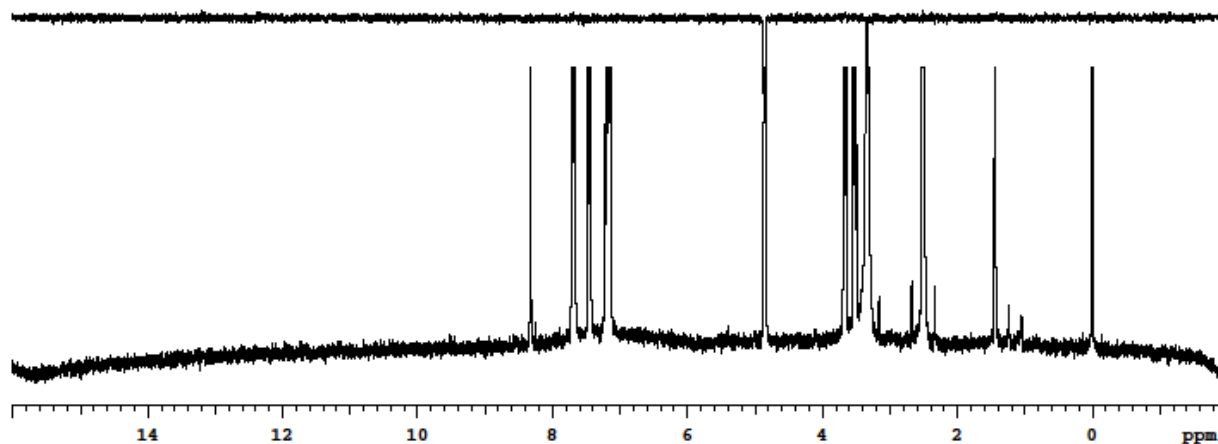
-----MS Spectrum-----



Compound 10c (Z-isomer) NOE analysis:

Sample code: C2072-179-FK1

Selective band center: 4.86 (ppm), width: 34.6 (Hz)
VARIAN 400MHz NMR
Solvent: dmsc
Date: Nov 14 2022



Plotname: C2072-179-FK1_NORSY1D_01_plot01

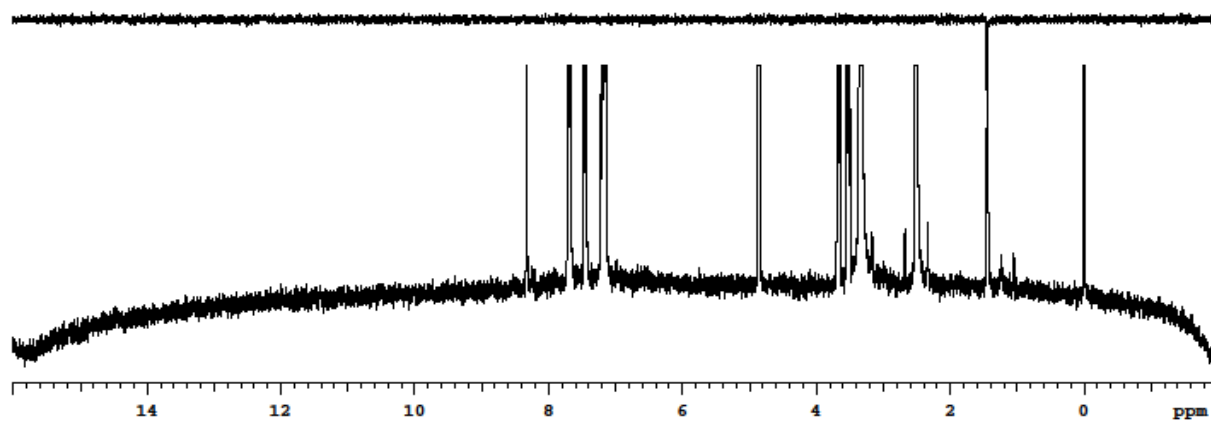
Sample code: C2072-179-FK1

Selective band center: 1.44 (ppm), width: 23.9 (Hz)

VARIAN 400MHz NMR

Solvent: dmsc

Date: Nov 14 2022



Plotname: C2072-179-FK1_NMRSTD_03_plot01

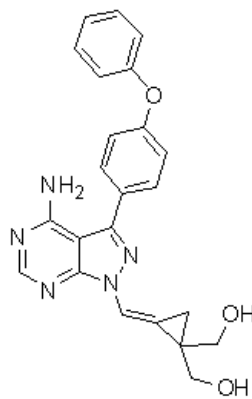
Compound 10c(Peak-2)

