

Total Synthesis and Biological Evaluation of Halofuginone and its analogs

A Thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

By

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November, 2022**

Dedicated to

My Mother

Because the Love of a mother starts before Birth

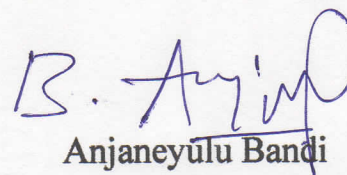
her Love will endure long after death

Declaration

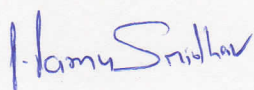
I hereby declare that, the overall material contained in this thesis entitled "**Total Synthesis and Biological Evaluation of Halofuginone and Its Analogs**" is the outcome of research accomplished by me in the school of chemistry, University of Hyderabad, Hyderabad, India, under the supervision of **Prof. Perali Ramu Sridhar**.

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Certificate

This is to certify that the thesis entitled "**Total Synthesis and Biological Evaluation of Halofuginone and Its Analogs**" submitted by **Mr. Anjaneyulu Bandi** bearing registration number **17CHPH11** in partial fulfilment of the requirements for award of Doctor of Philosophy in the school of chemistry is a bonafide work carried out by him under my supervision and guidance.

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1. Stereoselective total synthesis of all the stereoisomers of (+) and (-)-Febrifugine and Halofuginone.
Perali Ramu Sridhar, **Anjaneyulu Bandi**. *Tetrahedron Lett.*, **2020**, 61, 152151. DOI: 10.1016/j.tetlet.2020.152151.
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He has also made presentations in the following conferences:

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SYNOPSIS

The thesis entitled “**Total Synthesis and Biological Evaluation of Halofuginone and its analogs**” consists four chapters.

Chapter 1

Introduction and recent developments of Halofuginone

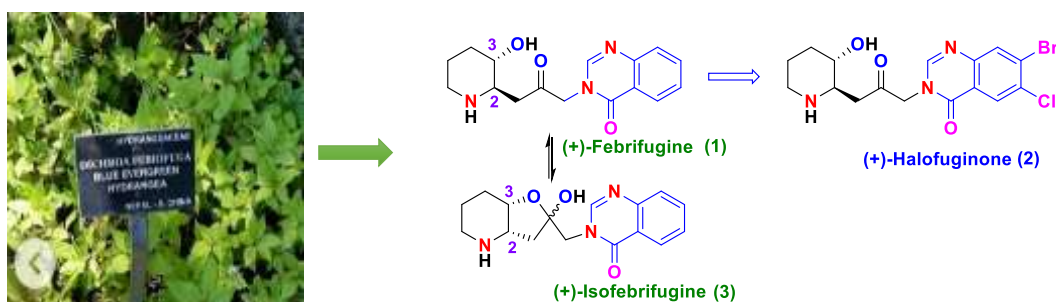


Figure-1: Evolution of Halofuginone from natural alkaloid febrifugine.

This chapter mainly describes a concerted effort to illustrate historical elements that contributed to difficulties in figuring out the structures of naturally occurring febrifugine **1** and isofebrifugine **3**, this was achieved by revealing the interconversion of febrifugine to isofebrifugine (Figure 1). Further highlight, how these problems were successfully overcome by chemical synthesis.

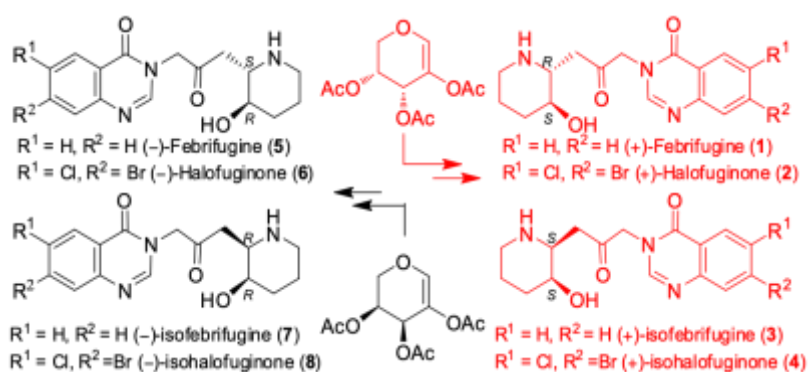
Structural identification of the exact structure of febrifugine and the various protocols for the synthesis of were discussed in this chapter. However, due to high potent and severe side effects, febrifugine precluded as drug molecule. Interestingly, a halogenated derivative of febrifugine named as halofuginone **2** was shown to be a better analogue in drug discovery. Initially, halofuginone was used as an antiprotozoal. The later part of this chapter deals with the literature methods to synthesize halofuginone and its biological importance were elaborated. It is interesting to note that halofuginone was found to be an important molecule in the fields of

fibrosis and angiogenesis. In addition, it has also equivalent biological significance in human biology towards anti-cancer, anti-inflammatory and auto immune disorders.

Chapter 2

Stereoselective total synthesis of all the stereoisomers of (+) and (-) Febrifugine and Halofuginone

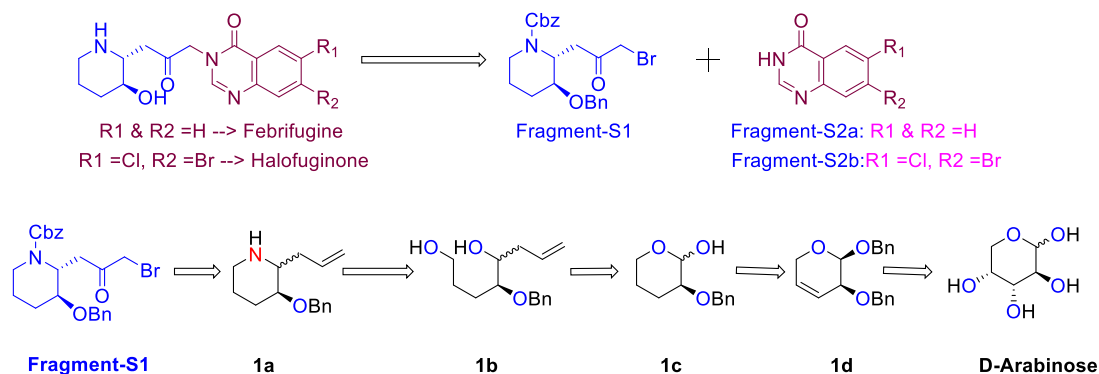
In this chapter an efficient approach for the stereoselective-synthesis of all possible stereoisomers of febrifugine and halofuginone were discussed. D-arabinose and L-arabinose, two pentose sugars that are naturally available, are utilized as the starting materials towards our chiral pool total synthesis.



Scheme-1: Total synthesis of all the stereoisomers of (+) and (-) febrifugine and halofuginone

Our protocol for the total synthesis of (+) series of febrifugine and halofuginone (**1-4**, Scheme 1) began with the use of D-arabinal as chiral pool starting material. 2,3,4-tri-O-acetyl-D-Arabinal was converted to the dihydropyranone, involving Ferrier-type rearrangement, followed by Luche reduction and benzylation of this alcohol, provided the compound **1d**. A one-pot regioselective hydrogenolysis with concomitant hydrogenation of the alkene provided the cyclic hemiacetal **1c**. Treatment of **1c** with allyl magnesium bromide furnished the diol **1b**, which were further mesylated to give the diastereomeric mixture of dimesylates. Regioselective substitution of the primary mesylate with an azide followed by cyclization provided the piperidine derivatives **1a**. Protection of the amine with -benzyloxycarbonyl group

and Wacker oxidation of the alkene group to provide the corresponding methyl ketone, followed by bromination produced the α -bromo ketone **fragment S1** (Scheme 1).



Scheme-2: Retrosynthetic approach of **fragment S1**

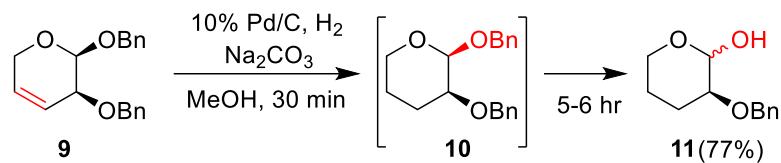
The obtained crude bromides were subjected to substitution reaction with quinazolinone (**S2a**) or 7-bromo-6-chloroquinazolin-4(3*H*)-one (**S2b**) in presence of base followed by deprotection of the Cbz-group, as well as the benzyl, with 6*N* HCl under reflux provided the (+)-febrifugine (**1**), (+)-Halofuginone (**2**), (+)-isofebrifugine (**3**), and (+)-isohalofuginone (**4**) as their HCl salts, respectively. In a similar fashion, starting from 2,3,4-tri-*O*-acetyl-L-Arabinal, (–)-febrifugine (**5**), (–)-Halofuginone (**6**), (–)-isofebrifugine (**7**), and (–)-isohalofuginone (**8**) were also synthesized as their HCl salts.

Chapter 3

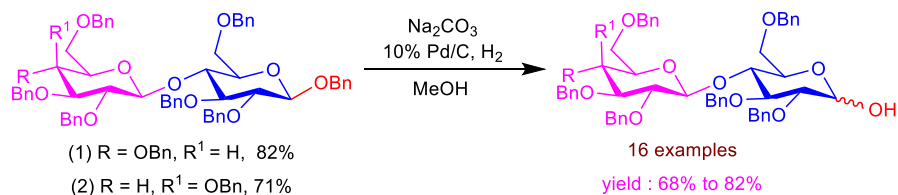
Regioselective anomeric O-benzyl deprotection in Carbohydrates

During our total synthesis of febrifugine and halofuginone, one of the transformations involves the conversion of the unsaturated benzyl acetal **9** to the saturated hemiacetals **11** through the intermediate formation of saturated acetal **10**. In this process, we observed that the hydrogenation of the alkene occurs within 30 minutes providing the product **10**. However, prolonged stirring for 5 - 6 hours afforded the regioselective hydrogenolysis to form product **11**

(Scheme 3). This observation prompted us to investigate the selective hydrogenolysis of anomeric *O*-benzyl group in various carbohydrate derivatives.



Scheme 3. Regioselective hydrogenolysis with concomitant hydrogenation of benzyl acetal.



Scheme 4. Regioselective anomeric *O*-benzyl deprotection in carbohydrates.

In this chapter, we disclose our findings on regioselective hydrogenolysis of the anomeric benzyl group using 10% Pd/C in the presence of 1 eq of sodium carbonate under the hydrogen atmosphere. The scope and the generality of the methodology were evaluated by applying it to several carbohydrate-derived hemiacetals. A number of mono-saccharides and disaccharides were studied under the hydrogenolysis conditions to provide the corresponding carbohydrate hemiacetals (Scheme 4).

Chapter 4

Synthesis and Biological evaluation of Halofuginone analogs

Halofuginone has acknowledged a lot of attention recently due to its broad spectrum of beneficial biochemical activity, that include its capability to treat autoimmune, cancer, and fibrosis-related diseases along with malaria. There are currently two documented action mechanisms postulated for halofuginone:

(1) Fibrosis and the fibroblast-to-myofibroblast transition are inhibited by blocking Smad3 phosphorylation downstream of the TGF signaling pathway.

(2) By activating the amino acid starvation and integrated stress responses, prolyl-tRNA synthetase (ProRS) activities in the blood stage of malaria and Th17 cell development are inhibited, which inhibits inflammation and the autoimmune response.

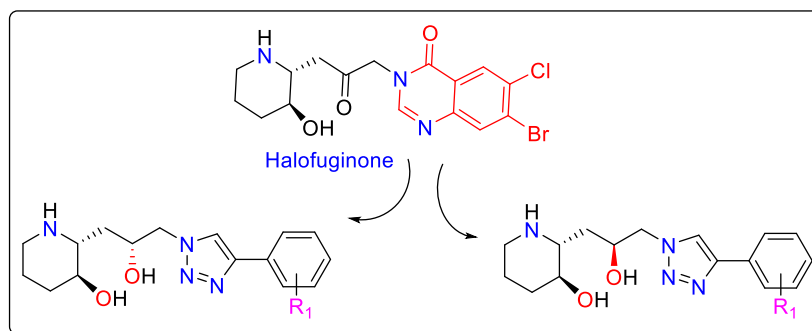


Figure-2: Synthesis of Halofuginone analogs.

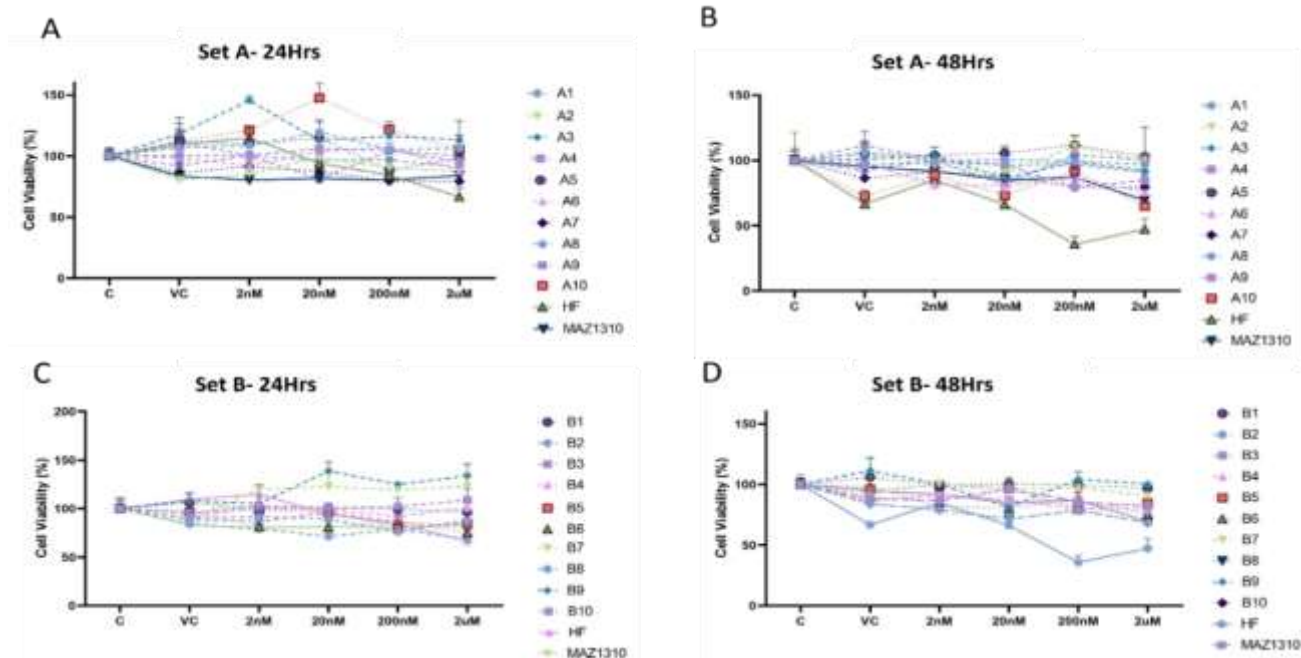
In order to investigate the biological possibility, in this chapter we have synthesized a series of halofuginone analogs. Mild modification of the intermediate compounds that are formed in the total synthesis were converted to an azido alcohol and used it in a click reaction with a series of aryl acetylenes to form the corresponding triazoles. Keeping the polar portion of the halofuginone intact, a number of analogs were synthesized. The obtained products were evaluated for the following biological studies.

Cell Proliferation Assay/ MTT assay

Shown below is the MTT assay performed for the 20 analogs of Halofuginone (HF) (10 each for A series and B series alongside the vehicle/solvent control designated as VC).

Therefore, HF, MAZ (standard inactive halofuginone derivative) and the chemically synthesized analogs are not cytotoxic up to 24 hours post treatment. Since the time period for all of our experiments is up to 12 hours, it is safe to conclude that the compounds would not induce cytotoxicity thereby affecting any molecular mechanism under study. Further experiments are in progress to assess the GCN2 (General Control Nonderepressible2)

activation of each of these compounds, since HF a known amino acid starvation mimetic acts through the activation of the GCN2 signaling pathway.



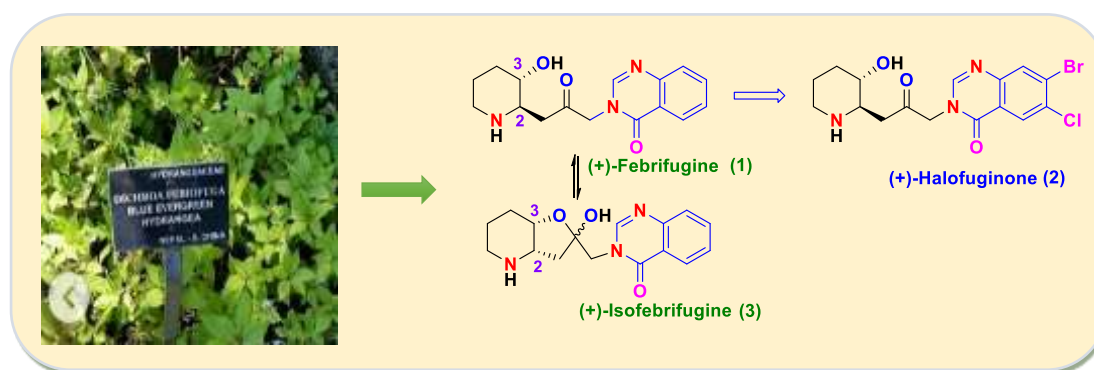
Chemically synthesized analogs of HF are not cytotoxic even at larger concentrations up to 200nM for 48 hrs. Graphs A, B, C and, D depict the cell viability percentage upon treatment with the compounds.

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CHAPTER 1

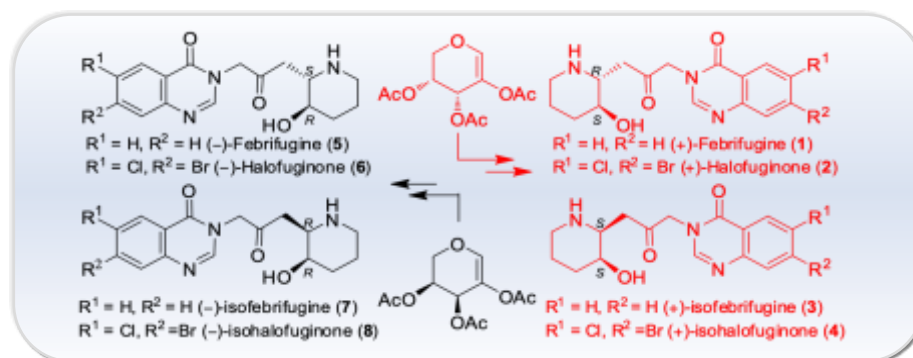
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CHAPTER 2

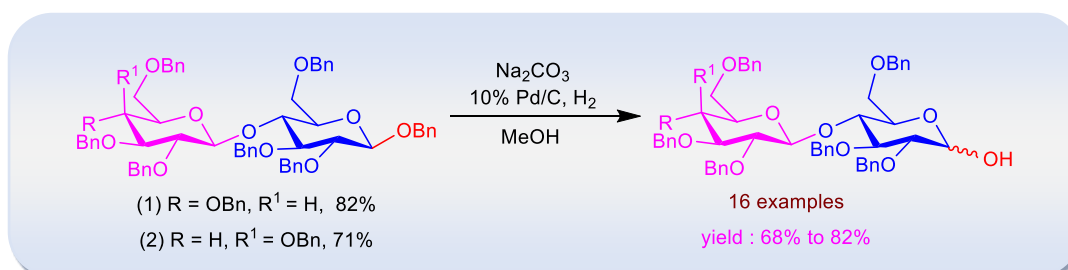
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CHAPTER 3

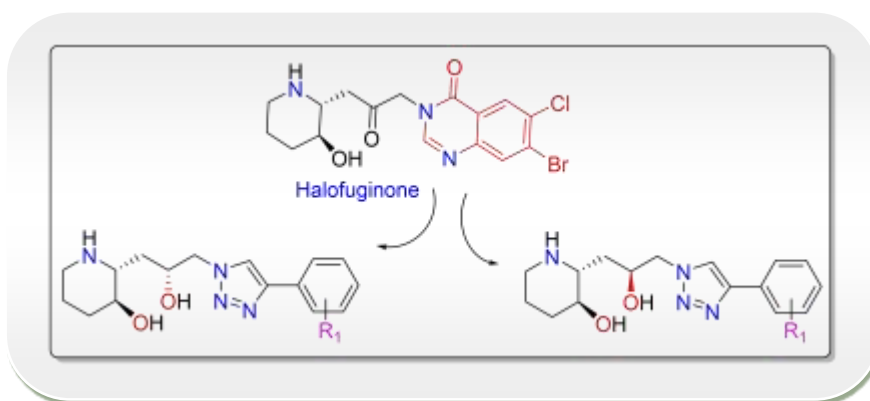
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CHAPTER 4

Synthesis and Biological evaluation of Halofuginone analogs



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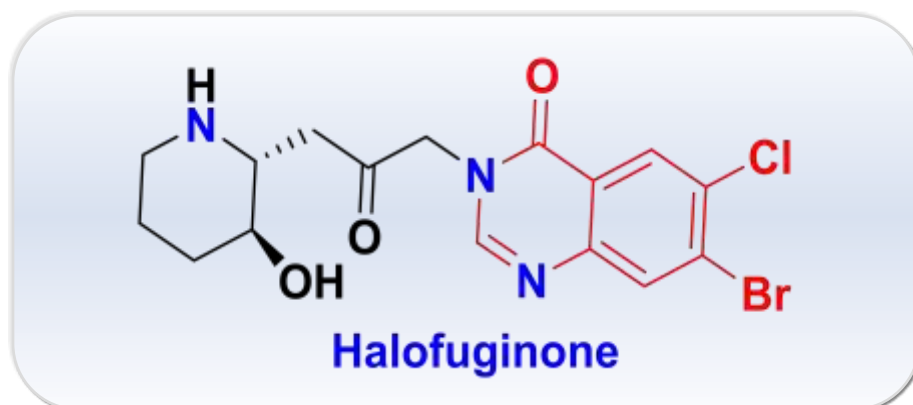
Abbreviations

Ac	: Acetyl
aq.	: Aqueous
atm	: atmosphere
AllyMgBr	: Allylmagnesium bromide
BF ₃ ·OEt ₂	: Boron trifluoride etherate
Bn	: Benzyl
BnOH	: Benzyl alcohol
c	: concentration
Calcd.	: calculated
CbzCl	: Benzyl chloroformate
CuCl	: Copper(I) Chloride
CaOAc	: Caesium acetate
DMAP	: dimethyl aminopyridine
DMF	: Dimethylformamide
DIPEA	: Di isopropyl ethyl amine
DBU	: 1,8-di-azabicyclo[5.4.0]undec-7-ene
EtOAc	: Ethyl acetate
Et ₃ N	: Triethylamine
ent	: enantiomer
HRMS	: high resolution mass spectrometry
IR	: Infrared
<i>J</i>	: coupling constant in Hz (NMR)
m	: multiplet
MsCl	: methane sulfonyl chloride
MHz	: megahertz
mL	: milliliter

mmol	: millimolar
NBS	: <i>N</i> -bromo succinimide
NMR	: nuclear magnetic resonance
NaBH ₄	: Sodium borohydride
NaN ₃	: Sodium azide
ORTEP	: Oak Ridge thermal ellipsoid plot
Ph	: Phenyl
PPh ₃	: Triphenylphosphine
Ppm	: parts per million
Pd/C	: Palladium on carbon
rt	: room temperature
R _f	: Retardation factor
Ref	: reference
S	: singlet
t	: triplet
TLC	: thin layer chromatography
THF	: tetrahydrofuran
TMSOTf	: trimethylsilyl trifluoromethane sulfonate
TBSCl	: tert-butyldimethylsilyl chloride
UV	: ultraviolet

Chapter-1

Introduction and Recent Developments of Halofuginone



1.1 Introduction

1.2 Results and Discussions

1.3 Conclusions

1.4 References

1.1 Introduction

1.1.1 Febrifugine

Dichroa febrifuga, a Chinese medicinal herb, its leaves and roots were used to isolate the (+)-febrifugine (1) and (+)-isofebrifugine (2) as isomeric quinazolinone alkaloids.¹ *Dichroa febrifuga*'s leaves (Shuu Chi) and roots (Chang Shan) have been utilized to treat malaria symptoms for ages. Chang Shan decoction is a key ingredient in traditional Chinese medicine is an herb, and has been used to treat several ailments, including stomach cancer.²⁻⁴ It was an unsuccessful medication candidate because of its great potency, extreme toxicity, and adverse effects such as nausea, liver damage and vomiting. Further research is needed to prepare analogues, explore biological assessment, and remove the risks of febrifugine.

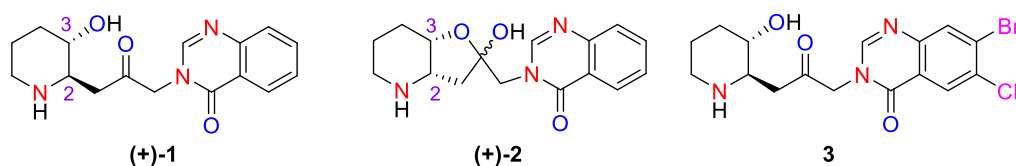
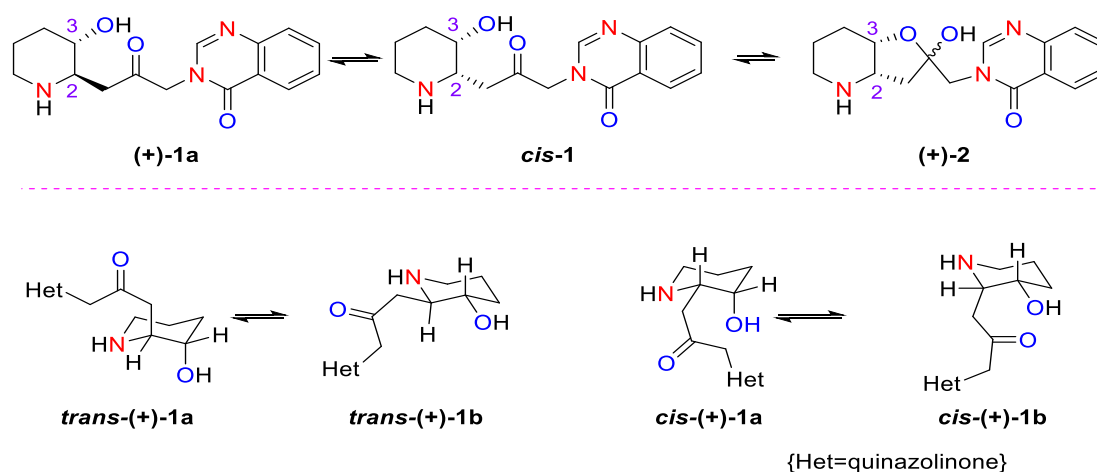


Figure 1. (+)-Febrifugine (1) (+)-Isofebrifugine (2) Halofuginone (3) chemical structure

These efforts potentially result in the identification of halofuginone (HF) (3), which has been created to strengthen the therapeutic potential of (1), halofuginone, which is utilized in the poultry sector as an antiprotozoal medicine in the racemic form. Studies examining the ideal intake of (3) for the treatment of poultry have indicated that, this substance actively inhibits the production of collagen,⁵ type 1 in both humans and birds, according to the research. These findings encouraged access to human medication trials.⁶ Surprisingly, A major medication called HF was created to inhibit unchecked collagen biosynthesis. A study was conducted on it to determine whether it has anti-cancer medication potential,⁷ and Duchenne muscular dystrophy is being studied as the focus of a clinical research right now.⁸

1.1.2 Isolation and structural analysis of Febrifugine

The structural interpretation of relative structure of (+)-febrifugine (**1**) & (+)-isofebrifugine (**2**) and absolute stereochemistry was extremely complicated when these compounds were first reported. This issue was resolved by showing that, under certain conditions, the sequence of the retro Hemiketal is a conjugate addition of conjugate additions synthesis can lead to the interconversion of febrifugine (**1**) and isofebrifugine (**2**) via *cis*-**1** (Scheme 1).^{9,10} According to Scheme 1, At the site of the hemiketal, either the chair form or the (+)-**2**'s hydroxyl group and the electrophilic ketone group are nearby. Contrarily, *trans*-(+)-**1** is either unable to produce the hemiketal in the di-axial or di-equatorial form or is less able to do so. Resulting of this unforeseen isomerization, initial reports failed to conclude the exact structure of (+)-**1**, errors concerning the accurate structure of these quinazolinone derivatives have been resolved by Artificial work produced by Kobayashi's team in 1999¹¹ and Harayama and Takeuchi in 2003.¹²



Scheme 1. Febrifugine (**1**) and isofebrifugine (**2**) interconversion

Crude Chang Shan extract from the plant *Dichroa febrifuga* Lour was shown by Chou and his team to be an effective treatment for tertian malaria in clinical cases in 1943. This represented the beginning of a legacy of febrifugine.^{4,13} It was observed that Chang Shan was only moderately more effective than crude extracts of Shuu Chii in controlling *Plasmodium*

gallinaceum in chicks. Isofebrifugine (2), which fails to kill *Plasmodium gallinaceum*, is observed by Koepfli *et al*, occurs most frequently in the *Dichroa febrifuga* roots. Finally, Lour explained this behavior change.¹ They also discovered that two alkaloids from Chang Shan, "dichroine A" (mp 230 °Celsius) & "dichroine B" (mp 237-238 °Celsius), had been isolated and were salts of dihydrochloride.¹⁴ Dichroine B, a quinazolinone derivative, is effective towards *Plasmodium gallinaceum* in hens, however, Dichroine A is ineffective.

Dichroine B's empirical formula was reported to be $C_{16}H_{19}O_3N_3$ in 1947.¹⁵ Later, two isomeric alkaloids known as febrifugine and isofebrifugine were isolated by Koepfli *et al*. from the same plant source. *Dichroa febrifuga* Lour was isolated first from both the leaves and the roots but was later separated just from the roots.¹ The dichroine B formula provided by Chou *et al*. agreed with a formula was developed empirically for these alkaloids.¹⁶ Koepfli *et al*. ascertained optical rotations and melting point of febrifugine (mp: 139-140 °Celsius; $[\alpha]_D^{25} = +6.0$ (c = 0.5, $CHCl_3$)) as well as isofebrifugine (mp: 129-130 °C; $[\alpha]_D^{25} = +121.0$ (c = 0.35, $CHCl_3$)). When 10 % more an Alkaloid in alcoholic solution received 12 M HCl, it quickly generated the salt of dihydrochloride (mp: 220-222 °C), proving that febrifugine was dibasic.

Dichroine A and B are isomers that may be interconverted into one another in the presence of alkali, heat, acid, hydrolysis, and even other solvents, according to a 1948 report by Chou *et al*.¹⁶ The stated melting points of Dichroine A & Dichroine B were discovered to (136 °C) and (145 °C) respectively and is more comparable with the figures for isofebrifugine and febrifugine, respectively, published by Koepfli *et al*. A structural pattern that was found in multiple alkaloids¹⁷ and was isolated as 3-*H*-quinazolin-4-one were described.

The heteroaromatic 4-quinazolinone entity was found in both dichroine alkaloids based on these and additional chemical degradation tests. The findings from this structural research together with Koepfli *et al*'s¹⁸ for this idea lead to a thoughtful suggestion for the framework of febrifugine & isofebrifugine (Fig. 2). It is challenging to determine the relative absolute configuration at each stereocenter due to structural interconversion of febrifugine &

isofebrifugine. Consequently, structure Z was proposed, which, will include an open hydroxyl ketone framework, unlike X & Y.

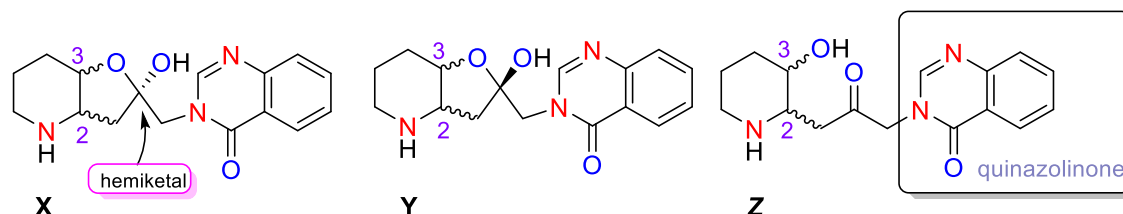
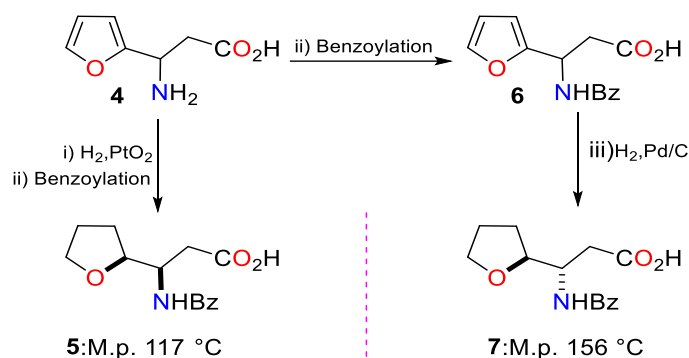


Figure 2. Febrifugine(X), isofebrifugine (Y), and American Cyanamid structure (Z) postulated by Koepfli

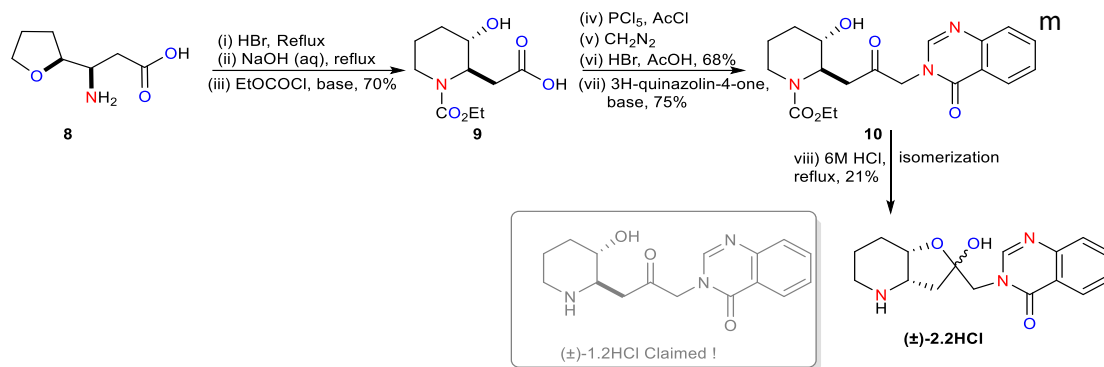
1.1.3 Efforts towards febrifugine and isofebrifugine structural interpretation by Baker's synthesis

Since their first publications, febrifugine (1) and isofebrifugine (2) have been common synthetic targets due to their emphasis on biological assessment and isolation.²⁰ Finally, the validity of the structures of (1) and (2) was attained as an outcome of these efforts, in addition to providing a way to improve natural resources and producing analogues for biological investigations. Innovators Baker and his team synthesized these alkaloids in the 1950's and provided compounds with a structure.²¹ Following Baker's initial racemic synthesis that was documented,^{21g} it is important to note that later research used the stereoselective reduction of substituted heteroaromatic molecules.²²⁻²⁴ In Baker's second method, a monosubstituted furan was reduced diastereoselectively, and the products were then elaborated into piperidines. With Adam's catalyst presence, (4) was treated with hydrogen to produce (5), and the resulting amino tetrahydrofuran was then N-benzoylated (Scheme 2). The melting point of this substance was 117 °Celsius.

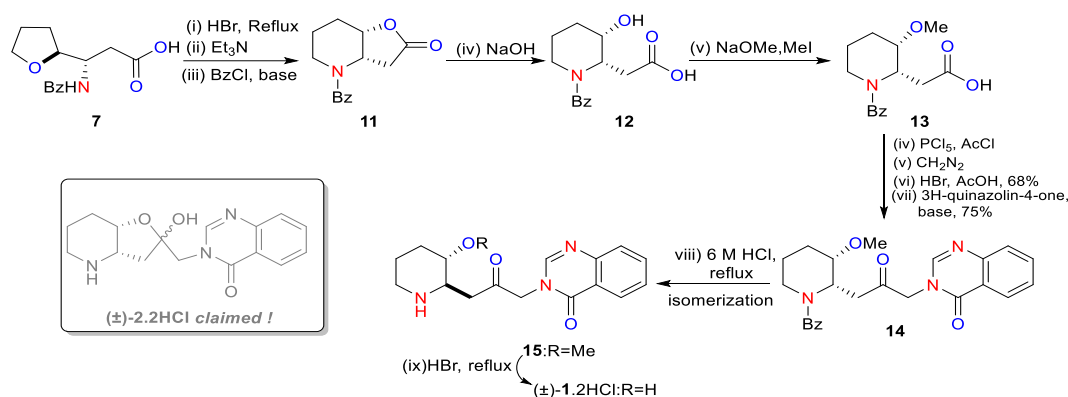


Scheme 2. 4- and 6-furan-2-yl (Furan-2-yl) 3-amino propanoic acid diastereoselective hydrogenation

On the other hand, N-benzoyl preservation of (4) results in (6), then Pd/C hydrogenation geared at isolating (7) yielded the same combustion study as (5) but it had a 156 °Celsius melting point. To access the febrifugine skeleton, Baker needs both diastereoisomeric materials because insufficient analytical capabilities make it impossible to evaluate their relative structures (Schemes 3 and 4). The stereochemistry of those isomers (5 and 7) was covered at this point. Takeuchi's 2003¹² reports served as the basis for the structures shown (Scheme 2). The tetrahydrofuran derivative (8) acid-promoted ring opening produced an intermediate bromohydrin hydrobromide, which was then further reacted with NaOH to produce a piperidine derivative (Scheme 3). (9) was isolated in three steps with a 70% yield after further N-protection by using ethyl chloroformate. Here it was believed that the 3-hydroxyl group would need to be protected to avoid lactonization in the following phase. O-protection was not necessary, and the relative transness of the piperidine (9) was shown by the hydroxy acid's resistance to lactonization. (9) was effectively transformed into N-protected (±)-febrifugine via methylation, bromination, and alkylation process (10). The protective group for the carbamate was eliminated in the existence of 6 M hydrochloric acid under reflux circumstances.



Scheme 3. synthesis of (±)-isofebrifugine by Baker. from tetrahydrofuran (8) 2HCl.



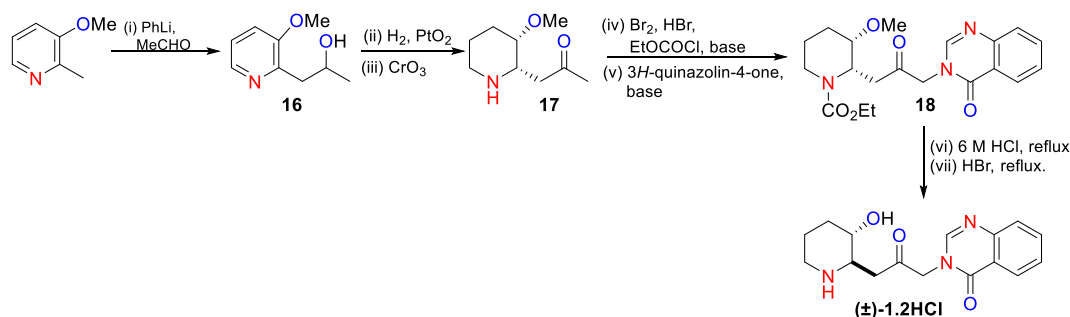
Scheme 4. (±)-Febrifugine synthesized by Baker. Tetrahydrofuran-derived 2HCl (7)

In Baker and his team's opinion, the *trans*-alkaloid (±)-Febrifugine.2HCl. had been identified. based on (9) resistances to undergoing lactonization, but after prolonged exposure to Hydrochloric acid, according to later research by Barringer *et al.*, In reality, isomerization (see Scheme 6)^{10a} had occurred, resulting in the formation of (±)-isofebrifugine dihydrochloride (2) in a yield of 7.4 % over a total of nine stages. Regarding its melting point & anti-malarial properties, the substance was contrasted to the hydrangea alkaloid that was isolated, and these tests made it abundantly clear that both substances were different from one another. As a result, it was wrongly assumed that Isofebrifugine's relative configuration has been *trans*-based on this prominent work.

Then, another isomer (7), created by the reaction of stereo-complementary hydrogenation (Scheme 2), was built for the anticipated structure of febrifugine. (7) allowed for the

bromohydrin hydrobromide to be heated to reflux while hydrobromic acid was present (Scheme 4). This bromohydrin hydrobromide was detached as a lactone, in contrast to Scheme 3, where (8) was treated similarly. The piperidine lactone (11) was made by closing the rings with triethylamine in chloroform and then N-protecting them. When NaOH was added to (11), it produced the difficult-to-handle hydroxyl acid (12), which quickly produced piperidine lactone (11) after re-lactonization.

To safeguard the hydroxyl group, a methyl ether was shown to be essential (13). The identical methylation, bromination, and alkylation procedure were used to create the N, O-protected (14) in four stages from (13). Final step: Using (15), (14) was twice deprotected to get what Baker had assumed would be (2) based on the straightforward lactonization. Information, including activities, matched the natural product febrifugine, as well as the substance that was isolated from this process did turn out to be different from the substance created by the reactions shown in Scheme 3.



Scheme 5: The production of (±)-Febrifugine using Baker's 2,3 disubstituted pyridine-based method. 2HCl

Baker & team were therefore mistaken in their assumption that there was a 2,3-*cis* correlation in febrifugine. It was later discovered, however, that the final stages of deprotection must have witnessed another unexpected isomerization. These results led Baker *et al.* to successfully isolate the trans-alkaloid (±)-1.2HCl.

Takeuchi *et al.* in 2003 explained the structural assignment error was caused by the isomerization of the baker's technique.¹² They synthesized (15) again and found that demethylation did not result in the isomerization of the stereo chemically pure dihydrochloride salt. It was noted, however, that the deprotected molecule (14), together with (15) (combined with diastereoisomers), this two *cis*-14 & *trans*-14, did undergo isomerization upon exposure to 6 M HCl under reflux conditions.

In 1953, Baker *et al.* developed and synthesized the occurs naturally febrifugine enantiomer using the sequence shown in (Scheme 4).²⁵ By crystallizing the brucine salts to resolve 3-amino-3-(tetrahydrofuran-2-yl) propanoic acid, optically active (7) was produced. In order to finish the synthesis of (+)-1.2HCl, this substance was then put through the same chemical processes as depicted in (Scheme 4). It was discovered that Comparable to the natural alkaloid was the synthetic (+)-1.2HCl.

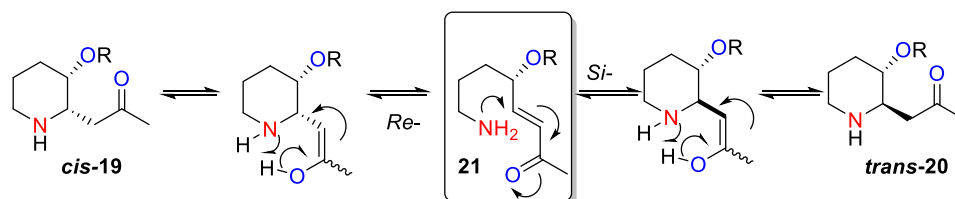
Based on earlier research and the hypothesis that a more powerfully Natural substance that prevents malaria has a relationship in 2,3-*cis*, in 1955, Baker *et al.* developed a more useful approach of synthesizing (±)-febrifugine (1) using the primary reaction involved 2,3-disubstituted pyridine (Scheme 5).^{26,27} As a result, the diastereoselective reduction of 16 using PtO₂ in a hydrogen environment was followed by the production the piperidine (17) with *cis*-2,3-disubstitute through the 16's oxidation. The methyl ketone that resulted from this process was subsequently selectively brominated with Br₂, HBr using ethyl chloroformate, N-protected, and alfa Bromo piperidine substituted with 3*H*-quinazoline-4-one to produce N, O-protected alkaloid (18). In a process that we now know is followed by isomerization, in the existence of 6M HCl under reflux, the group N-protecting was deprotected resulting in matching dihydrochloride. As soon as the reaction's result was exposed to 48% HBr in a reflux environment, the methyl ether was broken down in 10 stages, yielding (±)-1. dihydrochloric acid with a 2% overall yield.

Three separate syntheses of (±)-febrifugine were achieved by Baker *et al.* (1). 2HCl ^{21g,25,27} The natural isomer might also be prepared via early-stage resolution. A disadvantage of these

methods of synthesis was the need for robust conditions for the final deprotections, which resulted in the molecule's isomerization and led to the inaccurate assignment of the quinazoline alkaloid's relative stereochemistry.

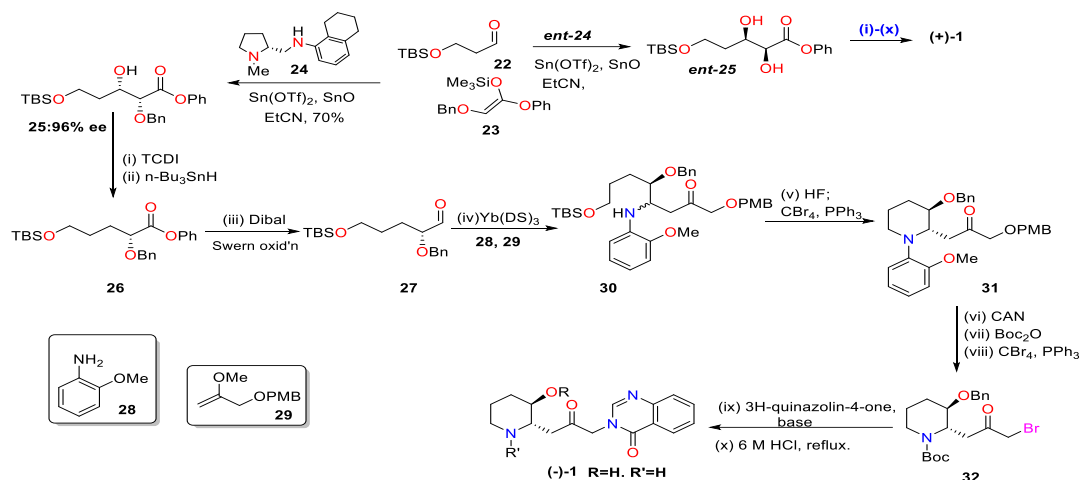
1.1.4 The structural confirmation of (+)-Febrifugine by Kobayashi's synthesis.

To comprehend how febrifugine and isofebrifugine relate to one another, Barringer *et al.*, 1973, established the equilibrium between both the 3-hydroxylated piperidines **19** and **20** in *cis* and *trans* (Scheme 6). (R = Et or Me) Alkyl ether was formed from hydroxyl group to prevent hemiketal production from the *cis*-2,3-diastereoisomer. Regarding the effects of pH, temperature, and solvent on the equilibrium between these isomers, research was done. A method involving base-catalyzed-elimination, conjugate addition, and rotation from One or both of the **21**'s diastereotopic alkenyl faces was postulated when it was shown that this isomerization was simple (Scheme 6).



Scheme 6: The *cis* and *trans* piperidines **19** and **20** are in equilibrium (R=Et, Me), which explains how febrifugine and isofebrifugine interconvert.

It was suggested that (+)-Febrifugine (**1**) displayed a *cis*-relative structure based on Baker's synthetic studies. Hill and Edwards suggested Baker's *cis*-relative configuration's absolute structure as the *cis*-relative configuration in 1962. But none of these presumptions is true.²⁸



Scheme 7: Febrifugine (-) and (+) were created utilizing the asymmetric aldol condensation-based synthesis of Kobayashi with Sn (II).

Last but not least, Kobayashi *et al.* designated the absolute configuration of the febrifugine in 1999 after completing the first asymmetrical synthesis of (+)-febrifugine (**1**).¹² The two stereoselective carbon-carbon bond formation processes used in this approach are used to introduce the stereogenic centers. According to Scheme 7, the synthesis started with an unsymmetrical aldol condensation of (**22**) Achiral Aldehyde with Achiral Silyl Enol Ether (**23**), which was done in diamine's existence. (**24**). The separated (**25**) esters & *ent*-**25** was all in excellent diastereomeric & excess enantiomeric, & the technique successfully induced asymmetry. An updated Barton-McCombie deoxygenation model was used to convert the chiral, entering enantioenriched ester (**25**) in (**26**), which was then reduced with DIBAL-H and finally oxidized using the Swern oxidation method to get the aldehyde (**27**) in 4 steps with a 55% yield.

In the existence of ytterbium tri-dodecyl sulfate ($\text{Yb}(\text{DS})_3$), functionalized enol ether (**29**), aldehyde (**27**), and 2-methoxyaniline (**28**) were subsequently transformed to β -aminomethyl ketone adduct (**30**) with a moderate diastereomeric excess underneath a three-component Mannich response in excellent yields (*anti*: *syn*; 60:40). The next two processes were then applied to this combination of diastereoisomers to synthesis piperidine (**31**) as the main component. Artificial (-)-febrifugine (**1**) was created through the Ceric (IV) ammonium nitrate

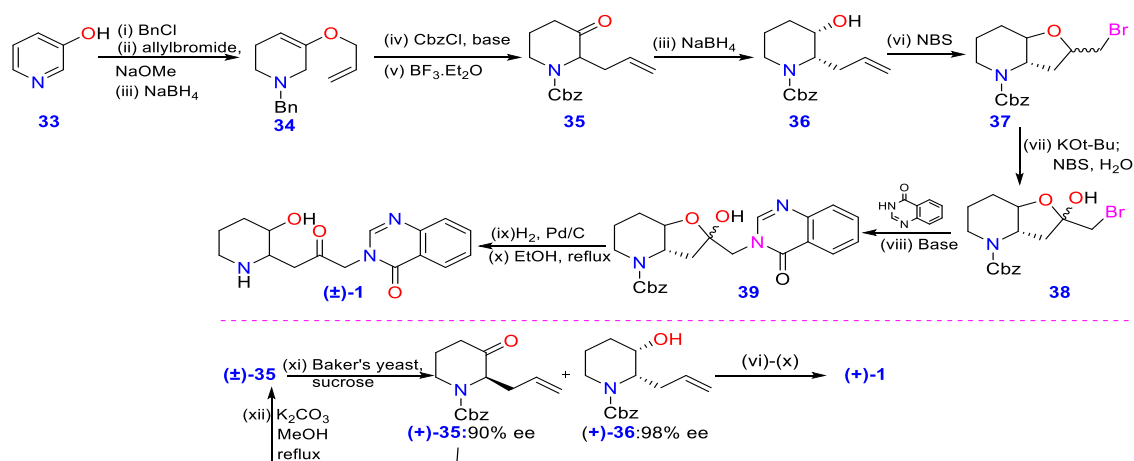
(CAN) was subjected to oxidative double deprotection and was then protected with N-tert-butyloxycarbonyl (Boc).

The synthesis procedure for synthetic (-)-febrifugine (**1**) was finished with a double-oxidative deprotection utilizing (CAN) N-tert-butyloxycarbonyl (Boc) protection with ceric (IV) ammonium nitrate, accompanied by the reaction of bromination. Piperidine that is N, O-protected was produced as a result shown in (**32**). The N, O-protected alkaloid was produced from this α -bromoketone by reacting it with 3H-quinazoline-4-one in the presence of potassium hydroxide. In 11% of the 13 reaction steps after deprotection with 6M HCl under reflux conditions for 35 min, (-)-febrifugine (**1**) was extracted.

Because more acid labile protecting groups were utilized, there may have been less HCl exposure, which may have prevented the isomerization issues caused by Baker's technique (i.e., O-benzyl and N-Boc). The antipode of natural sources febrifugine, (-)-**1**, had been created, as evidenced by antimalarial activity and optical rotation investigation of the final product after it had been separated. The chiral ester, *ent*-**25**, was then used to synthesis naturally occurring (+)-febrifugine (**1**) using the same method as described above. These results clearly showed that (+)-febrifugine's (**1**) absolute configuration is its native state (2R,3S). The cytotoxicity of synthetic (+)-febrifugine (**1**) against mouse mammary FM3A and artificial drugs' (+)-febrifugine (**1**) ability to prevent malaria against Plasmodium falciparum were examined in vitro. synthetic (+)-**1** When used against the FCR-3 strain, which is chloroquine-sensitive, synthetic (+)-**1** ($EC_{50} = 7.6 \times 10^{-11}$ M) exhibited comparable natural febrifugine, which is derived from the Dichroa febrifuga plant, in terms of antimalarial activity. When compared to its naturally occurring antipode, synthesized (-)-febrifugine (**1**) antimalarial activity ($EC_{50} = 2.0 \times 10^{-7}$ M) against the identical strain was noticeably lower.

The description of febrifugine and the effects of systematic structural modifications on antimalarial activity have been thoroughly analyzed by the Takeuchi research team over the last 15 years. The team has created a method to gain access to enantioenriched material during this time and published four different syntheses during that same timeframe. As depicted in Scheme 8, Takeuchi *et al.* revealed their preliminary ($\pm$)-febrifugine synthesis in 1999. (**1**).^{20f,g} Claisen rearrangement was used in this 12-step synthesis to make it easier to build the 2,3-

disubstituted piperidine molecule (**34–36**). The benzyloxy disubstituted piperidine molecule (**34–36**). The benzyloxy carbamate (Cbz) protecting group was deprotected in the penultimate step, yielding ($\pm$)-**2**, which effectively isomerized to ($\pm$)-febrifugine (**1**) in refluxing ethanol. Furthermore, this synthesis is noteworthy and unequivocally shows that it is possible to Synthetically alter the equilibrium between the two febrifugines, febrifugine (**1**) & isofebrifugine (**2**).



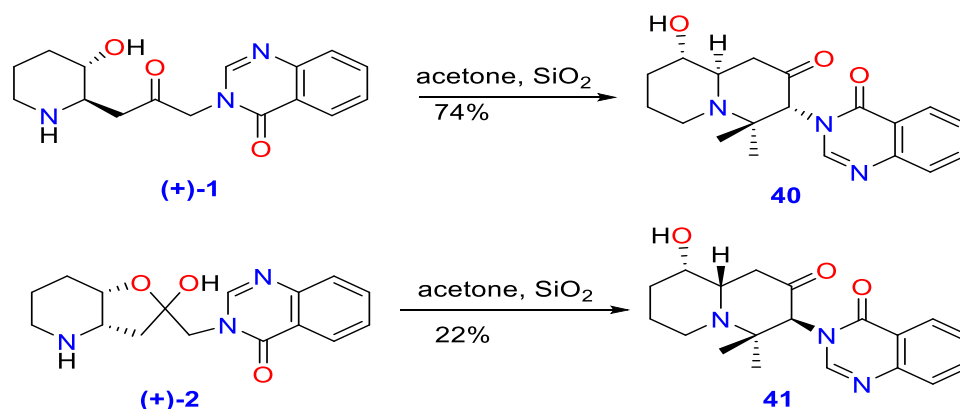
Scheme 8. Takeuchi's synthesis of ($\pm$)-**1** features the isomerization of ($\pm$)-**2** and the successive asymmetric variant.

extending the results of the earlier synthesis, Takeuchi *et al.* performed asymmetrically (+)-febrifugine synthesis (**1**) in 2000.^{20 h, i} By using Baker's yeast in this method, racemic (**35**) was optically resolved, resulting in the separation of (+)-**36** with 98% efficiency and 40% yield. The base had an impact on the chiral center's epimerization in (+)-**35**, which improved resolution.

It is frequently discussed how febrifugine is isomerized into isofebrifugine & vice versa in the syntheses of febrifugine and isofebrifugine. Given that this particular form of 2,3-disubstituted piperidine is a combination of *cis*- diastereoisomers and *trans*-diastereoisomers in nature, research by Barringer *et al.* on analogues of natural products¹⁰ showed that heating this mixture of piperidine in affected water the equilibrium in favor of the *trans*-diastereoisomer, while concentrated aqueous acid was added, the results were the opposite.

1.1.5 Design, synthesis, and biological evaluation of Febrifugine analogues

The most deceptive malaria-causing organism, *Plasmodium falciparum*, is very resistant to febrifugine, and febrifugine has potent antimalarial efficacy against it. However, because of the adverse effects such as vomiting, diarrhea, & liver damage, febrifugine cannot be used as an antimalarial medication.²⁹ Since febrifugine's original isolation in the 1950s, attempts have been conducted to develop analogues of it as possible antimalarial medicines. These studies were motivated by febrifugine's strong antimalarial activity.



Scheme 9. Bicyclic Febrifugine analogues **40** and **41** synthesis

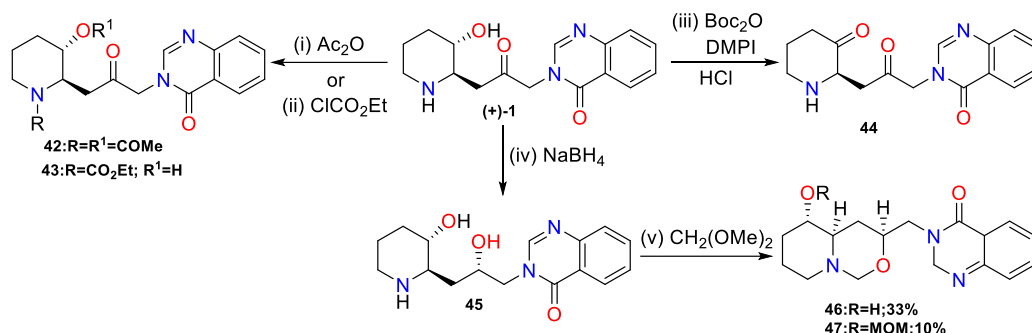
The biological testing of febrifugine analogues as prospective antimalarial medications in the 1970s revealed that the hydroxyl group, piperidine ring's nitrogen atom, and 4-quinazolinone moiety were required for antimalarial action.^{30,31} Additionally, it was established that the compound's absolute arrangement is crucial since the unnatural enantiomer has only mildly active properties.³²

The febrifugine bicycloacetone adducts **40** and **41** were created and studied by Takaya *et al.* in 1999. (Scheme 9).³³ Using a Mannich-type reaction with acetone and SiO₂, such bicyclo analogues have been produced from the natural alkaloids (+)-1 & (+)-2. As a result, the original alkaloid was presented in a locked conformation. Investigated were mouse mammary FM3A in vitro cytotoxicity and antimalarial activity against *Plasmodium falciparum*.

Chloroquine's EC_{50} value of (1.8×10^{-8}) M was much higher for analogues **40** ($EC_{50} = 1.6 \times 10^{-9}$ M) and **41** ($EC_{50} = 2.8 \times 10^{-9}$ M) than it was for the FCR-3 strain sensitive to chloroquine. These analogs demonstrated excellent antimalarial efficacy in opposition to the chloroquine-resistant K1 strain and were shown to be selective towards *Plasmodium falciparum*.

Several modifications in 2002, (+)-febrifugine **1** was present, and Kikuchi et al. investigated the structural alterations affected activity (Scheme **10**).³⁴ When (+)-febrifugine **1** was first bis-acetylated to produce **42**, its analogue's antimalarial activities were noticeably lower ($EC_{50} = 9.1 \times 10^{-7}$ M) than those of (+)-febrifugine **1** ($EC_{50} = 7.0 \times 10^{-10}$ M). The analog **43** was then produced by N-protecting (+)-febrifugine **1** in the existence of ethyl chloroformate. Similar to (+)-febrifugine **1**, Additionally, this analog's antimalarial activity has decreased ($EC_{50} = 4.8 \times 10^{-6}$ M).

Further research led to the discovery of the keto-analog **44**, which showed antimalarial properties with an EC_{50} of 2.0×10^{-8} M when (+)-**1** was converted to oxidation in the existence of Dess Martin Periodinane. Contrarily, the antimalarial activity of **45**, which was generated by a reduction in (+)-**1** when the presence of sodium borohydride ($NaBH_4$), was comparable to that of its ketone counterpart, **44**. Both of these analogues demonstrated strong *Plasmodium falciparum* selectivity. A combination of the cyclized compounds **46** and **47** was produced when the hydroxyl analogue **45** underwent cyclization during the existence of dimethoxymethane. These analogues **46** and **47** both exhibited strong activity against malaria, with **46** exhibiting particularly strong selectivity for *Plasmodium falciparum* ($EC_{50} = 3.7 \times 10^{-9}$ M & 8.6×10^{-9} M). Analogues of the same class generated from (+)-isofebrifugine **2** had noticeably low activity compared to those produced from (+)-febrifugine **1**.



Scheme 10. Kikuchi's alternative of (+)-febrifugine (1)

Using a 1,3-dipolar cycloaddition method, Kikuchi *et al.* had also prepared racemic febrifugine alternative **48–51** (Fig. 3).³⁴ To determine the most effective treatments, these analogs were evaluated for activity by the 4-quinazolinone ring's N-1 atom and the fused benzene moiety.

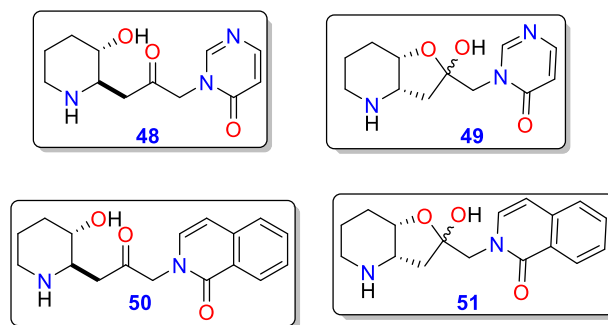


Figure 3. Quinazolinone ring alternative of (+)-Febrifugine 1

The modest antimalarial activity of all analogues was accompanied by a lack of selectivity in opposition to *Plasmodium falciparum*, highlighting the significance of the selectivity and antimalarial activity of the 4-quinazoline moiety.

Hirai *et al.* described the metabolic production of (+)-febrifugine (**1**) metabolites produced by mouse liver S9.³⁰ in 2003. Following an hour-long the metabolites **52** & **53** mentioned in (Fig. 4) have been isolated after (+)-febrifugine **1** was incubated with mouse liver S9. Then, using HPLC, they were isolated and purified. Identical incubations of the analogue of bicyclo **40** resulted in the isolation of two more metabolites, **54** and **55**. (Scheme 9). These four metabolites were synthesized via total synthesis after the structures of each were clarified by

NMR and mass spectrometric analyses. Kobayashi *et al.* observed that the antipode of (+)-febrifugine (**1**) has 1/2632 of the natural alkaloid's antimalarial effectiveness (Section 1.2.1)¹¹, allowing conclusions to be drawn about the respective EC₅₀ values of both compounds.

The *Plasmodium falciparum* parasite was used to measure the antimalarial activity (FCR-3 strain). While metabolite **53** (EC₅₀ = 6.6 x 10⁻⁶ M) shown modest limited selectivity and antimalarial activity in vitro, metabolite **52** (EC₅₀ = 2.2 x 10⁻⁹ M) demonstrated significant antimalarial activity with excellent selectivity. In vivo, **52** shown minimal toxicity and antimalarial efficacy that was equivalent to (+)-febrifugine (**1**) itself (ED₅₀ = 0.3 mg/kg/day) (ED₅₀ = 0.6 mg/Kg/day). Its "isofebrifugine" isomer **56** was also identified during the production of metabolite **52**, and evaluation of its antimalarial efficacy against the FCR-3 strain of *Plasmodium falciparum*. In vitro, **56** demonstrated potent antimalarial activity (EC₅₀ = 2.7 x 10⁻¹⁰ M), it was similar to (+)-febrifugine (**1**). Aside from that, it demonstrated outstanding *Plasmodium falciparum* activity and minimal toxicity (EC₅₀ = 2.9 x 10⁻⁶ M). Both **52** and **56** exhibited outstanding in vitro antimalarial activity, which suggests that a hydroxyl group in the 4-quinazolinone ring's C-6 position minimizes toxicity toward mammalian cells while retaining strong antimalarial activity.

After being **54** synthesized from the metabolite **36** (Scheme 8), **54** showed superb selectivity and strong activity against malaria in test vitro (EC₅₀ = 2.2 x 10⁻⁸ M) in opposition to *Plasmodium falciparum* (FCR-3 strain). Also noted that there was a low toxicity (EC₅₀ = 3.6 x 10⁻⁵ M) against mammalian cells. This metabolite has a low toxicity level and moderate antimalarial efficacy in vivo (ED₅₀ = 2.4 mg/kg/day). In 19 steps, D-aspartic acid was used to produce metabolite **55**. But **55** has limited antimalarial effect in opposition to *Plasmodium falciparum* in vitro (FCR-3 strain).

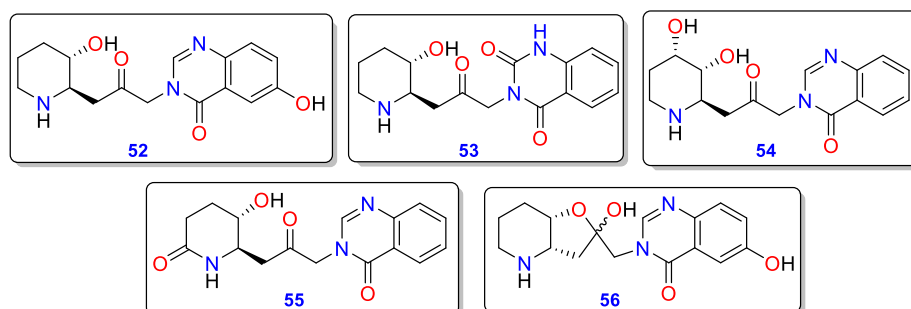
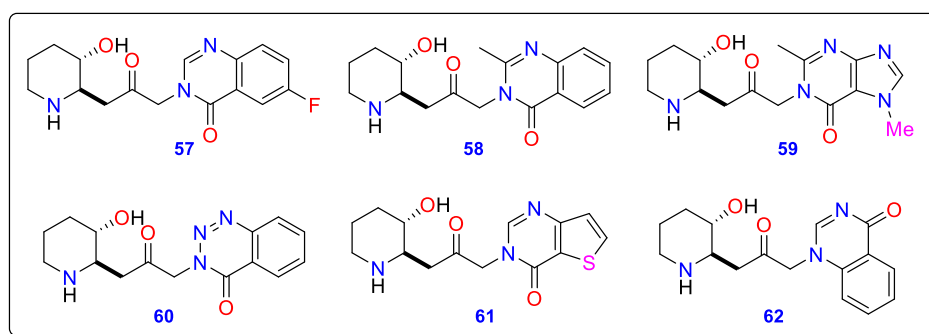


Figure 4. Metabolites containing (+)-Febrifugine (**1**), **52–55**, and artificial **56**

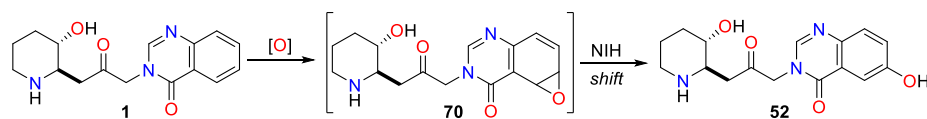
Several analogue's synthesis & biological evaluations were reported on by Kikuchi *et al.* in 2006 based on changes made to the piperidine ring, linker, and 4-quinazolinone ring.³⁶ The 4-quinazolinone ring underwent several changes, ultimately resulting in the separation of the analogs **57–62**. (Fig. 5). Using the method described by Takeuchi *et al.*, these analogues were produced as racemic mixes. Each of these analogue's antimalarial activity was evaluated in vitro against the chloroquine-sensitive FCR-3 and chloroquine-resistant K1 Plasmodium falciparum strains. Additionally, mouse L929 cell's cytotoxicity was assessed.

Although it was created to minimize metabolic oxidation, the fluorinated counterpart **57** demonstrated stronger and more effective against malaria than (+)-febrifugine (**1**) while also being more perilous. Analogue **61** had significant in vitro and in vivo antimalarial efficacy, in contrary to the other analogues shown in (**58–60**), which exhibited modest antimalarial activity stated for analogue with complete lack of antimalarial activity (**62**).

**Figure 5.** Racemic Quinazolinone alternative of Febrifugine

The fact that analogue **62** completely lost its antimalarial effectiveness shows that the heteroaromatic component's basic nitrogen group is required for antimalarial activity. Using the metabolite **52** shown in the (Fig. 4), first discovered by Hirai & his team, Zhu *et al.* produced & tested some new febrifugine analogues in 2006.³⁷ Zhu *et al.* produced analogues had fewer toxic properties than the original alkaloid. Based on these observations, it was hypothesized that cytochrome **P-450** enzymes may convert febrifugine into arene oxide **70**.

(Scheme 11). the extremely electrophilic intermediary (70) then responds indiscriminately with the host's proteins, DNA, RNA, or other macromolecules. The most likely transitory intermediary of the metabolite 52 is arene oxide (70).



Scheme 11. The NIH shift for febrifugine and its anticipated oxidative metabolism using arene oxide 70

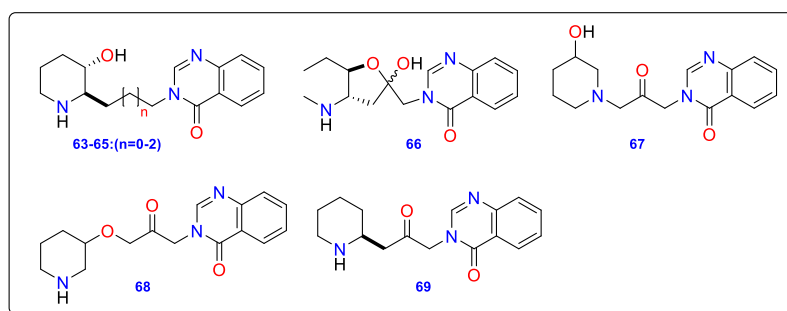
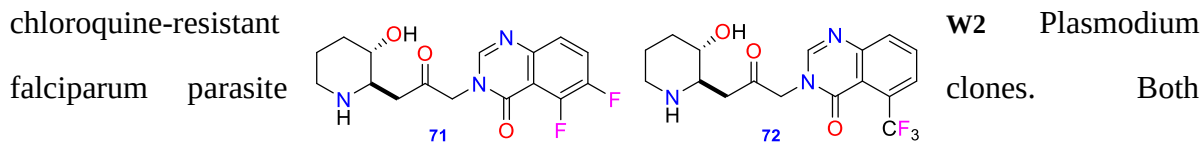


Figure 6. Alternatives to Febrifugine.

Novel febrifugine analogues with critical structural changes were created by Zhu *et al.* This study aimed to make the a fore mentioned procedure undesirable or unattainable. Two approaches were used to deal with this. First, the metabolism was stopped by substituting an element other than hydrogen in the locations of the 4-quinazolinone ring at C-5 or C-6. Alternately, by electrically modifying the aromatic ring, the molecule's oxidation potential was raised. A variety of analogues were created using Taniguchi *et al.*'s.^{20m} synthetic method and met the aforementioned requirements.

Two analogs, 71 & 72 depicted in the (Fig. 7), were discovered to be nearly four times more efficient in vitro than (+)-febrifugine (1) against the chloroquine-sensitive D6 and the chloroquine-resistant



analogues were attractive possibilities for the development and discovery of brand-new antimalarial medicines because they were, interestingly, less than about 100 times damaging to rat hepatocytes than (+)-1.

Figure 7. Quinazolinone analogs **71** & **72** of febrifugine

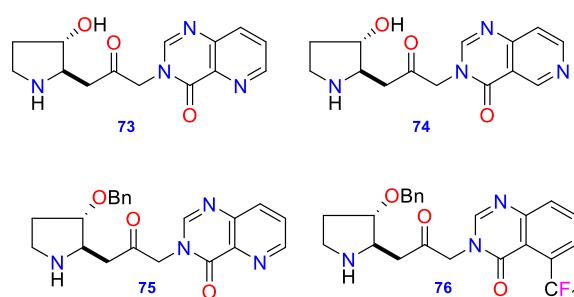


Figure 8. Based on the pyrrolidine analogues of Febrifugine

To investigate the isomerization of - isofebrifugine (**2**) and -febrifugine (**1**), Zhu *et al.* created a second set of analogues of febrifugine. in 2009. (See Schemes **1** and **6**).³⁸ As a possible biomolecule alkylating agent, the electrophilicity of the probable, unsaturated intermediate (Scheme **6** of type **21**) implied in this route was recognized. In this case, the construction of 5 - membered rings is entropically preferable than that compared with the six - membered rings. Therefore, it was predicted that the pyrrolidine component of febrifugine would replace the constituent of piperidine, leading to an analogue with less favorable isomerization. The antimalarial activity of each of the pyrrolidine analogues of the effectiveness of febrifugine was evaluated in mice both in vivo and in vitro against the chloroquine-resistant W2 strain of *Plasmodium falciparum*.

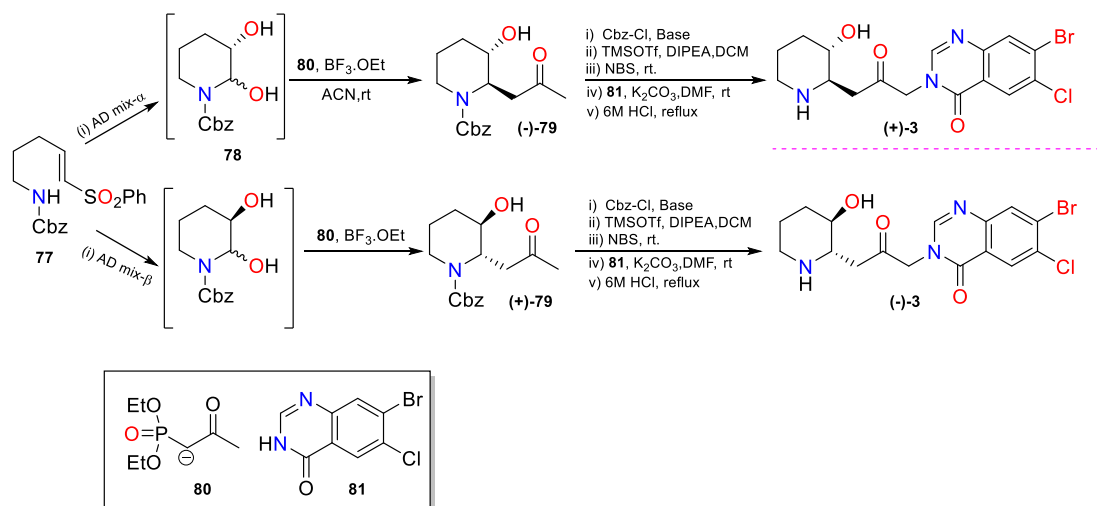
While exhibiting minimal toxicity, compared to (+)-febrifugine (**1**), analogues **73** & **74** both showed greater antimalarial efficacy. They were over four times more effective in vivo and had an antimalarial activity that was Compared to Febrifugine (**1**) in vitro, it is more than six times more potent. Additionally, both were 1.31 times less hazardous than the currently

accessible antimalarial medicine chloroquine and almost less harmful than febrifugine by nine times. The analogues **75** and **76**, which are also depicted in Figure **8**, likewise showed promising antimalarial activity in vitro, and in vivo, they were discovered to be nearly 16 times more effective than (+)-febrifugine (**1**). They both had a benzyloxy group on the ring of pyrrolidine. However, it was found that both of these analogues were more hazardous than their hydroxyl counterparts, **73** and **74**, by a factor of more than three.

1.2 Results and Discussions

1.2.1 Synthesis of Halofuginone

The halogenated analogue of febrifugine, halofuginone (**3**), was first created as a potential antimalarial medication in the late 1960s. in which one of this drug's metabolic activities is inhibited (Scheme **11**).



Scheme 12: (+)-Halofuginone and (-)-Halofuginone structures (**3**).

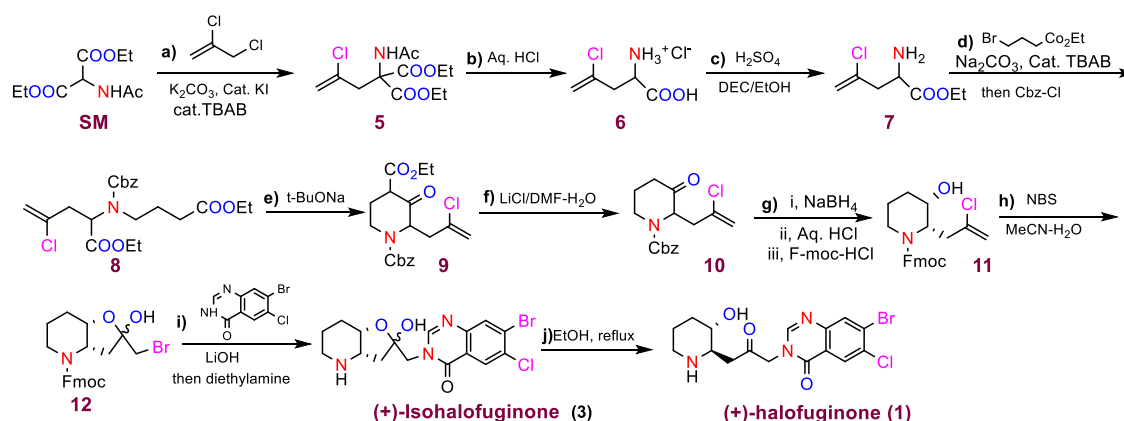
For broilers & turkeys, racemic salts of halofuginone hydrobromide has been employed as an anticoccidial feed additive⁵, which eventually led to the discloser that, (**3**) also exhibits mammalian biological features in addition to its antiprotozoal action. In 2005, Jiang *et al.* evaluated halofuginone's effectiveness against malaria.³⁹ Halofuginone's in vitro antimalarial

activity against the W2 *Plasmodium falciparum* strain has an IC_{50} of 0.145 ng/ml. In comparison, febrifugine's activity ($IC_{50} = 0.53 \text{ ng ml}^{-1}$) against the identical clones *Plasmodium falciparum* was less potent ($IC_{50} = 0.53 \text{ ng ml}^{-1}$). Halofuginone was shown to be 10 times more effective in vivo than febrifugine at treating *Plasmodium berghei* in mice. Halofuginone was shown to be deadly to mice at 0.5 mg/kg per day, whilst febrifugine was classified as toxic.

It is quite remarkable that just one extensive synthesis has been described in great specifics in the literature considering the current interest in HF (3) so far.^{20s} In this method (Scheme 12) utilizes asymmetric vinyl sulfone dihydroxylation (77) to produce *trans*-2,3-disubstituted piperidine (79) following intermediate (78) has undergone Horner-Wadsworth-Emmons olefination and been added to. The separation of either enantiomeric form of (79) was possible using both AD mix- α - and AD mix- β . In the end, the methyl group was functionalized by 7-Bromo-6-chloroquinazolin-4-one alkylation (81). following Takeuchi's technique,^{20j,k} to produce (+)- and (-)-3.

In 2019, Yehuva Jin *et al.*⁴⁰ reported It has become possible to completely synthesize halofuginone on a large scale. a yield of 17% overall 12 steps. Diethyl acetamido malonate was transformed into compound (5) by 2,3-dichloropropene alkylation. Aqueous HCl solution in refluxing condition (5) compounds was produced after decarboxylating one ester group, including hydrochloride of an amino acid (6). After the esterification process, (7) was produced, and it was then used in ethyl 4-bromobutyrate's N-substitution process. TBAI present in toluene in a catalytic amount was utilized along with anhydrous Na_2CO_3 . Compound (8) was obtained by adding dropwise amounts of Cbz-Cl to the reaction mixture following the N-substitution reaction, then treatment of *t*-BuONa in THF. Compound (9) was then produced. Compound (10) was prepared through Krapcho decarboxylation, which removed the ethoxy carbonyl functionality of compound (9). The cis alcohol isomer was produced by reducing the carbonyl group with $NaBH_4$. Followed by removing the Cbz group with aqueous HCl. and protecting the Compound (11) was produced when the N-atom of 10 was combined with Fmoc-Cl., further treating (11) with NBS in the existence of acetonitrile and water produced Bromo compound (12). The coupling product was prepared by gradually

adding the (12) in DMF solution with the lithium salt of preformed 7-Bromo-6-chloroquinazolin-4(3*H*)-one, which was then deprotected with diethyl amine to yield isohalofuginone (+)-3 with a trace quantity of halofuginone (+)-1 (5%). It was discovered that (1) isomerized with (3), further Isohalofuginone (+)-3 subjected Ethanol under reflux completely isomerized to Halofuginone (+)-1



Scheme 13: Large scale synthesis of Halofuginone

1.2.2 Biological strides of Halofuginone

Halofuginone, which developed into a physiologically active molecule, has garnered attention for a wide range of therapeutic uses, including the treatment of autoimmune, cancerous, and fibrotic disorders as well as malaria. There are now two documented mechanisms of action for halofuginone.

(1) The TGF signaling pathway's downstream Smad3 phosphorylation regulation prevents the transformation of fibroblasts into myofibroblasts and inhibits fibrosis.

(2) Integration of the response to stress and the activation of the protein starvation response, which decrease inflammation and the autoimmune response by inhibiting (ProRS) prolyl-tRNA synthetase activity during the blood stage of malaria and suppression of Th17 cell diversity.

1.2.3 Halofuginone and fibrosis

When an organ or tissue develops an excessive amount of fibrous connective tissue as a result of an accident or chronic inflammation, the organ will eventually collapse due to severe and persistent scarring. Halofuginone reduced the production of collagen by limiting the growth of fibroblasts into myofibroblasts in fibrosis-related animal models, where an excess of collagen is a defining feature of the condition.⁴¹ Halofuginone differs from all other antifibrotic drugs in that it also encouraged the resolution of existing fibrosis⁴² by influencing compensatory mechanisms in fibrotic tissue, such as matrix metalloproteinase⁴³ and triple-helix repeat in collagen with one system⁴⁴.

1.2.4 Halofuginone and cancer

It has been discovered that halofuginone inhibits the transition of fibroblasts into myofibroblasts, which is a feature of tumor cells as well as the quantity of stromal Extra Cellular Matrix (ECM) essential for tumor growth in a range of animal models. The growth of new blood vessels, known as angiogenesis, which is necessary for the growth of solid tumors & serves as a major route for metastasis, was also suppressed by HF. Significantly inhibiting impacts on basement membrane invasion, capillary tube formation, and vascular sprouting were seen when ECM synthesis was halofuginone-dependently inhibited, in addition to the implantation of sub-endothelial ECM in several experimental devices that portrayed the angiogenic cascade's sequential events.⁴⁵ Halofuginone is a prime option for integration therapy, as evidenced by its efficacy in the treatment of prostate cancer and pancreatic, as well as xenografts for Wilms' tumor.^{46,47} Halofuginone successfully reduced the doses of chemotherapeutic agents when used in integration therapy with additional cancer-fighting medication with diverse modalities, which lessens the burden of treatment placed on cancer patients.

Following repeated topical administrations, halofuginone's safety & tolerance profile were found to be acceptable when applied topically to healthy volunteers. In a patient with promyelocytic leukemia that had developed a serious cGvHD following a fruitful transplant of bone marrow, topical treatment of halofuginone led to a considerable decrease in skin

collagen production and an improvement in physiological indices.⁶ After three months of therapy, topical administration of halofuginone significantly decreased the average total Rodnan skin score in people with localized scleroderma.⁴⁸ Halofuginone's antifibrotic effects were also seen in people with Kaposi sarcoma related to AIDS.⁴⁹ The dosage of 0.5 mg/day was recommended for continuous oral administration for cancer patients that is advanced & progressing.⁷ Halofuginone showed excellent safety and tolerability profile, as well as encouraging results, in a Phase IIa research that investigated oral dosing for patients who had bladder superficial transitional cell carcinoma that returns frequently and underwent receiving systemic treatment. Halofuginone is now being tested for safety, tolerability, and phase Ib trial participants' pharmacokinetics for Duchenne muscular dystrophy (DMD).

1.3 Conclusion

In this introduction, we make a concerted effort to illustrate historical elements that contributed to difficulties in figuring out the structures of the synthesis of the innate febrifugine 1 and isofebrifugine 2, and the solutions to the aforementioned issues, are discussed. Furthermore, the wide range of febrifugine analogs developed for initiatives to combat malaria has been highlighted. The fact that the precise biological mechanism, or processes, underlying Febrifugine and isofebrifugine's antiprotozoal activities are not well understood is noteworthy. Exciting new findings on halofuginone 3, a substance first created as an antiprotozoal, are presented in the fields of fibrosis and angiogenesis.

Again, it's important to highlight that while equivalent research concerning human biology has not been carried out, through various malaria control initiatives, the febrifugine skeleton has been systematically altered. To the best of our knowledge, no research has ever been done into the ability that this type of substance's antiparasitic effect and the human biology it has been shown to affect may not be unrelated. Furthermore, rather than employing single optical isomers, racemic material has been utilized in a large number of the latest biological studies involving halofuginone.

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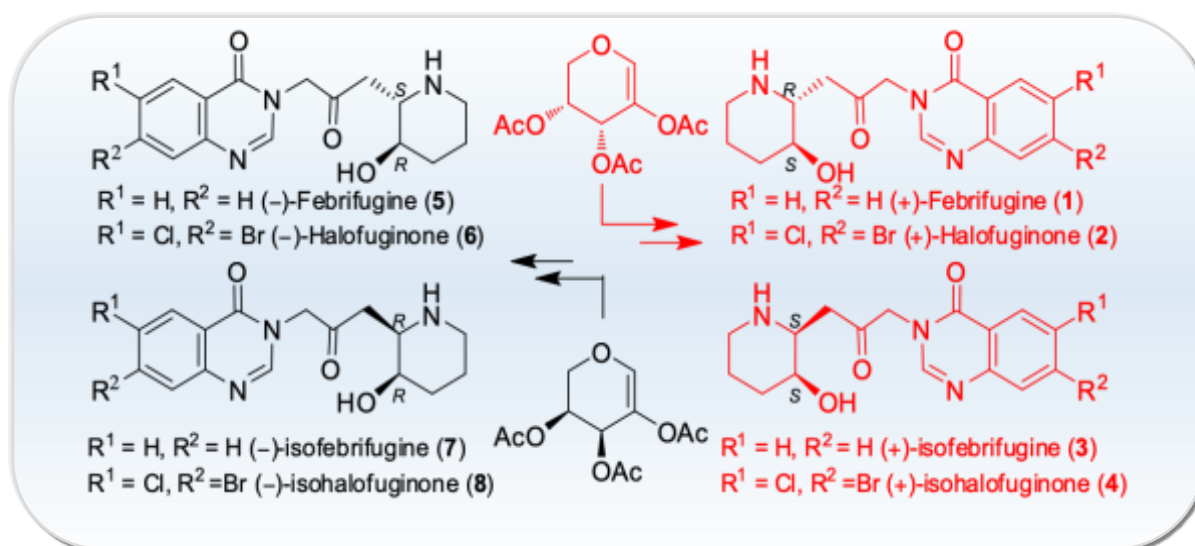
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Chapter-2

Stereoselective total synthesis of all the stereoisomers of (+) and (-) Febrifugine and Halofuginone



2.1 Introduction

2.4 Experimental section

2.2 Results and Discussions

2.5 References

2.3 Conclusions

2.1 Introduction

(+)-Febrifugine **1** and (+)-isofebrifugine **3** are natural alkaloids isolated from a Chinese medicinal plant, Ch'ang Shan (*Dichroa febrifuga*)¹ in 1940. Later they were also isolated from common garden plant, hydrangea.² For over 2000 years, the extracts of Ch'ang shan have been used as natural remedy for the treatment of stomach cancer and malaria. In solution, (+)-Febrifugine **1** slowly epimerizes into its diastereomer (+)-isofebrifugine **3**, which is comparatively less potent than **1**.³ Due to the facile epimerization of **1** to **3**, there have been a couple of structural revisions of these two natural products have been reported.⁵ Thus, these compounds have been the subject of interest concerning their structural and biological perspective.⁴ Although Baker and Co-workers reported the chemical structures and the racemic synthesis of **1** and **3**,⁶ the absolute stereochemistry of these compounds was revealed in 1999 by Kobayashi's total synthesis.⁷ Since then a couple of methods for the total synthesis of **1** and **3**, in both racemic and enantioselective fashion, have been reported.⁸ Although **1** was found to be an effective antimalarial and even more potent than chloroquine⁹ due to severe toxicity inducing side-effects¹⁰ like nausea, vomiting and liver damage associated with it have precluded its transformation into a medicine. In search of a better analog of **1** possessing improved activity and toxicity profile, the structure-activity studies led to the discovery of (+)-halofuginone **2**, in which the metabolically vulnerable quinazoline protons in **1** were replaced by chlorine and bromine atoms.

The biological properties of (+)-halofuginone **2** in mammals was initially came across during its usage as veterinary medicine to treat intestinal protozoal infections.¹¹ In the year 2000, (+)-halofuginone **2** has received orphan drug designation by the FDA for the treatment of scleroderma, a chronic connective tissue disease.¹² Currently, **2** is in phase II clinical trials as a therapeutic to treat cancer, muscular dystrophy and fibrotic diseases.¹³ Recently it was also found that **2** inhibits the Th17 cells, which play an important role in autoimmune diseases, by activation of amino acid starvation response (AAR) directly by inhibiting the prolyl-tRNA synthetase activity of glutamyl-prolyl-tRNA synthetase (EPRS).¹⁴

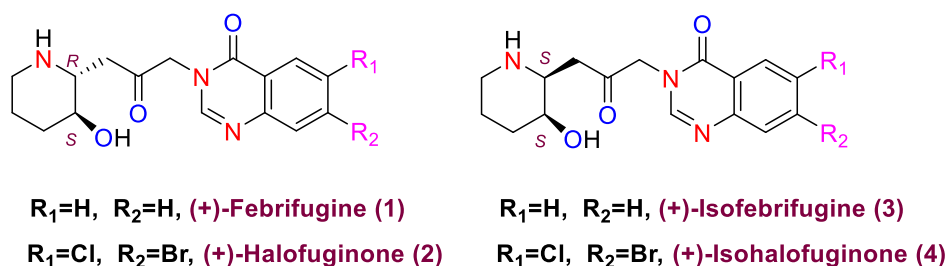
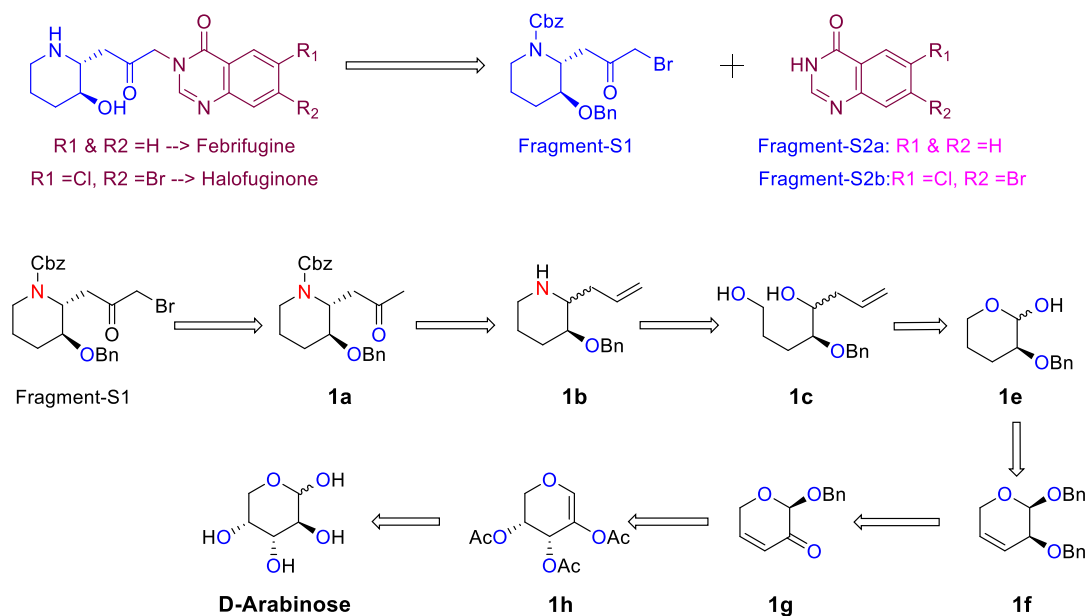


Figure 1: Molecular structures of (+)-Febrifugine (1), (+)-halofuginone (2), (+)-isofebrifugine (3) and (+)-isohalofuginone (4).

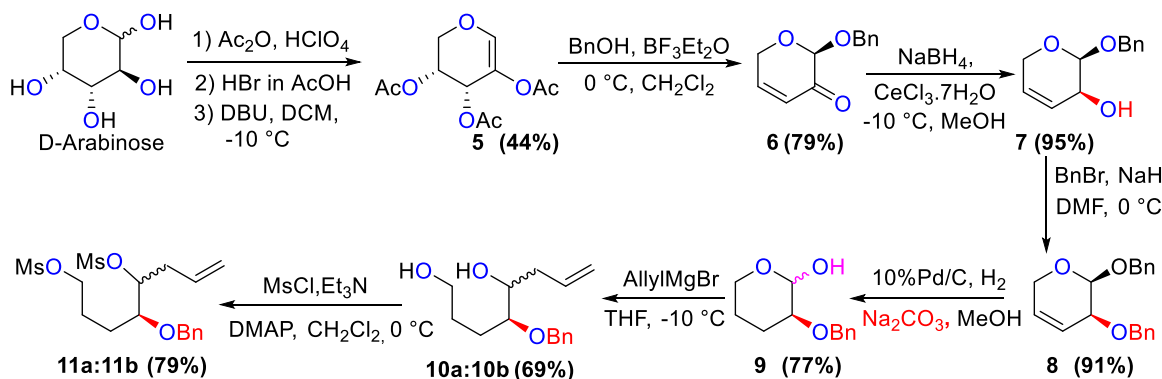
However, there were very few reports on the stereoselective synthesis of (+)-halofuginone (2) and (+)-isohalofuginone (4). Apart from this, the evaluation of biological properties of enantiomers of **1** to **4** is also very important in therapeutic perspective of these compounds. Thus, herein we report a stereoselective method for the total synthesis of all the stereoisomers of febrifugine and halofuginone.

2.2 Results and Discussions

a) Retrosynthesis approach



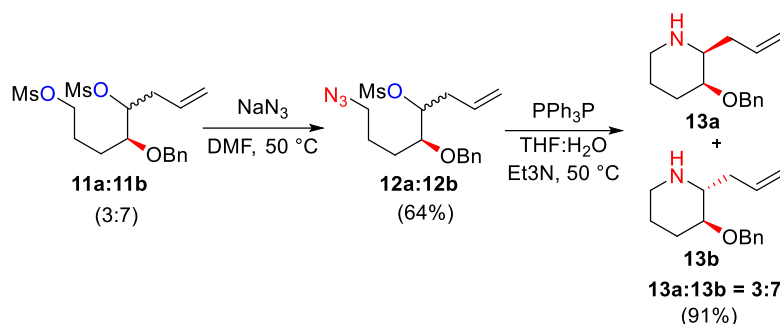
Our protocol for the total synthesis began with the use of D-arabinal as chiral pool starting material. Thus, D-arabinose was initially transformed to the 2-acetoxy-3,4-di-O-acetylglycal **5** involving peracetylation and glycosyl bromide formation using 33% HBr in acetic acid followed by 1,8-di-azabicyclo[5.4.0]undec-7-ene (DBU) mediated dehydrohalogenation reaction.¹⁵ Glycal **5** in presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as a promotor underwent a highly facial-diastereoselective glycosylation reaction with benzyl alcohol providing dihydropyranone **6**. Diastereoselective reduction of ketone in **6** under Luche conditions¹⁵ provided the allyl alcohol derivative **7** as a single diastereomer in good yield. Benzylation of this alcohol, to give **8**, followed by regioselective hydrogenolysis with concomitant hydrogenation of the alkene provided the cyclic hemiacetal **9**¹⁶ in 84 % yield, after two steps. Treatment of **9** with allyl magnesium bromide furnished the diols **10a** and **10b**, which were further mesylated to give the diastereomeric mixture of dimesylates **11a** and **11b**, in 3:7 ratio,¹⁷ respectively (Scheme 1).