¹H NMR-DMSO

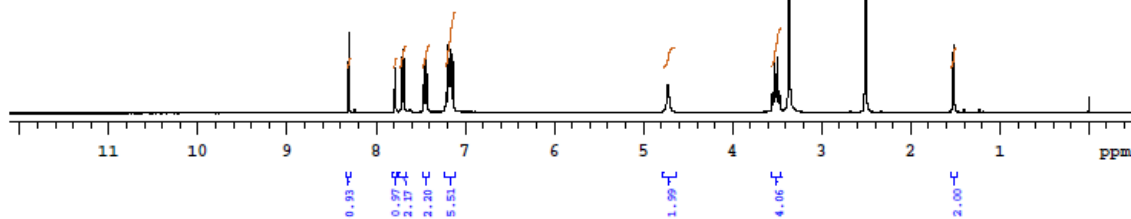
VARIAN 400MHz NMR

Solvent: dmsc

Date: Jul 19 2022



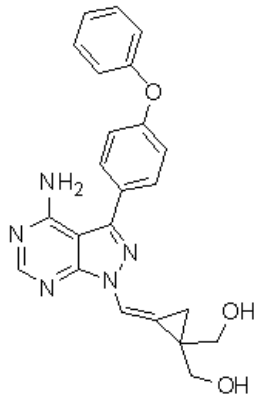
Compound 10c(Peak-2)



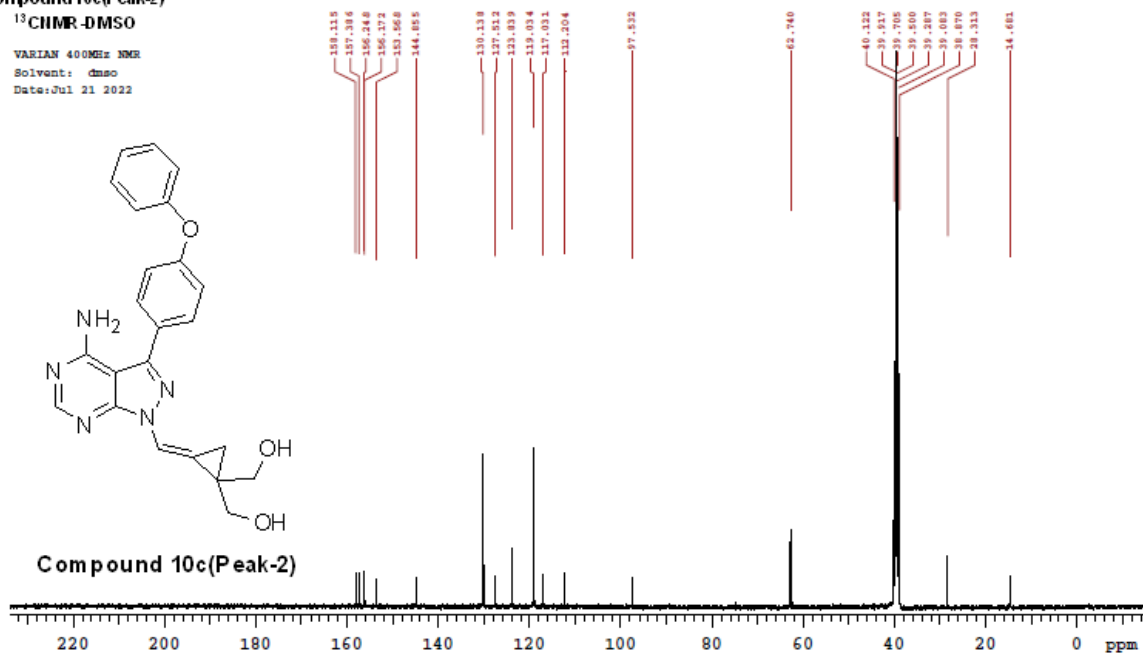
Compound 10c(Peak-2)

¹³CHMR-DMSO

VARIAN 400MHz NMR
Solvent: dmsc
Date: Jul 21 2022



Compound 10c(Peak-2)



1 **Table 1.** Design, Physico-chemical and pharmacokinetic properties of pyrimidine-based carbocyclic nucleoside derivatives.

Compound	Physico-chemical properties										Pharmacokinetic Properties		
	MW	HA	AHA	RBs	HBA	HBD	MR	TPSA	iLOGP	Violation	GI absorption	BBB permeant	Pgp substrate
8a (E&Z)	247.25	18	9	3	5	3	65.29	110.08	1.55	0	High	No	No
8b (E&Z)	371.17	19	9	3	4	2	80.78	71.17	2.69	0	High	Yes	Yes
8c (E&Z)	324.17	19	9	3	4	2	75.76	71.17	2.71	0	High	Yes	Yes
8d (E&Z)	261.28	19	9	4	5	2	69.58	80.4	2.51	0	High	No	Yes
8e (E&Z)	387.17	20	9	4	5	2	82.3	80.4	2.86	0	High	No	Yes
8f (E&Z)	350.21	21	9	4	4	2	83.26	71.17	2.79	0	High	Yes	Yes
8g (E&Z)	372.16	19	9	3	4	3	80.21	97.19	2.07	0	High	No	Yes
8h (E&Z)	372.16	19	9	3	4	3	80.21	97.19	2.07	0	High	No	Yes
10a (E&Z)	247.25	18	9	3	5	3	65.29	110.08	1.55	0	High	No	No
10b (E&Z)	373.15	19	9	3	5	3	78.01	110.08	1.9	0	High	No	Yes
10c (E&Z)	415.44	31	21	6	6	3	117.24	119.31	3.34	0	High	No	Yes