Scheme 1: Synthesis of dimesylate precursor for the piperidine ring formation

Regioselective nucleophilic substitution of the primary mesylate in **11a** and **11b** with an azide provided the azido mesylates **12a** and **12b**. Conversion of the azide to amine under Staudinger reduction conditions followed Et_3N assisted cyclization provided the piperidine derivatives **13a** and **13b** in a 3:7 ratio, respectively. Fortunately, we were able to separate

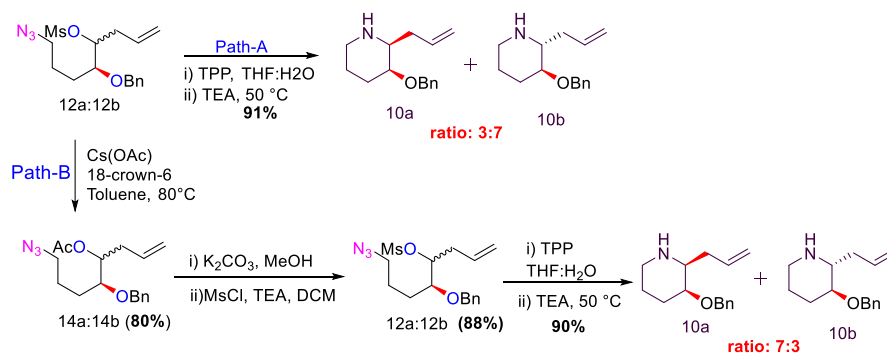
these two diastereomeric piperidines using the silica gel column chromatography and assigned the configuration at the two stereocenters successfully (Scheme 2).



Scheme 2: Stereoselective synthesis of the piperidine framework of (+)-febrifugine and (+)-halofuginone

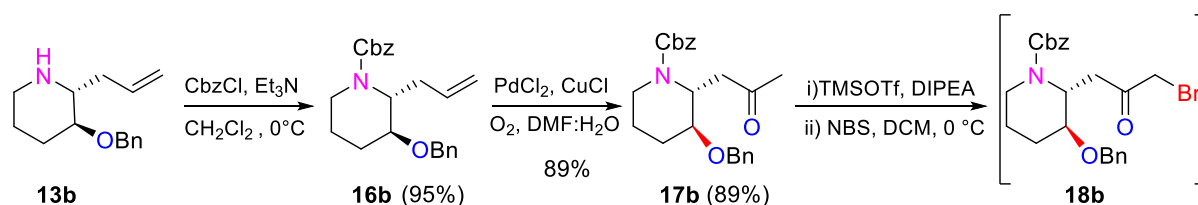
Inversion of Stereocenter:

To obtain the minor diastereomer **13a** in good quantity, we planned to invert the stereocentre at mesylate carbon in the azido mesylate mixture **12a** and **12b**. Towards this, substitution of the secondary mesylate in the azido mesylates **12a** and **12b** with cesium acetate provided the diastereomeric mixture of azido acetates **14a** and **14b** which were upon deacetylation gave the azido alcohols **15a** and **15b** in excellent yield. Mesylation of this alcohol to give the azido mesylates **12a** and **12b** followed by a one-pot reductive cyclization provided the piperidine derivatives **13a** and **13b** in 7:3 ratio, respectively (Scheme 3). The structure **13b** was further confirmed by crystallization of the corresponding hydrochloride salt (Figure 2).¹⁸

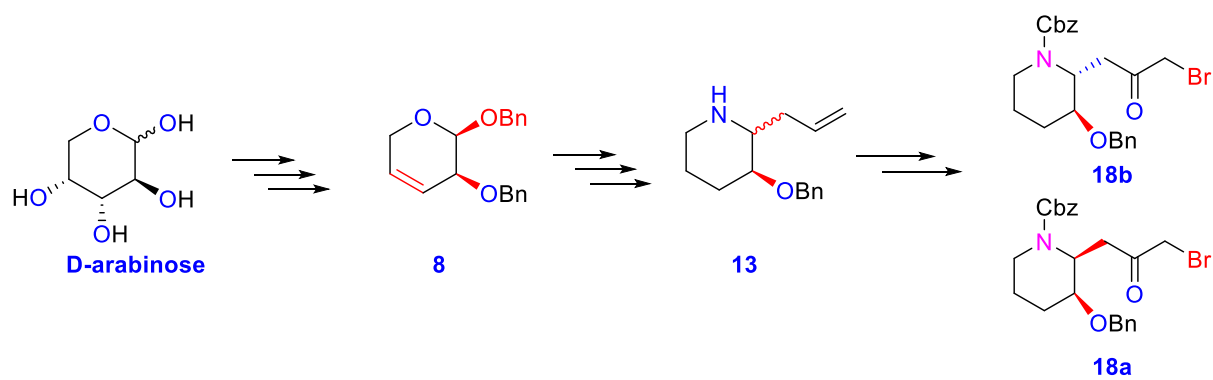


Scheme 3: Stereoselective synthesis of the piperidine framework.

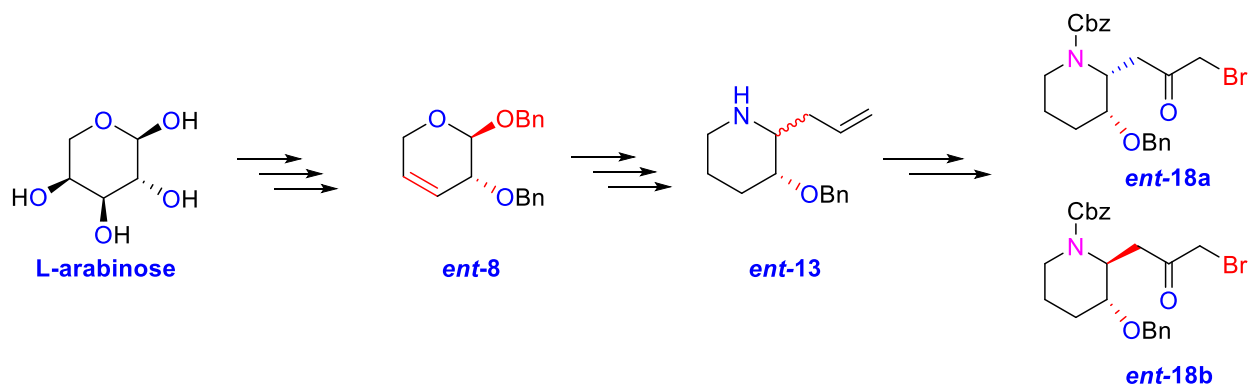
Our next objective was the conversion of the enantiomerically pure piperidine derivatives to all the stereoisomers of febrifugine and halofuginone. Towards this, the free NH present in **13a** and **13b** was protected by using Cbz-Cl to give the compounds **16a** and **16b** in excellent yield (~94%).¹⁹ Although, various approaches have been reported to convert the alkene group present in the compounds **16a** and **16b** into the corresponding methyl ketone, we chose to use the Wacker oxidation protocol to obtain the keto-derivatives **17a** and **17b** in excellent yield. Conversion of this ketone to the silyl enol ether using TMSOTf and DIPEA followed by bromination with NBS produced the α -bromo ketones **18a** and **18b**. Attempts to purify the **18a** and **18b** using column chromatography were not successful. Thus, the obtained crude bromides were subjected to substitution reaction with quinazolinone that resulted in the formation of protected (+)-isofebrifugine **19a** and (+)-febrifugine **19b**^{8r} in good yield. Finally, deprotection of the Cbz-group, as well as the benzyl, was commenced by refluxing the compounds **19a** and **19b** in aqueous 6N hydrochloric acid to obtain the (+)-isofebrifugine **20a** and the (+)-febrifugine **20b** as their di-hydrochloric acid salt, respectively. On the other hand, the substitution of the α -bromo ketones **18a** and **18b** with 7-bromo-6-chloro-4-hydroxyquinazoline provided the protected (+)-halofuginone derivatives **21a** and **21b**. Removal of the protecting groups by refluxing in 6N hydrobromic acid in water afforded (+)-isohalofuginone **22a** and (+)-halofuginone **22b** as their di-HBr salts (Scheme 5).



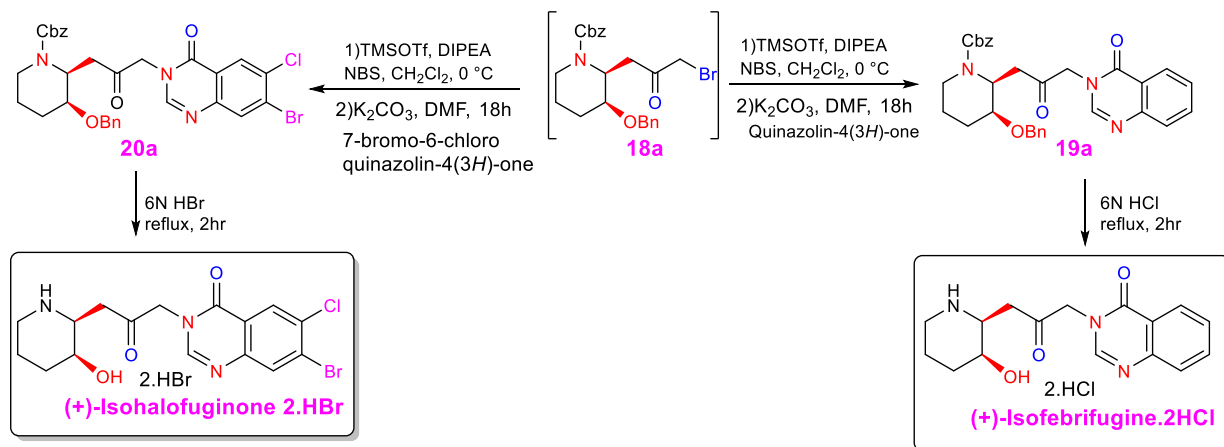
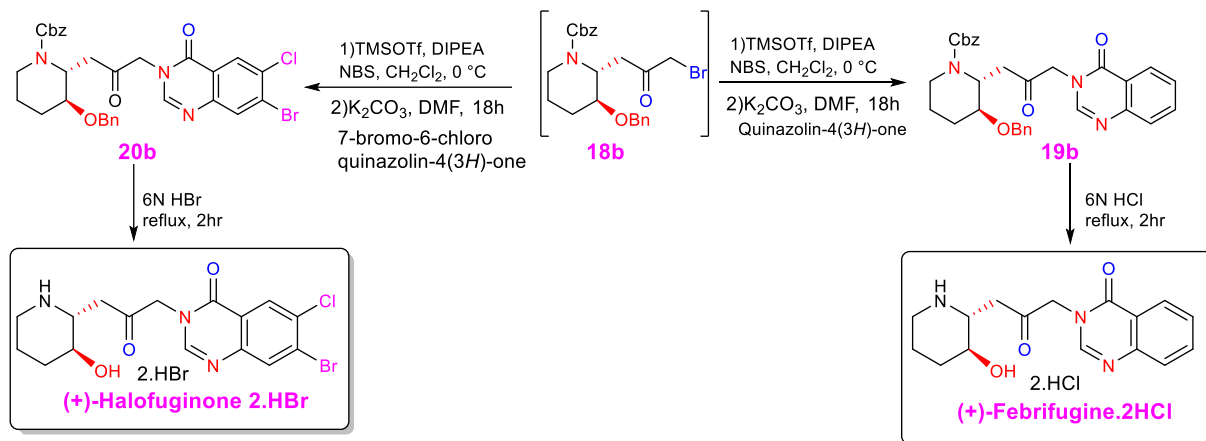
From D-Arabinose



From L-Arabinose

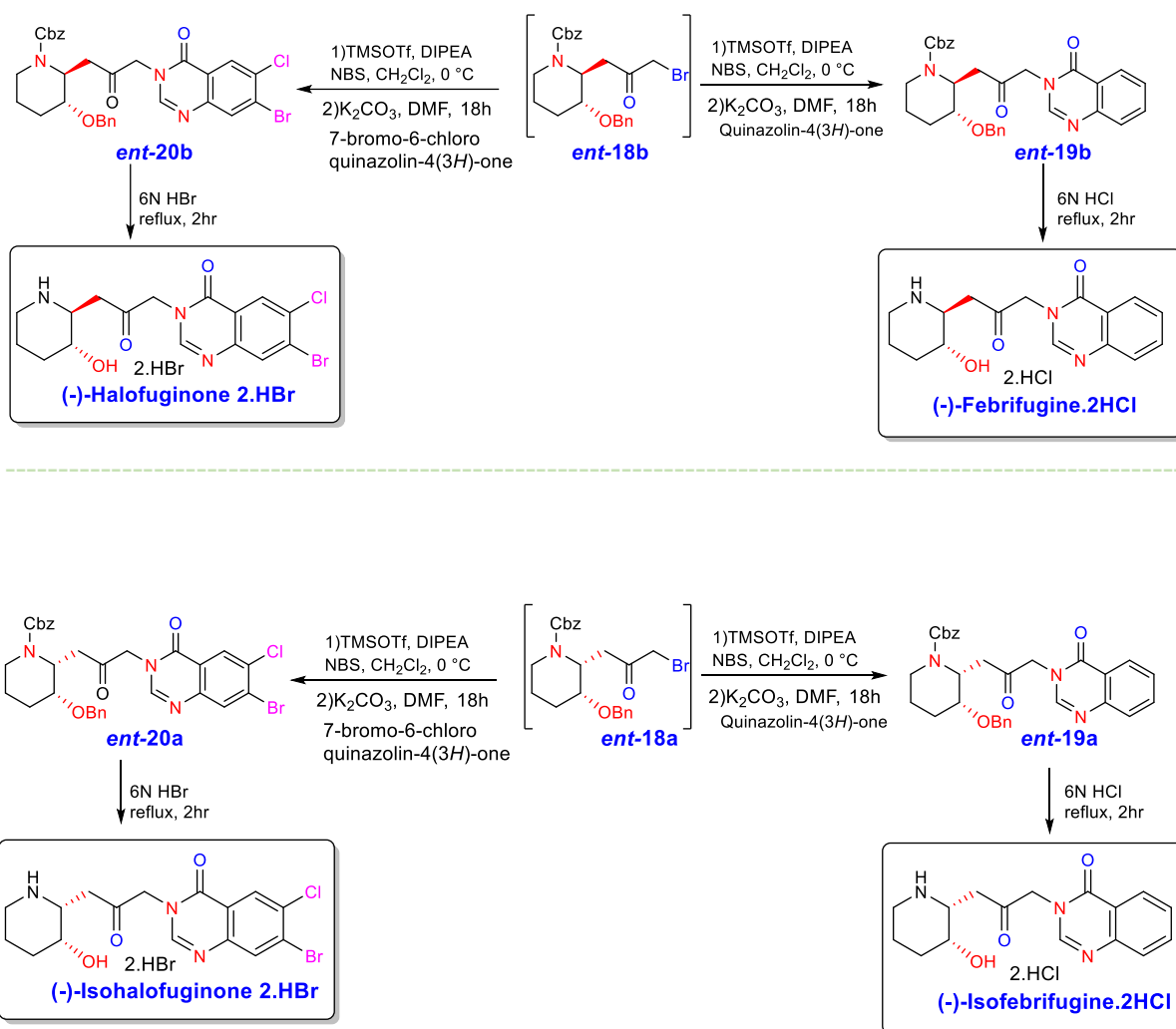


From D-Arabinose



Scheme 5: Completion of the total synthesis of (+)-febrifugine and (+)-halofuginone and their diastereomers.

From L-Arabinose

**Scheme 6:** Total synthesis of (-)-febrifugine and (-)-halofuginone and their diastereomers.

Performing the identical sequence of reactions starting from *ent*-**13a** provided the (-)-isofebrifugine **20c**, (-)-isohalofuginone **22c** and starting from *ent*-**13b** provided (-)-febrifugine **20d**, (-)-halofuginone **22d** (Scheme 6). The structure of the *ent*-**21a** was confirmed by the crystallization of this compound before subjecting it to the final deprotection reaction (Figure 2).²⁰

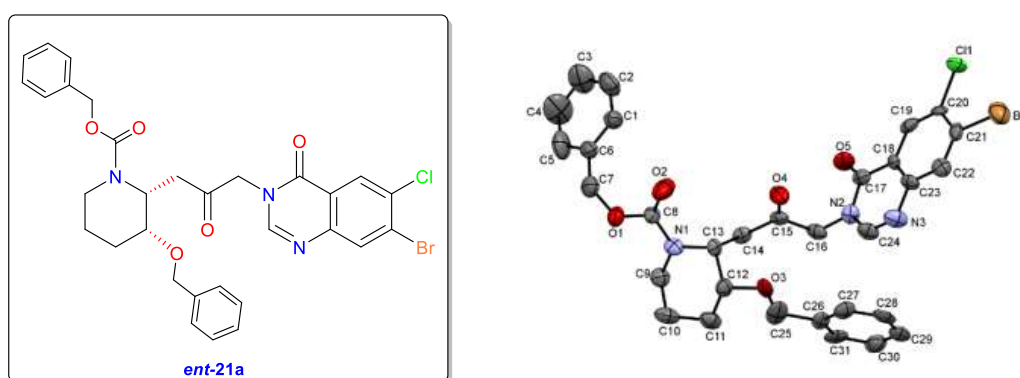
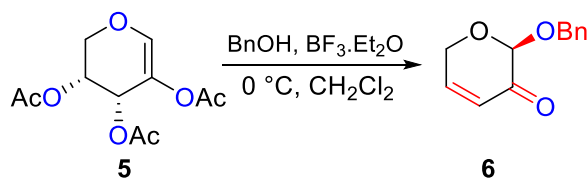


Figure 2: ORTEP diagram of compound *ent*-**21a**

2.3 Conclusions:

In conclusion, an efficient protocol for the total synthesis of all the possible stereoisomers of febrifugine and halofuginone have been achieved using naturally abundant pentose sugars, D-arabinose and L-arabinose as chiral pool starting materials. The protocol is amicable to scale up. To date, most of the synthetic analogs of febrifugine and halofuginone were mostly comprise modification on the quinazolinone ring, whereas the alterations on the piperidine ring are not much explored. The present protocol paves the way to acquire molecules possessing the structural variation on the piperidine framework of this highly important molecular scaffold. Synthesis of piperidine ring modified halofuginone analogs is in progress.

2.4 Experimental section:



(S)-2-(benzyloxy)-2H-pyran-3(6H)-one (6):

To a stirred solution of compound (3*R*,4*R*)-3,4-dihydro-2*H*-pyran-3,4,5-triyl triacetate **5** (20.0 g, 77.45 mmol) in dry dichloromethane (200 mL), was added benzyl alcohol (10.05 g, 9.7 mL, 92.94 mmol) at rt, cooled to 0 °C, then BF₃·OEt₂ (45-49 %) (21.98 g, 19.11 mL, 154.90 mmol) was added drop wise and the stirring was continued for 30 min at the same temperature. After completion of the reaction (monitored by TLC), it was diluted with dichloromethane (100 mL). The obtained solution was washed with saturated NaHCO₃ solution (50 mL), water (100 mL) and brine solution. The organic layer was dried over Na₂SO₄ and filtered. Evaporation of the solvent under reduced pressure afforded the crude product which was purified by flash column chromatography over silicagel (hexanes/ethyl acetate) provided (S)-2-(benzyloxy)-2*H*-pyran-3(6*H*)-one (**12.5 g, 79%**) as a colourless liquid.

TLC: R_f = 0.50 (30% EtOAc in Hexanes).

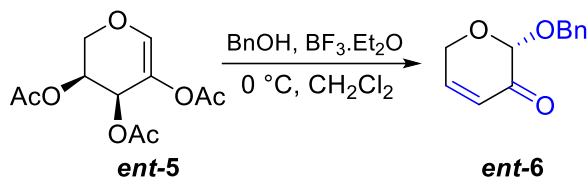
SOR: $[\alpha]_D^{25} = -220.68$ (*c* = 0.5, CHCl₃) {Lit. $[\alpha]_D^{20} -248.3$ (*c* 1.03, CHCl₃)}.

¹H NMR (500 MHz, CDCl₃): δ = 7.32-7.39 (m, 5H), 7.05-7.08 (m, 1H), 6.16 (d, 1H, *J* = 10.5 Hz), 4.96 (s, 1 H), 4.85 (d, 1H, *J* = 11.5 Hz), 4.74 (d, 1H, *J* = 12.0 Hz), 4.58 (dt, 1H, *J* = 2.5 Hz, 19.0 Hz), 4.33 (ddd, 1H, *J* = 1.5 Hz, *J* = 4.0 Hz, *J* = 19.0 Hz).

¹³C NMR (125 MHz, CDCl₃): δ = 188.55, 147.80, 136.76, 128.54, 128.09, 128.05, 124.87, 97.07, 70.81, 59.74 ppm.

IR (neat): 3031, 2929, 1733, 1696, 1454 cm⁻¹.

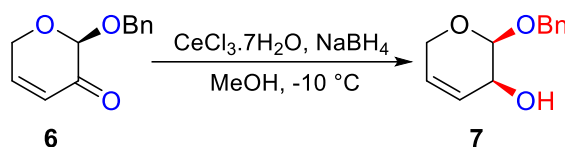
HRMS (ESI-TOF) *m/z*: [M + Na]⁺ Calcd. for C₁₂H₁₂O₃Na 227.0684; found 227.0681.



(*R*)-2-(benzyloxy)-2*H*-pyran-3(6*H*)-one (*ent-6*).

An identical procedure described for **6**, compound *ent-6* was synthesized from *ent-5*.

SOR: $[\alpha]_D^{25} = +145.8$ ($c = 0.5$, CHCl_3).



(2*S*,3*S*)-2-(benzyloxy)-3,6-dihydro-2*H*-pyran-3-ol (7**):**

Sodium borohydride (2.22 g, 58.76 mmol) was added portion wise to a stirred solution of (*S*)-2-(benzyloxy)-2*H*-pyran-3(6*H*)-one **6** (12.0 g, 58.76 mmol) in methanol (150 mL) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (5.80 g, 15.57 mmol) at -10°C . The resultant reaction mixture was stirred for 1 hr at -10°C . After completion of reaction (monitored by TLC), the reaction mass was quenched with saturated NH_4Cl solution. The solution volume was reduced to half by means of concentrated under reduced pressure, then extracted with diethyl ether (2 x 100 mL). The ether layers were washed with water and brine solution, dried over Na_2SO_4 , filtered followed by solvent evaporation under reduced pressure. Purification of the afforded crude product by flash column chromatography over silicagel (hexanes/ethyl acetate) provided compound **7**, (11.51 g, 95%) as a colourless less solid.

TLC: $R_f = 0.40$ (30% EtOAc in Hexanes).

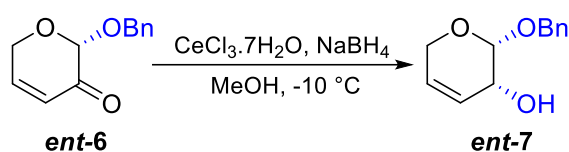
SOR: $[\alpha]_D^{25} = -112.68$ ($c = 0.5$, CHCl_3) {Lit. $[\alpha]_D^{25} -132.3$ (c 1.0, CHCl_3)}.

^1H NMR (400 MHz, CDCl_3): δ = 7.32-7.39 (m, 5H), 5.82-5.85 (m, 1H), 5.75-5.78 (m, 1H), 5.00 (d, 1H, J = 4.0 Hz), 4.88 (d, 1H, J = 12.0 Hz), 4.66 (d, 1H, J = 12.0 Hz), 4.19-4.24 (m, 2H), 4.05-4.10 (m, 1H), 2.28 (d, 1H, J = 10.4 Hz).

^{13}C NMR (100 MHz, CDCl_3): δ = 137.29, 128.56, 128.03, 128.01, 127.05, 126.15, 95.85, 69.97, 64.18, 60.24 ppm.

IR (neat): 3333, 3032, 2943, 2919, 2898, 2855, 1496, 1449 cm^{-1} .

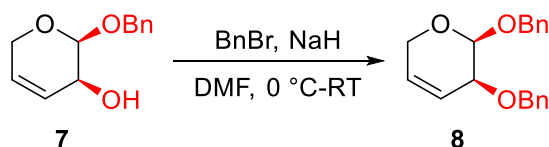
HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_3\text{Na}$ 229.0835; found 229.0836.



(2R,3R)-2-(benzyloxy)-3,6-dihydro-2H-pyran-3-ol (*ent*-7).

An identical procedure described for **7** was used to synthesize *ent*-7 from *ent*-6.

SOR: $[\alpha]_D^{25} = +111.5$ (c = 1.0, CHCl_3).



(2S,3S)-2,3-bis(benzyloxy)-3,6-dihydro-2H-pyran (8**):**

A stirred solution of compound (2S,3S)-2-(benzyloxy)-3,6-dihydro-2H-pyran-3-ol **7** (11.0 g, 53.33 mmol) in dry DMF (100 mL) at 0 °C was added sodium hydride (3.20 g (60 %), 80.00 mmol) in portions. The reaction mixture was stirred for 20 min at 0 °C then added benzyl bromide (10.94 g, 7.6 mL, 63.96 mmol) and stirred for 1 hr at rt. After completion of the reaction (monitored by TLC), the reaction mass was poured on ice water (100 mL) and stirred for 15 min. The hazy suspension was extracted with diethyl ether (3 x 100 mL). The combined organic layers were washed with water and brine solution, dried over Na_2SO_4 , and filtered. Evaporation of the solvent under reduced pressure followed by purification by flash

column chromatography over silicagel (hexanes/ethyl acetate) provided compound (2*S*,3*S*)-2,3-bis(benzyloxy)-3,6-dihydro-2*H*-pyran (**8**) (14.4 g, 91%) as a colourless liquid.

TLC: R_f = 0.65 (20% EtOAc in Hexanes).

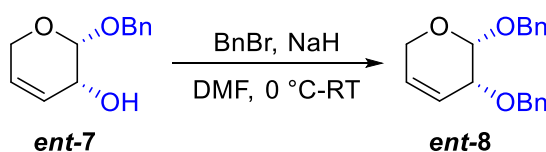
SOR: $[\alpha]_D^{25}$ = -97.40 (c = 0.5, CHCl₃).

¹H NMR (500 MHz, CDCl₃): δ = 7.28-7.45 (m, 10H), 5.80-5.88 (m, 1H), 5.77-5.80 (m, 1H), 4.98 (d, 1H, J = 3.5 Hz), 4.89 (d, 1H, J = 12.5 Hz), 4.67 (d, 1H, J = 12.5 Hz), 4.58 (q, 2H, J = 12.0 Hz), 4.22-4.27 (m, 1H), 4.11-4.12 (m, 1H), 4.05-4.08 (m, 1H).

¹³C NMR (125 MHz, CDCl₃): δ = 138.33, 137.68, 128.38, 128.31, 128.20, 127.76, 127.73, 127.58, 127.36, 123.87, 94.35, 70.97, 70.80, 69.32, 60.54 ppm.

IR (neat): 3029, 2923, 2851, 1736, 1495, 1452 cm⁻¹.

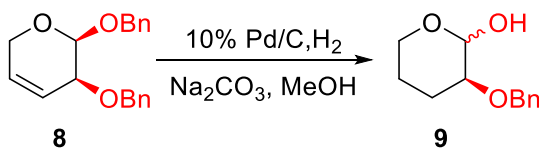
HRMS (ESI-TOF) m/z : $[M+Na]^+$ Calcd. for C₁₉H₂₀O₃Na 319.1305, found: 319.1311.



(2*R*,3*R*)-2,3-bis(benzyloxy)-3,6-dihydro-2*H*-pyran (*ent*-8):

An identical procedure described for **8** was used to synthesize *ent*-8 from *ent*-7.

SOR: $[\alpha]_D^{25}$ = +70.0 (c = 1.0, CHCl₃).



(3*S*)-3-(benzyloxy) tetrahydro-2*H*-pyran-2-ol (9**).**

To a stirred solution of (2*S*,3*S*)-2,3-bis(benzyloxy)-3,6-dihydro-2*H*-pyran **8** (5.0 g, 16.87 mmol) in methanol (100 mL) at rt, was added sodium carbonate (1.78 g, 16.87 mmol). The reaction mixture was stirred for 10 min, then Palladium on activated carbon (10 wt. %) (540 mg) was added under nitrogen atmosphere. After degassing the reaction mixture for 5 min, the stirring was continued under hydrogen atmosphere (using balloon) for 5-6 hr at rt. After

completion of the reaction (monitored by TLC) the suspension was filtered through a small pad of celite, and the filter cake was washed with methanol (20 mL). Evaporation of the methanol under reduced pressure followed by purification of the afforded crude product by flash column chromatography over silica gel (hexanes/ethyl acetate) provided an anomeric mixture of compound **9** (2.70 g, 77 %) as a colourless semisolid.

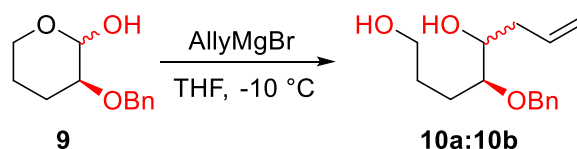
TLC: R_f = 0.60 (50% EtOAc in hexanes).

^1H NMR (500 MHz, CDCl_3): δ = 7.28-7.39 (m, 5H), 4.94-4.96 (m, 0.5H), 4.79-4.81 (m, 0.5H), 4.67-4.69 (m, 1.5H), 4.55 (d, 0.5H, J = 12.0 Hz), 3.95-3.98 (m, 1H), 3.52-3.55 (m, 1.5H), 3.27-3.29 (m, 0.5H), 2.05-2.08 (m, 0.5H), 1.95-2.00 (m, 0.5H), 1.60-1.81 (m, 2H), 1.49-1.55 (m, 1H);

^{13}C NMR (125 MHz, CDCl_3): δ = 138.56, 137.96, 128.51, 128.38, 127.89, 127.82, 127.73, 127.60, 96.69, 92.57, 76.06, 74.44, 71.62, 70.87, 63.57, 62.13, 26.32, 24.39, 23.12, 22.28 ppm.

IR (neat): 3305, 3058, 3030, 2945, 2882, 1718, 1696, 1496, 1452, 1373 cm^{-1} .

HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ Calcd. for $\text{C}_{12}\text{H}_{16}\text{O}_3\text{Na}$ 231.0997, found: 231.0997.



(4S, 5R)-4-(benzyloxy)oct-7-ene-1,5-diol (10a) and (4S,5S)-4-(benzyloxy)oct-7-ene-1,5-diol (10b).

To a stirred solution of compound (3S)-3-(benzyloxy)tetrahydro-2H-pyran-2-ol **9** (1.2 g, 5.76 mmol) in dry THF (30 mL) at -10 °C, was added allylmagnesium bromide (1 M in diethyl ether) (23 mL, 23.05 mmol) dropwise over a period of 20 min. Stirring was continued at -10 °C until the completion of the reaction ~3-4 hr (monitored by TLC). The reaction was quenched by the addition of saturated NH_4Cl solution (20 mL) and the resulting suspension was extracted with ethyl acetate (2 x 50 mL). The combined ethyl acetate layers were washed

with water and brine solution, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the afforded crude product by flash column chromatography over silicagel (hexanes/ethyl acetate) provided an inseparable diastereomeric mixture of diols (**10a:10b**) (1.0 g, 69 %) as a colourless liquid.

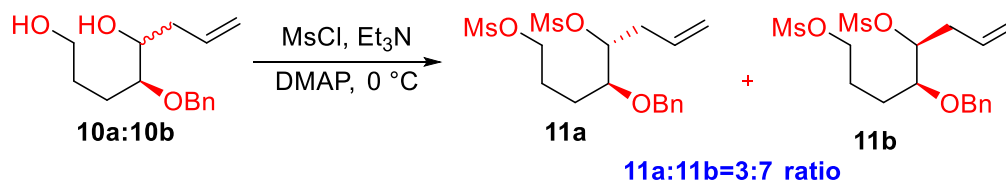
TLC: R_f = 0.30 (50% EtOAc in Hexanes).

¹H NMR (500 MHz, CDCl₃): δ = 7.30-7.37 (m, 5H), 5.83-5.87 (m, 1H), 5.10-5.14 (m, 2H), 4.54-4.67 (m, 2H), 3.82-3.86 (m, 0.36H), 3.68-3.70 (m, 0.64H), 3.61-3.64 (m, 2H), 3.40-3.42 (m, 1H), 2.34-2.36 (m, 1H), 2.25-2.28 (m, 1H), 1.74-1.76 (m, 2H), 1.64-1.68 (m, 2H).

¹³C NMR (125 MHz, CDCl₃): δ = 138.17, 134.93, 134.90, 128.50, 128.48, 127.95, 127.89, 127.84, 117.84, 117.49, 81.47, 81.12, 72.51, 72.04, 71.87, 71.12, 62.76, 37.86, 37.21, 28.47, 28.31, 26.43, 25.40 ppm.

IR (neat): 3370, 2936, 1710, 1640, 1495, 1452 cm⁻¹.

HRMS (ESI-TOF) m/z: [M+Na]⁺ calcd for C₁₅H₂₂O₃Na 273.1467, found: 273.1460.



(4*S*,5*R*)-4-(benzyloxy)oct-7-ene-1,5-diyl dimethanesulfonate (11a) and (4*S*,5*S*)-4-(benzyloxy)oct-7-ene-1,5-diyl dimethanesulfonate (11b).

A stirred solution of the above (4*S*)-4-(benzyloxy)oct-7-ene-1,5-diol mixture (**10a:10b**) (1.0 g, 3.99 mmol) in dry dichloromethane (15 mL) at 0 °C was added triethylamine (1.41 g, 1.95 mL, 13.99 mmol). After 10 min DMAP (25 mg) was added followed by methanesulfonyl chloride (1.60 g, 1.08 mL, 13.99 mmol) dropwise at 0 °C and stirring was continued for 3 hr at the same temperature. After completion of the reaction (monitored by TLC) dichloromethane (20 mL) and satd., NaHCO₃ solution was added successively. The reaction mixture was transferred into a separating funnel, the organic layer was separated and the

aqueous layer was extracted with dichloromethane (2x20 mL). The combined dichloromethane layers were washed with water and brine solution, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the afforded crude product by flash column chromatography over silicagel (hexanes/ethyl acetate) provided an inseparable diastereomeric mixture of compounds **11a:11b** (1.35 g, 83%) as colourless liquid. **TLC:** R_f = 0.70 (50 % EtOAc in Hexanes).

11a (selected data):

¹H NMR (500 MHz, CDCl₃): δ = 7.34-7.38 (m, 5H), 5.17-5.24 (m, 1H), 5.20-5.24 (m, 2H), 4.93-4.96 (m, 1H), 4.77 (d, 1H, *J* = 11.0 Hz), 4.50 (d, 1H, *J* = 11.0 Hz), 4.18-4.21 (m, 2H), 3.60-3.63 (m, 1H), 3.03 (s, 3H), 2.99 (s, 3H), 2.55-2.63 (m, 1H), 2.37-2.44 (m, 1H), 1.95-1.99 (m, 1H), 1.75-1.81 (m, 1H), 1.68-1.73 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 137.42, 132.56, 128.56, 128.30, 128.14, 119.25, 82.63, 78.79, 72.45, 69.62, 38.93, 35.20, 31.53, 25.57, 25.36 ppm.

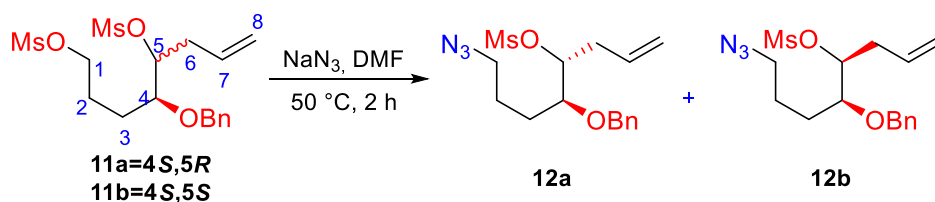
11b (selected data):

¹H NMR (500 MHz, CDCl₃): δ = 7.34-7.38 (m, 5H), 5.17-5.24 (m, 1H), 5.17-5.20 (m, 2H), 4.73-4.77 (m, 1H), 4.65 (d, 1H, *J* = 11.5 Hz), 4.60 (d, 1H, *J* = 11.5 Hz), 4.18-4.21 (m, 2H), 3.68-3.71 (m, 1H), 3.00 (s, 3H), 2.98 (s, 3H), 2.55-2.63 (m, 1H), 2.37-2.44 (m, 1H), 1.87-1.90 (m, 1H), 1.75-1.81 (m, 2H), 1.68-1.73 (m, 1H).

¹³C NMR (125 MHz, CDCl₃): δ = 137.64, 132.83, 128.56, 128.14, 128.11, 119.18, 81.51, 78.34, 72.86, 69.59, 38.61, 37.38, 34.15, 25.33, 25.13 ppm.

IR (neat): 2923, 1712, 1642, 1453, 1346, 1169 cm⁻¹.

HRMS (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₁₇H₂₆O₇S₂Na 429.1012, found: 429.1012.



(4R,5S)-8-azido-5-(benzyloxy)oct-1-en-4-yl methanesulfonate (12a) and **(4S,5S)-8-azido-5-(benzyloxy)oct-1-en-4-yl methanesulfonate (12b)**.

To a stirred solution of compounds **11a** and **11b** (200 mg, 0.49 mmol) in dry DMF (3 mL) was added sodium azide (38 mg, 0.59 mmol) the resultant mixture was stirred at 50 °C for 1 hr. After completion of the reaction, the temperature was brought to room temperature and diluted with ice water. The obtained solution was extracted with ethyl acetate (2 x 20 mL). The combined ethyl acetate layers were washed with water, brine solution, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the afforded crude product by flash column chromatography over silicagel (hexanes/ethyl acetate) provided compound an inseparable diastereomeric mixture of **12a** and **12b**, 3:7 ratio respectively (112 mg, 64%) as colourless liquid.

TLC: R_f = 0.45 (20 % EtOAc in Hexanes).

12a (selected data):

¹H NMR (500 MHz, CDCl₃): δ = 7.32-7.38 (m, 5H), 5.79-5.85 (m, 1H), 5.19-5.24 (m, 2H), 4.93-4.96 (m, 1H), 4.76 (d, 1H, *J* = 11.0 Hz), 4.50 (d, 1H, *J* = 11.0 Hz), 3.57-3.60 (m, 1H), 3.24-3.28 (m, 2H), 3.02 (s, 3H), 2.55-2.61 (m, 1H), 2.38-2.42 (m, 1H), 1.80-1.87 (m, 1H), 1.68-1.76 (m, 1H), 1.58-1.65 (m, 2H).

¹³C NMR (125 MHz, CDCl₃): δ = 137.53, 132.65, 128.54, 128.27, 128.05, 119.14, 82.77, 79.04, 72.42, 51.21, 38.90, 35.26, 26.71, 25.11, ppm.

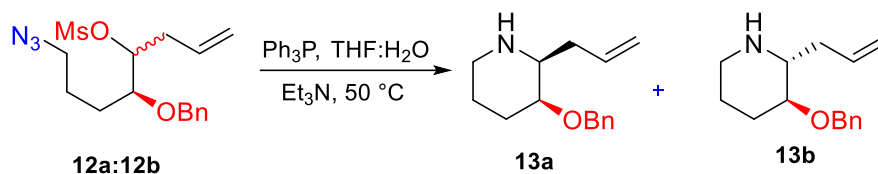
12b (selected data):

¹H-NMR (500 MHz, CDCl₃): δ = 7.32-7.38 (m, 5H), 5.79-5.85 (m, 1H), 5.17-5.21 (m, 2H), 4.72-4.75 (m, 1H), 4.64 (d, 1H, *J* = 11.5 Hz), 4.60 (d, 1H, *J* = 11.5 Hz), 3.65-3.68 (m, 1H), 3.25-3.28 (m, 2H), 2.96 (s, 3H), 2.59-2.63 (m, 1H), 2.42-2.44 (m, 1H), 1.68-1.76 (m, 2H), 1.58-1.65 (m, 2H).

¹³C-NMR (125 MHz, CDCl₃): δ = 137.75, 132.83, 128.54, 128.10, 128.05, 119.12, 81.86, 78.59, 72.84, 51.28, 38.58, 34.40, 26.52, 24.80, ppm.

IR (neat): 3035, 2950, 2092, 1348, 1170, 1067 cm^{-1} .

HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{23}\text{N}_3\text{NaO}_4\text{S}$ 376.1301, found: 376.1306.



(2*S*,3*S*)-2-allyl-3-(benzyloxy)piperidine (13a) and (2*R*,3*S*)-2-allyl-3-benzyloxy)piperidine (13b):

To a stirred solution of diastereomeric mixture of **12a** and **12b**, (300 mg, 0.849 mmol) in dry THF (10 mL) was added triphenylphosphine (0.33 g, 1.27 mmol). After 1 hr, water (0.85 mL, 2.83 vol) was added. After 15 minutes triethylamine (1.0 mL, 3.3 vol) was added to the reaction mixture and stirred at 50-55 °C for 10 hrs. The reaction mixture was diluted with ethyl acetate and washed with water. The combined organic extracts were dried over Na_2SO_4 filtered followed by solvent evaporation under reduced pressure. The obtained crude product that was purified by column chromatography over silica gel (eluted in 2% methanol in chloroform. afforded **13a** (53 mg) and **13b** (126 mg) (13a & 13b, 91%) as colourless semisolid.

Compound 13a:

TLC: R_f = 0.50 (10 % MeOH in CHCl_3).

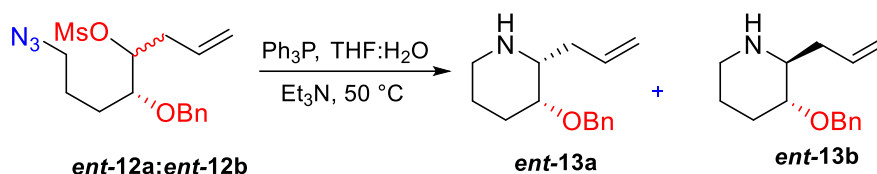
SOR: $[\alpha]_D^{25} = 32.23$ ($c = 1.3$, CHCl_3).

^1H NMR (500 MHz, CDCl_3): δ = 7.25-7.38 (m, 5H), 6.23 (bs, 1H), 5.60-5.70 (m, 1H), 5.03-5.87 (m, 2H), 4.64 (d, 1H, $J = 12.0$ Hz), 4.40 (d, 1H, $J = 12.0$ Hz), 3.58 (s, 1H), 3.29 (d, 1H, $J = 12.8$ Hz), 2.92 (ddd, 1H, $J = 1.6$ Hz, $J = 6.0$ Hz, $J = 8.4$ Hz), 2.78 (td, 1H, $J = 3.2$ Hz, $J = 12.8$ Hz), 2.46-2.54 (m, 2H), 2.10 (dd, 1H, $J = 2.0$ Hz, $J = 14.0$ Hz), 1.86-2.03 (m, 1H), 1.49-1.54 (m, 1H), 1.36-1.44 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 138.04, 133.37, 128.37, 127.78, 127.65, 118.65, 70.55, 70.49, 58.89, 44.91, 34.60, 25.99, 18.58 ppm.

IR (neat): 3393, 2936, 2859, 1640, 1452, 1090, 1064 cm^{-1} .

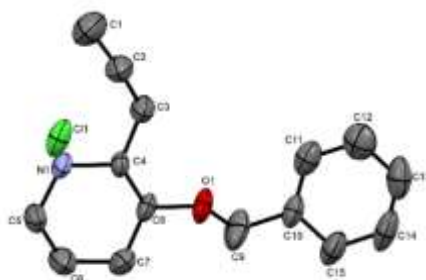
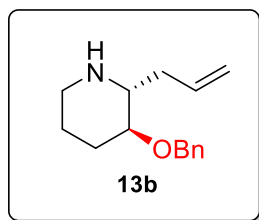
HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{21}\text{NONa}$ 232.1696, found: 232.1697.



(2R,3R)-2-allyl-3-(benzyloxy)piperidine (*ent*-13a):

An identical procedure described for the synthesis of **13a** (from compound **8**), was used to synthesize **ent-13a** from **ent-8**.

SOR: $[\alpha]_D^{25} = -37.33$ ($c = 1.2$, CHCl_3).



The ORTEP diagram of compound **13b**.HCl.

Compound 13b:

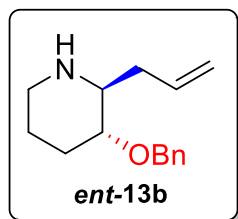
TLC: $R_f = 0.55$ (10 % MeOH in CHCl_3).

SOR: $[\alpha]_D^{25} = 32.22$ ($c = 1.0$, CHCl_3).

^1H NMR (500 MHz, CDCl_3): δ = 7.28-7.37 (m, 5H), 7.17 (bs, 1H), 5.85-5.96 (m, 1H), 5.18-5.25 (m, 2H), 3.55 (td, 1H, $J = 4.0$ Hz, $J = 9.6$ Hz), 3.33 (dt, 1H, $J = 2.4$ Hz, $J = 12.4$ Hz), 2.91-2.96 (m, 1H), 2.73-2.84 (m, 2H), 2.58 (dt, 1H, $J = 7.6$ Hz, $J = 15.6$ Hz), 2.25-2.29 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 137.79, 132.51, 128.49, 127.89, 127.78, 119.85, 75.28, 71.25, 59.57, 44.23, 34.31, 28.40, 21.09 ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{21}\text{NONa}$ 232.1696, found: 232.1697.

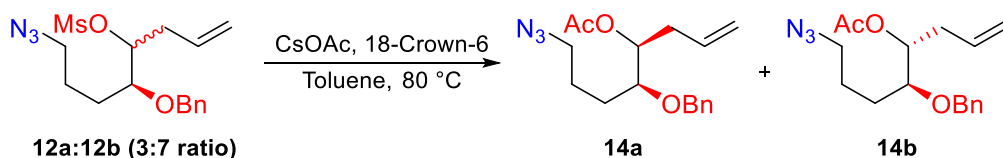


(2*S*,3*R*)-2-allyl-3-(benzyloxy) piperidine (*ent*-13b):

An identical procedure described for the synthesis of **13b** (from compound **8**), was used to synthesize *ent*-**13b** from *ent*-**8**.

SOR: $[\alpha]_D^{25} = -45.32$ ($c = 1.0$, CHCl_3).

Inversion of Stereo centre:



(4*S*,5*S*)-8-azido-5-(benzyloxy)oct-1-en-4-yl acetate (14a) and (4*R*,5*S*)-8-azido-5-(benzyloxy)oct-1-en-4-yl acetate (14b).

To a stirred solution of a diastereomeric mixture of compounds **12a and 12b** (3:7 ratio), (1.0 g, 2.82 mmol) in dry toluene (15 mL) at room temperature was added caesium acetate (1.62 g, 8.48 mmol), followed by 18-crown-6 (1.12 g, 4.21 mmol). The resultant suspension was stirred at 80 °C for 36 hrs. After completion of the reaction (confirmed by TLC) the temperature was brought to 25 °C and a saturated solution of NaHCO_3 and diethyl ether were

added. The organic layer was separated and the aqueous layer was extracted with diethyl ether 2 x 50 mL. The combined ethereal layers were dried over Na₂SO₄, filtered and concentrated. Purification of the afforded crude product by flash column chromatography over silicagel (hexanes/ethyl acetate) provided compound **14a** and **14b** (720 mg, 80% an inseparable mixture of diastereomers) as a colourless liquid.

TLC: R_f = 0.55 (10 % EtOAc in Hexanes).

Compound 14a (selected data):

¹H NMR (500 MHz, CDCl₃): δ = 7.31-7.37 (m, 5H), 5.70-5.78 (m, 1H), 5.16-5.20 (m, 1H), 5.10-5.14 (m, 2H), 4.66 (d, 1H, *J* = 12.0 Hz), 4.59 (d, 1H, *J* = 11.5 Hz), 3.47-3.51 (m, 1H), 3.21-3.30 (m, 2H), 2.30-2.49 (m, 2H), 2.07 (s, 3H), 1.67-1.72 (m, 1H), 1.62-1.65 (m, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 170.63, 138.10, 133.84, 128.45, 128.09, 128.01, 117.75, 78.20, 73.10, 72.51, 51.37, 34.13, 27.06, 25.12, 21.13.

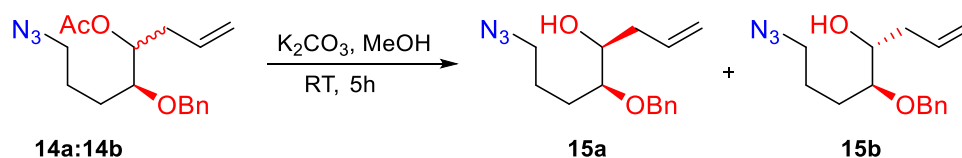
Compound 14b (selected data):

¹H NMR (500 MHz, CDCl₃): δ = 7.31-7.37 (m, 5H), 5.72-5.70 (m, 1H), 5.16-5.20 (m, 1H), 5.06-5.12 (m, 2H), 4.70 (d, 1H, *J* = 11.5 Hz), 4.48 (d, 1H, *J* = 11.5 Hz), 3.47-3.51 (m, 1H), 3.21-3.30 (m, 2H), 2.30-2.49 (m, 2H), 2.08 (s, 3H), 1.78 (m, 1H), 1.62-1.65 (m, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 170.52, 138.05, 133.73, 128.45, 128.09, 127.84, 117.81, 78.86, 73.18, 72.12, 51.37, 34.57, 27.22, 25.02, 21.13.

IR (neat): 3415, 3068, 3030, 2929, 2093, 1733, 1641, 1495, 1452, 1369, 1232, 1067, 1024 cm⁻¹.

HRMS (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₁₇H₂₃N₃NaO₃ 340.1632, found: 340.1582.



(4S,5S)-8-azido-5-(benzyloxy)oct-1-en-4-ol (15a) and (4R,5S)-8-azido-5-(benzyloxy)oct-1-en-4-ol (15b):

A stirred solution of diastereomeric mixture of compounds **14a** and **14b**, (500 mg, 1.57 mmol) in dry methanol (15 mL) was added K₂CO₃ (108 mg, 0.782 mmol). After completion of the reaction (~5 hr, confirmed by TLC) methanol was evaporated under reduced pressure and the crude reaction mixture was subjected to flash column chromatography over silicagel (hexanes/ethyl acetate) provided **15a** and **15b** (400 mg, 92%) an inseparable diastereomeric mixture of alcohols in 7:3 ratio, respectively, as colourless liquid.

TLC: R_f = 0.35 (10 % EtOAc in Hexanes).

Compound **15a** (selected peaks)

¹H NMR (500 MHz, CDCl₃): δ = 7.32-7.38 (m, 5H), 5.83-5.91 (m, 1H), 5.17-5.20 (m, 2H), 4.65 (d, 1H, *J* = 11.5 Hz), 4.57 (d, 1H, *J* = 11.5 Hz), 3.87 (dt, 1H, *J* = 4.5 Hz, *J* = 7.0 Hz), 3.39-3.43 (m, 1H), 3.27-3.32 (m, 2H), 2.23-2.26 (m, 2H), 1.79-1.86 (m, 1H), 1.59-1.79 (m, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 138.10, 134.72, 128.53, 128.51, 127.89, 117.67, 80.67, 72.62, 71.88, 51.58, 37.96, 27.32, 24.69 ppm.

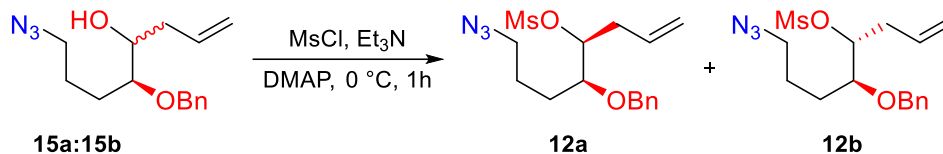
Compound **15b** (selected peaks)

¹H NMR (500 MHz, CDCl₃): δ = 7.32-7.38 (m, 5H), 5.83-5.91 (m, 1H), 5.12-5.17 (m, 2H), 4.65 (d, 1H, *J* = 11.5 Hz), 4.56 (d, 1H, *J* = 11.5 Hz), 3.77 (dt, 1H, *J* = 5.0 Hz, *J* = 7.5 Hz), 3.39-3.43 (m, 1H), 3.23-3.30 (m, 2H), 2.29-2.40 (m, 2H), 1.59-1.79 (m, 4H).

¹³C NMR (125 MHz, CDCl₃): δ = 138.16, 134.69, 128.53, 128.51, 127.93, 118.06, 80.84, 72.06, 70.92, 51.55, 37.13, 26.05, 24.91 ppm.

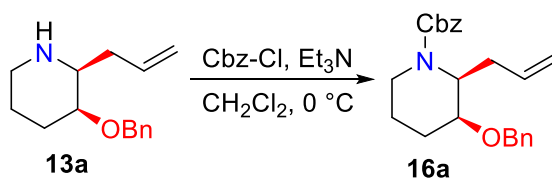
IR (neat): $\tilde{\nu}$ = 3357, 3065, 3029, 2951, 2924, 2866, 2093, 1721, 1639, 1494, 1453, 1070, 737 cm⁻¹.

HRMS (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₁₅H₂₁N₃NaO₂ 298.1526, found: 298.1424.



(4*S*,5*S*)-8-azido-5-(benzyloxy)oct-1-en-4-yl methanesulfonate (12a) and (4*R*,5*S*)-8-azido-5-(benzyloxy)oct-1-en-4-yl methanesulfonate (12b):

To a stirred solution of **15a** and **15b**, (350 mg, 1.27 mmol) in dry dichloromethane (5 mL) at 0 °C was added triethylamine (385 mg, 0.5 mL, 3.81 mmol). After 10 min stirring at this temperature methanesulfonyl chloride (218 mg, 0.15 mL, 1.9 mmol) was added dropwise and stirring was continued for 1 hr at the same temperature. After completion of the reaction (monitored by TLC) dichloromethane (20 mL) and satd., NaHCO₃ solution were added successively. The reaction mass was transferred into a separating funnel, the organic layer was separated and the aqueous layer was extracted with dichloromethane (2x20 mL). The combined dichloromethane layers were washed with water and brine solution, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the afforded crude product by flash column chromatography over silicagel (hexanes/ethyl acetate) provided an inseparable diastereomeric mixture of compounds **12a:12b** (382 mg, 85%) as colourless liquid.



(2*S*,3*S*)-Benzyl 2-allyl-3-(benzyloxy)piperidine-1-carboxylate (16a):

To a stirred solution of compound **13a** (500 mg, 2.16 mmol) in dry dichloromethane (15 mL) and triethyl amine (0.75 mL, 5.4 mmol), DMAP (100 mg) at 0 °C was added benzyl chloroformate (0.46 mL, 3.24 mmol). The reaction mixture was stirred for 2 hr at 0 °C. After

completion of the reaction (by TLC monitoring) it was diluted with dichloromethane (50 mL) and the obtained solution was washed with saturated NaHCO_3 solution, water and brine solution. The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Purification of the obtained crude product by flash column chromatography (hexanes: ethyl acetate) afforded compound **16a** (740 mg, 94%) as colourless liquid.

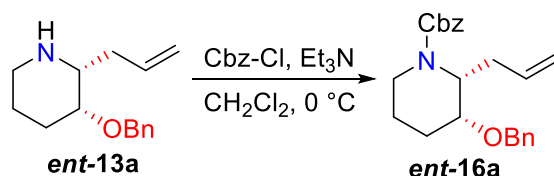
SOR: $[\alpha]_D^{25} = +25.2$ ($c = 1$, CHCl_3).

$^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta = 7.29\text{--}7.35$ (m, 10H), 5.63–5.86 (m, 1H (rotamers)), 4.96–5.20 (m, 4H), 4.55–4.82 (m, 3H), 4.97–4.09 (m, 1H (rotamers), 3.58 (bs, 1H), 2.76–2.86 (m, 1H), 2.43–2.47 (m, 2H), 1.90–1.94 (m, 1H), 1.49–1.77 (m, 4H).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): $\delta = 155.78, 138.33, 136.90, (135.11, 134.96), 127.97, 127.70, 127.63, 127.58, (117.08, 116.86), (75.95, 75.74), 70.53, 67.11, (53.20, 52.46), (38.15, 37.85), 28.55, (25.57, 25.28), (24.46, 23.98)$ ppm (peaks shown in the bracket are rotamers).

IR (neat): 3071, 3029, 2942, 2862, 1690, 1495, 1424, 1348, 1247, 1090 cm^{-1} .

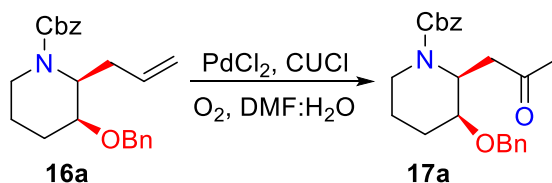
HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{NO}_3$ 366.2064, found: 366.2063.



(2R,3R)-Benzyl 2-allyl-3-(benzyloxy)piperidine-1-carboxylate (*ent*-16a).

An identical procedure described for the synthesis of **16a** (from compound **13a**), was used to synthesize *ent*-**16a** from *ent*-**13a**.

SOR: $[\alpha]_D^{25} = -37.33$ ($c = 1.2$, CHCl_3).



(2S, 3S)-Benzyl 3-(benzyloxy)-2-(2-oxopropyl)piperidine-1-carboxylate (17a):

To a stirred solution of DMF: water (10:1) (3 mL) was added CuCl (203 mg, 2.05 mmol) and palladium chloride (36 mg, 0.205 mmol) at room temperature stir for 1 hr under oxygen atmosphere. Then added Benzyl (2S,3S)-2-allyl-3-(benzyloxy)piperidine-1-carboxylate **16a** (750 mg, 2.05 mmol) in DMF: water (10:1) (2 mL) at rt. stir for 3 hr at same temperature, After completion of the reaction (by TLC monitoring) reaction mixture quenched with 20 % KHSO₄ solution (10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 30 mL). The combined ethereal layers were washed with saturated NaHCO₃ solution and brine solution with dried over Na₂SO₄, filtered and concentrated. Purification of the afforded crude product by flash column chromatography over silicagel (hexanes/ethyl acetate) provided compound *benzyl (2S,3S)-3-(benzyloxy)-2-(2-oxopropyl) piperidine-1-carboxylate* **17a** (700 mg, 89 %) as colourless liquid.

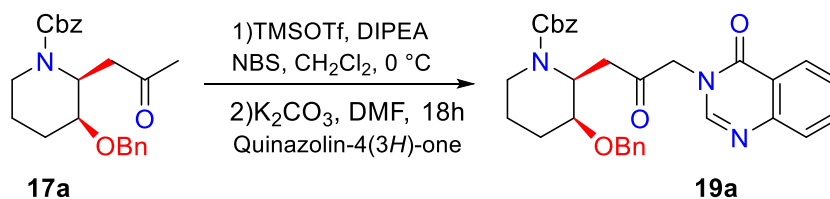
TLC: R_f = 0.2 (20 % EtOAc in Hexanes).

SOR: $[\alpha]_D^{25} = +11.36$ (c 1.0, CHCl₃). IR (neat): 3034, 2940, 2864, 1690, 1496, 1420, 1349, 1305, 1250, 1075 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.28–7.38 (m, 10 H), 5.16–5.23 (m, 3H), 4.55–4.59 (m, 2H), 3.99–4.06 (m, 1H), 3.55 (br s, 1H), 2.54–2.92 (m, 2H), 2.54 (bs, 1H), 2.08 and 2.20 (2 x br s, total 3H), 1.93 (d, 1H, *J* = 9.2 Hz), 1.72 (d, 1H, *J* = 11.2 Hz), 1.32–1.60 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ (rotamers) = 207.16, 206.31, 155.36, 138.16, 136.62, 128.53, 128.48, 128.05, 127.91, 127.76, 127.68, 75.28, 67.39, 50.36, 39.77, 38.69, 30.40, 29.7, 25.55, 24.14, 23.78 ppm. IR (NEAT): 3030, 2944, 2865, 1689, 1496, 1423, 1355, 1307, 1260, 1166, 1047 cm⁻¹.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₃H₂₈NO₄ 382.2013; found: 382.2017.



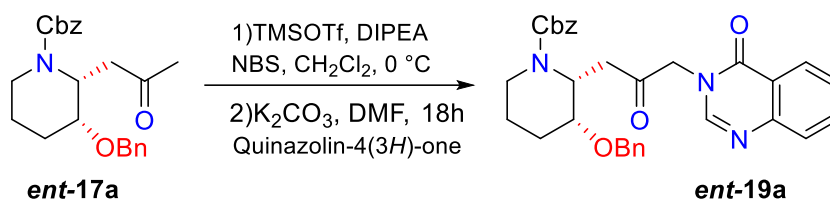
(2S,3S)-benzyl 3-(benzyloxy)-2-(2-oxo-3-(4-oxoquinazolin-3(4H)-yl)propyl)piperidine-1-carboxylate (19a):

To a stirred solution of Benzyl (2R,3S)-3-(benzyloxy)-2-(2-oxopropyl) piperidine-1-carboxylate **17a** (300 mg, 0.78 mmol, 1.0 eq.) in dry dichloromethane (10 mL) was added TMSOTf (350 mg, 0.28 mL, 1.57 mmol) and DIPEA (202 mg, 0.27 mL, 1.57 mmol) under N₂ at 0 °C. The reaction mixture was stirred 1hr at the same temperature. Then added NBS (N-Bromosuccinamide) (279 mg, 1.57 mmol). The reaction mixture was warmed to room temperature and stirred for a further 90 min. After completion of the reaction (confirmed by TLC) the reaction mass poured on ice water (~25 mL) Compound extracted with ethyl acetate (2 x 30 ml). The combined organic layers were washed with water and brine solution, then dried over Na₂SO₄, filtered, and concentrated in *vacuo* to afford the crude brominated intermediate. R_f = 0.55 (30 % EtOAc in Hexanes); To a stirred solution of the crude brominated intermediate in DMF (7 mL) was added quinazolin-4(3H)-one (172 mg, 1.17 mmol, 1.5 eq.) and K₂CO₃ (162 mg, 1.17 mmol, 1.5 eq). The reaction mixture was stirred at room temperature for 16 h. The resultant mixture was diluted with EtOAc (20 mL), washed with water (10 mL), and back extracted with EtOAc (20 mL). The combined organic layers were washed with brine (20 mL), The combined organic extracts were dried over NaSO₄ Filtration followed by solvent evaporation under reduced pressure afforded the crude product. Purification by flash column chromatography using silica gel (Hexanes-EtOAc) afforded the compound **19a** (145 mg, 35%) **TLC:** R_f = 0.6 (80 % EtOAc in Hexanes).

SOR: $[\alpha]_D^{25} = +34.6$ (c = 1.25, CHCl₃).

¹H NMR (500 MHz, CDCl₃) (rotamers): δ = 8.28 (bs, 1H), 7.75-7.78 (m, 3H), 7.50-7.53 (m, 1H), 7.30–7.37 (m, 10H), 5.01–5.15 (m, 4H), 4.79 (m, 1H), 4.48-4.58 (m, 2H), 3.99-4.12 (m, 1H), 3.63 (m, 1H), 3.12 (m, 1H), 2.53-2.78 (m, 2H), 2.00 (m, 1H), 1.75 (m, 1H), 1.53 (m, 2H). **¹³C NMR (125 MHz, CDCl₃) (rotamers):** δ = 200.89, 162.44, 160.87, 155.86, 148.15, 146.76, 137.80, 136.20, 134.26, 128.55, 128.45, 128.03, 127.78, 127.68, 127.48, 126.62, 121.78, 75.32, 70.98, 67.53, 53.66, 50.90, 38.69, 36.62, 25.03, 23.66.

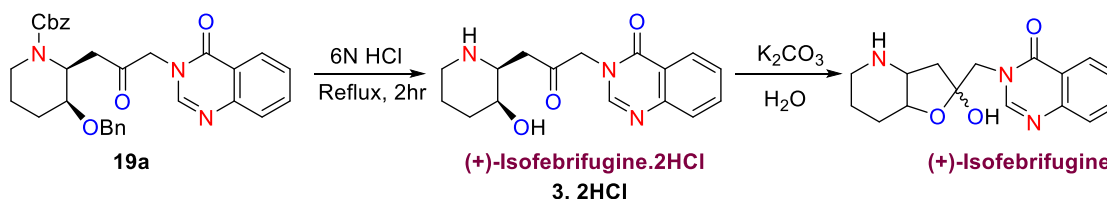
HRMS (ESI-TOF) m/z : $[M+H]^+$ calcd for $C_{31}H_{32}N_3O_5$ 526.2336; found: 526.2335.



(2*R*,3*R*)-benzyl 3-(benzyloxy)-2-(2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)propyl)piperidine-1-carboxylate (**ent-19a**).

An identical procedure described for the synthesis of **19a** (from compound **17a**), was used to synthesize **ent-19a** from **ent-17a**.

SOR: $[\alpha]_D^{25} = -49.2$ ($c = 0.875$, $CHCl_3$).



(+)-isofebrifugine .2HCl. (3 .2HCl).

A solution of benzyl (2*S*,3*S*)-3-(benzyloxy)-2-(2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl) propyl) piperidine-1-carboxylate **19a** (120 mg, 0.22 mmol) in 6 N HCl (7 mL) was stirred at reflux for 2 h. The solvent was removed under reduced pressure and recrystallization of the residue from ethanol provided (+)-isofebrifugine.2HCl (**3 .2HCl**) (35 mg, 40%) as a white solid. The obtained salt was dissolved in water pH was adjusted to 9 using K_2CO_3 solution and extracted with chloroform (2 x 10 mL). The combined extracts were concentrated and purified by flash column chromatography to obtain the (+)-isofebrifugine (free base) as a white solid. (15 mg).

SOR: $[\alpha]_D^{25} = 69.07$ ($c = 0.38$, $CHCl_3$) {Lit.^{8r} $[\alpha]_D^{25} = 75.6$ ($c = 0.50$, $CHCl_3$)}

^1H NMR (500 MHz, $CDCl_3$); $\delta = 8.30$ -8.32 (m, 2H), 7.70-7.78 (m, 2H), 7.50 (ddd, 1H, $J = 1.0$ Hz, $J = 7.0$ Hz, $J = 8.0$ Hz), 4.46 (d, 1H, $J = 14.0$ Hz), 4.16 (d, 1H, $J = 14.0$ Hz), 3.88-

3.89 (m, 1H), 3.29 (t, 1H, $J = 3.0$ Hz), 2.97-3.00 (m, 1H), 2.51-2.56 (m, 1H), 2.06-2.14 (m, 2H), 1.78-1.90 (m, 2H), 1.51-1.58 (m, 2H) ppm.

^{13}C NMR (125 MHz, CDCl_3): 161.46, 148.22, 148.05, 134.33, 127.50, 127.09, 126.88, 121.90, 105.47, 77.79, 55.70, 49.83, 44.55, 43.34, 26.82, 20.11 ppm.

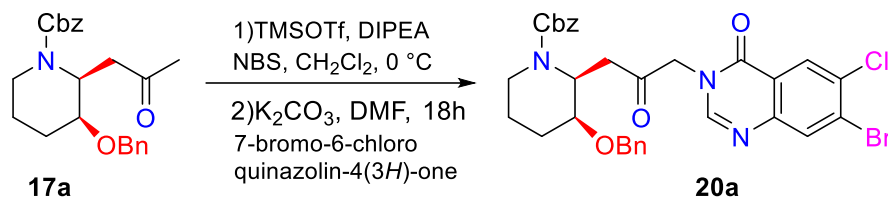
HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_3$: 302.1499; found: 302.1497.

Analytical data of the synthesized one is in accordance with the reported natural product.

(-)-Isofebrifugine .2HCl (*ent*-3 .2HCl).

An identical procedure described for the synthesis of **20a** (from compound **19a**), was used to synthesize *ent*-3 from *ent*-19a. The obtained salt was further converted to (-)-Isofebrifugine (free base) as reported above.

SOR: $[\alpha]_D^{25} = -56.60$ ($c = 0.25$, CHCl_3).



Benzyl(3*S*)-3-(benzyloxy)-2-(3-(7-bromo-6-chloro-4-oxoquinazolin-3(4*H*)-yl)-2-oxopropyl) piperidine-1-carboxylate (20a**):**

A stirred solution of benzyl (2*R*,3*S*)-benzyl 3-(benzyloxy)-2-(2-oxopropyl)piperidine-1-carboxylate (**17a**) (100 mg, 0.262 mmol) in dry dichloromethane (5 mL) was added TMSOTf (116 mg, 0.1 mL, 0.502 mmol, 1.99 eq.) and DIPEA (67 mg, 0.18 mL, 0.518 mmol, 2.0 eq.). The resultant mixture was stirred at 0 °C for 60 min. then added NBS (102 mg, 0.573 mmol, 2.0 eq). stir for 1 hr rt. The resultant mixture was poured on ice (20 ml) extract with ethyl acetate (2 x 20 mL) and combined organic layers and washed with water and brine solution, dried over Na_2SO_4 , filtered, and concentrated in *vacuo* to afford the crude brominated intermediate. $R_f = 0.55$ (30% EtOAc-hexanes); To a stirred solution of the crude brominated intermediate in DMF (5 mL) was added 7-bromo-6-chloroquinazolin-4(3*H*)-one (85 mg, 0.32

mmol, 1.5 eq.) and K_2CO_3 (45 mg, 0.32 mmol, 1.5 eq.). The reaction mixture was stirred at room temperature for 16 h. The resultant mixture was diluted with EtOAc (20 mL), washed with water (10 mL), and back extracted with EtOAc (20 mL). The combined organic layers were washed with brine (20 mL). The combined organic extracts were dried over $NaSO_4$. Filtration followed by solvent evaporation under reduced pressure afforded the crude product. Purification by flash column chromatography using silica gel (Hexanes-EtOAc) afforded the compound **20a** (68 mg, 40%).

TLC: R_f = 0.6 (80 % EtOAc in Hexanes).

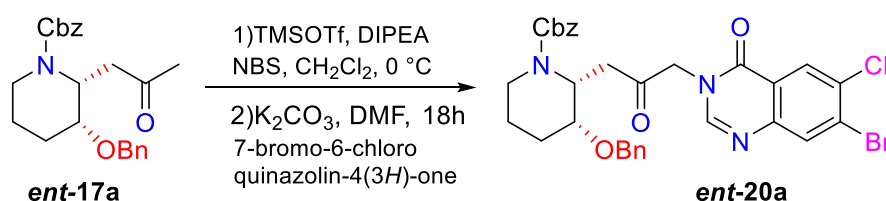
SOR: $[\alpha]_D^{25} = 24.8$ ($c = 0.75$, $CHCl_3$).

^1H NMR (400 MHz, DMSO- d_6 , 333 K): δ = 8.18 (s, 1H) 8.09 (s, 1H) 8.04 (s, 1H), 7.31-7.32 (m, 10H), 4.99-5.12 (m, 5H), 4.55 (d, 1H, $J = 12.4$ Hz), 4.50 (d, 1H, $J = 12.4$ Hz), 3.87 (d, 1H, $J = 13.2$ Hz), 3.50-3.52 (m, 1H), 3.07 (dd, 1H, $J = 4.8$ Hz, $J = 16.0$ Hz), 2.84-2.91 (m, 2H), 1.87-1.89 (m, 1H), 1.66-1.69 (m, 1H), 1.52-1.62 (m, 1H), 1.32-1.36 (m, 1H) ppm.

^{13}C NMR (100 MHz, DMSO- d_6 , 333 K): δ 201.62, 159.10, 155.09, 149.94, 147.81, 138.86, 137.37, 132.87, 132.24, 128.77, 128.68, 128.14, 127.88, 127.77, 127.45, 122.36, 79.62, 75.32, 70.26, 66.94, 54.84, 50.35, 38.92, 36.40, 29.39, 25.41, 24.03 ppm.

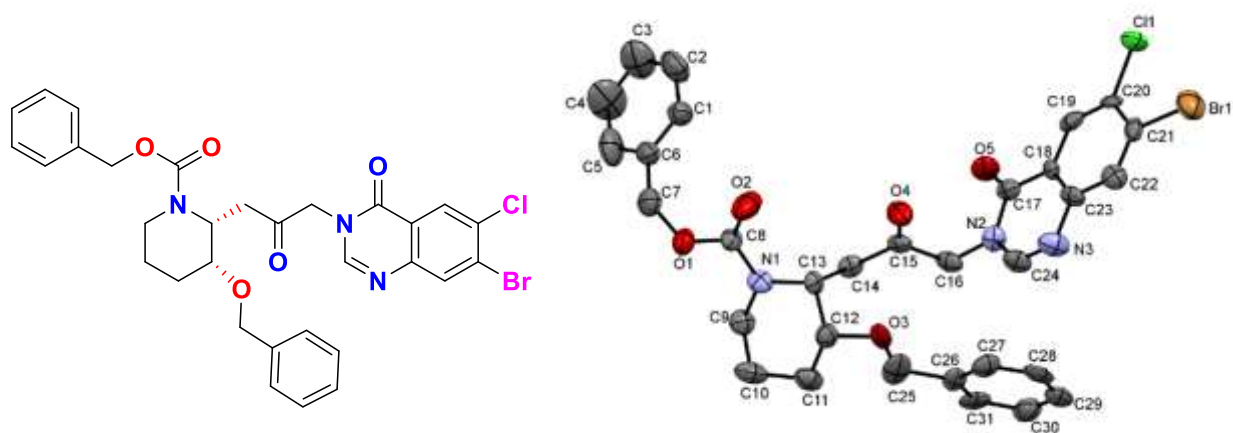
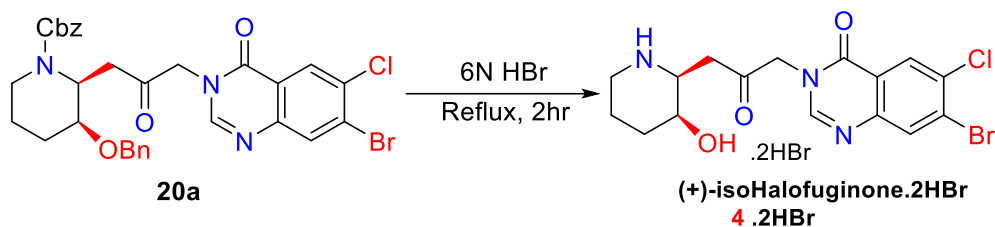
IR (neat) 3065, 2954, 2872, 1730, 1679, 1601, 1493, 1444, 1355, 1261, 1081 cm^{-1} .

HRMS (ESI-TOF) m/z : $[M+H]^+$ calcd for $C_{31}H_{30}BrClN_3O_5$ 638.1057, found 638.1059.



Benzyl (2*R*,3*R*)-3-(benzyloxy)-2-(3-(7-bromo-6-chloro-4-oxoquinazolin-3(4*H*)-yl)-2-oxopropyl) piperidine-1-carboxylate (*ent*-20a).

An identical procedure described for the synthesis of **21a** (from compound **17a**), was used to synthesize *ent*-20a from *ent*-17a. $[\alpha]_D^{25} = -25.4$ ($c = 1.0$, $CHCl_3$). (The crystal structure of compound *ent*-20a is also provided).

ORTEP diagram of compound **ent-21a****(+)-isoHalofuginone & (-)-isoHalofuginone.****(+)-isoHalofuginone.2HBr (4.2HBr):**

A solution of benzyl (2*S*,3*S*)-3-(benzyloxy)-2-(3-(7-bromo-6-chloro-4-oxoquinazolin-3(4*H*)-yl)-2-oxopropyl) piperidine-1-carboxylate **20a** (120 mg, 0.18 mmol) in aqueous HBr (6 M, 10 mL), was stirred at reflux for 2 h. The solvent was removed under reduced pressure and recrystallization of the residue from ethanol provided (+)-isohalofuginone .2HBr (**4.2HBr**) (56 mg, 51%).

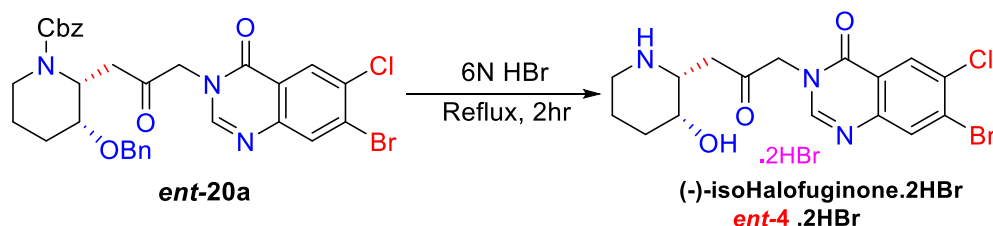
SOR: $[\alpha]_D^{25} = 25.7$ ($c = 0.5$, (CH₃)₂SO).

¹H NMR (500 MHz, DMSO-*d*₆): δ : 8.57-8.64 (m, 2H), 8.27 (s, 1H), 8.23 (s, 1H), 8.19 (s, 1H), 5.03-5.12 (m, 2H), 3.46-3.50 (m, 1H), 3.30-3.33 (m, 1H), 3.23 (dd, 1H, $J = 5.5$ Hz, $J =$

17.5 Hz), 3.14-3.17 (m, 1H), 2.87-2.93 (m, 2H), 1.90-1.93 (m, 1H), 1.80-1.83 (m, 1H), 1.57-1.62 (m, 1H), 1.41-1.49 (m, 1H) ppm.

^{13}C NMR (125 MHz, DMSO- d_6): δ (ppm): 201.24, 159.27, 149.97, 147.59, 132.81, 132.46, 129.04, 127.37, 122.13, 67.24, 56.56, 54.89, 43.60, 39.50, 30.85, 20.54 ppm.

HRMS (ESI-TOF) m/z : $[M+H]^+$ calcd for $\text{C}_{16}\text{H}_{18}\text{BrClN}_3\text{O}_3$ 414.0215, Found: 414.0215.

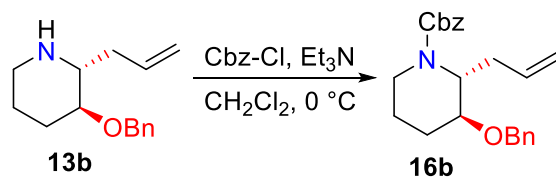


(-)-isoHalofuginone.2HBr (ent-4 .2HBr)

An identical procedure described for the synthesis of **22a** (from compound **20a**), was used to synthesize (-)-isohalofuginone .2HBr (**ent-4 .2HBr**) from **ent-21a**.

SOR: $[\alpha]_D^{25} = -22.7$ ($c = 0.5$, $(\text{CH}_3)_2\text{SO}$).

(+)-Febrifugine And (-)-Febrifugine:



(2R,3S)-Benzyl 2-allyl-3-(benzyloxy) piperidine-1-carboxylate (16b):

SOR: $[\alpha]_D^{25} = -22$ ($c = 1.55$, CHCl_3).

^1H NMR (400 MHz, CDCl_3): $\delta = 7.27$ -7.34 (m, 10H), 5.63-5.86 (m, 1H), 5.02-5.16 (m, 4H), 4.47-4.66 (m, 3H), 4.05-4.25 (m, 1H), 3.48 (bs, 1H), 2.91 (t, 1H, $J = 12.0$ Hz), 2.38-2.46 (m, 1H), 2.17-2.30 (m, 1H), 1.189-1.97 (m, 2H), 1.67-1.75 (m, 2H), 1.37-1.50 (m, 1H).

^{13}C -NMR (100 MHz, CDCl_3): δ = 156.20, 138.69, 137.09, 134.41, 128.42, 128.32, 127.79, 127.72, 127.41, 117.31, 73.30, 70.04, 66.93, 52.45, 38.89, 33.83, 23.92, 19.60 ppm.

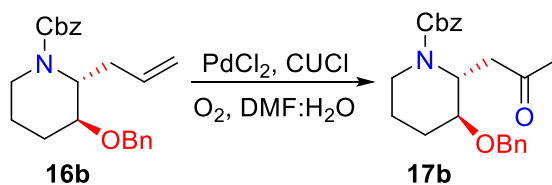
IR (neat): 3069, 3030, 2944, 2865, 1689, 1496, 1423, 1355, 1260, 1166, 1047 cm^{-1} .

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{NO}_3$ 366.2064, found: 366.2063.

(2S,3R)-Benzyl 2-allyl-3-(benzyloxy) piperidine-1-carboxylate (*ent*-16b).

An identical procedure described for the synthesis of **16b** (from compound **13b**), was used to synthesize *ent*-**16b** from *ent*-**13b**.

SOR: $[\alpha]_D^{25} = +12.0$ ($c = 0.5$, CHCl_3).

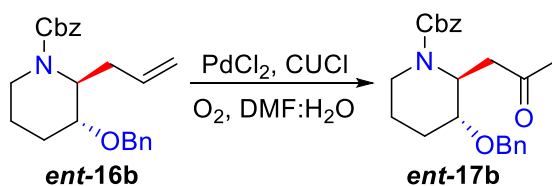


(2R,3S)-benzyl 3-(benzyloxy)-2-(2-oxopropyl) piperidine-1-carboxylate (17b):

SOR: $[\alpha]_D^{25} = -17.66$ ($c = 1.0$, CHCl_3).

^1H NMR (500 MHz, CDCl_3): δ = 7.26–7.33 (m, 10H), 5.11–5.14 (m, 2H), 5.01 (bs, 1H), 4.62–4.73 (m, 1H), 4.53 (d, 1H, $J = 10.0$ Hz), 4.08–4.16 (m, 1H), 3.44 (br s, 1H), 2.86 (br s, 1H), 2.61–2.71 (m, 2H), 2.06–2.17 (m, 3H), 1.87–1.93 (m, 2H), 1.61–1.74 (m, 2H), 1.42 (br s, 1H). **^{13}C NMR (125 MHz, CDCl_3):** δ = 205.9, 155.91, 138.61, 136.79, 128.45, 128.30, 127.89, 127.77, 127.42, 73.28, 70.21, 67.17, 49.73, 43.71, 39.54, 30.02, 24.42, 19.52 ppm. IR (NEAT): 3034, 2940, 2864, 1690, 1496, 1420, 1349, 1305, 1250, 1075 cm^{-1} .

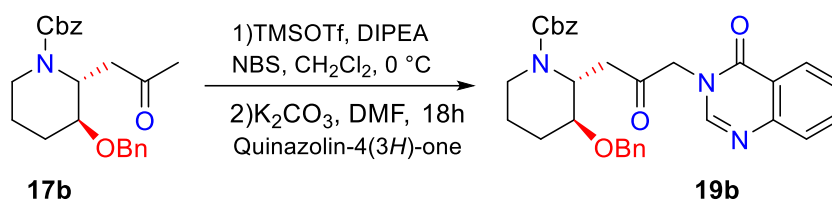
HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{NO}_4$ calcd: 382.2013; found: 382.2017.



(2*S*,3*R*)-benzyl 3-(benzyloxy)-2-(2-oxopropyl) piperidine-1-carboxylate (*ent*-17b).

An identical procedure described for the synthesis of **17b** (from compound **16b**), was used to synthesize *ent*-**17b** from *ent*-**16b**.

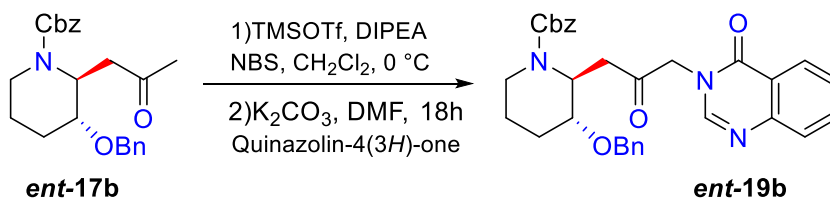
SOR: $[\alpha]_D^{25} = 17.05$ ($c = 0.55$, CHCl_3).

**(2*R*,3*S*)-benzyl 3-(benzyloxy)-2-(2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)propyl)piperidine-1-carboxylate (**19b**):**

^1H NMR (500 MHz, CDCl_3): $\delta = 8.27$ (dd, 1H, $J = 1.5$ Hz, $J = 8.0$ Hz), 7.71-7.84 (m, 3H), 7.50-7.53 (m, 1H), 7.28-7.30 (m, 10H), 5.18 (d, 1H, $J = 12.5$ Hz), 5.12 (d, 1H, $J = 12.5$ Hz), 5.01 (t, 1H, $J = 7.0$ Hz), 4.95 (bs, 1H), 4.66 (d, 1H, $J = 12.0$ Hz), 4.54 (d, 1H, $J = 11.5$ Hz), 4.07 (br s, 1H), 3.53 (br s, 1H), 2.99 (br s, 1H), 2.86 (dd, 1H, $J = 7.0$ Hz, $J = 14.5$ Hz), 2.77-2.81 (m, 1H), 1.86-1.93 (m, 2H), 1.64-1.71 (m, 1H), 1.44-1.46 (m, 1H).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 200.09$, 160.98, 154.6, 148.27, 146.56, 138.30, 136.52, 134.73, 134.52, 128.54, 128.40, 128.36, 128.26, 128.06, 127.67, 127.37, 126.70, 121.81, 73.68, 70.44, 67.43, 53.94, 51.1, 40.96, 39.57, 24.30, 19.41.

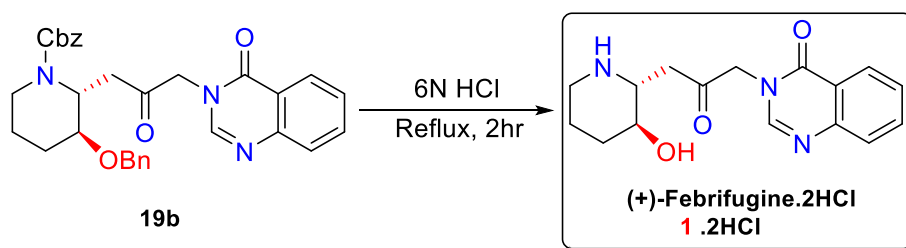
HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{31}\text{H}_{32}\text{N}_3\text{O}_5$ 526.2336; found: 526.2338.



(2S,3R)-benzyl 3-(benzyloxy)-2-(2-oxo-3-(4-oxoquinazolin-3(4H)-yl)propyl)piperidine-1-carboxylate (*ent*-19b):

An identical procedure described for the synthesis of **19b** (from compound **17b**), was used to synthesize *ent*-**19b** from *ent*-**17b**.

SOR: $[\alpha]_D^{25} = +39.0$ ($c = 1.0$, CHCl_3).



(+)-Febrifugine .2HCl (1 .2HCl).

A solution of benzyl (2*R*,3*S*)-3-(benzyloxy)-2-(2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl) propyl) piperidine-1-carboxylate **19b** (150 mg, 0.28 mmol) in 6 N HCl (7 mL) was stirred at reflux for 2 h. The solvent was removed under reduced pressure and recrystallization of the residue from ethanol provided (+)-Febrifugine.2HCl (**1** .2HCl) (53 mg, 50%) as a white solid.

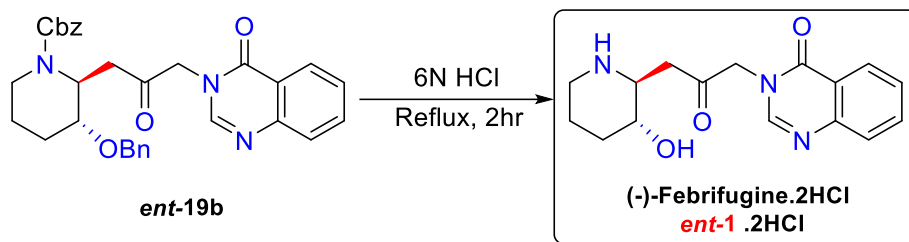
SOR: $[\alpha]_D^{25} = 20.5$ ($c = 0.1$, EtOH), {Lit.⁷: $[\alpha]_D^{25} = 26.6$ ($c = 0.1$, EtOH)}.

¹H NMR (500 MHz, CD₃OD): $\delta = 9.07$ (s, 1H), 8.34 (dd, 1H, $J = 1.5$ Hz, $J = 8.5$ Hz) 8.04 (td, 1H, $J = 1.5$ Hz, $J = 8.5$ Hz), 7.80 (d, 1H, $J = 8.5$ Hz), 7.75 (t, 1H, $J = 8.0$ Hz), 5.27 (d, 1H, $J = 17.5$ Hz), 5.23 (d, 1H, $J = 17.5$ Hz), 3.44-3.53 (m, 2H), 3.32-3.34 (m, 1H), 3.13 (dd, 1H, $J = 7.0$ Hz, $J = 17.5$ Hz), 3.03 (td, 1H, $J = 3.5$ Hz, $J = 12.5$ Hz), 2.10-2.14 (m, 1H), 2.00-2.06 (m, 1H), 1.76-1.85 (m, 1H), 1.57-1.66 (m, 1H) ppm.

¹³C NMR (125 MHz, CD₃OD): δ 201.38, 160.40, 151.46, 142.67, 137.45, 130.41, 128.47, 123.89, 121.73, 68.29, 58.10, 56.30, 44.93, 40.08, 31.62, 21.44 ppm. IR (neat): 3371, 2948, 2805, 1719, 1659, 1612 cm^{-1} .

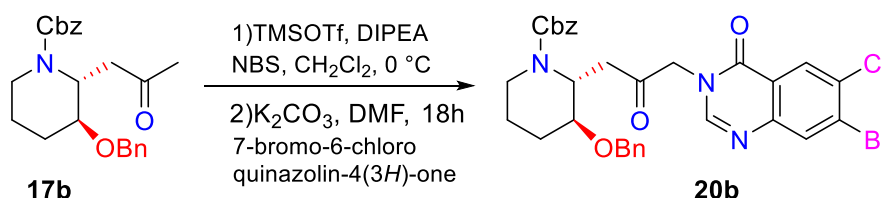
HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{20}\text{N}_3\text{O}_3$ 302.1499; found: 302.1499.

Analytical data of the synthesized one is in accordance with the reported natural product.

**(-)-Febrifugine .2HCl (ent-1 .2HCl).**

An identical procedure described for the synthesis of **1 .2HCl** (from compound **19b**), was used to synthesize (-)-febrifugine 2.HCl (**ent-1 .2HCl**) from **ent-19b**.

SOR: $[\alpha]_D^{25} = -28.60$ ($c = 0.8$, EtOH). {Lit.^{8r} $[\alpha]_D^{25} = -18.3$ ($c = 0.5$, EtOH)}.

(+)-Halofuginone and (-)-Halofuginone:**(2R,3S)-benzyl 3-(benzyloxy)-2-(3-(7-bromo-6-chloro-4-oxoquinazolin-3(4H)-yl)-2-oxopropyl)piperidine-1-carboxylate (20b):**

A stirred solution of benzyl (2R,3S)-benzyl 3-(benzyloxy)-2-(2-oxopropyl)piperidine-1-carboxylate (**17b**) (200 mg, 0.52 mmol) in dry dichloromethane (5 mL) was added TMSOTf (231.8 mg, 0.188 mL, 1.04 mmol, 1.99 eq.) and DIPEA (135 mg, 0.18 mL, 1.046 mmol, 2.0 eq.). The resultant mixture was stirred at 0 °C for 60 min. then added NBS (186 mg, 1.048 mmol, 2.0 eq). stir for 1 hr rt. The resultant mixture was poured on ice (20 ml) extract with ethyl acetate (2 x 20 mL) and combined organic layers and washed with water and brine solution, dried over Na₂SO₄, filtered, and concentrated in *vacuo* to afford the crude

brominated intermediate. $R_f = 0.55$ (30% EtOAc-hexanes); To a stirred solution of the crude brominated intermediate in DMF (7 mL) was added 7-bromo-6-chloroquinazolin-4(3*H*)-one (203 mg, 0.78 mmol, 1.5 eq.) and K_2CO_3 (108 mg, 0.78 mmol, 1.5 eq.). The reaction mixture was stirred at room temperature for 16 h. The resultant mixture was diluted with EtOAc (20 mL), washed with water (10 mL), and back extracted with EtOAc (20 mL). The combined organic layers were washed with brine (20 mL), The combined organic extracts were dried over $NaSO_4$ Filtration followed by solvent evaporation under reduced pressure afforded the crude product. Purification by flash column chromatography using silica gel (Hexanes-EtOAc) afforded the compound **20b** (205 mg, 49%).

TLC: $R_f = 0.6$ (80 % EtOAc in Hexanes).

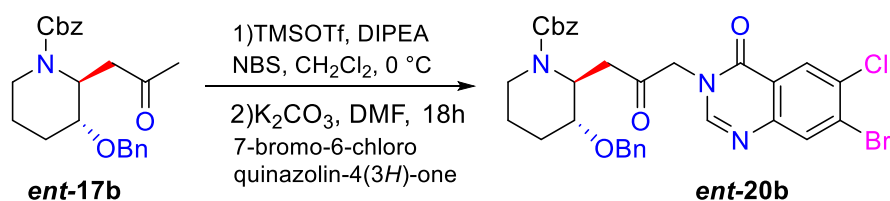
SOR: $[\alpha]_D^{25} = -22.7$ ($c = 1.00$, $CHCl_3$); Lit. $[\alpha]_D^{25} = -29.3$ ($c = 1.00$, $CHCl_3$);

^1H NMR (400 MHz, $CDCl_3$, T = 323 K): $\delta = 8.30$ (s, 1H) 8.05 (s, 1H) 7.77 (s(br), 1H), 7.27-7.33 (m, 10H), 5.18 (d, 1H, $J = 12.4$ Hz), 5.12 (d, 1H, $J = 12.4$ Hz). 4.95 (t, 1H, $J = 8.4$ Hz), 4.81 (s(br), 2H), 4.64 (d, 1H, $J = 12.0$ Hz), 4.55 (d, 1H, $J = 12.0$ Hz), 4.08 (d, 1H, $J = 13.2$ Hz), 3.52 (d, 1H, $J = 2.4$ Hz), 3.00 (t, 1H, $J = 12.4$ Hz), 2.86 (dd, 1H, $J = 8.8$ Hz, $J = 14.4$ Hz), 2.75 (dd, 1H, $J = 6.0$ Hz, $J = 14.4$ Hz), 1.89-2.03 (m, 2H), 1.64-1.72 (m, 1H), 1.47-1.48 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$, T = 323 K): 199.45, 159.48, 156.29, 147.70, 147.30, 138.30, 136.58, 133.58, 132.84, 129.44, 128.49, 128.44, 128.35, 128.01, 127.72, 127.57, 127.50, 121.90, 73.90, 70.52, 67.42, 53.82, 51.08, 41.07, 39.65, 24.33, 19.43 ppm.

IR (neat) 3021, 2957, 2859, 1679, 1605, 1447, 1424, 1381 cm^{-1} .

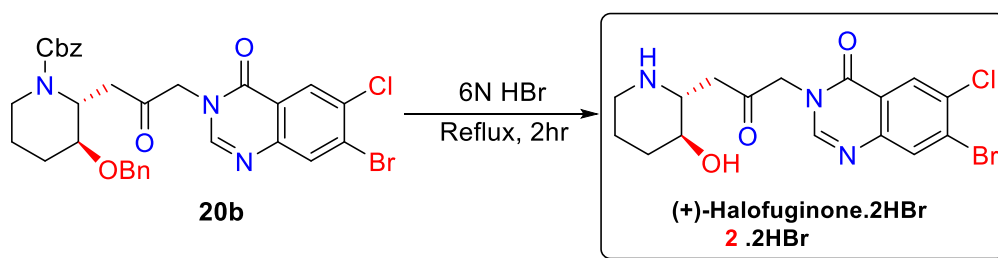
HRMS (ESI-TOF) m/z : $[M+H]^+$ calcd for $C_{31}H_{30}BrClN_3O_5$ 638.1052, found 638.1055.



Benzyl (2*S*,3*R*)-3-(benzyloxy)-2-(3-(7-bromo-6-chloro-4-oxoquinazolin-3(4*H*)-yl)-2-oxopropyl)piperidine-1-carboxylate (*ent*-20*b*).

An identical procedure described for the synthesis of **20*b*** (from compound **17*b***), was used to synthesize *ent*-20*b* from *ent*-17*b*.

SOR: $[\alpha]_D^{25} = -20.4$ ($c = 1.0$, CHCl_3).



(+)-Halofuginone.2HBr (2.2HBr):

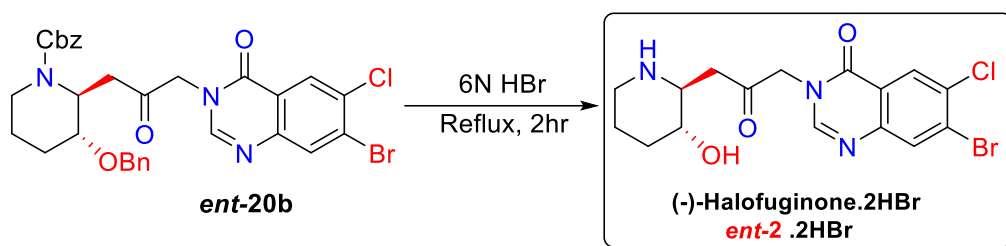
A solution of benzyl (2*R*,3*S*)-3-(benzyloxy)-2-(3-(7-bromo-6-chloro-4-oxoquinazolin-3(4*H*)-yl)-2-oxopropyl) piperidine-1-carboxylate **20*b*** (150 mg, 0.23 mmol) in aqueous HBr (6 M, 10 mL), was stirred at reflux for 2 h. The solvent was removed under reduced pressure and recrystallization of the residue from ethanol provided (+)-halofuginone .2HBr (**2.2HBr**) (70 mg, 51%).

SOR: $[\alpha]_D^{25} = 12.7$ ($c = 0.5$, $(\text{CH}_3)_2\text{SO}$) {Lit:^{8q}. $[\alpha]_D^{25} = 7.3$ ($c = 0.5$, $(\text{CH}_3)_2\text{SO}$)}.

¹H NMR (500 MHz, DMSO-*d*₆), δ (ppm): 8.69 (m, 2H), 8.29 (s, 1H), 8.21 (s, 1H), 8.17 (s, 1H), 5.12 (d, 1H, $J = 18.0$ Hz), 5.07 (d, 1H, $J = 18.0$ Hz), 3.49-3.52 (m, 1H), 3.32 (bs, 1H), 3.23 (dd, 1H, $J = 2.5$ Hz, $J = 17.5$ Hz), 3.15 (d, 1H, $J = 12.0$ Hz), 2.92-2.94 (m, 1H), 2.89-2.90 (m, 1H), 1.91-1.93 (m, 1H), 1.79-1.82 (m, 1H), 1.61-1.64 (m, 1H), 1.42-1.48 (m, 1H).

¹³C NMR (125 MHz, DMSO-*d*₆), δ (ppm): 200.68, 158.64, 149.52, 147.22, 132.40, 131.79, 128.41, 126.84, 121.71, 66.70, 56.13, 54.36, 42.99, 39.02, 30.47, 20.10. IR (neat), ν (cm⁻¹): 3322, 3189, 2936, 2810, 1727, 1677.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{18}\text{BrClN}_3\text{O}_3$ 414.0215, Found: 414.0215.



(-)-Halofuginone.2HBr (ent-2 .2HBr).

An identical procedure described for the synthesis of **22b** (from compound **20b**), was used to synthesize (-)-halofuginone .2HBr (**ent-2 .2HBr**) from **ent-20b**.

SOR: $[\alpha]_D^{25} = -17.2$ ($c = 0.5$, $(CH_3)_2SO$) {Lit: $[\alpha]_D^{25} : -11.2$ ($c = 0.5$, $(CH_3)_2SO$)}.

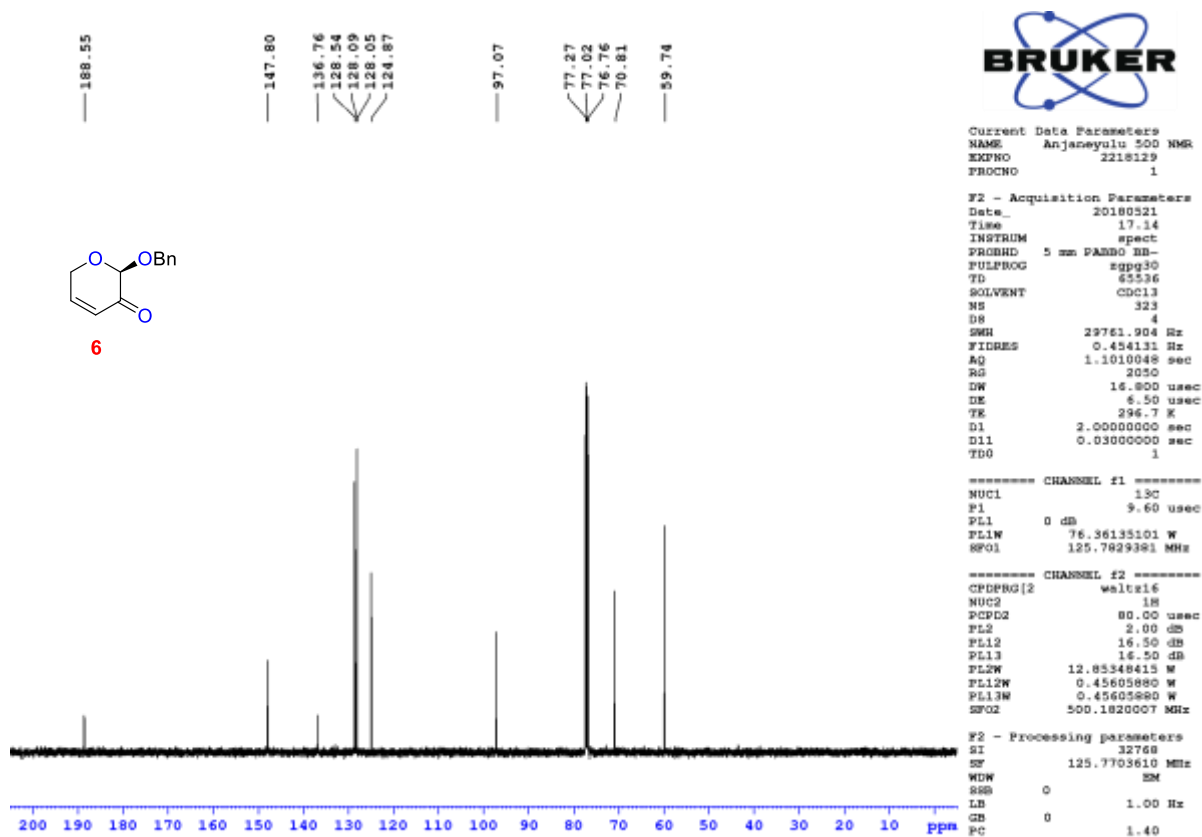
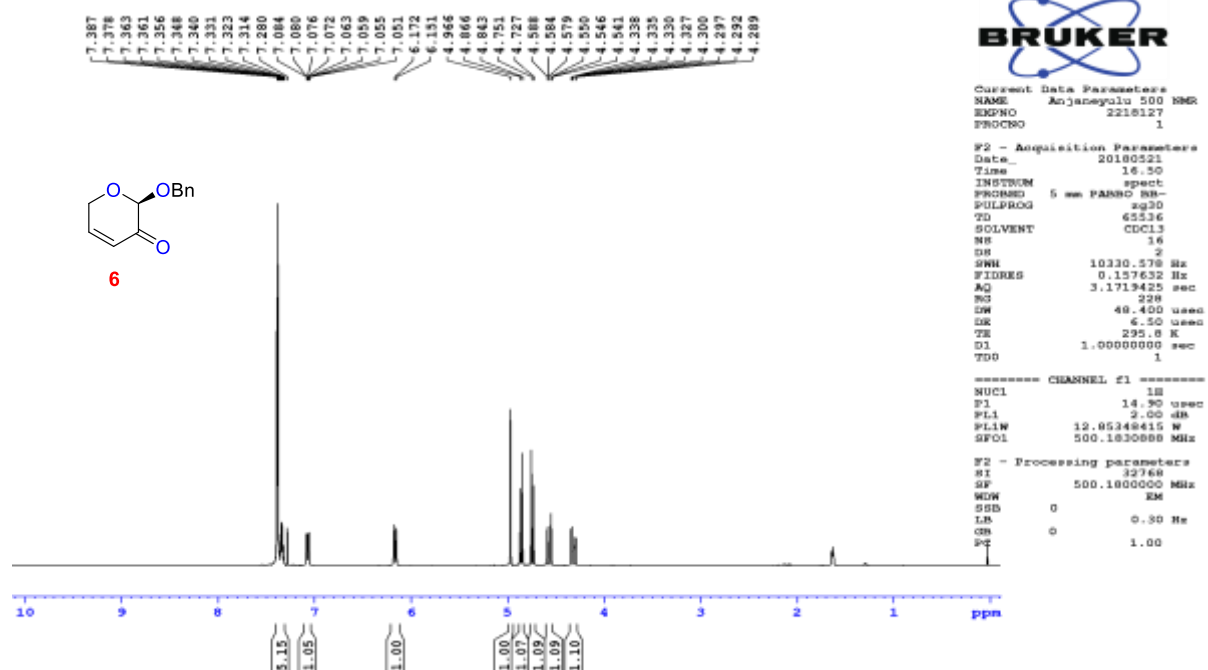
2.5 References and notes

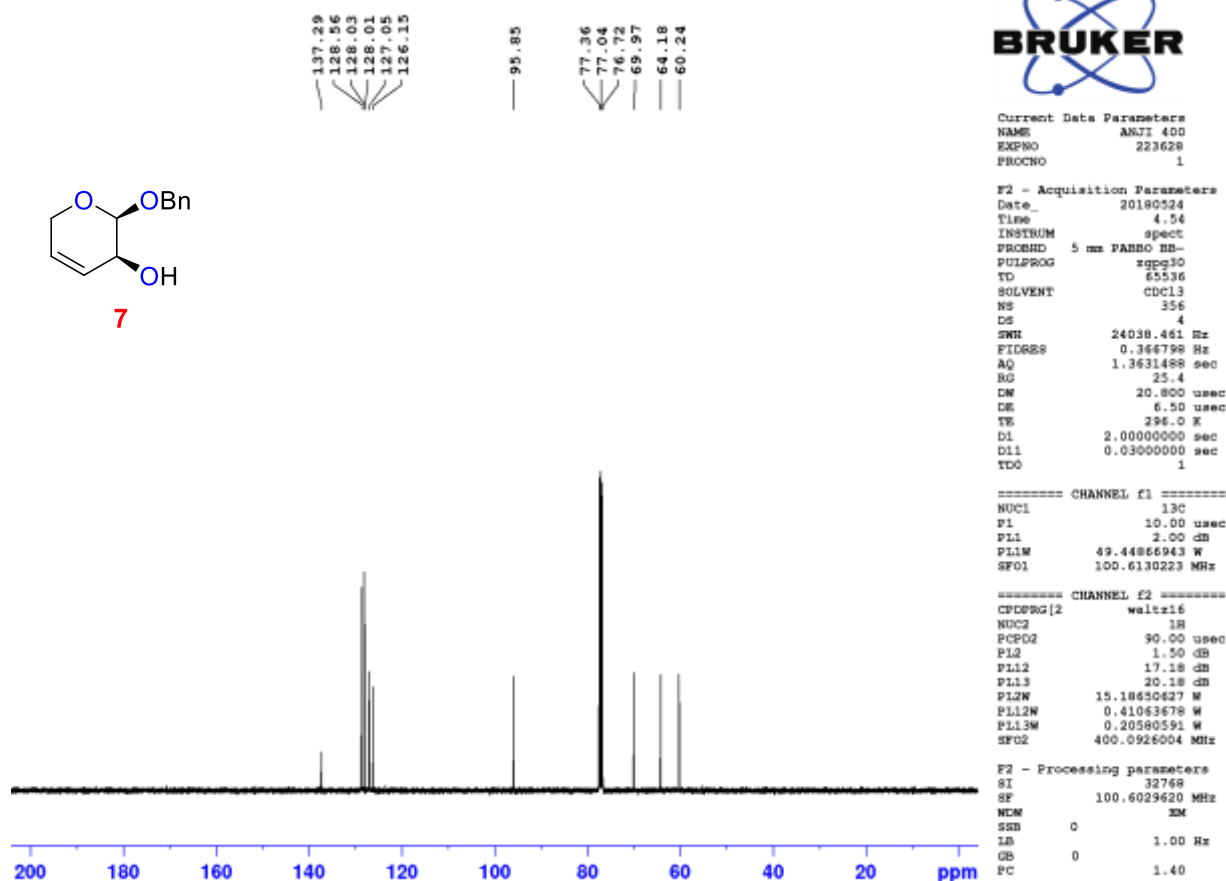
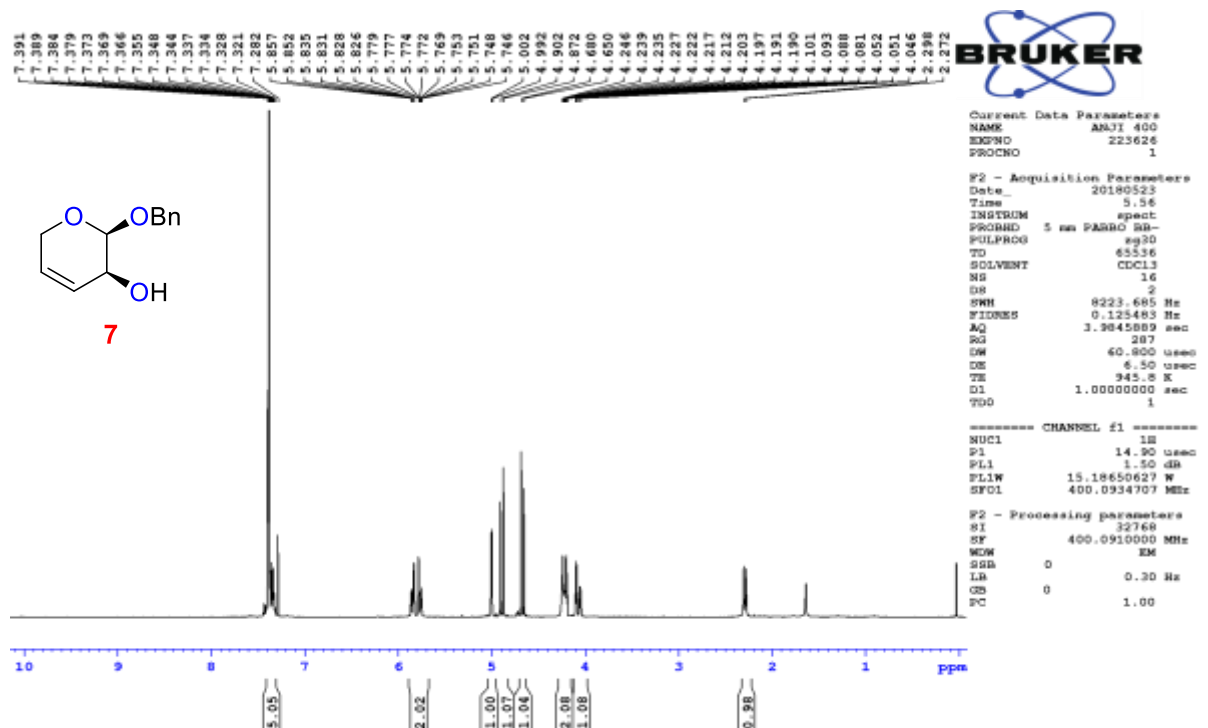
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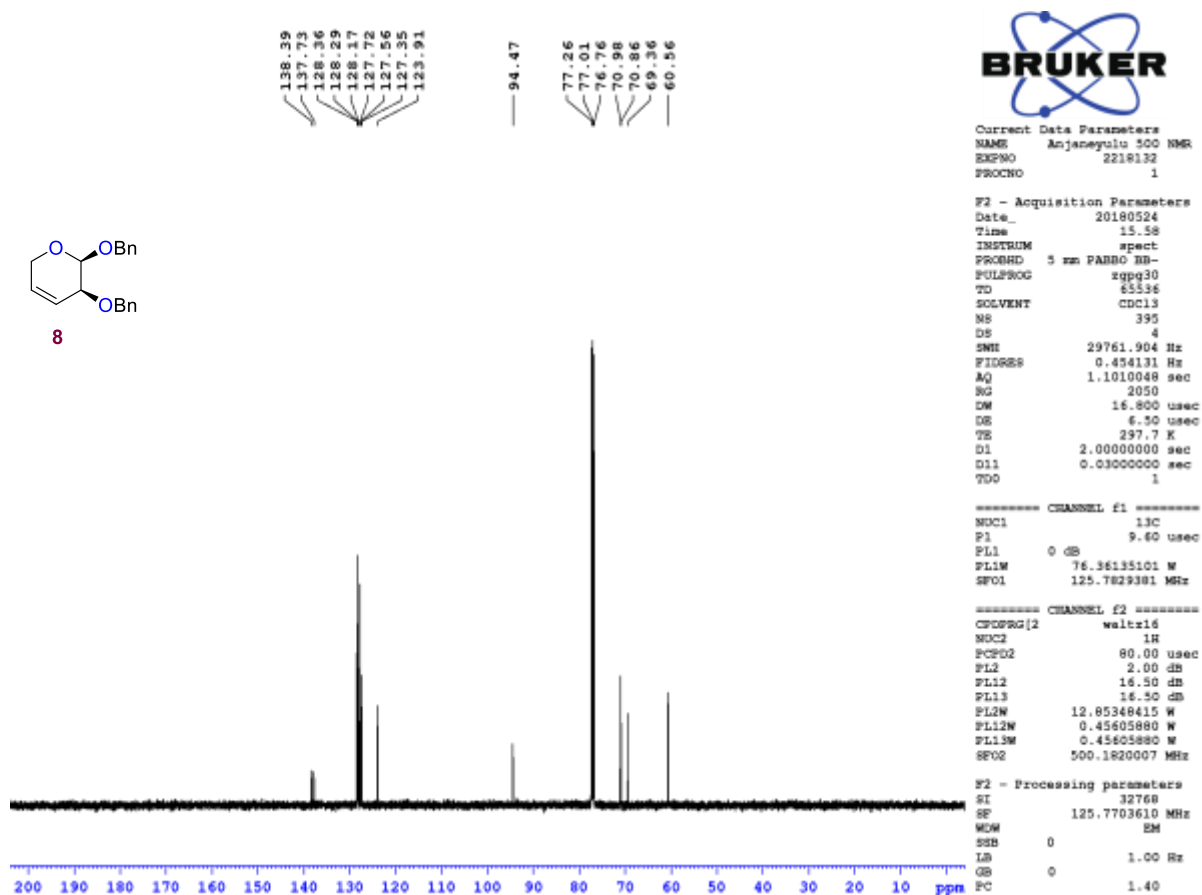
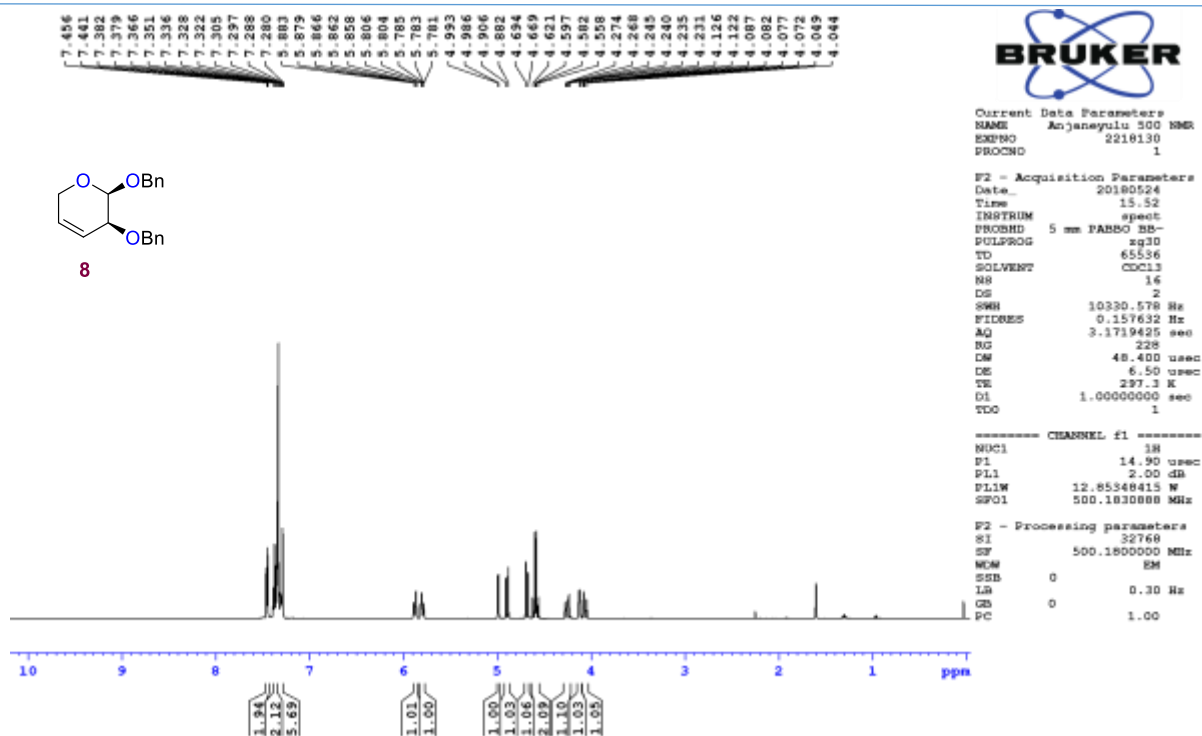
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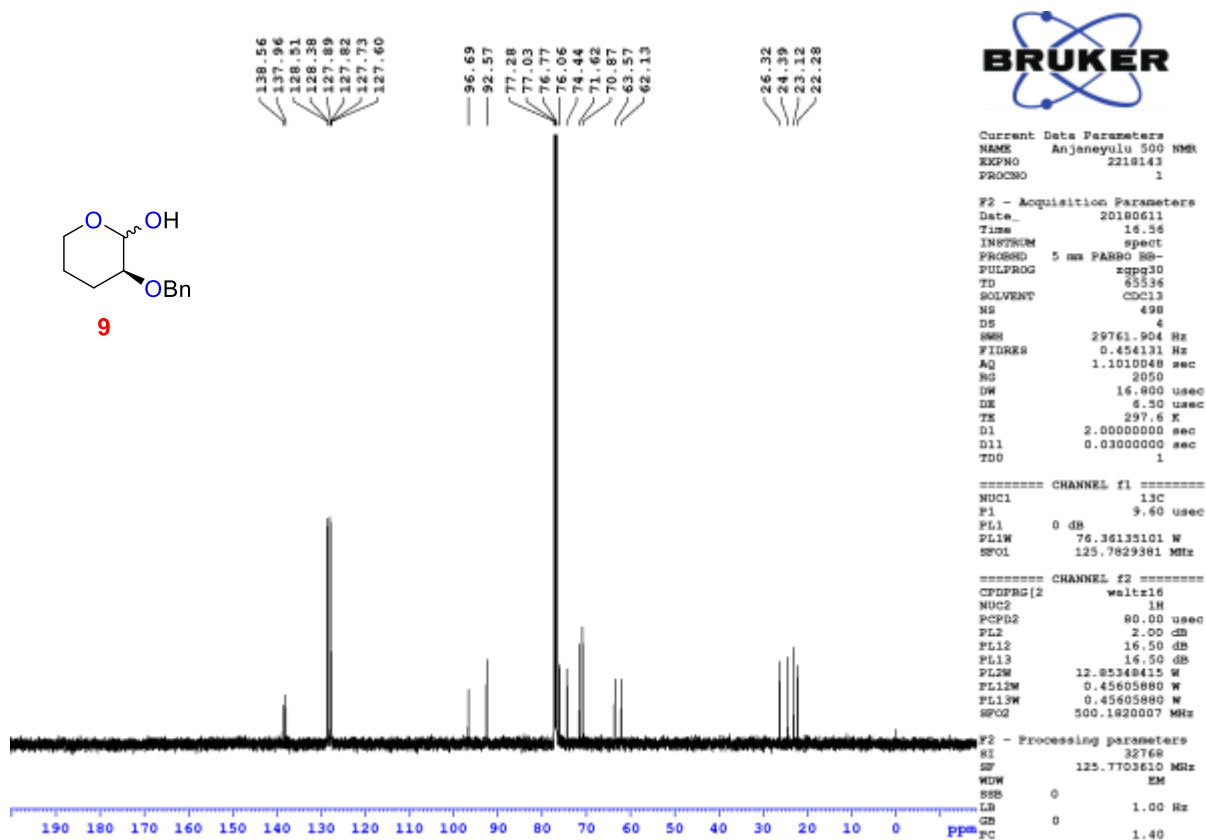
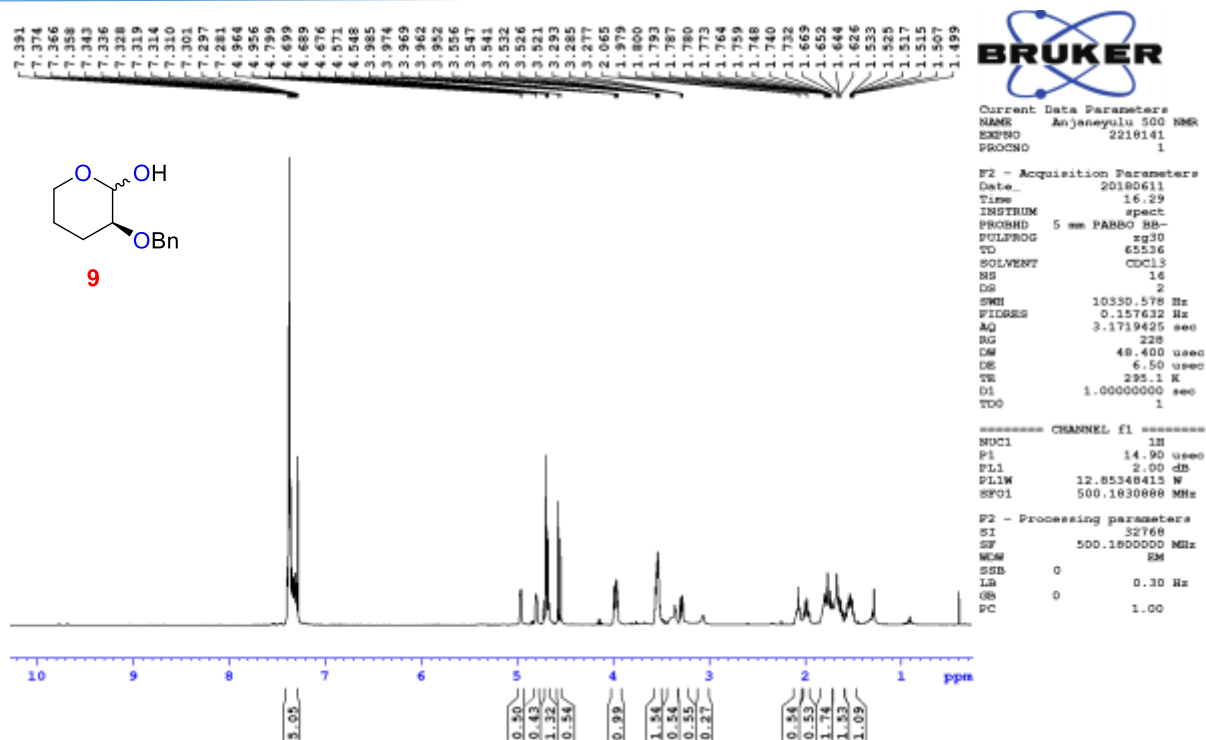
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17. The absolute stereochemistry of the products was made based on the known compounds synthesized in later stages.
18. Crystal data for compound **13b** have been deposited in CCDC with number: 1945942. formula: C₁₅H₂₂ClNO, formula weight = 267.78, monoclinic, space group P 2₁, a = 8.2091 (11) Å, b = 7.0970 (8) Å, c = 12.9662 (15) Å, V = 753.63(16) Å³, Z = 2, Mo-K_α radiation (λ = 0.71073), T = 299 K; R₁ = 0.0486, wR₂ = 0.1175 [*I* ≥ 2σ (*I*)].
19. The free base of **3** .2HCl was found to be in the form of hemiketal.
20. Crystal data for compound **ent-20a** have been deposited in CCDC with number: 1974727. Formula: C₃₁H₂₉BrClN₃O₅, formula weight = 638.93, monoclinic, space group P 2₁, a = 6.1629 (10) Å, b = 16.075 (3) Å, c = 14.710 (3) Å, V = 1435.5(5) Å³, Z = 2, Mo-K_α radiation (λ = 0.71073), T = 100 K; R₁ = 0.0771, wR₂ = 0.1348 [*I* ≥ 2σ (*I*)].

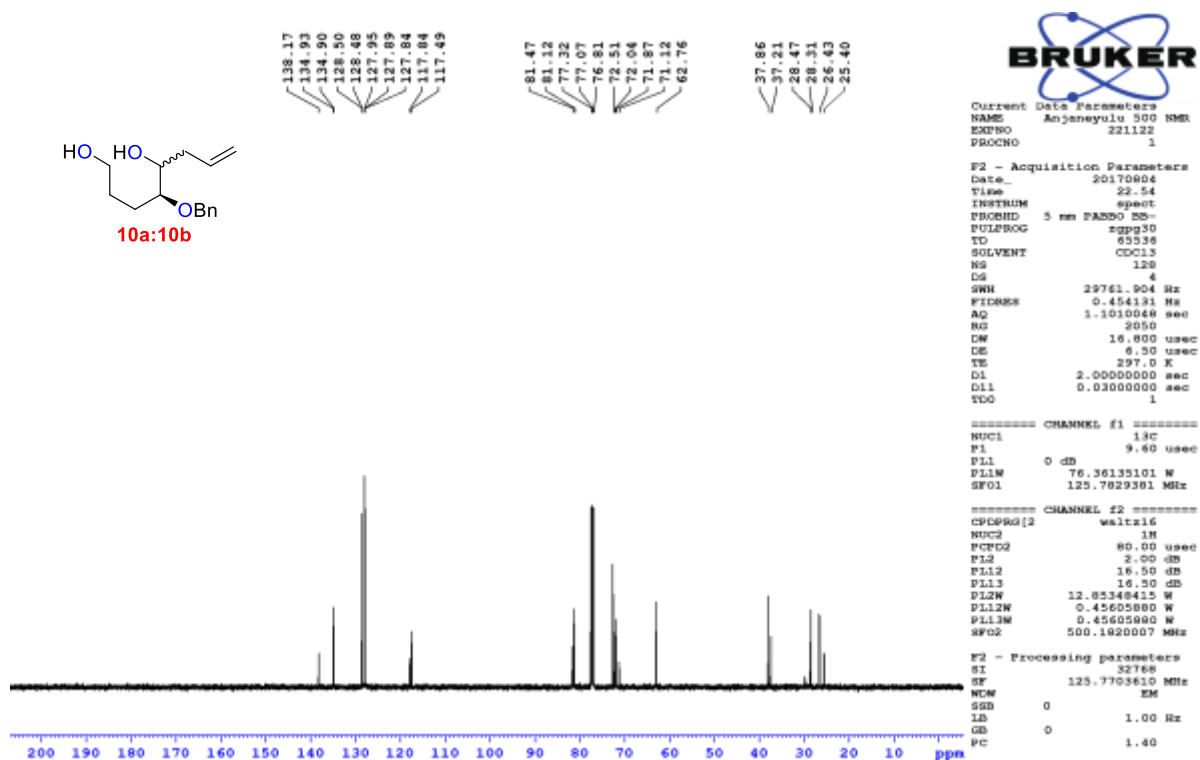
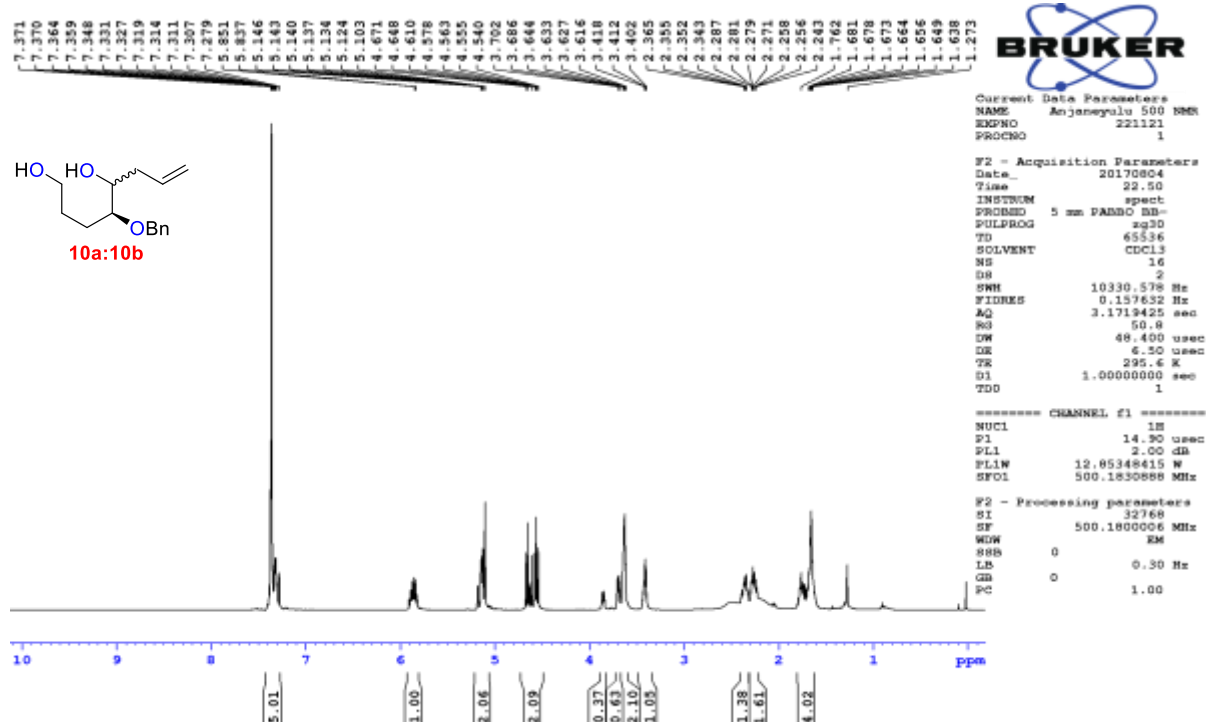




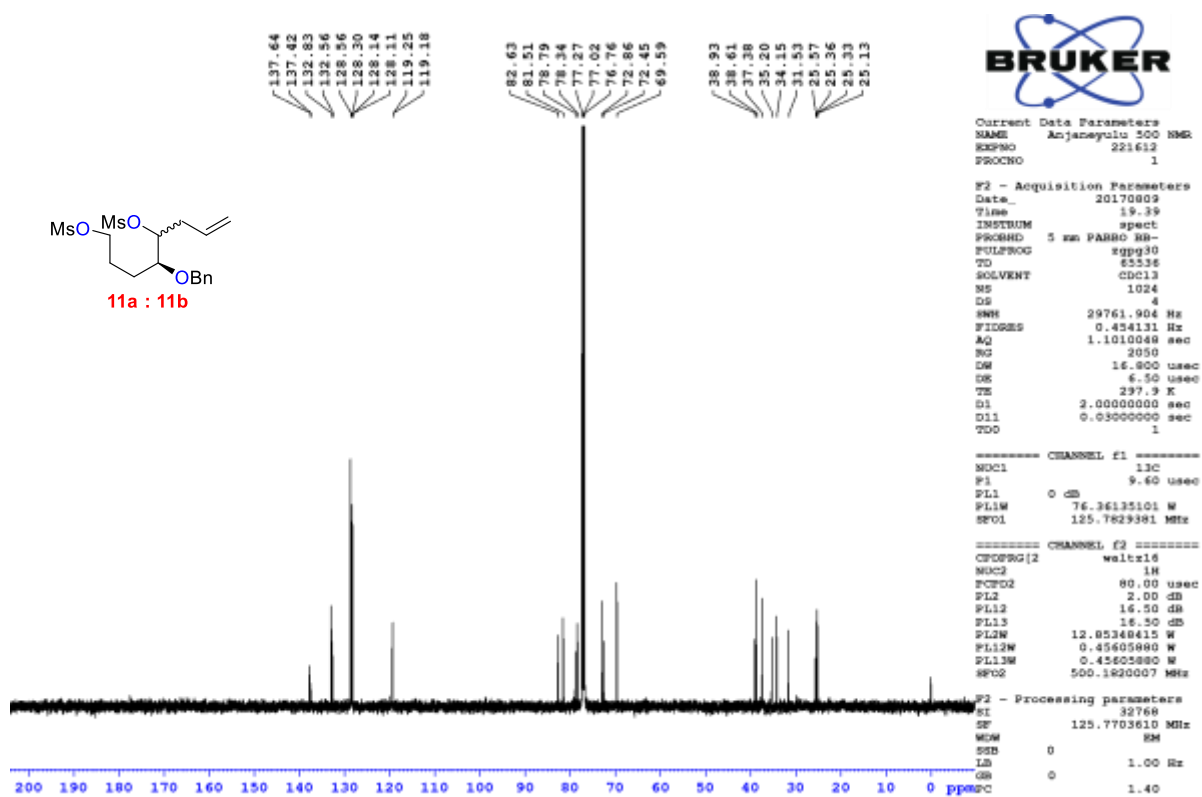
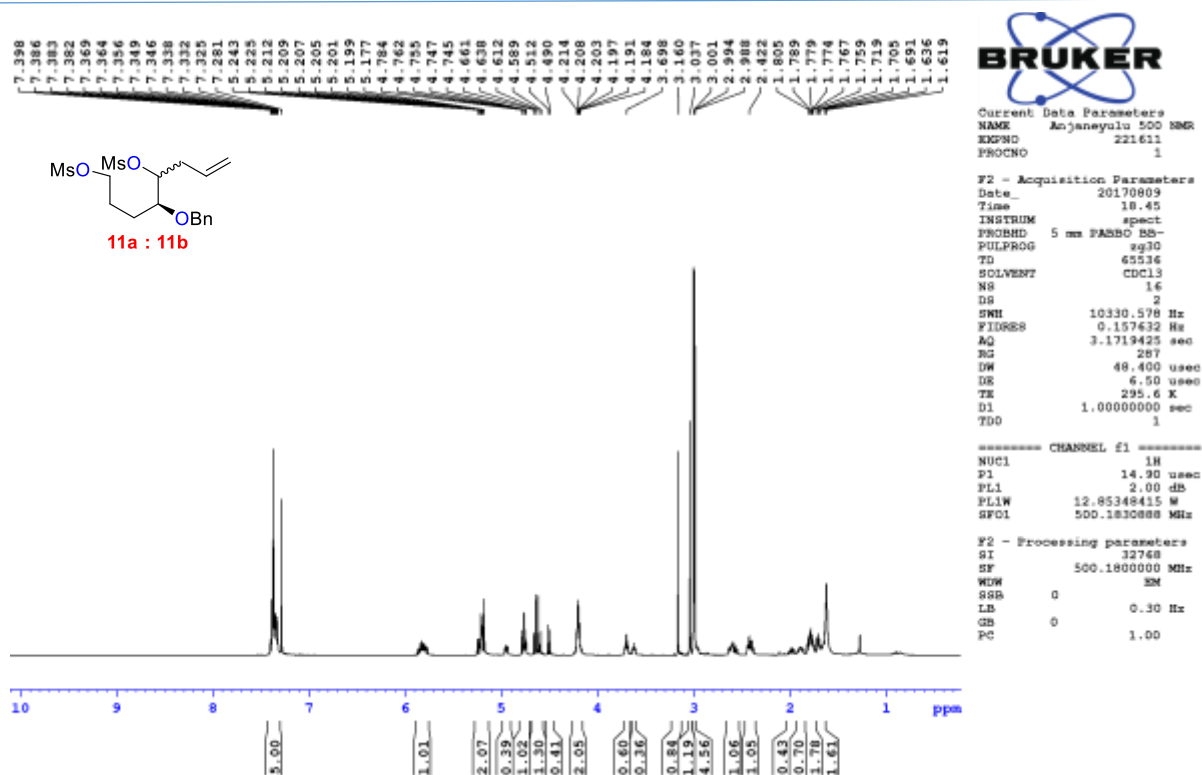


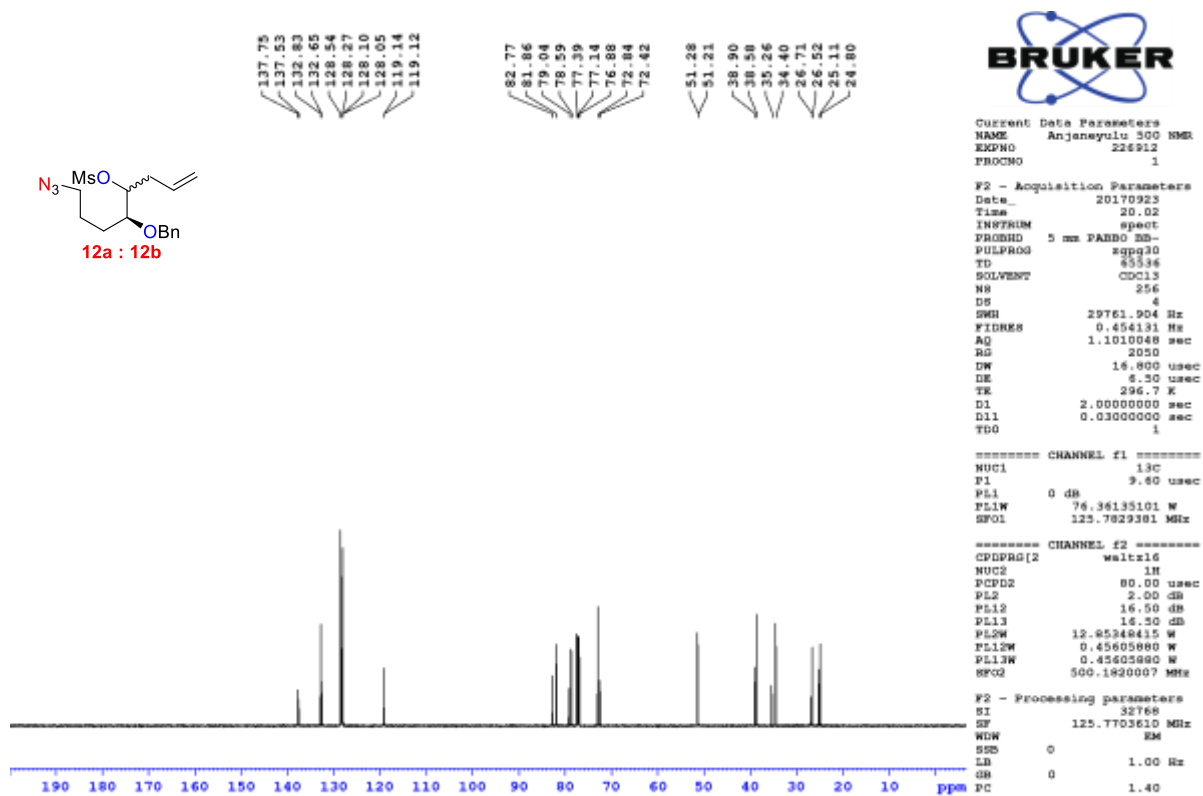
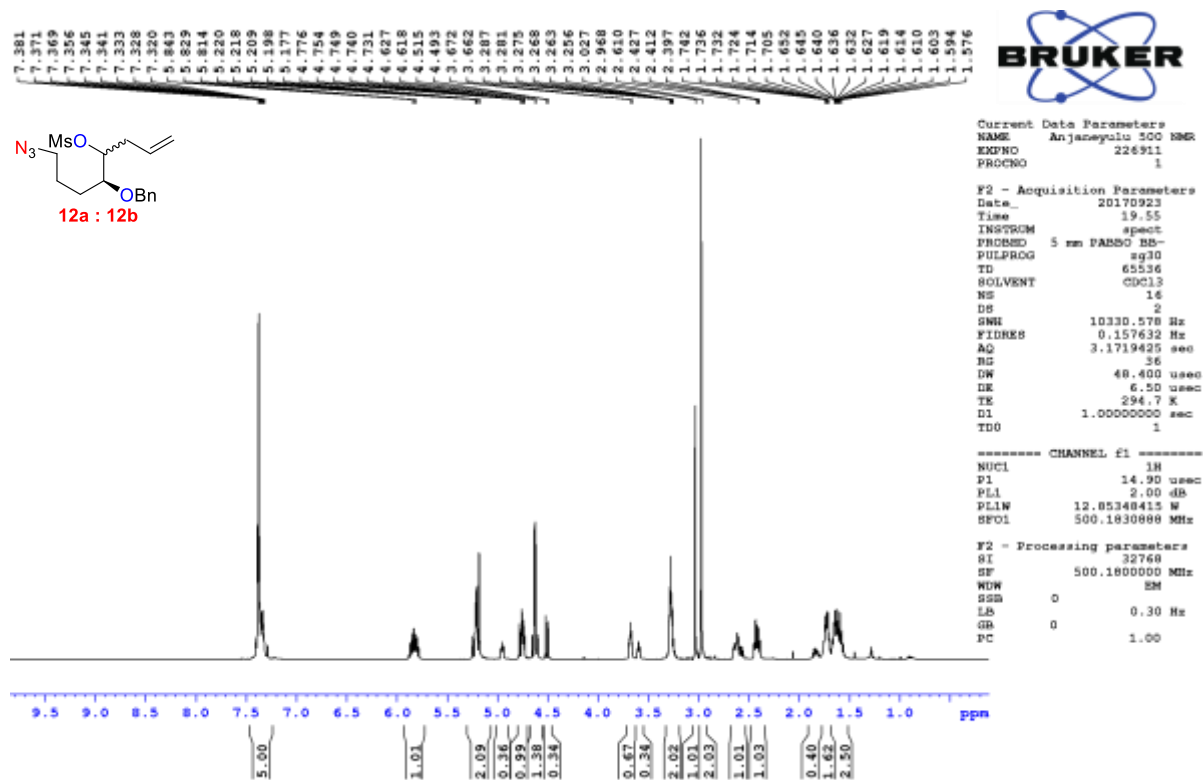
Total synthesis of *Febrifugine* and *Halofuginone*

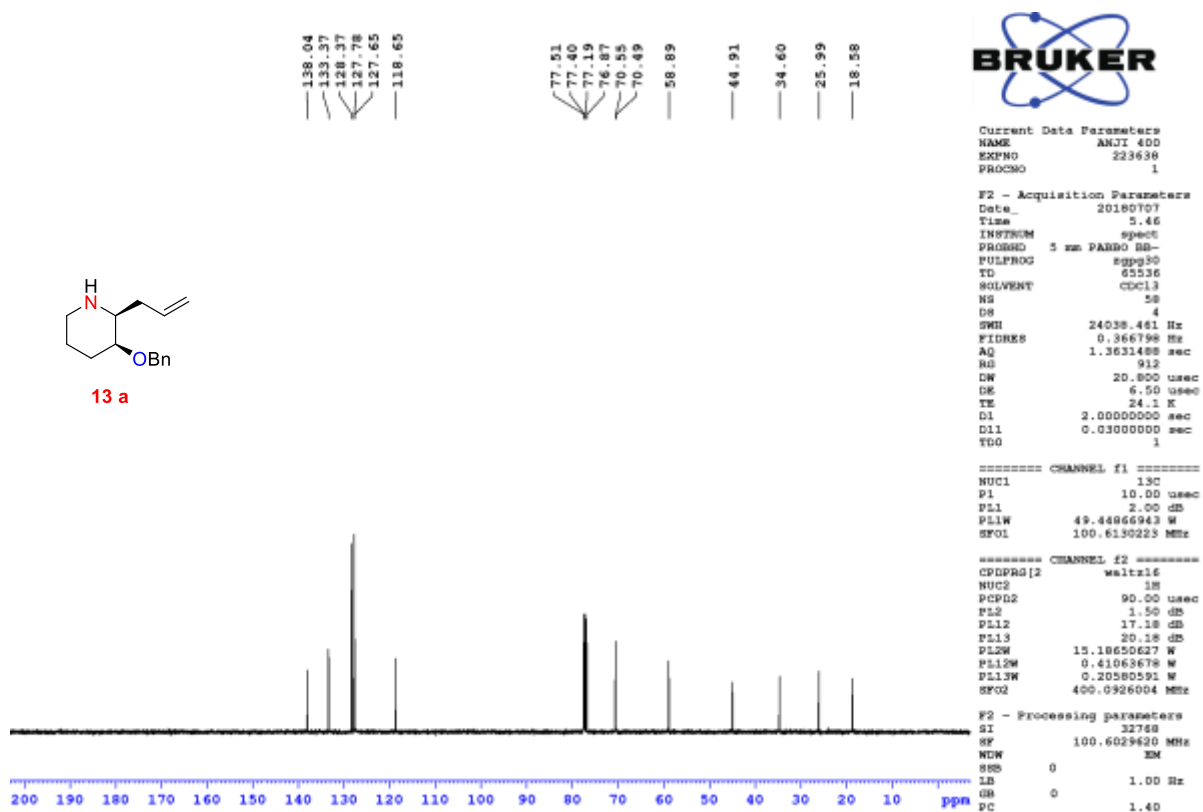
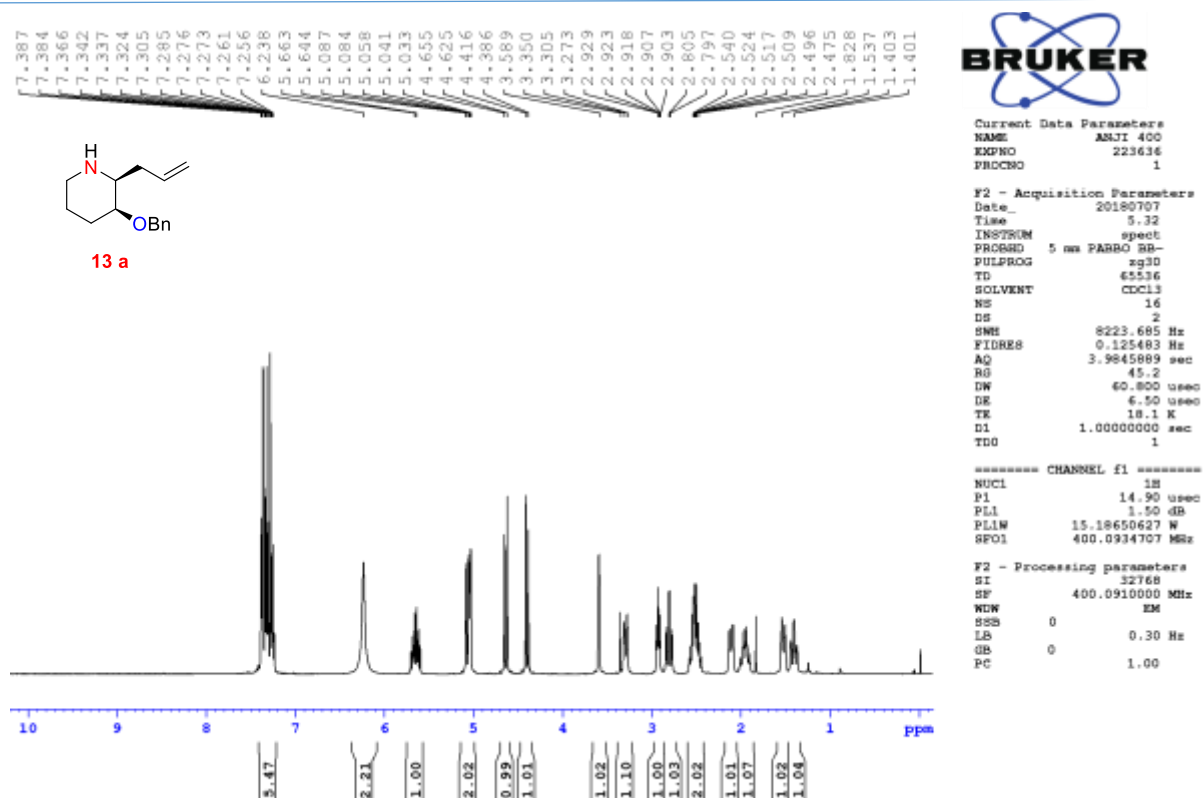


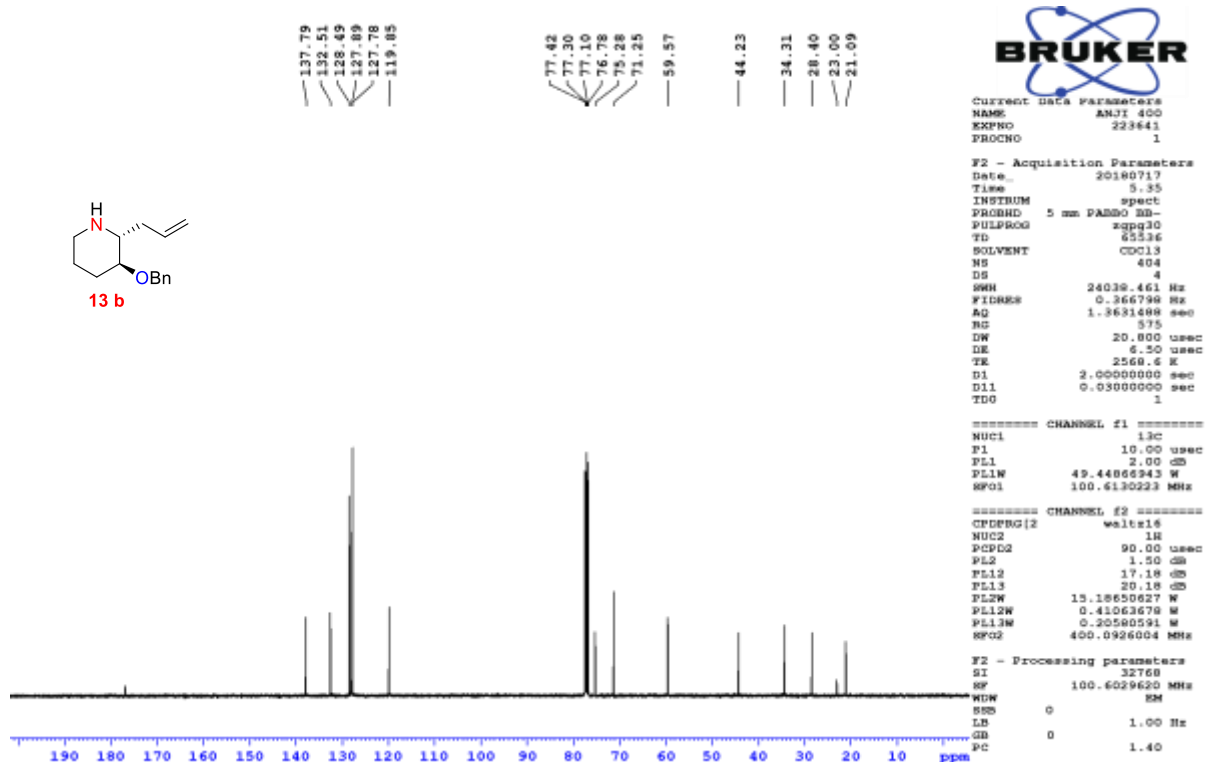
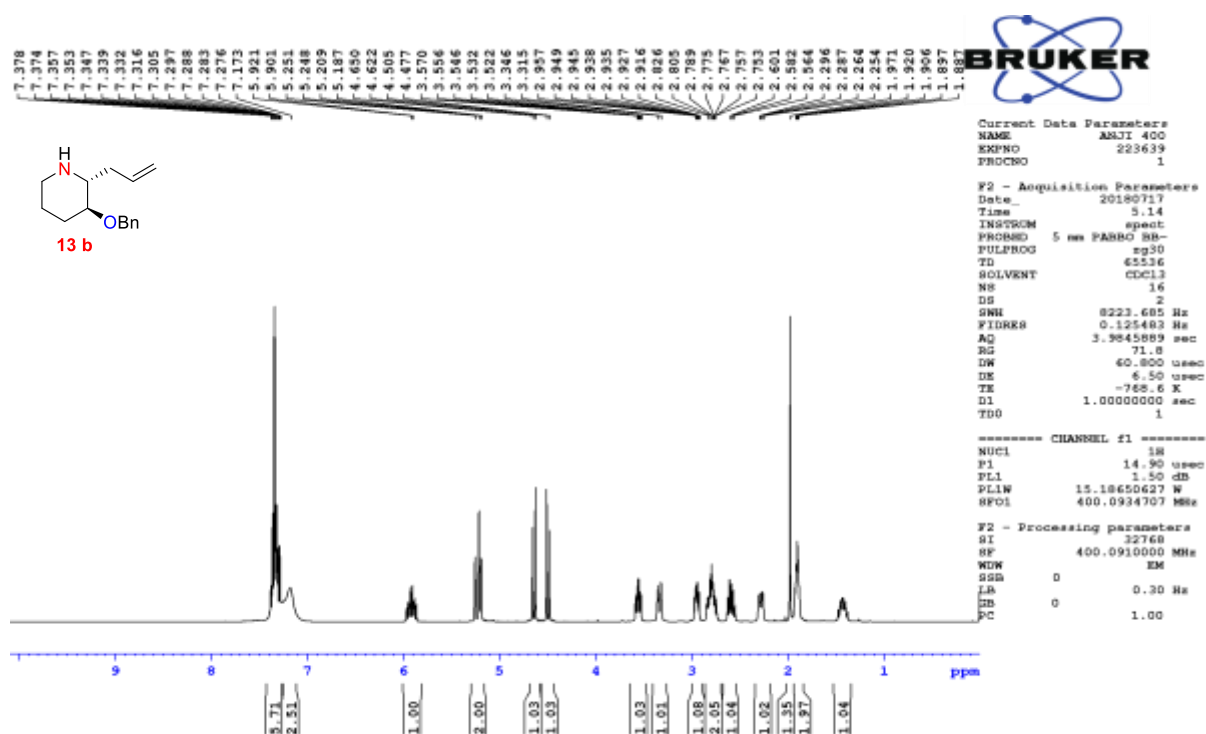


Total synthesis of *Febrifugine* and *Halofuginone*



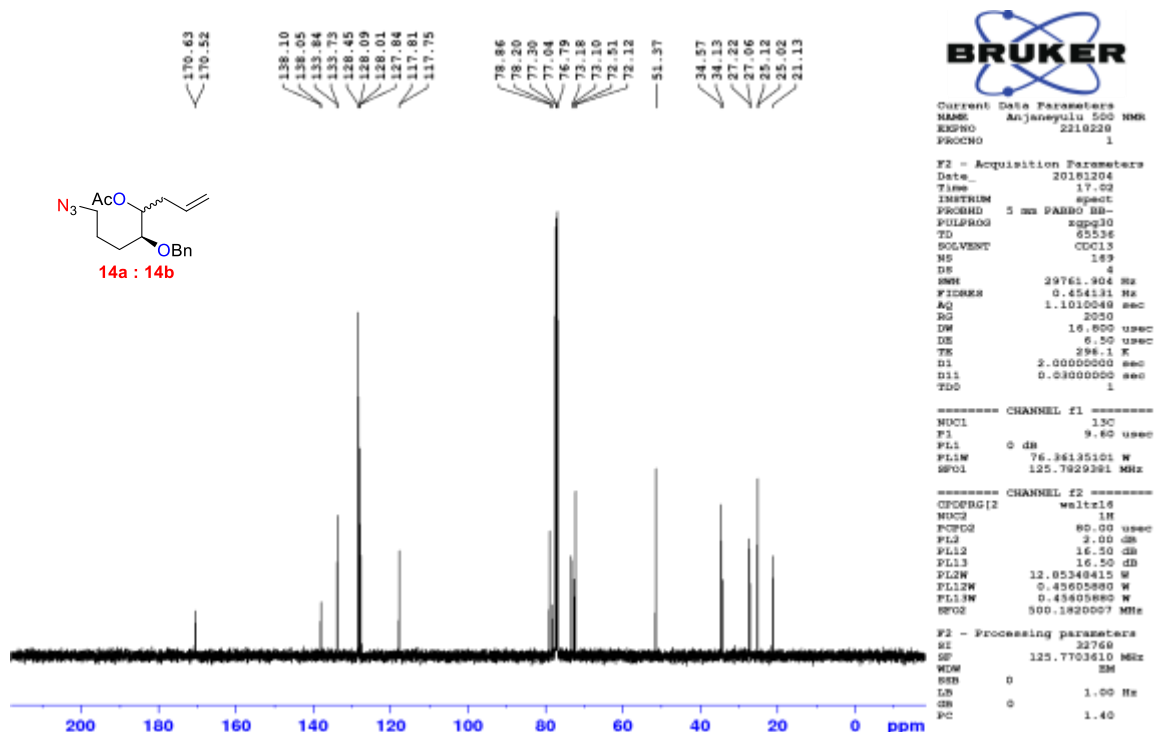
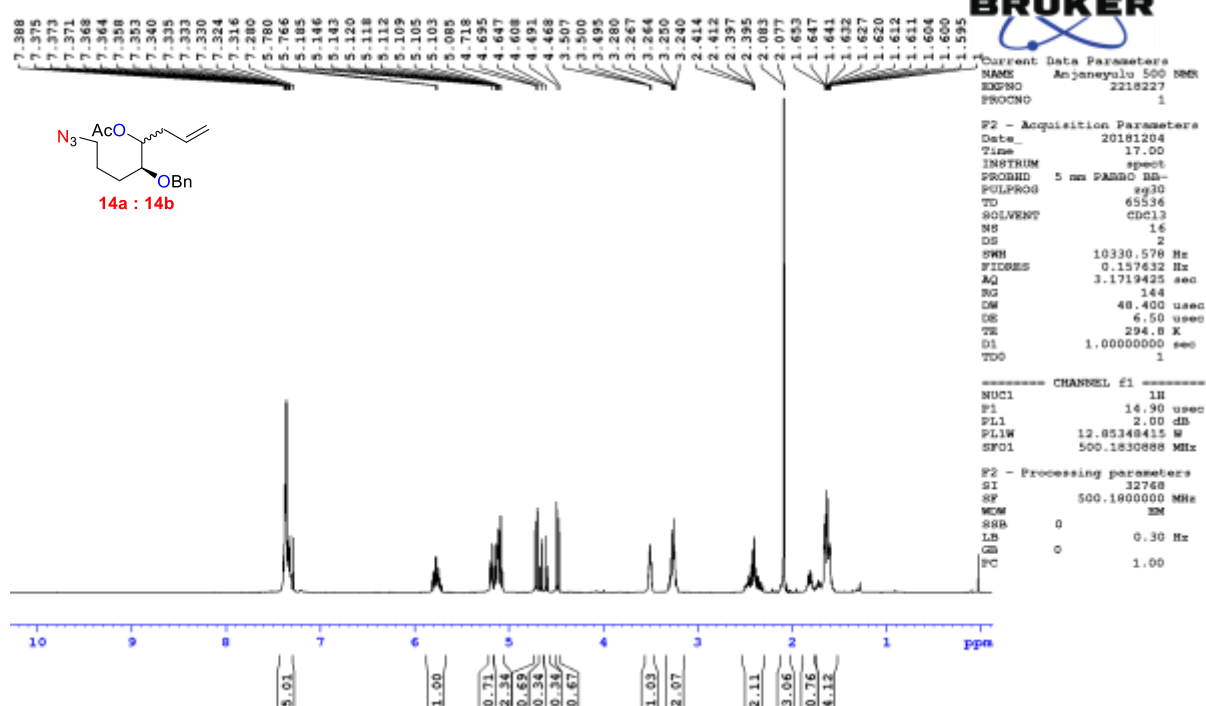


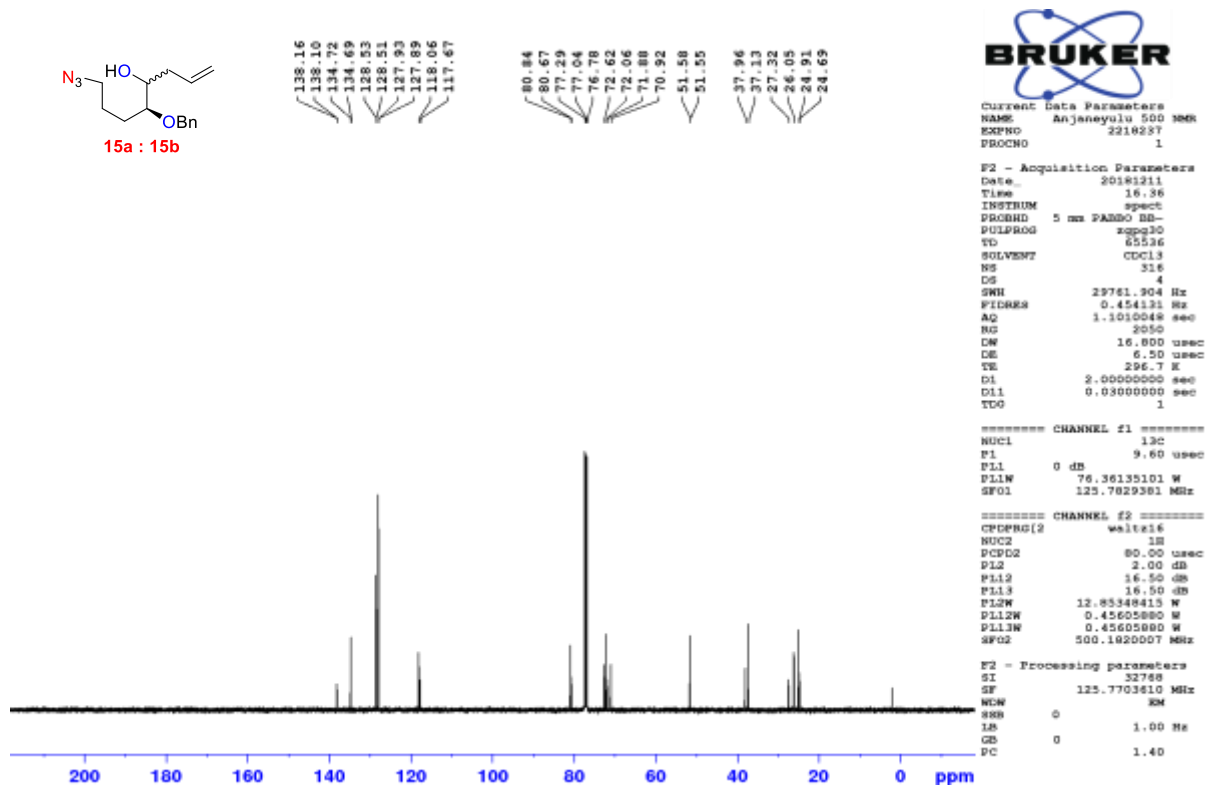
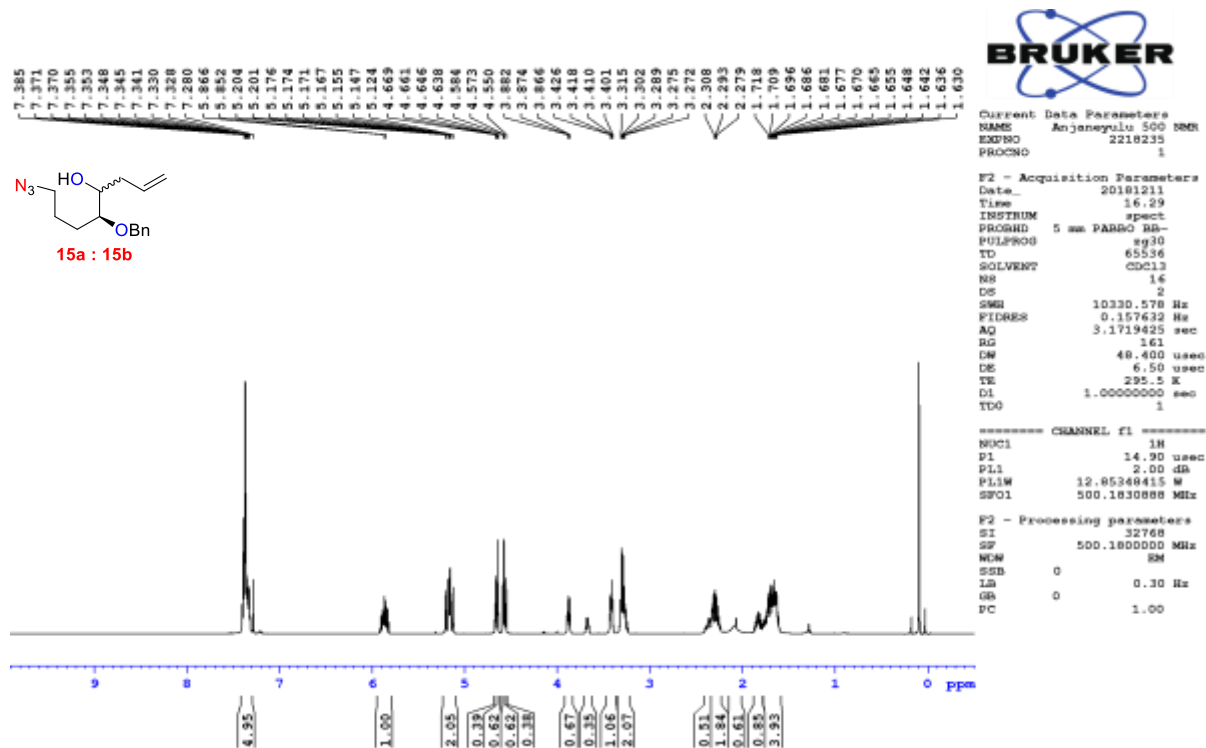


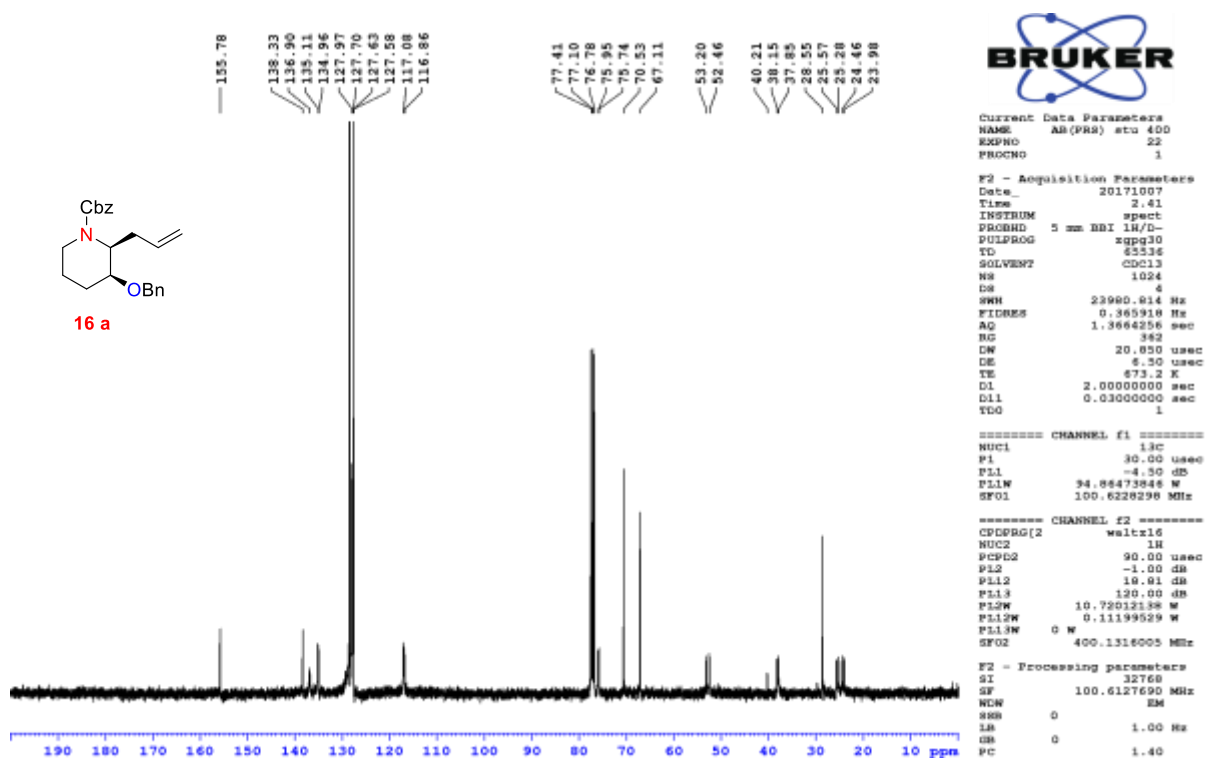
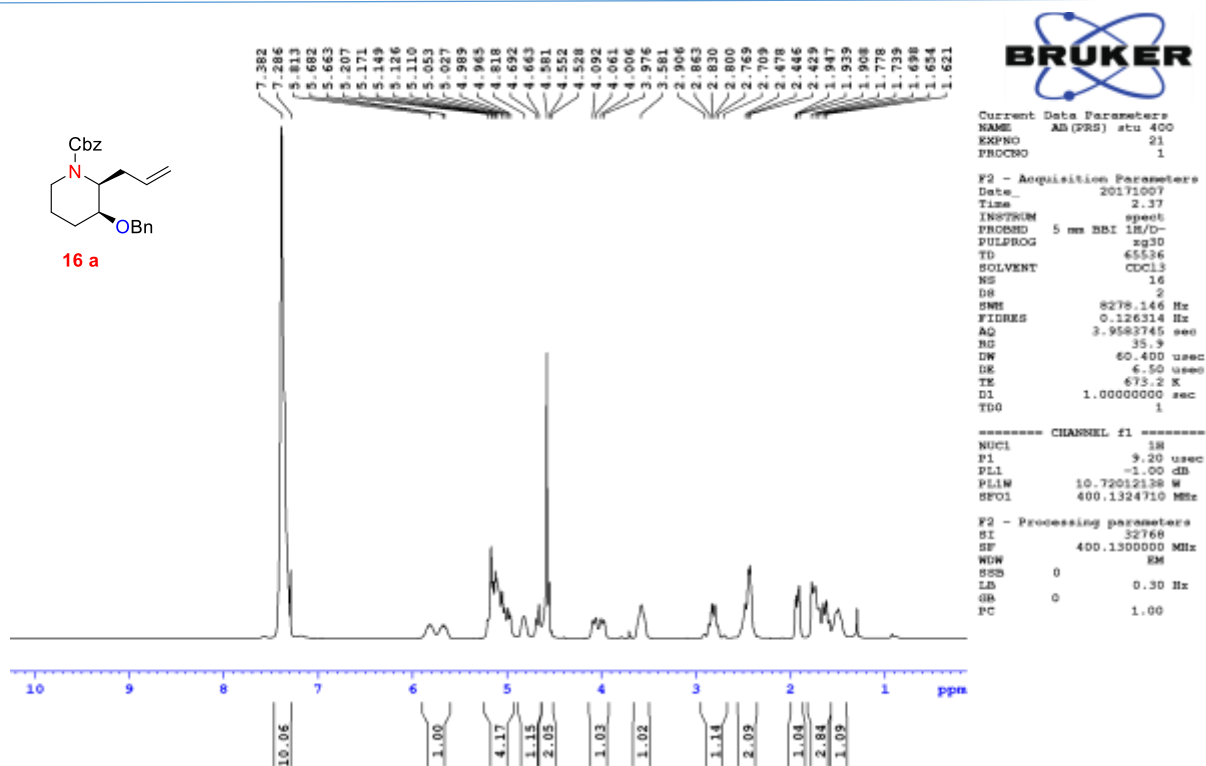


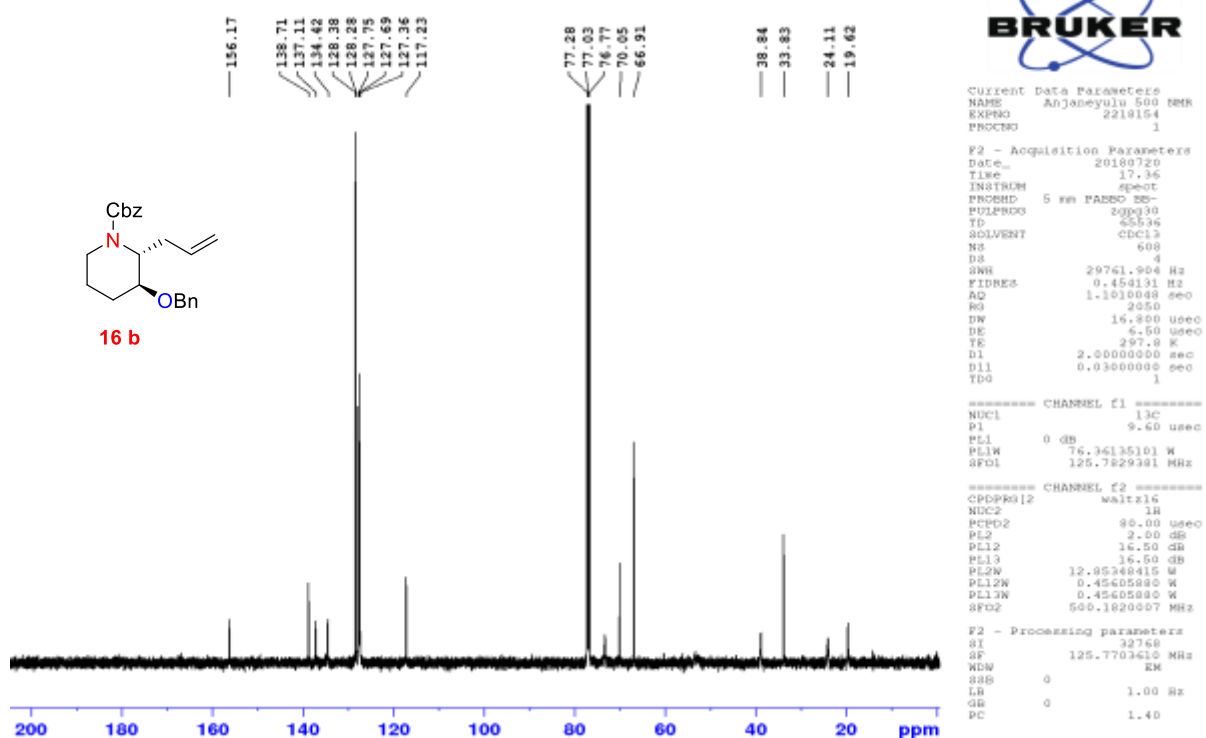
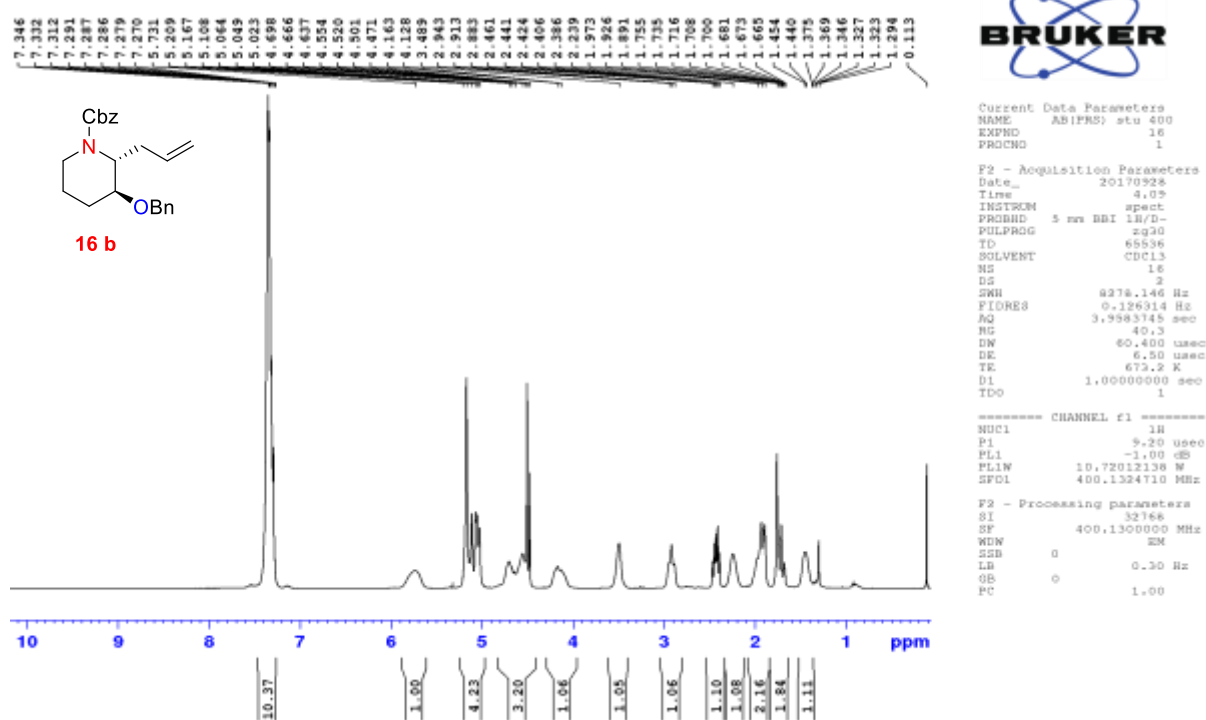
Total synthesis of *Febrifugine* and *Halofuginone*

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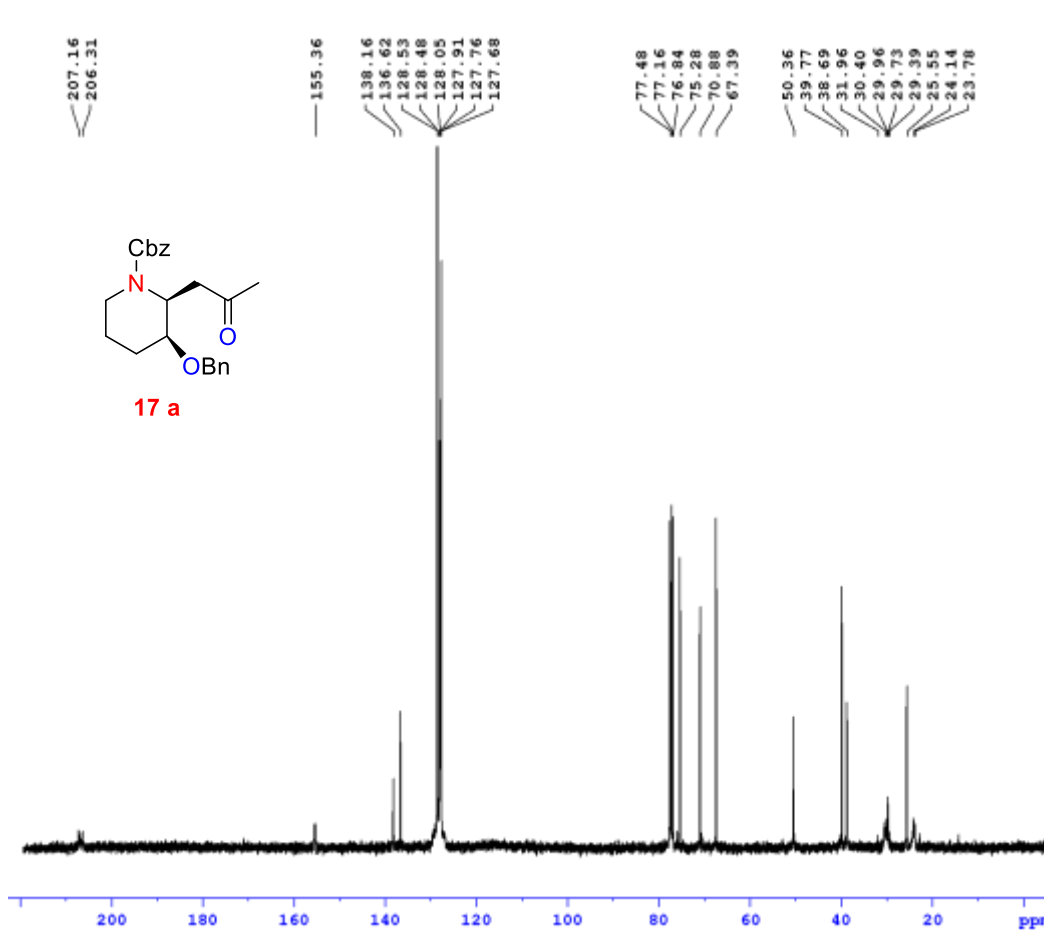
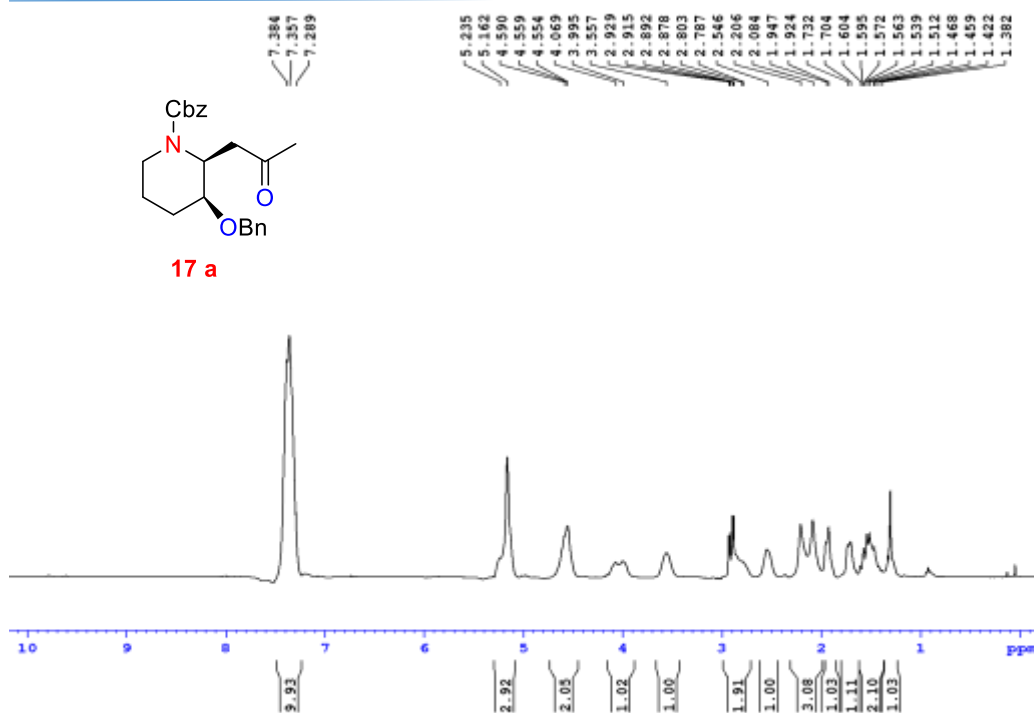


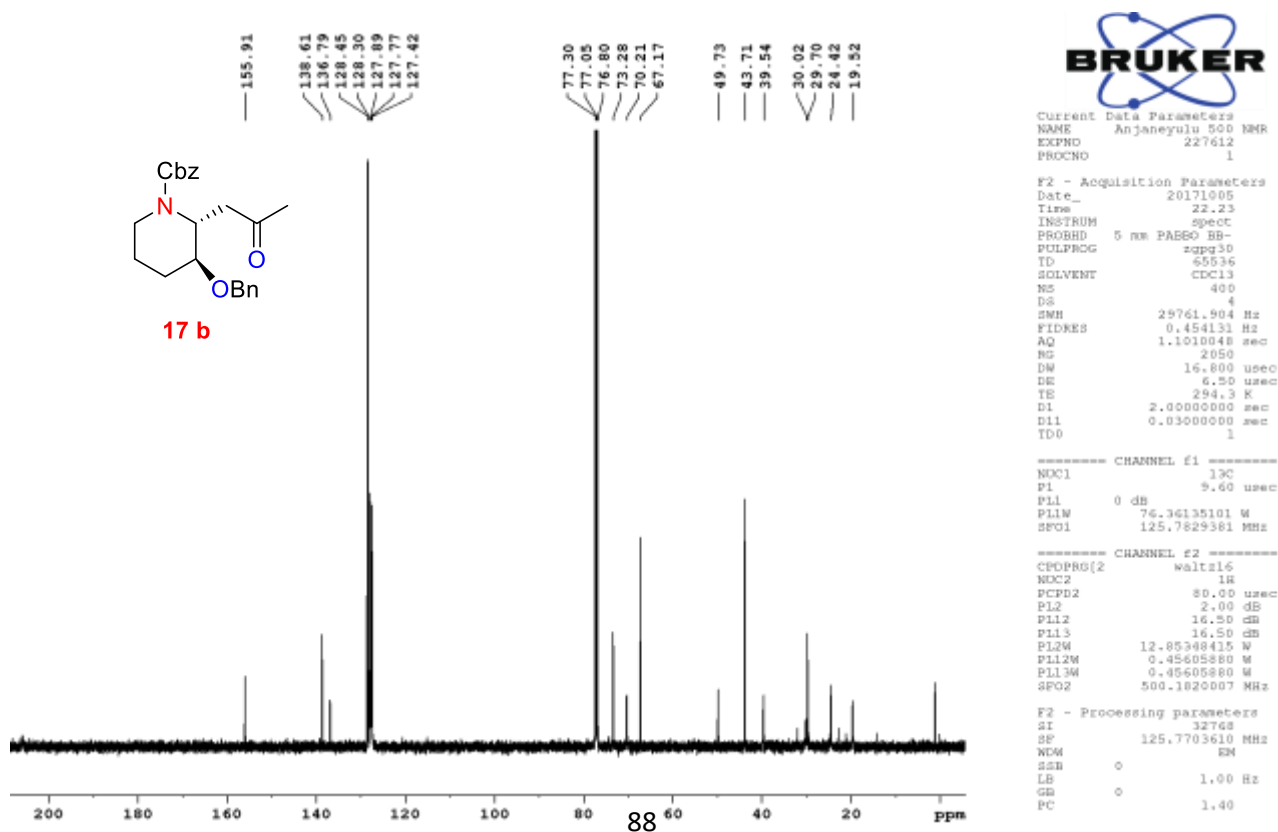
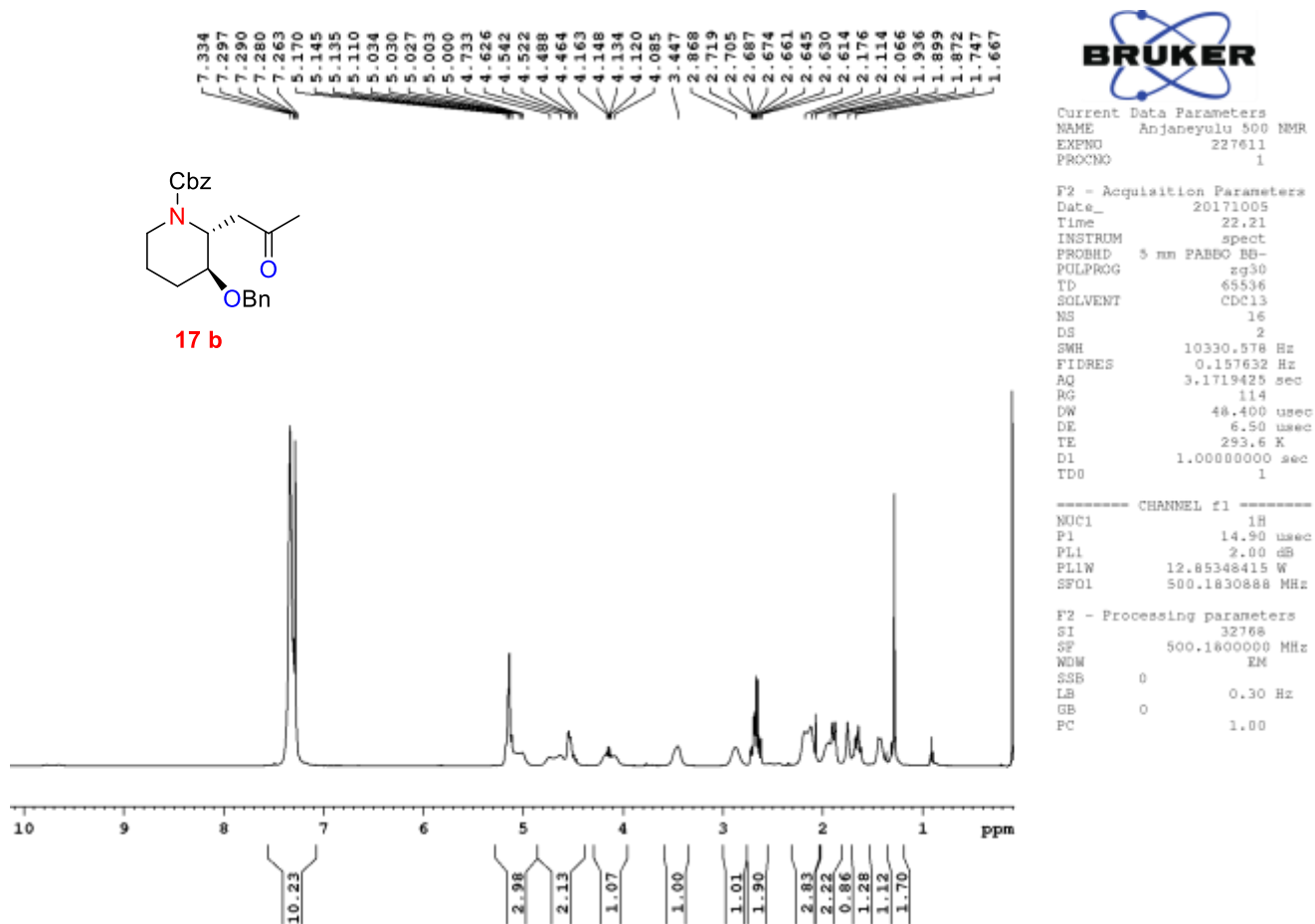