2 (a) Design of the molecules (b) MLP 3D representation of the molecule, **8a** (c) Web representation of the physico-chemical properties of
3 molecule, **8a**

Table 2: Docking and Amino Acid interactions of the synthesized compounds

S. No.	Compd.	Docking score (kcal/mol)	Amino Acid Interactions
1	8a(Z - isomer)	-8.6	His280, Gln279, Phe303, Glc601, Glu277, Asp352, Arg442-Van Der Waals; Glu411, Gln353-Carbon Hydrogen Bond; Arg315-Unfavorable Donor Donor; Tyr158-Pi-Pi T-Shaped
2	8b(Z- isomer)	-8.5	Glu277, Phe178, Phe159, Arg442, Glu411, Phe303, Tyr158, Gln279, Phe314, Pro312, Leu313-Van Der Waals; Arg315- Carbon Hydrogen Bond; Glc601, Asp352-Conventional Hydrogen Bond; His280-Pi-Alkyl
3	8b(E- isomer)	-9.4	Tyr72, His112, Val216, Phe178, Glu411, Arg315, Arg446, His351, Glu277, Phe159, Gln353- Van Der Waals; Glc601-Unfavorable Bump; Asp215, Asp352- Carbon Hydrogen Bond; Gln182, Asp69, Arg442- Conventional Hydrogen Bond; Phe303-Pi-Pi Stacked; Tyr158-Pi-Alkyl
4	8c(Z- isomer)	-8.7	Tyr72, Arg446, His351, Asp69, Arg442, Phe178, Gln279, Asp215, His112, Val216, Glu277, Gln353, Asp307, Phe159, Tyr158-Van Der Waals; Glc601- Unfavorable Bump; Asp352- Carbon Hydrogen Bond; Arg315-Conventional Hydrogen Bond; Glu411-