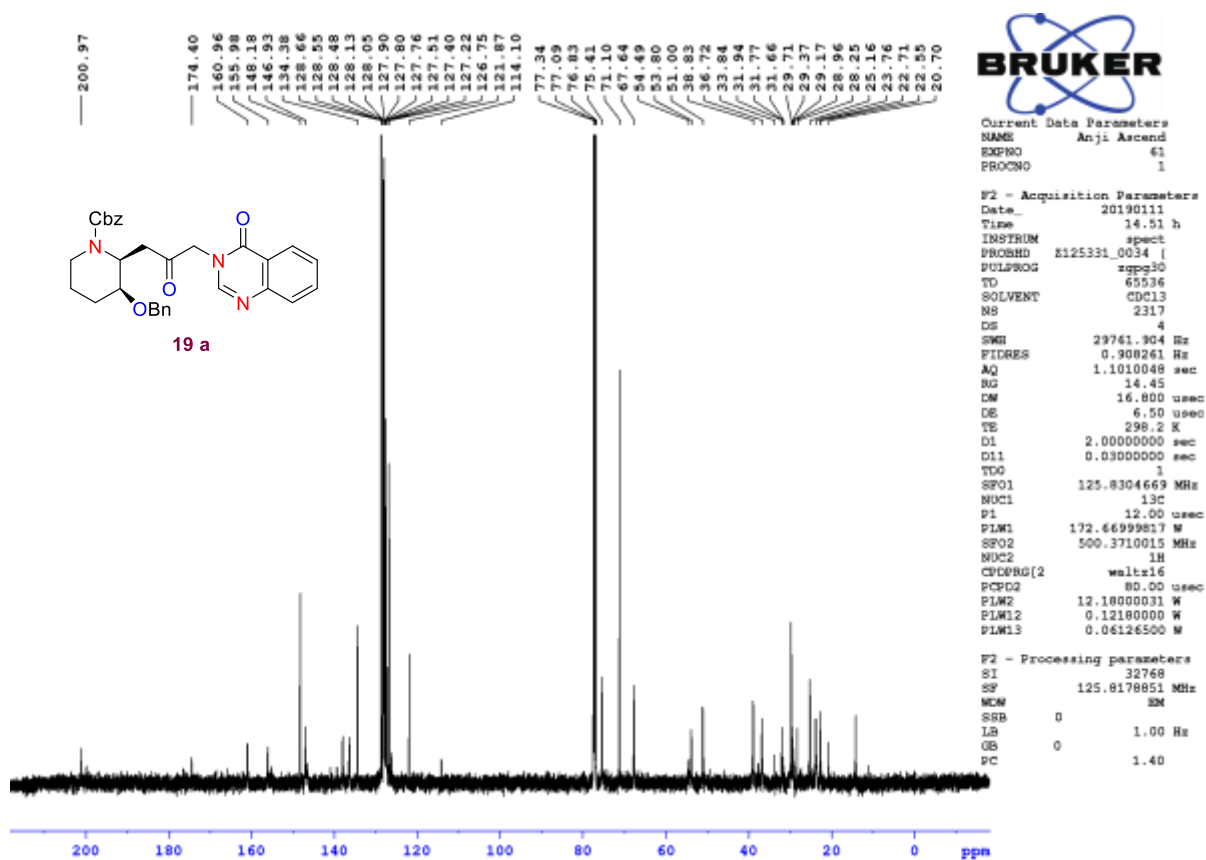
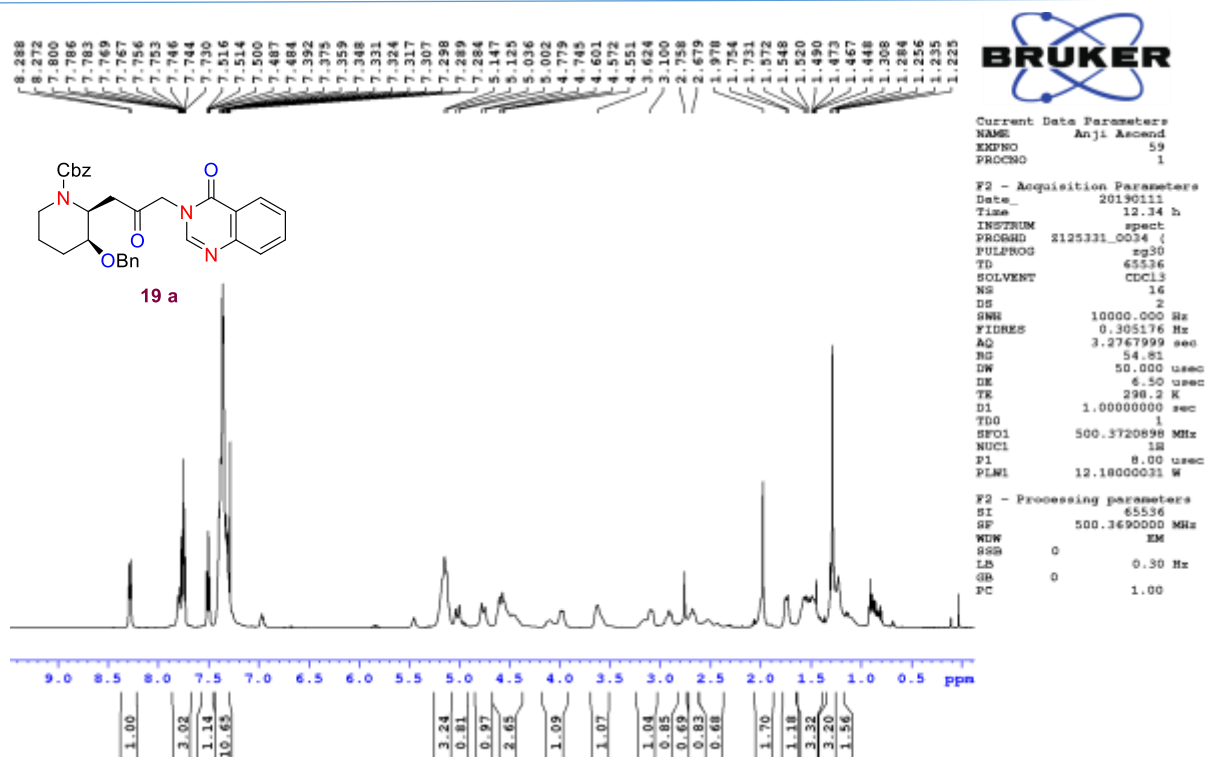




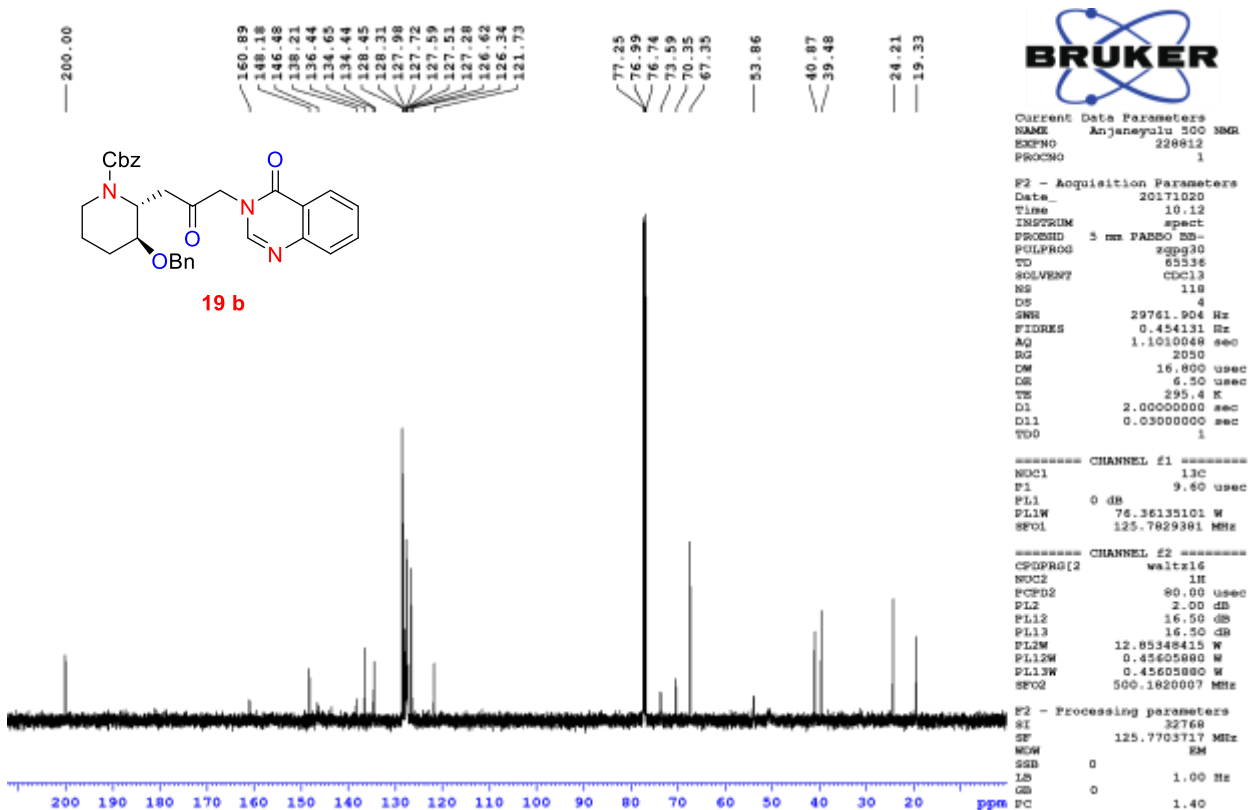
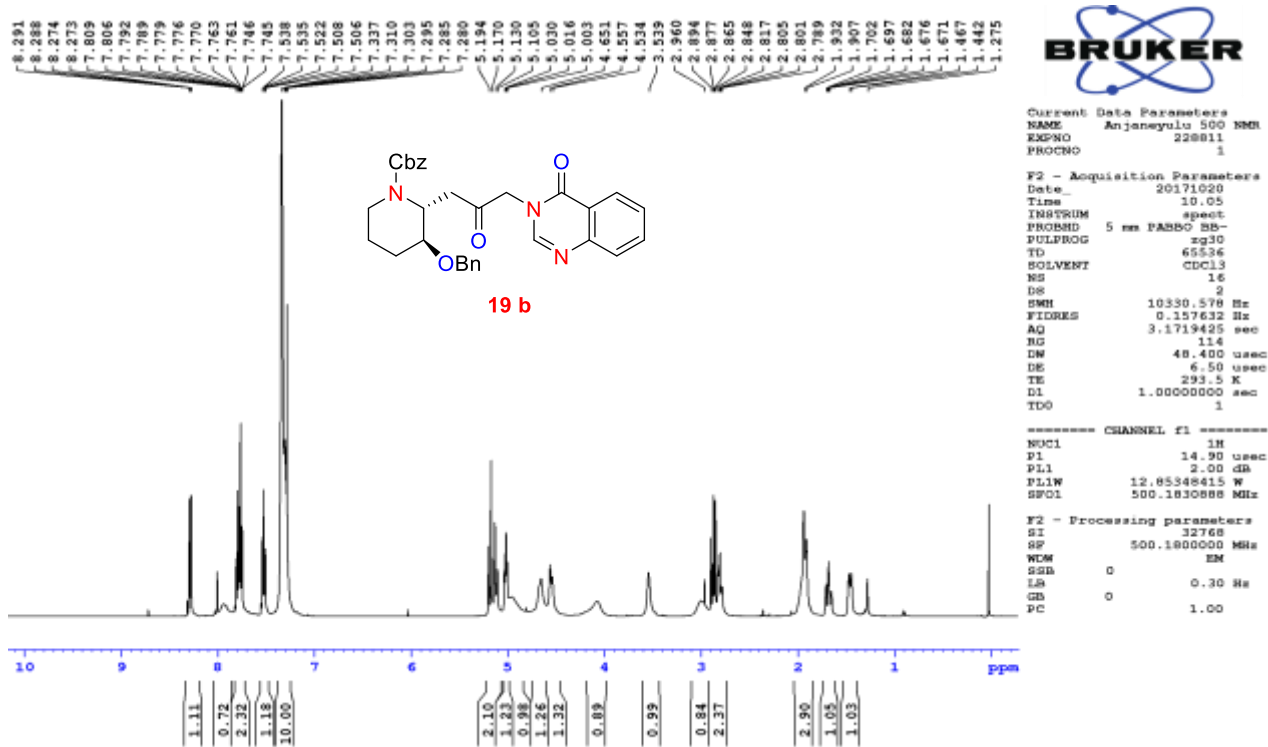
Total synthesis of *Febrifugine* and *Halofuginone*



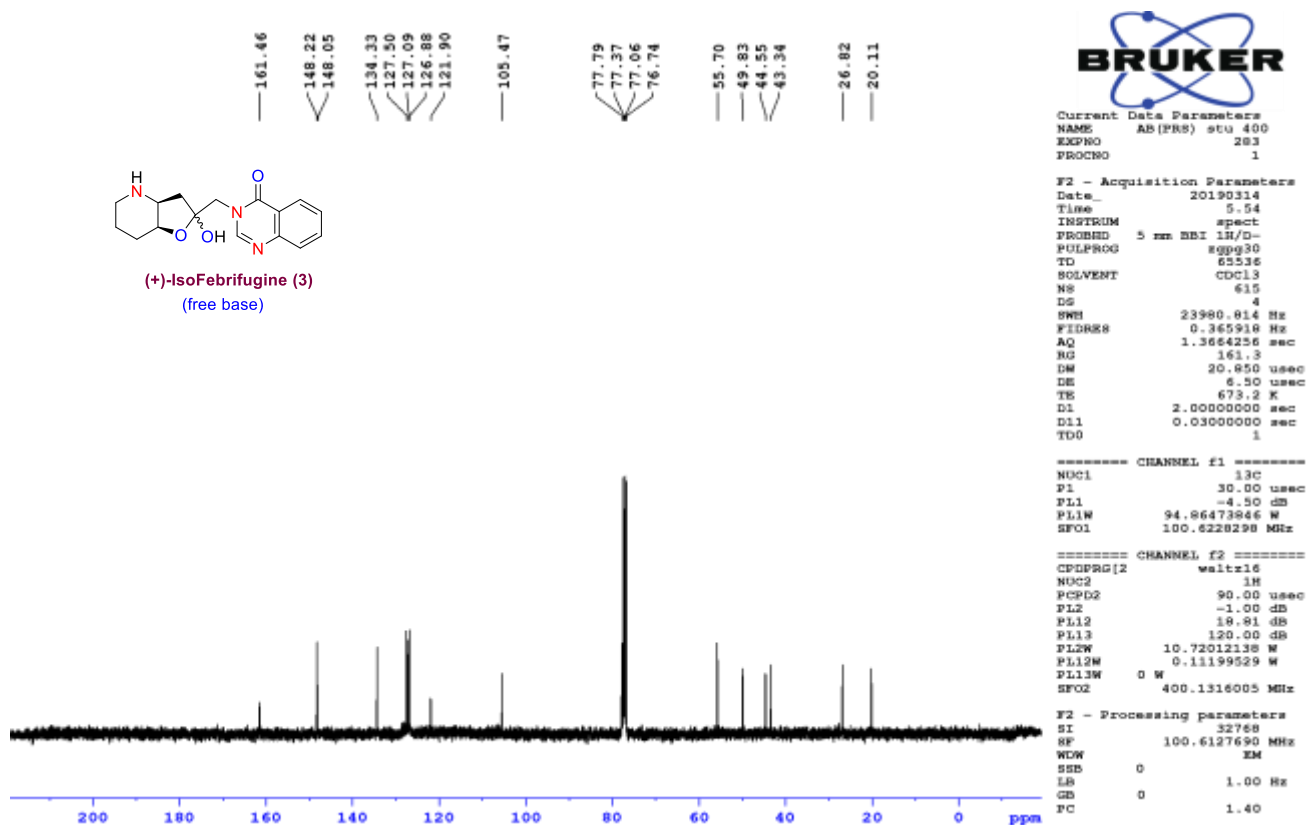
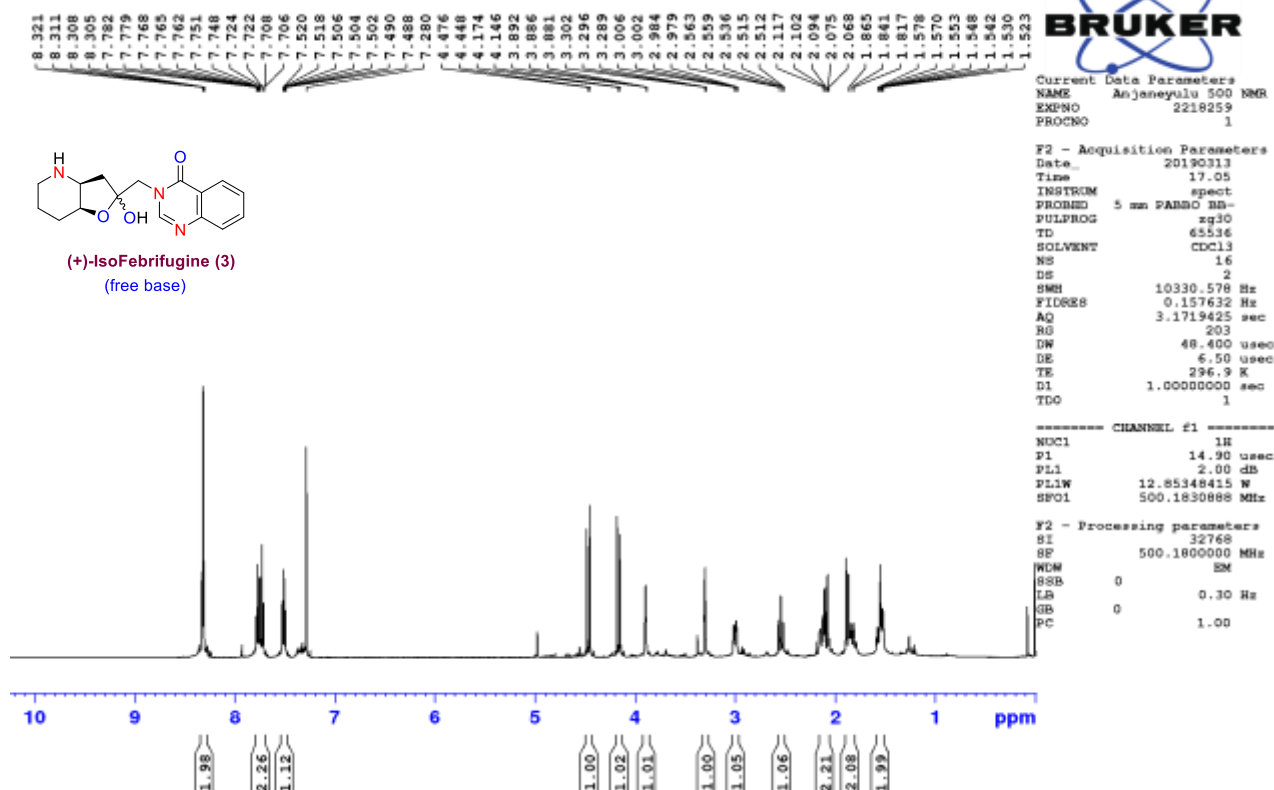


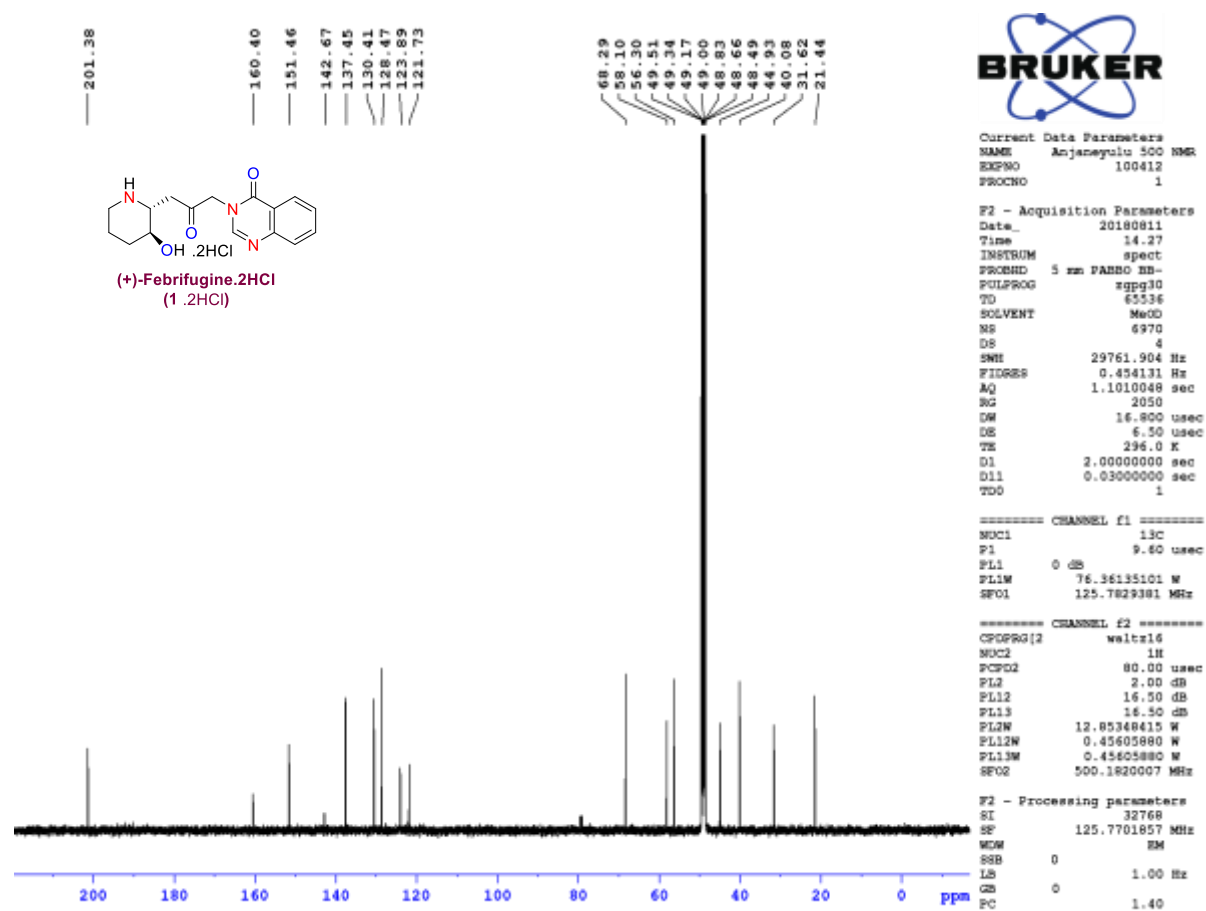
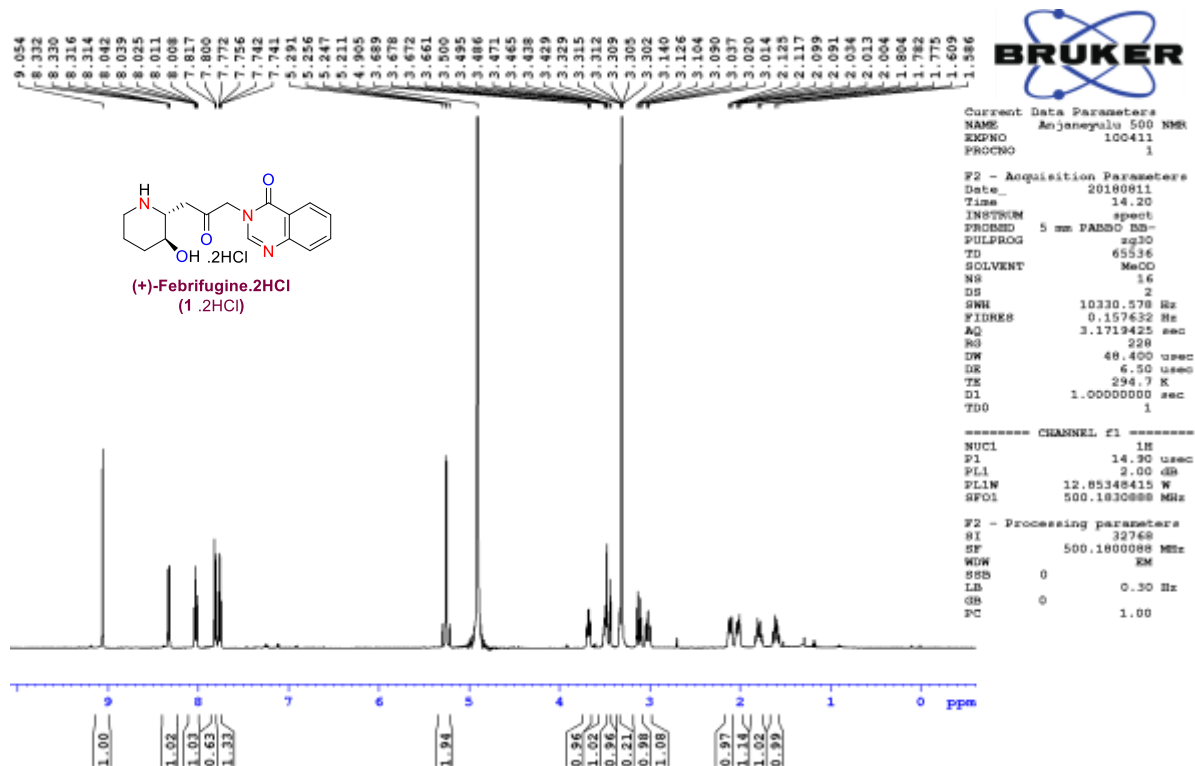


Chapter-2



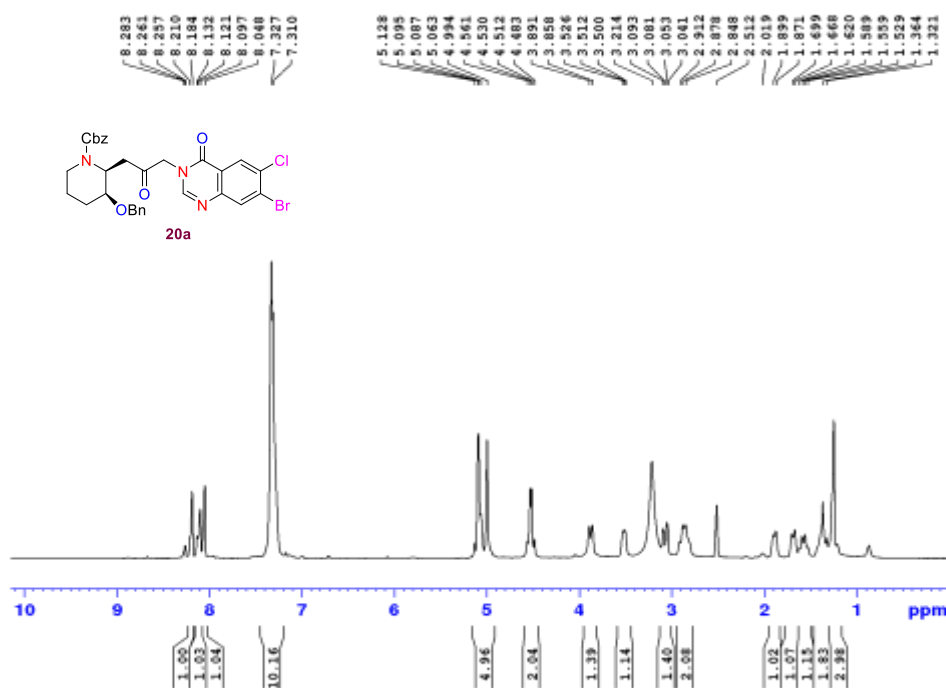
Total synthesis of *Febrifugine* and *Halofuginone*





Total synthesis of *Febrifugine* and *Halofuginone*

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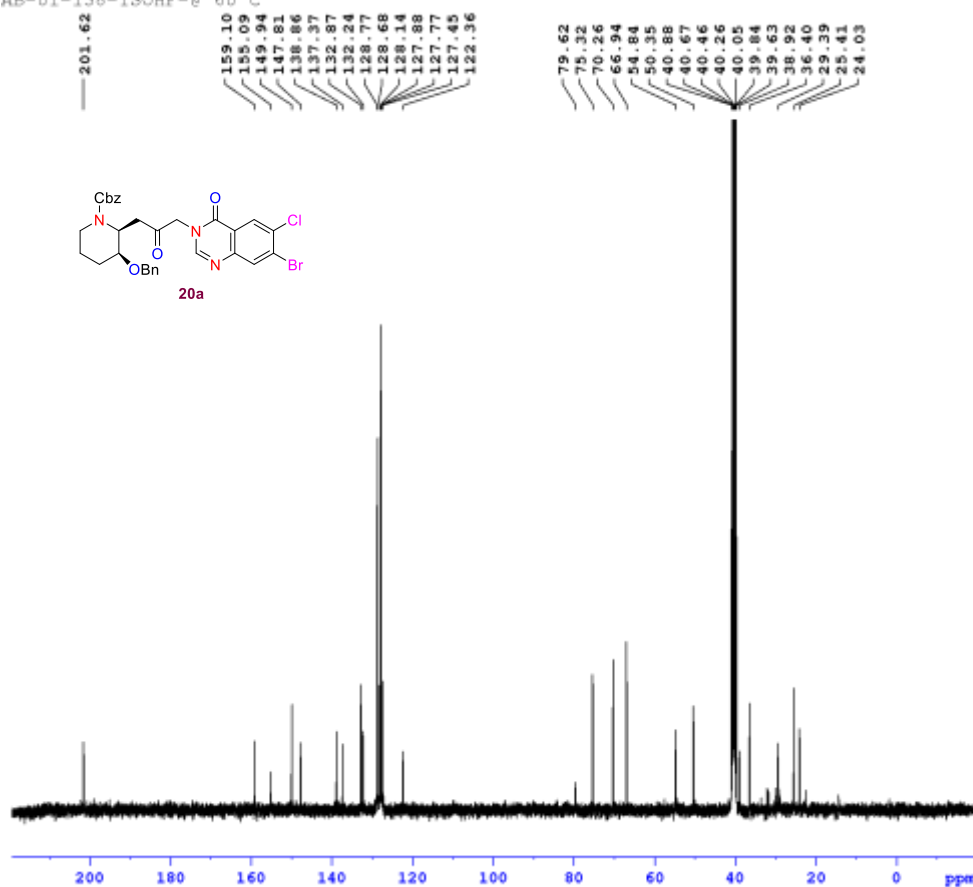
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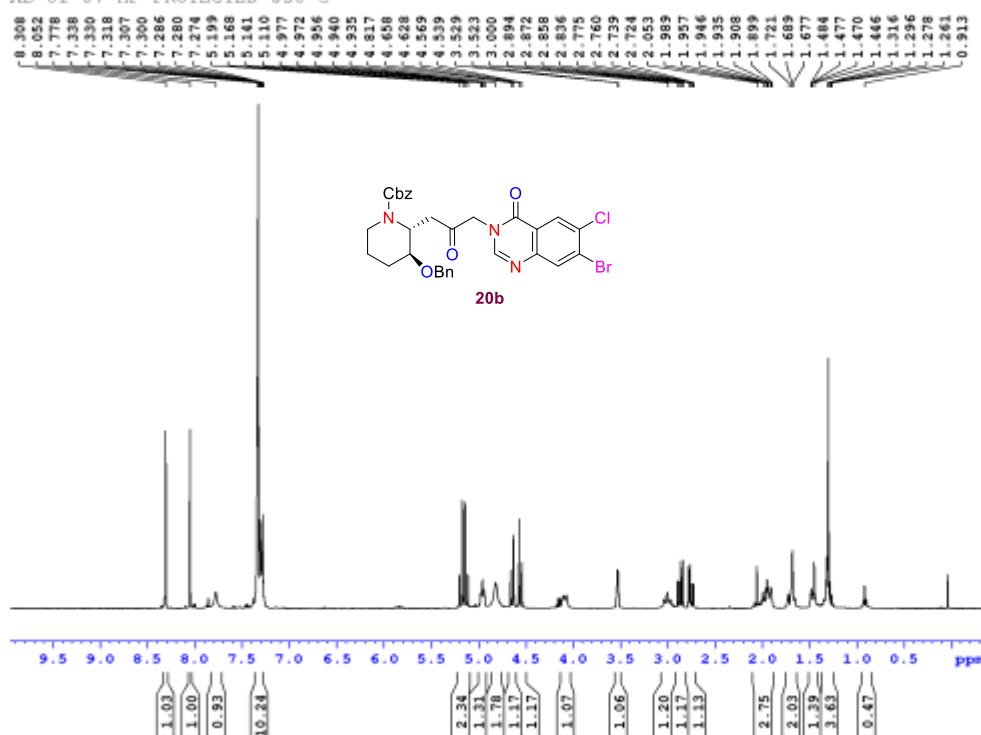
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AB-01-07 HF PROTECTED 850'C



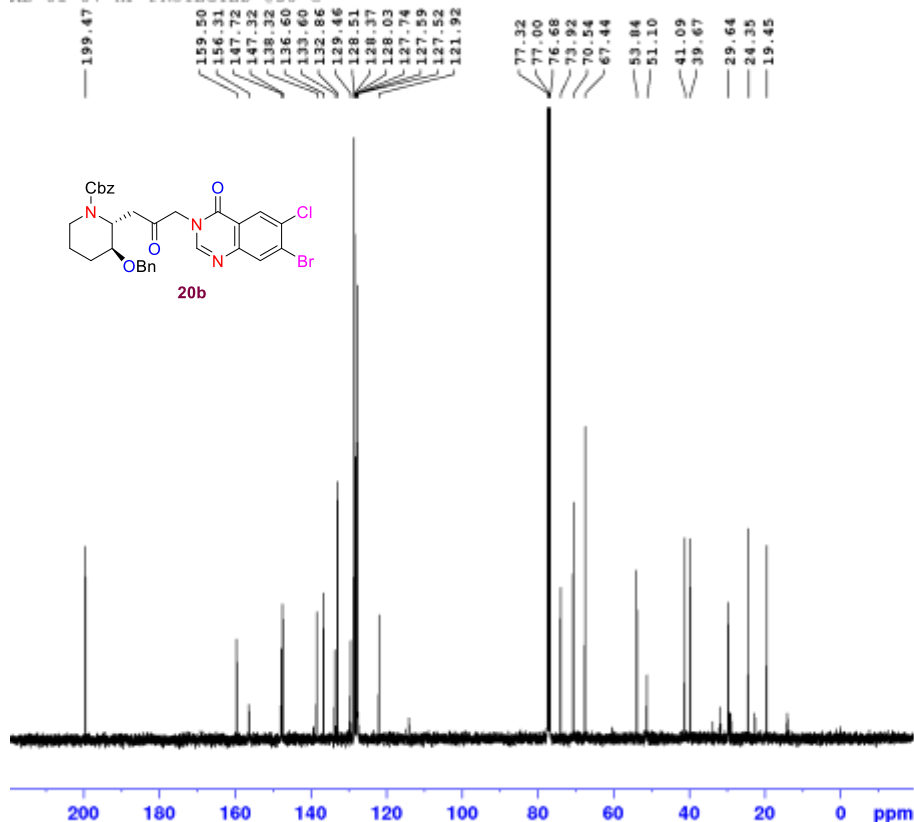
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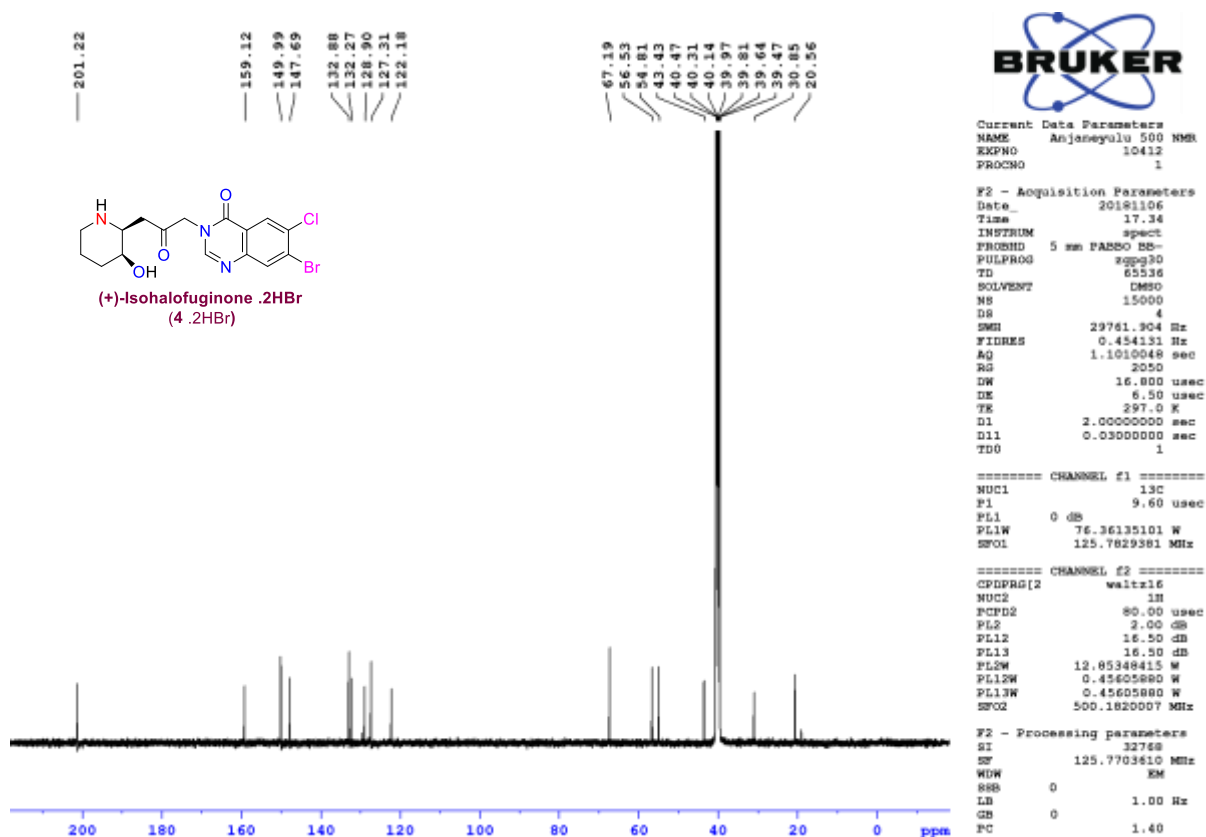
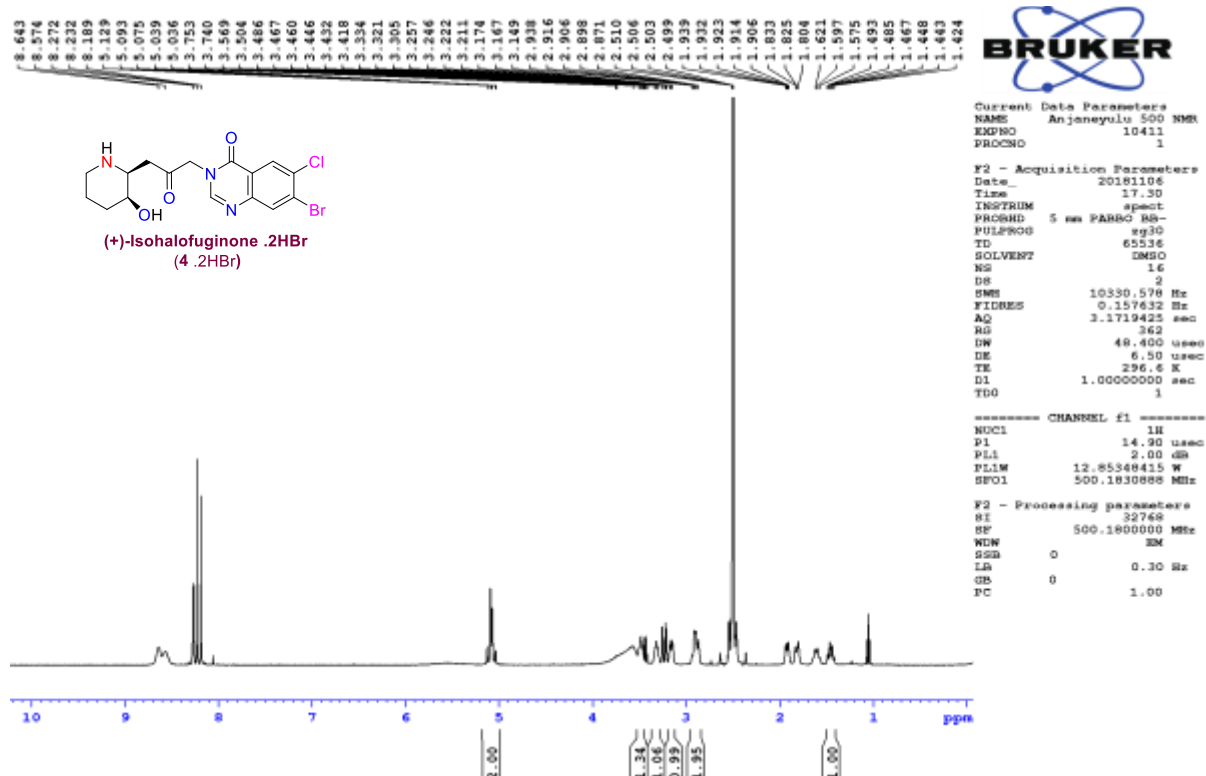
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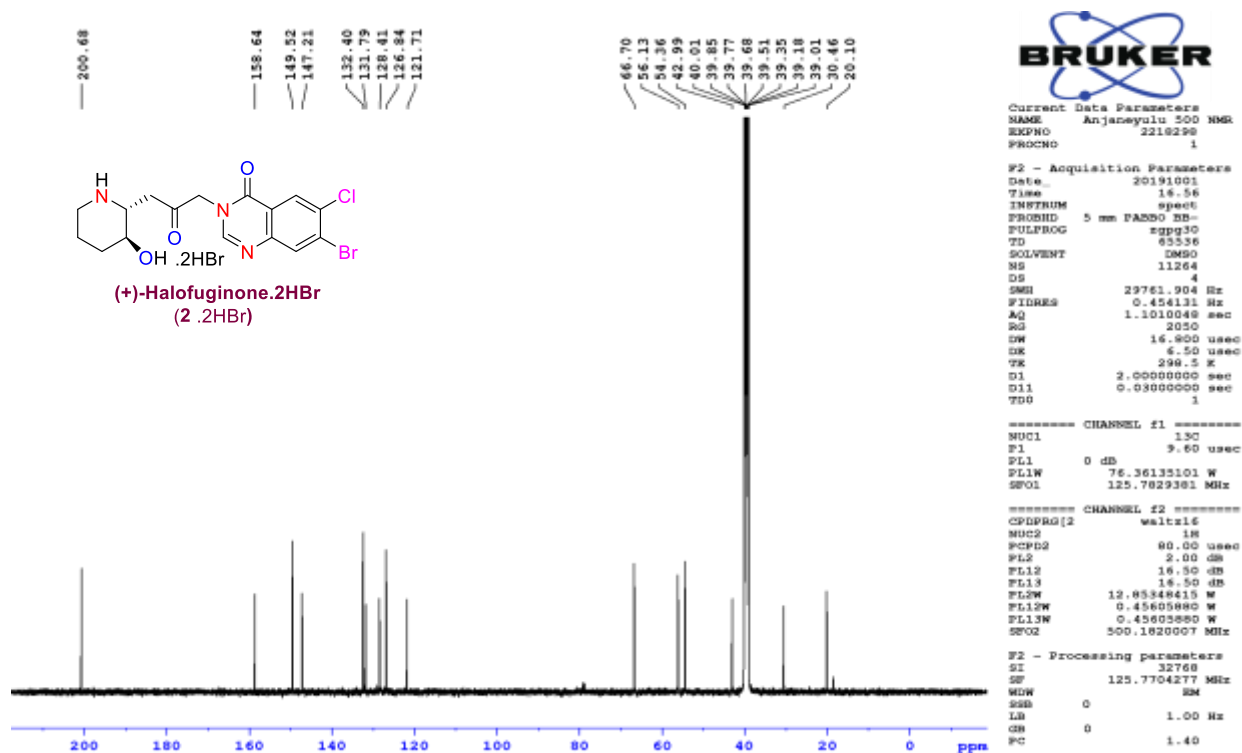
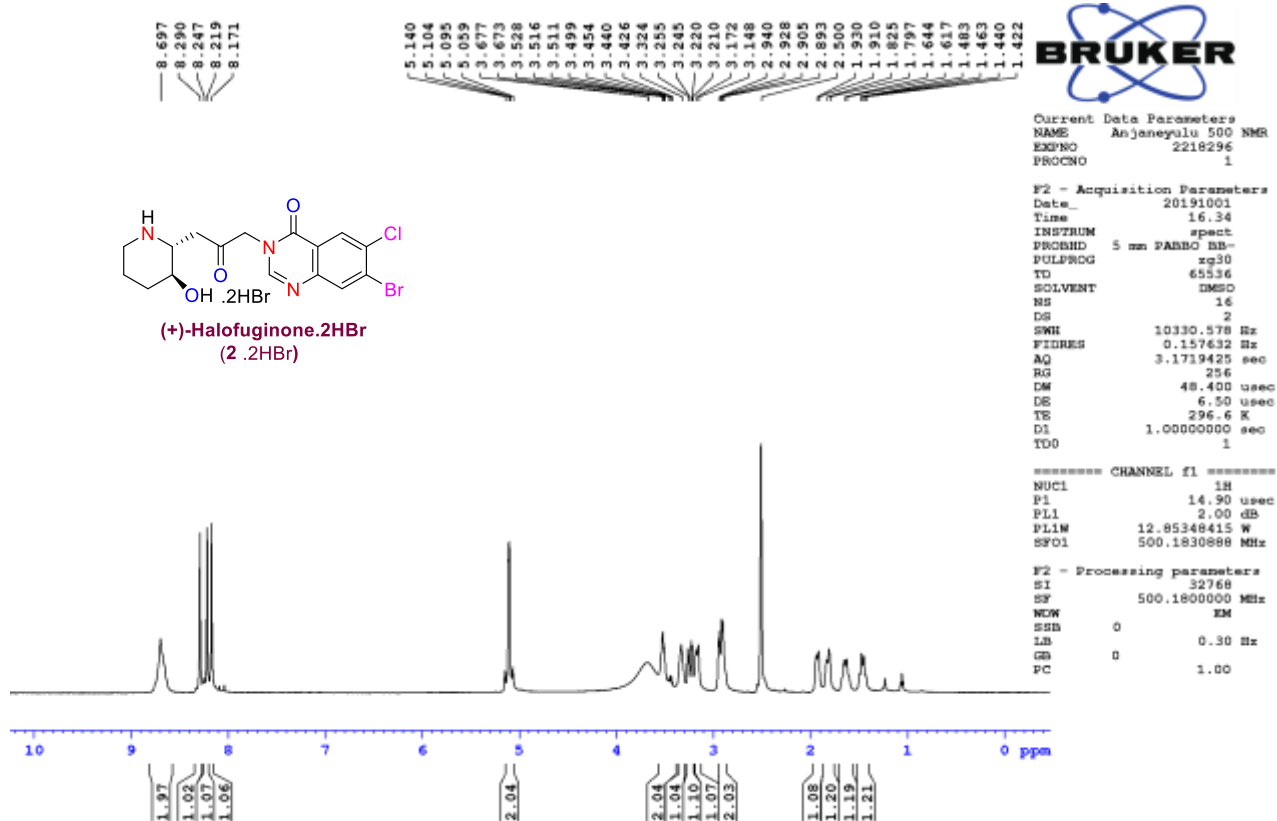
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NUC2 1H
PCPD2 90.00 usec
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PL12 17.18 dB
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PL1W 0.41063678 W
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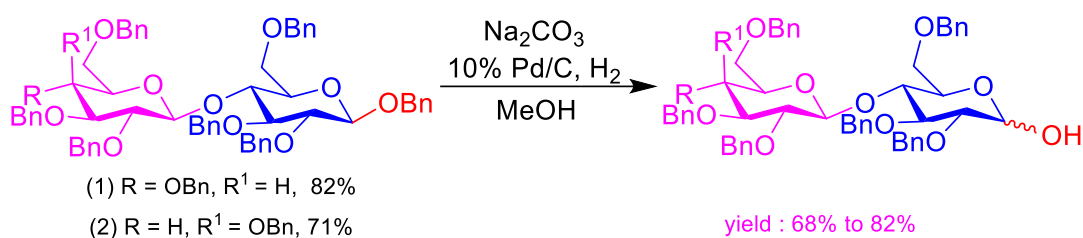
Total synthesis of *Febrifugine* and *Halofuginone*





Chapter-3

Regioselective anomeric O-benzyl deprotection in Carbohydrates



3.1 Introduction

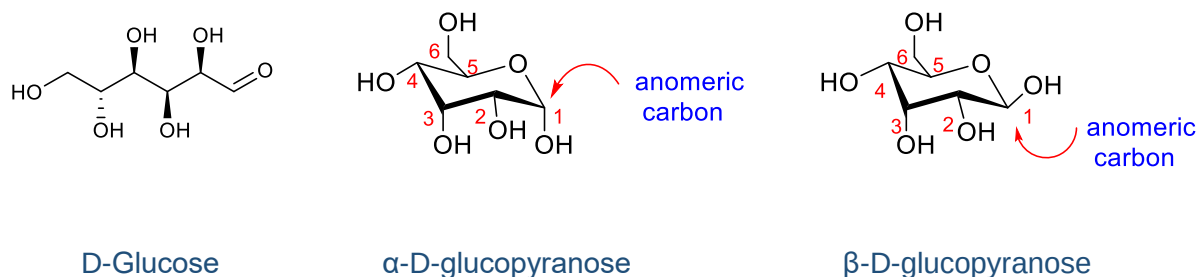
3.4 Experimental section

3.2 Results and Discussions

3.5 References

3.3 Conclusions

3.1 Introduction

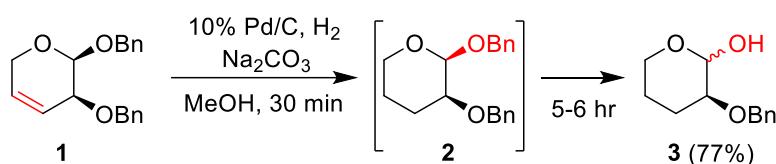


In the cyclic form of a sugar, the anomeric carbon is the carbon that was part of the carbonyl group in the straight-chain structure. Majority of the sugar chemistry belong to the anomeric carbon atom. Despite great advances, the stereo controlled synthesis of glycosides with a desired anomeric orientation remains a challenge. Many natural products and biologically active molecules having specified configuration at anomeric position.

Benzyl is one of the widely used protective groups for hydroxyl function in synthetic organic chemistry. It is due to its ease of installation, stability, non-migratory aptitude, and mild deprotection conditions of the benzyl group.¹ The typical deprotection of benzyl ethers to form the corresponding alcohol involves the hydrogenolysis reaction using Pd/C under hydrogen atmosphere. Apart from benzyl ethers, the commonly used *O*-benzylidene acetals undergo partial² or complete³ deprotection under hydrogenolysis conditions. Due to the electron-donating nature of this protecting group, glycosyl donors or acceptors protected with the benzyl group are called armed donors or armed acceptors, respectively.^{4,5} In this context, benzyl protection for non-anomeric hydroxyl function in oligosaccharide synthesis is perhaps, a necessary scenario. Interestingly, a couple of methods have been reported for the regioselective removal of the benzyl protecting group from non-anomeric positions.^{6,7} However, when it comes to anomeric position, benzyl as a protective group did not get much application in oligosaccharide synthesis. This is primarily due to the difficulty in selective deprotection of the anomeric benzyl group in the presence of non-anomeric benzyl protected hydroxyls, which

requires strong acidic conditions.⁸ A catalytic transfer hydrogenation has been reported for the regioselective anomeric *O*-benzyl deprotection.^{9,10}

In continuation of our research on the application of carbohydrate substrates in the total synthesis of natural products, we required a transformation in which the unsaturated benzyl acetal **1** be converted to the corresponding saturated acetal derivative **2**. Towards this, we subjected compound **1** to hydrogenation reaction using catalytic 10% Pd/C under hydrogen atmosphere in the presence of sodium carbonate.¹¹ In this process, we observed that the hydrogenation of the alkene occurs within 30 minutes providing the product **2**. However, prolonged stirring for 5 – 6 hours afforded the regioselective hydrogenolysis product **3** (Scheme 1).¹² This observation prompted us to investigate the selective hydrogenolysis of anomeric *O*-benzyl group in various carbohydrate derivatives.



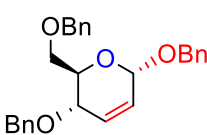
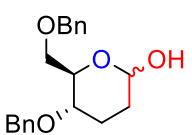
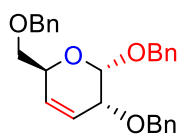
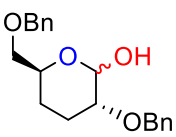
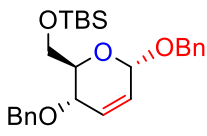
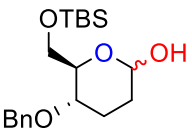
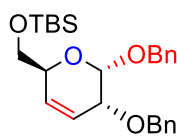
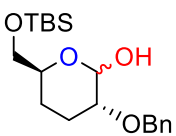
Scheme 1. Regioselective hydrogenolysis with concomitant hydrogenation of benzyl acetal.

3.2 Results and Discussion

Initially, we focused on one-pot hydrogenation of olefin followed by regioselective hydrogenolysis in various benzyl protected unsaturated glycosides. Thus, 2,3-unsaturated and 3,4-unsaturated benzyl glycosides **4** and **6** were subjected to 10% Pd/C, H₂ in methanol with 1 equivalent of sodium carbonate. As expected, both the compounds provided the hemiacetals **5**¹³ and **7** in good yield (Table 1, entries 1 and 2). Likewise, 6-*O*-*tert*-butyldimethylsilyl protected 2,3-unsaturated and 3,4-unsaturated benzyl glycosides **8** and **10**, also provided the hemiacetals **9** and **11** without affecting the *O*-benzyl at C-4 and C-2 position, respectively, while *tert*-butyldimethylsilyl is also intact (Table1, entries 3 and 4).

To investigate the stability of other common hydroxyl protective groups under the anomeric debenzylation reaction conditions, we planned to synthesize a series of benzyl glycosides that possessed various orthogonal protecting groups, including benzyl ethers at the

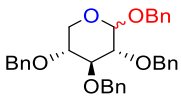
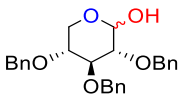
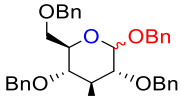
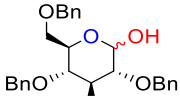
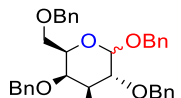
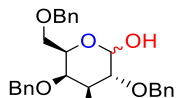
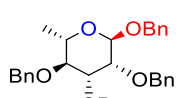
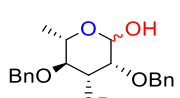
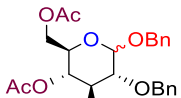
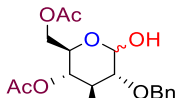
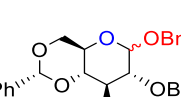
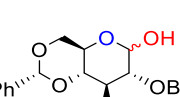
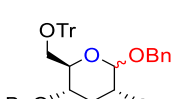
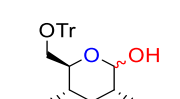
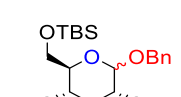
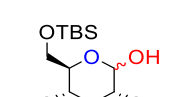
Table 1. Regioselective hydrogenolysis of the unsaturated benzyl glycosides

Entry No.	Substrate	Time (hr)	Product	Yield % ^[a]
1	 4	10	 5	77
2	 6	10	 7	81
3	 8	10	 9	82
4	 10	8	 11	85

[a] Yield refers to pure and isolated products.

non-anomeric position. Thus, perbenzylated hexoses like the perbenzylated D-xylose **12**,^[10] D-glucose **14**,¹⁴ D-galactose **16**¹⁵ and L-rhamnose **18**¹⁶ upon treatment with 10% Pd/C, H₂ in methanol in the presence of sodium carbonate (1 equivalent) afforded the hemiacetals **13**¹⁷, **15**¹⁵, **17**¹⁵ and **19**¹⁸, respectively, in excellent yield. In all the above transformations, no detectable amount of the products derived from hydrogenolysis of non-anomeric benzyl groups was observed, (Table 2, entries 1-4).

Table 2. Protective group tolerance in the regioselective hydrogenolysis of the anomeric benzyl

Entry No.	Substrate	Time (hr)	Product	Yield %
5 group		8		70
	12		13	
6		5		71
	14		15	
7		6		72
	16		17	
8		10		75
	18		19	
9 ^[a]		6		75
	20		21	
10		9		68
	22		23	
11		5		80
	24		25	
12		10		72
	26		27	

[a] yield refers to pure and isolated products. [b] tetrahydrofuran (THF) was used as a solvent in place of methanol.

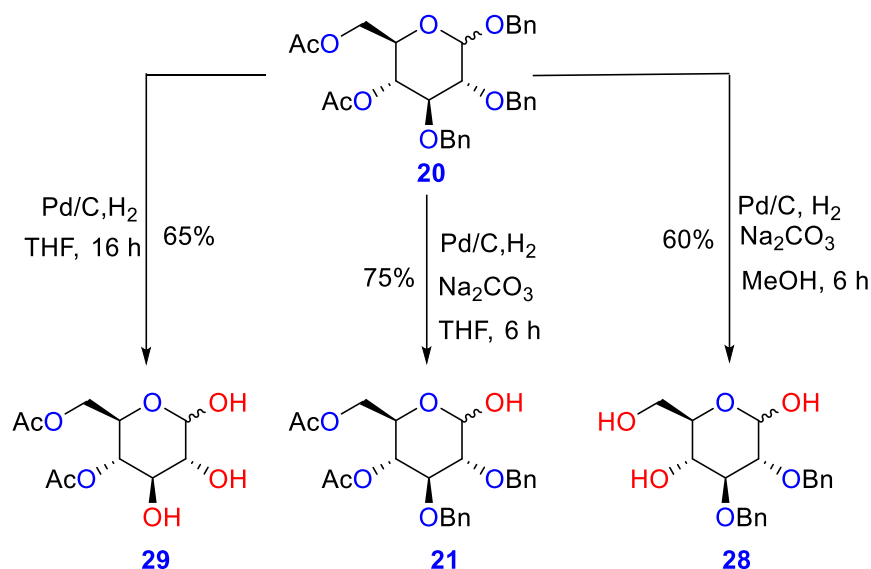
One of the widely used protecting groups for hydroxyl function in carbohydrate chemistry is the corresponding acetate ester. In view of evaluating the stability of this base sensitive protective group, benzyl 4,6-di-O-acetyl-2,3-di-O-benzyl glucoside **20** was prepared and subjected to Pd/C/H₂ with 1 equivalent of sodium carbonate in dry THF. Interestingly, the

reaction proceeded smoothly, without affecting the acetyl protecting group, and provided the hemiacetals **21** (Table 2, entry 5). Further, to evaluate the stability of acid-sensitive protecting groups, like benzylidene, trityl, and *tert*-butyldimethylsilyl, benzyl glycosides **22**¹⁰, **24**¹⁰ and **26** were synthesized and subjected to the above regioselective anomeric debenzylation reaction conditions. Again, it was shown that these protective groups are stable, and the only products isolated were the corresponding hemiacetals **23**¹⁹, **25**¹⁰ and **27**, respectively, in good yield ((Table 2, entries 6-8). These results show that the OTBS, OAc, benzylidene acetal, and trityl protecting groups were stable under the present regioselective anomeric benzyl deprotection reaction conditions.

Proving the versatility of the reaction to obtain glycosylation precursors of monosaccharides, we further plan to scrutinize the scope of the reaction in various benzyl and benzylidene-protected disaccharides. Thus, perbenzyl disaccharide derivatives of lactose **28**,²⁰ maltose **30** and cellobiose **32** were evaluated for hemiacetal formation. Interestingly these disaccharides upon above-developed hydrogenolysis reaction conditions provided the disaccharide hemiacetals **29**, **31**²¹, and **33**, respectively, in moderate yield (Table 3, entries 1,2 &3). Similarly, benzylidene protected lactose **34** upon subjecting to regioselective hydrogenolysis conditions provided the corresponding hemiacetal **35**²², in good yield (Table 3, entry 4).

To emphasize the importance of the present methodology, compound **20** was subjected to hydrogenolysis in the presence of Na₂CO₃ in methanol solvent. As expected, de-acetylation along with regioselective hydrogenolysis was observed by isolating the compound **28**. On the other hand, when hydrogenolysis was performed in THF solvent in the absence of Na₂CO₃ provided the diacetate **29** in moderate yield, where all the benzyl groups were deprotected (Scheme 2).²¹

We further scrutinize the method by change the solvent system and presence and absence of sodium carbonate in reaction, results depicted the importance of sodium carbonate as below.



3.3 Conclusions

In conclusion, regioselective hydrogenolysis of the anomeric benzyl group is reported using 10% Pd/C in the presence of 1 eq of sodium carbonate under the hydrogen atmosphere. The scope and the generality of the methodology were evaluated by applying it to synthesize several carbohydrate-derived hemiacetals. In general, the hydrogenolysis is orthogonally selective in the presence of benzylidene, benzyl, TBDMS, trityl and acetate protective groups. The methodology is equally applicable in the case of disaccharide derivatives. The synthesis of biologically important oligosaccharides using the present methodology is in progress. However, at present, the influence of sodium carbonate and the reason for the regioselective hydrogenolysis of the anomeric benzyl group under the prescribed reaction conditions is not clearly understood, which may require further research.

3.4 Experimental section

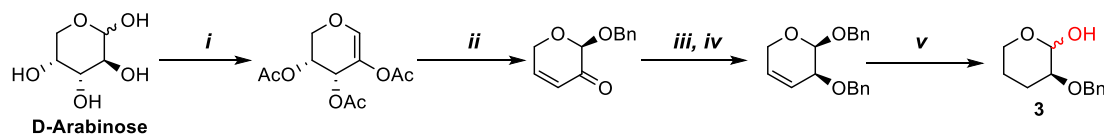
3.4.1 General Methods

General procedure for hydrogenolysis of benzyl acetals:

To a stirred solution of benzyl acetal (1.0 equi) in methanol (20 vol) at rt, was added sodium carbonate (1.0 equi). The reaction mixture was stirred for 10 min, then Palladium (10 wt. %) on activated carbon (100 mg/gr) was added under nitrogen atmosphere. After degassing the reaction mixture for 5 min, the stirring was continued under hydrogen atmosphere (using balloon) for 4-10 hr at rt. After completion of the reaction (monitored by TLC) the suspension was filtered through a small pad of celite, and the filter cake was washed with methanol. Evaporation of the methanol under reduced pressure followed by purification of the afforded crude product by flash column chromatography over silica gel (hexanes/ethyl acetate) provided the corresponding mixture of hemiacetal.

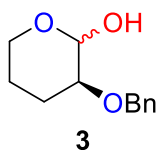
3.4.2 Experimental procedures and spectral data

Synthesis of (3S)-3-(benzyloxy) tetrahydro-2H-pyran-2-ol (3)



i, (a) Ac_2O , HClO_4 , 33% HBr in AcOH , (b) DBU , DCM , $-10\text{ }^\circ\text{C}$; **ii**, BnOH , $\text{BF}_3\cdot\text{OEt}_2$, Dry DCM , $0\text{ }^\circ\text{C}$; **iii**, NaBH_4 , $\text{CeCl}_3\cdot 7\text{H}_2\text{O}$, MeOH , $-10\text{ }^\circ\text{C}$, **iv**, BnBr , NaH , DMF ; **v**, 10% Pd/C , Na_2CO_3 , H_2 , MeOH

(3S)-3-(benzyloxy)tetrahydro-2H-pyran-2-ol (3)



Yield: 3.8 gm, 77%, R_f : 0.6 (50 % EtOAc /hexane)

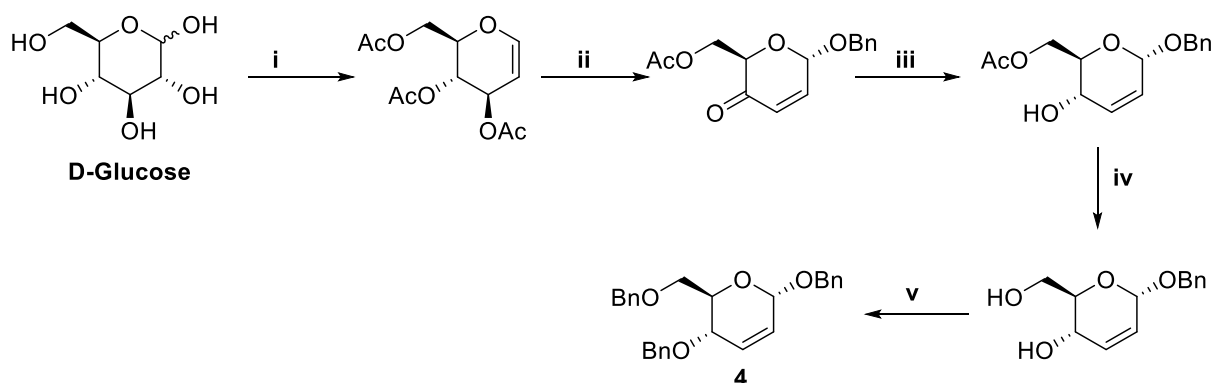
IR (neat): 3305, 3058, 3030, 2945, 2882, 1718, 1696, 1496, 1452, 1373 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.28-7.39 (m, 5H), 4.94-4.96 (m, 0.5H), 4.79-4.81 (m, 0.5H), 4.67-4.69 (m, 1.5H), 4.55 (d, 0.5H, J = 12.0 Hz), 3.95-3.98 (m, 1H), 3.52-3.55 (m, 1.5H), 3.27-3.29 (m, 0.5H), 2.05-2.08 (m, 0.5H), 1.95-2.00 (m, 0.5H), 1.60-1.81 (m, 2H), 1.49-1.55 (m, 1H)

^{13}C NMR (125 MHz, CDCl_3): δ = 138.56, 137.96, 128.51, 128.38, 127.89, 127.82, 127.73, 127.60, 96.69(β), 92.57(α), 76.06, 74.44, 71.62, 70.87, 63.57, 62.13, 26.32, 24.39, 23.12, 22.28 ppm.

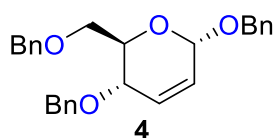
HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$: calcd for $\text{C}_{12}\text{H}_{16}\text{O}_3\text{Na}$ 231.0997, found: 231.0997.

(2R,3S,6S)-3,6-bis(benzyloxy)-2-((benzyloxy)methyl)-3,6-dihydro-2H-pyran (4)



i, (a) Ac_2O , HClO_4 , 33% HBr in AcOH , (b) Activated Zinc, saturated NaH_2PO_4 , acetone; **ii,** BnOH , $\text{BF}_3\cdot\text{OEt}_2$, DCM , 0°C ; **iii,** NaBH_4 , $\text{CeCl}_3\cdot 7\text{H}_2\text{O}$, MeOH , -10°C **iv,** K_2CO_3 , MeOH ; **v,** BnBr , NaH , DMF .

(2R,3S,6S)-3,6-bis(benzyloxy)-2-((benzyloxy)methyl)-3,6-dihydro-2H-pyran (4)



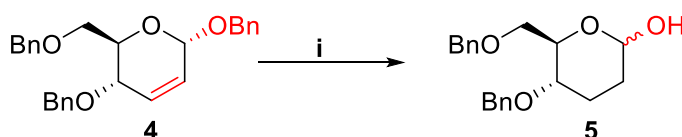
Yield: 100 mg, 90%, R_f : 0.6 (10% EtOAc /hexane):

IR (neat): 3059, 3028, 2933, 2896, 2871, 2809, 1604, 1496, 1480, 1452, 1407, 1039 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ 7.26-7.38 (m, 15H), 6.11 (d, 1H, J = 10.5 Hz), 5.80-5.83 (m, 1H), 5.15 (bs, 1H), 4.84 (d, 1H, J = 12.0 Hz), 4.67 (d, 1H, J = 12.5 Hz), 4.62 (dd, 2H, J = 3.0 Hz, J = 11.5 Hz), 4.54 (d, 1H, J = 12.0 Hz), 4.47 (d, 1H, J = 11.5 Hz), 4.22 (d, 1H, J = 9.5 Hz), 4.02-4.05 (m, 1H), 3.75 (dd, 1H, J = 4.0 Hz, J = 10.5 Hz), 3.66 (d, 1H, J = 11.0 Hz).

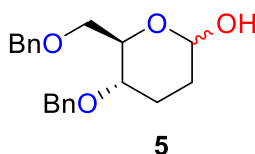
^{13}C NMR (125 MHz, CDCl_3): δ 138.2, 138.1, 130.8, 128.3, 128.3, 128.0, 127.8, 127.7, 127.6, 126.5, 93.9(α), 73.4, 71.0, 70.4, 70.0, 69.3, 68.8.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{27}\text{H}_{28}\text{O}_4\text{Na}$ 439.1885, found 439.1880.



i, Na_2CO_3 , 10% Pd/C, H_2 , MeOH, 77%

(5*S*, 6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-ol (5)



Yield: 115 mg, 77%, R_f : 0.4 (50% EtOAc/hexane). α/β :1.3/1

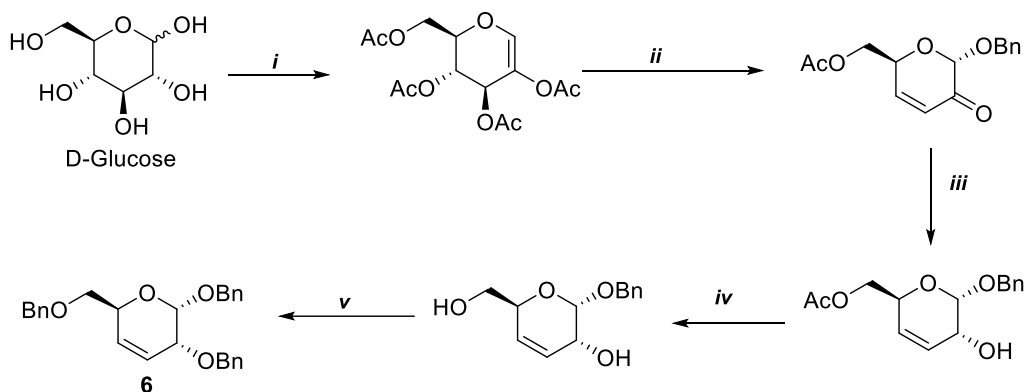
IR (neat): 3389, 3062, 3032, 2932, 2856, 1664 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ 7.24-7.38 (m, 23H), 5.30 (s, 1.3H), 4.79 (d, 1H, J = 7.5 Hz), 4.64 (d, 1.3H, J = 2.0 Hz), 4.61 (s, 2.3H), 4.54-4.60 (m, 3.3H), 4.43 (d, 1.3H, J = 4.0 Hz), 4.41 (d, 1H, J = 4.0 Hz), 4.09 (ddd, 1.3H, J = 2.0 Hz, J = 5.5 Hz, J = 9.5 Hz), 3.73-3.79 (m, 2.3H), 3.72 (d, 1H, J = 2.5 Hz), 3.66-3.70 (m, 2.3H), 3.60 (ddd, 1H, J = 2.0 Hz, J = 5.5 Hz, J = 9.0 Hz), 3.38-3.48 (m, 2.3H), 3.21 (s, 1.3H), 2.21-2.25 (m, 1H), 2.02-2.06 (m, 1.3H), 1.84-1.94 (m, 4.6H), 1.70-1.76 (m, 1.3H), 1.49-1.51 (d, 1H, J = 9.5 Hz).

^{13}C NMR (125 MHz, CDCl_3): δ 138.4, 138.2, 138.1, 128.3, 128.3, 127.9, 127.6, 127.6, 127.6, 127.6, 127.5, 95.9(β), 90.9(α), 78.0, 73.5, 73.4, 73.2, 72.6, 71.3, 71.1, 70.6, 69.7, 31.3, 28.9, 27.2, 23.2.

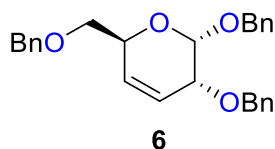
HRMS (ESI-TOF) m/z : $[M+Na]^+$ calcd for $C_{20}H_{24}O_4Na$ 351.1567, found 351.1568.

Synthesis of (2*S*,3*R*,6*S*)-2,3-bis(benzyloxy)-6-((benzyloxy)methyl)-3,6-dihydro-2*H*-pyran (6)



i, (a) Ac_2O , $HClO_4$, 33% HBr in $AcOH$, (b) DBU , DCM , $-10\text{ }^\circ C$; **ii**, $BnOH$, $BF_3 \cdot OEt_2$, Dry DCM , $0\text{ }^\circ C$; **iii**, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, $MeOH$, $-10\text{ }^\circ C$; **iv**, K_2CO_3 , $MeOH$; **v**, $BnBr$, NaH , DMF .

(2*S*,3*R*,6*S*)-2,3-bis(benzyloxy)-6-((benzyloxy)methyl)-3,6-dihydro-2*H*-pyran (6)



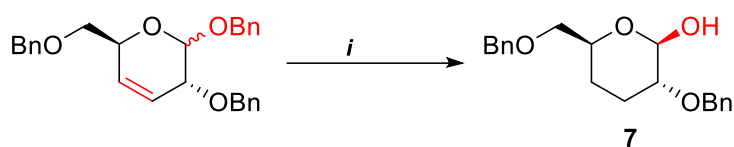
Yield: 450 mg, 85%, R_f : 0.7 (10% $EtOAc$ /hexane);

IR (neat): 3094, 3059, 3029, 2855, 2862, 1495, 1452, 1365, 1307, 1093, 1071, 1021 cm^{-1} .

^1H NMR (500 MHz, $CDCl_3$): δ 7.27-7.46 (m, 15H), 5.84-5.87 (m, 1H), 5.81 (dt, 1H, $J = 1.5$ Hz, $J = 11.0$ Hz), 5.13 (d, 1H, $J = 4.0$ Hz), 4.86 (d, 1H, $J = 12.5$ Hz), 4.69 (d, 1H, $J = 12.5$ Hz), 4.60 (ddd, 2H, $J = 12.5$ Hz, $J = 3.0$ Hz, $J = 15.5$ Hz), 4.54 (ddd, 2H, $J = 12.5$ Hz, $J = 1.0$ Hz, $J = 13.5$ Hz), 4.39-4.42 (m, 1H), 4.16-4.18 (m, 1H), 3.54 (d, 2H, $J = 5.5$ Hz).

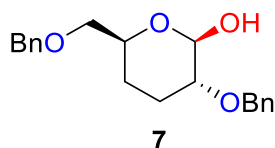
^{13}C NMR (125 MHz, $CDCl_3$): δ 138.0, 138.0, 137.6, 128.3, 128.3, 128.3, 128.2, 127.7, 127.7, 127.6, 126.6, 127.4, 125.5, 94.28 (α), 73.4, 72.0, 70.8, 70.7, 69.3, 68.2.

HRMS (ESI-TOF) m/z : $[M+Na]^+$ calcd for $C_{20}H_{24}O_4Na$ 351.1572, found 351.1568.



i, 10% Pd/C, Na₂CO₃, H₂, MeOH, 81%

(2R,3R,6S)-3-(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-ol (7)



Yield: 220 mg, 81%, α/β :0.4/1, R_f: 0.4 (50% EtOAc/hexane),

data for β isomer:

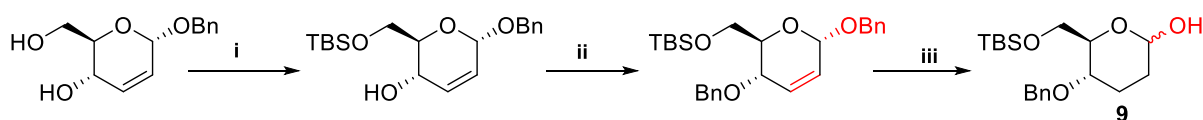
IR (neat): 3427, 3029, 2923, 2856, 2361, 1730, 1495, 1453 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 7.28-7.37 (m, 10H), 4.95 (d, 1H, J = 3.5 Hz), 4.82 (d, 1H, J = 12.0 Hz), 4.54-4.58 (m, 3H), 3.92-3.96 (m, 1H), 3.63-3.69 (m, 1H), 3.44-3.50 (m, 2H), 1.90-1.94 (m, 2H), 1.68-1.77 (m, 2H), 1.49-1.58 (m, 1H).

¹³C NMR (125 MHz, CDCl₃): δ 138.3, 137.6, 128.4, 128.3, 128.0, 127.8, 127.6, 127.5, 97.7(β), 73.3, 72.6, 69.2, 68.1, 67.8, 27.4, 26.9.

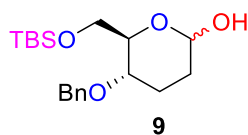
HRMS (ESI-TOF) m/z : [M+Na]⁺ calcd for C₂₀H₂₄O₄Na 351.1572, found 351.1568.

Synthesis of (5S,6R)-5-(benzyloxy)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-ol (9)



i, TBS-Cl, imidazole, DMF, 68 %; **ii**, BnBr, NaH, DMF 85%; **iii**, Na₂CO₃, 10% Pd/C, H₂, MeOH, 82%

(5S,6R)-5-(benzyloxy)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-ol (9)



Yield: 150 mg, 82%, R_f: 0.4 (30% EtOAc/hexane). α/β :0.25/1

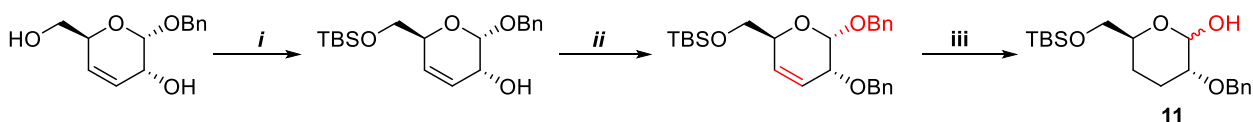
IR (neat): 3425, 2927, 2855, 1737, 1495, 1458 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 7.27-7.37 (m, 6.25H), 4.88 (d, 0.25H, J = 3.5 Hz), 4.85 (d, 1H, J = 3.0 Hz), 4.72 (d, 0.25H, J = 12.0 Hz), 4.71 (d, 1H, J = 12.0 Hz), 4.49 (d, 1H, J = 12.0 Hz), 4.47 (d, 0.25H, J = 12.0 Hz), 3.84 (dd, 1H, J = 4.0 Hz, J = 9.5 Hz), 3.80 (ddd, 0.25H, J = 3.0 Hz, J = 6.0 Hz, J = 14.5 Hz), 3.73-3.76 (m, 1H), 3.69-3.72 (m, 0.25H), 3.58-3.67 (m, 2.5H), 3.33 (s, 1H), 2.98-2.04 (m, 0.25H), 1.86-1.89 (m, 3H), 1.69-1.83 (m, 2H), 0.92 (s, 9H), 0.89 (s, 2.25H), 0.12 (s, 3H), 0.11 (s, 3H), 0.09 (s, 0.75H), 0.08 (s, 0.75H).

¹³C NMR (125 MHz, CDCl₃): δ 138.0, 137.9, 128.3, 128.3, 127.8, 127.7, 127.6, 127.5, 95.5(β), 95.4(α), 73.6, 71.4, 70.2, 68.6, 67.4, 66.2, 62.7, 29.3, 28.8, 27.9, 26.3, 25.8, 25.7, 18.2, 17.9, -4.1, -4.9, -5.5, -5.6.

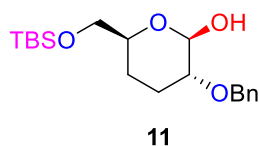
HRMS (ESI-TOF) m/z : [M+Na]⁺ calcd for C₁₉H₃₂O₄SiNa 375.1968, found 375.1966.

Synthesis of (2*R*,3*R*,6*S*)-3-(benzyloxy)-6-(((*tert*-utyldimethylsilyl)oxy)methyl)tetrahydro-2*H*-pyran-2-ol (11)



i, TBS-Cl, imidazole, DMF, 68 %; **ii,** BnBr, NaH, DMF 80 %; **iii,** Na₂CO₃, 10% Pd/C, H₂, MeOH, 85 %

(2*R*,3*R*,6*S*)-3-(benzyloxy)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydro-2*H*-pyran-2-ol (11)



Yield: 120 mg, 85%, α/β :0.2/1, R_f: 0.4 (30 % EtOAc/hexane)

data for β isomer:

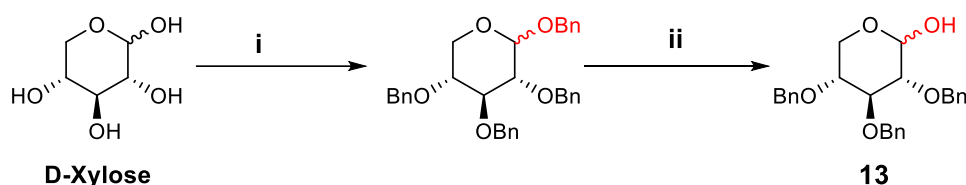
IR (neat): 3582, 3053, 2953, 2929, 2856, 2307, 1457, 1361, 1264, 1095 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 7.32-7.38 (m, 5H), 4.92 (d, 1H, J = 3.5 Hz), 4.83 (d, 1H, J = 11.5 Hz), 4.54 (d, 1H, J = 12.0 Hz), 3.77-3.82 (m, 1H), 3.62 (m, 2H), 3.55 (dd, 1H, J = 5.0 Hz, J = 10.5 Hz), 1.91-1.95 (m, 1H), 1.90 (d, 1H, J = 11.0 Hz), 1.71-1.80 (m, 2H), 0.92 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 137.7, 128.4, 128.0, 127.8, 97.5(β), 69.4, 69.0, 68.3, 66.0, 27.4, 26.8, 25.9, 18.3, -5.2, -5.3.

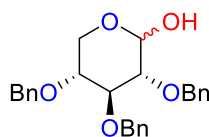
HRMS (ESI-TOF) m/z :[M] calcd for C₁₉H₃₂O₄Si 352.2070, found 252.2293.

Synthesis of 2,3,4-tri-O-benzyl- α/β -D-xylopyranose (13)



i, BnBr, NaH, DMF 85%; ii, Na₂CO₃, 10% Pd/C, H₂, MeOH, 70%.

2,3,4-tri-O-benzyl- α/β -D-xylopyranose (13)



Yield: 150 mg, 70%, R_f: 0.2 (30% EtOAc/hexane). α/β :1/1

IR (neat): 3342, 3062, 3028, 2922, 1495, 1452, 1358, 1143, 1116, 1069 cm⁻¹

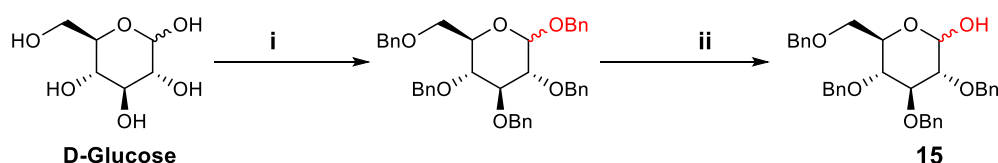
¹H NMR (500 MHz, CDCl₃): δ 7.28-7.36 (m, 30H), 5.11 (t, 1H, J = 3.0 Hz), 4.83-4.91 (m, 5H), 4.77 (d, 2H, J = 11.0 Hz), 4.72 (dd, 2H, J = 1.5 Hz, J = 11.5 Hz), 4.62-4.69 (m, 4H), 3.94-

3.97 (m, 1H), 3.87 (t, 1H, $J = 8.5$ Hz), 3.80 (t, 1H, $J = 10.5$ Hz), 3.67 (dd, 1H, $J = 5.0$ Hz, $J = 11.0$ Hz), 3.58-3.64 (m, 2H), 3.53-3.57 (m, 1H), 3.48 (dd, 1H, $J = 3.5$ Hz, $J = 9.0$ Hz), 3.25-3.36 (m, 3H), 3.05 (d, 1H, $J = 2.5$ Hz)

^{13}C NMR (125 MHz, CDCl_3): δ 138.6, 138.5, 138.3, 138.2, 138.1, 137.8, 128.5, 128.4, 128.4, 128.4, 128.3, 128.0, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 127.7, 127.6, 97.7(β), 91.5(α), 83.2, 82.3, 80.5, 79.5, 77.5, 77.5, 75.4, 75.4, 74.7, 73.4, 73.2, 73.2, 63.7, 60.4.

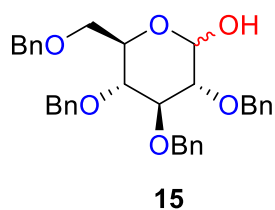
HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{28}\text{O}_5\text{Na}$ 443.1834, found 443.1812.

Synthesis of 2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranose (15)



i, BnBr, NaH, DMF 85%; **ii**, Na_2CO_3 , 10% Pd/C, H_2 , MeOH, 71%

2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranose (15)



Yield: 1.82 gm, 71%, R_f : 0.4 (50% EtOAc/hexane). α/β :2/1

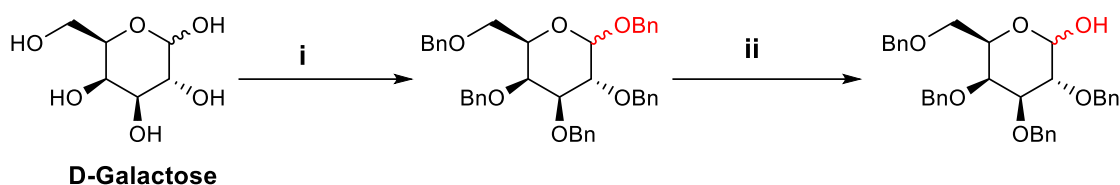
IR (neat): 3351, 3061, 3028, 2906, 2858, 1494, 1451, 1356, 1144, 1072 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ 7.28-7.40 (m, 27H), 7.16-7.19 (m, 3H), 5.26 (d, 1H, $J = 2.5$ Hz), 4.95-4.99 (m, 2H), 4.83-4.89 (m, 3H), 4.80 (s, 0.5H), 4.78 (s, 1H), 4.71-4.75 (m, 2H), 4.63 (d, 0.5H, $J = 5.5$ Hz), 4.60 (d, 1H, $J = 5.5$ Hz), 4.56 (d, 1.5H, $J = 12.0$ Hz), 4.52 (d, 1.5H, $J = 12.0$ Hz), 4.07-4.09 (m, 1H), 3.99-4.04 (m, 1H), 3.73 (dd, 1.5H, $J = 4.0$ Hz, $J = 10.5$ Hz), 3.65-3.70 (m, 3H), 3.61 (dd, 1.5H, $J = 4.5$ Hz, $J = 9.5$ Hz), 3.50-3.58 (m, 1H), 3.21 (bs, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ 138.7, 138.5, 138.3, 138.2, 138.0, 137.8, 137.8, 128.5, 128.4, 128.3, 128.3, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 127.6, 126.9, 97.5(β), 91.3(α), 84.5, 83.1, 81.7, 80.0, 77.8, 77.7, 75.6, 75.6, 74.9, 74.7, 73.5, 73.4, 73.2, 70.3, 68.9, 68.6.

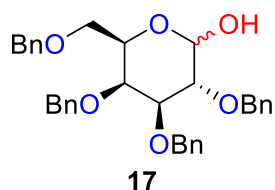
HRMS (ESI-TOF) m/z : $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{34}\text{H}_{40}\text{NO}_6$ 558.2856, found 558.2940.

Synthesis of 2,3,4,6-tetra-*O*-benzyl- α/β -D-galactopyranose: (17)



i, BnBr, NaH, DMF 85 %; **ii**, Na_2CO_3 , 10 % Pd/C, H_2 , MeOH, 72%

2,3,4,6-tetra-*O*-benzyl- α/β -D-galactopyranose (17)



Yield: 82 mg 72%, R_f : 0.6 (50% EtOAc/hexane). α/β :1/0.4

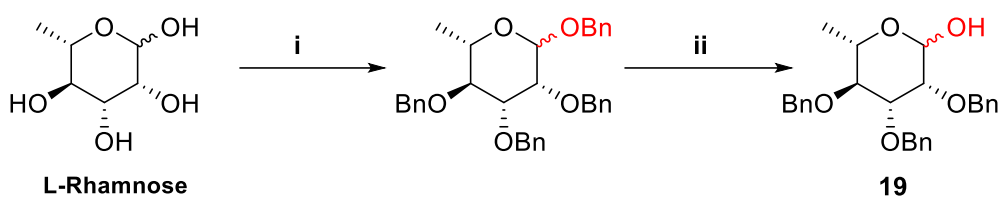
IR (neat): 3413, 3029, 2865, 1604, 1495, 1452, 1362, 1206, 1058 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ 7.23-7.38 (m, 28H), 5.27 (d, 1H, $J = 3.5$ Hz), 4.90-4.94 (m, 2H), 4.80-4.82 (m, 1.4H), 4.76 (d, 1.4H, $J = 13.5$ Hz), 4.68-4.73 (m, 2H), 4.63-4.65 (m, 0.4H), 4.56-4.60 (m, 1.4H), 4.56 (d, 1.4H, $J = 12.0$ Hz), 4.39 (d, 1H, $J = 12.0$ Hz), 4.38 (d, 0.4H, $J = 11.5$ Hz), 4.15 (t, 1H, $J = 6.5$ Hz), 4.02 (dd, 1H, $J = 3.5$ Hz, $J = 10.0$ Hz), 3.94 (d, 1H, $J = 2.0$ Hz), 3.91 (dd, 1H, $J = 2.5$ Hz, $J = 9.5$ Hz), 3.87 (d, 0.4H, $J = 2.5$ Hz), 3.75 (dd, 0.4H, $J = 7.5$ Hz, $J = 9.5$ Hz), 3.57-3.61 (m, 0.8H), 3.44-3.54 (m, 3.2H), 3.17 (bs, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ 138.5, 138.5, 138.4, 138.4, 138.3, 138.1, 137.8, 137.6, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 127.5, 127.4, 97.7(β), 91.8(α), 82.1, 80.6, 78.6, 76.5, 75.0, 74.6, 74.5, 73.5, 73.5, 73.4, 72.9, 72.8, 69.4, 68.9, 68.8.

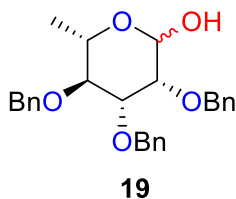
HRMS (ESI-TOF) m/z: $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{34}\text{H}_{40}\text{NO}_6$ 558.2856, found 558.2859.

Synthesis of 2,3,4-tri-O-benzyl- α/β -L-rhamnose (19)



i, BnBr, NaH, DMF 85%; **ii**, Na_2CO_3 , 10% Pd/C, H_2 , MeOH, 75%

2,3,4-tri-O-benzyl- α/β -L-rhamnose (19)



Yield: 170 mg, 75%, R_f : 0.3 (30% EtOAc/hexane). α/β :1/1

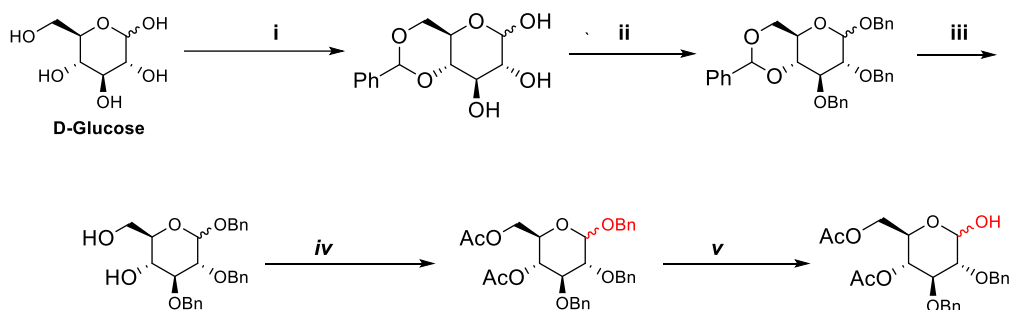
IR (neat) 3323, 3062, 3027, 2910, 2872, 1950, 1883, 1495, 1452, 1091, 1064 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ 7.29-7.40 (m, 30H), 5.11-5.17 (m, 2H), 4.96 (dd, 2H, $J = 7.0$ Hz, $J = 10.5$ Hz), 4.64-4.80 (m, 10H), 3.91-3.98 (m, 3H), 3.82-3.86 (m, 2H), 3.64-3.70 (m, 2H), 3.59-3.60 (m, 1H), 3.36-3.41 (m, 1H), 2.91(d, $J = 3.0$ Hz), 1.35 (dd, 6H, $J = 6.0$ Hz, $J = 11.5$ Hz).

^{13}C NMR (100 MHz, CDCl_3): δ 138.6, 138.5, 138.3, 138.2, 138.0, 137.9, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5, 93.3(β), 92.9(α), 83.0, 80.5, 79.9, 79.6, 75.4, 75.3, 75.0, 74.9, 72.9, 72.2, 71.6, 68.2, 18.0, 17.9.

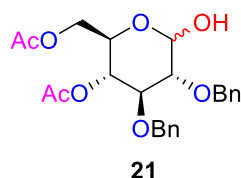
HRMS (ESI-TOF) m/z : $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{27}\text{H}_{34}\text{NO}_5$ 452.2437, found 452.2447.

Synthesis of 2,3-di-*O*-benzyl-4,6-di-*O*-acetyl- α/β -D-glucopyranose (21)



i, Benzaldehyde dimethylacetal, *p*-TSA, DMF, 75%; **ii**, BnBr, NaH, DMF 75%; **iii**, (8:2) Acetic acid:water, 80 °C, 16 h, 70%; **iv**, Ac_2O , Pyridine; **v**, Na_2CO_3 , 10% Pd/C, H_2 , THF, 75 %

2,3-di-*O*-benzyl-4,6-di-*O*-acetyl- α/β -D-glucopyranose (21)



Yield: 125 mg, 75%, R_f : 0.2 (30% EtOAc/hexane). α/β :1/0.3

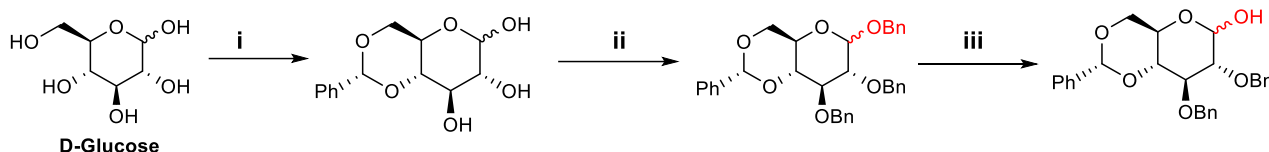
IR (neat): 3368, 3064, 3031, 2921, 2880, 1971, 1740, 1717, 1495, 1453, 1378, 1243, 1113, 1042 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ 7.26-7.41 (m, 13H), 5.22 (d, 1H, J = 3.2 Hz), 5.02-5.08 (m, 1.3H), 4.96 (d, 0.3H, J = 11.2 Hz), 4.89 (d, 1H, J = 11.6 Hz), 4.86 (d, 0.3H, J = 12.0 Hz), 4.76-4.82 (m, 1.6H), 4.64-4.71 (m, 2.3H), 4.24 (dd, 1H, J = 4.8 Hz, J = 12.4 Hz), 4.11-4.21 (m, 1.6H), 4.05 (dd, 1H, J = 2.4 Hz, J = 12.4 Hz), 3.96 (t, 1H, J = 9.2 Hz), 3.59-3.66 (m, 1.6H), 3.38-3.51 (m, 1.3H), 2.09 (s, 0.9H), 2.08 (s, 3H), 1.95 (s, 3H), 1.95 (s, 0.9H)

^{13}C NMR (100 MHz, CDCl_3): δ 170.9, 169.7, 169.6, 138.2, 138.1, 138.0, 137.5, 128.5, 128.4, 128.3, 128.1, 128.1, 128.0, 127.8, 127.8, 127.7, 127.6, 97.4(β), 91.2(α), 82.8, 81.4, 79.6, 78.7, 75.3, 75.1, 74.8, 73.4, 71.9, 69.6, 69.4, 67.7, 62.4, 20.7.

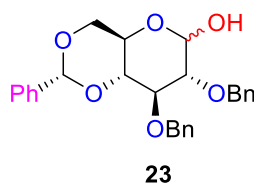
HRMS (ESI-TOF) m/z : $[M+NH_4]^+$ calcd for $C_{24}H_{32}NO_8$ 462.2128, found 462.2148.

Synthesis of 2,3-di-O-benzyl-4,6-O-benzylidene-D-glucopyranoside(23)



i, Benzaldehyde dimethylacetal, *p*-TSA, DMF, 75% ; **ii**, BnBr, NaH, DMF 75%; **iii**, Na_2CO_3 , 10% Pd/C, H_2 , MeOH, 68%

2,3-di-O-benzyl-4,6-O-benzylidene-D-glucopyranoside(23)



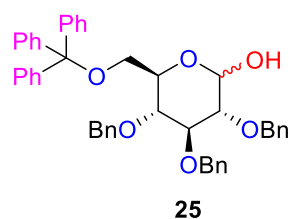
Yield: 68 mg, 68%, R_f : 0.3 (40% EtOAc/hexane). α/β :1/0.6

IR (neat): 3427, 3088, 3062, 3031, 2874, 1948, 1497, 1452, 1386, 1091 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 7.48-7.51 (m, 3H), 7.28-7.41 (m, 21H), 5.58 (s, 0.6H), 5.57 (s, 1H), 5.19 (d, 1H, $J = 3.5$ Hz), 4.95 (d, 1H, $J = 11.0$ Hz), 4.94 (d, 0.6H, $J = 11.0$ Hz), 4.90 (d, 0.6H, $J = 11.0$ Hz), 4.85 (d, 1H, $J = 1.5$ Hz), 4.82-4.83 (m, 1.2H), 4.80-4.82 (m, 1.6H), 4.72 (d, 1H, $J = 11.5$ Hz), 4.35 (dd, 0.6H, $J = 5.0$ Hz, $J = 10.5$ Hz), 4.30 (dd, 1H, $J = 5.0$ Hz, $J = 10.0$ Hz), 4.08 (td, 1H, $J = 5.0$ Hz, $J = 10.0$ Hz), 4.02 (t, 1H, $J = 9.0$ Hz), 3.77-3.81 (m, 1.2H), 3.71 (t, 0.6H, $J = 9.0$ Hz), 3.71 (t, 1H, $J = 10.5$ Hz), 3.64 (t, 1H, $J = 9.5$ Hz), 3.61 (dd, 1H, $J = 3.5$ Hz, $J = 9.0$ Hz), 3.46 (td, 0.6H, $J = 5.0$ Hz, $J = 9.5$ Hz), 3.42 (t, 0.6H, $J = 8.0$ Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 138.4, 138.1, 137.6, 137.3, 137.2, 128.9, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 126.0, 125.9, 101.2, 101.1, 97.8(β), 92.2(α), 83.0, 81.9, 81.5, 80.8, 79.3, 78.3, 75.3, 75.2, 75.1, 73.8, 68.9, 68.7, 66.2, 62.5.

HRMS (ESI-TOF) m/z : $[M+Na]^+$ calcd for $C_{27}H_{28}NaO_6$ 471.1784, found 471.1776.

2,3,4-tri-O-benzyl-6-O-trityl- α/β -D-Glucopyranose (25)

Yield: 150 mg, 80%, R_f : 0.2 (30% EtOAc/hexane). α/β :1/0.5

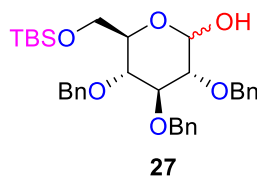
IR (neat): 3410, 3085, 3059, 3028, 2940, 2895, 2870, 1955, 1876, 1597, 1492, 1450, 1091 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ 7.18-7.39 (m, 42H), 7.12-7.14 (m, 1H), 7.07-7.09 (m, 2H), 5.21 (dd, 1H, $J = 2.0$ Hz, $J = 3.0$ Hz), 4.87 (d, 0.5H, $J = 11.0$ Hz), 4.77-4.84 (m, 4H), 4.76 (d, 1H, $J = 4.0$ Hz), 4.72 (d, 1H, $J = 6.5$ Hz), 4.69 (d, 0.5H, $J = 4.0$ Hz), 4.66 (s, 0.5H), 4.58 (t, 0.5H, $J = 7.0$ Hz), 4.48 (d, 0.5H, $J = 11.5$ Hz), 4.42 (d, 1H, $J = 11.5$ Hz), 4.12 (t, 1H, $J = 6.5$ Hz), 4.03 (d, 1H, $J = 2.0$ Hz), 3.97 (dd, 1H, $J = 3.5$ Hz, $J = 10.0$ Hz), 3.94 (d, 0.5H, $J = 2.5$ Hz), 3.91 (dd, 1H, $J = 2.5$ Hz, $J = 10.0$ Hz), 3.68 (dd, 0.5H, $J = 7.5$ Hz, $J = 9.5$ Hz), 3.50 (dd, 0.5H, $J = 3.0$ Hz, $J = 10.0$ Hz), 3.47 (dd, 0.5H, $J = 5.5$ Hz, $J = 9.0$ Hz), 3.38-3.43 (m, 1.5H), 3.30 (t, 0.5H, $J = 8.5$ Hz), 3.20 (t, 1H, $J = 8.0$ Hz), 3.04-3.05 (m, 0.5H), 2.90-2.91 (m, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ 143.8, 143.8, 138.7, 138.6, 138.5, 138.5, 138.5, 138.1, 128.6, 128.6, 128.4, 128.4, 128.3, 128.2, 128.0, 128.0, 128.0, 127.8, 127.8, 127.6, 127.6, 127.5, 127.5, 127.3, 127.3, 127.1, 127.0, 97.7(β), 91.9(α), 87.1, 86.9, 82.1, 80.8, 78.6, 76.6, 75.2, 75.0, 74.6, 74.5, 74.1, 73.8, 73.5, 73.0, 72.9, 70.0, 62.4, 62.3.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{46}\text{H}_{48}\text{NO}_6$ 710.3482, found 710.3477.

2,3,4-tri-O-benzyl-6-O-(tert-butyl dimethyl silyl)- α/β -D-Glucopyranose (27)



Yield: 150 mg, 80%, R_f: 0.2 (30% EtOAc/hexane). α/β :1/0.5

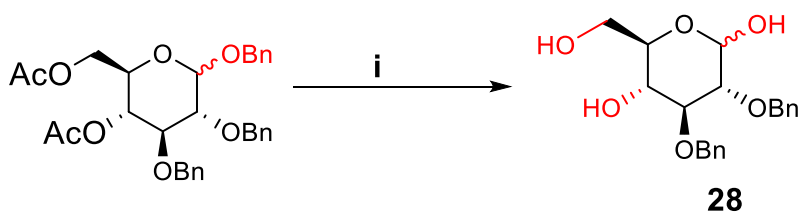
IR (neat): 3409, 3037, 2957, 2929, 2859, 2153, 1458, 1369, 1248, 1090, 1058 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 7.27-7.40 (m, 22.5H), 5.28 (s, 1H), 4.91-4.98 (m, 2H), 4.79-4.85 (m, 3H), 4.71-4.77 (m, 3H), 4.62-4.67 (m, 2H), 4.04 (dd, 1H, J = 3.5 Hz, J = 10.0 Hz), 3.97-4.00 (m, 2H), 3.90-3.93 (m, 1.5H), 3.70-3.77 (m, 2H), 3.64-3.68 (m, 1H), 3.55 (dd, 0.5H, J = 3.0 Hz, J = 10.0 Hz), 3.22-3.31 (m, 0.5H), 3.03-3.08 (m, 1H), 0.89 (s, 4.5H), 0.89 (s, 9H), 0.05 (s, 6H), 0.05 (s, 3H).

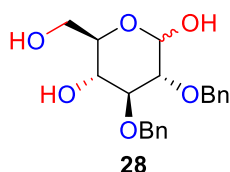
¹³C NMR (125 MHz, CDCl₃): δ 138.8, 138.7, 138.6, 138.6, 138.4, 138.2, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.6, 127.6, 127.5, 127.5, 127.4, 97.8(β), 91.9(α), 82.2, 80.9, 78.7, 77.2, 75.3, 75.0, 74.8, 74.8, 74.6, 73.5, 72.9, 72.8, 71.2, 61.3, 61.3, 25.9, 18.2, -5.4, -5.4.

HRMS (ESI-TOF) m/z: [M+NH₄]⁺ calcd for C₃₃H₄₈NO₆Si 582.3251, found 582.3245.

Synthesis of 2,3-di-O-benzyl- α/β -D-glucopyranose (28)



i, Na₂CO₃, 10% Pd/C, H₂, MeOH, 60 %

2,3-di-O-benzyl- α/β -D-glucopyranose (28)

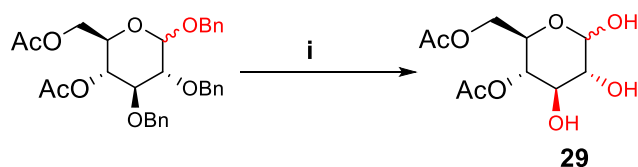
Yield: 62 mg, 60%, R_f : 0.2 (10% MeOH/ CHCl_3). α/β :0.6/1

IR (neat): 3394, 3334, 3027, 2918, 2888, 2854, 1604, 1496, 1452, 1153, 1030 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ 7.27-7.34 (m, 16H), 5.20 (d, 1H, $J = 3.5$ Hz), 4.93 (dd, 2H, $J = 11.5$ Hz, $J = 23.5$ Hz), 4.67-4.75 (m, 4.2H), 4.44-4.64 (m, 1H), 4.29 (bs, 0.6H), 4.13-4.16 (m, 0.6H), 3.77-4.05 (m, 4.2H), 3.66-3.74 (m, 2H), 3.43-3.57 (m, 3H), 3.33-3.37 (m, 1.6H), 3.12-3.17 (m, 1.6H), 3.04 (q, 0.6H, $J = 7.5$ Hz).

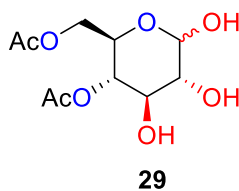
^{13}C NMR (125 MHz, CDCl_3): δ 138.6, 138.4, 138.3, 137.7, 128.5, 128.5, 128.4, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 97.5(β), 91.0(α), 84.0, 82.8, 81.0, 79.8, 75.5, 75.3, 74.6, 72.9, 71.3, 70.5, 70.0, 62.4, 62.0.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{O}_6$ Na 383.1471, found 383.1481.

Synthesis of 4,6-di-O-acetyl- α/β -D-glucopyranose (29)

i, 10 % Pd/C, H_2 , THF, 65%

4,6-di-O-acetyl- α/β -D-glucopyranose (29)



Yield: 64 mg, 65%, R_f : 0.2 (15% MeOH/ CHCl_3). α/β :1/1

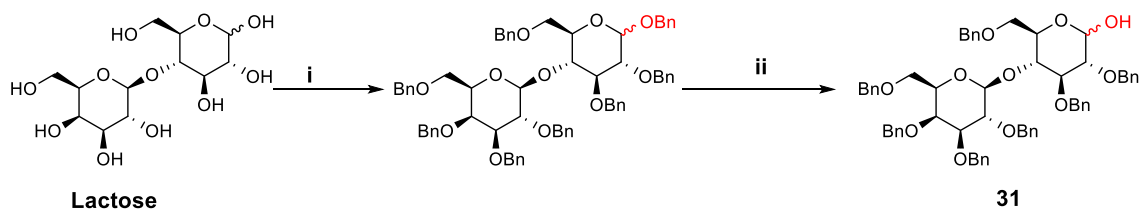
IR (neat): 3341, 2943, 1739, 1708, 1452, 1366, 1316, 1272, 1227, 1159, 1110, 1025 cm^{-1} .

^1H NMR (400 MHz, DMSO-d_6): δ 6.86 (d, 1H, $J = 6.4$ Hz), 6.61 (d, 1H, $J = 4.4$ Hz), 5.25 (d, 1H, $J = 4.8$ Hz), 5.16 (d, 1H, $J = 4.0$ Hz), 5.10 (d, 1H, $J = 4.8$ Hz), 4.96 (t, 1H, $J = 4.0$ Hz), 4.83 (d, 1H, $J = 5.6$ Hz), 4.58 (t, 2H, $J = 9.2$ Hz), 4.40 (t, 1H, $J = 7.2$ Hz), 3.89-4.03 (m, 5H), 3.54-3.64 (m, 2H), 3.34-3.38 (m, 1H), 3.25 (bs, 1H), 3.01 (bs, 1H), 2.02 (s, 6H), 1.99 (s, 3H), 1.99 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 170.6, 170.6, 170.1, 97.1(β), 92.4(α), 74.9, 73.8, 72.2, 71.7, 71.3, 70.9, 70.5, 66.7, 63.1, 62.9, 21.0, 20.8.

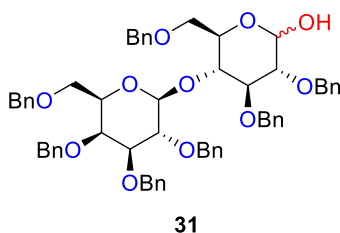
HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{17}\text{O}_8$ 265.0923, found 265.1443.

Synthesis of 2,3,6-tri-O-benzyl-4-(2',3',4',6'-tetra-O-benzyl- β -D-galactopyranosyl)- α/β -D-glucopyranose



i, BnBr, NaH, DMF 75%; **ii**, Na_2CO_3 , 10% Pd/C, H_2 , MeOH, 71%

2,3,6-tri-*O*-benzyl-4-(2',3',4',6'-tetra-*O*-benzyl- β -D-galactopyranosyl)- α/β -D-glucopyranose (31)



Yield: 120 mg, 71%, R_f : 0.3 (50% EtOAc/hexane). α/β :1/0.7

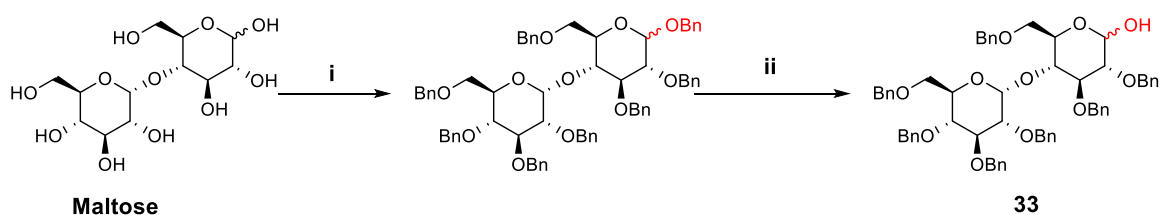
IR (neat): 3342, 3098, 3062, 2935, 2869, 1735, 1589, 1495, 1358, 1215, 1145, 1023 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ 7.16-7.41 (m, 60H), 5.20-5.21 (m, 1H), 5.11 (d, 1H, $J = 10.5$ Hz), 5.08 (d, 0.7H, $J = 10.5$ Hz), 5.01 (d, 1H, $J = 11.5$ Hz), 5.00 (d, 0.7H, $J = 11.5$ Hz), 4.86-4.92 (m, 1.7H), 4.79-4.86 (m, 3.4H), 4.71-4.76 (m, 5.1H), 4.68-4.70 (m, 2H), 4.53-4.60 (m, 3.4H), 4.35-4.44 (m, 5.1H), 4.29 (d, 1H, $J = 6.0$ Hz), 4.27 (d, 0.7H, $J = 5.5$ Hz), 3.94-3.99 (m, 4.4H), 3.87-3.91 (m, 2H), 3.77-3.80 (m, 2.4H), 3.69-3.72 (m, 0.7H), 3.54-3.60 (m, 4.4H), 3.36-3.43 (m, 6.8H), 3.12 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 139.2, 139.0, 138.9, 138.7, 138.5, 138.4, 138.4, 138.1, 138.0, 138.0, 137.9, 128.3, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.4, 127.4, 127.3, 127.3, 127.0, 102.8, 102.7, 97.3(β), 91.3(α), 82.7, 82.6, 82.4, 82.3, 79.8, 79.0, 76.4, 75.3, 75.1, 74.9, 74.8, 74.6, 73.6, 73.5, 73.3, 73.0, 73.0, 72.9, 72.5, 72.5, 70.3, 68.3, 68.1, 68.0.

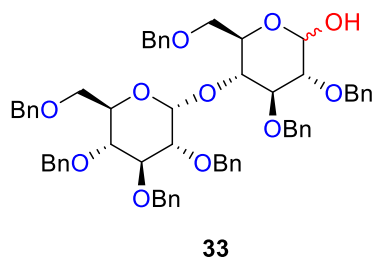
HRMS (ESI-TOF) m/z : $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{61}\text{H}_{68}\text{NO}_{11}$ 990.4792, found 990.4795.

Synthesis of 2,3,6-tri-*O*-benzyl-4-*O*-(2',3',4',6'-tetra-*O*-benzyl- α -D-glucopyranosyl)- α/β -glucopyranose (33)



i, BnBr, NaH, DMF 75%; **ii,** Na_2CO_3 , 10% Pd/C, H_2 , MeOH, 74%

2,3,6-tri-O-benzyl-4-O-(2',3',4',6'-tetra-O-benzyl- α -D-glucopyranosyl)- α/β -glucopyranose (33)



Yield: 300 mg, 74%, R_f: 0.3 (30% EtOAc/hexane). α/β :1/0.4

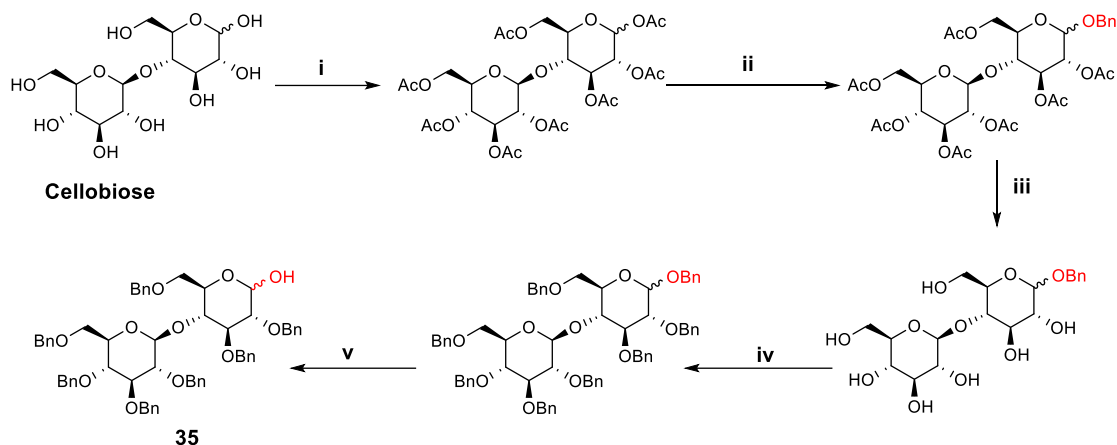
IR (neat): 3091, 3062, 3028, 2921, 2863, 1711, 1589, 1495, 1452, 1359, 1208, 1145, 1091 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 7.10-7.31 (m, 49H), 5.65 (d, 1H, J = 3.5 Hz), 5.64 (d, 0.4H, J = 3.5 Hz), 5.25 (d, 1H, J = 3.5 Hz), 4.92-4.98 (m, 1.8H), 4.85-4.90 (m, 2.4H), 4.82 (d, 1H, J = 8.0 Hz), 4.76-4.79 (m, 3H), 4.68 (s, 0.4H), 4.64-4.66 (m, 1.2H), 4.61 (s, 1H), 4.58-4.59 (m, 1.2H), 4.56 (d, 0.4H, J = 4.0 Hz), 4.49-4.55 (m, 5.4H), 4.42-4.47 (m, 2H), 4.34 (d, 0.4H, J = 12.5 Hz), 4.31 (d, 1H, J = 12.0 Hz), 4.14 (dq, 1H, J = 2.0 Hz, J = 9.5 Hz), 4.08 (t, 1H, J = 8.5 Hz), 4.00-4.04 (m, 1.6H), 3.92 (t, 1H, J = 9.5 Hz), 3.87 (t, 0.4H, J = 9.5 Hz), 3.78-3.82 (m, 1.4H), 3.72-3.75 (m, 1.8H), 3.62-3.68 (m, 4.2H), 3.47-3.55 (m, 3.2H), 3.40-3.42 (m, 1.4H).

¹³C NMR (125 MHz, CDCl₃): δ 138.8, 138.7, 138.7, 138.7, 138.4, 138.4, 138.1, 138.1, 137.9, 137.9, 137.6, 128.5, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 127.7, 127.6, 127.6, 127.5, 127.5, 127.4, 127.1, 126.7, 126.6, 97.4(β), 96.9, 96.8, 90.8(α), 84.3, 83.1, 81.9, 81.3, 79.9, 79.4, 79.3, 77.7, 75.5, 74.9, 74.9, 74.4, 74.4, 74.2, 73.9, 73.5, 73.4, 73.2, 73.1, 72.9, 72.9, 71.1, 71.0, 69.9, 69.4, 69.1, 68.2.

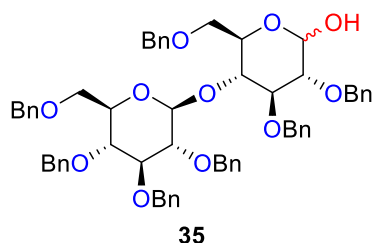
HRMS (ESI-TOF) m/z: [M+Na]⁺ calcd for C₆₁H₆₄NaO₁₁ 995.4346, found 995.4265.

Synthesis of 2,3,6-tri-*O*-benzyl-4-*O*-(2',3',4',6'-tetra-*O*-benzyl- β -D-glucopyranosyl)- α/β -glucopyranose (35)



i, Ac₂O, Pyridine, 100 %; **ii**, (a) HBr, AcOH, CH₂Cl₂; (b) BnOH, Hg(OAc)₂, 72 %; **iii**, NaOMe, MeOH, 98%; **iv**, BnBr, NaH, DMF 75%; **v**, Na₂CO₃, 10% Pd/C, H₂, MeOH, 82%

2,3,6-tri-*O*-benzyl-4-*O*-(2',3',4',6'-tetra-*O*-benzyl- β -D-glucopyranosyl)- α/β -glucopyranose (35)



Yield: 1.87 gm, 82%, R_f: 0.3 (30% EtOAc/hexane). α/β :1/0.8

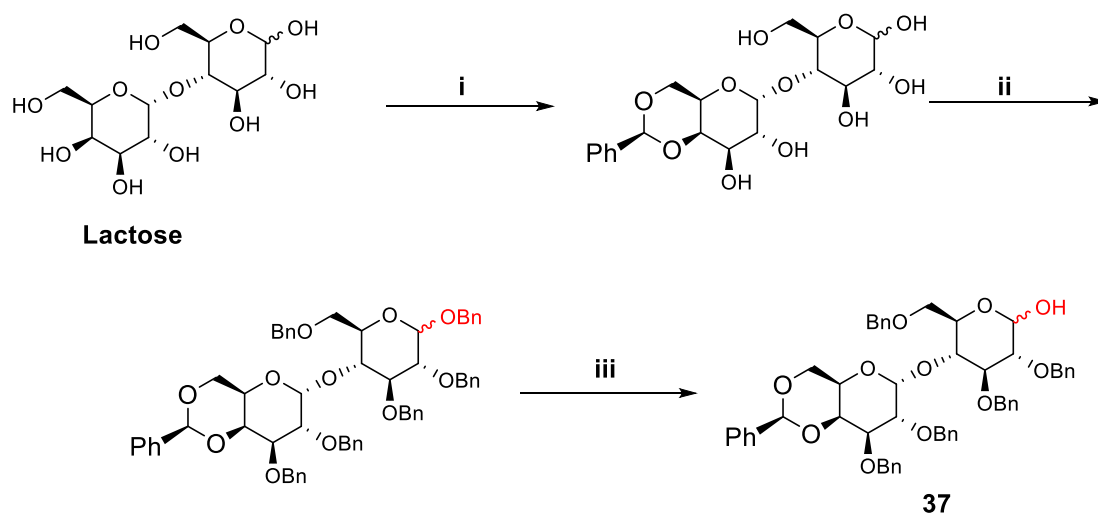
IR (neat): 3412, 3029, 2921, 1495, 1453, 1360, 1208, 1068 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 7.21-7.46 (m, 63H), 5.22 (d, 1H, *J* = 3.5 Hz), 5.16 (d, 1H, *J* = 11.5 Hz), 5.13 (d, 0.8H, *J* = 11.5 Hz), 4.91-4.95 (m, 2.6H), 4.83-4.89 (m, 5.4H), 4.77-4.81 (m, 6H), 4.70 (d, 1H, *J* = 7.5 Hz), 4.67 (d, 1H, *J* = 12.0 Hz), 4.56-4.63 (m, 3.6H), 4.42-4.50 (m, 7.2H), 4.00-4.07 (m, 3.4H), 3.90-3.94 (m, 2H), 3.82 (dd, 1H, *J* = 4.5 Hz, *J* = 11.0 Hz), 3.76 (td, 1.6H, *J* = 1.5 Hz, *J* = 11.0 Hz), 3.71 (dd, 1H, *J* = 1.5 Hz, *J* = 7.0 Hz), 3.64-3.69 (m, 3.4H), 3.52-3.63 (m, 6H), 3.33-3.46 (m, 5H), 3.27 (bs, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ 139.3, 139.1, 138.5, 138.5, 138.5, 138.4, 138.2, 138.2, 137.9, 137.8, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.7, 127.7, 127.7, 127.6, 127.6, 127.5, 127.5, 127.5, 127.3, 127.3, 127.1, 102.6, 102.5, 97.3(β), 91.3(α), 84.8, 84.8, 82.7, 82.6, 82.6, 82.5, 79.9, 78.9, 78.0, 77.9, 76.6, 76.4, 75.5, 75.1, 75.0, 75.0, 74.9, 74.9, 74.8, 74.7, 74.7, 73.5, 73.3, 73.3, 73.2, 70.3, 68.9, 68.9, 68.1, 67.9.

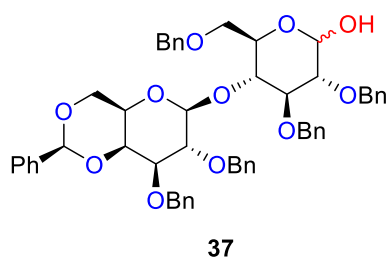
HRMS (ESI-TOF) m/z : $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{61}\text{H}_{68}\text{NO}_{11}$ 990.4792, found 990.4616.

Synthesis of 2,3,6-tri-O-benzyl-4-O-(2',3'-di-O-benzyl-4',6'-O-benzylidene- β -D-galactopyranosyl)- α/β -glucopyranose (37)



i, Benzaldehyde dimethylacetal, *p*-TSA, DMF, 75% ; **ii**, BnBr, NaH, DMF 75%; **iii**, Na_2CO_3 , 10% Pd/C, H_2 , MeOH, 68%

2,3,6-tri-O-benzyl-4-O-(2',3'-di-O-benzyl-4',6'-O-benzylidene- β -D-galactopyranosyl)- α/β -glucopyranose (37)



Yield:150mg, 72%, R_f: 0.2 (50% EtOAc/hexane). α/β :1/0.4

IR (neat): 3382, 3089, 3045, 2922, 1495, 1452, 1358, 1273, 1216, 1095 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 7.56-7.58 (m, 4H), 7.31-7.45 (m, 30H), 7.24-7.26 (m, 11H), 5.52 (d, 1H, J = 1.0 Hz), 5.51 (d, 0.5H, J = 1.0 Hz), 5.29 (dd, 1H, J = 2.0 Hz, J = 10.5 Hz), 5.22-5.25 (m, 1.5H), 4.93 (td, 0.5H, J = 1.5 Hz, J = 11.0 Hz), 4.86-4.88 (m, 1.5H), 4.80-4.85 (m, 4H), 4.76-4.78 (m, 3H), 4.69-4.72 (m, 1.5H), 4.60 (d, 0.5H, J = 1.0 Hz), 4.55-4.58 (m, 1H), 4.45 (dd, 0.5H, J = 2.0 Hz, J = 8.0 Hz), 4.41 (dd, 1H, J = 2.5 Hz, J = 8.0 Hz), 4.25-4.32 (m, 3H), 4.07 (d, 1.5H, J = 3.0 Hz), 3.95-4.02 (m, 5H), 3.87-3.92 (m, 2H), 3.81 (td, 2H, J = 2.5 Hz, J = 10.0 Hz), 3.66-3.72 (m, 1H), 3.59-3.63 (m, 2.5H), 3.36-3.44 (m, 3H), 2.98 (s, 1.5H).

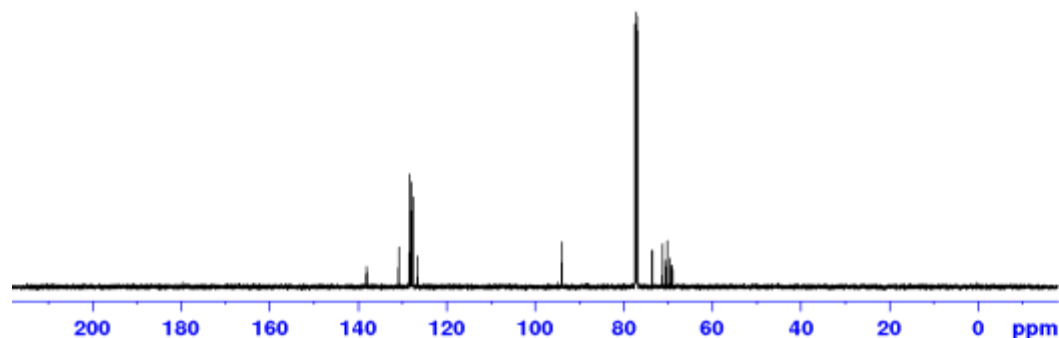
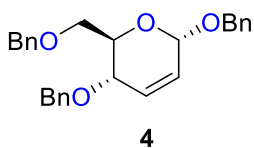
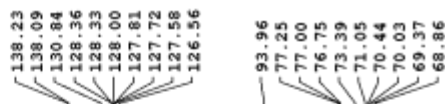
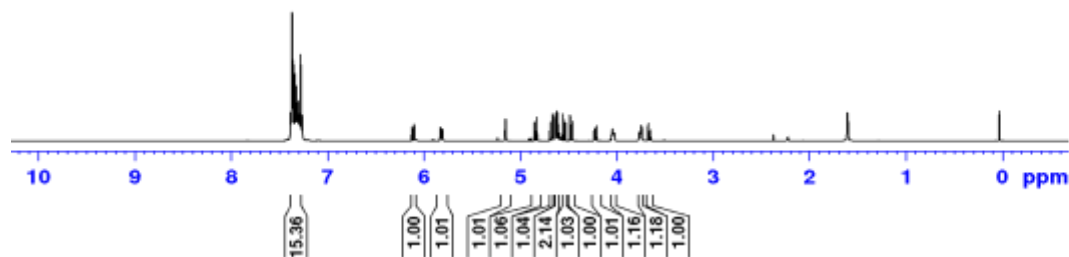
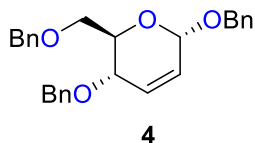
¹³C NMR (125 MHz, CDCl₃): δ 138.9, 138.9, 138.7, 138.4, 138.4, 138.3, 138.2, 138.1, 138.0, 138.0, 128.8, 128.7, 128.5, 128.3, 128.3, 128.2, 128.2, 128.1, 128.0, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 127.5, 127.4, 127.2, 126.5, 126.5, 102.9, 102.8, 101.4, 101.3, 97.3(β), 91.2(α), 82.8, 82.7, 79.9, 79.6, 79.4, 79.2, 78.7, 77.4, 77.3, 75.8, 75.6, 75.2, 74.8, 74.8, 76.6, 73.5, 72.9, 71.5, 71.5, 70.3, 68.9, 68.2, 68.0, 66.3, 66.2.

HRMS (ESI-TOF) m/z: [M+NH₄]⁺ calcd for C₅₄H₆₀NO₁₁ 898.4166, found 898.4138.

3.5 References

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Current Data Parameters
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PROCNO 1

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SOLVENT CDCl3
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DS 2
SWH 10330.576 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 256
DM 48.400 usec
DE 6.50 usec
TE 297.6 K
D1 1.00000000 sec
TD0 1

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P1 14.90 usec
PL1 2.00 dB
PL1W 12.85346415 W
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F2 - Processing parameters
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WDW EM
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LB 0.30 Hz
GB 0
PC 1.00



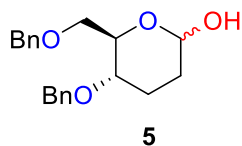
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EXPNO 2218217
PROCNO 1

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PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 386
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SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 2050
DM 16.800 usec
DE 6.50 usec
TE 299.4 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

===== CHANNEL f1 =====
NUC1 13C
P1 9.60 usec
PL1 0 dB
PL1W 76.36135101 W
SFO1 125.7829381 MHz

===== CHANNEL f2 =====
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NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.50 dB
PL13 16.50 dB
PL2W 12.85346415 W
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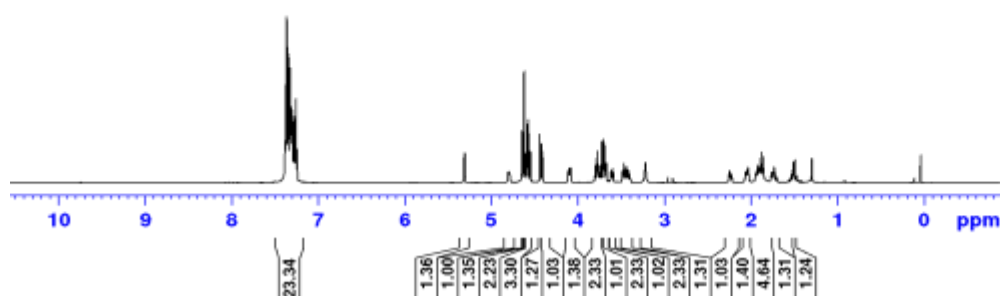
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Current Data Parameters
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EXPNO 104
PROCNO 1

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SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767995 sec
RG 101
DW 50.000 usec
DE 13.04 usec
TE 298.9 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
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F2 - Processing parameters
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SSB 0
LB 0.30 Hz
GB 0
PC 1.00



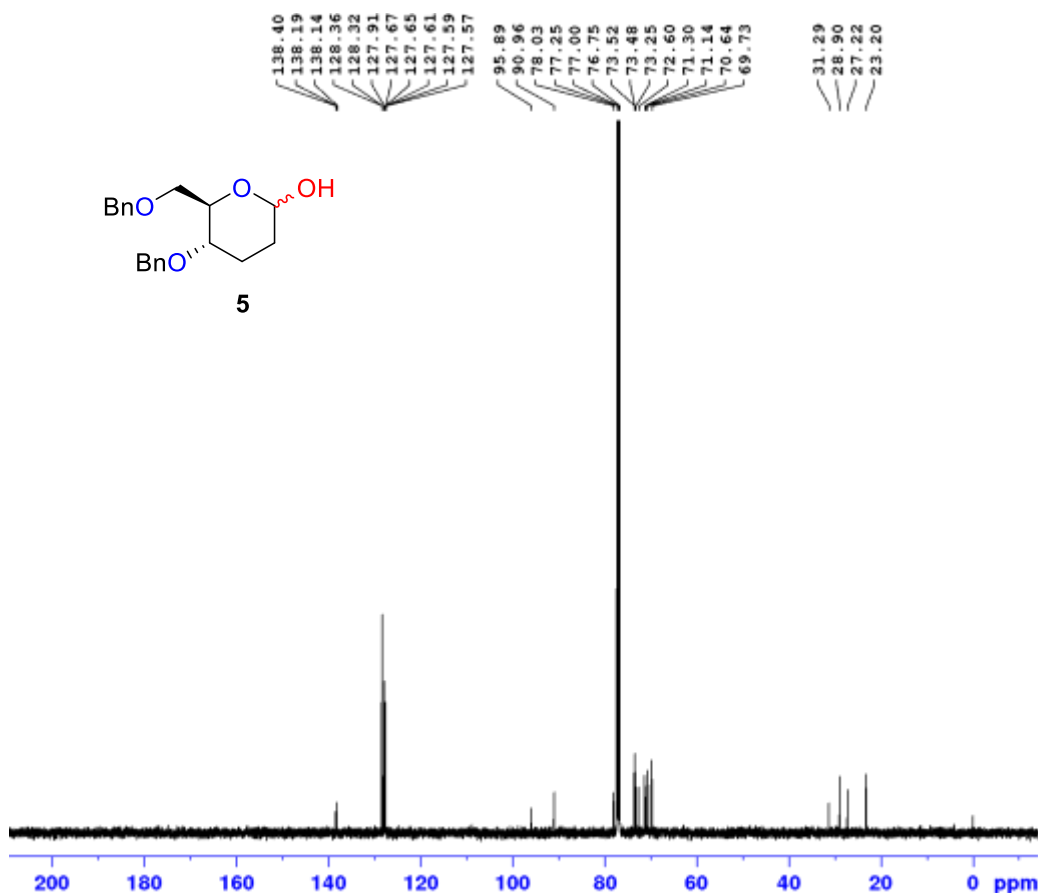
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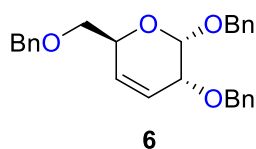
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TD 65536
SOLVENT CDCl3
NS 1024
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FIDRES 0.454131 Hz
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RG 2050
DW 16.800 usec
DE 6.50 usec
TE 297.8 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

===== CHANNEL f1 =====
NUC1 13C
P1 9.60 usec
PL1 0 dB
PL1W 76.36135101 W
SFO1 125.7829381 MHz

===== CHANNEL f2 =====
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NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.50 dB
PL13 16.50 dB
PL1W 12.85348415 W
PL12W 0.45605880 W
PL13W 0.45605880 W
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F2 - Processing parameters
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SSB 0
LB 1.00 Hz
GB 0
PC 1.40

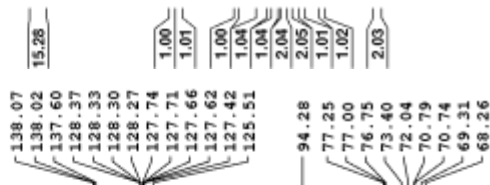
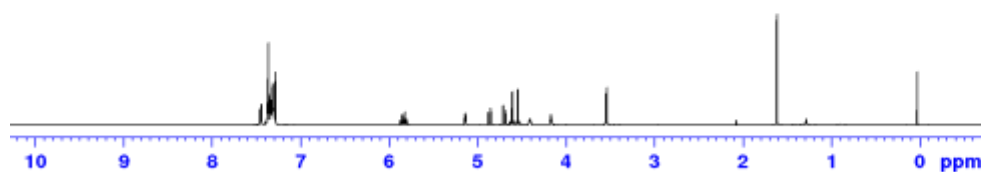




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PROCNO 1

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SOLVENT CDCl3
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FIDRES 0.305178 Hz
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RG 124.09
DW 50.000 usec
DE 6.50 usec
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TD0 1
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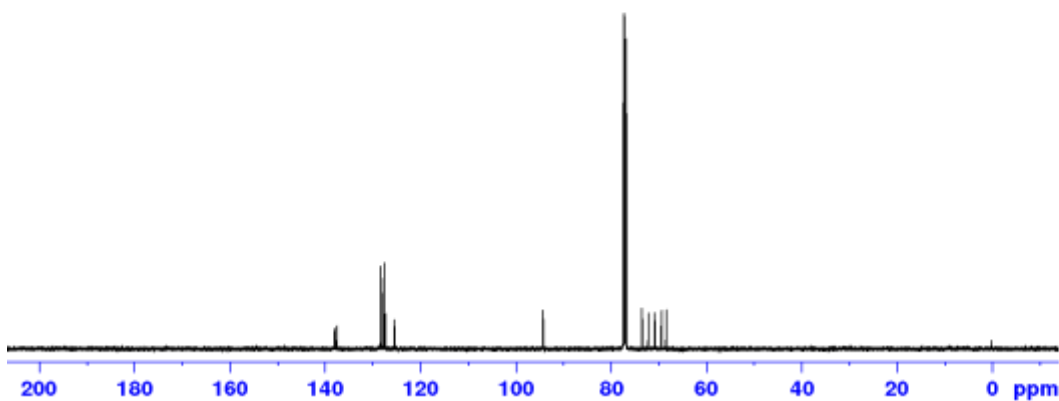
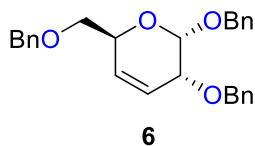
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GB 0
PC 1.00

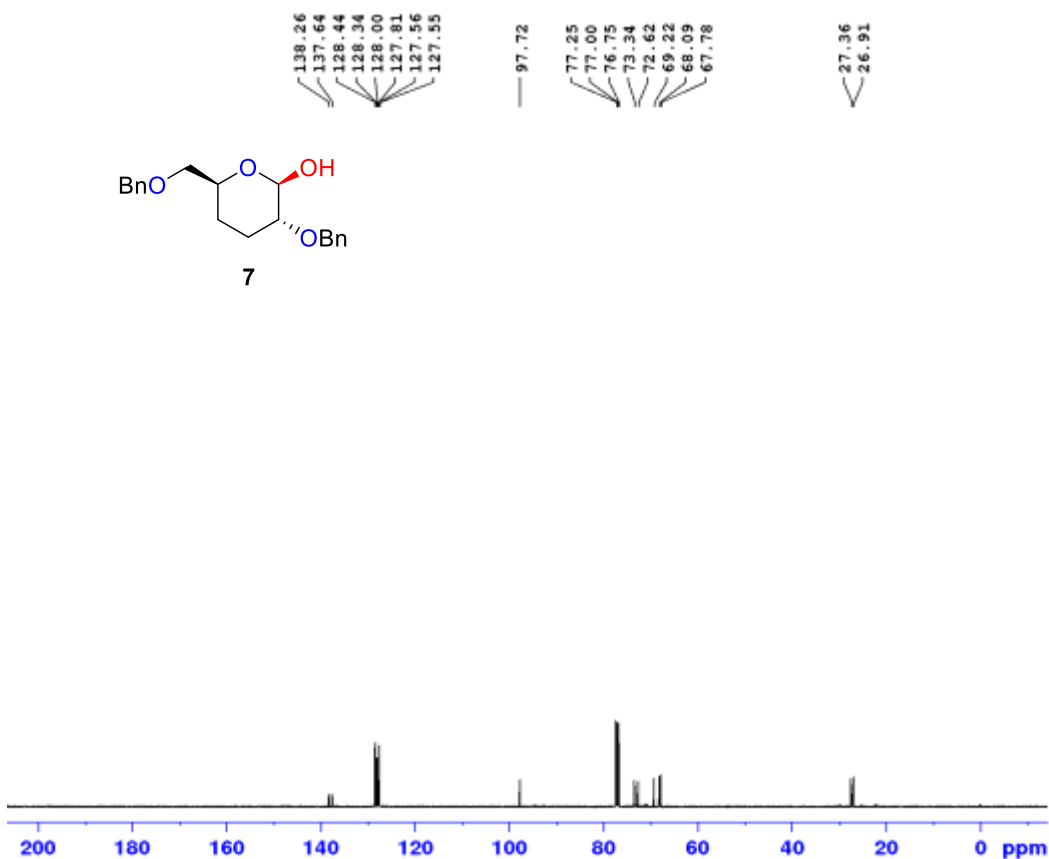
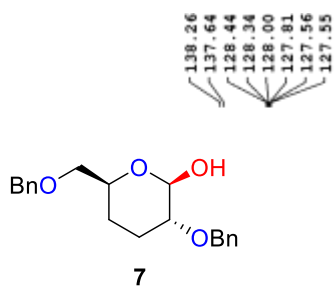
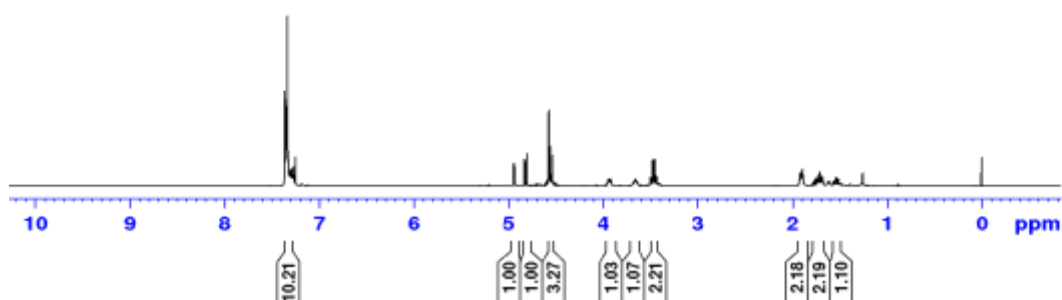
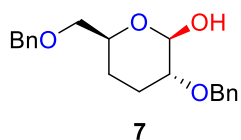


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EXPNO 157
PROCNO 1

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PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 914
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 192.83
DW 16.800 usec
DE 6.50 usec
TE 295.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8304669 MHz
NUC1 13C
P1 12.00 usec
PLW1 172.66999817 W
SFO2 500.3710013 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 80.00 usec
PLM2 12.18000031 W
PLW2 0.12180000 W
PLW13 0.06126500 W

F2 - Processing parameters
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LB 1.00 Hz
GB 0
PC 1.40





Current Data Parameters
NAME Anji Ascend
EXPNO 387
PROCNO 1

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Time 17.51 h
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PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
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FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 69.79
DW 50.000 usec
DE 6.50 usec
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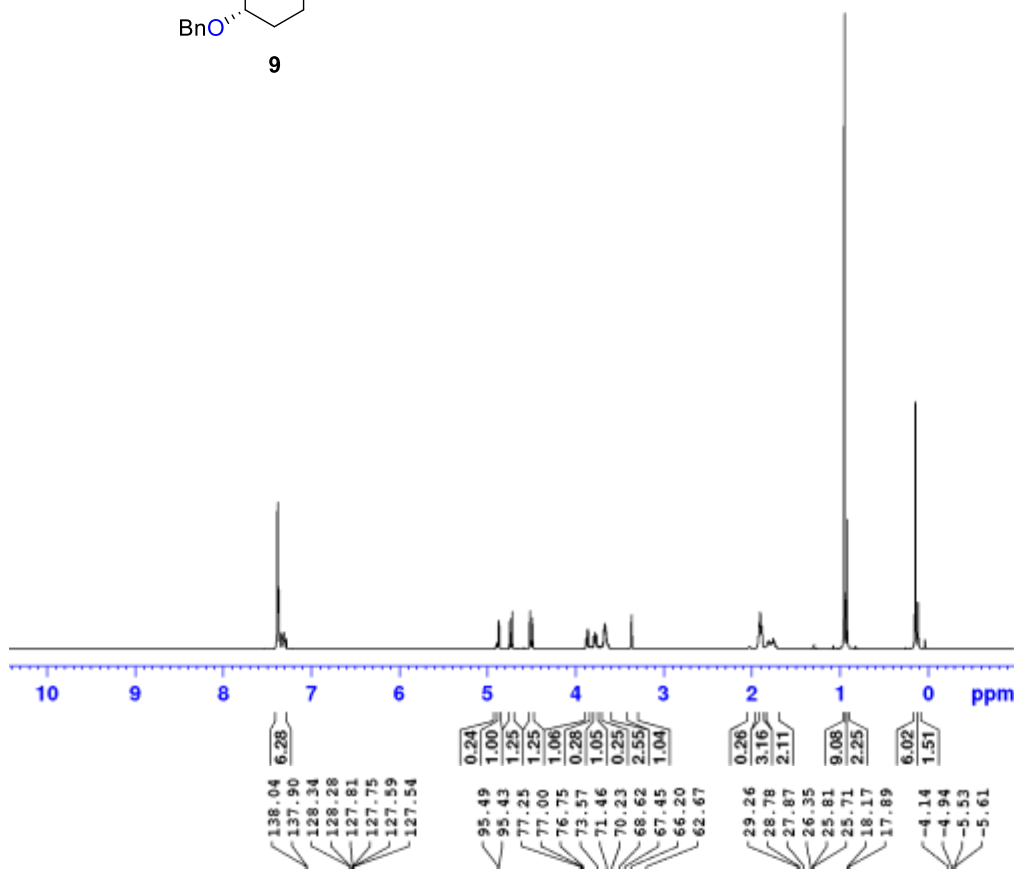
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Current Data Parameters
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EXPNO 389
PROCNO 1

F2 - Acquisition Parameters
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TD 65536
SOLVENT CDCl3
NS 551
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 192.83
DW 16.800 usec
DE 6.50 usec
TE 299.4 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8304669 MHz
NDC1 13C
P1 10.00 usec
PLW1 115.01000214 W
SFO2 500.3710015 MHz
NDC2 1H
CPDPRG[2] waltz16
PCPD2 80.00 usec
PLW2 23.23100090 W
PLW12 0.36298999 W
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GB 0
PC 1.40



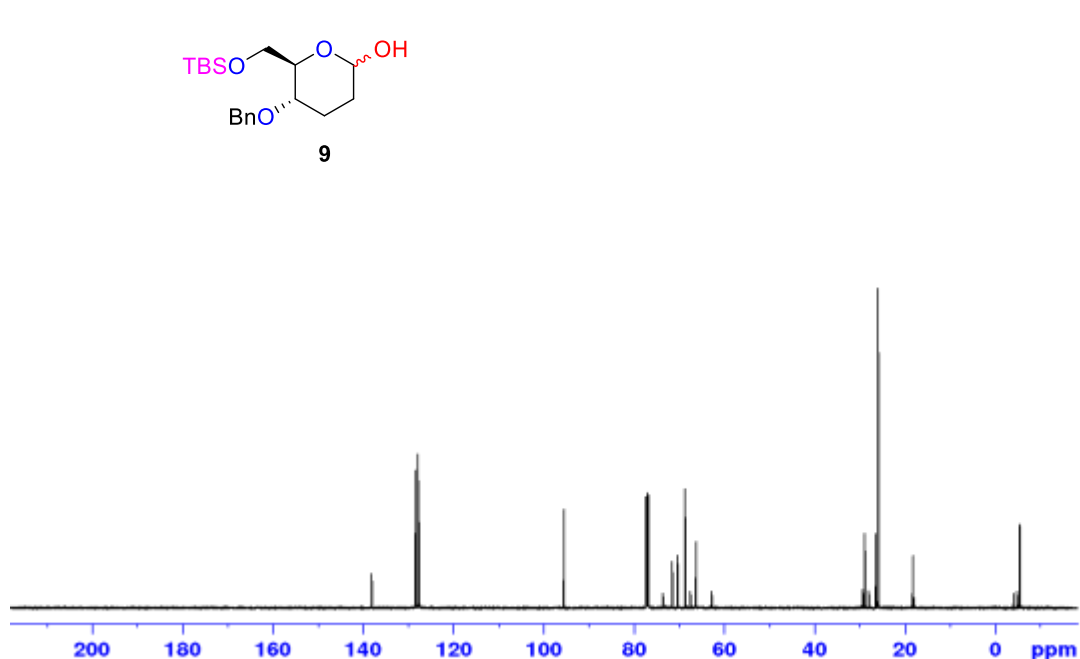
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PROCNO        1

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PULPROG       zg30
TD            65536
SOLVENT       CDCl3
NS            16
DS            2
SWH           10000.000 Hz
FIDRES        0.305176 Hz
AQ            3.2767999 sec
RG            57
DM            50.000 usec
DE            13.04 usec
TE            297.1 K
D1            1.00000000 sec
TD0           1
SFO1          500.1630666 MHz
NUC1          1H
P0            5.00 usec
P1            15.00 usec
PLW1          4.64679985 W

F2 - Processing parameters
SI            65536
SF            500.1600000 MHz
WDW           EM
SSB           0
LB            0.30 Hz
GB            0
PC            1.00

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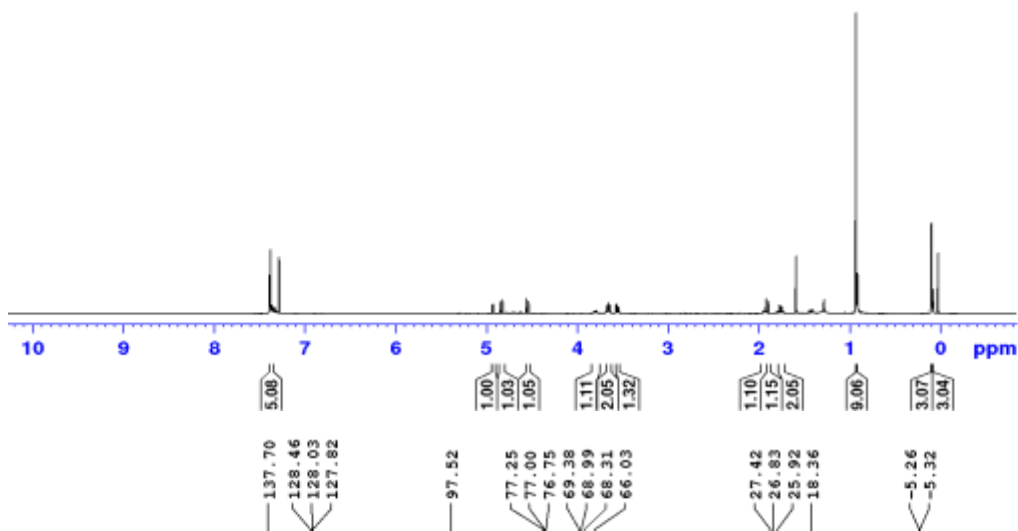
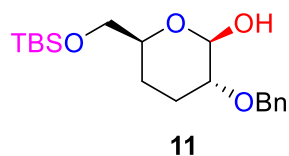
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Current Data Parameters
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EXPNO         188
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SOLVENT       CDCl3
NS            287
DS            4
SWH           29761.904 Hz
FIDRES        0.908261 Hz
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RG            203
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DE            6.50 usec
TE            297.9 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0           1
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NUC1          13C
P0            3.33 usec
P1            10.00 usec
PLW1          64.00399780 W
SF02          500.1820007 MHz
NUC2          1H
CPDPRG2       waltz65
PCPD2         80.00 usec
PLW2          4.84679985 W
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PLW13         0.08570800 W

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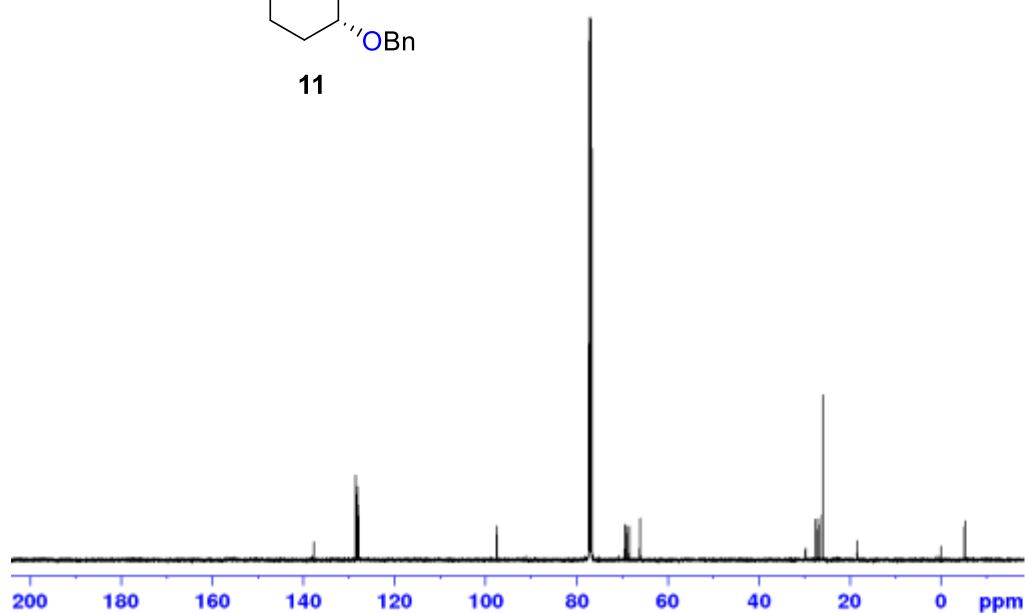
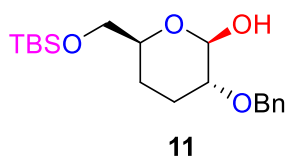
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EXPNO 133
PROCNO 1

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TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.309176 Hz
AQ 3.2767999 sec
RG 362
DN 50.000 usec
DE 13.04 usec
TE 298.5 K
D1 1.00000000 sec
TD0 1
SF01 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLN1 4.84679985 W

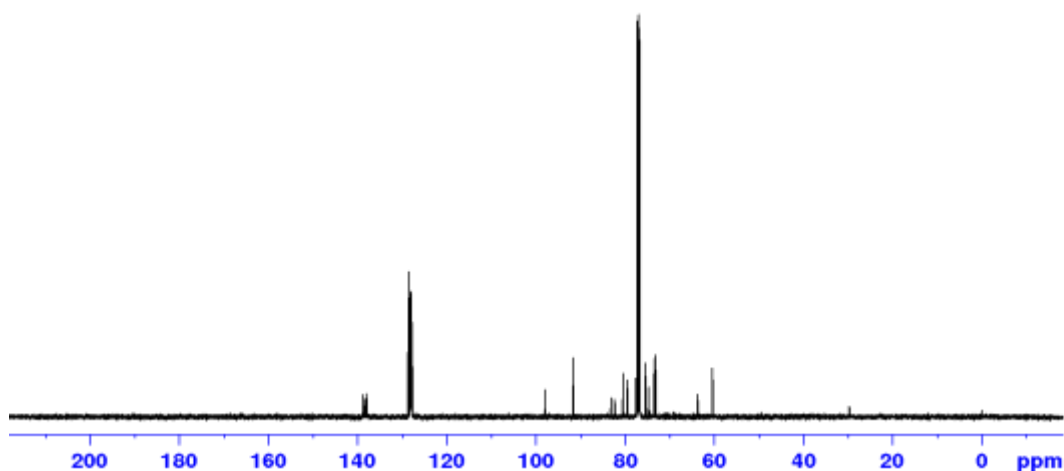
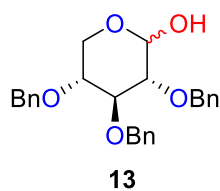
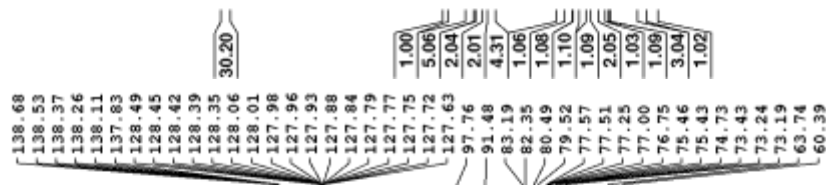
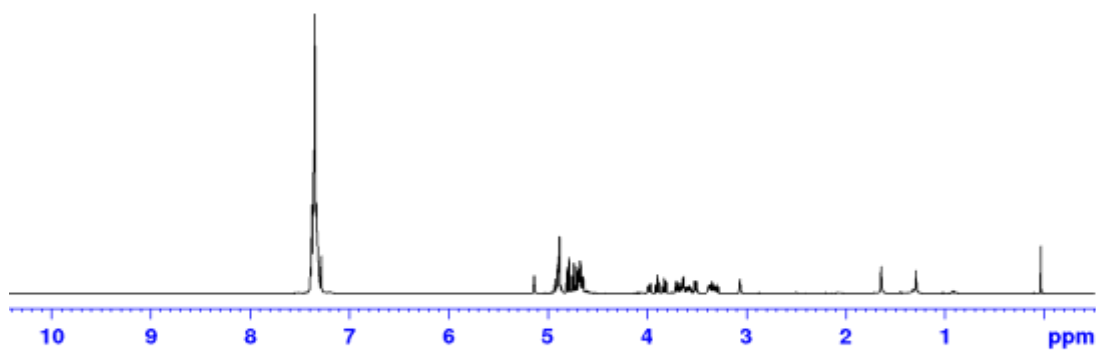
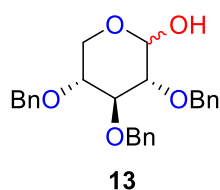
F2 - Processing parameters
SI 65536
SF 500.1800000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME AB-500
EXPNO 135
PROCNO 1

F2 - Acquisition Parameters
Date_ 20210324
Time 14.43 h
INSTRUM spect
PROBHD Z109128_0042
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 2170
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 203
DN 16.800 usec
DE 6.50 usec
TE 299.8 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SF01 125.7629381 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLN1 64.00399780 W
SF02 500.1820007 MHz
NUC2 1H
CPDPRG2 wait65
PCPD2 80.00 usec
PLN2 4.84679985 W
PLN12 0.17039999 W
PLN13 0.08570800 W

F2 - Processing parameters
SI 32768
SF 125.7703606 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Current Data Parameters
NAME Anjaneyulu 500 NMR
EXPNO 2218317
PROCNO 1

F2 - Acquisition Parameters
Date_ 20191213
Time 17.00
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 181
DW 48.400 usec
DE 6.50 usec
TE 295.4 K
D1 1.00000000 sec
TD0 1

===== CHANNEL f1 =====
NUC1 1H
P1 14.90 usec
PL1 2.00 dB
PL1W 12.85346415 W
SFO1 500.1630668 MHz

F2 - Processing parameters
SI 32768
SF 500.1800000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



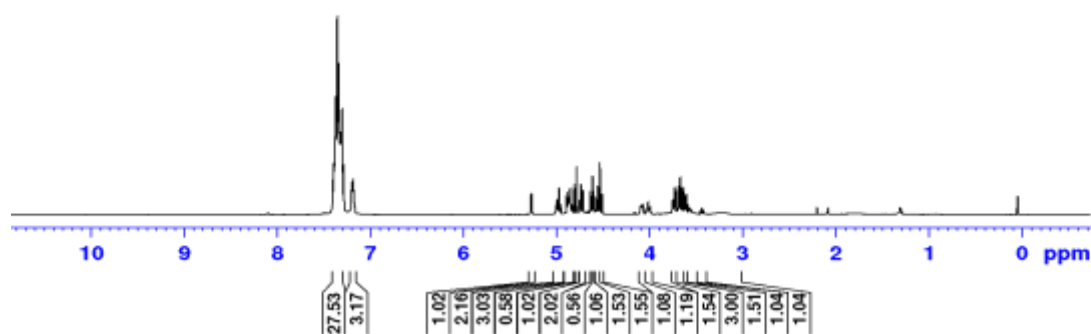
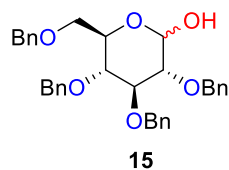
Current Data Parameters
NAME Anjaneyulu 500 NMR
EXPNO 2218322
PROCNO 1

F2 - Acquisition Parameters
Date_ 20191217
Time 15.06
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 889
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 2050
DW 16.800 usec
DE 6.50 usec
TE 299.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

===== CHANNEL f1 =====
NUC1 13C
P1 9.60 usec
PL1 0 dB
PL1W 76.36135101 W
SFO1 125.7829381 MHz

===== CHANNEL f2 =====
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.30 dB
PL13 16.30 dB
PL1W 12.85346415 W
PL12W 0.45605880 W
PL13W 0.45605880 W
SFO2 500.1820007 MHz

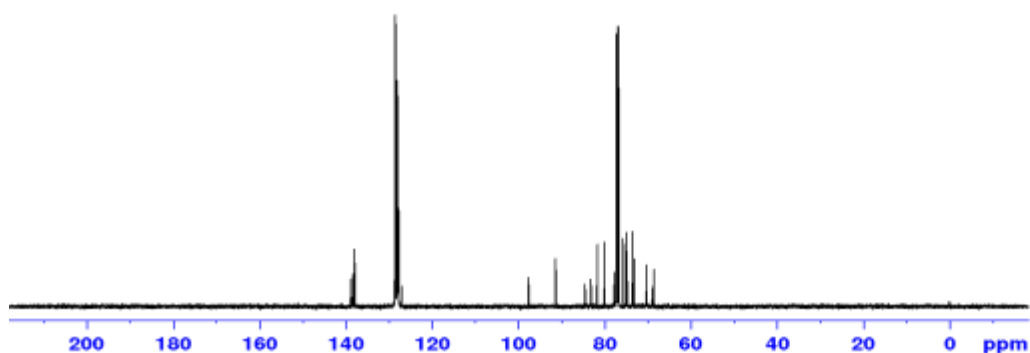
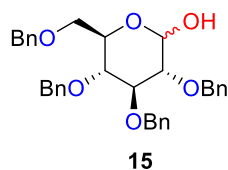
F2 - Processing parameters
SI 32768
SF 125.7703631 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Current Data Parameters
NAME Anji Ascend
EXPNO 247
PROCNO 1

F2 - Acquisition Parameters
Date_ 20200318
Time 9.43 h
INSTRUM spect
PROBHD Z119470_0291 f
PULPROG zg30
TD 65536
SOLVENT CDC13
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 54.81
DM 50.000 usec
DE 6.50 usec
TE 303.6 K
D1 1.00000000 sec
TDO 1
SFO1 500.3720696 MHz
NUC1 1H
P1 10.00 usec
PLW1 23.23100090 W

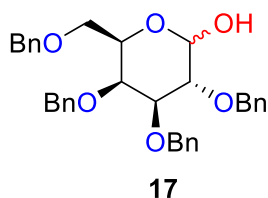
F2 - Processing parameters
SI 65536
SF 500.3690000 MHz
NDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME Anji Ascend
EXPNO 249
PROCNO 1

F2 - Acquisition Parameters
Date_ 20200318
Time 10.17 h
INSTRUM spect
PROBHD Z119470_0291 f
PULPROG zgpg30
TD 65536
SOLVENT CDC13
NS 446
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 192.83
DM 16.600 usec
DE 6.50 usec
TE 303.5 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1
SFO1 125.8304669 MHz
NUC1 13C
P1 10.00 usec
PLM1 115.01000214 M
SFO2 500.3710015 MHz
NUC2 1H
CPOPRG12 waltz16
PCPD2 80.00 usec
PLM2 23.23100090 W
PLM12 0.36298999 W
PLM13 0.18257999 W

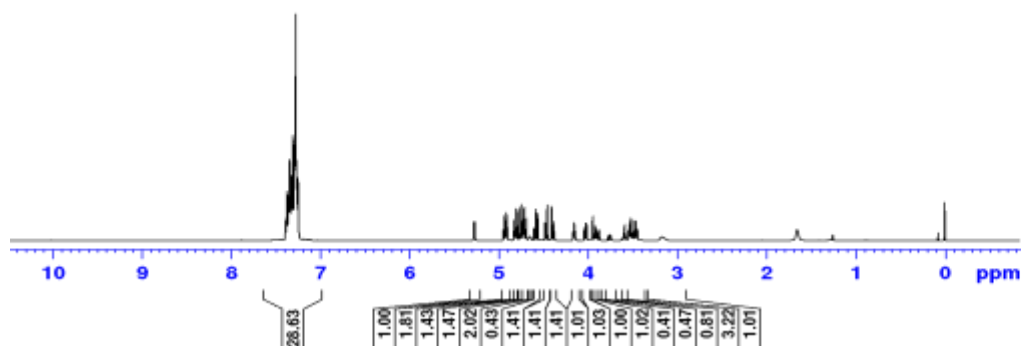
F2 - Processing parameters
SI 32768
SF 125.8176913 MHz
NDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Current Data Parameters
NAME Anji Ascend
EXPNO 335
PROCNO 1

F2 - Acquisition Parameters
Date_ 20201228
Time 13.27 h
INSTRUM spect
PROBHD Z119470_0291
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 62.04
DM 50.000 usec
DE 6.50 usec
TE 294.6 K
D1 1.00000000 sec
TD0 1
SFO1 500.3720896 MHz
NUC1 1H
P1 10.00 usec
PLM1 23.23100090 W

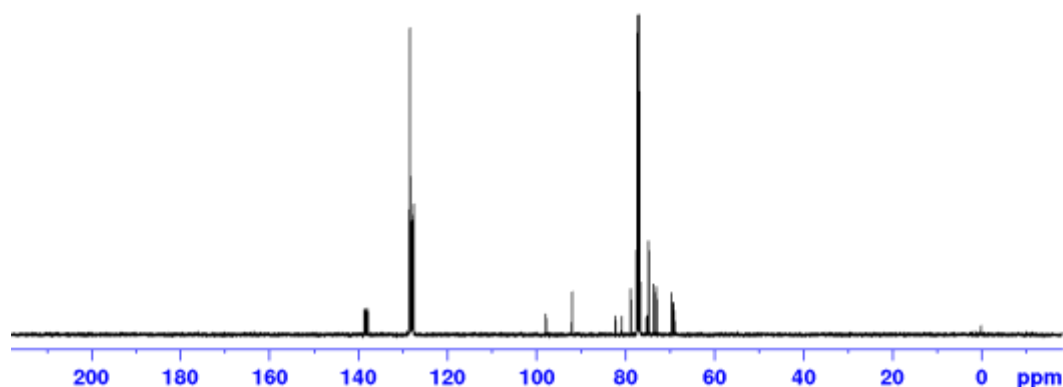
F2 - Processing parameters
SI 65536
SF 500.3690195 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

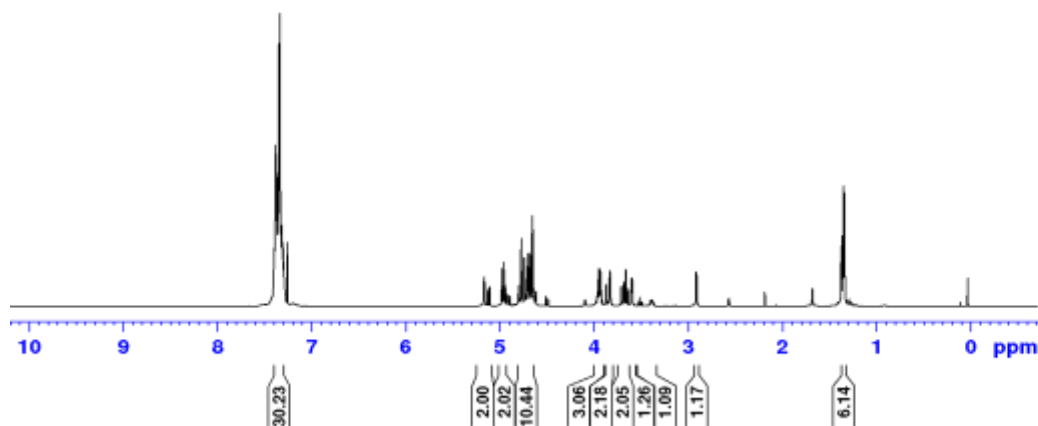
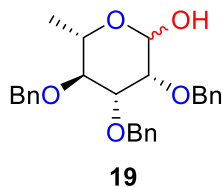


Current Data Parameters
NAME Anji Ascend
EXPNO 337
PROCNO 1

F2 - Acquisition Parameters
Date_ 20201228
Time 16.05 h
INSTRUM spect
PROBHD Z119470_0291
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 460
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 152.9
DM 16.800 usec
DE 6.50 usec
TE 295.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8304669 MHz
NUC1 13C
P1 10.00 usec
PLM1 115.01000214 W
SFO2 500.3710015 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 80.00 usec
PLM2 23.23100090 W
PLM12 0.36298999 W
PLM13 0.18257999 W

F2 - Processing parameters
SI 32768
SF 125.8178931 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

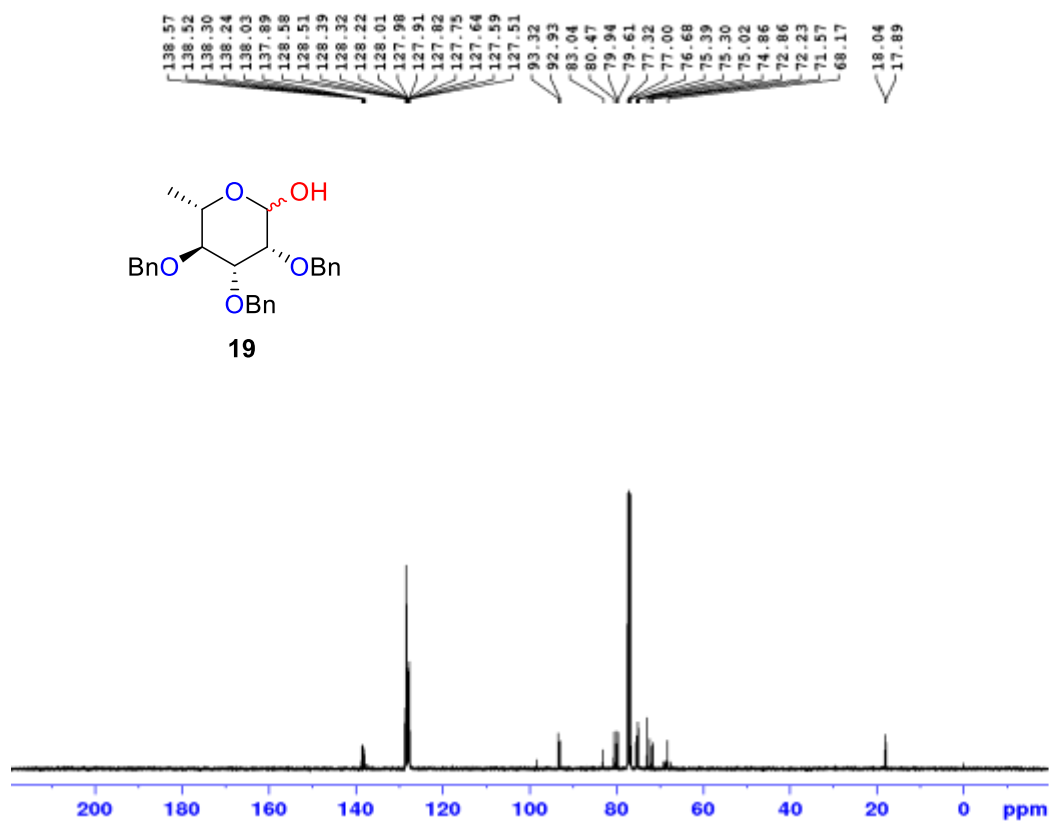
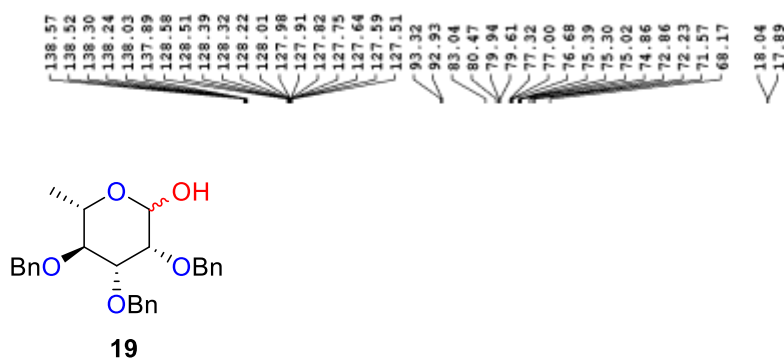




Current Data Parameters
NAME AB-500
EXPNO 124
PROCNO 1

F2 - Acquisition Parameters
Date_ 20210305
Time 12.59 h
INSTRUM spect
PROBHD H109128_0042 (zg30)
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 80.6
DM 50.000 usec
DE 13.04 usec
TE 298.0 K
D1 1.00000000 sec
TDO 1
SFO1 500.1830666 MHz
NUC1 1H
PO 5.00 usec
PL 15.00 usec
PLW1 4.84679985 W

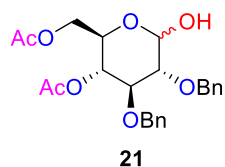
F2 - Processing parameters
SI 65536
SF 500.1800109 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME AB-400 New
EXPNO 99
PROCNO 1

F2 - Acquisition Parameters
Date_ 20210401
Time 13.47 h
INSTRUM spect
PROBHD H108618_0098 (zgpg30)
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 814
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 203
DM 20.800 usec
DE 6.50 usec
TE 299.4 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1
SFO1 100.6130223 MHz
NUC1 13C
PO 3.33 usec
PL 10.00 usec
PLW1 49.4399863 W
SFO2 400.0926004 MHz
NUC2 1H
CPDPRG2 waltz165
PCPD2 90.00 usec
PLN2 15.18599987 W
PLN12 0.41622999 W
PLN13 0.20936000 W

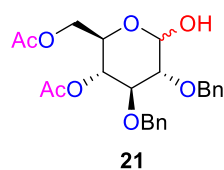
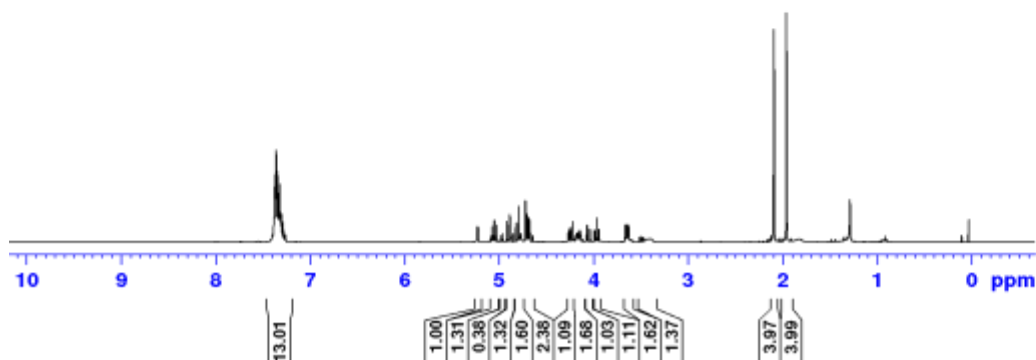
F2 - Processing parameters
SI 32768
SF 100.6029693 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Current Data Parameters
NAME AB-400 New
EXPNO 21
PROCNO 1

F2 - Acquisition Parameters
Date_ 20200626
Time 16.05 h
INSTRUM spect
PROBHD Z108618_0098 1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 128
DM 62.400 usec
DE 16.93 usec
TE 296.1 K
D1 1.00000000 sec
TD0 1
SFO1 400.0934706 MHz
NUC1 1H
PO 4.97 usec
P1 14.90 usec
PLW1 15.18599987 W

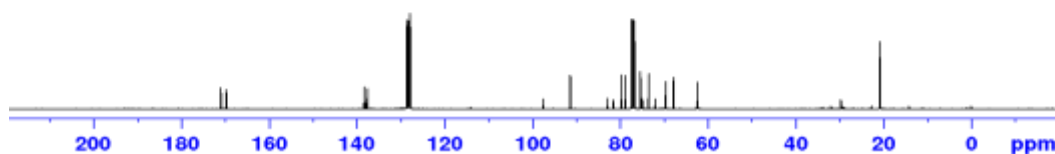
F2 - Processing parameters
SI 65536
SF 400.0910000 MHz
WUN EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

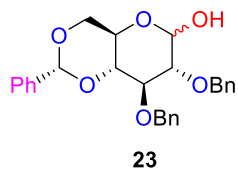


Current Data Parameters
NAME AB-400 New
EXPNO 22
PROCNO 1

F2 - Acquisition Parameters
Date_ 20200627
Time 16.27 h
INSTRUM spect
PROBHD Z108618_0098 1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 25600
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 203
DM 20.800 usec
DE 6.50 usec
TE 296.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6130223 MHz
NUC1 13C
PO 3.33 usec
P1 10.00 usec
PLW1 49.43999863 W
SFO2 400.0926004 MHz
NUC2 1H
CPDPRG12 waltz16
PCPD2 90.00 usec
PLW2 15.18599987 W
PLW12 0.41622999 W
PLW13 0.20936000 W

F2 - Processing parameters
SI 32768
SF 100.6029692 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

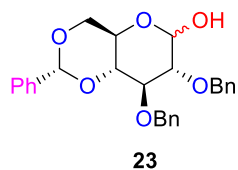
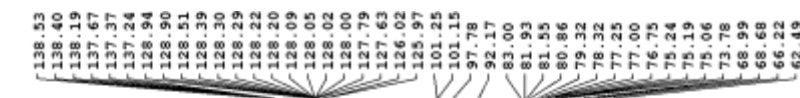
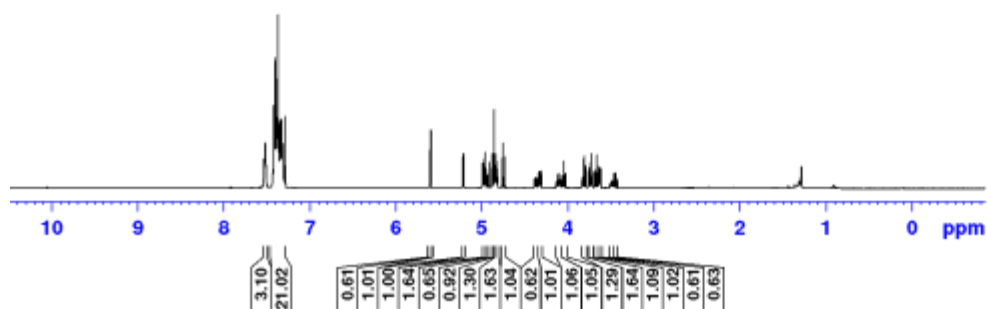




Current Data Parameters
NAME AB-900
EXPNO 224
PROCNO 1

F2 - Acquisition Parameters
Date_ 20211011
Time 10.44 h
INSTRUM spect
PROBHD Z109128_0042 {
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SMH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 181
DW 50.000 usec
DE 13.04 usec
TE 294.7 K
D1 1.00000000 sec
TDO 1
SFO1 500.1830886 MHz
NUC1 1H
PO 5.00 usec
PI 15.00 usec
PLW1 4.84679985 W

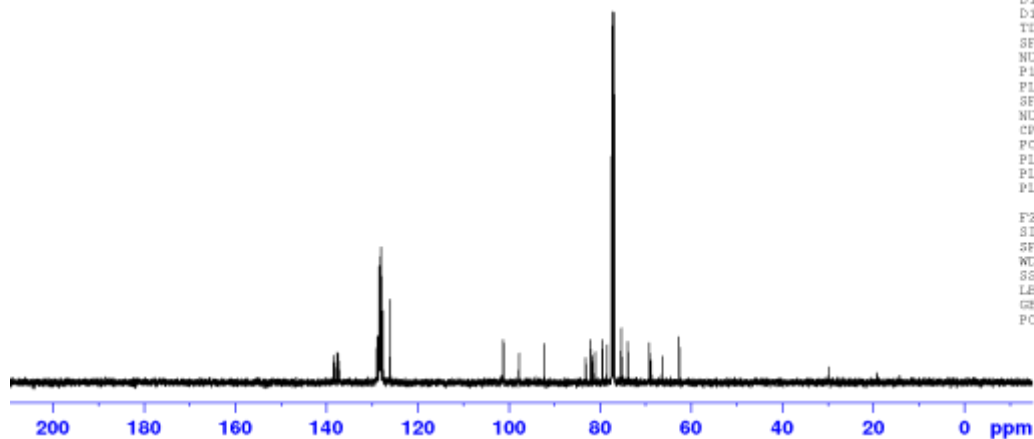
F2 - Processing parameters
SI 65536
SF 500.1800000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

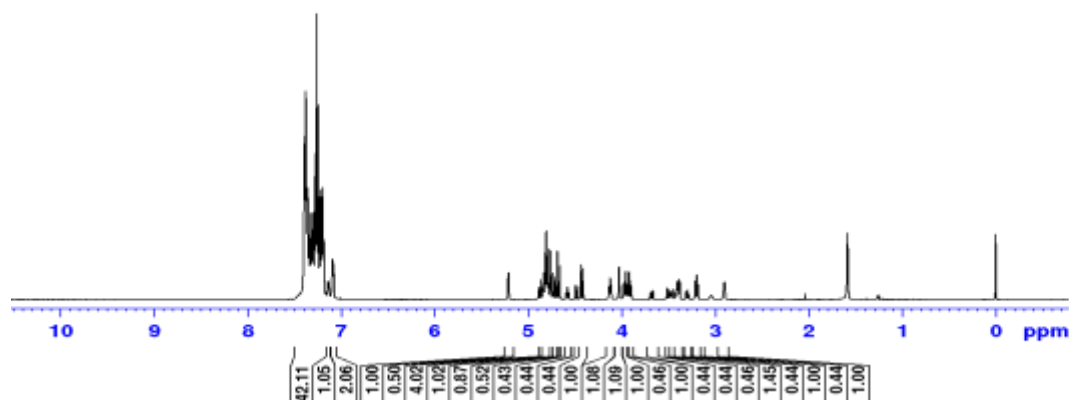
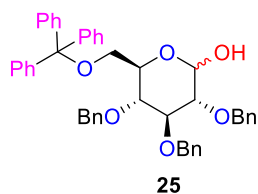


Current Data Parameters
NAME Anji Ascend
EXPNO 239
PROCNO 1

F2 - Acquisition Parameters
Date_ 20200302
Time 15.29 h
INSTRUM spect
PROBHD Z125331_0034 {
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 465
DS 4
SMH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 192.83
DW 16.800 usec
DE 6.50 usec
TE 300.6 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1
SFO1 125.8304669 MHz
NUC1 13C
PI 12.00 usec
PLM1 172.66999817 W
SFO2 500.3710015 MHz
NDC2 1E
CPDPRG[2] waltz16
PCPD2 80.00 usec
PLM2 12.18000031 W
PLM12 0.12180000 W
PLM13 0.06126500 W

F2 - Processing parameters
SI 32768
SF 125.8174921 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40





Current Data Parameters
NAME AB-500
EXPNO 171
PROCNO 1

F2 - Acquisition Parameters
Date_ 20210709
Time 15.28 h
INSTRUM spect
PROBHD Z109128_0042 (6536
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SMH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 144
DW 50.000 usec
DE 13.04 usec
TE 299.1 K
D1 1.00000000 sec
TD0 1
SFO1 500.130888 MHz
NUC1 1H
PO 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W

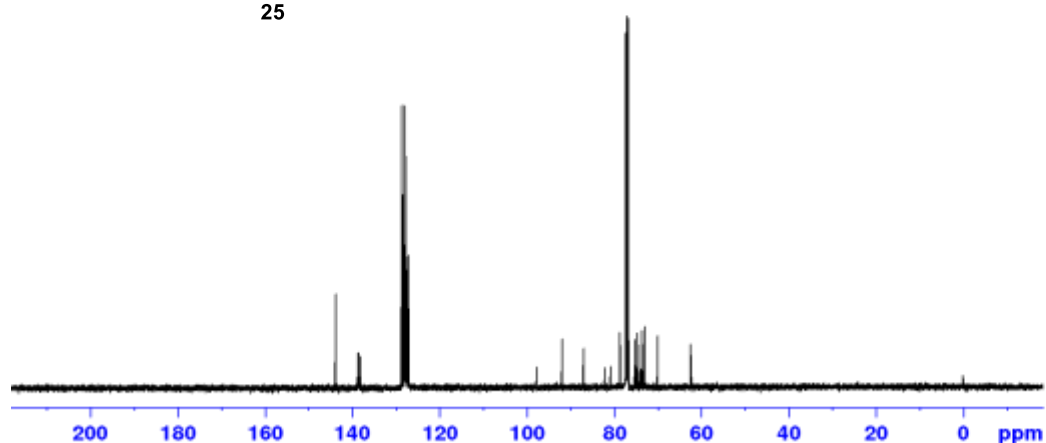
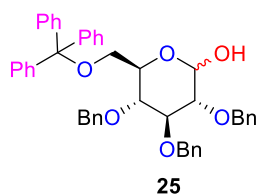
F2 - Processing parameters
SI 6536
SF 500.130888 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

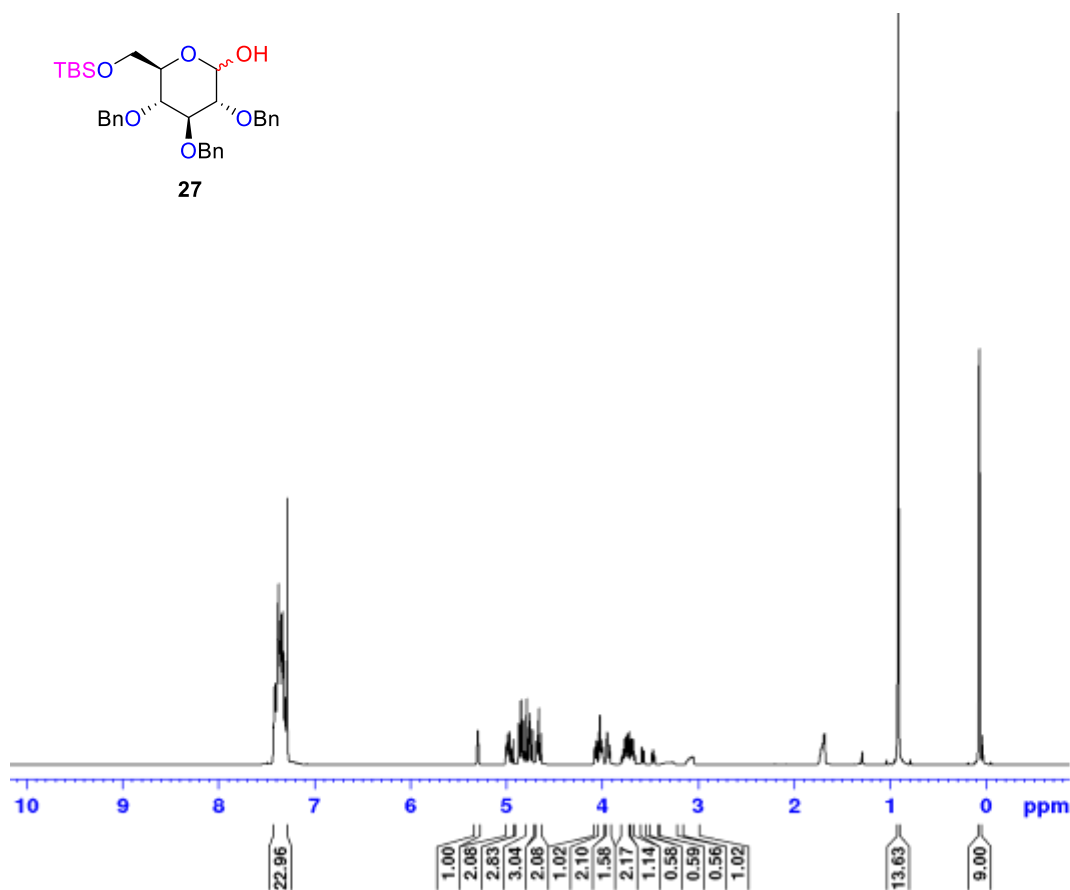
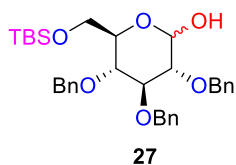


Current Data Parameters
NAME AB-500
EXPNO 173
PROCNO 1

F2 - Acquisition Parameters
Date_ 20210709
Time 16.09 h
INSTRUM spect
PROBHD Z109128_0042 (6536
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 514
DS 4
SMH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 299.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.7829381 MHz
NUC1 13C
PO 3.33 usec
P1 10.00 usec
PLW1 64.00399780 W
SFO2 500.130888 MHz
NUC2 1H
CPDPRG[2] waltz165
PCPD2 80.00 usec
PLW2 4.84679985 W
PLW12 0.17039999 W
PLW13 0.08570880 W

F2 - Processing parameters
SI 32768
SF 125.7703652 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

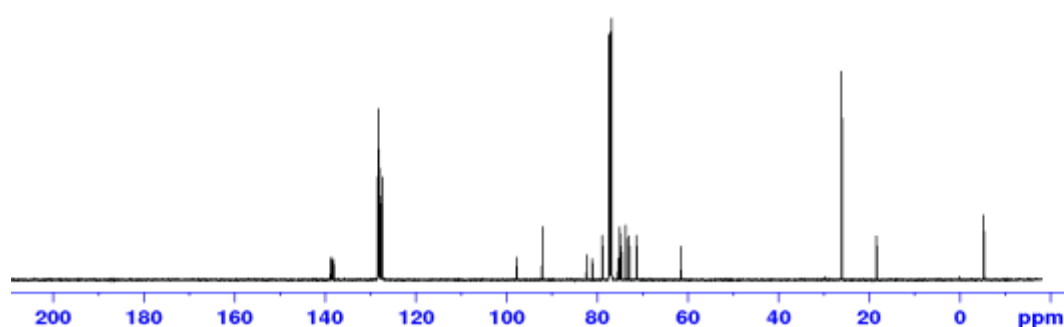
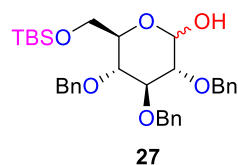




Current Data Parameters
NAME AB-500
EXPNO 180
PROCNO 1

F2 - Acquisition Parameters
Date_ 20210722
Time 13.31 h
INSTRUM spect
PROBHD Z109128_0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 101
DW 50.000 usec
DE 13.04 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1
SF01 500.1830886 MHz
NUC1 1H
PO 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W

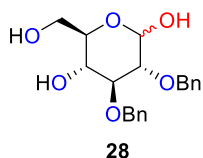
F2 - Processing parameters
SI 65536
SF 500.1800000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME AB-500
EXPNO 182
PROCNO 1

F2 - Acquisition Parameters
Date_ 20210722
Time 15.04 h
INSTRUM spect
PROBHD Z109128_0042 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1488
DS 4
SWH 29761.904 Hz
FIDRES 0.906261 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 299.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SF01 125.7629381 MHz
NUC1 13C
PO 3.33 usec
P1 10.00 usec
PLW1 64.00399780 W
SF02 500.1820007 MHz
NUC2 1H
CPDPRG2 waltz65
PCPD2 80.00 usec
PLW2 4.84679985 W
PLW12 0.17039999 W
PLW13 0.08570800 W