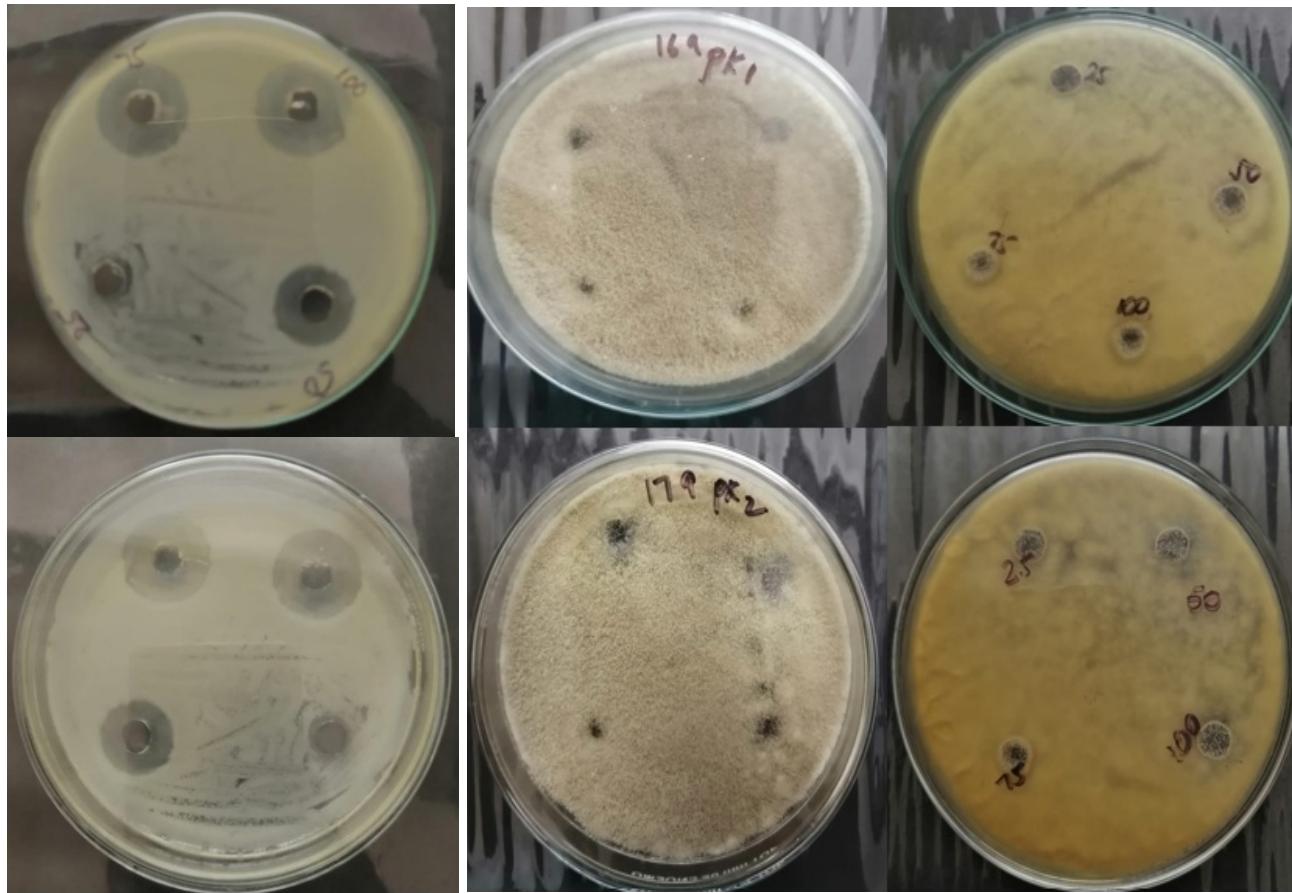
Attractive Charge; Phe303-Pi-Alkyl

5	8c(E-isomer)	-7.1	Val109, His112, Phe178, Val216, Tyr158, Gln279, Asp307, Tyr72, Arg446, His351, Asp69, Arg442, Glu277, Phe159, Gln353, Arg315-Van Der Waals; Glc601-Unfavorable Bump; Asp215 Conventional Hydrogen Bond; Asp352-Carbon Hydrogen Bond; Glu411-Attractive Bond; Phe303-Pi-Pi T-Shaped
6	8f(E-isomer)	-7.9	Tyr72, His112, Val109, Phe178, Phe159, Tyr158, Arg315, Asp307, His280, His351, Val216, Arg213, Asp352, Glu277-Van Der Waals; Glc601-Unfavorable Bump; Asp215-Conventional Hydrogen Bond; Asp69-Carbon Hydrogen Bond; Glu411, Arg442-Attractive Charge; Phe303-Pi-Pi T- Shaped
7	10a(E-isomer)	-10.3	His351, Tyr72, Asp69, Phe159, Phe178, Tyr158, Phe303, Val216, Gln353, Arg315, Asp307-Van Der Waals; Glc601-Unfavorable Bump; Gln279, Arg442, Glu277, Asp215, Arg213-Conventional Hydrogen Bond; Asp352-Carbon Hydrogen Bond; Glu411-Attractive Charge
8	10b(Z-isomer)	-7.9	Arg446, Asp69, Phe178, Phe159, Arg442, Gln279, Tyr72, Val109, His112, Val216, Glu277, Gln353, Asp307-Van Der Waals; Glc601-Unfavorable Bump;

			Asp215, Arg315-Conventional Hydrogen Bond; Asp352-Carbon Hydrogen Bond; Glu411-Attractive Charge; His280, Tyr158, Phe303-Pi-Alkyl
9	10b(E- isomer)	-8.3	Arg446, Asp69, His112, Phe178, Phe159, Gln279, Asp307, Arg315, Gln353, Val216, Glu277, Arg213-Van Der Waals; His351, Glc601-Unfavorable Bump; Arg442-Conventional Hydrogen Bond; Tyr72, Asp352, Asp215-Carbon Hydrogen Bond; Phe303-Pi-Pi T- Shaped; His280, Tyr158-Pi-Alkyl; Glu411-Attractive Charge
10	10c(Z- isomer)	-8.3	Leu313, Phe314, Glu411, Asp352, Phe159, Asp69, His112, Asp215, Tyr72, Glu277, Phe303, Gln279, Ser157, Ser240, Lys156-Van Der Waals; Glc601- Unfavorable Bump; Arg442, His280-Conventional Hydrogen Bond; Phe178-Pi-Pi Stacked; Tyr158 -Pi-Pi T-Shaped; Val216, Arg315-Pi-Alkyl
11	10c(E- isomer)	-8.7	ASN415, GLY160, LYS156, LEU313, PHE314, GLU411, PHE159, PHE178, PRO312, TYR158, SER311, GLN279, PHE303, GLU277, VAL216-Van der Waals; HIS280, GLC601-Unfavorable Bump; SER157, ASP307-Conventional Hydrogen Bond; ARG315-Pi-Alkyl; ARG442, ASP352-Attractive Charge