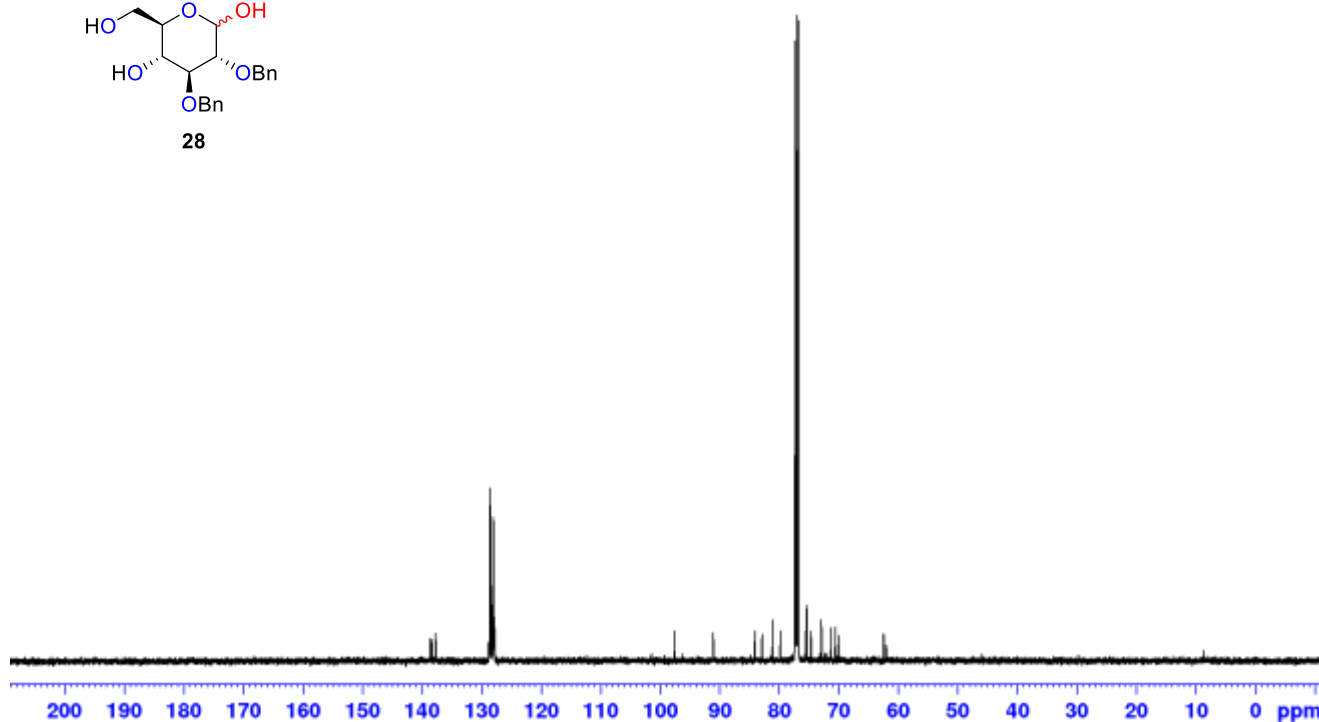
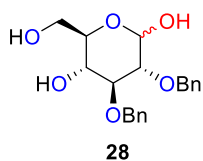
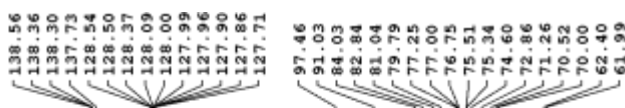
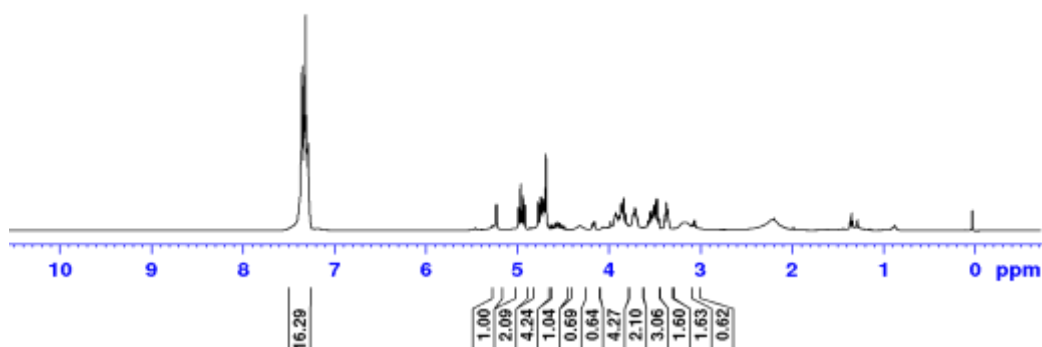
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EXPNO 209
PROCNO 1

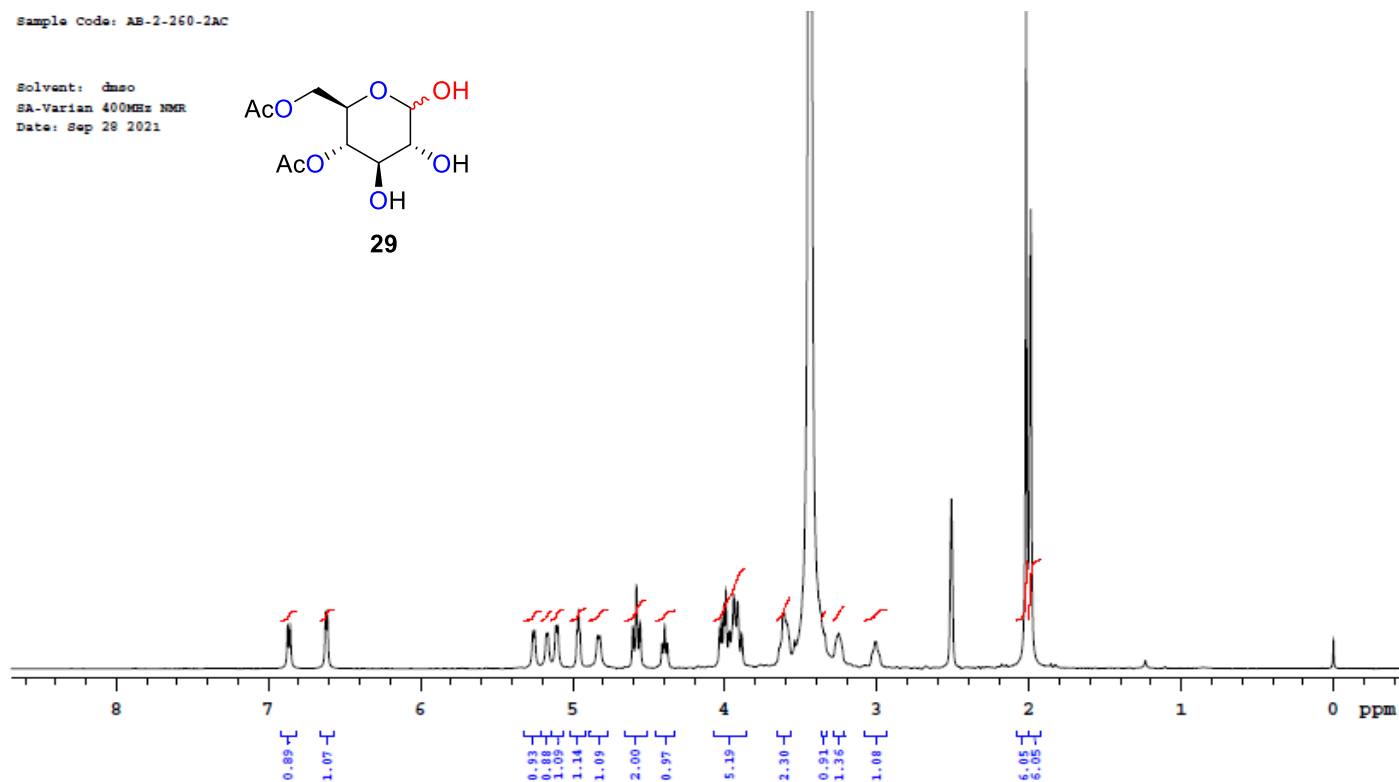
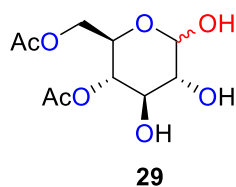
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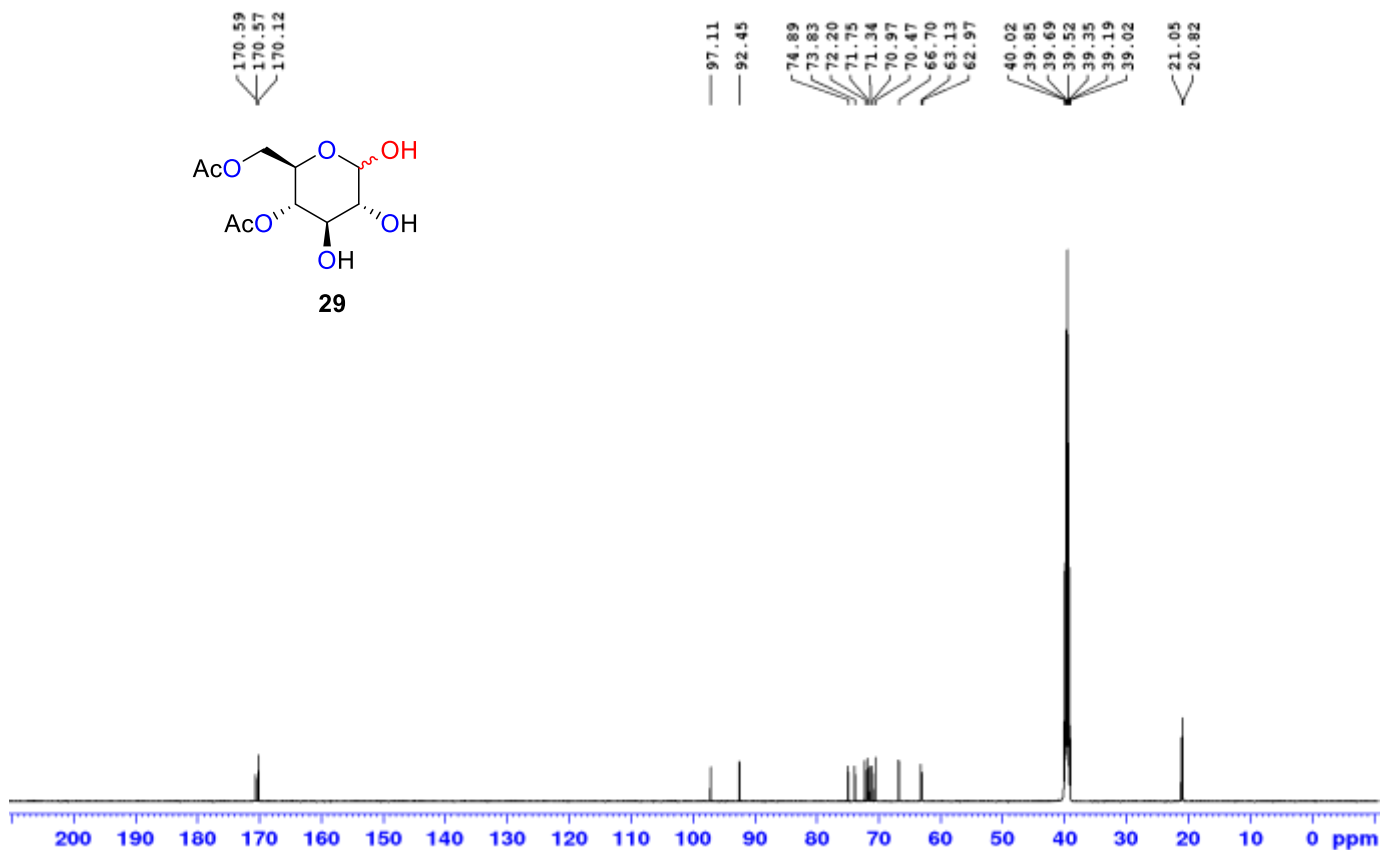
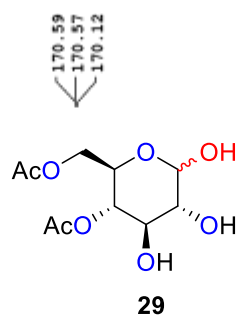


Sample Code: AB-2-260-2AC

Solvent: dmsc
SA-Varian 400MHz NMR
Date: Sep 28 2021



Plotname: AB-2-260-2AC_PROTON_20210928_01_plot06

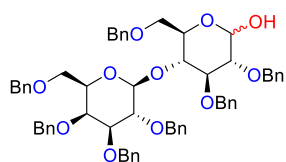




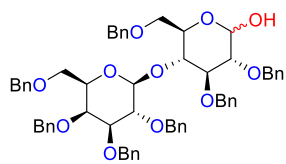
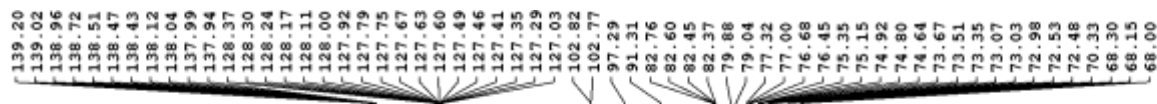
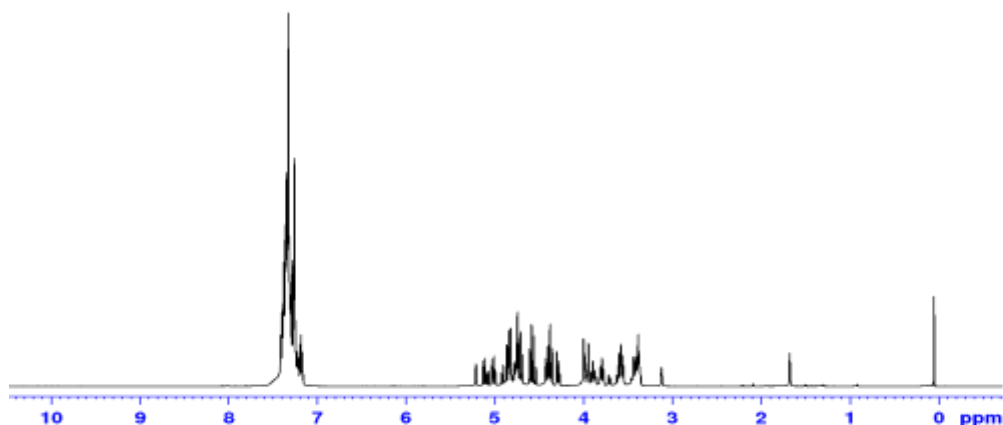
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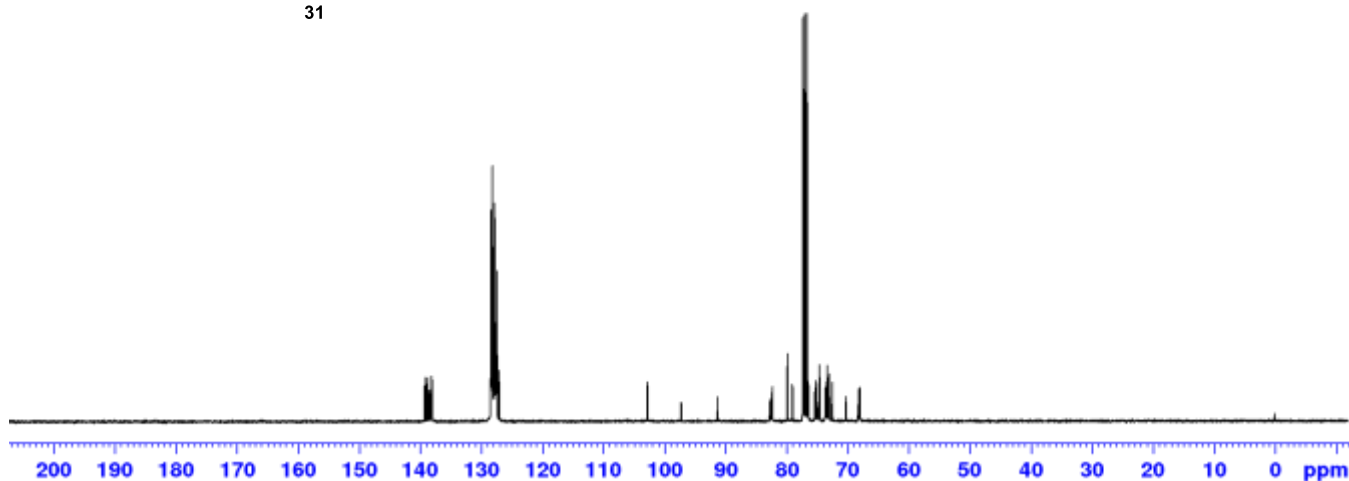
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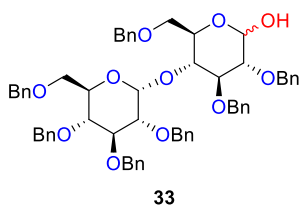


31



31

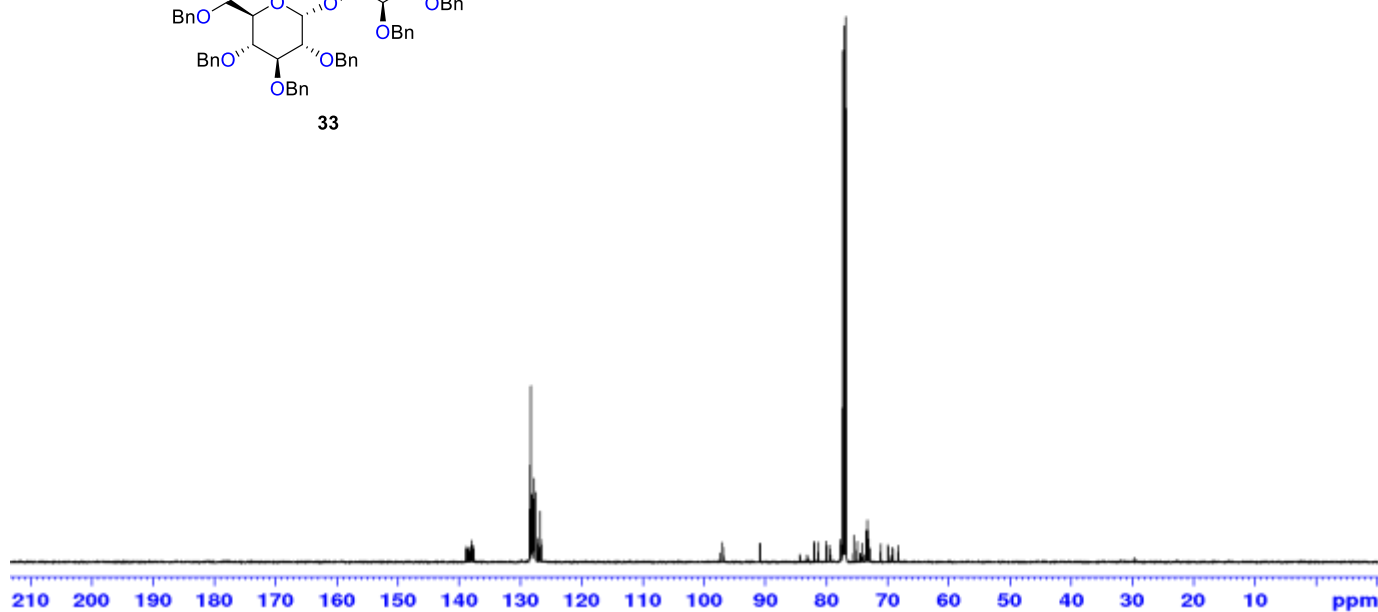
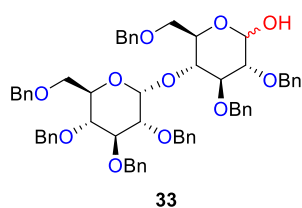
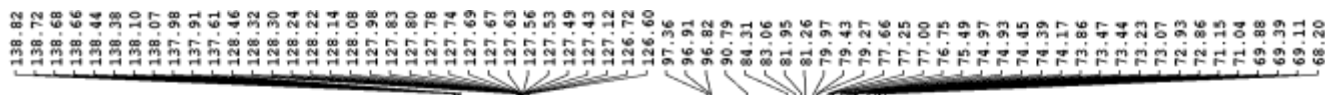
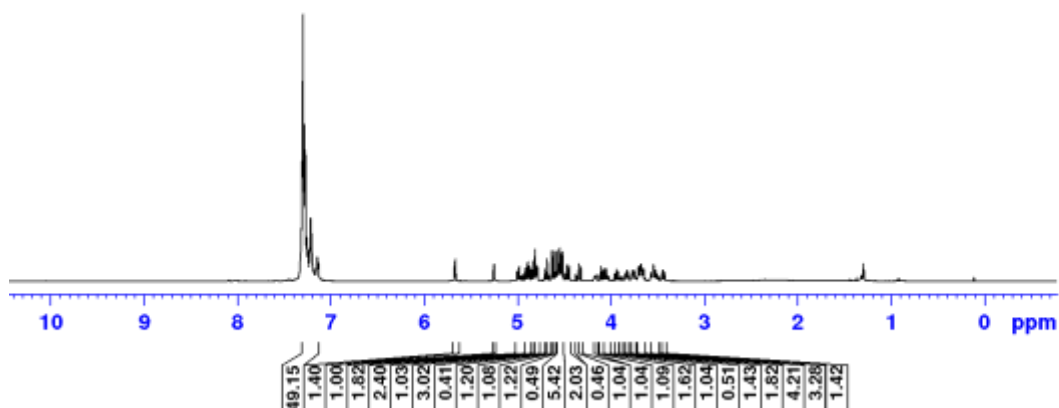


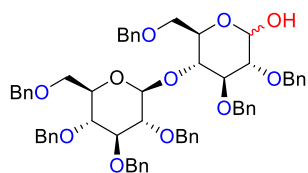


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TD0 1
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PO 5.00 usec
P1 15.00 usec
PLW1 4.84679985 M

F2 - Processing parameters
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35

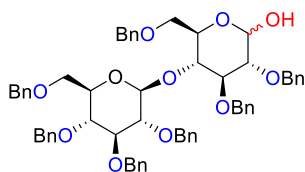
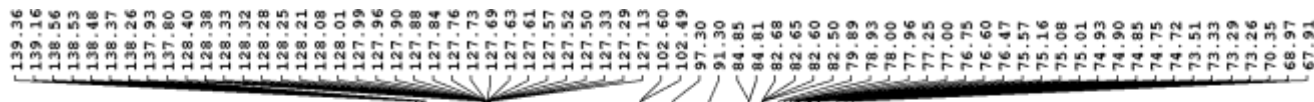
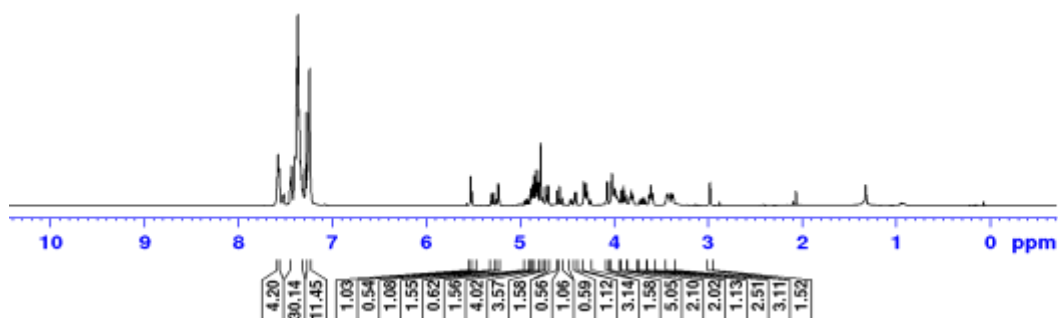


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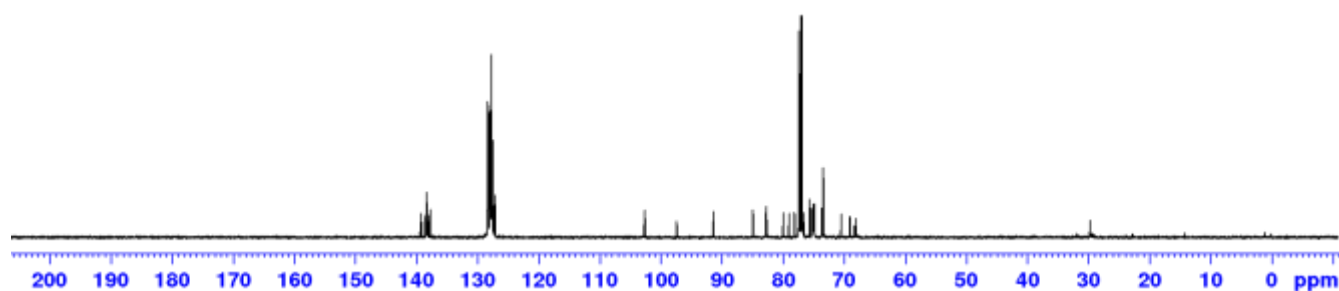
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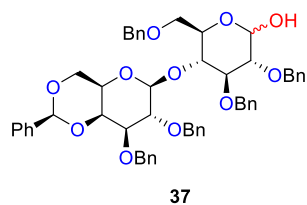
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35

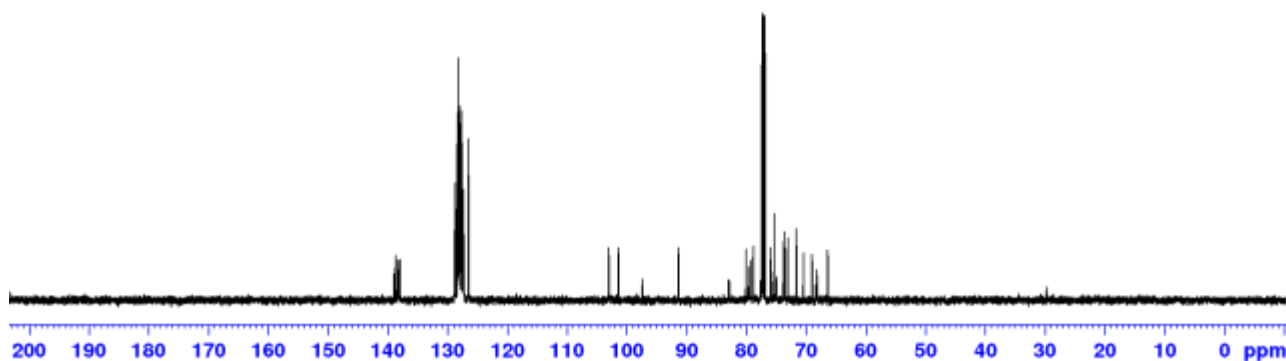
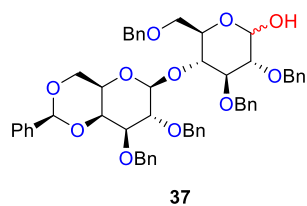
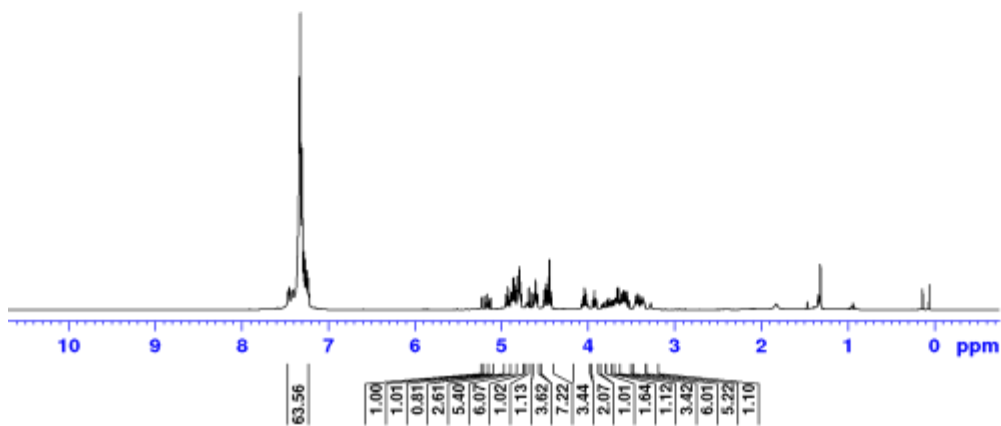




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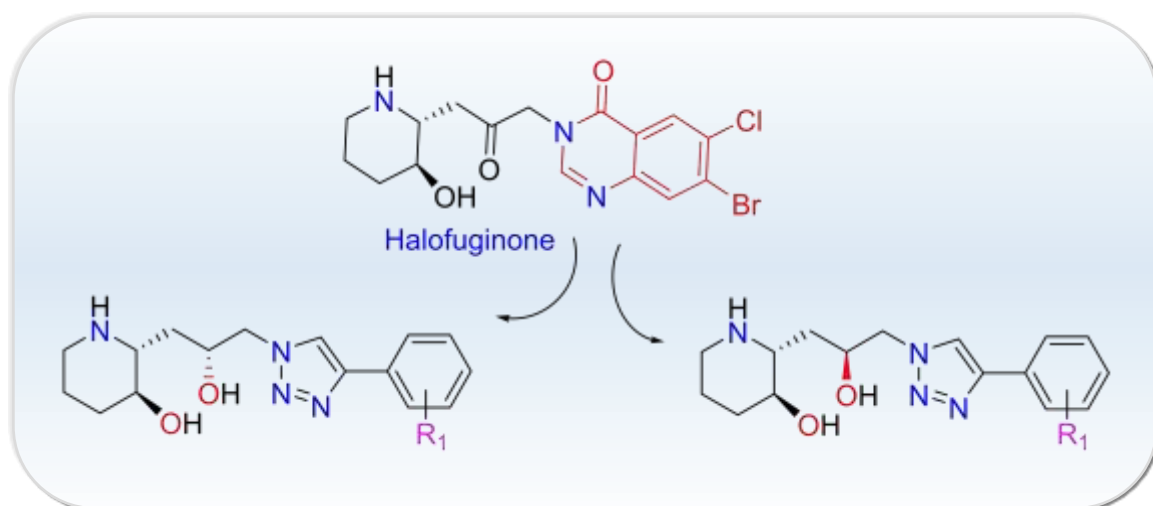
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P1 15.00 usec
PLN1 4.64679985 W

F2 - Processing parameters
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SF 500.1800000 MHz
WDW EM
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LB 0.30 Hz
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PC 1.00



Chapter-4

Synthesis and Biological evaluation of Halofuginone analogs



4.1 Introduction

4.2 Results and Discussions

4.3 Conclusions

4.4 Experimental section

4.5 References

4.1 Introduction

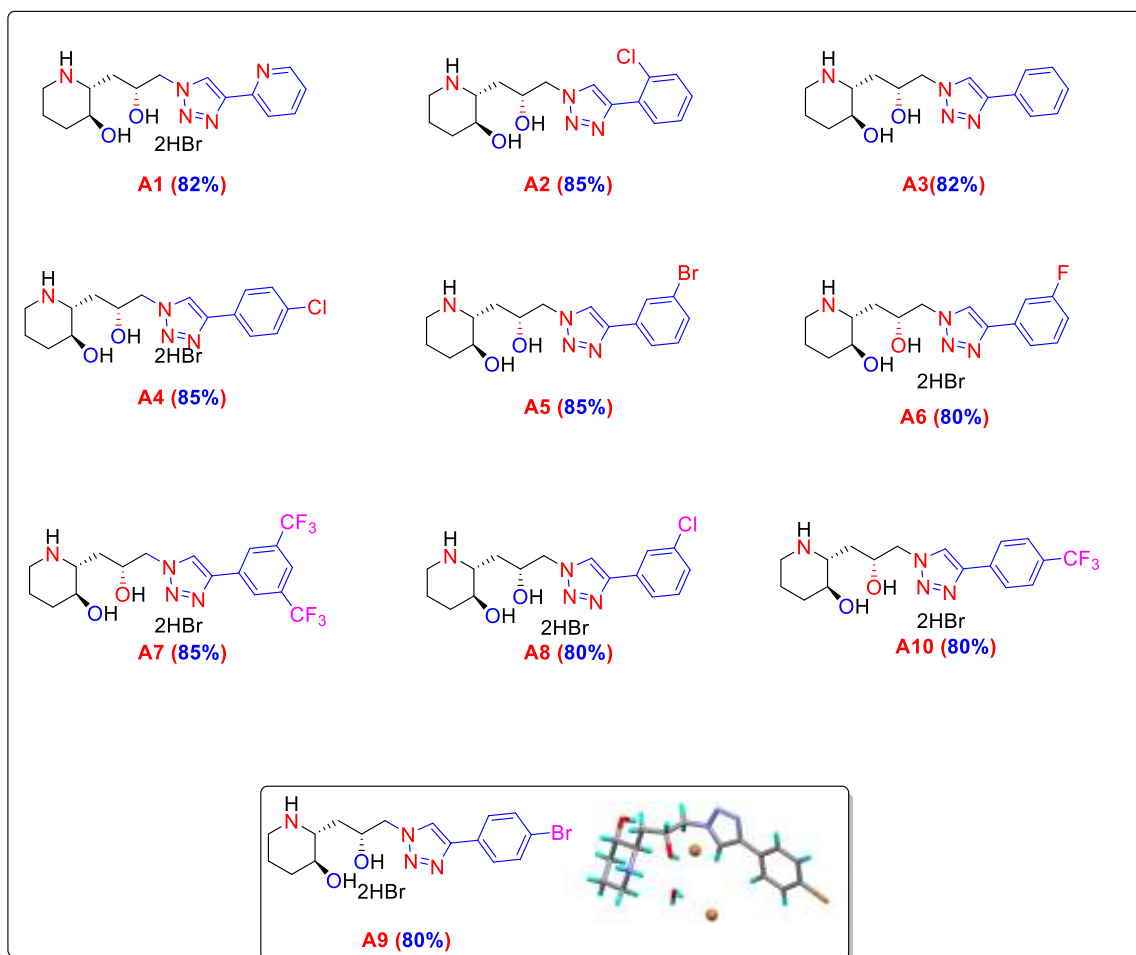
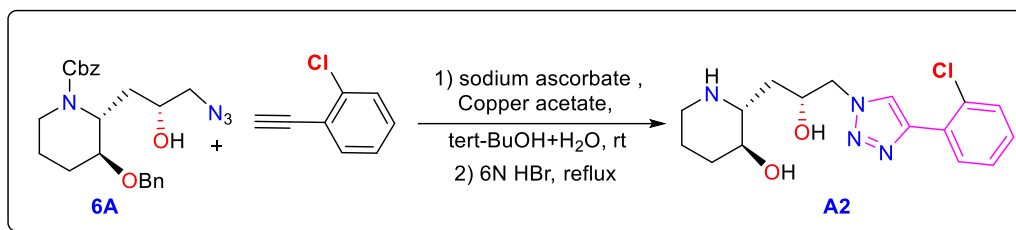
The Chinese medicinal plant *Dichroa febrifuga*, often known as Chinese quinine and a member of the Saxifragaceae family, contains (+)-febrifugine and (+)-isofebrifugine in its roots and leaves. These tests also revealed that at least one of the other plants from the Saxifragaceae family has febrifugine.¹ These attempts ultimately fell short of producing a malaria cure for humans because of unpleasant side effects such as nausea, vomiting, and liver poisoning. However, a racemic version of an analogue halofuginone that was created to increase the therapeutic potential has been utilized as an antiprotozoal drug in the poultry sector. It was discovered through research on the best dosage of ($\pm$)-halofuginone for the treatment of chickens that this substance is also a potent inhibitor of type 1 collagen manufacture in humans.² When these compounds were originally discovered in the middle of the 20th century, structural elucidation made it extremely difficult to determine their relative and absolute stereochemistry. The history of febrifuge today dates back to 1943 when Chou and colleagues discovered that a crude extract of Chang Shan from the *Dichroa febrifuga* Lour plant may be utilized to treat tertian malaria patients clinically. Chang Shan was shown to be five times less effective than Shuu Chii's crude extracts at preventing *Plasmodium gallinaceum* in chicks.³ Febrifugine was shown to be 100 times more effective than quinine, the antimalarial medicine of choice at the time, over *Plasmodium Lophurae* in ducks, although isofebrifugine had only moderate action against the same malaria strain. No known parasite is resistant to febrifugine. The side effects of febrifugine, including diarrhea, vomiting, and liver damage, have prevented its usage as an antimalarial medication.⁴ A derivative of febrifugine known as halofuginone was initially developed in the late 1960's as a potential antimalarial drug in which one of the pharmaceutical's metabolic pathways was blocked. It was discovered that HF (3), in addition to having antiprotozoal activity and mammalian biological features, racemic halofuginone's hydrobromide salt, which has been employed as an anticoccidial feed additive for broilers and turkeys.

Halofuginone has been discovered to stop tumor development and formation in several animal models, including chemically produced bladder carcinoma and hepatocellular carcinoma metastasis.^{5, 6} HF is being employed as a coccidiostat against infections caused by *Eimeria* and *Cryptosporidium*.⁷ Studies on HF indicate that it may be useful in treating fibrotic illness, cancer, and scleroderma. Prolyl-tRNA synthetase (PRS), an enzyme belonging to the family of aminoacyl-tRNA synthetases (aaRS), has recently been identified as the molecular target of HF in humans. These latter ones, which link amino acids to appropriate tRNAs for protein translation in an aminoacylation step, are ancient enzymes that translate genetic code. Studies on HF show promise. We and other researchers have examined crucial cellular procedures in malaria parasites, including lipid import and nucleosome assembly.⁸ However, the search for effective malaria parasite inhibitors against these protein targets has been impeded by the absence of experimentally validated "hit" molecules. Thankfully, a number of groups have been examining the structure-function characteristics of aaRSs found in malaria parasites. The present multidrug anti-malarial therapy can benefit from adding a medication component that targets parasitic aaRSs.⁹

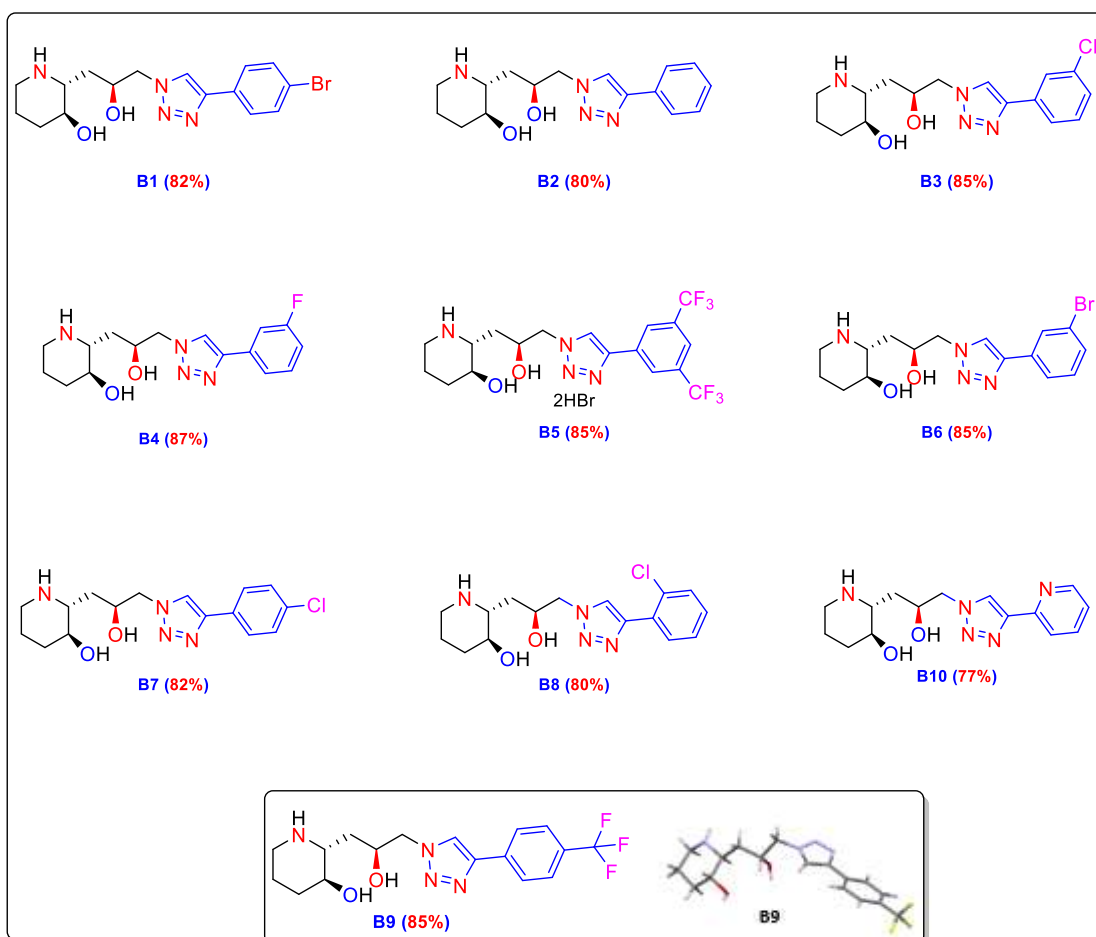
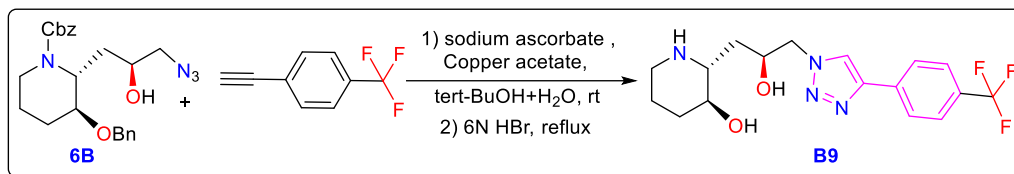
The advent and rapid spread of parasites that are resistant to drugs emphasizes the necessity of finding ways to weaken these parasites in order to eventually get rid of or control their infestations. Therefore, it is crucial to find novel druggable targets and chemical families of anti-parasitic drugs. Targeting parasite enzymes involved in protein synthesis has been shown to be useful in a number of recent investigations. Consequently, our work offers the groundwork for tailoring quinazolinone-based derivatives for the development of leads against parasites that cause malaria, leishmaniasis, toxoplasmosis, cryptosporidiosis, and coccidiosis.¹⁰

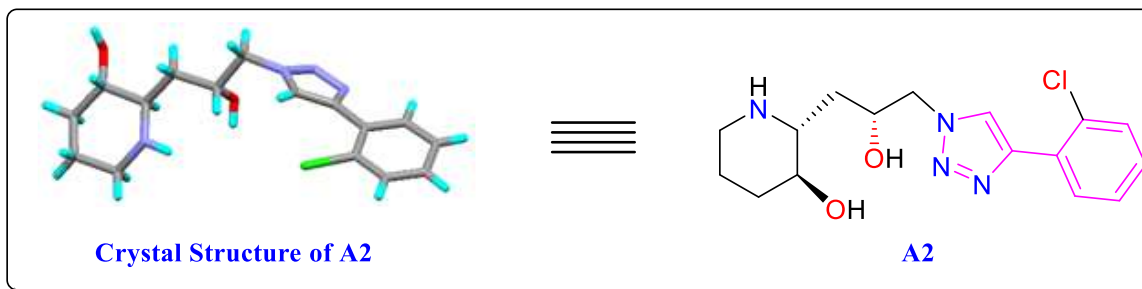
When administered in combination therapy with various cancer-fighting drugs using a variety of modalities, halofuginone successfully decreased the dosages of chemotherapeutic agents, reducing the burden of treatment on cancer patients. The precise biological mechanism or mechanisms, underlying febrifugine, and isofebrifugine's antiprotozoal action are not fully understood. We looked at how HF and its stereoisomers, which are produced chemically,

Synthesis of Halofuginone analogs-A series



Synthesis of Halofuginone analogs-B series





This compound crystallizes in P21 space group and its asymmetric unit is composed of one unit of **A2** molecule. In this molecule, interplanar angle between benzene ring and triazole ring is found to be 23.59°. Like the previous compound, here also each **A2** molecule is connected with four **A2** molecules via O-H $\cdots$ O and O-H $\cdots$ N hydrogen bonds which are propagated along ab-plane leading to the formation of a two-dimensional hydrogen-bonded layered network.

Datablock: PRS36

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	Calculated	Reported	
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Hall group	P 2yb	P 2yb	
Moiety formula	C16 H21 Cl N4 O2	?	
Sum formula	C16 H21 Cl N4 O2	C16 H21 Cl N4 O2	
Mr	336.82	336.82	
Dx, g cm-3	1.330	1.330	
Z	2	2	
Mu (mm-1)	0.242	0.242	
F000	356.0	356.0	
F000'	356.42		
h, k, lmax	7, 12, 21	7, 11, 20	
Nref	3731 [1982]	2889	
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test-name_ALERT_alert-type_alert-level.

Click on the hyperlinks for more details of the test.

● Alert level B

PLAT340_ALERT_3_B Low Bond Precision on C-C Bonds 0.01333 Ang.

● Alert level C

PLAT026_ALERT_3_C Ratio Observed / Unique Reflections (too) Low ..	49% Check
PLAT029_ALERT_3_C _diffn_measured_fraction_theta_full value Low .	0.973 Why?
PLAT052_ALERT_1_C Info on Absorption Correction Method Not Given	Please Do !
PLAT230_ALERT_2_C Hirshfeld Test Diff for C009 --C00E .	5.3 s.u.
PLAT234_ALERT_4_C Large Hirshfeld Difference C008 --C00F .	0.17 Ang.
PLAT234_ALERT_4_C Large Hirshfeld Difference C00F --C00K .	0.16 Ang.
PLAT420_ALERT_2_C D-H Bond Without Acceptor N005 --H005 .	Please Check
PLAT911_ALERT_3_C Missing FCF Refl Between Thmin & STh/L= 0.600	43 Report
PLAT915_ALERT_3_C No Flack x Check Done: Low Friedel Pair Coverage	61 %

● Alert level G

PLAT007_ALERT_5_G Number of Unrefined Donor-H Atoms	2 Report
PLAT199_ALERT_1_G Reported _cell_measurement_temperature (K)	293 Check
PLAT200_ALERT_1_G Reported _diffn_ambient_temperature (K)	293 Check
PLAT720_ALERT_4_G Number of Unusual/Non-Standard Labels	44 Note
PLAT791_ALERT_4_G Model has Chirality at C006 (Sohnke SpGr)	R Verify
PLAT791_ALERT_4_G Model has Chirality at C007 (Sohnke SpGr)	S Verify
PLAT791_ALERT_4_G Model has Chirality at C009 (Sohnke SpGr)	R Verify
PLAT883_ALERT_1_G No Info/Value for _atom_sites_solution_primary .	Please Do !
PLAT910_ALERT_3_G Missing # of FCF Reflection(s) Below Theta(Min).	1 Note
PLAT912_ALERT_4_G Missing # of FCF Reflections Above STh/L= 0.600	120 Note
PLAT941_ALERT_3_G Average HKL Measurement Multiplicity	3.3 Low
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density.	0 Info

- 0 **ALERT level A** = Most likely a serious problem - resolve or explain
 1 **ALERT level B** = A potentially serious problem, consider carefully
 9 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
 12 **ALERT level G** = General information/check it is not something unexpected

- 4 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
 3 ALERT type 2 Indicator that the structure model may be wrong or deficient
 7 ALERT type 3 Indicator that the structure quality may be low
 7 ALERT type 4 Improvement, methodology, query or suggestion
 1 ALERT type 5 Informative message, check
-

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

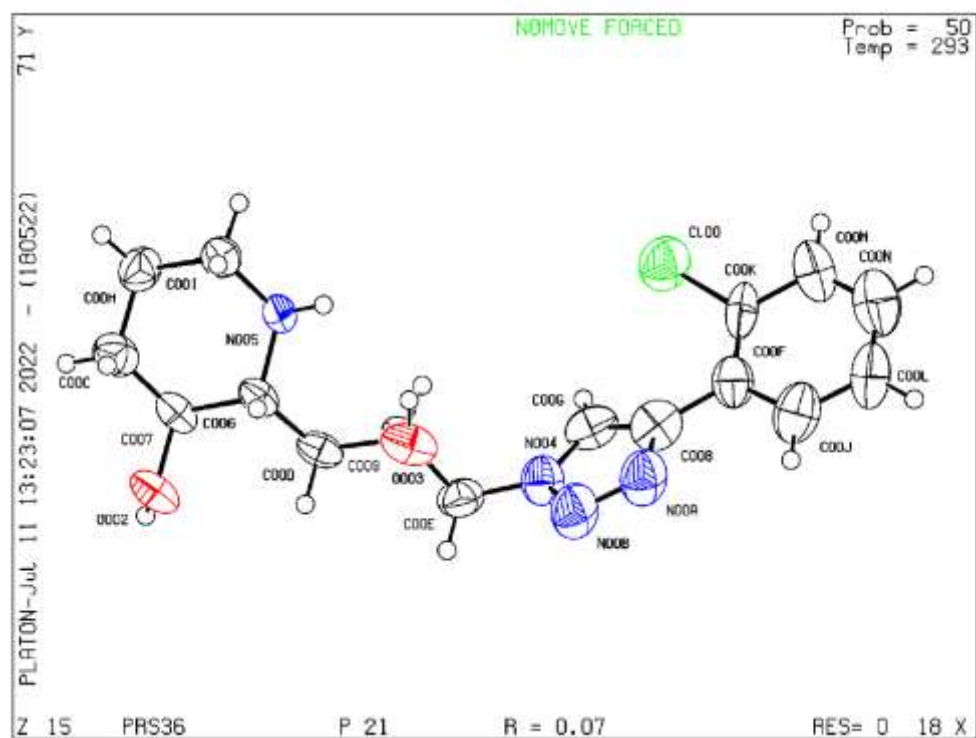
A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

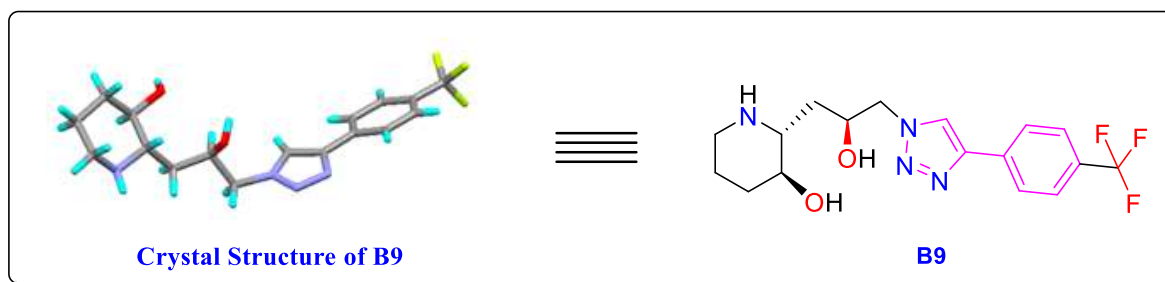
Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 18/05/2022; check.def file version of 17/05/2022

Datablock PRS36 - ellipsoid plot





This compound crystallizes in $P2_12_12_1$ space group and its asymmetric unit comprises one unit of **B9** molecule. In this molecule, benzene ring and triazole ring are found almost coplanar (Interplanar angle: 16.19°). Each **B9** molecule is connected to four **B9** molecules through $O\cdots O$ and $O-H\cdots N$ hydrogen bonds. These hydrogen bonds are propagated along *ab*-plane to form a two dimensional hydrogen-bonded layered network.

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	Calculated	Reported	
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Hall group	P 2ac 2ab	P 2ac 2ab	
Moiety formula	C17 H21 F3 N4 O2	?	
Sum formula	C17 H21 F3 N4 O2	C17 H21 F3 N4 O2	
Mr	370.38	370.38	
Dx, g cm-3	1.399	1.399	
Z	4	4	
Mu (mm-1)	0.115	0.115	
F000	776.0	776.0	
F000'	776.45		
h, k, lmax	7, 12, 40	6, 12, 39	
Nref	3926 [2302]	3674	
Tmin, Tmax	0.962, 0.973		
Tmin'	0.962		
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		0.1679 (3674)	
S = 0.788	Npar= 240		

The following ALERTS were generated. Each ALERT has the format

test-name_ALERT_alert-type_alert-level.

Click on the hyperlinks for more details of the test.

Alert level C

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                   outside the range 0.80 <> 2.00
                   Goodness of fit given =      0.788
STRVA01_ALERT_2_C      Chirality of atom sites is inverted?
                   From the CIF: _refine_ls_abs_structure_Flack      1.900
                   From the CIF: _refine_ls_abs_structure_Flack_su    0.900
PLAT052_ALERT_1_C Info on Absorption Correction Method      Not Given      Please Do !
PLAT242_ALERT_2_C Low   'MainMol' Ueq as Compared to Neighbors of      C00I Check
PLAT340_ALERT_3_C Low Bond Precision on C-C Bonds ..... 0.00719 Ang.
PLAT420_ALERT_2_C D-H Bond Without Acceptor N004      --H004      . Please Check
PLAT907_ALERT_2_C Flack x > 0.5, Structure Needs to be Inverted? . 1.90 Check
PLAT911_ALERT_3_C Missing FCF Refl Between Thmin & STh/L= 0.600      2 Report
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Alert level G

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PLAT007_ALERT_5_G Number of Unrefined Donor-H Atoms ..... 2 Report
PLAT032_ALERT_4_G Std. Uncertainty on Flack Parameter Value High . 0.900 Report
PLAT199_ALERT_1_G Reported _cell_measurement_temperature ..... (K) 293 Check
PLAT200_ALERT_1_G Reported _diffrn_ambient_temperature ..... (K) 293 Check
PLAT242_ALERT_2_G Low   'MainMol' Ueq as Compared to Neighbors of      C00O Check
PLAT720_ALERT_4_G Number of Unusual/Non-Standard Labels ..... 47 Note
PLAT791_ALERT_4_G Model has Chirality at C007      (Sohnke SpGr) S Verify
PLAT791_ALERT_4_G Model has Chirality at C009      (Sohnke SpGr) R Verify
PLAT791_ALERT_4_G Model has Chirality at C00B      (Sohnke SpGr) R Verify
PLAT883_ALERT_1_G No Info/Value for _atom_sites_solution_primary . Please Do !
PLAT910_ALERT_3_G Missing # of FCF Reflection(s) Below Theta(Min). 1 Note
PLAT912_ALERT_4_G Missing # of FCF Reflections Above STh/L= 0.600 73 Note
PLAT916_ALERT_2_G Hooft y and Flack x Parameter Values Differ by . 0.30 Check
PLAT933_ALERT_2_G Number of HKL-OMIT Records in Embedded .res File 2 Note
PLAT965_ALERT_2_G The SHELXL WEIGHT Optimisation has not Converged Please Check
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density. 0 Info
```

```
0 ALERT level A = Most likely a serious problem - resolve or explain
0 ALERT level B = A potentially serious problem, consider carefully
8 ALERT level C = Check. Ensure it is not caused by an omission or oversight
16 ALERT level G = General information/check it is not something unexpected
```

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4 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
10 ALERT type 2 Indicator that the structure model may be wrong or deficient
3 ALERT type 3 Indicator that the structure quality may be low
6 ALERT type 4 Improvement, methodology, query or suggestion
1 ALERT type 5 Informative message, check
```

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

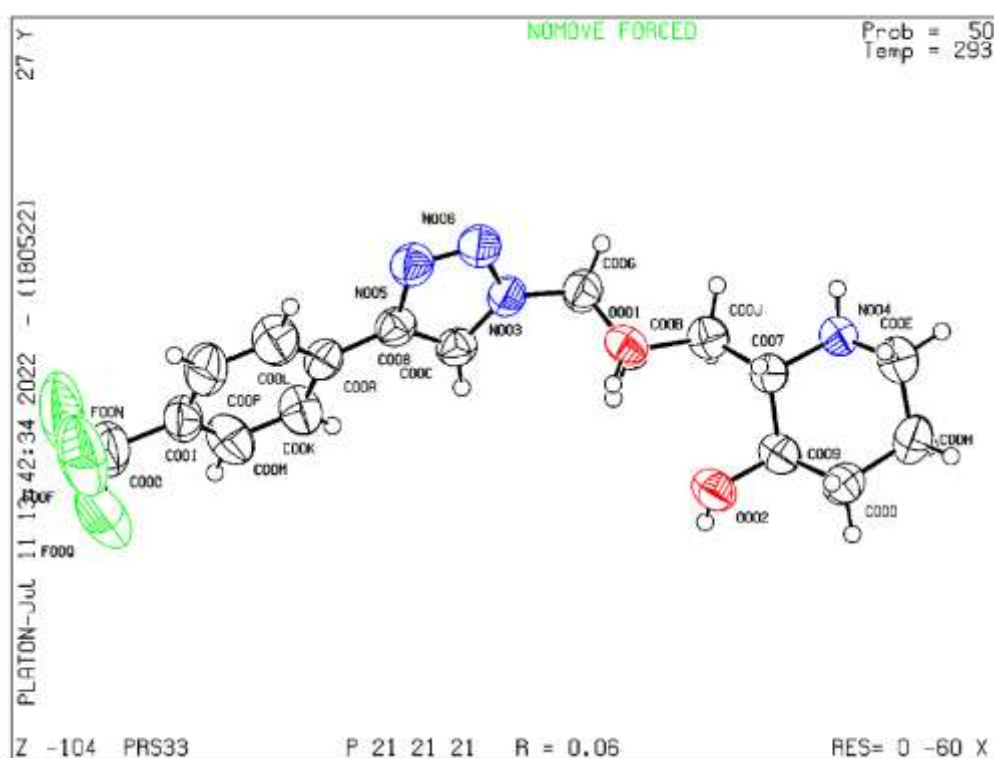
A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 18/05/2022; check.def file version of 17/05/2022

Datablock PRS33 - ellipsoid plot



FLOW CYTOMETRIC ANALYSIS

4.2.2 Flow Cytometry gating for p-GCN2 in HepG2 cells for A-Series compounds

Flow cytometry refers to the measurement of cells based on the scattering of light and fluorescence properties. This method is used to measure size, shape, density, DNA, RNA and protein content, internal or external receptors, membrane structures, Apoptosis and necrosis, calcium flux, intracellular pH, etc. By using the gating graph plotted against the amount of side scattering and Fluorescence isothiocyanate we have analyzed the percentage of HepG2 cells affected by the treatment of the chemically synthesized analogues of halofuginone. The reaction is carried out in the presence of suitable control and the vehicle methanol is added to remove the excess amount of water and vehicle DMSO is added as the solvent. The following figure 4.1 shows the HepG2 cell p-GCN2 flow cytometry gating for the A-Series compound.

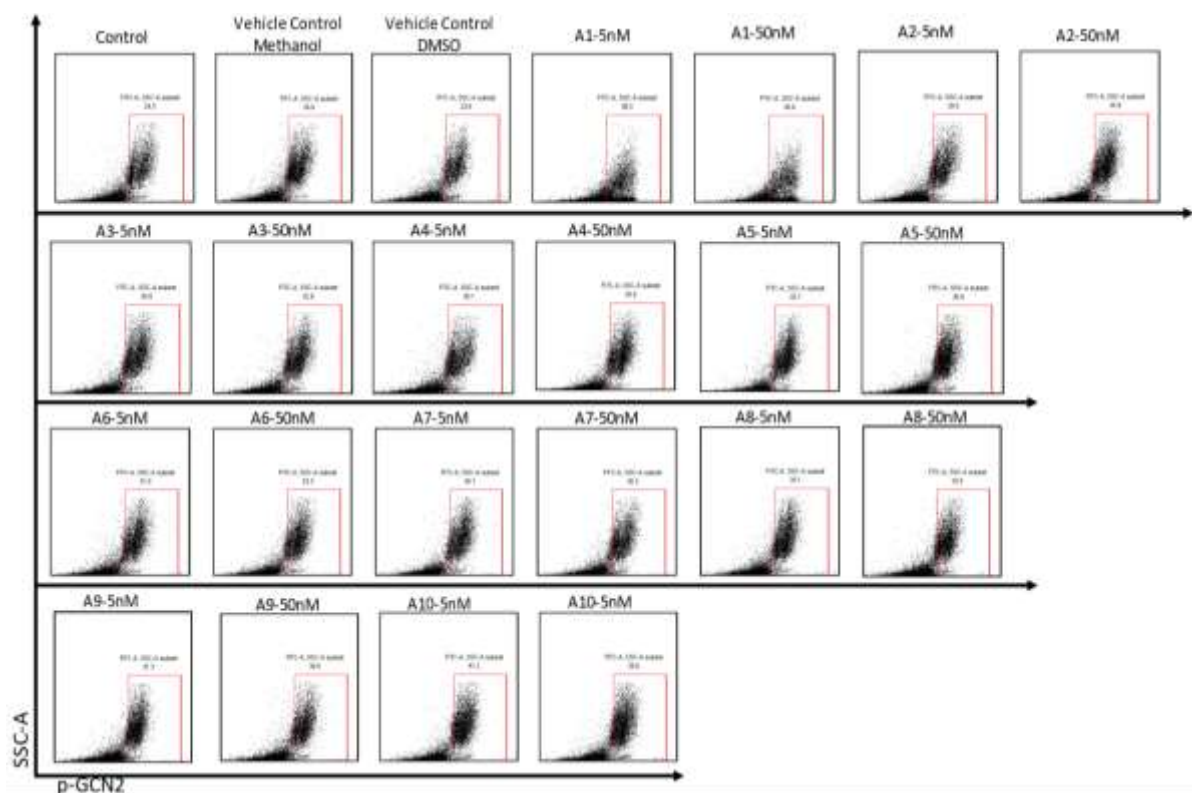
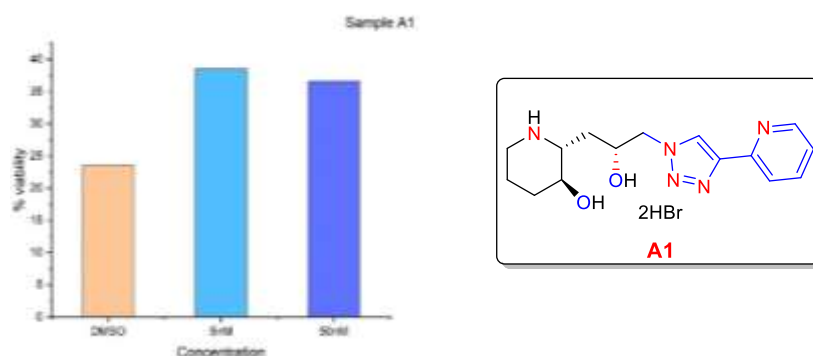
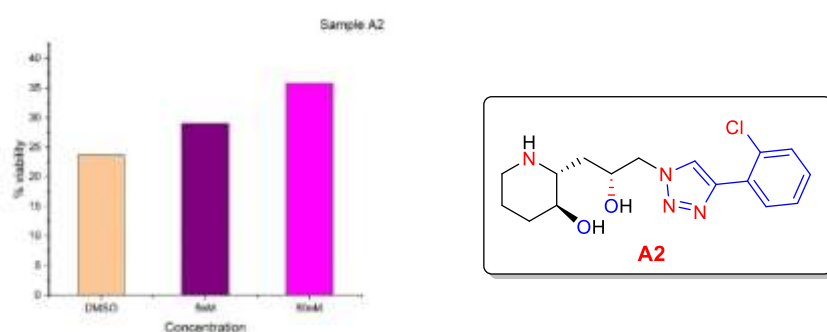


Figure 4.1 Flow Cytometry gating for p-GCN2 in HepG2 cells for A-Series compounds**Figure 4.2: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample A1**

In figure 4.2, the comparison between DMSO, 5nM, and 50nM for sample A1 is illustrated. In terms of the graphical representation, the percentage of viability in DMSO obtained is 23.6% which is lower than the other concentrations such as 5nM and 50nM. On treatment 5nM sample with HepG2 cells showed 38.5% cell viability which is a little bit higher than that treated with 50nM concentration with 36.6% viability.

**Figure 4.3: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample A2**

The contrast between DMSO, 5nM and 50nM for sample A2 is shown in figure 4.3. According to the graphical representation, the viability percentage in DMSO achieved is 23.6%, which is lower than the viability percentages at other doses like 5nM and 50nM. HepG2

cell viability after treatment with a 5nM sample was 29%, somewhat lower than that after treatment with a 50nM concentration, which was 35.8%.

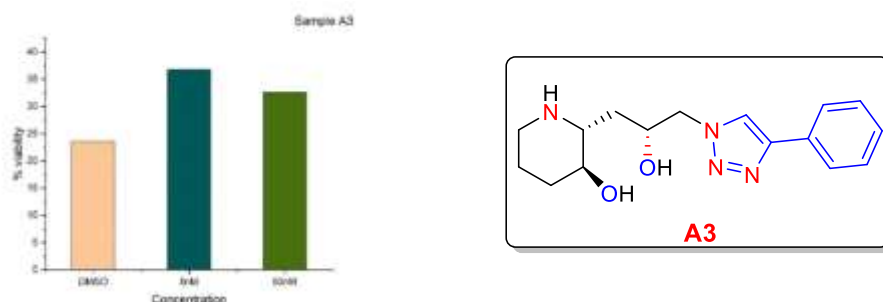


Figure 4.4: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample A3

Figure 4.4 shows the contrast between DMSO at 5nM and 50nM for sample A3. The viability percentage in DMSO was 23.6% according to the graphical representation, which is less than the viability percentages at other doses like 5nM and 50nM. HepG2 cells treated with a 5nM sample showed 36.8% cell viability after treatment, which is 4.2% greater than cells treated with a 50nM concentration, which had 32.6% viability.

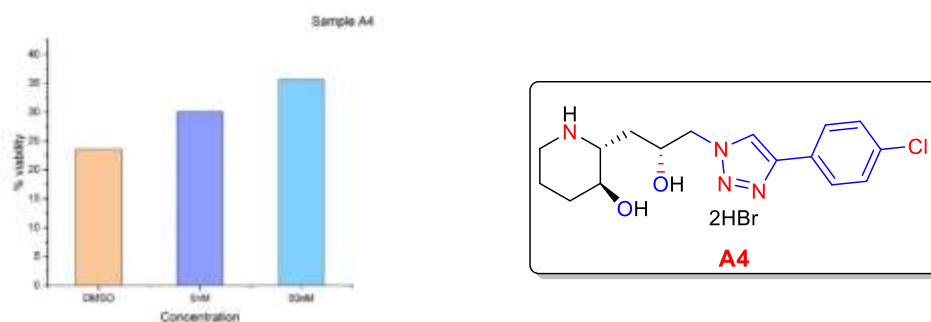


Figure 4.5: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample A4

Concentrations of DMSO 5nM and 50nM for sample A4 are compared and shown side by side in figure 4.5. When compared to other concentrations like 5nM and 50nM, the percentage of viability in DMSO was obtained to be 23.6%, which is lower. HepG2 cell viability after treatment with a 5nM sample was 30.1%, a small increase in the cell viability over the 35.6% viability of cells after treatment with a 50nM concentration.

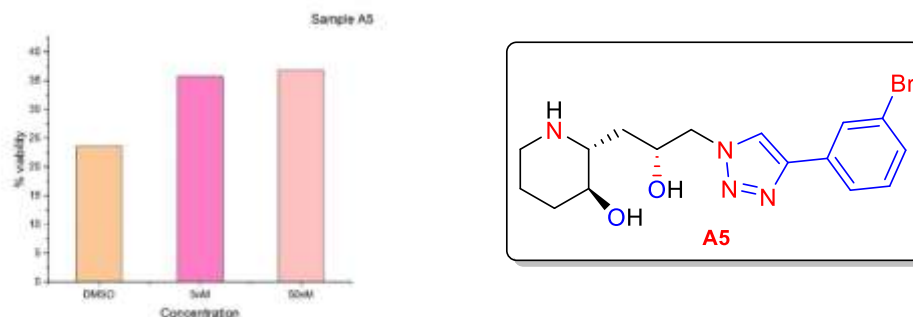


Figure 4.6: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample A5

Figure 4.6 compares the effects of DMSO at 5nM and 50nM for specimen A5. In regards to the graphical depiction, the viability percentage in DMSO achieved is 23.6%, which is smaller than the other dosages like 5nM and 50nM. HepG2 cells treated with a 5nM sample had a cell viability of 38.5% after treatment, which is almost unchanged from the cells treated with a 50nM dosage, which had a viability of 36.6%.

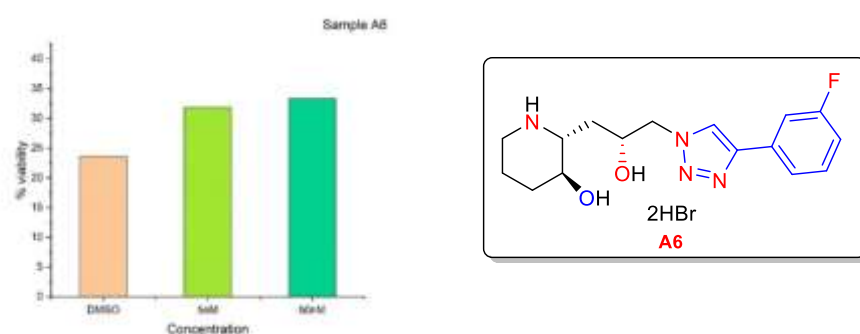


Figure 4.7: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample A6

For specimen A6, Figure 4.7 contrasts the effects of DMSO at 5nM and 50nM. The viability percentage in DMSO attained, according to the graphical representation, is 23.6%, which is lower than the viability percentages at other dosages like 5nM and 50nM. After

treatment, HepG2 cells treated with a 5nM sample had a cell viability of 31.9%, which is nearly unchanged from the viability of cells treated with a 50nM dosage, which was 33.3%.

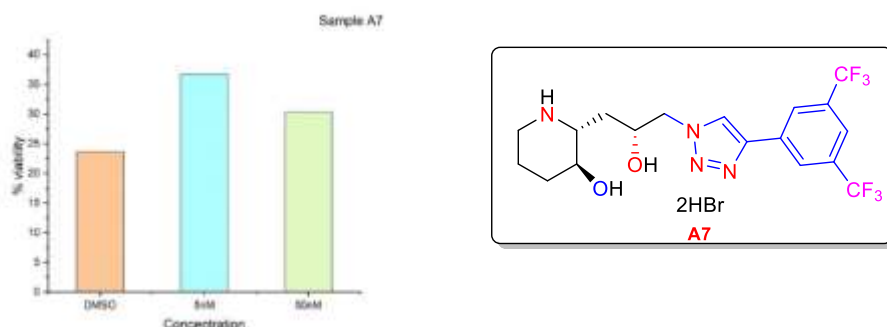


Figure 4.8: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample A7

The effects of DMSO at 5nM and 50nM for specimen A7 are contrasted in Figure 4.8. According to the graphical representation, the viability percentage for DMSO attained is 23.6%, which is lower than the viability percentages for other dosages like 5nM and 50nM. The viability of HepG2 cells treated with a 5nM sample was 36.7% following treatment, which is about 6.4% higher than the viability of cells treated with a 50nM dosage, which was 30.3%.

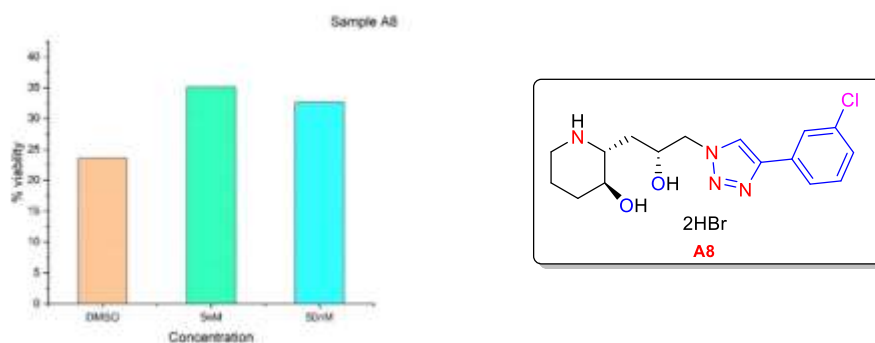


Figure 4.9: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample A8

DMSO's effects on specimen A8 at 5nM and 50nM are contrasted in Figure 4.9. According to the graphical representation, the viability percentage in DMSO attained is 23.6%,

which is lower than the concentrations of 5nM and 50nM. Following treatment, the HepG2 group treated with a 5nM sample exhibited cell viability of 35.1%, which is 2.5% more than the viability of 32.6% seen in cells treated with a 50nM dosage.

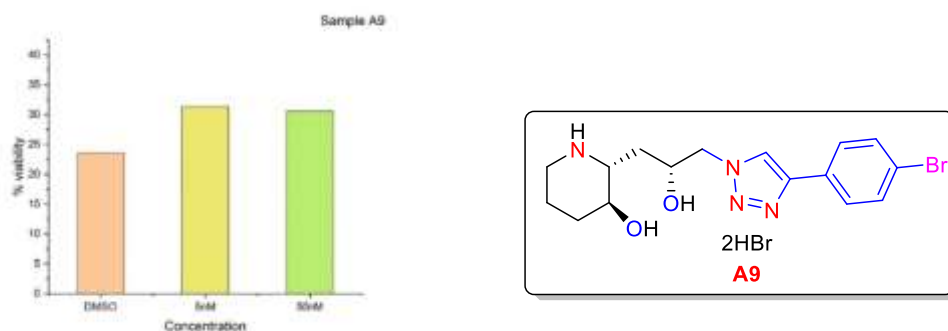


Figure 4.10: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample A9

For specimen A9, Figure 4.10 contrasts the effects of DMSO at 5nM and 50nM. The viability % in DMSO attained, according to the graphical representation, is 23.6%, which is lower than the viability percentages at other levels like 5nM and 50nM. After administration, HepG2 cells treated with a 5nM sampling had a cell viability of 31.3%, which is nearly unchanged from the viability of cells treated with a 50nM dosage, which was 30.6 %.

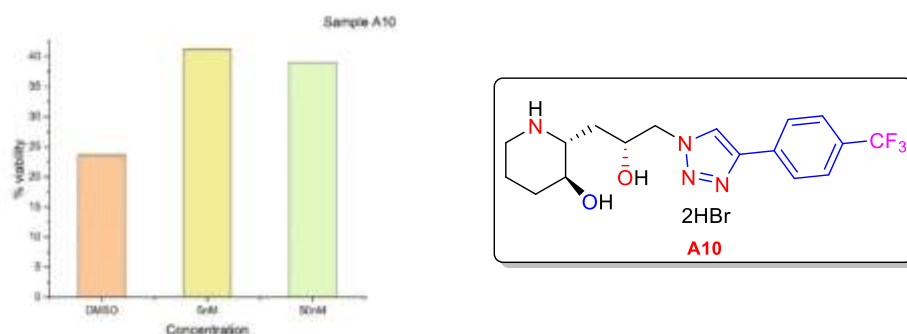
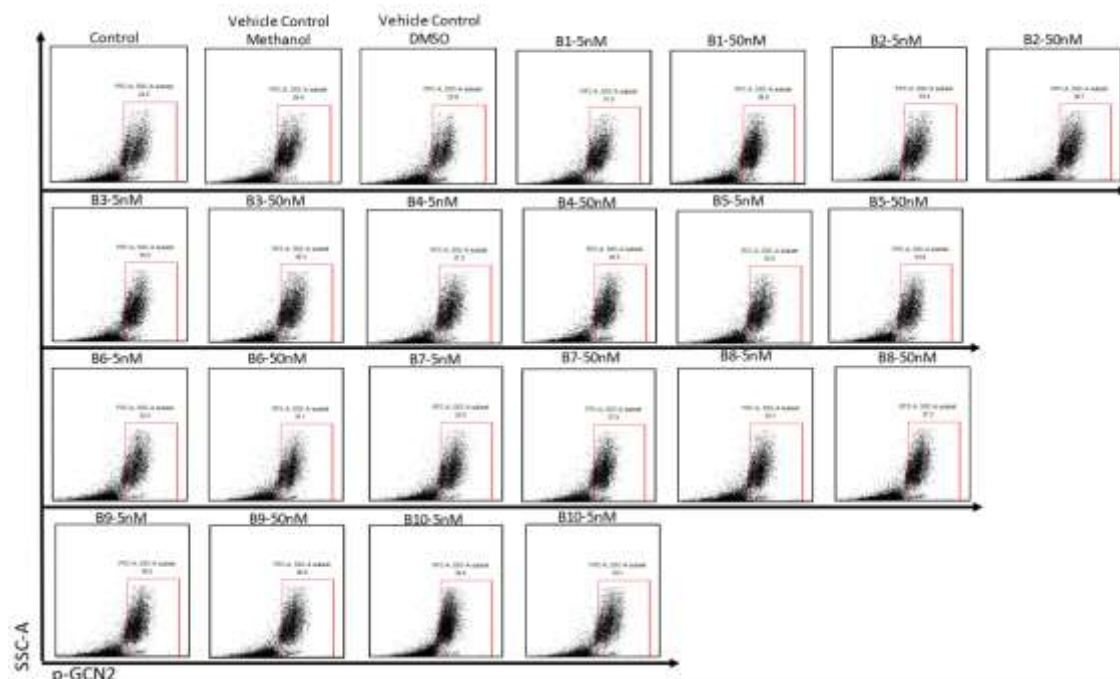


Figure 4.11: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample A10

The effects of DMSO at 5nM and 50nM for specimen A10 are contrasted in Figure 4.11. According to the graphical representation, the viability percentage for DMSO attained is 23.6%, which is lower than the viability percentages for other dosages like 5nM and 50nM.

4.2.3 Flow Cytometry gating for p-GCN2 in HepG2 cells for B-Series compounds



The viability of HepG2 cells treated with a 5nM sample was 41.2% following treatment, which is a little higher than the viability of cells treated with a 50nM dosage, which was 39%.

Figure 4.12: Flow Cytometry gating for p-GCN2 in HepG2 cells for B-Series compounds

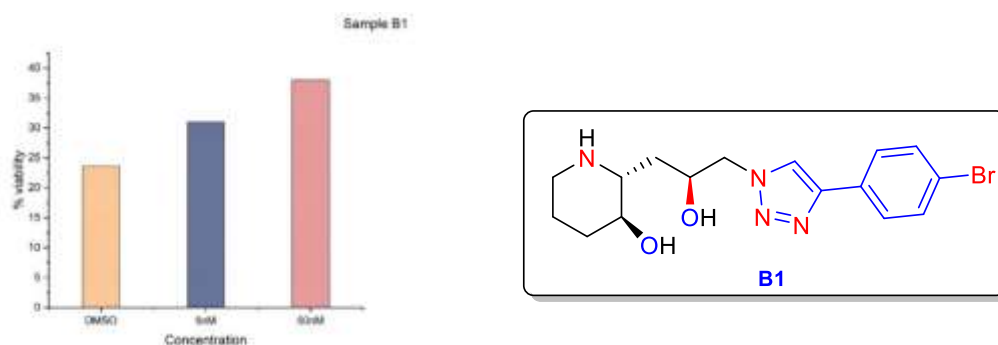


Figure 4.13: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample B1

In figure 4.13, the comparison between DMSO, 5nM, and 50nM for sample B1 is illustrated. In terms of the graphical representation, the percentage of viability in DMSO obtained is 23.6% which is lower than the other concentrations such as 5nM and 50nM. On

treatment 5nM sample with HepG2 cells showed 31% cell viability which is a very low 7% than that treated with 50nM concentration with 38% viability.

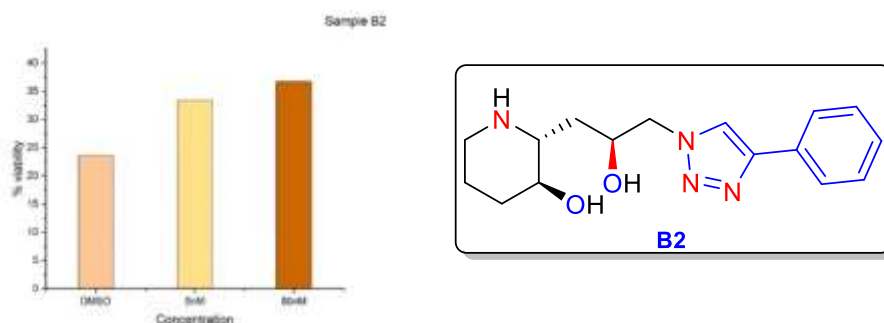


Figure 4.14: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample B2

The contrast between DMSO, 5nM and 50nM for sample B2 is shown in figure 4.14. According to the graphical representation, the viability percentage in DMSO achieved is 23.6%, which is lower than the viability percentages at other doses like 5nM and 50nM. HepG2 cell viability after treatment with a 5nM sample was 33.4%, somewhat lower than that after treatment with a 50nM concentration, which was 36.7%.

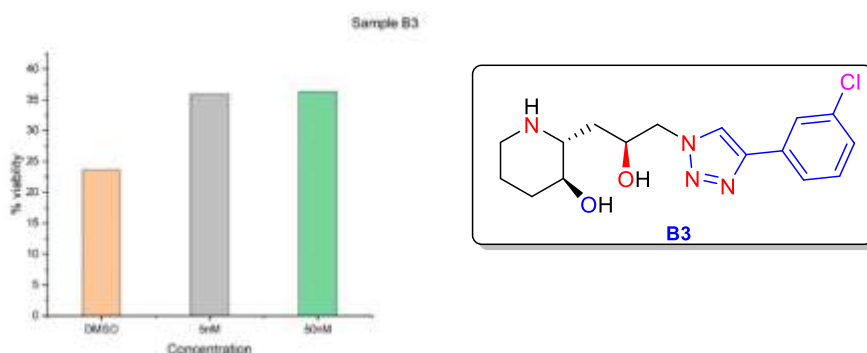


Figure 4.15: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample B3

Figure 4.15 shows the contrast between DMSO at 5nM and 50nM for sample B3. The viability percentage in DMSO was 23.6% according to the graphical representation, which is less than the viability percentages at other doses like 5nM and 50nM. HepG2 cells treated with

a 5nM sample showed 35.9% cell viability after treatment, which is almost the same that the cells treated with a 50nM concentration, which had 36.3% viability.

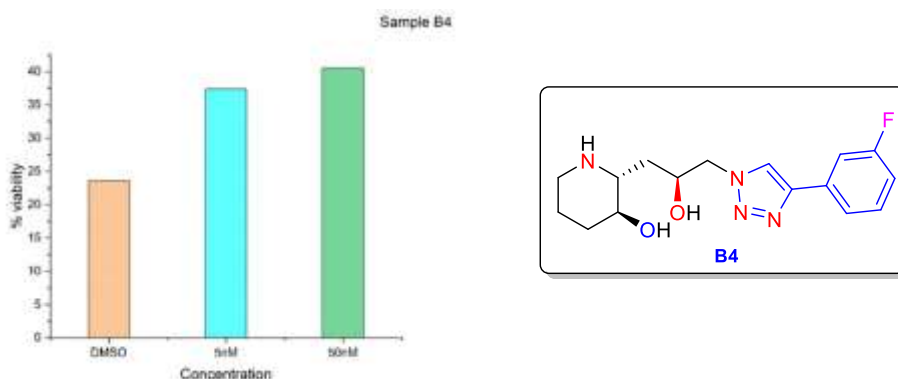


Figure 4.16: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample B4

Concentrations of DMSO 5nM and 50nM for sample B4 are compared and shown side by side in figure 4.16. When compared to other concentrations like 5nM and 50nM, the percentage of viability in DMSO was obtained to be 23.6%, which is lower. HepG2 cell viability after treatment with a 5nM sample was 37.3%, a small increase in the cell viability over the 40.5% viability of cells after treatment with a 50nM concentration.

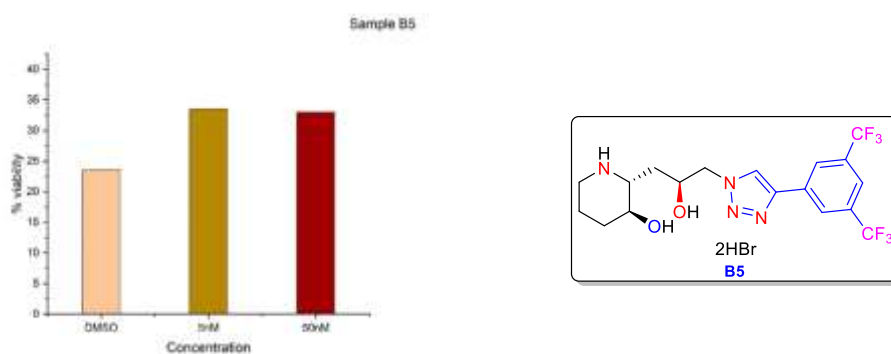


Figure 4.17: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample B5

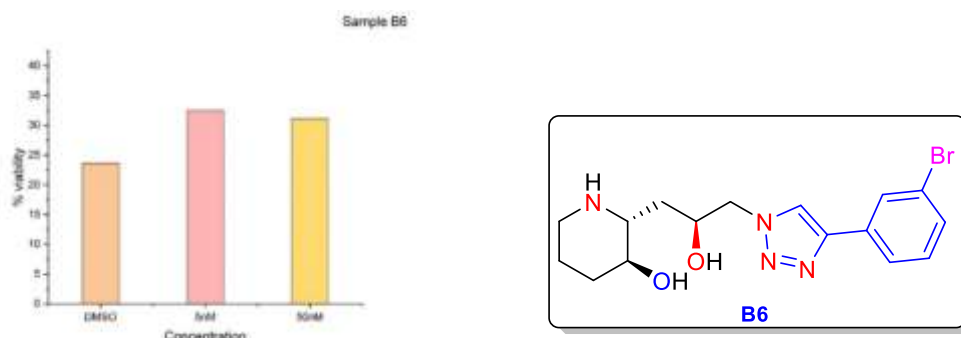


Figure 4.17 compares the effects of DMSO at 5nM and 50nM for specimen B5. In regards to the graphical depiction, the viability percentage in DMSO achieved is 23.6%, which is smaller than the other dosages like 5nM and 50nM. HepG2 cells treated with a 5nM sample had a cell viability of 33.5% after treatment, which is almost unchanged from the cells treated with a 50nM dosage, which had a viability of 33%.

Figure 4.18: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample B6

For specimen B6, Figure 4.18 contrasts the effects of DMSO at 5nM and 50nM. The viability percentage in DMSO attained, according to the graphical representation, is 23.6%, which is lower than the viability percentages at other dosages like 5nM and 50nM. After treatment, HepG2 cells treated with a 5nM sample had a cell viability of 32.5%, which is nearly unchanged from the viability of cells treated with a 50nM dosage, which was 31.1%.

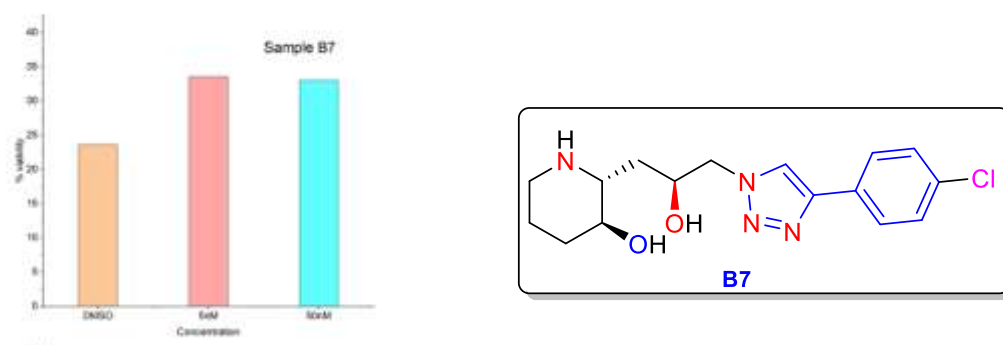


Figure 4.19: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample B7

The effects of DMSO at 5nM and 50nM for specimen B7 are contrasted in Figure 4.19. According to the graphical representation, the viability percentage for DMSO attained is 23.6%, which is lower than the viability percentages for other dosages like 5nM and 50nM. The viability of HepG2 cells treated with a 5nM sample was 33.5% following treatment, which is about 4.4% higher than the viability of cells treated with a 50nM dosage, which was 37.9%.

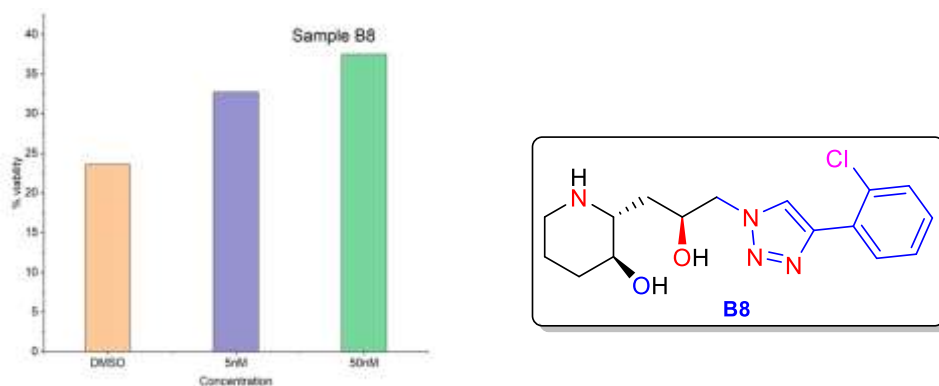


Figure 4.20: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample B8

DMSO's effects on specimen B8 at 5nM and 50nM are contrasted in Figure 4.20. According to the graphical representation, the viability percentage in DMSO attained is 23.6%, which is lower than the concentrations of 5nM and 50nM. Following treatment, the HepG2 group treated with a 5nM sample exhibited cell viability of 32.7 %, which is 4.8% less than the viability of 37.5% seen in cells treated with a 50nM dosage.

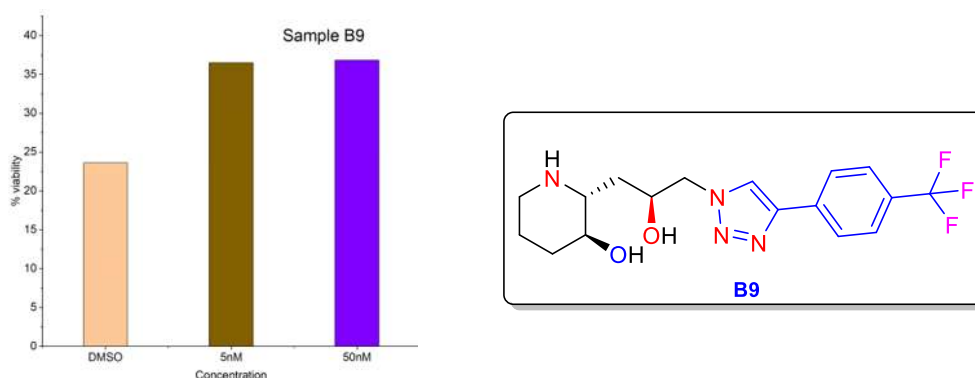


Figure 4.21: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample B9

For specimen B9, Figure 4.21 contrasts the effects of DMSO at 5nM and 50nM. The viability % in DMSO attained, according to the graphical representation, is 23.6%, which is lower than the viability percentages at other levels like 5nM and 50nM. After administration, HepG2 cells treated with a 5nM sampling had a cell viability of 36.5%, which is nearly unchanged from the viability of cells treated with a 50nM dosage, which was 36.8%.

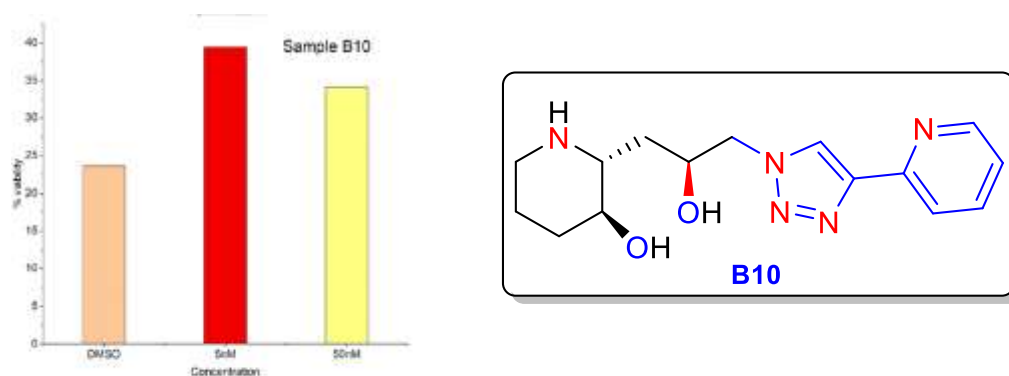


Figure 4.22: Comparison of %viability DMSO, 5nM, and 50nM concentration with sample B10

The effects of DMSO at 5nM and 50nM for specimen B10 are contrasted in Figure 4.22. According to the graphical representation, the viability percentage for DMSO attained is 23.6%, which is lower than the viability percentages for other dosages like 5nM and 50nM. The viability of HepG2 cells treated with a 5nM sample was 39.4% following treatment, which is 5.3% higher than the viability of cells treated with a 50nM dosage, which was 34.1%.

4.2.4 Cell Viability study using MTT Assay

The MTT test is still one of the most useful and well-liked viability assays that rely on living cells converting substrate into chromogenic product. A sensitive test with outstanding linearity up to 106 cells per well is the end result. Similar to the alamarBlue assay, exposure to a toxin can induce cell stress without directly causing cell death, and small tweaks in metabolic activity can result in substantial increases in MTT. For cells cultured in several wells, either adherent or non-adherent, the test has been standardised. A typical 96-well plate is used in the protocol. The 20 Halofuginone analogs were tested using the MTT method, with 10 of each series (A and B) and the vehicle/solvent control (VC) being used. In this study the cell viability is plotted

against concentration. Also different values are observed at different concentration (5nM and 50nM) respectively for the time interval of 24 Hrs and 48 Hrs.

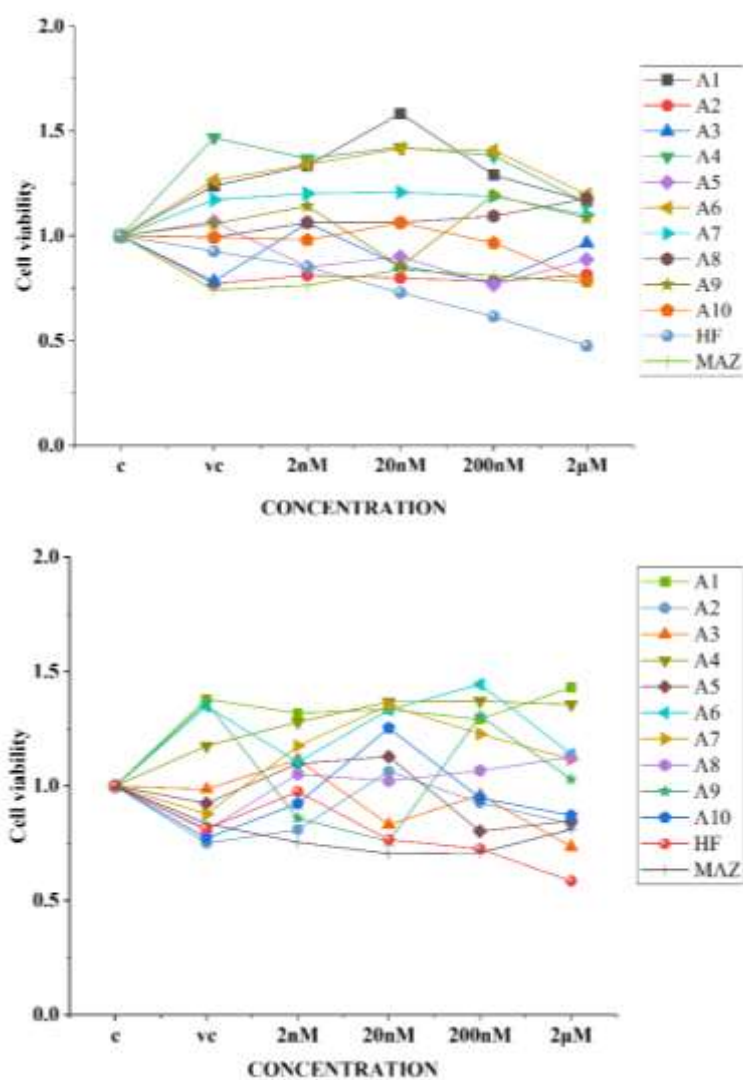


Figure 4.23: Comparison of cell viability with concentration for 5nM and 50nM in

Set- A in 24 Hrs

The above figure 4.23 shows the comparison of cell viability with concentration for 5nM in Set – A including sample A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, HF and MAZ at 24 Hrs. From the graph it is concluded that sample A1 shows highest cell viability of 1.58% for 20nM concentration and sample HF shows the lowest cell viability of 0.93% in 2μM.

Similarly on observing the cell viability with concentration for 50nM in Set – A at 24 Hrs, it is concluded that sample A6 shows the highest cell viability of 1.44% for 200nM and the lowest cell viability is seen in sample HF of 0.58% in 2 μ M.

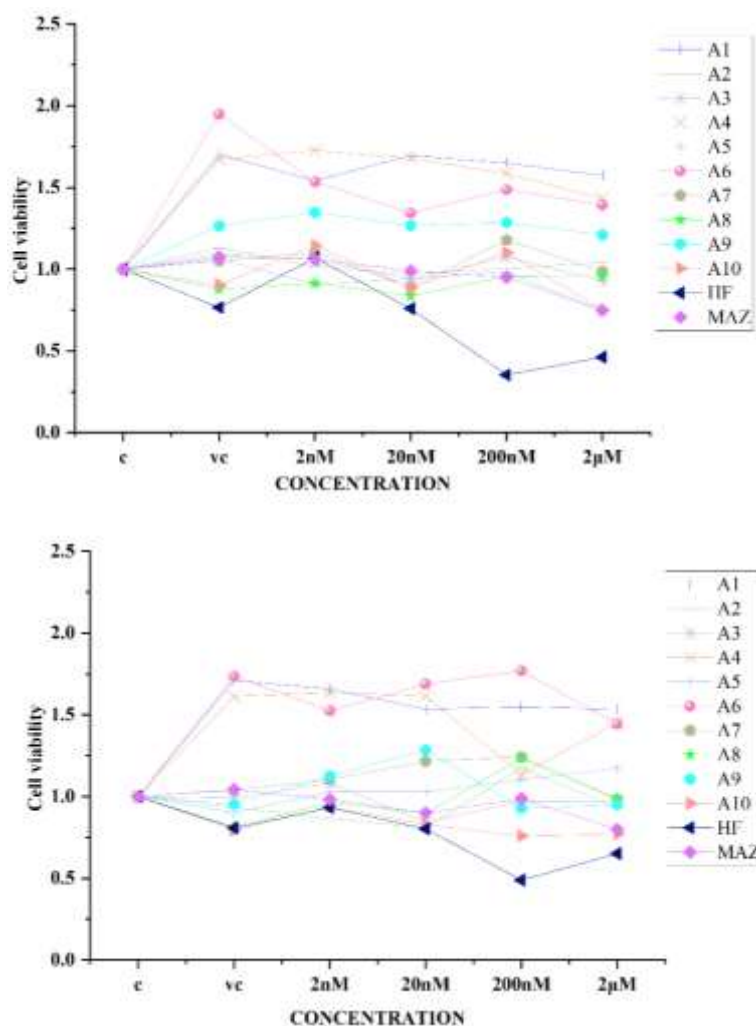


Figure 4.24: Comparison of cell viability with concentration for 5nM and 50nM in Set- A in 48 Hrs

The assessment of cell viability with concentrations for 5nM in Set A, which includes sample A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, HF, and MAZ at 48 Hours, is shown in figure 4.24 above. The graph indicates that sample HF has the lowest cell viability of 0.35% at 200nM and sample A6 has the maximum cell viability at 1.95% when adding vehicle control concentration. Similar to this, it is determined that sample A6 exhibits the maximum cell

viability, measuring 1.96% for 200nM, while sample HF exhibits the lowest vitality, measuring 0.48% for 200nM.

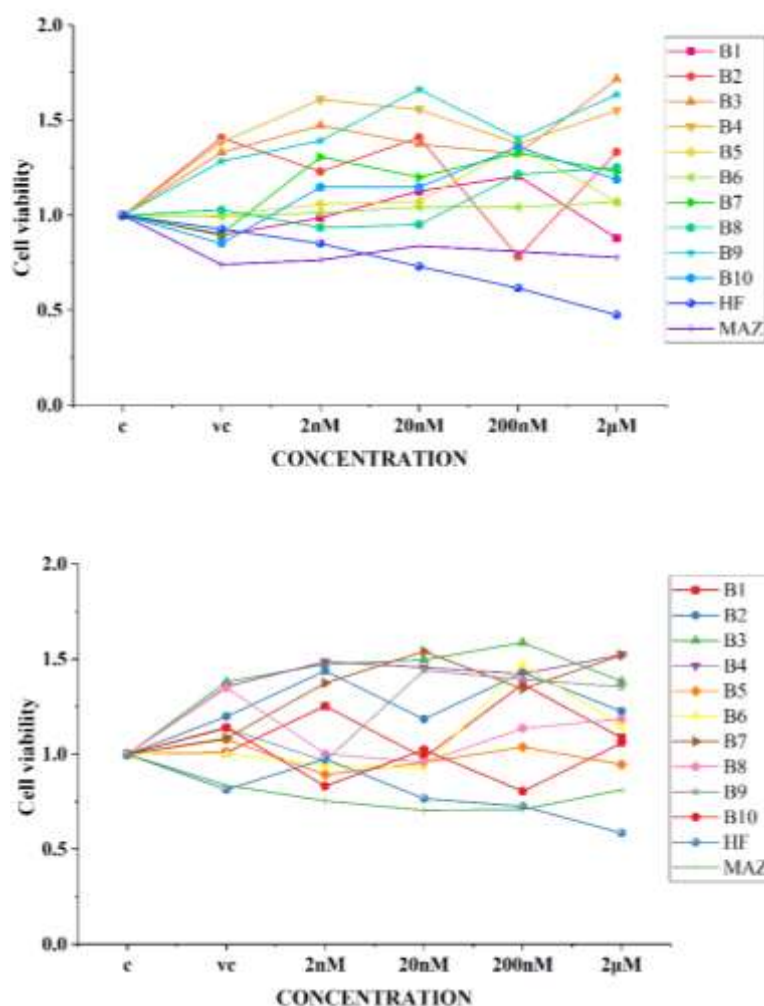


Figure 4.25: Comparison of cell viability with concentration for 5nM and 50nM in Set- B in 24 Hrs

Figure 4.25 above illustrates the evaluation of cell viability with concentrations for 5nM in Set B, which contains sample B1, B2, B3, B4, B5, B6, B7, B8, B9, B10, HF, and MAZ at 24 Hours. The graph shows that, sample B3 has the highest cell viability of 1.72% at 2μM and sample HF has the lowest cell viability at 2μM, which is 0.47%. Similarly the second part of the graph leads to the conclusion that sample B3 has the highest cell viability, measuring 1.58% for 200nM, and sample HF has the lowest vitality, measuring 0.58% for 2μM.

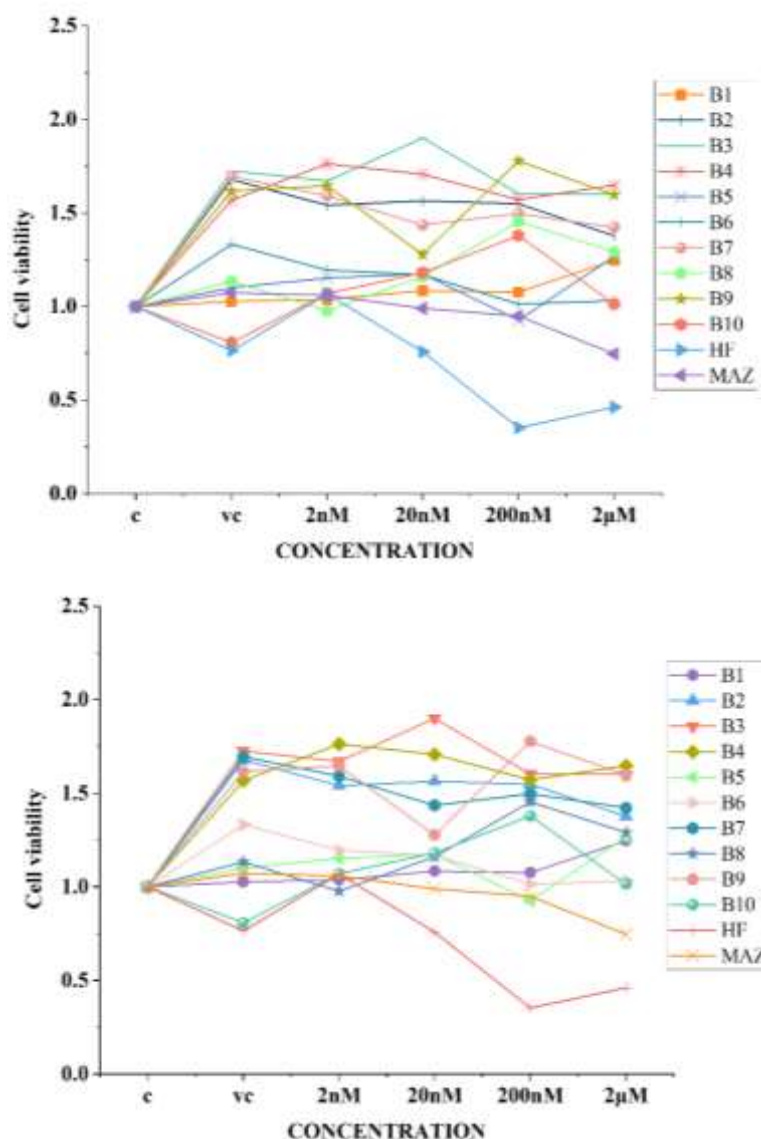


Figure 4.26: Comparison of cell viability with concentration for 5nM and 50nM in Set- B in 48 Hrs

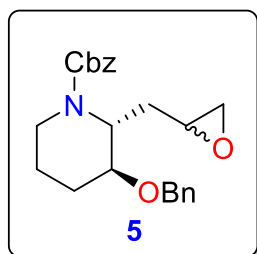
The above figure 4.26 shows the variation of cell viability with concentration for 5nM in Set – B including, sample B1, B2, B3, B4, B5, B6, B7, B8, B9, B10, HF and MAZ at 48 Hrs. From the graph it is concluded that sample B3 shows highest cell viability of 2.03% for 20nM concentration and sample HF shows the lowest cell viability of 0.35% in 200nM. Similarly on observing the cell viability with concentration for 50nM in Set – B at 24 Hrs, it is concluded that sample B3 shows the highest cell viability of 1.82% for 20nM and the lowest cell viability is seen in sample HF of 0.48% in 200M.

4.3 Conclusion

From the flow cytometry analysis, it is concluded that from the set – A, sample A10 shows the highest % viability within the concentration 5nM and 50nM of viability 41.2% and 39% respectively. While the sample A2 shows the lowest percent viability of 29% at 5nM concentration and A7 shows lowest viability of percent at 50nM concentration of 30.3%. Similarly on interpreting set – B, it is found that sample B10 shows the highest percent of viability with the concentration 5nM of 39.4% and B4 shows the high value for 50nM concentration of 40.5%. Also the sample B1 shows the lowest value for 5nM concentration with 31% cell viability and sample B5 shows the lowest value 33% survivability for a 50 nM concentration. The MTT Assay results indicate that chemically produced HF analogues are not harmful, even when used at higher concentrations up to 200 nM for 48 hours. The graph 4.23, 4.24, 4.25 and 4.26 show the percentage of cells that survive after exposure to the compounds. It is safe to assume that the compounds do not cause cytotoxicity, which would damage any molecular mechanism under investigation.

4.4 Experimental procedures and spectral data

Benzyl (2R,3S)-3-(benzyloxy)-2-(oxiran-2-ylmethyl)piperidine-1-carboxylate (5):



To a stirred solution of benzyl (2R,3S)-2-allyl-3-(benzyloxy)piperidine-1-carboxylate (**4**) (3.0 gr, 8.2 mmol) in dichloromethane and water (1:1) (100 mL), was added sodium bicarbonate (1.72 gr, 20.4 mmol) followed by m-CPBA (2.1 gr, 12.28 mmol) at 0 °C. The resultant mixture was stirred for 48 hr at room temperature, after completion of the reaction (confirmed by TLC), the reaction mixture was poured on 10% sodium thiosulphate solution and extracted with ethyl acetate 3x50 ml, combined organic layers were washed with 0.5 M NaOH solution, water and brine solution. The organic layer were dried over Na₂SO₄, filtered and concentrated. Purification of the afforded crude product by flash column chromatography over silicagel (hexanes/ethyl acetate) provided compound **5**.

Yield: 500 mg, 80%,

TLC: R_f: 0.4 (30% EtOAc/hexane)

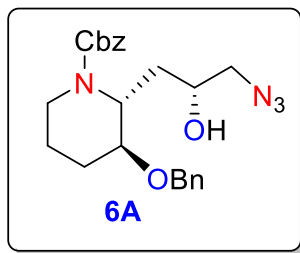
¹H-NMR (500 MHz, CDCl₃): δ = 7.28-7.35 (m, 10H), 5.13-5.18 (m, 2H), 4.84 (d, 1H, *J* = 13.0 Hz), 4.51 (t, 1H, *J* = 12.0 Hz), 4.12-4.20 (m, 1H), 3.50 (t, 1H, *J* = 25.5 Hz), 2.85-2.96 (m, 2H), 2.67 (s, 1H), 2.42 (q, 1H, *J* = 3.0 Hz), 1.90-2.02 (m, 3H), 1.57-1.68 (m, 3H), 1.41-1.44 (m, 1H).

¹³C-NMR (125 MHz, CDCl₃): δ = 156.1, 138.6, 138.5, 137.0, 128.5, 128.4, 127.9, 127.9, 127.5, 127.5, 73.8, 70.1, 67.1, 49.9, 46.9, 46.5, 39.9, 32.6, 32.2, 24.7, 24.2, 19.6 ppm.

HRMS (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₃H₂₇NO₄+Na⁺ 404.1832, found 404.1833.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm⁻¹.

General procedure for synthesis of Benzyl (2R,3S)-2-((R)-3-azido-2-hydroxypropyl)-3-(benzyloxy)piperidine-1-carboxylate (6A):



To a stirred solution of Benzyl (2R,3S)-3-(benzyloxy)-2-(oxiran-2-ylmethyl)piperidine-1-carboxylate (5) (2.5 gr, 6.5 mmol) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (3.27 mmol) in acetonitrile and water (9:1) (70 mL), was added sodium azide (0.5 gr, 7.8 mmol) at room temperature. The resultant mixture was stirred for 10 hr at reflux temperature, after completion of the reaction (confirmed by TLC), the reaction mixture was diluted with ethyl acetate 25 ml washed with water and brine solution. The organic layer were dried over Na_2SO_4 , filtered and concentrated. Purification of the afforded crude product by flash column chromatography over silicagel (hexanes/ethyl acetate) provided compound **6A & 6B** (1 :1) yield: 500 mg, 90%,

TLC: R_f : 0.4 (30% EtOAc/hexane)

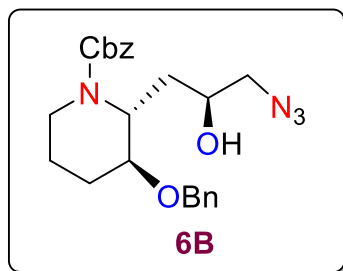
^1H NMR (500 MHz, CDCl_3): δ 7.29-7.38 (m, 10H), 5.17 (dd, 2H, $J = 12.0$ Hz, $J = 24$ Hz), 4.74 (d, 1H, $J = 12.0$ Hz), 4.65 (d, 1H, $J = 12.0$ Hz), 4.51 (d, 1H, $J = 11.5$ Hz), 4.43 (s, 1H), 4.13 (d, 1H, $J = 7.0$ Hz), 3.63 (s, 1H), 3.48 (s, 1H), 3.34 (q, 1H, $J = 6.5$ Hz), 3.22 (dd, 1H, $J = 4.0$ Hz, $J = 12$ Hz), 2.81 (td, 1H, $J = 2.5$ Hz, $J = 13$ Hz), 1.93-1.99 (m, 3H), 1.80 (td, 1H, $J = 2.5$ Hz, $J = 14.5$ Hz), 1.60-1.65 (m, 1H), 1.29-1.45 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 157.6, 138.2, 136.2, 128.5, 128.3, 128.0, 127.7, 127.4, 77.3, 74.2, 70.0, 67.6, 66.7, 55.8, 50.0, 38.9, 33.4, 24.2, 19.3$ ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_4+\text{H}^+$ 425.2183, found 425.2189.

IR (neat): 3415, 3066, 3035, 2921, 2868, 2098, 1679, 1491, 1425, 1315, 1261, 1205, 1085, cm^{-1} .

Benzyl (2R,3S)-2-((S)-3-azido-2-hydroxypropyl)-3-(benzyloxy)piperidine-1-carboxylate (6B):



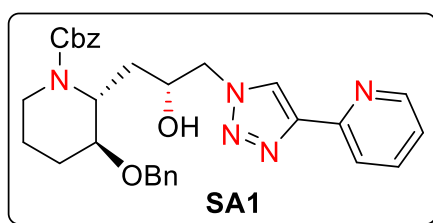
^1H NMR (500 MHz, CDCl_3): δ 7.30-7.34 (m, 10H), 5.17 (dd, 2H, $J = 4.5$ Hz, $J = 19$ Hz), 4.59 (d, 1H, $J = 24.0$ Hz), 4.51 (d, 1H, $J = 11.0$ Hz), 4.0-4.16 (m, 1H), 3.74-3.85 (m, 1H), 3.34 (d, 1H, $J = 24.0$ Hz), 2.95 (s, 1H), 1.89 (d, 4H, $J = 14.0$ Hz), 1.65 (td, 1H, $J = 2.0$ Hz, $J = 13.5$ Hz), 1.54-1.58 (m, 3H), 1.41-1.44 (m, 1H), 1.28 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 156.7, 138.3, 136.5, 128.5, 128.3, 128.0, 127.8, 127.5, 74.2, 70.1, 69.2, 67.3, 56.2, 51.2, 39.2, 36.6, 33.9, 29.6, 24.0, 19.4$ ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_4+\text{H}^+$ 425.2183, found 425.2189.

IR (neat): 3412, 3062, 3030, 2927, 2865, 2097, 1669, 1495, 1426, 1311, 1260, 1089, cm^{-1} .

General procedure for synthesis of Benzyl (2R,3S)-3-(benzyloxy)-2-((R)-2-hydroxy-3-(4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)propyl)piperidine-1-carboxylate (SA1):



To a stirred solution of Benzyl (2R,3S)-2-((R)-3-azido-2-hydroxypropyl)-3-(benzyloxy)piperidine-1-carboxylate **6A** (0.3 mmol) and 2-pyridylacetylene (0.3 mmol) in *tert*-Butanol and water (1:1) (5 mL), was added sodium ascorbate (0.13 mmol) and copper acetate (0.06 mmol). The reaction was stirred at room temperature for 10 h, after completion of the reaction (confirmed by TLC), the reaction mixture was diluted with ethyl acetate 25 mL washed

with water and brine solution. The organic layer were dried over Na₂SO₄, filtered and concentrated. Purification of the afforded crude product by flash column chromatography over silicagel (hexanes/ethyl acetate) provided compound **SA1**.

Yield: 300 mg, 90%,

TLC: R_f: 0.2 (50% EtOAc/hexane)

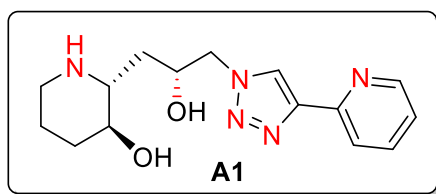
¹H NMR (500 MHz, CDCl₃): δ 8.61 (bs, 1H), 8.36 (s, 1H), 8.15 (d, 1H, *J* = 8.0 Hz), 7.77 (dt, 1H, *J* = 2.0 Hz, *J* = 17.5.0 Hz), 7.21-7.29 (m, 11H), 5.12 (bs, 2H), 4.67 (d, 1H, *J* = 12.0 Hz), 4.53-4.61 (m, 2H), 4.46 (d, 1H, *J* = 12 Hz), 4.33-4.37 (m, 1H), 4.01 (d, 1H, *J*=13.5), 3.81 (bs, 1H), 3.42 (s, 1H), 2.75 (dt, 1H, *J* = 2.5 Hz, *J* = 16.0 Hz), 1.85-1.91 (m, 3H), 1.55 (t, 1H, *J* = 13.5 Hz), 1.38-1.42 (m, 1H), 1.27-1.32 (m, 1H).

¹³C NMR (125 MHz, CDCl₃): δ = 157.6, 150.3, 149.4, 148.1, 138.2, 136.9, 136.2, 128.5, 128.3, 128.1, 127.8, 127.4, 123.7, 122.8, 120.2, 74.3, 70.2, 67.7, 66.3, 55.4, 50.2, 39.1, 33.4, 29.6, 24.3, 19.3 ppm.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₃₀H₃₃N₅O₄+H⁺ 528.2605, found 528.2601.

IR (neat): 3399, 3059, 2925, 2856, 2024, 1685, 1601, 1495, 1469, 1421, 1351, 1128, cm⁻¹.

General procedure for synthesis of (2R,3S)-2-((R)-2-hydroxy-3-(4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)propyl)piperidin-3-ol (A1**):**



A solution of Benzyl (2R,3S)-3-(benzyloxy)-2-((R)-2-hydroxy-3-(4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl) propyl) piperidine-1-carboxylate **SA1** (200 mg, 3.8 mmol) in aqueous HBr (6 M, 10 mL), was stirred at reflux for 2 h. The solvent was removed by concentration under reduced pressure. Purification of the afforded crude product by flash column chromatography over silicagel (0.1 % Ammonia in MeOH/ Chloroform) provided compound **A1** as off white solid.

Yield: 120 mg, 85%,

TLC: R_f : 0.2 (20% MeOH/CHCl₃).

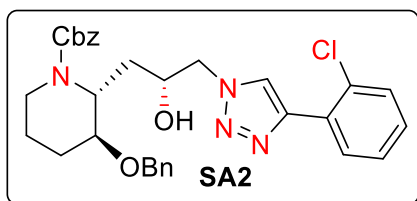
¹H NMR (500 MHz, CD₃OD): δ 9.08 (bs, 1H), 8.80 (d, 1H, $J=6$ Hz), 8.67 (t, 1H, $J=7.5$ Hz), 8.54 (d, 1H, $J=8$ Hz), 8.01 (t, 1H, $J=6.5$ Hz), 4.74 (dd, 1H, $J=4$ Hz, $J=10$ Hz), 4.63 (dd, 1H, $J=7$ Hz, $J=14$ Hz), 4.46-4.51 (m, 1H), 3.69 (dt, 1H, $J=4$ Hz, $J=9.5$ Hz), 3.25-3.27 (m, 1H), 2.98 (dt, 1H, $J=3.5$ Hz, $J=12.5$ Hz), 2.05-2.12 (m, 3H), 1.97-2.20 (m, 1H), 1.75-1.83 (m, 1H), 1.54-1.62 (m, 1H), 1.25-1.34 (m, 1H).

¹³C NMR (125 MHz, CD₃OD): δ = 148.6, 144.9, 142.7, 140.1, 128.9, 126.8, 125.5, 68.1, 67.4, 59.8, 57.2, 45.0, 33.7, 31.9, 21.6 ppm.

HRMS (ESI-TOF) m/z : $[M+H]^+$ calcd for C₁₅H₂₁N₅O₂+H⁺ 304.1768, found 304.1762.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm⁻¹.

Benzyl (2R,3S)-3-(benzyloxy)-2-((R)-3-(4-(2-chlorophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidine-1-carboxylate (SA2):



Yield: 300 mg, 90%,

TLC: R_f : 0.3 (50% EtOAc/hexane)

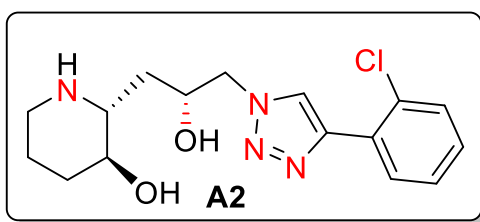
¹H NMR (500 MHz, CDCl₃): δ 8.41 (s, 1H), 8.25 (dd, 1H, $J = 2.0$ Hz, $J = 8.0$ Hz), 7.47 (d, 1H, $J = 7.5$ Hz), 7.39 (td, 1H, $J = 1.5$ Hz, $J = 7.5.0$ Hz), 7.27-7.33 (m, 13H), 5.14 (dd, 2H, $J = 8.0$ Hz, $J = 20.0$ Hz), 4.70 (d, 1H, $J = 16.0$ Hz), 4.60 (t, 3H, $J = 19.5$ Hz), 4.49 (d, 1H, $J = 12.0$ Hz), 4.36 (q, 1H, $J = 7.0$ Hz), 4.10 (d, 1H, $J=12.5$), 3.84 (bs, 1H), 3.46 (s, 1H), 2.80 (td, 1H, $J = 3.0$ Hz, $J = 13.5$ Hz), 1.88-1.96 (m, 4H), 1.60 (t, 1H, $J = 14.5$ Hz), 1.41-1.45 (m, 1H), 1.29-1.34 (m, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ = 157.5, 143.7, 138.2, 136.2, 131.2, 130.1, 129.6, 129.3, 128.8, 128.4, 128.3, 128.0, 127.7, 127.4, 127.4, 127, 124.9, 74.2, 70.1, 67.6, 66.3, 55.2, 50.2, 39.1, 33.4, 24.2, 19.3 ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{31}\text{H}_{33}\text{ClN}_4\text{O}_4+\text{H}^+$ 561.2263, found 561.2260.

IR (neat): 3330, 2929, 2862, 1677, 1451, 1426, 1314, 1258, 1128, 1089 cm^{-1} .

(2R,3S)-2-((R)-3-(4-(2-chlorophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidin-3-ol (A2):



Yield: 120 mg, 80%,

TLC: R_f : 0.2 (20% MeOH/ CHCl_3).

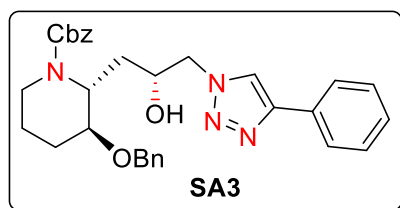
^1H NMR (500 MHz, CD_3OD): δ 8.52(s, 1H), 8.01 (dd, 1H, J = 2.0 Hz, J = 8 Hz), 7.52 (dd, 1H, J = 1.5 Hz, J = 8 Hz), 7.41 (td, 1H, J = 1.5 Hz, J = 8 Hz), 7.35 (td, 1H, J = 2.0 Hz, J = 7.5 Hz), 4.55 (dd, 1H, J = 4.0 Hz, J = 13.5 Hz), 4.45 (dd, 1H, J = 7.5 Hz, J = 14 Hz), 4.27-4.32 (m, 1H), 3.18 (td, 1H, J = 4.5 Hz, J = 10.5 Hz), 2.91 (dt, 1H, J = 1.5 Hz, J = 12.0 Hz), 2.54-2.58 (m, 1H), 2.48 (td, 1H, J = 3.0 Hz, J = 12.5 Hz), 2.03-2.06 (m, 1H), 1.95-2.00 (m, 1H), 1.70-1.73 (m, 1H), 1.56-1.60 (m, 1H), 1.48-1.54 (m, 1H).

^{13}C NMR (125 MHz, CD_3OD): δ = 144.9, 132.7, 131.4, 130.9, 130.5, 128.3, 126.4, 72.5, 68.7, 60.9, 57.6, 46.7, 38.3, 35.0, 26.4 ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{21}\text{ClN}_4\text{O}_2+\text{H}^+$ 337.1426, found 337.1425.

IR (neat): 3401, 2944, 2859, 1676, 1606, 1572, 1425, 1258, 1198, 1128 cm^{-1} .

Benzyl (2R,3S)-3-(benzyloxy)-2-((R)-2-hydroxy-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propyl)piperidine-1-carboxylate (SA3):



Yield: 320 mg, 90%,

TLC: R_f : 0.2 (50% EtOAc/hexane)

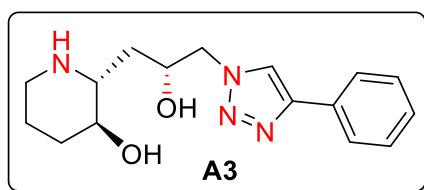
^1H NMR (500 MHz, CDCl_3): δ 8.0 (s, 1H), 7.84 (d, 1H, $J = 7.5$ Hz), 7.61 (t, 2H, $J = 7.5$ Hz), 7.24-7.33 (m, 11H), 5.11 (dd, 2H, $J = 12.5$ Hz, $J = 19.5$ Hz), 4.65 (d, 1H, $J = 12$ Hz), 4.51-4.59 (m, 2H), 4.45 (d, 1H, $J = 12$ Hz), 4.27-4.321 (m, 1H), 4.06 (d, 1H, $J = 12.5$ Hz), 3.76 (s, 1H), 3.41 (s, 1H), 2.77 (dt, 1H, $J = 3$ Hz, $J = 13.5$ Hz), 1.88-1.93 (m, 3H), 1.57 (m, 1H), 1.39 (m, 1H), 1.25 (m, 2H).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 157.6, 147.5, 138.2, 136.2, 130.7, 128.7, 128.4, 128.3, 128.1, 128.0, 127.6, 127.5, 127.4, 125.6, 121.4, 77.2, 74.3, 70.1, 67.7, 66.4, 55.2, 50.3, 39.1, 33.3, 29.6, 33.3, 29.6, 24.2, 19.3$ ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{31}\text{H}_{34}\text{N}_4\text{O}_4+\text{H}^+$ 527.2653, found 527.2651.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

(2R,3S)-2-((R)-2-hydroxy-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propyl)piperidin-3-ol (A3):



Yield: 200 mg, 90%,

TLC: R_f: 0.2 (50% EtOAc/hexane)

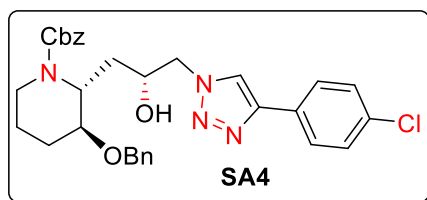
¹H NMR (500 MHz, CD₃OD): δ 8.37 (s, 1H), 7.81 (d, 2H, *J* = 7.5 Hz), 7.61 (t, 2H, *J* = 7.5 Hz), 7.32-7.35(m, 1H), 4.85 (s, 1H), 4.51-4.61(m, 2H), 4.43-4.46(m, 1H), 3.65(dt, 1H, *J* = 4 Hz, *J* = 10 Hz), 3.30-3.32 (m, 1H), 3.18-3.22 (m, 1H), 2.9 (dt, 1H, *J* = 3.5 Hz, *J* = 12.5 Hz), 2.08-2.12 (m, 1H), 1.94-2.03 (m, 3H), 1.72-1.81 (m, 1H), 1.51-1.59 (m, 1H).

¹³C NMR (125 MHz, CD₃OD): δ = 148.7, 131.7, 130.0, 129.4, 126.6, 123.5, 68.1, 67.5, 59.9, 56.8, 45.0, 33.7, 32.1, 21.7 ppm.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₆H₂₂N₄O₄+H⁺ 303.1816, found 303.1815.

IR (neat): 3330, 2948, 2869, 1678, 1491, 1453, 1353, 1289, 1298, 1232 cm⁻¹.

Benzyl (2R,3S)-3-(benzyloxy)-2-((R)-3-(4-(4-chlorophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidine-1-carboxylate (SA4):



Yield: 100 mg, 90%,

TLC: R_f: 0.3 (50% EtOAc/hexane)

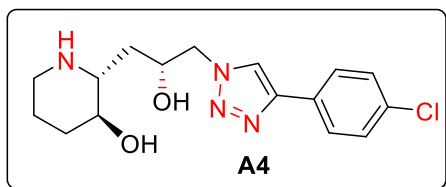
¹H NMR (500 MHz, CDCl₃): δ 8.01 (s, 1H), 7.81 (d, 2H, *J* = 8 Hz), 7.61 (d, 2H, *J* = 8.5 Hz), 7.27-7.33(m, 10H), 5.11 (dd, 2H, *J* = 6.0 Hz, *J* = 12 Hz), 4.68 (d, 1H, *J* = 12.5 Hz), 4.55-4.62(m, 2H), 4.49 (d, 1H, *J* = 12 Hz), 4.29 (q, 1H, *J* = 7 Hz), 4.10 (d, 1H, *J* = 13 Hz), 3.79 (bs, 1H), 3.45 (s, 1H), 2.81 (dt, 1H, *J* = 3.0 Hz, *J* = 13.5 Hz), 1.88-1.95 (m, 3H), 1.60 (t, 1H, *J* = 14 Hz), 1.42(d, 1H, *J* = 13 Hz), 1.29 (dt, 1H, *J* = 3.0 Hz, *J* = 11.5 Hz).

¹³C NMR (125 MHz, CDCl₃): δ = 157.6, 146.4, 138.2, 136.1, 133.6, 129.2, 128.9, 128.4, 128.3, 128.1, 127.6, 127.5, 127.4, 126.8, 121.4, 74.3, 70.1, 67.7, 66.3, 55.3, 50.3, 39.1, 33.3, 24.1, 19.2 ppm.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₃₁H₃₃BrN₄O₄+H⁺ 605.1758, found 605.1756.

IR (neat): 3399, 3138, 3030, 2929, 2862, 1677, 1451, 1426, 1314, 1258, 1197, 1128, cm^{-1} .

(2R,3S)-2-((R)-3-(4-(4-chlorophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidin-3-ol (A4):



Yield: 120 mg, 85%,

TLC: R_f : 0.2 (20% MeOH/ CHCl_3).

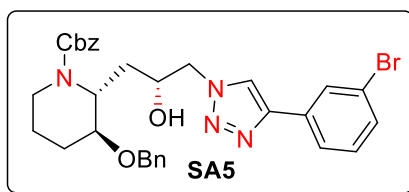
^1H NMR (500 MHz, CD_3OD): δ 8.74 (bs, 1H), 7.85 (d, 2H, $J = 8.5$ Hz), 7.53 (d, 2H, $J = 8.5$ Hz), 4.70-4.75(m, 1H), 4.62-4.66(m, 1H), 4.52 (t, 1H, $J = 3.0$ Hz), 3.69 (td, 1H, $J = 3.0$ Hz, $J = 9.0$ Hz), 3.27-3.28(m, 1H), 2.96 (td, 1H, $J = 2.5$ Hz, $J = 12.0$ Hz), 2.08-2.2.15(m, 3H), 1.98-2.03(m, 1H), 1.76 (q, 1H, $J = 12.5$ Hz), 1.56-1.63(m, 1H).

^{13}C NMR (125 MHz, CD_3OD): $\delta = 146.1, 136.4, 130.5, 128.8, 128.7, 125.3, 68.1, 67.5, 67.4, 59.9, 5.1, 57.9, 45.04, 33.6, 32.0, 21.6$ ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{21}\text{ClN}_4\text{O}_2+\text{H}^+$ 337.1426, found 337.1425.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

Benzyl (2R,3S)-3-(benzyloxy)-2-((R)-3-(4-(3-bromophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidine-1-carboxylate (SA5):



Yield: 300 mg, 90 %.

TLC: R_f : 0.2 (50% EtOAc/hexane)

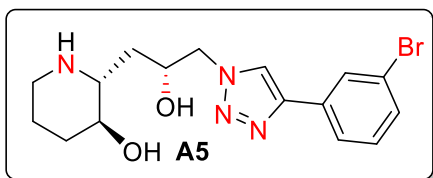
¹H NMR (500 MHz, CDCl₃): δ 8.04 (d, 1H, *J* = 6.0 Hz), 7.80 (d, 1H, *J* = 7.5 Hz), 7.47 (d, 1H, *J* = 7.5 Hz), 7.28-7.34 (m, 13H), 5.11 (dd, 2H, *J* = 12.0 Hz, *J* = 22.5 Hz), 4.68 (d, 1H, *J* = 11.0 Hz), 4.56-4.62 (m, 2H), 4.49 (d, 1H, *J* = 12 Hz), 4.33 (q, 1H, *J* = 7.0 Hz), 4.11 (d, 1H, *J* = 13.5 Hz), 3.80 (bs, 1H), 3.45 (s, 1H), 2.81 (td, 1H, *J* = 3.5 Hz, *J* = 13.5 Hz), 1.88-1.99 (m, 3H), 1.76 (bs, 1H), 1.60 (t, 1H, *J* = 14.0 Hz), 1.42-1.46 (m, 1H), 1.28 (t, 1H, *J* = 10.0 Hz).

¹³C NMR (125 MHz, CDCl₃): δ = 157.7, 146.2, 138.2, 136.2, 132.6, 130.9, 130.4, 128.6, 128.5, 128.3, 128.1, 127.7, 127.5, 127.4, 124.2, 122.9, 121.8, 74.3, 70.2, 67.8, 66.3, 55.3, 50.3, 39.2, 33.3, 24.2, 19.3 ppm.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₃₁H₃₃BrN₄O₄+H⁺ 605.1758, found 605.1758.

IR (neat): 3401, 3126, 2945, 2865, 2071, 1682, 1454, 1426, 1351, 1315, 1259, 1198, 1068, 1027, 970 cm⁻¹.

(2R,3S)-2-((R)-3-(4-(3-bromophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidin-3-ol (A5):



Yield: 120 mg, 85%,

TLC: R_f: 0.2 (20% MeOH/CHCl₃).

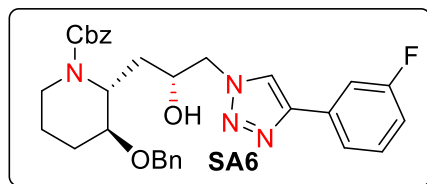
¹H NMR (500 MHz, CD₃OD): δ 8.48 (bs, 1H), 8.04 (bs, 1H), 7.81 (d, 1H, *J* = 7.5 Hz), 7.51 (d, 1H, *J* = 9.0 Hz), 7.38 (t, 1H, *J* = 7.0 Hz), 4.60 (dd, 1H, *J* = 3.0 Hz, *J* = 13.5 Hz), 4.54 (dd, 1H, *J* = 6.5 Hz, *J* = 13.5 Hz), 4.47 (bs, 1H), 3.71 (bs, 1H), 3.32 (d, 2H, *J* = 12.5 Hz), 3.24 (d, 1H, *J* = 4.0 Hz), 2.96 (t, 1H, *J* = 12.0 Hz), 2.11-2.13 (m, 1H), 1.98-2.04 (m, 3H), 1.79-1.82 (m, 1H), 1.54-1.62 (m, 1H).

¹³C NMR (125 MHz, CD₃OD): δ = 147.2, 134.0, 132.1, 131.8, 129.4, 125.4, 124.0, 123.9, 68.2, 67.5, 59.9, 56.8, 45.1, 33.8, 32.1, 21.7 ppm.

HRMS (ESI-TOF) m/z : $[M+H]^+$ calcd for $C_{16}H_{21}BrN_4O_2+H^+$ 381.0921, found 381.0926.

IR (neat): 3399, 3138, 3030, 2929, 2862, 1677, 1451, 1426, 1314, 1258, 1128, 1089 cm^{-1} .

Benzyl (2R,3S)-3-(benzyloxy)-2-((R)-3-(4-(3-fluorophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidine-1-carboxylate (SA6):



Yield: 300 mg, 90%.

TLC: R_f : 0.2 (50% EtOAc/hexane)

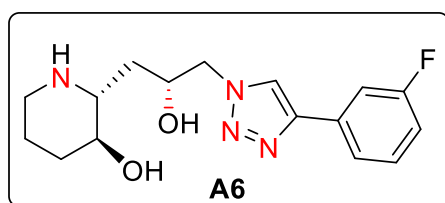
^1H NMR (500 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.61 (t, 2H, $J = 10.5$ Hz), 7.38-7.72 (m, 1H), 7.26-7.33 (m, 10H), 7.04 (dt, 1H, $J = 1$ Hz, 19.0 Hz), 5.15 (dd, 2H, $J = 8.0$ Hz, 20 Hz), 4.68 (d, 1H, $J = 4.8$ Hz), 4.56-4.62 (m, 2H), 4.49 (d, 1H, $J = 12.0$ Hz), 4.33 (m, 1H), 4.10-4.15 (m, 1H), 3.79 (bs, 1H), 3.45 (s, 1H), 2.81 (dt, 1H, $J = 3$ Hz, 23.0 Hz), 1.81-1.95 (m, 3H), 1.61 (t, 1H, $J = 15.0$ Hz), 1.41-1.45 (m, 1H), 1.26-1.32 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 164.1, 162.1, 157.6, 146.4, 138.2, 136.1, 130.4, 130.3, 128.4, 128.3, 128.1, 127.6, 127.5, 127.4, 121.8, 121.2, 114.8, 114.7, 112.6, 112.4, 74.3, 70.1, 67.7, 66.3, 55.3, 50.3, 39.1, 33.3, 24.1, 19.3$ ppm.

HRMS (ESI-TOF) m/z : $[M+H]^+$ calcd for $C_{31}H_{33}FN_4O_4+H^+$ 545.2559, found 545.2557.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

(2R,3S)-2-((R)-3-(4-(3-fluorophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidin-3-ol (A6):



Yield: 100 mg, 85%,

TLC: R_f: 0.2 (20% MeOH/CHCl₃).

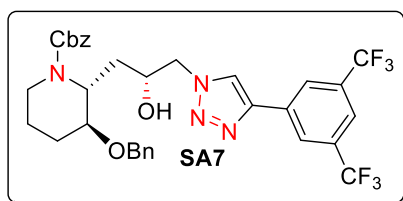
¹H NMR (500 MHz, CD₃OD): δ 8.42 (s, 1H), 7.61 (dt, 1H, *J* = 3.5 Hz, *J* = 11.5 Hz), 7.42-7.46 (m, 1H), 7.07 (td, 1H, *J* = 2.5 Hz, *J* = 8.0 Hz), 4.60 (dd, 1H, *J* = 4.0 Hz, *J* = 14.0 Hz), 4.49 (dd, 1H, *J* = 6.5 Hz, *J* = 14.0 Hz), 4.37-4.39(m, 1H), 3.85 (t, 1H, *J* = 4.5 Hz), 3.15-3.19 (m, 1H), 3.03 (bs, 1H), 2.81-2.86 (m, 1H), 2.75 (s, 2H), 2.13 (dt, 1H, *J* = 3.5 Hz, 15.5 Hz), 1.91-1.96 (m, 3H), 1.71-1.76(m, 1H), 1.54-1.58(m, 1H).

¹³C NMR (125 MHz, CD₃OD): δ = 165.6, 163.6, 146.3, 132.3, 132.3, 125.4, 123.0, 117.1, 116.9, 113.9, 113.7, 68.1, 67.5, 59.9, 58.3, 57.7, 45.0, 33.6, 32.0, 21.6 ppm.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₆H₂₁FN₄O₂+H⁺ 321.1721, found 321.1720.

IR (neat): 3103, 3021, 2921, 2849, 2808, 2675, 2266, 1601, 1397, 1399, 1248 cm⁻¹.

Benzyl (2R,3S)-3-(benzyloxy)-2-((R)-3-(4-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidine-1-carboxylate (SA7):



Yield: 280 mg, 90%,

TLC: R_f: 0.2 (50% EtOAc/hexane)

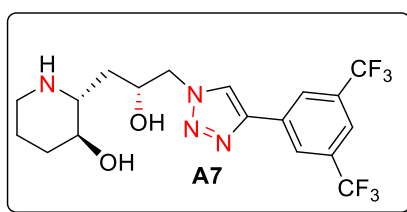
¹H NMR (500 MHz, CDCl₃): δ 8.33 (s, 1H), 8.19 (s, 1H), 7.85 (s, 1H), 7.28-7.34 (m, 10H), 5.14 (dd, 2H, *J* = 12 Hz, *J* = 18.5 Hz), 4.74 (bs, 1H), 4.67 (d, 1H, *J* = 12 Hz), 4.59-4.63 (m, 2H), 4.50 (d, 1H, *J* = 12.0 Hz), 4.34 (q, 1H, *J* = 7 Hz), 4.13 (d, 1H, *J* = 12 Hz), 3.80 (bs, 1H), 3.46 (s, 1H), 2.83 (dt, 1H, *J* = 2.5 Hz, *J* = 10.5 Hz), 1.9-1.97 (m, 3H), 1.74 (bs, 1H), 1.59 (t, 1H, *J* = 14 Hz), 1.47(d, 1H, *J* = 12.5 Hz), 1.27 (t, 1H, *J* = 16.5 Hz).

^{13}C NMR (125 MHz, CDCl_3): δ = 157.8, 145.0, 138.3, 136.2, 133.0, 132.7, 132.4, 132.1, 131.9, 128.5, 128.4, 128.1, 127.7, 127.6, 127.5, 125.6, 124.4, 122.5, 122.2, 121.4, 120.0, 70.2, 67.8, 66.3, 55.5, 50.5, 39.3, 33.4, 29.7, 24.2, 19.3 ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{32}\text{F}_6\text{N}_4\text{O}_4+\text{H}^+$ 663.2401, found 663.2401.

IR (neat): 3411, 2943, 2865, 1672, 1496, 1427, 1351, 1322, 1276, 1174, 1127, 1085 cm^{-1} .

(2R,3S)-2-((R)-3-(4-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidin-3-ol (A7):



Yield: 80 mg, 85 %.

TLC: R_f : 0.2 (20% MeOH/ CHCl_3).

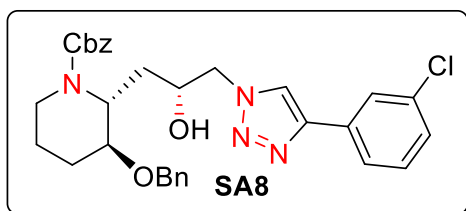
^1H NMR (500 MHz, CD_3OD): δ 8.70 (s, 1H), 8.45 (s, 2H), 7.93 (s, 1H), 4.64 (dd, 1H, J = 3.5 Hz, J = 13.5 Hz), 4.56 (dd, 1H, J = 7.0 Hz, J = 14 Hz), 4.47-4.48(m, 1H), 4.33(q, 1H, J = 7.0 Hz), 3.31 (d, 1H, J = 11 Hz), 4.47-4.48(m, 1H), 2.94 (t, 1H, J = 10.5 Hz), 2.11-2.14 (m, 1H), 2.94 (t, 2H, J = 5.5 Hz), 1.98(d, 1H, J = 14 Hz), 1.76 (q, 1H, J = 12.0 Hz), 1.55 (q, 1H, J = 10.5 Hz).

^{13}C NMR (125 MHz, CD_3OD): δ = 145.8, 134.7, 133.6, 133.3, 132.3, 129.8, 126.7, 125.8, 125.1, 123.6, 122.3, 68.1, 67.5, 59.9, 56.9, 45.1, 33.7, 32.1, 21.7 ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{20}\text{F}_6\text{N}_4\text{O}_2+\text{H}^+$ 439.1563, found 439.1565.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

benzyl (2R,3S)-3-(benzyloxy)-2-((R)-3-(4-(3-chlorophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidine-1-carboxylate (SA8):



Yield: 200 mg, 90%,

TLC: R_f: 0.2 (50% EtOAc/hexane)

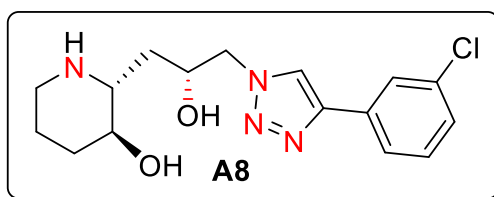
¹H NMR (500 MHz, CDCl₃): δ 8.04 (s, 1H), 7.88 (s, 1H), 7.74 (d, 1H, J = 7 Hz), 7.28-7.38 (m, 14H), 5.11 (dd, 2H, J = 7.0 Hz, J = 19.0 Hz), 4.68 (d, 2H, J = 12.5 Hz), 4.55-4.62 (m, 2H), 4.49 (d, 1H, J = 12 Hz), 7.74 (q, 1H, J = 6.5 Hz), 4.10 (d, 1H, J = 12.5 Hz), 3.80 (s, 1H), 3.45 (s, 1H), 2.79 (t, 1H, J = 11.5 Hz), 1.88-1.95 (m, 3H), 1.58 (t, 1H, J = 13.0 Hz), 1.42 (d, 1H, J = 12.5 Hz), 1.27 (t, 1H, J = 12.0 Hz).

¹³C NMR (125 MHz, CDCl₃): δ = 157.5, 146.2, 138.2, 136.1, 134.6, 132.4, 130.0, 128.4, 128.2, 128.0, 127.9, 127.5, 127.4, 127.3, 125.6, 123.6, 121.7, 74.2, 70.1, 67.6, 66.3, 55.3, 50.3, 39.1, 33.3, 24.1, 19.2 ppm.

HRMS (ESI-TOF) m/z : [M+H]⁺ calcd for C₃₁H₃₃ClN₄O₄+H⁺ 561.2263, found 561.2261.

IR (neat): 3399, 2957, 2924, 2862, 2026, 1662, 1454, 1350, 1261, 1196, 1075, 1046 cm⁻¹.

(2R,3S)-2-((R)-3-(4-(3-chlorophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidine-3-ol (A8):



Yield: 60 mg, 85%,

TLC: R_f: 0.2 (20% MeOH/CHCl₃).

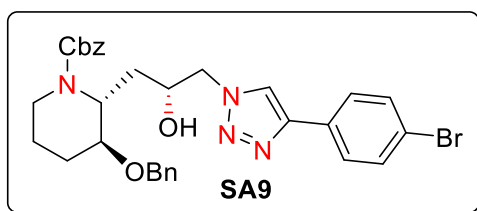
^1H NMR (500 MHz, CD_3OD): δ 8.77 (bs, 1H), 7.89 (bs, 1H), 7.77 (d, 1H, $J = 8.0$ Hz), 7.50 (t, 1H, $J = 11.5$ Hz), 7.45 (d, 1H, $J = 7.5$ Hz), 4.71-4.74 (m, 1H), 4.62-4.66 (m, 1H), 4.51 (bs, 1H), 3.69 (t, 1H, $J = 3.5$ Hz), 3.26 (d, 1H, $J = 3.5$ Hz), 2.98 (t, 1H, $J = 11.5$ Hz), 2.08-2.13 (m, 3H), 1.97-2.01 (m, 1H), 1.75 (q, 1H, $J = 12.5$ Hz), 1.54-1.62 (m, 1H).

^{13}C NMR (125 MHz, CD_3OD): $\delta = 146.2, 136.1, 131.9, 130.1, 126.9, 125.4, 68.1, 67.5, 59.9, 57.7, 45.1, 33.6, 32.0, 21.6$ ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{21}\text{ClN}_4\text{O}_2+\text{H}^+$ 337.1426, found 337.1426.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

benzyl (2R,3S)-3-(benzyloxy)-2-((R)-3-(4-(4-bromophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidine-1-carboxylate (SA9):



Yield: 180 mg, 85%.

TLC: R_f : 0.3 (50% EtOAc/hexane)

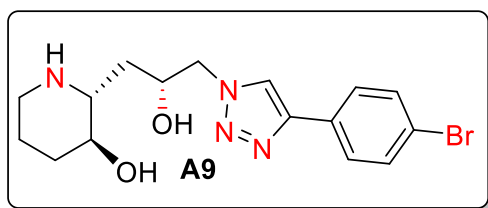
^1H NMR (500 MHz, CDCl_3): δ 7.98(s, 1H), 7.68 (d, 1H, $J = 8.0$ Hz), 7.50 (d, 1H, $J = 8.0$ Hz), 7.23-7.28 (m, 10H), 5.06 (dd, 2H, $J = 5.0$ Hz, $J = 12.5$ Hz), 4.65 (t, 2H, $J = 12.0$ Hz), 4.44-4.57 (m, 3H), 4.23(q, 1H, $J = 7.5$ Hz), 4.05 (d, 1H, $J = 6.0$ Hz), 3.76(bs, 1H), 3.41(s, 1H), 2.75 (dd, 1H, $J = 3.0$ Hz, $J = 13.5$ Hz), 1.85 (t, 3H, $J = 14.5$ Hz), 1.53 (t, 2H, $J = 12.0$ Hz), 1.37 (d, 1H, $J = 12.0$ Hz), 1.23 (t, 1H, $J = 13.0$ Hz).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 157.4, 146.3, 138.1, 136.1, 131.7, 129.5, 128.3, 128.2, 127.9, 127.5, 127.3, 127.3, 127.0, 121.6, 121.4, 74.1, 69.9, 67.5, 66.6, 66.2, 55.2, 50.2, 39.0, 33.2, 24.0, 19.1$ ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{31}\text{H}_{33}\text{FN}_4\text{O}_4+\text{H}^+$ 545.2559, found 545.2557.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

(2R,3S)-2-((R)-3-(4-(4-bromophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidin-3-ol (A9):



Yield: 50 mg, 85%,

TLC: R_f: 0.2 (20% MeOH/CHCl₃)

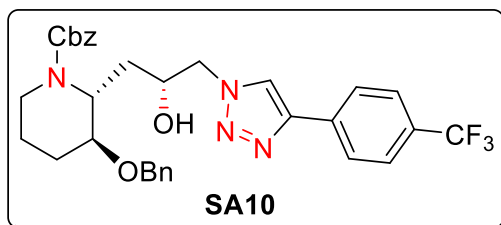
¹H NMR (500 MHz, CD₃OD): δ 8.59(s, 1H), 7.77-7.79(m, 2H), 7.66(d, 2H, *J* = 8.5 Hz), 4.65-4.69(m, 1H), 4.46-4.51(m, 1H), 3.72(dt, 1H, *J* = 4.0 Hz, *J* = 9.5 Hz), 3.3(t, 1H, *J* = 3.5 Hz), 3.23-3.27(m, 1H), 2.97 (dt, 1H, *J* = 3.5 Hz, *J* = 12.5 Hz), 2.10-2.14(m, 1H), 2.06(t, 2H, *J* = 6 Hz), 1.98-2.03(m, 1H), 1.74-1.82(m, 1H), 1.55-1.63(m, 1H).

¹³C NMR (125 MHz, CD₃OD): δ = 145.7, 133.5, 129.0, 127.8, 125.7, 124.7, 68.0, 67.4, 59.8, 58.1, 45.0, 33.6, 32.0, 21.6 ppm.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₆H₂₁FN₄O₂+H⁺ 321.1721, found 321.1725.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm⁻¹.

Benzyl(2R,3S)-3-(benzyloxy)-2-((R)-2-hydroxy-3-(4-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)propyl)piperidine-1-carboxylate (SA10):



Yield: 150 mg, 90%,

TLC: R_f: 0.3 (50% EtOAc/hexane)

¹H NMR (500 MHz, CDCl₃): δ 8.12 (s, 1H), 7.98 (d, 2H, *J* = 7.5 Hz), 7.69 (d, 2H, *J* = 7.5 Hz), 7.28-7.33 (m, 10H), 7.98 (dd, 2H, *J* = 5.5 Hz, *J* = 12.0 Hz), 4.77 (s, 1H), 4.7 (d, 1H, *J* = 12.0 Hz), 4.60 (t, 2H, *J* = 11.5 Hz), 4.50 (d, 2H, *J* = 12.0 Hz), 4.31 (q, 1H, *J* = 7.0 Hz), 4.31-

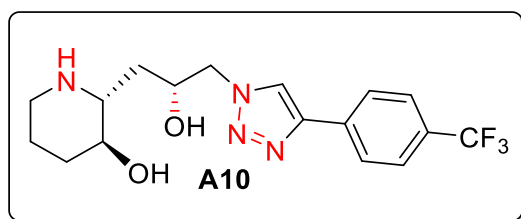
4.15 (m, 1H), 3.82 (bs, 1H), 3.47 (s, 1H), 2.84 (t, 1H, $J = 11.5$ Hz), 1.91-1.96 (m, 3H), 1.62 (t, 1H, $J = 13.5$ Hz), 1.44 (d, 1H, $J = 12.5$ Hz), 1.28-1.34 (m, 1H).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 157.6, 146.1, 138.1, 136.1, 134.1, 128.4, 128.3, 128.0, 127.5, 127.4, 127.3, 125.7, 125.6, 125.6, 122.2, 74.2, 70.1, 67.6, 66.3, 55.3, 50.3, 39.1, 33.3, 24.1, 19.2$ ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{32}\text{H}_{33}\text{FN}_4\text{O}_4+\text{H}^+$ 595.2527, found 595.2527.

IR (neat): 3402, 2946, 2859, 2166, 1677, 1621, 1496, 1621, 1496, 1323, 1259, 1062 cm^{-1} .

(2R,3S)-2-((R)-2-hydroxy-3-(4-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)propyl)piperidin-3-ol (A10):



Yield: 120 mg, 85%,

TLC: R_f : 0.2 (20% MeOH/ CHCl_3).

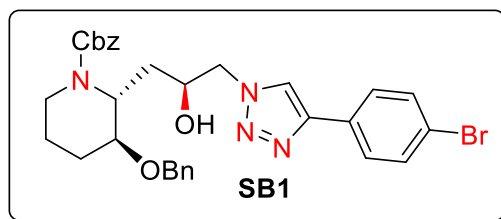
^1H NMR (500 MHz, CD_3OD): δ 8.52 (s, 1H), 8.02 (d, 1H, $J = 8$ Hz), 7.72 (d, 1H, $J = 8.5$ Hz), 4.57 (dq, 2H, $J = 7.0$ Hz, $J = 14$ Hz), 4.43-4.45 (m, 1H), 3.68 (td, 1H, $J = 4.0$ Hz, $J = 10.0$ Hz), 3.27 (bs, 1H), 3.19-3.23 (m, 1H), 2.91 (td, 1H, $J = 2.0$ Hz, $J = 12.0$ Hz), 2.09-2.12 (m, 1H), 1.96-2.03 (m, 3H), 1.73-1.80 (m, 1H), 1.57 (qd, 1H, $J = 3.5$ Hz, $J = 13.5$ Hz).

^{13}C NMR (125 MHz, CD_3OD): $\delta = 147.2, 135.6, 131.1, 130.8, 127.0, 126.9, 124.6, 68.1, 67.5, 59.9, 56.9, 45.0, 33.7, 32.1, 21.7$ ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{21}\text{F}_3\text{N}_4\text{O}_2+\text{H}^+$ 371.1689, found 371.1685.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

benzyl (2R,3S)-3-(benzyloxy)-2-((S)-3-(4-(4-bromophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidine-1-carboxylate (SB1):



Yield: 170 mg, 85%,

TLC: R_f : 0.3 (50% EtOAc/hexane).

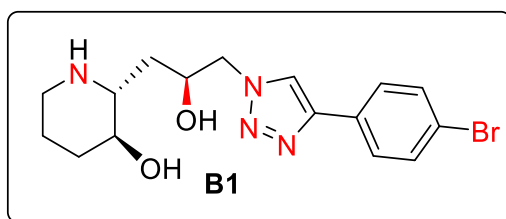
^1H NMR (500 MHz, CDCl_3): δ 7.9 (bs, 1H), 7.62 (bs, 1.5H), 7.51-7.56 (m, 2.6 H), 7.27-7.32 (m, 10H), 5.16 (bs, 2H), 4.54-4.67 (m, 3H), 4.37 (bs, 1H), 4.27 (bs, 1H), 4.11 (bs, 2H), 3.45 (bs, 1H), 2.92 (bs, 1H), 1.91-1.96 (m, 3H), 1.57-1.65 (m, 2H), 1.39-1.42 (m, 1H), 1.28-1.131 (m, 1H).

^{13}C NMR (125 MHz, CDCl_3): δ = 156.2, 146.1, 138.3, 136.4, 131.8, 128.4, 128.2, 127.9, 127.3, 126.9, 121.8, 121.4, 74.15, 70.0, 68.5, 67.2, 55.3, 51.0, 39.1, 33.7, 29.5, 23.9, 19.3 ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{31}\text{H}_{33}\text{FN}_4\text{O}_4+\text{Na}^+$ 629.1557, found 629.1570.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

(2R,3S)-2-((S)-3-(4-(4-bromophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidin-3-ol (B1):



Yield: 50 mg, 85%,

TLC: R_f : 0.2 (20% MeOH/ CHCl_3).

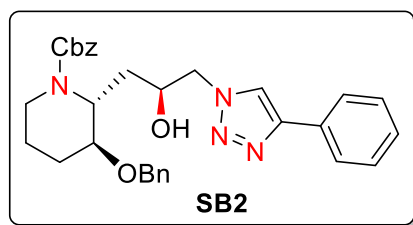
^1H NMR (500 MHz, CD_3OD): δ 8.42 (s, 1H), 7.73 (d, 2H, J = 6.5 Hz), 7.57 (d, 2H, J = 6.0 Hz), 4.58 (dd, 1H, J = 3.0 Hz, J = 14.0 Hz), 4.51 (dd, 2H, J = 6.0 Hz, J = 14.5 Hz), 4.40 (bs, 1H), 3.56 (d, 1H, J = 4.5 Hz), 3.32 (bs, 0.5H), 3.26 (d, 1H, J = 12.5 Hz), 3.14-3.15 (m, 1H), 2.94 (t, 1H, J = 12.5 Hz), 2.33 (d, 1H, J = 14.5 Hz), 2.06 (d, 1H, J = 15.6 Hz), 1.94 (d, 1H, J = 14.5 Hz), 1.70-1.75 (m, 1H), 1.52-1.62 (m, 1H).

^{13}C NMR (125 MHz, CD_3OD): δ = 147.6, 133.1, 130.9, 128.3, 123.8, 122.9, 70.45, 68.8, 62.1, 57.1, 44.7, 33.8, 31.9, 21.6 ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{21}\text{FN}_4\text{O}_2+\text{H}^+$ 321.1721, found 321.1725.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

Benzyl (2R,3S)-3-(benzyloxy)-2-((S)-2-hydroxy-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propyl)piperidine-1-carboxylate (SB2)



Yield: 300 mg, 90%,

TLC: R_f : 0.2 (50% EtOAc/hexane)

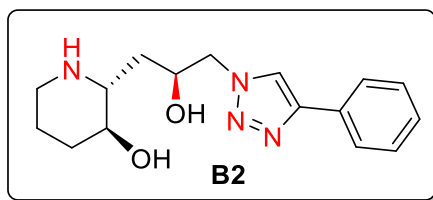
^1H NMR (500 MHz, CDCl_3): δ 7.68-7.99 (m, 3H), 7.57-7.59 (m, 0.5H), 7.40-7.3 (m, 2H), 7.27-7.35 (m, 15H), 5.19 (bs, 2H), 4.61-4.66 (m, 1.5H), 4.56-4.58 (m, 1H), 4.50 (d, 1H, J = 12.0 Hz), 4.38 (bs, 1H), 3.45-3.47 (m, 1H), 2.90-2.93 (m, 1H), 1.88-1.96 (m, 3.5H), 1.57-1.65 (m, 2H), 1.39 (d, 1H, J = 13.0 Hz).

^{13}C NMR (125 MHz, CDCl_3): δ = 156.8, 147.3, 138.3, 136.5, 130.4, 129.6, 128.7, 128.4, 128.3, 128.1, 128.0, 127.4, 125.5, 74.3, 70.1, 68.8, 67.3, 55.2, 51.2, 39.2, 33.8, 29.6, 24.0, 19.3 ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{31}\text{H}_{34}\text{N}_4\text{O}_4+\text{H}^+$ 526.2580, found 526.2581.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

(2R,3S)-2-((S)-2-hydroxy-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propyl)piperidin-3-ol (B2):



Yield: 120 mg, 85%,

TLC: R_f : 0.2 (20% MeOH/ CHCl_3).

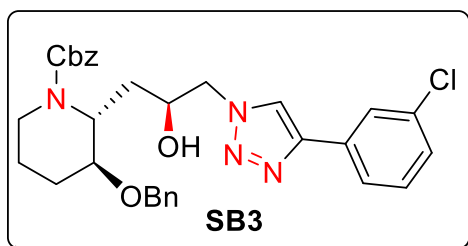
^1H NMR (500 MHz, CD_3OD): δ 8.35 (s, 1H), 7.83 (d, 2H, $J = 7.0$ Hz), 7.44 (t, 2H, $J = 8.0$ Hz), 7.35 (t, 1H, $J = 7.5$ Hz), 4.62 (dd, 1H, $J = 4.0$ Hz, $J = 14.0$ Hz), 4.62 (dd, 1H, $J = 6.0$ Hz, $J = 14.0$ Hz), 4.31-4.36 (m, 1H), 3.32-3.35 (m, 1H), 3.06 (d, 1H, $J = 12.5$ Hz), 2.81 (t, 1H, $J = 9.0$ Hz), 2.73 (td, 1H, $J = 3.0$ Hz, $J = 12.5$ Hz), 2.05 (dt, 1H, $J = 3.0$ Hz, $J = 14.5$ Hz), 2.03-2.06 (m, 1H), 1.80-1.84 (m, 1H), 1.56-1.65 (m, 1H), 1.40-1.49 (m, 2H).

^{13}C NMR (125 MHz, CD_3OD): $\delta = 148.6, 131.7, 130.0, 129.3, 126.6, 123.4, 71.1, 70.6, 62.9, 57.3, 45.6, 35.3, 33.4, 23.9$ ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{22}\text{N}_4\text{O}_2+\text{H}^+$ 303.1816, found 303.1815.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

Benzyl (2R,3S)-3-(benzyloxy)-2-((S)-3-(4-(3-chlorophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidine-1-carboxylate (SB3):



Yield: 300 mg, 90%,

TLC: R_f : 0.2 (50% EtOAc/hexane)

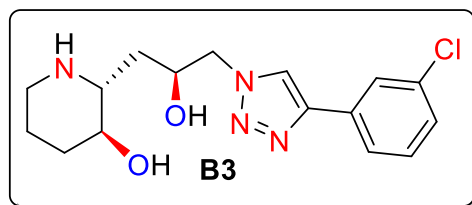
^1H NMR (500 MHz, CDCl_3): δ 7.89 (bs, 1H), 7.80 (bs, 1H), 7.67 (bs, 1H), 7.27-7.37 (m, 11H), 5.16 (bs, 2H), 4.56-4.63 (m, 2H), 4.50 (d, 1H, $J = 12.0$ Hz), 4.37 (bs, 1H), 4.10 (bs, 2H), 3.44 (bs, 1H), 2.89 (t, 1H, $J = 12.5$ Hz), 1.84-1.96 (m, 3H), 1.54-1.65 (m, 2H), 1.41 (d, 1H, $J = 12.5$ Hz), 1.28-1.29 (m, 11H).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 157.5, 146.2, 138.2, 136.1, 134.6, 132.4, 130.0, 128.4, 128.2, 128.0, 127.9, 127.5, 127.4, 127.3, 125.6, 123.6, 121.7, 74.2, 70.1, 67.6, 66.3, 55.3, 50.3, 39.1, 33.3, 24.1, 19.2$ ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{31}\text{H}_{33}\text{ClN}_4\text{O}_4+\text{H}^+$ 561.2263, found 561.2261.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

(2R,3S)-2-((R)-3-(4-(3-chlorophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidin-3-ol (B3):



Yield: 120 mg, 85%,

TLC: R_f : 0.2 (20% MeOH/ CHCl_3).

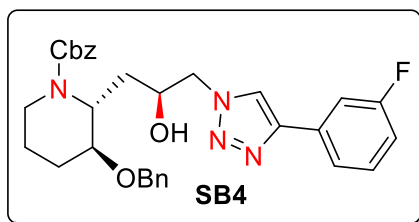
^1H NMR (500 MHz, CD_3OD): δ 8.42 (s, 1H), 7.87 (bs, 1H), 7.55 (d, 2H, $J = 6.5$ Hz), 7.43 (t, 1H, $J = 8.0$ Hz), 7.36 (d, 1H, $J = 8.0$ Hz), 4.56 (dd, 1H, $J = 4.0$ Hz, $J = 14.0$ Hz), 4.47 (dd, 1H, $J = 6.5$ Hz, $J = 14.0$ Hz), 4.32-4.36 (m, 1H), 3.32-3.33 (m, 1H), 3.08 (d, 1H, $J = 12.5$ Hz), 2.81-2.84 (m, 1H), 2.75 (t, 1H, $J = 12.5$ Hz), 2.25 (dd, 1H, $J = 3.0$ Hz, $J = 15.0$ Hz), 2.04-2.07 (m, 1H), 1.82-1.86 (m, 1H), 1.59-1.66 (m, 1H), 1.41-1.50 (m, 2H).

^{13}C NMR (125 MHz, CD_3OD): 147.2, 135.9, 133.8, 131.6, 129.1, 126.4, 124.9, 123.9, 71.0, 70.5, 62.8, 57.3, 45.5, 35.2, 33.4, 23.8.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{21}\text{ClN}_4\text{O}_2+\text{H}^+$ 337.1426, found 337.1421.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

benzyl (2R,3S)-3-(benzyloxy)-2-((S)-3-(4-(3-fluorophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidine-1-carboxylate (SB4):



Yield: 300 mg, 90%,

TLC: R_f : 0.2 (50% EtOAc/hexane)

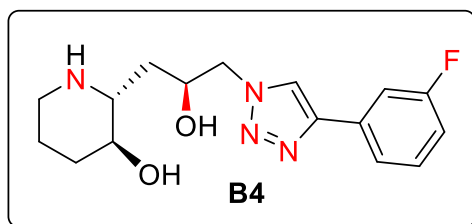
^1H NMR (500 MHz, CDCl_3): δ 7.87-8.01 (m, 1H), 7.49-7.57 (m, 3H), 7.23-7.38 (m, 10H), 6.96 (td, 1H, $J = 2.0$ Hz, $J = 8.0$ Hz), 5.10 (bs, 2H), 4.52-4.64 (m, 3H), 4.66 (d, 1H, $J = 12.0$ Hz), 4.34 (bs, 1H), 4.09 (bs, 2H), 3.42 (s, 1H), 2.87 (s, 1H), 1.84-1.92 (m, 3H), 1.54-1.62 (m, 2H), 1.36 (d, 1H, $J = 13\text{Hz}$), 1.25 (bs, 1H)

^{13}C NMR (100 MHz, CDCl_3): 164.2, 161.8, 156.8, 146.2, 138.3, 136.5, 132.5, 130.4, 130.3, 128.4, 128.3, 127.9, 127.4, 121.6, 121.1, 114.9, 114.7, 112.5, 112.3, 74.2, 70.1, 68.7, 67.3, 55.3, 51.2, 39.2, 33.8, 29.6, 23.9, 19.3.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{31}\text{H}_{33}\text{FN}_4\text{O}_4+\text{H}^+$ 545.2559, found 545.2556.

IR (neat): 3103, 3021, 2921, 2849, 2808, 2675, 2266, 1601, 1397, 1399, 1248 cm^{-1} .

(2R,3S)-2-((S)-3-(4-(3-fluorophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidin-3-ol (B4):



Yield: 120 mg, 85%,

TLC: R_f : 0.2 (20% MeOH/ CHCl_3).

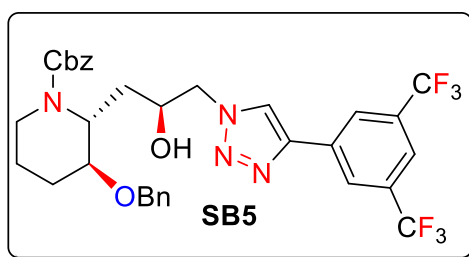
^1H NMR (500 MHz, CD_3OD): δ 8.38 (s, 1H), 7.65 (d, 1H, J = 8.0 Hz), 7.58 (dd, 1H, J = 2.0 Hz, J = 10.5 Hz), 7.44-7.49 (m, 1H), 7.08 (td, 1H, J = 2.0 Hz, J = 8.0 Hz), 4.53 (dd, 1H, J = 4.0 Hz, J = 14.0 Hz), 4.42 (dd, 1H, J = 6.5 Hz, J = 14.0 Hz), 4.26 (m, 1H), 3.19 (td, 1H, J = 4.5 Hz, J = 10.5 Hz), 2.94 (d, 1H, J = 12.0 Hz), 2.57-2.62 (m, 2H), 2.17 (dt, 1H, J = 3.0 Hz, J = 14.5 Hz), 2.02-2.05 (m, 1H), 1.73-1.76 (m, 1H), 1.51-1.58 (m, 1H), 1.30-1.43 (m, 3H).

^{13}C NMR (125 MHz, CD_3OD): 164.2, 162.3, 146.1, 146.1, 132.8, 132.8, 130.5, 130.5, 122.5, 121.1, 121.0, 114.5, 114.3, 111.9, 111.7, 70.3, 70.1, 62.1, 56.1, 44.7, 34.8, 33.1, 24.1.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{21}\text{FN}_4\text{O}_2+\text{H}^+$ 321.1721, found 321.1720.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

benzyl (2R,3S)-3-(benzyloxy)-2-((R)-3-(4-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidine-1-carboxylate (SB5):



Yield: 300 mg, 90%,

TLC: R_f : 0.2 (50% EtOAc/hexan)

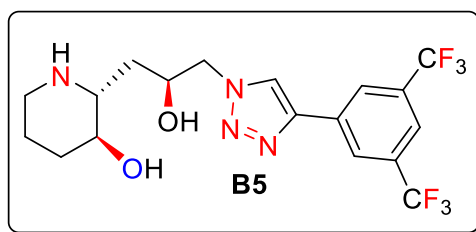
^1H NMR (500 MHz, CDCl_3): δ 8.27 (bs, 2H), 8.05 (bs, 1H), 7.84 (s, 1H), 7.27-7.34 (m, 10H), 4.62 (bs, 2H), 4.52 (d, 1H, J = 12 Hz), 4.40 (bs, 1H), 4.11 (bs, 3H), 3.45 (s, 1H), 2.93 (t, 1H, J = 12.5 Hz), 1.91-1.98 (m, 3H), 1.84 (bs, 1H), 1.60-1.66 (m, 2H), 1.42 (d, 1H, J = 13.0 Hz), 1.28 (bs, 1H), 0.87-0.91 (m, 1H).

^{13}C NMR (125 MHz, CDCl_3): 157.5, 146.2, 138.2, 136.1, 134.6, 132.4, 130.0, 128.4, 128.2, 128.0, 127.9, 127.5, 127.4, 127.3, 125.6, 123.6, 121.7, 74.2, 70.1, 67.6, 66.3, 55.3, 50.3, 39.1, 33.3, 24.1, 19.2.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{32}\text{F}_6\text{N}_4\text{O}_4+\text{H}^+$ 663.2401, found 663.2401.

IR (neat): 3411, 2943, 2865, 1672, 1496, 1427, 1351, 1322, 1276, 1174, 1127, 1085 cm^{-1} .

(2R,3S)-2-((R)-3-(4-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidin-3-ol (B5):



Yield: 120 mg, 85%,

TLC: R_f : 0.2 (20% MeOH/ CHCl_3).

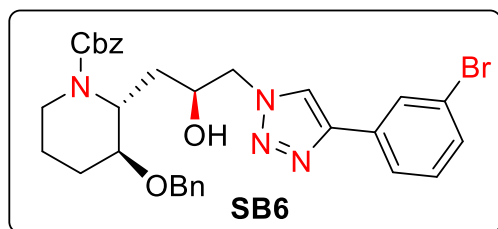
^1H NMR (500 MHz, CD_3OD): δ 8.73 (s, 1H), 8.47 (s, 2H), 7.96 (s, 1H), 4.64 (dd, 1H, $J = 4.0$ Hz, $J = 14.0$ Hz), 4.57 (dd, 1H, $J = 6.0$ Hz, $J = 14$ Hz), 4.24-4.44 (m, 1H), 3.56 (td, 1H, $J = 4.0$ Hz, $J = 9.5$ Hz), 3.27-3.30 (m, 1H), 3.17 (td, 1H, $J = 3.5$ Hz, $J = 9.0$ Hz), 2.97 (td, 1H, $J = 3.0$ Hz, $J = 12.5$ Hz), 2.35 (dt, 1H, $J = 3.0$ Hz, $J = 15.0$ Hz), 2.06-2.11 (m, 1H), 1.97-2.02 (m, 1H), 1.72-1.78 (m, 1H) 1.54-1.62 (m, 2H).

^{13}C NMR (125 MHz, CD_3OD): 157.5, 146.2, 138.2, 136.1, 134.6, 132.4, 130.0, 128.4, 128.2, 128.0, 127.9, 127.5, 127.4, 127.3, 125.6, 123.6, 121.7, 74.2, 70.1, 67.6, 66.3, 55.3, 50.3, 39.1, 33.3, 24.1, 19.2.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{20}\text{F}_6\text{N}_4\text{O}_2+\text{H}^+$ 439.1563, found 439.1561.

IR (neat): 3402, 2946, 2859, 2166, 1677, 1621, 1496, 1621, 1496, 1426, 1323, 1259, 1121, 1062 cm^{-1} .

Benzyl (2R,3S)-3-(benzyloxy)-2-((S)-3-(4-(3-bromophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidine-1-carboxylate (SB6):



Yield: 300 mg, 90%,

TLC: R_f: 0.2 (50% EtOAc/hexane)

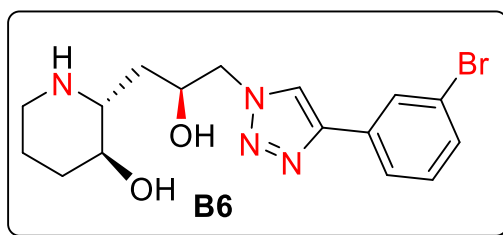
¹H NMR (500 MHz, CDCl₃): δ 7.84-8.02 (m, 2H), 7.55-7.65 (m, 1H), 7.44 (d, 1H, *J* = 8.5 Hz), 7.24-7.32 (m, 10H), 5.09 (bs, 2H), 4.57-4.69 (m, 2H), 4.63-4.69 (m, 2H), 4.52 (d, 1H, *J* = 12.0 Hz), 4.38 (bs, 2H), 4.12 (bs, 2H), 3.46 (d, 1H, *J* = 14.5 Hz), 3.66 (d, 1H, *J* = 3.5 Hz), 1.88-1.96 (m, 3H), 1.57-1.65 (m, 2H), 1.39 (d, 1H, *J* = 13.0 Hz).

¹³C NMR (125 MHz, CDCl₃): 156.7, 155.9, 145.8, 138.3, 136.4, 132.4, 130.9, 130.3, 129.5, 128.4, 128.2, 127.9, 127.4, 127.1, 123.9, 122.8, 121.6, 77.2, 74.2, 70.1, 68.6, 67.2, 55.4, 51.1, 39.2, 38.8, 33.7, 33.0, 29.6, 23.9, 19.3.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₃₁H₃₃BrN₄O₄+H⁺ 605.1758, found 605.1758.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm⁻¹.

(2R,3S)-2-((S)-3-(4-(3-bromophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidin-3-ol (B6):



Yield: 120 mg, 85%,

TLC: R_f: 0.2 (20% MeOH/CHCl₃).

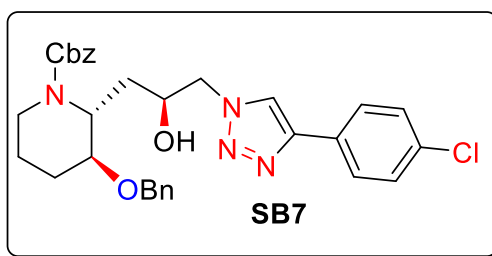
¹H NMR (500 MHz, CD₃OD): δ 8.47 (s, 1H), 8.05 (bs, 1H), 7.83 (d, 1H, *J* = 7.5 Hz), 7.51 (d, 2H, *J* = 8.0 Hz), 7.38 (t, 1H, *J* = 8.0 Hz), 4.60 (dd, 1H, *J* = 4.0 Hz, *J* = 14.0 Hz), 4.56 (dd, 1H, *J* = 5.5 Hz, *J* = 14.0 Hz), 4.40-4.42 (m, 1H), 3.58 (td, 1H, *J* = 4.0 Hz, *J* = 9.5 Hz), 3.28 (dt, 1H, *J* = 3.5 Hz, *J* = 13.0 Hz), 3.17 (td, 1H, *J* = 3.0 Hz, *J* = 8.5 Hz), 3.00 (td, 1H, *J* = 3.5 Hz, *J* = 12.5 Hz), 2.34 (dt, 1H, *J* = 3.0 Hz, *J* = 15.0 Hz), 2.06-2.10 (m, 1H), 1.96-2.00 (m, 1H), 1.70-1.78 (m, 1H), 1.53-1.61 (m, 2H).

¹³C NMR (125 MHz, CD₃OD): δ = 147.2, 134.0, 132.2, 131.8, 129.4, 125.4, 124.1, 123.9, 70.4, 68.8, 62.1, 57.2, 44.7, 33.7, 31.8, 21.4 ppm.

HRMS (ESI-TOF) m/z : $[M+H]^+$ calcd for C₁₆H₂₁BrN₄O₂+H⁺ 381.0921, found 381.0920.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm⁻¹.

benzyl (2R,3S)-3-(benzyloxy)-2-((R)-3-(4-(4-chlorophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidine-1-carboxylate (SB7):



Yield: 100 mg, 90 %,

TLC: R_f: 0.3 (50 % EtOAc/hexane).

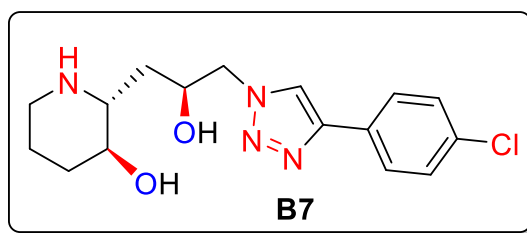
¹H NMR (500 MHz, CDCl₃): δ 8.01(s, 1H), 7.80 (d, 2H, J = 8 Hz), 7.43 (d, 2H, J = 8.5 Hz), 7.27-7.7.33 (m, 10H), 5.12-5.18 (m, 2H), 4.68 (d, 1H, J = 12.5 Hz), 4.55-4.62 (m, 2H), 4.49 (d, 2H, J =12 Hz), 4.29-4.4.34 (m, 1H), 4.11 (d, 1H, J = 13 Hz), 3.79 (bs, 1H), 3.46 (s, 1H), 2.81 (td, 1H, J = 2.5 Hz, J = 13.5 Hz), 1.88-1.95 (m, 3H), 1.6 (t, 1H, J = 13.5 Hz), 1.43 (d, 1H, J = 13 Hz), 1.29 (td, 2H, J = 2.5 Hz, J = 11.5 Hz).

¹³C NMR (125 MHz, CDCl₃): δ = 157.4, 146.3, 138.1, 136.1, 131.7, 129.5, 128.3, 128.2, 127.9, 127.5, 127.3, 127.3, 127.0, 121.6, 121.4, 74.1, 70.0, 67.5, 66.6, 66.2, 55.2, 50.2, 39.0, 33.2, 24.0, 19.14 ppm.

HRMS (ESI-TOF) m/z : $[M+H]^+$ calcd for C₃₁H₃₃BrN₄O₄+H⁺ 605.1758, found 605.1758.

IR (neat): 3399, 3138, 3030, 2929, 2862, 1677, 1451, 1426, 1314, 1258, 1197, 1128, 1089 cm⁻¹.

(2R,3S)-2-((R)-3-(4-(4-chlorophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidin-3-ol (B7):



Yield: 120 mg, 85%,

TLC: R_f : 0.2 (20% MeOH/ CHCl_3).

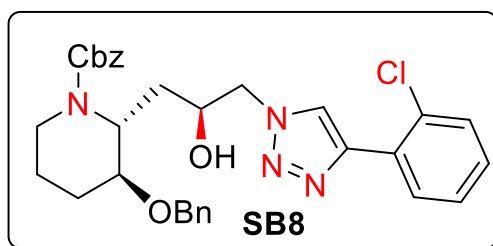
^1H NMR (500 MHz, CD_3OD): δ 8.35(s, 1H), 7.81 (d, 2H, J = 8.5 Hz), 7.45 (d, 2H, J = 8.5 Hz), 4.52 (dd, 1H, J = 4.0 Hz, J = 14.0 Hz), 4.42 (dd, 1H, J = 6.0 Hz, J = 14.0 Hz), 4.28-4.32 (m, 1H), 3.21 (td, 1H, J = 4.5 Hz, J = 10.0 Hz), 2.96 (d, 1H, J = 12.5 Hz), 2.58-2.64 (m, 2H), 2.17 (dt, 1H, J = 3.5 Hz, J = 14.0 Hz), 2.02-2.05 (m, 1H), 1.74-1.78(m, 1H), 1.52-1.59(m, 1H), 1.32-1.44(m, 2H) .

^{13}C NMR (125 MHz, CD_3OD): δ = 147.5, 135.0, 130.6, 130.1, 128.1, 123.5, 71.6, 71.5, 63.4, 57.5, 46.1, 36.1, 34.3, 25.3 ppm.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{21}\text{ClN}_4\text{O}_2+\text{H}^+$ 337.1426, found 337.1426.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

benzyl (2R,3S)-3-(benzyloxy)-2-((S)-3-(4-(2-chlorophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidine-1-carboxylate (SB8):



Yield: 300 mg, 90%,

TLC: R_f: 0.2 (50% EtOAc/hexane)

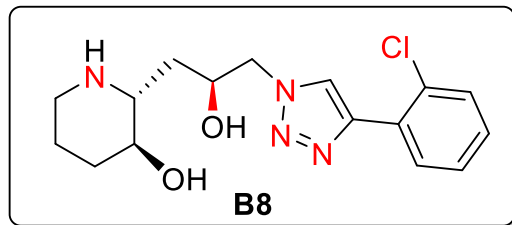
¹H NMR (500 MHz, CDCl₃): δ 8.33 (bs, 1H), 8.20 (d, 1H, *J* = 8.5 Hz), 7.44 (dd, 1H, *J* = 1.0 Hz, *J* = 8.0 Hz), 7.36 (dd, 1H, *J* = 1.5 Hz, *J* = 7.5 Hz), 7.27-7.32 (m, 10H), 5.15 (bs, 2H), 4.64-4.67 (m, 2H), 4.54 (d, 1H, *J* = 12.5 Hz), 4.35-4.52 (m, 2H), 4.08-4.13 (m, 2H), 3.40 (bs, 1H), 2.91 (t, 1H, *J* = 12.0 Hz), 1.83-1.95 (m, 3.5H), 1.60-1.65 (m, 1H), 1.54 (bs, 1H), 1.40-1.45 (m, 1H), 1.28 (bs, 1H).

¹³C NMR (125 MHz, CDCl₃): 156.9, 143.8, 138.4, 136.5, 131.3, 130.2, 129.7, 129.6, 129.2, 129.1, 128.5, 128.4, 128.1, 127.7, 127.5, 127.2, 124.8, 77.2, 74.4, 70.2, 69.0, 67.5, 55.3, 51.4, 39.3, 33.9, 29.7, 24.1, 19.4.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₃₁H₃₃ClN₄O₄+H⁺ 561.2263, found 561.2260.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm⁻¹.

(2R,3S)-2-((S)-3-(4-(2-chlorophenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxypropyl)piperidin-3-ol (B8):



Yield: 100 mg, 85%.

TLC: R_f: 0.2 (20% MeOH/CHCl₃).

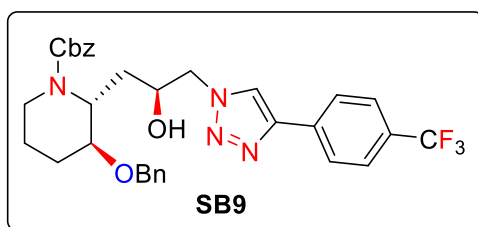
¹H NMR (500 MHz, CD₃OD): δ 8.51 (s, 1H), 8.01 (dd, 1H, *J* = 1.5 Hz, *J* = 7.5 Hz), 7.52 (dd, 1H, *J* = 1.0 Hz, *J* = 8.0 Hz), 7.43 (td, 1H, *J* = 1.5 Hz, *J* = 7.5 Hz), 7.35 (td, 1H, *J* = 2.0 Hz, *J* = 8.0 Hz), 4.55 (dd, 1H, *J* = 3.5 Hz, *J* = 14.0 Hz), 4.43 (dd, 2H, *J* = 7.0 Hz, *J* = 14.0 Hz), 4.28-4.30 (m, 1H), 3.14-3.19 (m, 1H), 2.88 (dt, 1H, *J* = 2.0 Hz, *J* = 12.5 Hz), 2.48-2.55 (m, 2H), 2.15 (dt, 1H, *J* = 3.0 Hz, *J* = 14.0 Hz), 2.01-2.05 (m, 1H), 1.69-1.72 (m, 1H), 1.51-1.53 (m, 1H), 1.30-1.37 (m, 2H).

¹³C NMR (125 MHz, CD₃OD): δ = 144.8, 132.7, 131.4, 130.9, 130.5, 130.5, 128.3, 126.4, 72.3, 71.7, 57.5, 46.5, 36.9, 35.0, 26.3 ppm.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₆H₂₁ClN₄O₂+H⁺ 337.1426, found 337.1422.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

Benzyl(2R,3S)-3-(benzyloxy)-2-((R)-2-hydroxy-3-(4-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)propyl)piperidine-1-carboxylate (SB9):



Yield: 150 mg, 90%,

TLC: R_f : 0.3 (50% EtOAc/hexane)

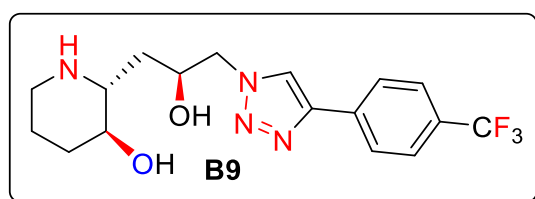
^1H NMR (500 MHz, CDCl_3): δ 7.98 (bs, 1H), 7.91 (bs, 2H), 7.67 (d, 2H, $J = 8.0$ Hz), 7.28-7.32 (m, 10H), 5.17 (bs, 2H), 4.62 (bs, 2H), 4.51 (d, 1H, $J = 12.0$ Hz), 4.39 (bs, 1H), 4.19 (bs, 3H), 3.45 (bs, 1H), 2.91 (t, 1H, $J = 12.5$ Hz), 1.79-1.97 (m, 4H), 1.57-1.66 (m, 2H), 3.75 (d, 1H, $J = 13.0$ Hz).

^{13}C NMR (125 MHz, CDCl_3): 156.8, 145.9, 138.3, 136.5, 133.8, 130.2, 130.2, 129.9, 129.6, 129.5, 129.4, 128.4, 128.3, 127.9, 127.4, 125.7, 125.7, 125.5, 125.1, 122.9, 122.1, 77.2, 74.3, 70.1, 68.7, 67.3, 55.4, 51.3, 39.2, 33.9, 29.6.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{32}\text{H}_{33}\text{FN}_4\text{O}_4+\text{H}^+$ 595.2527, found 595.2530.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

(2R,3S)-2-((R)-2-hydroxy-3-(4-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)propyl)piperidin-3-ol (B9):



Yield: 70 mg, 85%,

TLC: R_f: 0.2 (20% MeOH/CHCl₃).

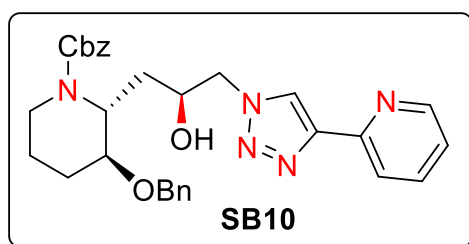
¹H NMR (500 MHz, CD₃OD): δ 8.48 (s, 1H), 8.04 (d, 2H, *J* = 8.0 Hz), 7.76 (d, 2H, *J* = 8.5 Hz), 4.56 (dd, 1H, *J* = 4.0 Hz, *J* = 14.0 Hz), 4.45 (dd, 1H, *J* = 7.5 Hz, *J* = 14.0 Hz), 4.30-4.35 (m, 1H), 4.47 (td, 1H, *J* = 4.0 Hz, *J* = 10.0 Hz), 2.99 (d, 1H, *J* = 12.5 Hz), 2.62-2.69 (m, 2H), 2.23 (dt, 1H, *J* = 3.0 Hz, *J* = 14.5 Hz), 2.03-2.06 (m, 1H), 1.76-1.80 (m, 1H), 1.52-1.62 (m, 1H), 1.35-1.46 (m, 2H).

¹³C NMR (125 MHz, CD₃OD): 147.1, 135.7, 131.1, 130.8, 127.0, 126.9, 126.9, 124.4, 71.3, 63.2, 57.5, 45.9, 35.9, 34.1, 24.9.

HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₇H₂₁F₃N₄O₂+H⁺ 371.1689, found 371.1682.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm⁻¹.

benzyl (2R,3S)-3-(benzyloxy)-2-((S)-2-hydroxy-3-(4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)propyl)piperidine-1-carboxylate (SB10):



Yield: 200 mg, 90%,

TLC: R_f: 0.2 (50% EtOAc/hexane)

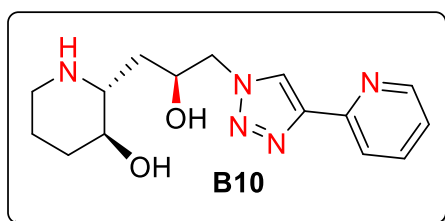
¹H NMR (500 MHz, CDCl₃): δ 8.61 (bs, 1H), 8.36 (s, 1H), 8.15 (d, 1H, *J* = 8.0 Hz), 7.77 (dt, 1H, *J* = 2.0 Hz, *J* = 17.5 Hz), 7.21-7.29 (m, 11H), 5.12 (bs, 2H), 4.67 (d, 1H, *J* = 12.0 Hz), 4.53-4.61 (m, 2H), 4.46 (d, 1H, *J* = 12 Hz), 4.33-4.37 (m, 1H), 4.01 (d, 1H, *J* = 13.5), 3.81 (bs, 1H), 3.42 (s, 1H), 2.75 (dt, 1H, *J* = 2.5 Hz, *J* = 16.0 Hz), 1.85-1.91 (m, 3H), 1.55 (t, 1H, *J* = 13.5 Hz), 1.38-1.42 (m, 1H), 1.27-1.32 (m, 1H).

^{13}C NMR (125 MHz, CDCl_3): 157.6, 150.3, 149.4, 148.1, 138.2, 136.9, 136.2, 128.5, 128.3, 128.1, 127.8, 127.4, 123.7, 122.8, 120.2, 74.3, 70.2, 67.7, 66.3, 55.4, 50.2, 39.1, 33.4, 29.6, 24.3, 19.3.

HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{33}\text{N}_5\text{O}_4+\text{H}^+$ 528.2605, found 528.2601.

IR (neat): 3399, 3059, 2925, 2856, 2024, 1685, 1601, 1495, 1469, 1421, 1351, 1128, 1084, 1045 cm^{-1} .

(2R,3S)-2-((S)-2-hydroxy-3-(4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)propyl)piperidin-3-ol (B10):



Yield: 80 mg, 85%.

TLC: R_f : 0.2 (20% MeOH/ CHCl_3).