6	8f(E - isomer)	-7.9	91.714	0	0	0	0	0	0	0	0
7	10a(E - isomer)	-10.3	48.638	0	0	1.1±0.15	1.4±0.1	0	0	0.9±0.05	1.2±0.15
8	10b(Z - isomer)	-7.9	68.771	0.5±0.1	1.1±0.15	2±0.2	2.2±0.25	0	0	0	0
9	10b(E - isomer)	-8.3	56.519	0.2	0.3±0.05	0.4±0.1	0.4±0.15	0	0	0	0
10	10c(Z - isomer)	-8.3	74.69	0.2	0.2	0.3±0.5	0.3±0.5	0	0	0	0
11	10c (E - isomer)	-8.7	56.278	0.2	0.3±0.05	0.3	0.4±0.05	0	0	0	0
12	*Std.	-8.5	35.91	3.5±0.05	3.5±0.05	5.5±0.05	7.0±0.25	5.5±0.05	6.1±0.05	9.1±0.05	10±0.05

Figures



A

B

Figure 1: Zone of inhibition

(A) against *Bacillus cereus* at 25 μ l, 50 μ l, 75 μ l and 100 μ l

(B) against *Aspergillus niger* was not observed

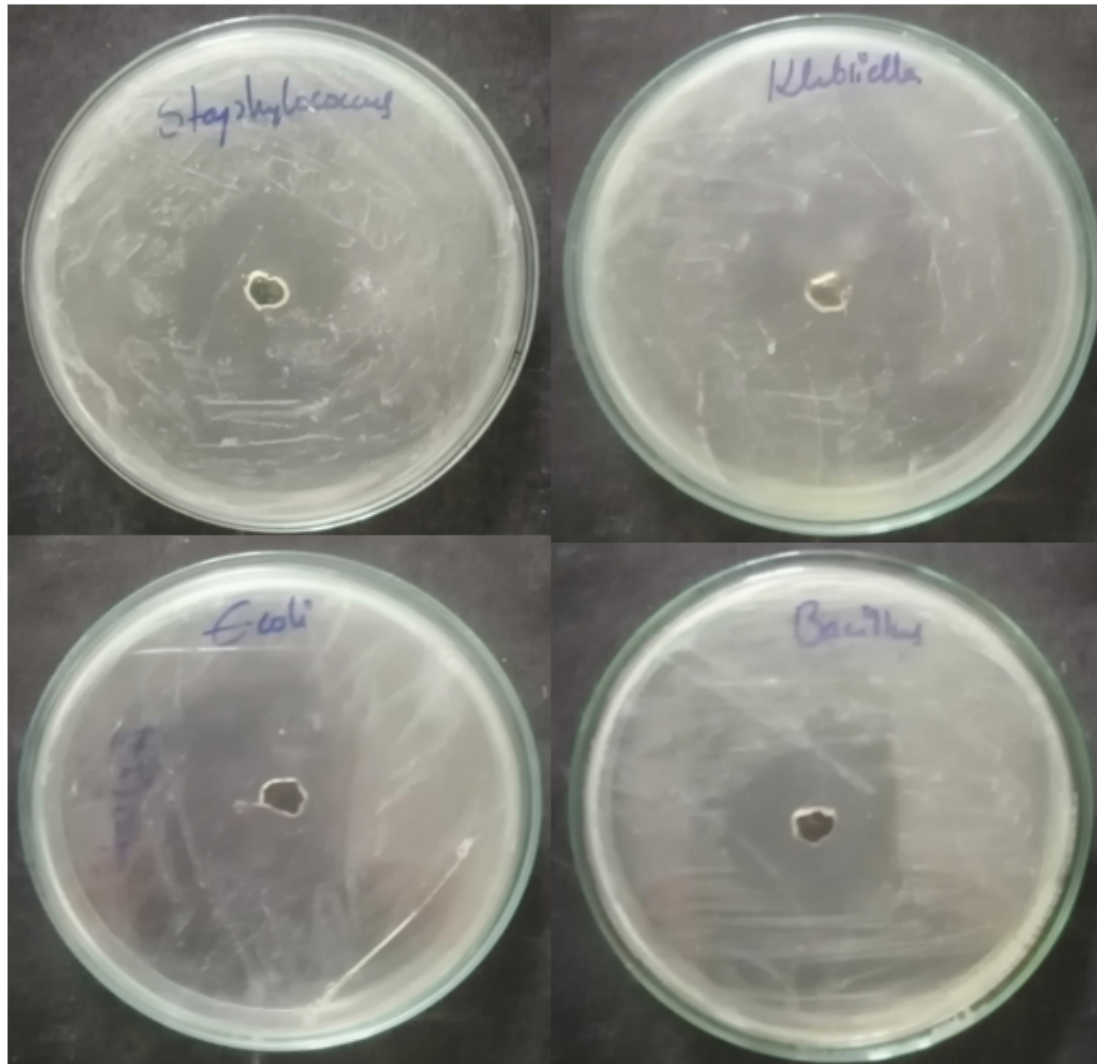
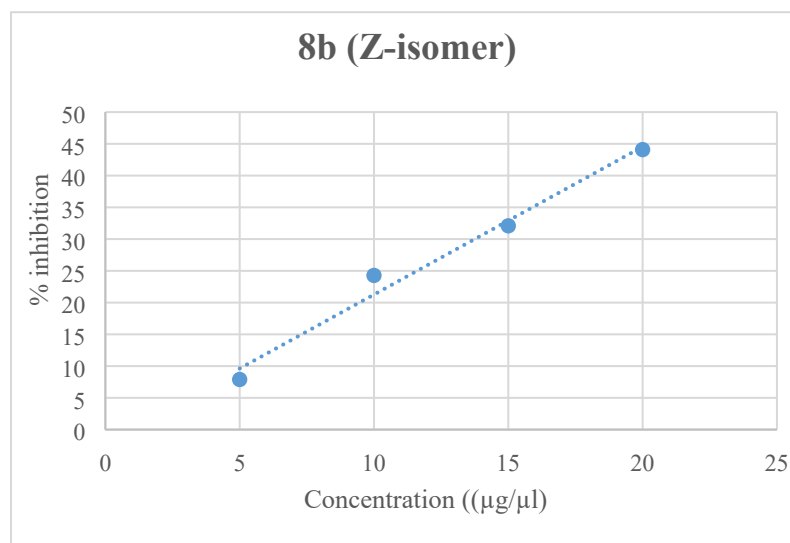
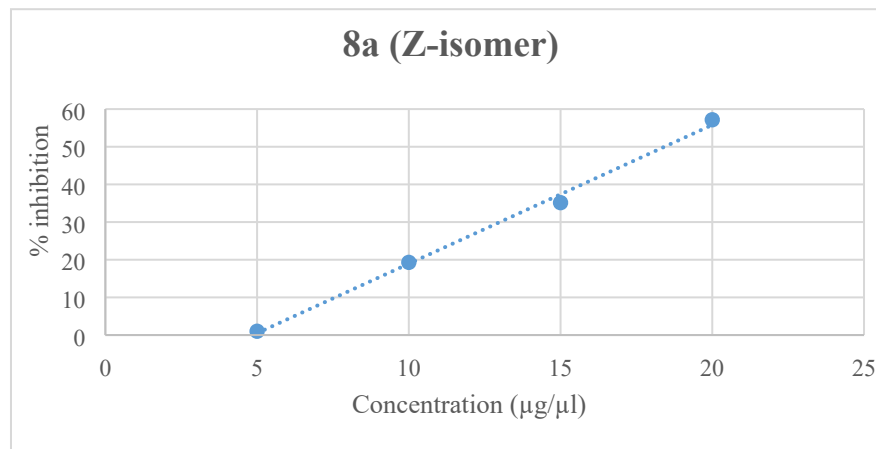
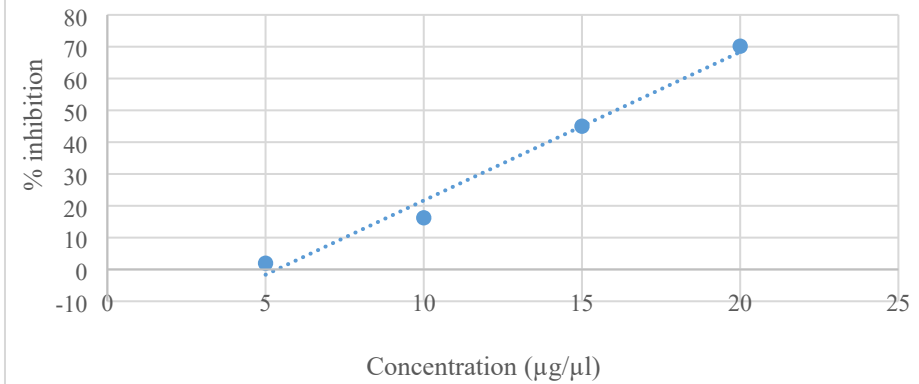


Figure 2: Ciprofloxacin control against the test organisms showing Zone of Inhibition

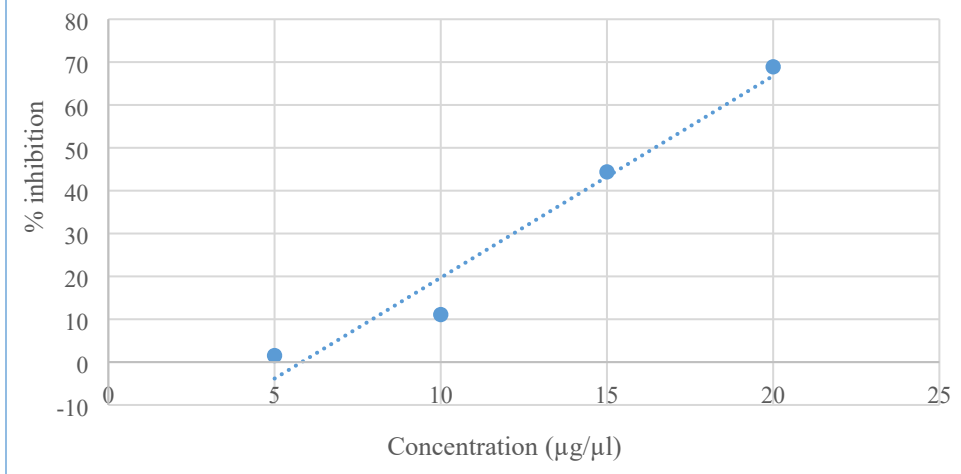
1. Graphs for the determination of IC50

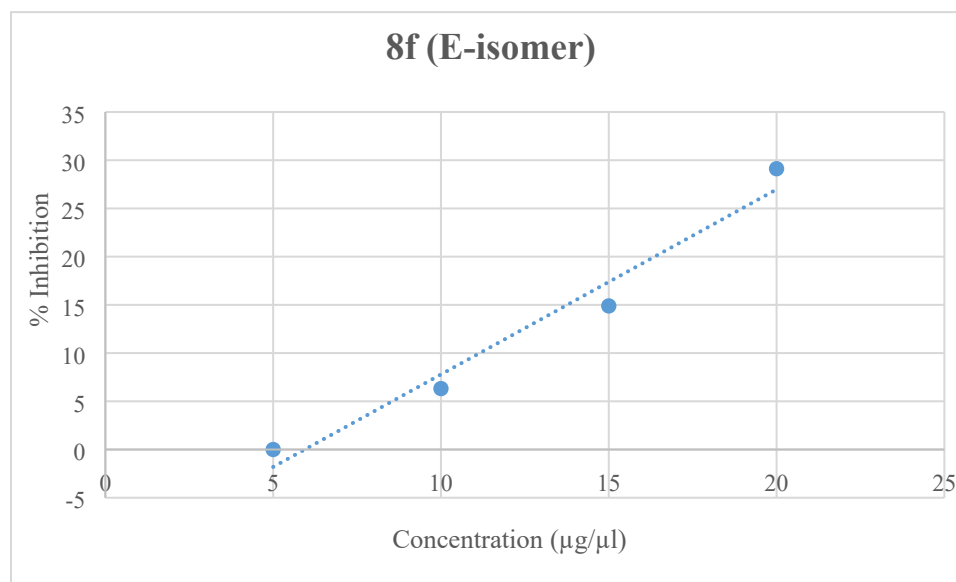
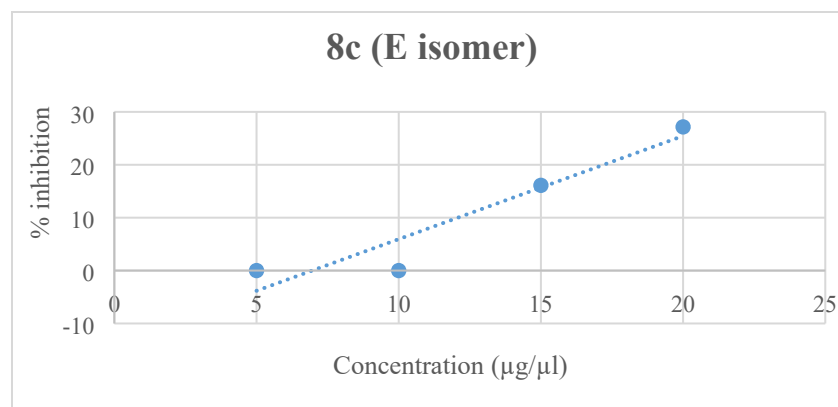


8b (E-isomer)

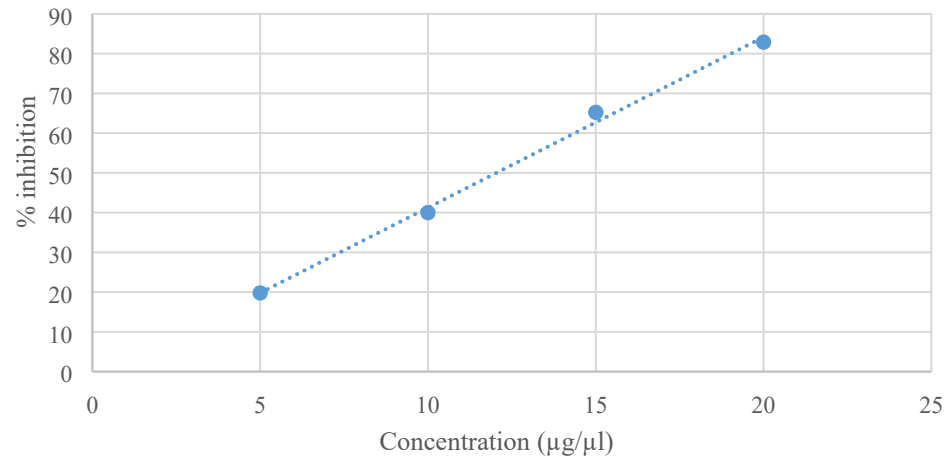


8c (Z-isomer)

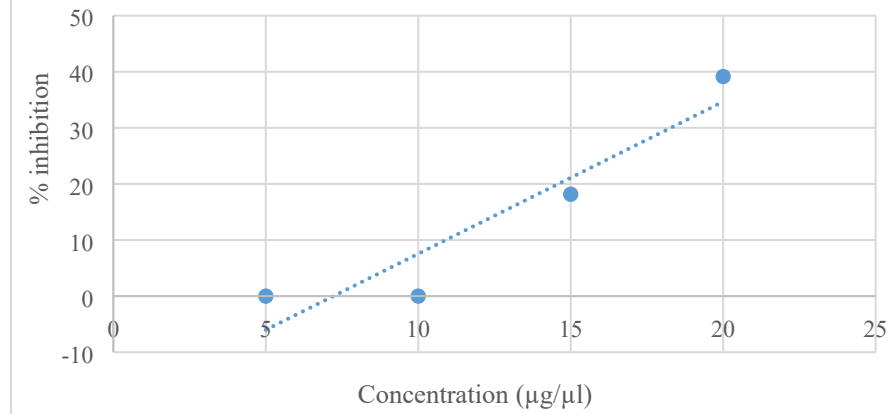




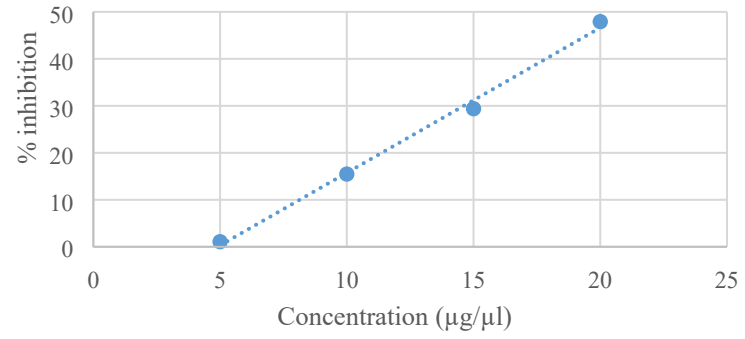
10a (E-isomer)



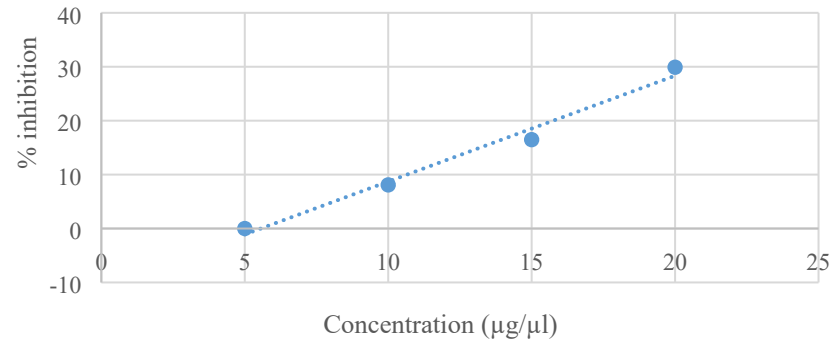
10b (Z-isomer)



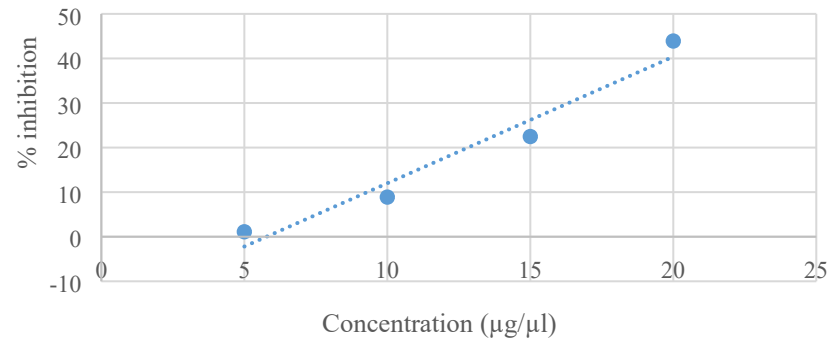
10b (E-isomer)



10c (Z-isomer)



10c (E-isomer)



Acarbose