^1H NMR (500 MHz, CD_3OD): δ 8.06 (d, 1H, $J=7.0$ Hz), 7.93 (t, 1H, $J=7.5$ Hz), 7.40 (t, 1H, $J=5.5$ Hz), 4.63 (dd, 1H, $J=3.5$ Hz, $J=14.0$ Hz), 4.56 (dd, 1H, $J=6.0$ Hz, $J=14$ Hz), 7.40 (t, 1H, $J=4.0$ Hz), 3.61 (bs, 1H), 3.28-3.33 (m, 1H), 3.18-3.21 (m, 1H), 3.00 (t, 1H, $J=12.0$ Hz), 2.35 (d, 1H, $J=15.0$ Hz), 2.07-2.10 (m, 1H), 1.95 (dt, 1H, $J=4.0$ Hz, $J=14.5$ Hz), 1.73-1.78 (m, 1H), 1.54-1.63 (m, 2H).

^{13}C NMR (125 MHz, CD_3OD): 148.6, 144.9, 142.7, 140.1, 128.9, 126.8, 125.5, 68.1, 67.4, 59.8, 57.2, 45.0, 33.7, 31.9, 23.4, 21.6.

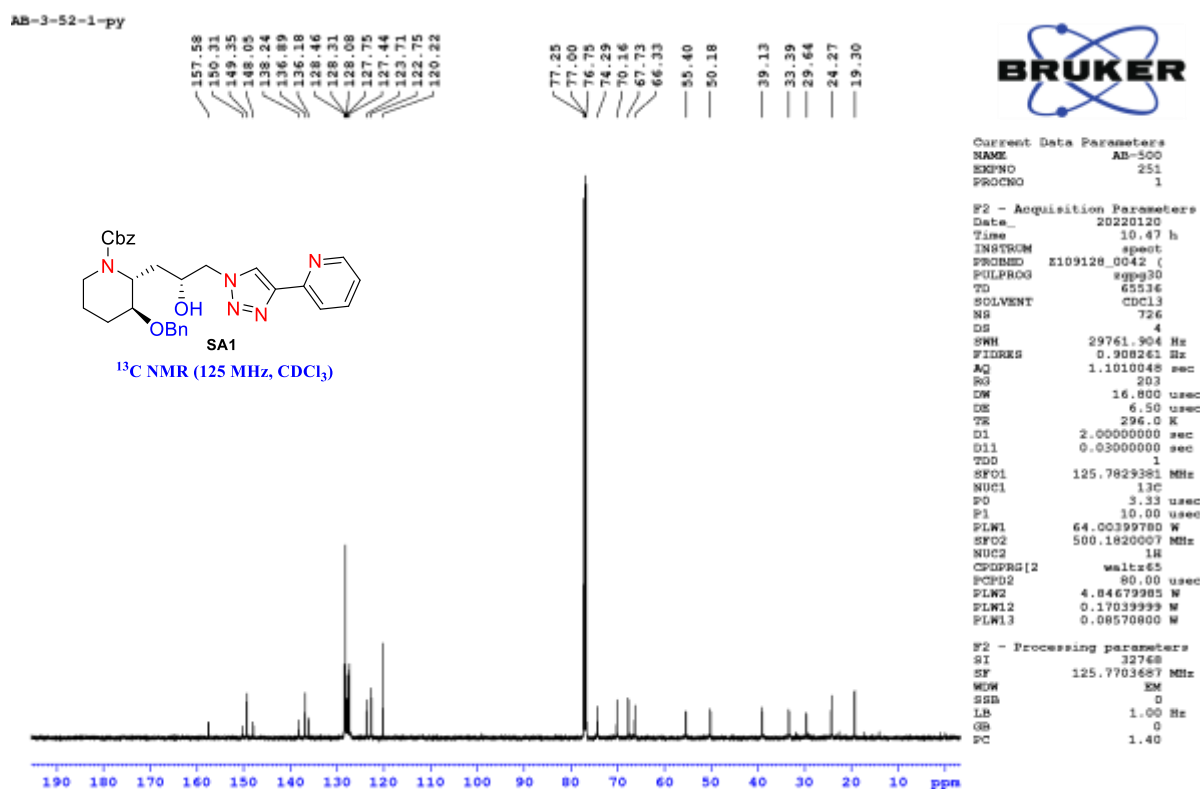
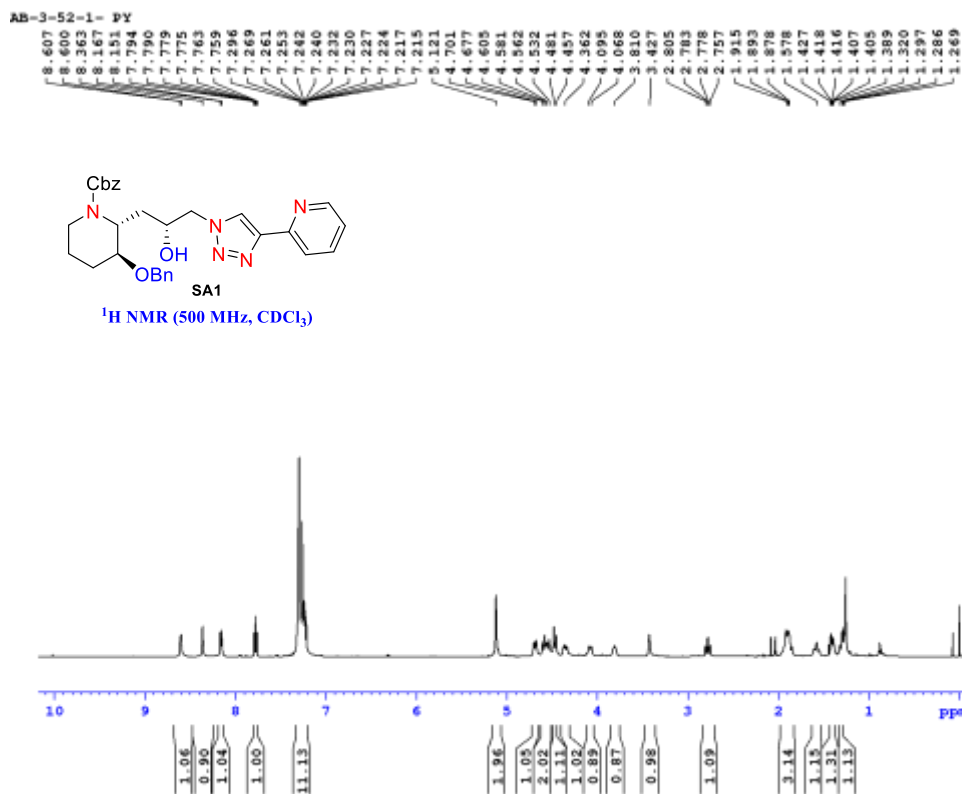
HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{21}\text{N}_5\text{O}_2+\text{H}^+$ 304.1768, found 304.1762.

IR (neat): 3030, 2941, 2862, 1688, 1495, 1423, 1313, 1249, 1198, 1132 cm^{-1} .

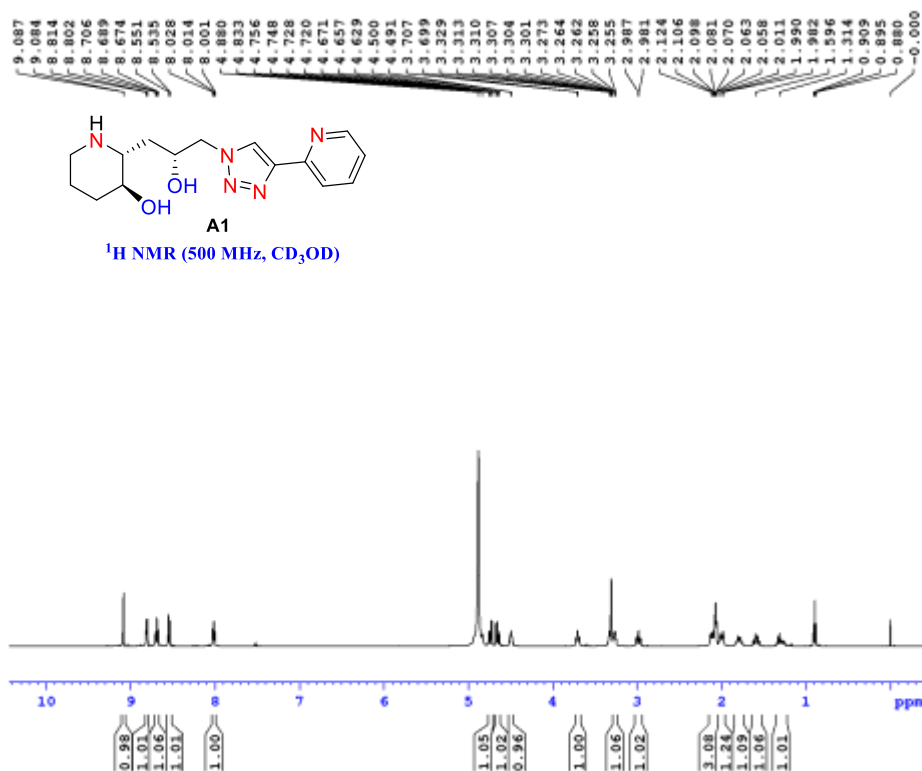
4.5 Reference:

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AB-3-60-1-PY

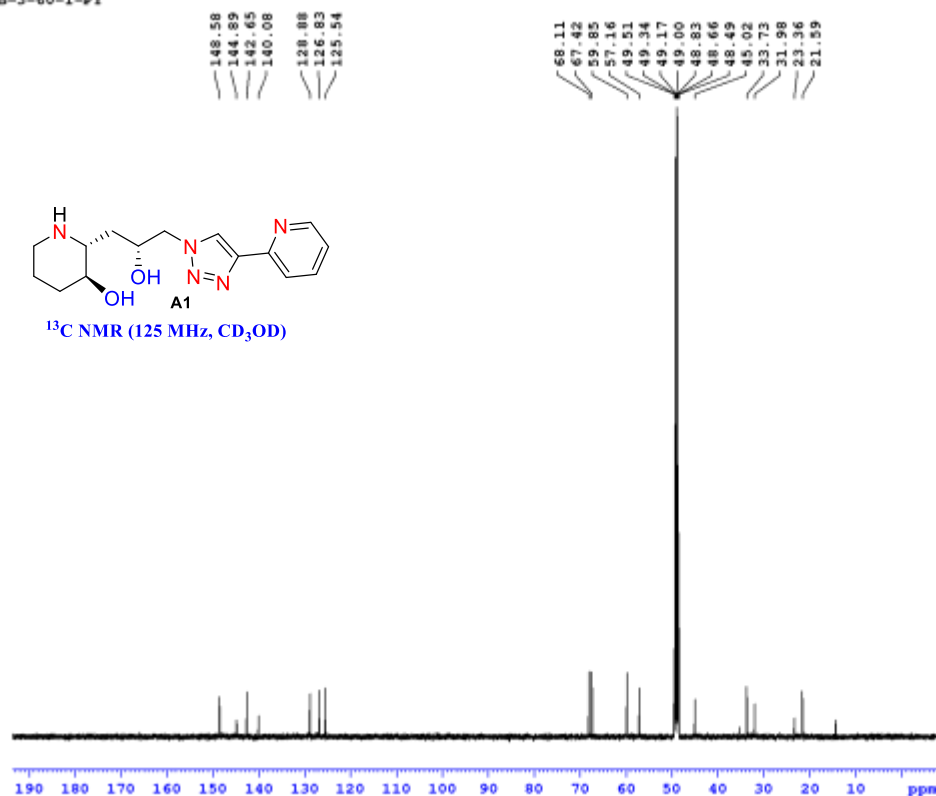


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 PROCNO 1

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 SOLVENT MeOD
 NS 16
 DS 2
 SWE 10000.000 Hz
 FIDRES 0.305176 Hz
 AQ 3.2767999 sec
 RG 95.6
 DW 50.000 usec
 DE 6.50 usec
 TE 298.2 K
 D1 1.00000000 sec
 TDO 1
 SFO1 500.3720098 MHz
 NUC1 1H
 P1 8.00 usec
 PLW1 12.18000031 W

F2 - Processing parameters
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 WDW EM
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 PC 1.00

AB-3-60-1-PY

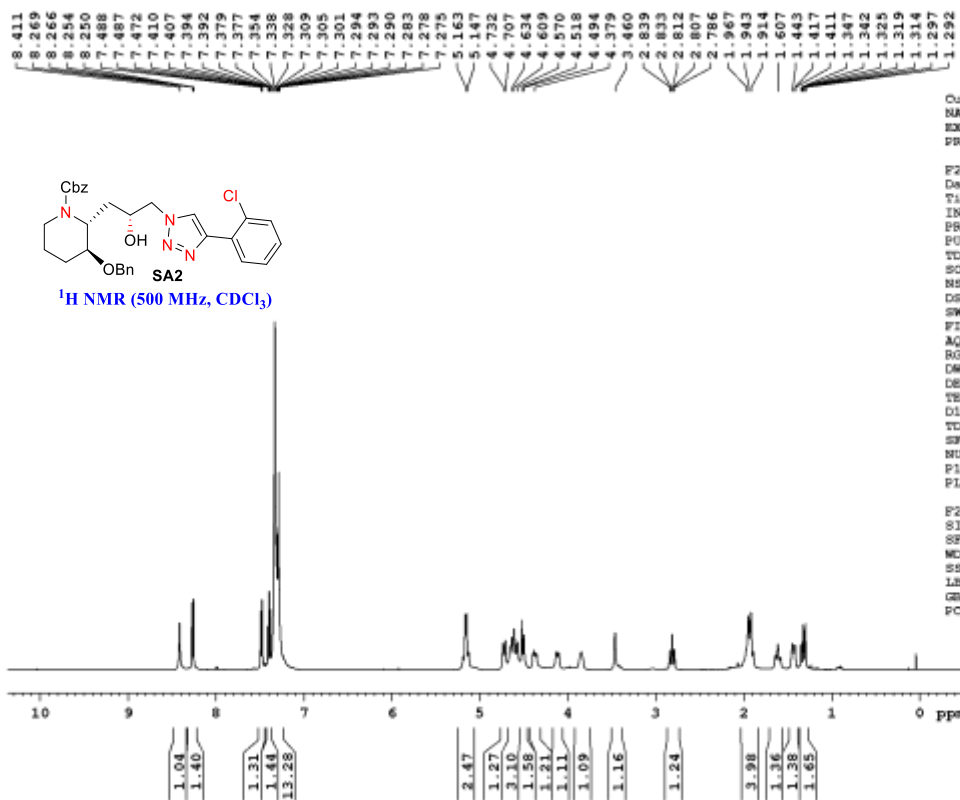


Current Data Parameters
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 EXPNO 503
 PROCNO 1

F2 - Acquisition Parameters
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 PULPROG zgpg30
 TD 65536
 SOLVENT MeOD
 NS 1524
 DS 4
 SWE 29761.904 Hz
 FIDRES 0.908261 Hz
 AQ 1.1010048 sec
 RG 15.92
 DW 16.800 usec
 DE 6.50 usec
 TE 298.2 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TDO 1
 SFO1 125.8304669 MHz
 NUC1 13C
 P1 12.00 usec
 PLW1 172.66999817 W
 SFO2 500.3710015 MHz
 NUC2 1H
 CPDPRG2 waltz16
 PCPD2 80.00 usec
 PLW2 12.18000031 W
 PLW12 0.12180000 W
 PLW13 0.06126500 W

F2 - Processing parameters
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 SSB 0
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 GB 0
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AB-3-103-1-2 C1

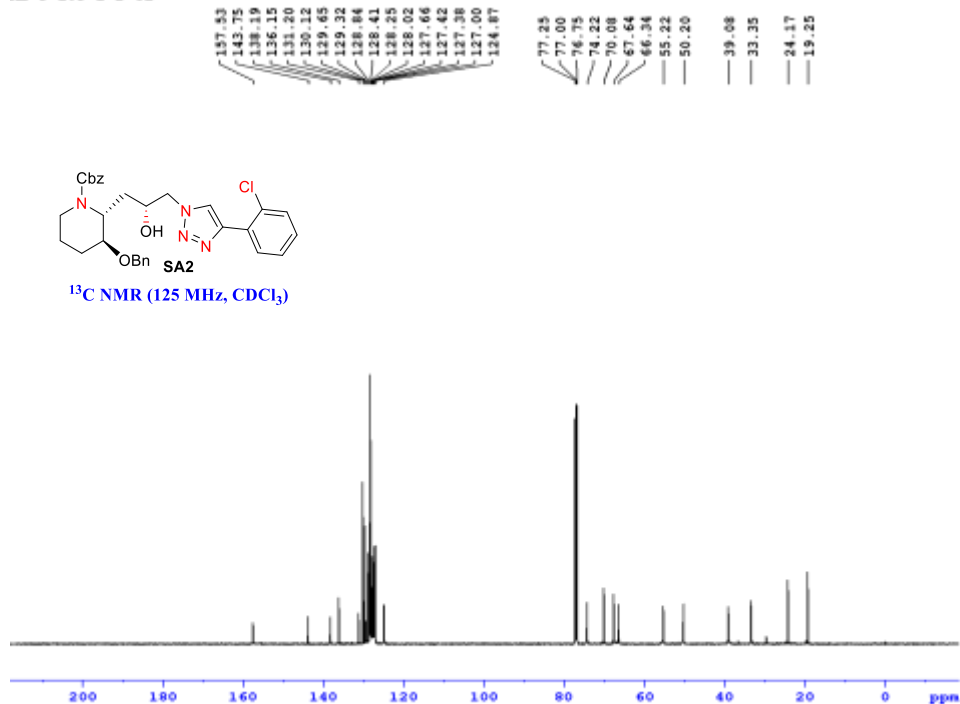


Current Data Parameters
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PROCNO 1

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PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 31.25
CW 50.000 used
DE 6.50 usec
TE 298.5 K
D1 1.00000000 sec
TDO 1
SFO1 500.3720898 MHz
NUC1 1H
P1 10.00 usec
PLW1 23.23100090 W

F2 - Processing parameters
SI 65536
SF 500.3690000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

AB-3-103-1-2 C1

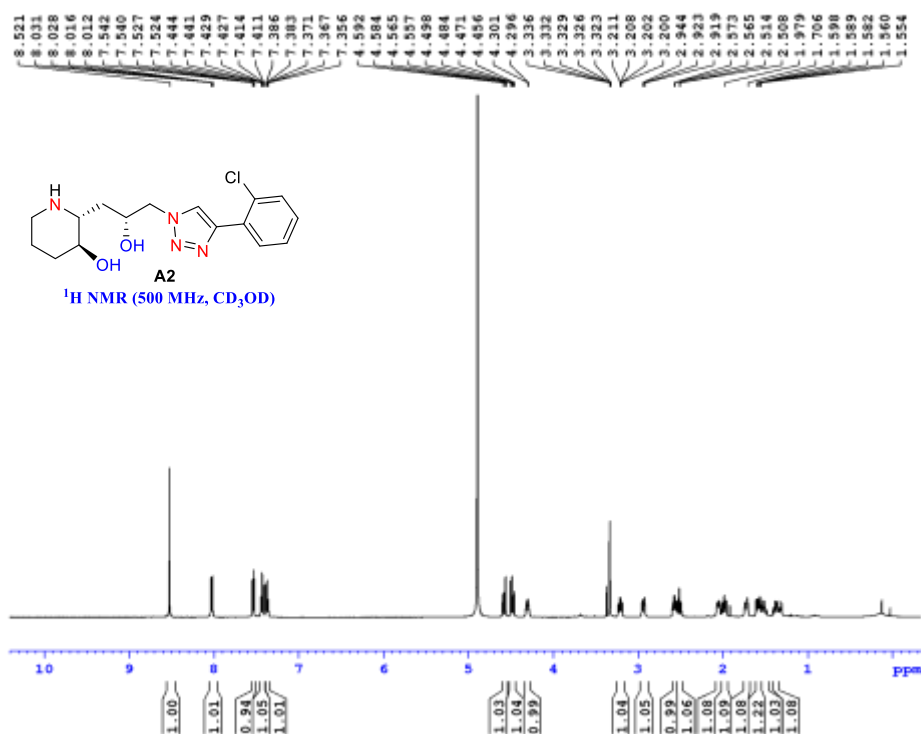


Current Data Parameters
NAME AB-500 Ascend
EXPNO 521
PROCNO 1

F2 - Acquisition Parameters
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Time 14.20 h
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PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 2102
DS 4
SWH 29761.304 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 192.83
CW 16.000 used
DE 6.50 usec
TE 299.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1
SFO1 125.8304669 MHz
NUC1 13C
P1 10.00 usec
PLW1 115.01000214 W
SFO2 500.3710015 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 80.00 usec
PLW2 23.23100090 W
PLW12 0.36298999 W
PLW13 0.18257999 W

F2 - Processing parameters
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WDW EM
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GB 0
PC 1.40

AB-3-107-1-2C1

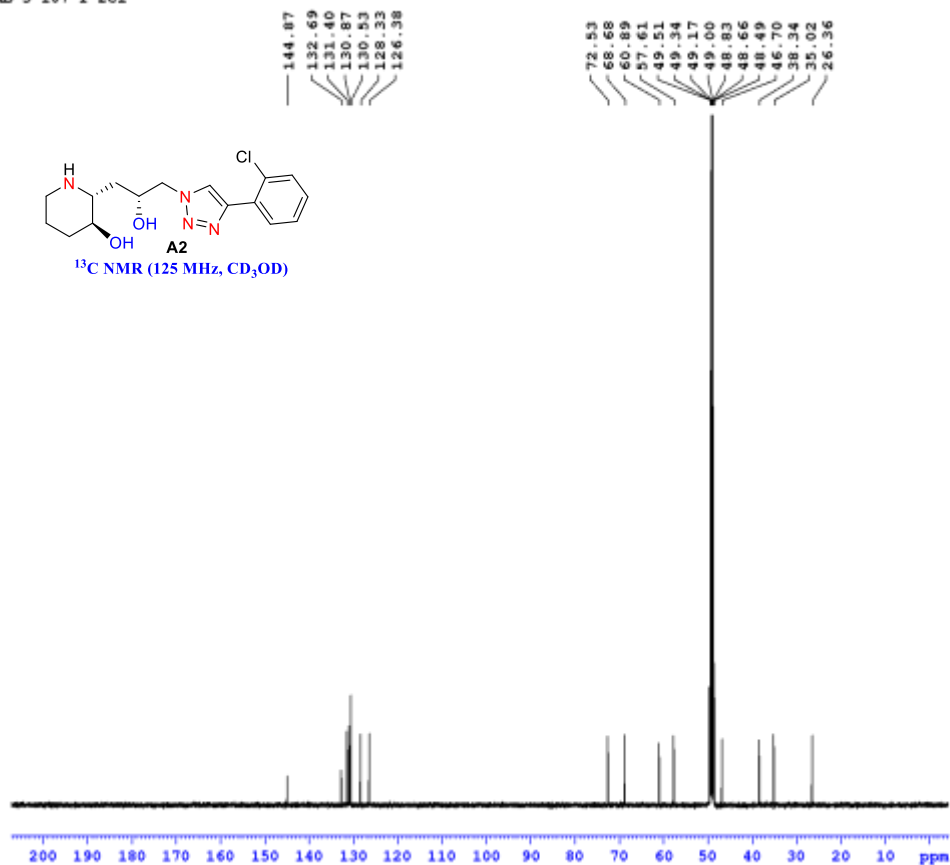


Current Data Parameters
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EXPNO 345
PROCNO 1

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TD 65536
SOLVENT MeOD
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 144
DW 50.000 usec
DE 13.04 usec
TE 300.6 K
D1 1.00000000 sec
TDO 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W

F2 - Processing parameters
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SF 500.1800000 MHz
WDW EM
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LB 0.30 Hz
GB 0
PC 1.00

AB-3-107-1-2C1

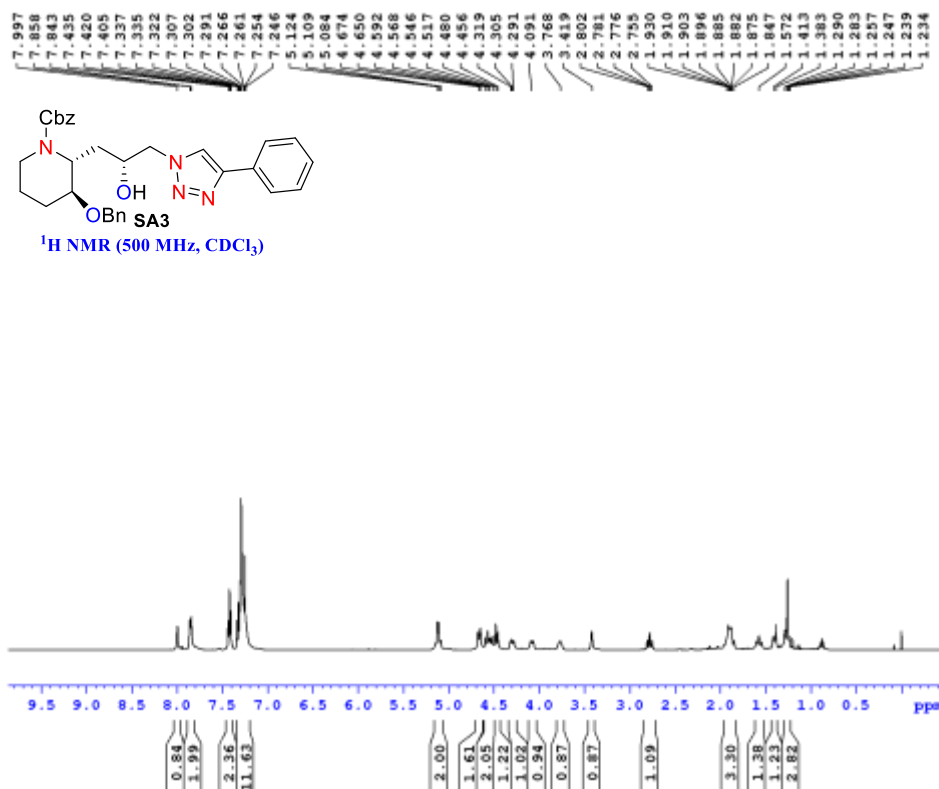


Current Data Parameters
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EXPNO 347
PROCNO 1

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TD 65536
SOLVENT MeOD
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SWH 23761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 301.4 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1
SFO1 125.7829381 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 64.00399780 W
SFO2 500.1820007 MHz
NUC2 1H
CPDPRG2 waltz65
PCPD2 80.00 usec
PLW2 4.84679985 W
PLW12 0.17039999 W
PLW13 0.08570800 W

F2 - Processing parameters
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WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

AB-3-43-SPOT-1

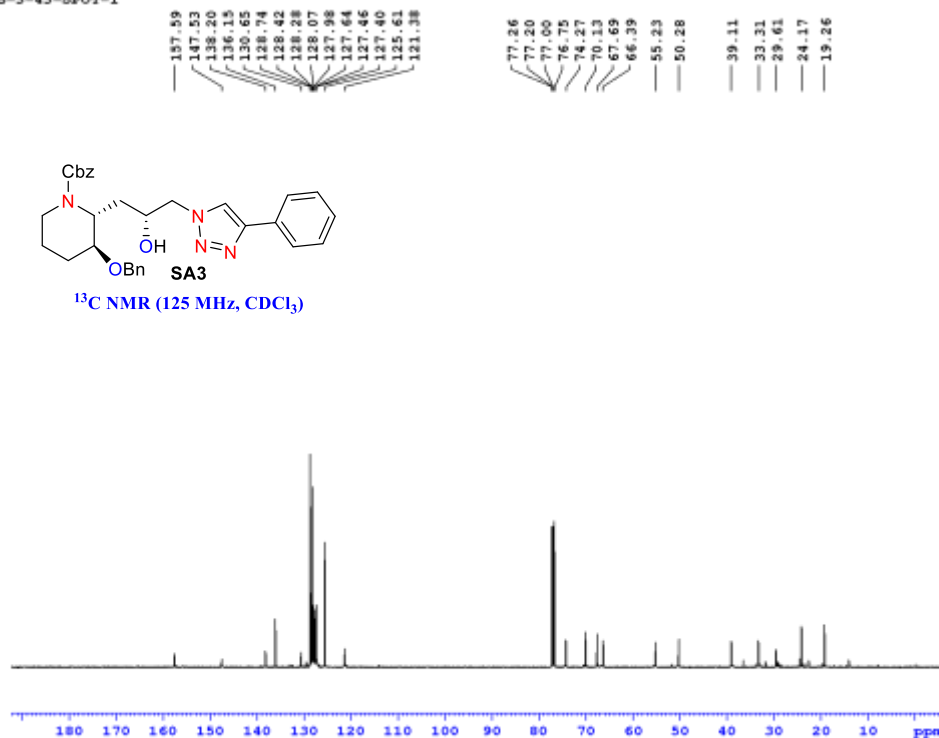


Current Data Parameters
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EXPNO 438
PROCNO 1

F2 - Acquisition Parameters
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PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 31.25
DM 50.000 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
SFO1 500.3720898 MHz
NUC1 1H
P1 10.00 usec
PLW1 23.23100090 W

F2 - Processing parameters
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SF 500.3690187 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

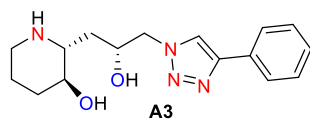
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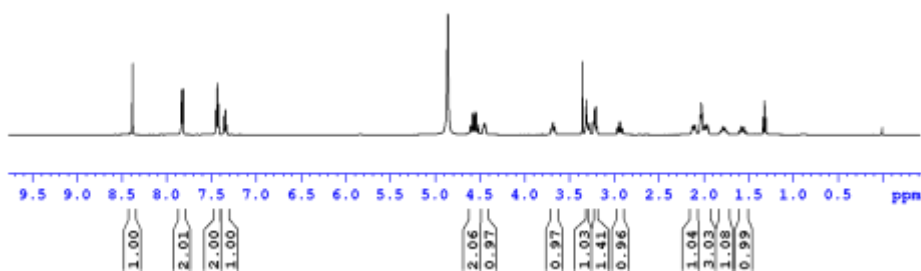
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EXPNO 440
PROCNO 1

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PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1766
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 192.83
DM 16.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8304669 MHz
NUC1 13C
P1 10.00 usec
PLW1 115.01000214 W
SFO2 500.3710015 MHz
NUC2 1H
CDPRG12 waltz16
PCPD2 80.00 usec
PLW2 23.23100090 W
PLW12 0.36298999 W
PLW13 0.18257999 W

F2 - Processing parameters
SI 52768
SF 125.8178986 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



¹H NMR (500 MHz, CD₃OD)



```

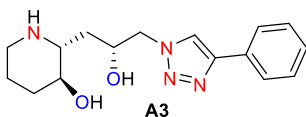
Current Data Parameters
NAME          AB-500 Ascend
RGFWND        486
PROCNO        1

F2 - Acquisition Parameters
Date_         20220401
Time          10.01 h
INSTRUM       spect
PROBHD        E125331_0034
PULPROG       zg30
TD            65536
SOLVENT       MeOD
NS            16
DS            2
SWH            10000.000 Hz
FIDRES        0.305176 Hz
AQ            3.2767999 sec
RG            76.68
DW            50.000 usec
DE            6.50 usec
TE            298.2 K
D1            1.00000000 sec
TDO           1
SFO1          500.372089 MHz
NUC1           1H
P1            8.00 usec
PLW1          12.18000031 W

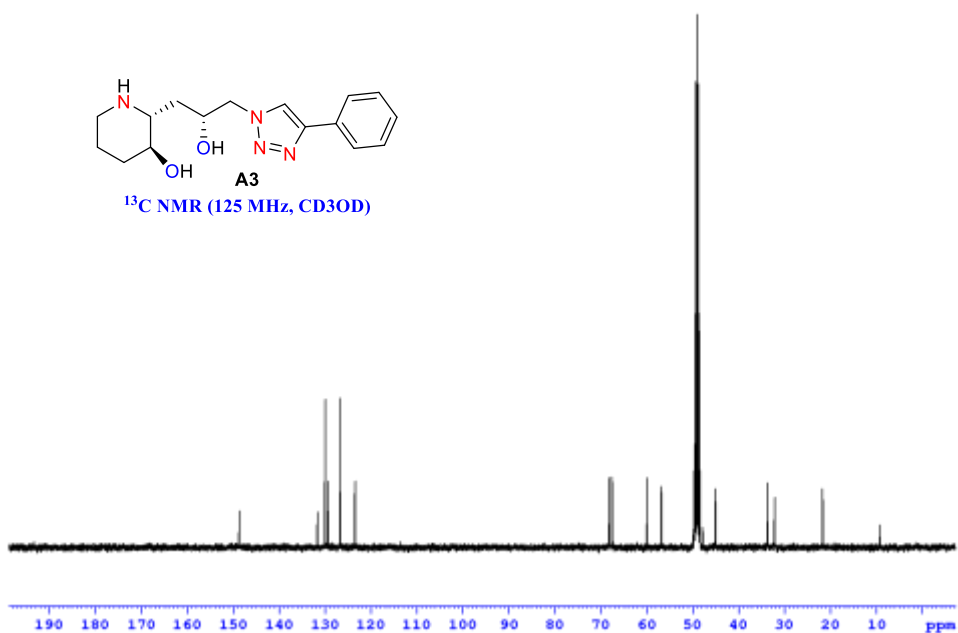
F2 - Processing parameters
SI            65536
SF            500.3690108 MHz
WDW           EM
SSB           0
LB            0.30 Hz
GB            0
PC            1.00

```

AB-3-43-1-Ph



^{13}C NMR (125 MHz, CD_3OD)



```

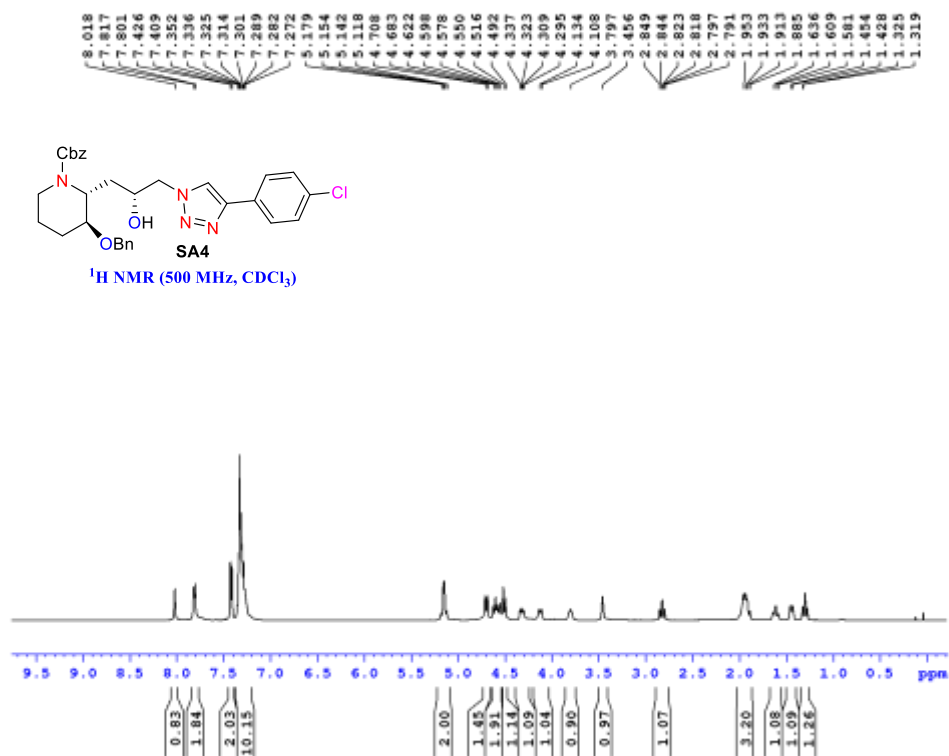
Current Data Parameters
NAME          AS-400
EXPNO         167
PROCNO        1

F2 - Acquisition Parameters
Date_         20220404
Time          10:49 h
INSTRUM       spect
PROBHD        X108618_0098 h
PULPROG       zgpg30
TD            65536
SOLVENT       MeOD
NS            1024
DS            4
SWH           24038.461 Hz
FIDRES        0.733596 Hz
AQ            1.3631488 sec
RG            203
DM            20.800 usec
DE            6.50 usec
TE            433.1 K
D1            2.0000000 sec
d11           0.0300000 sec
TD0           1
SFO1          100.6130223 MHz
NUC1          13C
P0            1.30 usec
PC1           3.00 usec
PLW1          49.4399963 W
SFO2          400.0926004 MHz
NUC2          1H
CPCORRG[2]   waltz165
PCPD2         90.00 usec
PLW2          15.18599907 W
PLW12         0.41622999 W
PLW13         0.2093600 W

F2 - Processing parameters
SI            32768
SF            100.6028254 MHz
RG            8M
NW            0
LB            1.00 Hz
GB            0
PC            1.40

```

AB-3-54-1-4C1

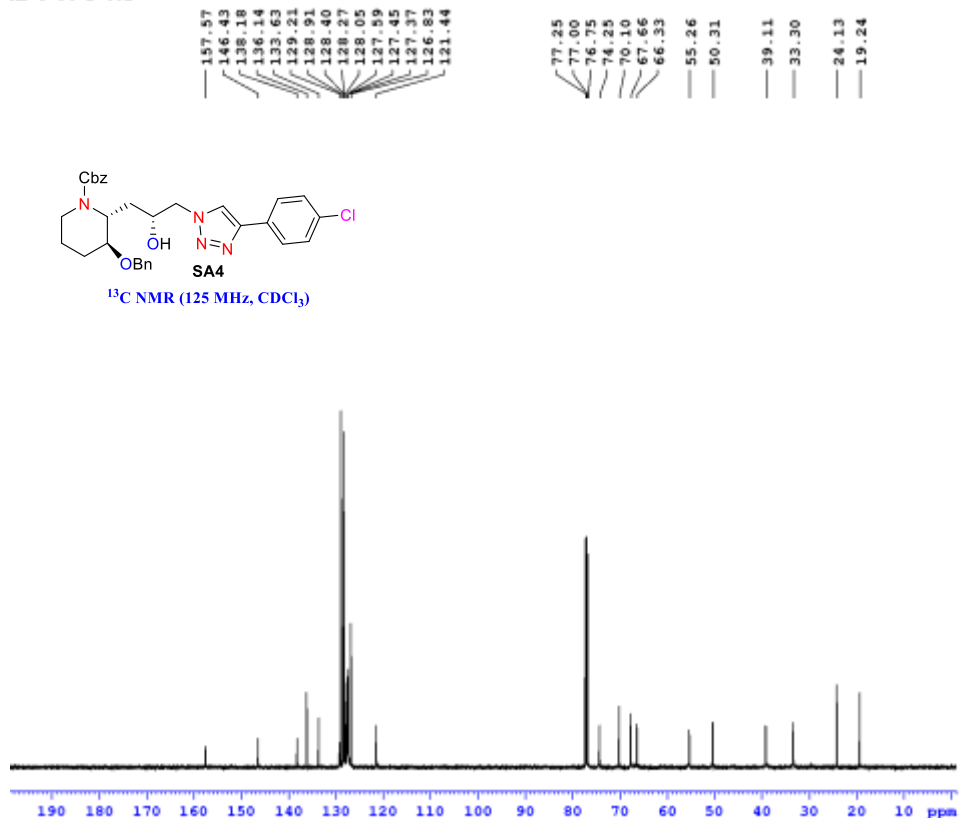


Current Data Parameters
NAME AB-500
EXPNO 302
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220404
Time 16.41 h
INSTRUM spect
PROBHD E109128.0042 (zg30)
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 57
DM 50.000 usec
DE 13.04 usec
TE 298.5 K
D1 1.00000000 sec
TDO 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W

F2 - Processing parameters
SI 65536
SF 500.1800000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

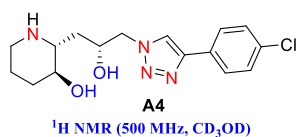
AB-3-54-1-4C1



Current Data Parameters
NAME AB-500
EXPNO 306
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220405
Time 10.14 h
INSTRUM spect
PROBHD E109128.0042 (zgpg30)
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 341
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 203
DM 16.800 usec
DE 6.50 usec
TE 296.6 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1
SFO1 125.7829381 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 64.00399780 W
SFO2 500.1820007 MHz
NUC2 1H
CPOPRG2 waltz16
PCPD2 80.00 usec
PLW2 4.84679985 W
PLW12 0.17039999 W
PLW13 0.08570800 W

F2 - Processing parameters
SI 32768
SF 125.7703765 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



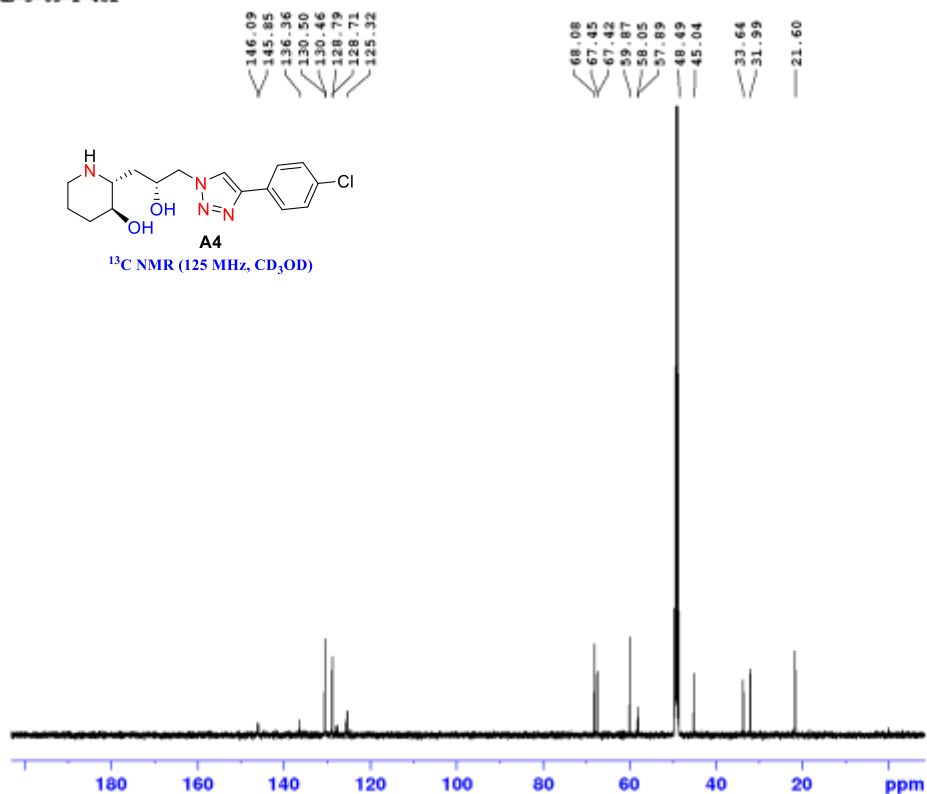
```

Current Data Parameters
NAME          AB-500
EXPNO         311
PROCNO        1

F2 - Acquisition Parameters
Date_         20220407
Time          16.57 h
INSTRUM       spect
PROCNO        109128_0042
PULPROG       zg30
TD            65536
SOLVENT       MeCO
NS            16
DS            2
SWH           10000.000 Hz
FIDRES        0.305176 Hz
AQ            3.2767999 sec
RG            144
CW            50.000 usec
DE            13.04 usec
TE            297.3 K
D1            1.00000000 sec
TDO           1
SFO1          500.1830886 MHz
NUC1           1H
PC            15.00 usec
PL1           0.00000000
PL2           4.84679985 W

F2 - Processing parameters
SI            65536
SF            500.1800000 MHz
WDW           EM
SSB           0
GB            0.00 Hz
PC            1.00

```



```

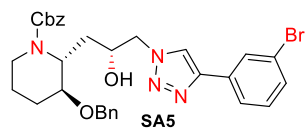
Current Data Parameters
NAME          ABC-500
EXPNO         313
PROCNO        1

F2 - Acquisition Parameters
Date_         20220405
Time          10.23 h
INSTRUM       spect
PROBHD        2109128_xq43
PULPROG       zgpg30
TD            65536
SOLVENT       MeCO
NS            1024
DS            4
SWH           23761.904  Hz
FIDRES       0.308261  Hz
AQ           1.1010048  sec
RG           203
CW           16.800  usec
DE           6.50  usec
TE           239.8  K
D1           2.00000000  sec
D11          0.03000000  sec
TD0          1
SF01         125.7829381  MHz
NUC1          13C
P0           3.33  usec
S1           10.00  usec
PLW1         44.00399780  W
SF02         500.18200007  MHz
NUC2          1H
CPCPD03[0]   waltz165
PCPD02       80.00  usec
PLW2         4.84673985  W
PLW12        0.17039999  W
PLW13        0.08570800  W

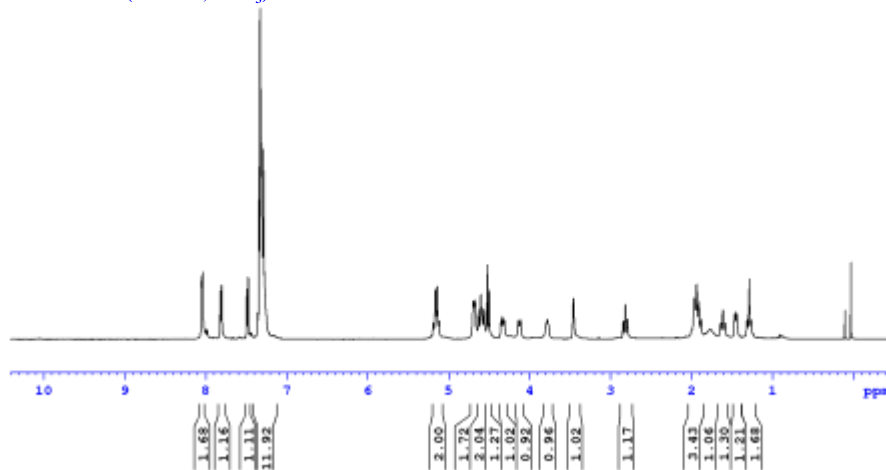
F2 - Processing parameters
SI            32768
SF            125.7701877  MHz
MCM           EM
SQR           0
LA            1.00  Hz
GB            0
PC            1.40

```

AB-3-102-1-3Br



¹H NMR (500 MHz, CDCl₃)

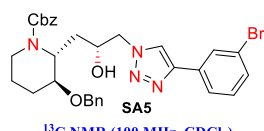


Current Data Parameters
NAME 500
EXPNO 142
PROCNO 1

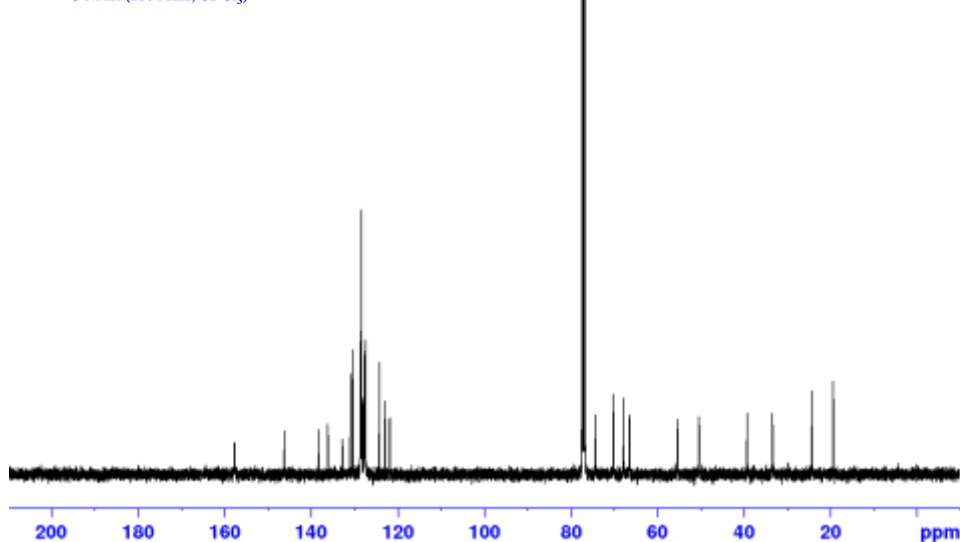
F2 - Acquisition Parameters
Date_ 20220505
Time 14.37 h
INSTRUM spect
PROBHD Z109128.0042 ()
PULPROG zg30
TD 65536
SOLVENT cdcl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767939 sec
RG 128
CW 50.000 usec
DE 13.04 usec
TE 1787.8 K
D1 1.00000000 sec
TD0 1
SFO1 500.1330886 MHz
NUC1 13C
P0 5.00 usec
P1 15.00 usec
PL1 4.84673985 W

F2 - Processing parameters
SI 65536
SF 500.1330886 MHz
WDW EM
SSB 0
LA 0.30 Hz
GB 0
PC 1.00

AB-3-102-1-3Br



¹³C NMR (100 MHz, CDCl₃)

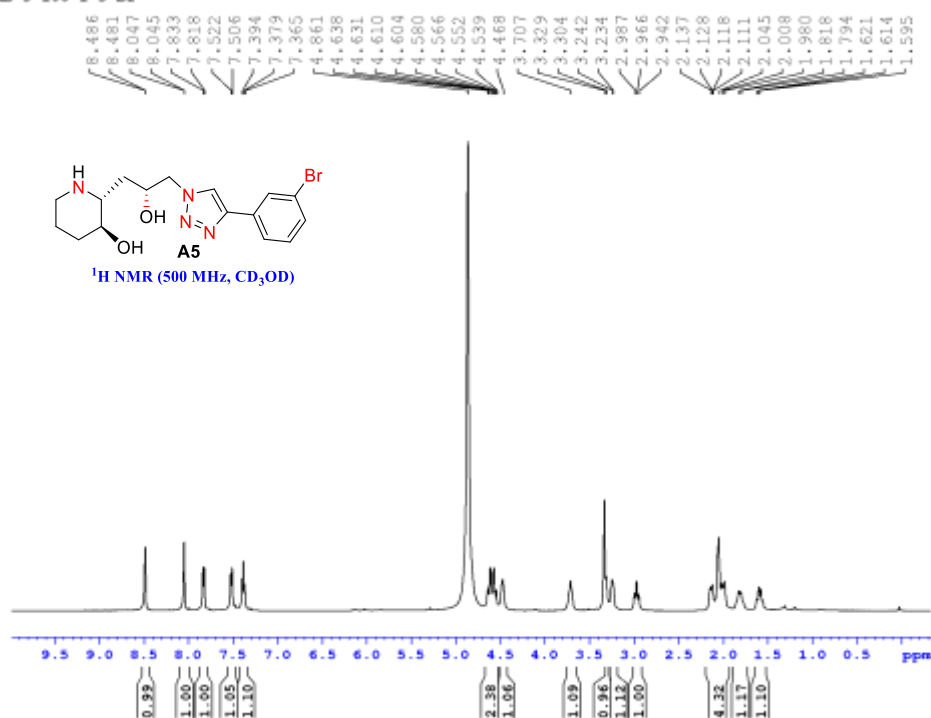


CUX
NAME AB-400
EXPNO 182
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220505
Time 12.28 h
INSTRUM spect
PROBHD Z108618.0098 ()
PULPROG zgpg30
TD 65536
SOLVENT cdcl3
NS 1024
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 203
CW 20.800 usec
DE 6.50 usec
TE 298.7 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6130223 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 49.43399863 W
SFO2 400.0926004 MHz
NUC2 1H
PCPDG[2] waltz165
PCPD2 90.00 usec
PLW2 15.18599987 W
PLW12 0.41422999 W
PLW13 0.20936000 W

F2 - Processing parameters
SI 32768
SF 100.6029700 MHz
WDW EM
SSB 0
LA 1.00 Hz
GB 0
PC 1.40

AB-3-108-1-3 Br

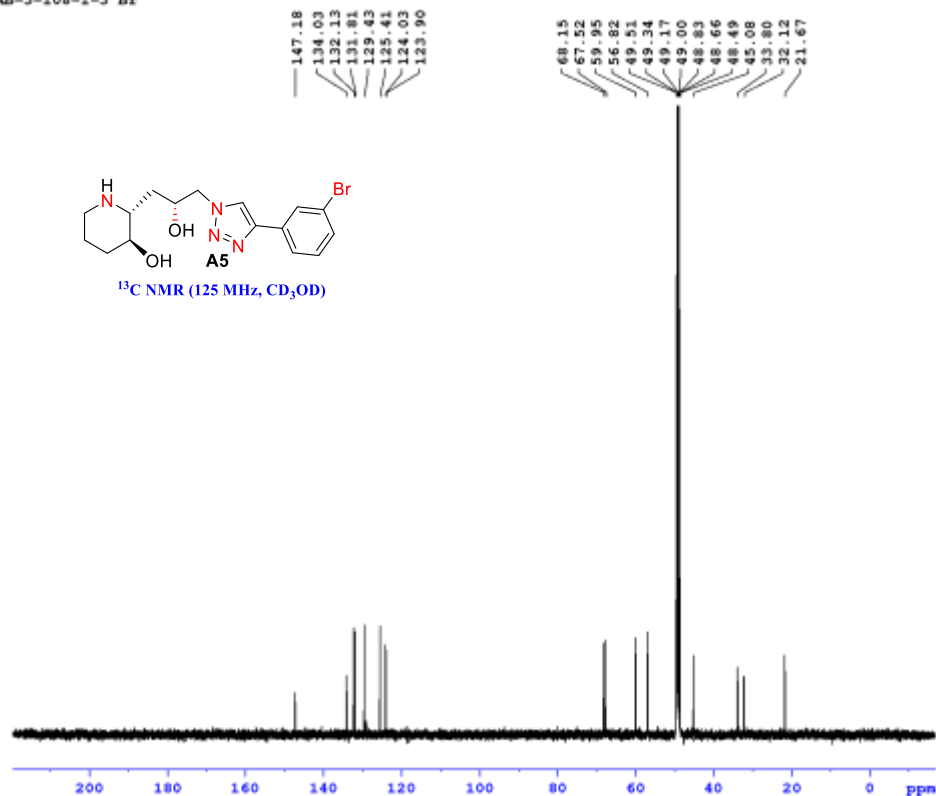


Current Data Parameters
NAME AB-500 Ascend
EXPNO 525
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220509
Time 16.06 h
INSTRUM spect
PROBHD Z119470.D291 (eg30
PULPROG zg30
TD 65536
SOLVENT MeOD
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 76.68
DW 50.000 usec
DE 6.50 usec
TE 298.5 K
D1 1.0000000 sec
TD0 1
SFO1 500.3720898 MHz
NUC1 1H
P1 10.00 usec
PLW1 23.23100090 W

F2 - Processing parameters
SI 65536
SF 500.3690000 MHz
WDW EM
SSB 0
LA 0.30 Hz
GB 0
PC 1.00

AB-3-108-1-3 Br

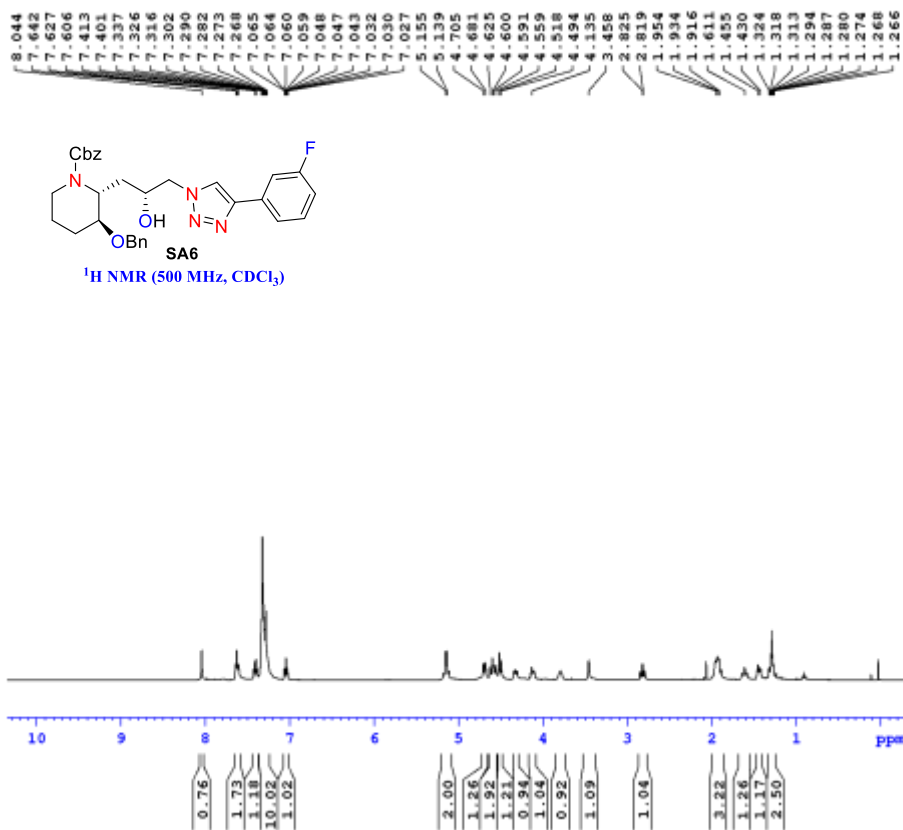


Current Data Parameters
NAME AB-500
EXPNO 349
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220511
Time 10.29 h
INSTRUM spect
PROBHD Z109128.0042 (zgpg30
PULPROG zgpg30
TD 65536
SOLVENT MeOD
NS 815
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 302.1 K
D1 2.0000000 sec
D11 0.0300000 sec
TD0 1
SFO1 125.7829381 MHz
NUC1 13C
PC 3.33 usec
P1 10.00 usec
PLW1 64.00399780 W
SFO2 500.1820007 MHz
NUC2 1H
CDEPRG[2] waltz65
PCPD2 80.00 usec
PLW2 4.84679985 W
PLW12 0.17039999 W
PLW13 0.08570800 W

F2 - Processing parameters
SI 32768
SF 125.7701881 MHz
WDW EM
SSB 0
LA 1.00 Hz
GB 0
PC 1.40

AB-3-51-1-3F

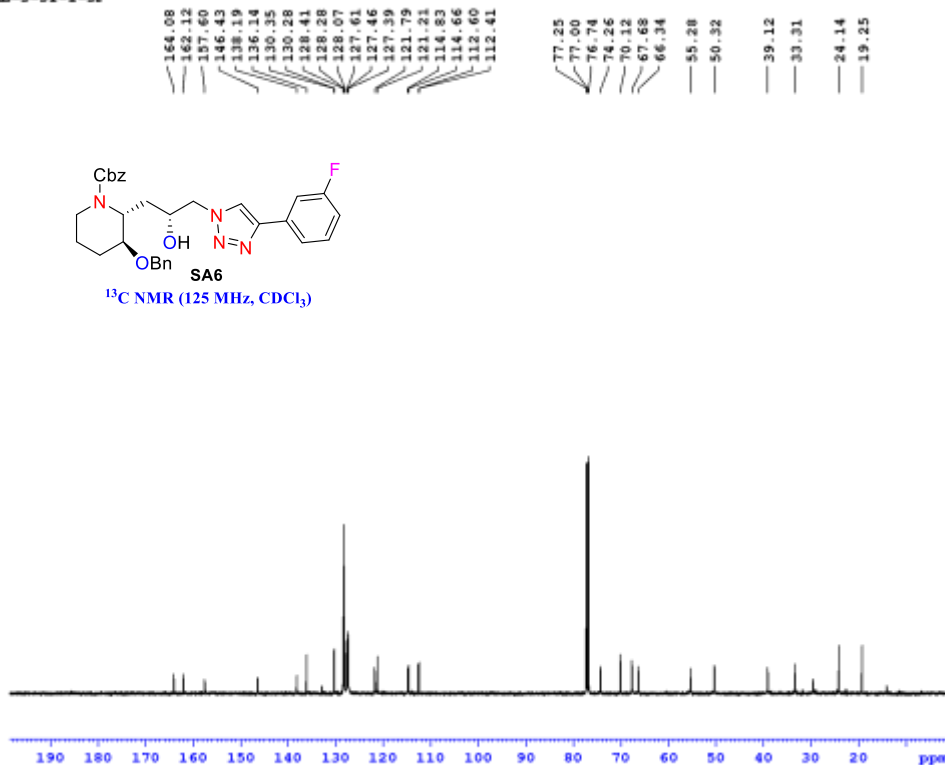


Current Data Parameters
NAME AB-500
EXPNO 252
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220124
Time 17.51 h
INSTRUM spect
PROBHD 5109128_0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 71.8
DM 50.000 usec
DE 13.04 usec
TE 296.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
PC 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W

F2 - Processing parameters
SI 65536
SF 500.1800000 MHz
WDM RM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

AB-3-51-1-3F

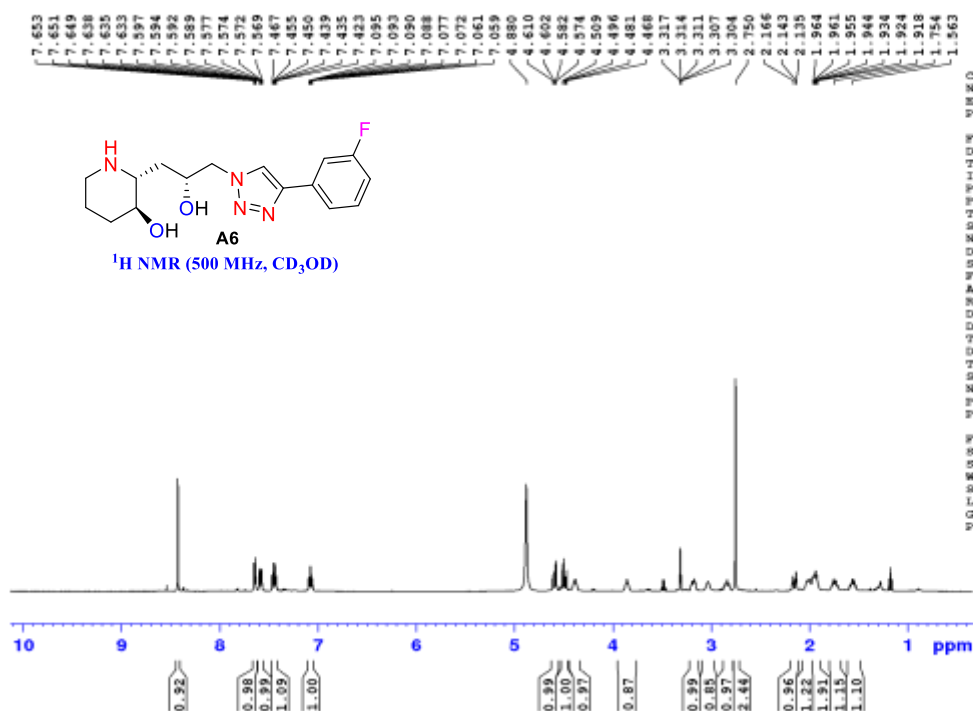


Current Data Parameters
NAME AB-500
EXPNO 254
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220125
Time 15.47 h
INSTRUM spect
PROBHD 5109128_0042 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 362
DS 4
SWH 29761.904 Hz
FIDRES 0.308261 Hz
AQ 1.1010048 sec
RG 203
DM 16.800 usec
DE 6.50 usec
TE 297.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.7829381 MHz
NUC1 13C
PC 3.33 usec
P1 10.00 usec
PLW1 64.00399780 W
SFO2 500.1820007 MHz
NUC2 1H
CPDPRG2 waltz165
PCPD2 80.00 usec
PLW2 4.84679985 W
PLW12 0.17039999 W
PLW13 0.08570800 W

F2 - Processing parameters
SI 32768
SF 125.7703746 MHz
WDM RM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

AB-3-61-1-3F

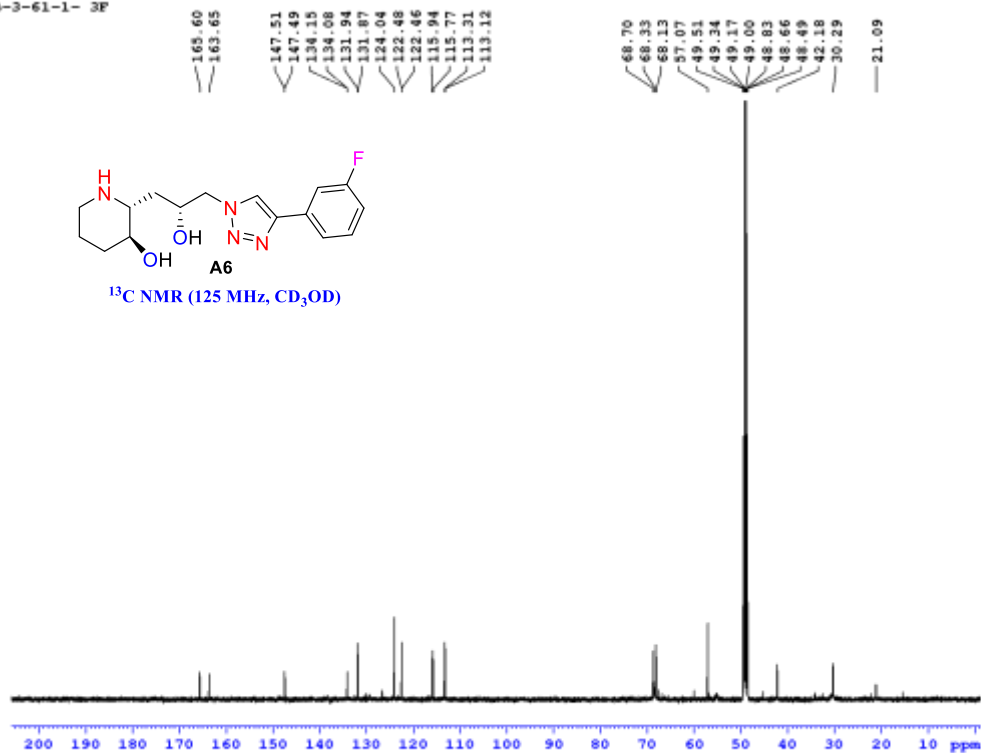


Current Data Parameters
 NAME Ascend-500
 EXPNO 489
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220401
 Time 10.20 h
 INSTRUM spect
 PROBRD E125331_0034 (
 PULPROG zg30
 TD 65536
 SOLVENT MeOD
 NS 16
 DS 2
 SWH 10000.000 Hz
 FIDRES 0.305176 Hz
 AQ 3.2747999 sec
 RG 54.81
 DW 50.000 usec
 DE 6.50 usec
 TE 298.1 K
 D1 1.00000000 sec
 TD0 1
 SFO1 500.3720898 MHz
 NUC1 1H
 P1 8.00 usec
 PLW1 12.18000031 W

F2 - Processing parameters
 SI 65536
 SF 500.3630091 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

AB-3-61-1- 3F

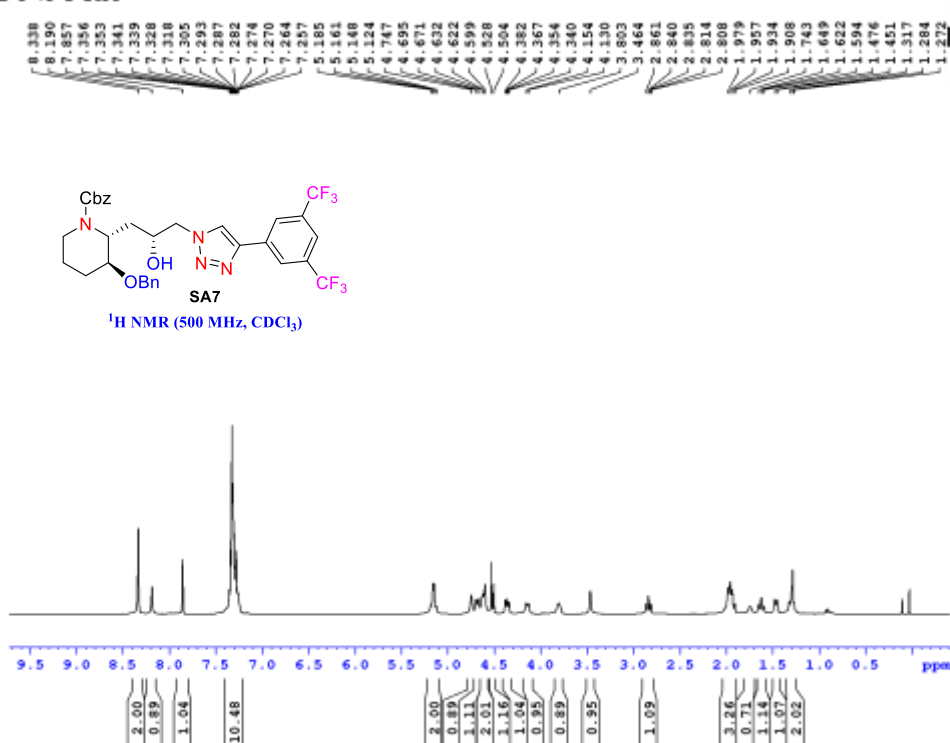


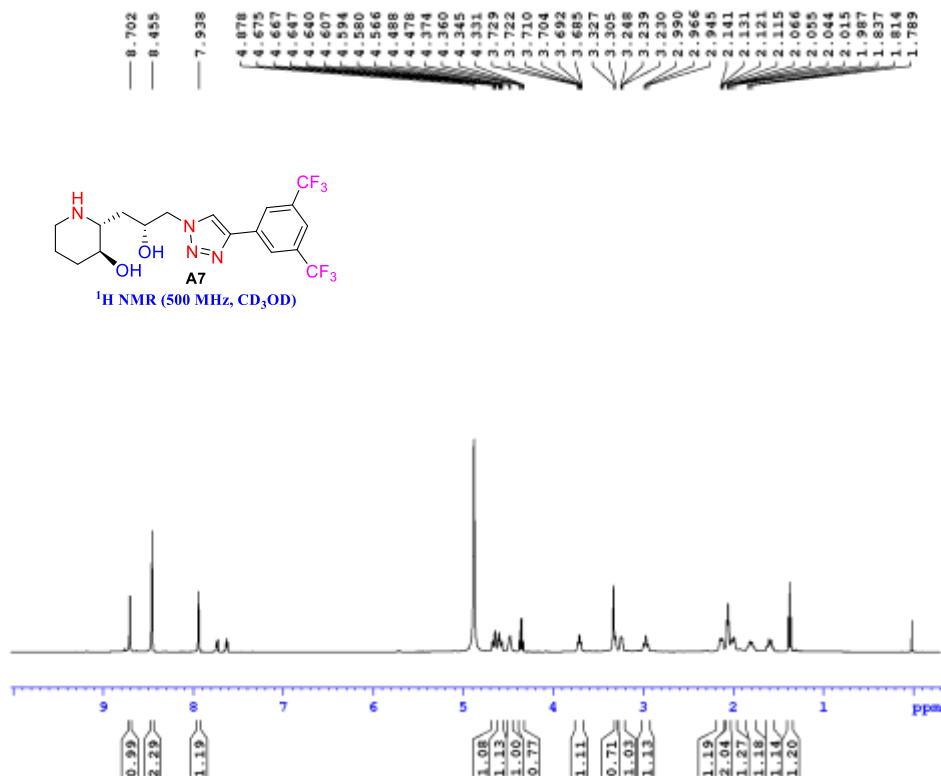
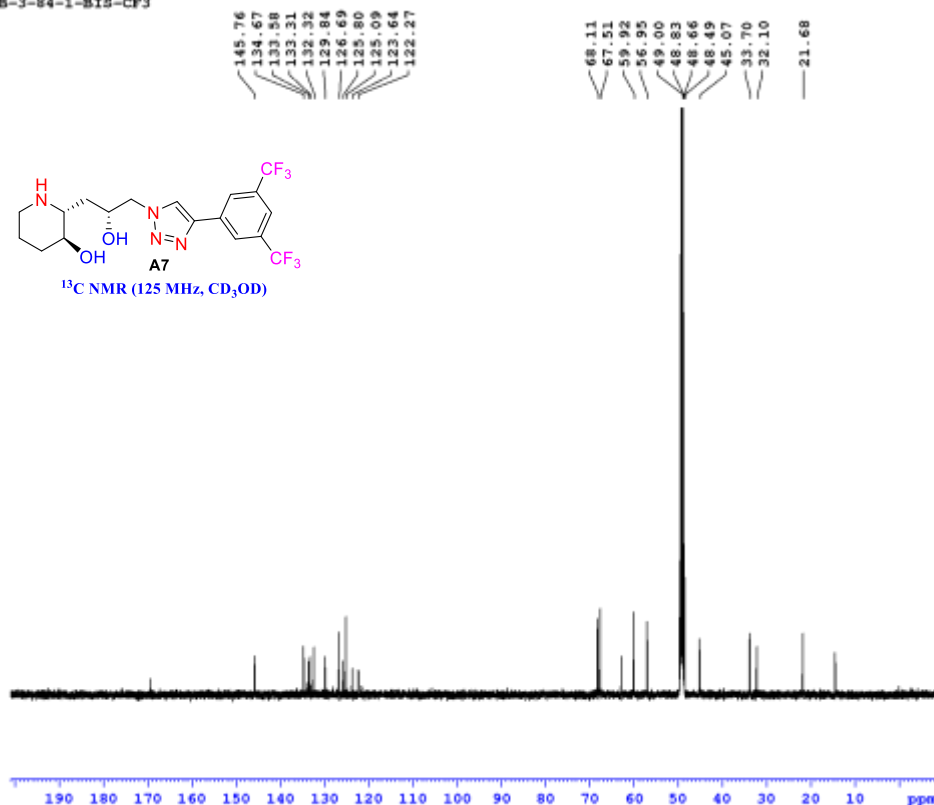
Current Data Parameters
 NAME AB-500 Ascend
 EXPNO 496
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220406
 Time 9.40 h
 INSTRUM spect
 PROBRD E125331_0034 (
 PULPROG zgpg30
 TD 65536
 SOLVENT MeOD
 NS 1687
 DS 4
 SWH 29761.904 Hz
 FIDRES 0.908261 Hz
 AQ 1.1010048 sec
 RG 22.23
 DW 16.800 usec
 DE 6.50 usec
 TE 299.2 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1
 SFO1 125.8304669 MHz
 NUC1 13C
 P1 12.00 usec
 PLW1 172.66999817 W
 SFO2 500.3710015 MHz
 NUC2 1H
 CPDPRG2 waltz16
 PCPD2 80.00 usec
 PLW2 12.18000031 W
 PLW12 0.12180000 W
 PLW13 0.06126500 W

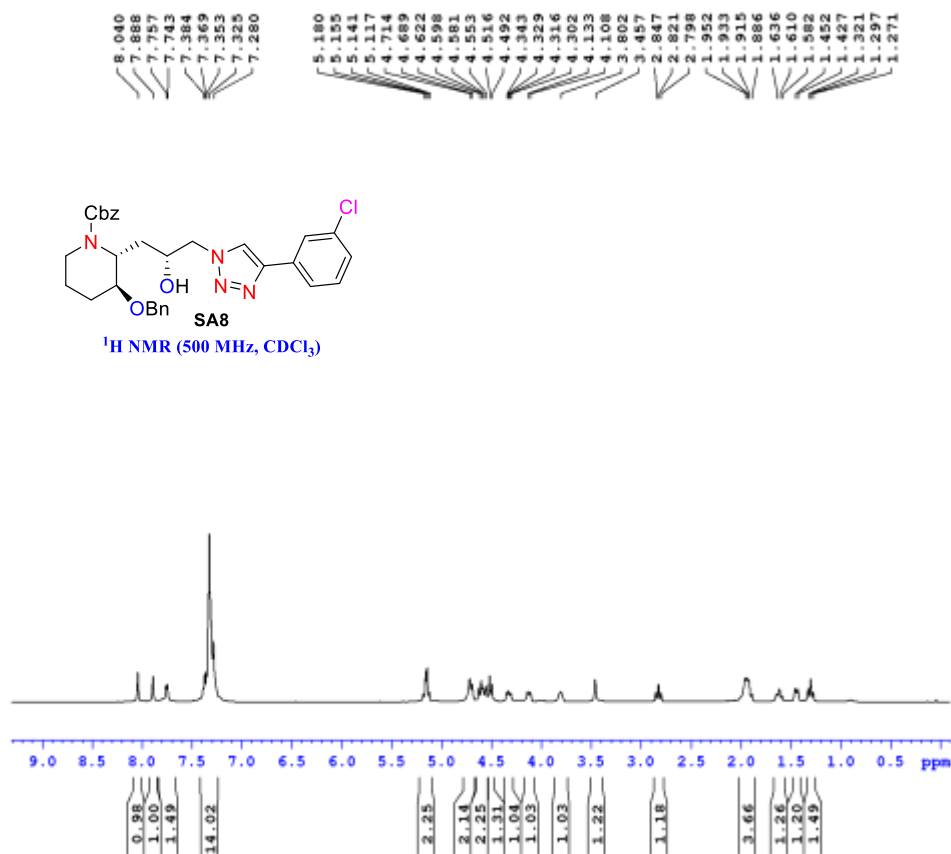
F2 - Processing parameters
 SI 32768
 SF 125.8177124 MHz
 WDW EM
 SSB 0
 LB 0.0 Hz
 GB 0
 PC 1.40

AB-3-73-1-2CF3



AB-3-84-1-Bis-CF₃AB-3-84-1-Bis-CF₃

AB-3-77-1-C1

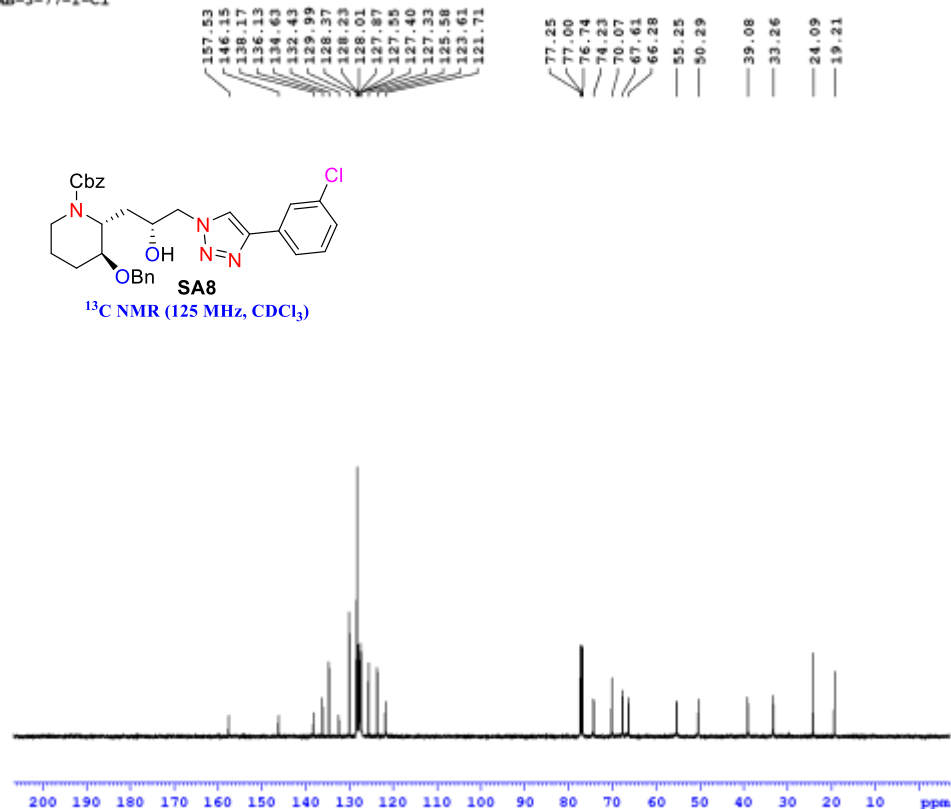


Current Data Parameters
NAME AB-500
EXPNO 277
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220310
Time 13.13 h
INSTRUM spect
PROBHD E109128.0042 (4
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 32
DW 50.000 usec
DE 13.04 usec
TE 297.1 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P1 5.00 usec
PL1 15.00 usec
PLW1 4.84679985 W

F2 - Processing parameters
SI 65536
SF 500.1800000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

AB-3-77-1-C1

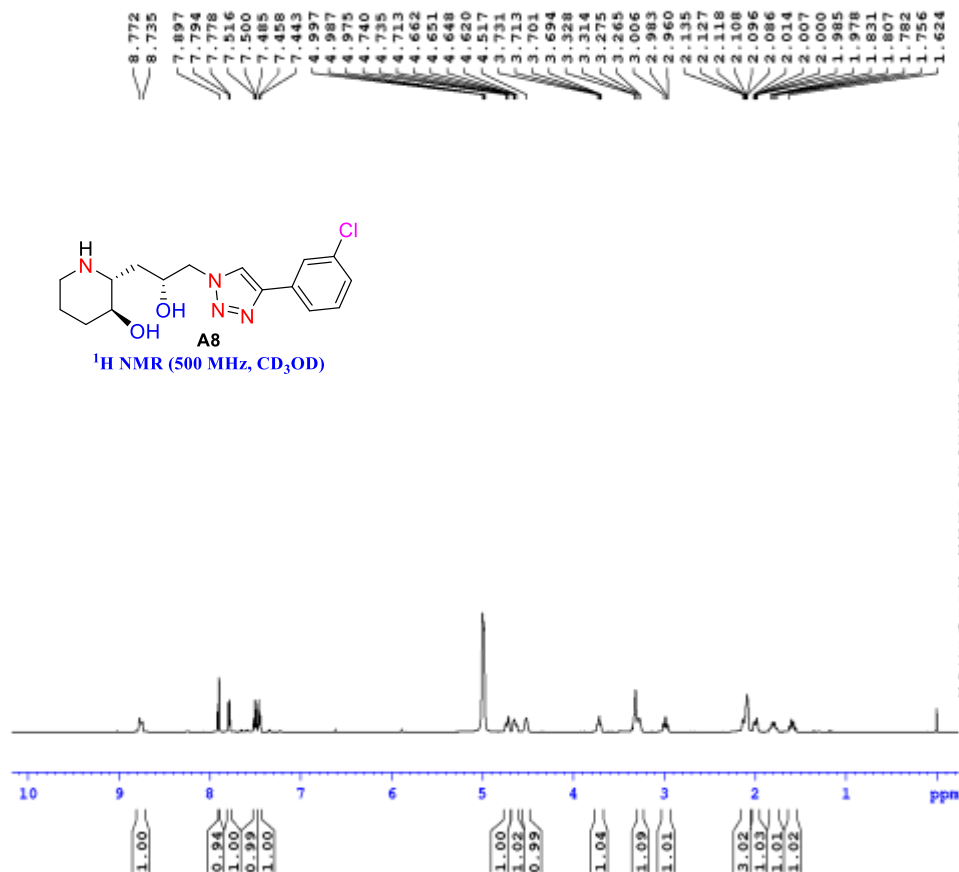


Current Data Parameters
NAME AB-500
EXPNO 278
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220310
Time 13.27 h
INSTRUM spect
PROBHD E109128.0042 (4
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 297.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.7829381 MHz
NUC1 13C
P1 3.33 usec
PL1 10.00 usec
PLW1 64.00399780 W
SFO2 500.1820007 MHz
NUC2 1H
CPDPRG2 waltz165
PCPD2 80.00 usec
PLW2 4.84679985 W
PLW12 0.17033939 W
PLW13 0.08570800 W

F2 - Processing parameters
SI 32768
SF 125.7703813 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

AB-3-88-1-3CL

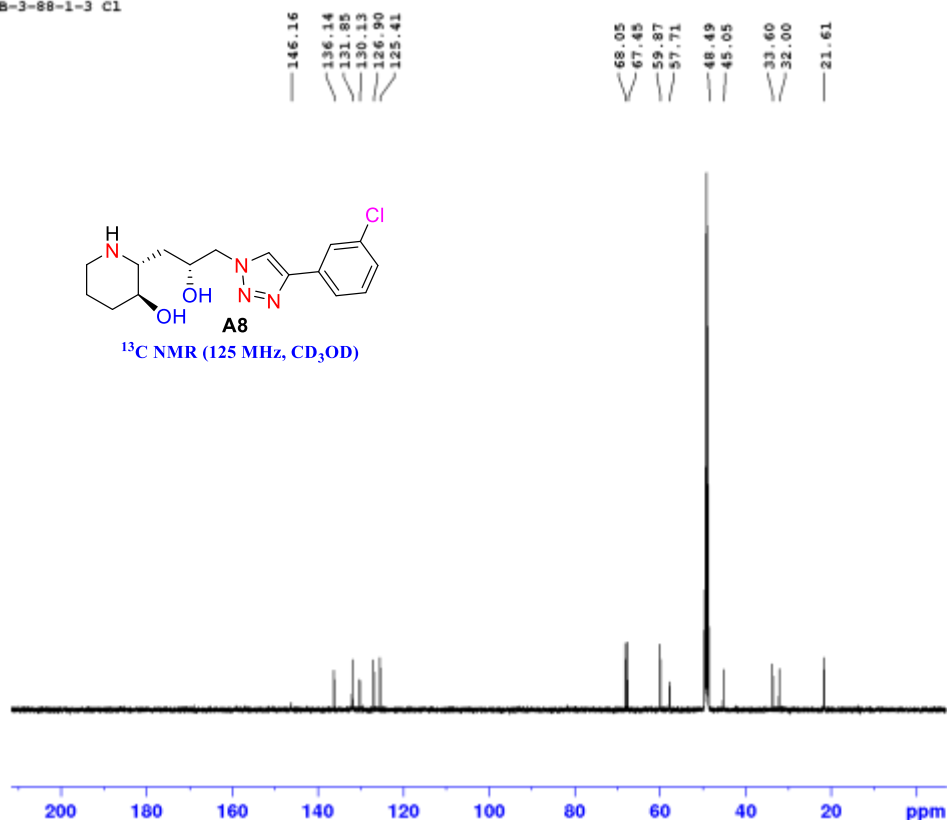


Current Data Parameters
 NAME AB-500 Ascend
 EXPNO 487
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220401
 Time 10.07 h
 INSTRUM spect
 PROBHD X125331_0034 (
 PULPROG zg30
 TD 65536
 SOLVENT MeOD
 NS 16
 DS 2
 SWH 10000.000 Hz
 FIDRES 0.305176 Hz
 AQ 3.2767999 sec
 RG 95.6
 DW 50.000 usec
 DE 6.50 usec
 TE 298.1 K
 D1 1.00000000 sec
 TDO 1
 SFO1 500.3720898 MHz
 NUC1 1H
 P1 8.00 usec
 PLW1 12.18000031 W

F2 - Processing parameters
 SI 65536
 SF 500.3690060 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

AB-3-88-1-3 C1

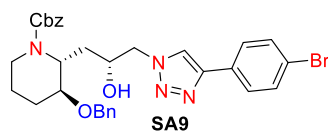


Current Data Parameters
 NAME AB-500
 EXPNO 108
 PROCNO 1

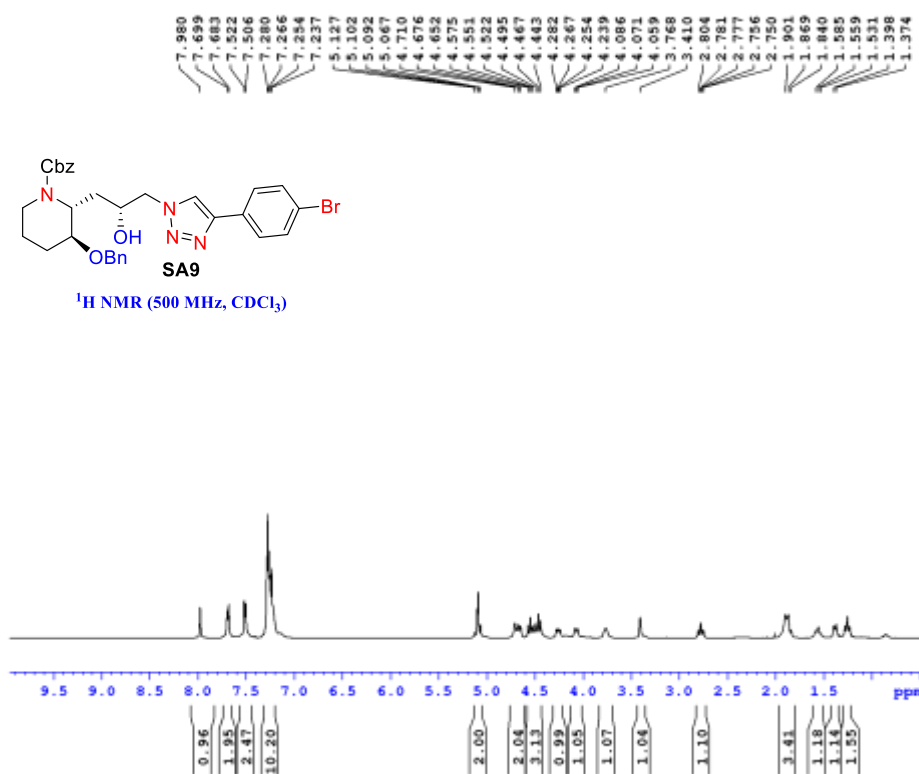
F2 - Acquisition Parameters
 Date_ 20220405
 Time 14.44 h
 INSTRUM spect
 PROBHD X109128_0042 (
 PULPROG zgpg30
 TD 65536
 SOLVENT MeOD
 NS 488
 DS 4
 SWH 29761.904 Hz
 FIDRES 0.908261 Hz
 AQ 1.1010048 sec
 RG 203
 DW 16.800 usec
 DE 6.50 usec
 TE 298.1 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TDO 1
 SFO1 125.7829381 MHz
 NUC1 13C
 P0 3.33 usec
 P1 10.00 usec
 PLW1 64.00399780 W
 SFO2 500.1820007 MHz
 NUC2 1H
 CPOPRG2 waltz45
 PCPD2 80.00 usec
 PLW2 4.84679985 W
 PLW12 0.17039999 W
 PLW13 0.08570800 W

F2 - Processing parameters
 SI 32768
 SF 125.7701906 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

AB-3-76-1- BR



¹H NMR (500 MHz, CDCl₃)

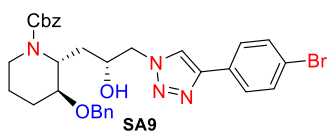


Current Data Parameters
NAME AB-500 Ascend
EXPNO 459
PROCNO 1

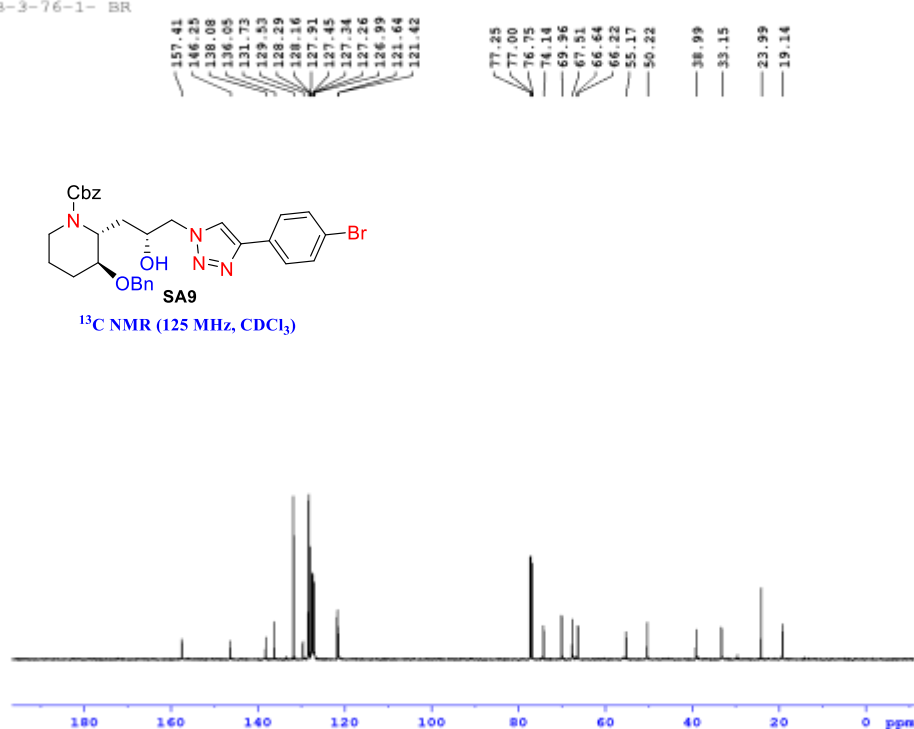
F2 - Acquisition Parameters
Date_ 20220310
Time 12.53 h
INSTRUM spect
PROBHD Z119470_0291 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 12.76
CW 50.000 usec
DE 6.50 usec
TE 294.9 K
D1 1.00000000 sec
TDO 1
SFO1 500.3720898 MHz
NUC1 1H
P1 10.00 usec
PLW1 23.23100090 W

F2 - Processing parameters
SI 65536
SF 500.3690234 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

AB-3-76-1- BR



¹³C NMR (125 MHz, CDCl₃)

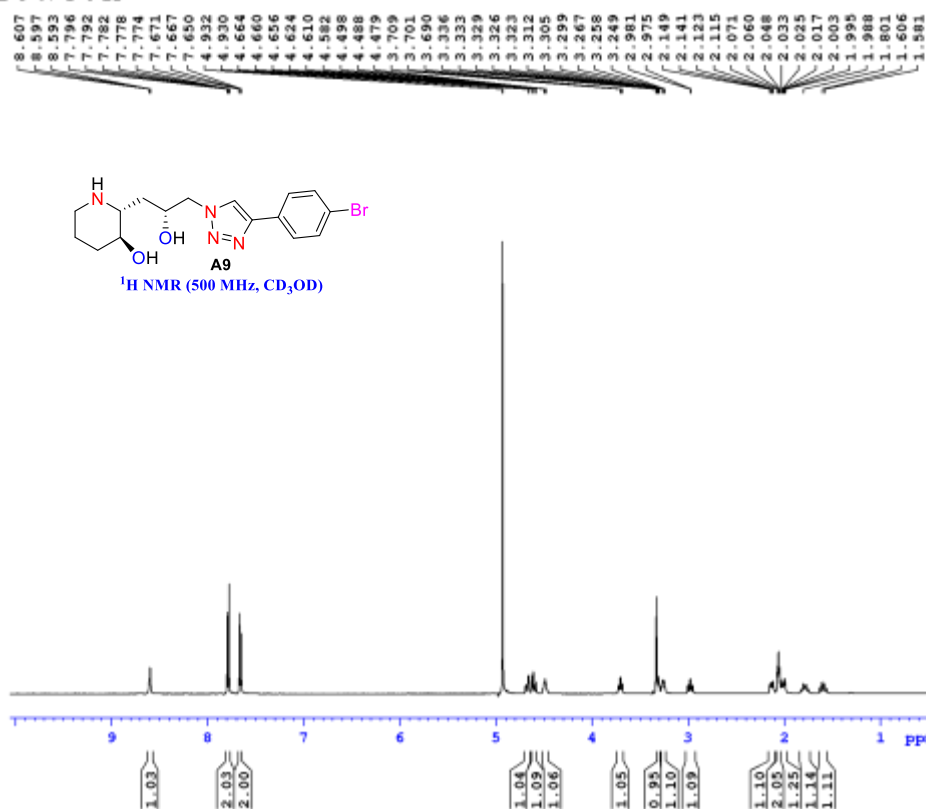


Current Data Parameters
NAME AB-500 Ascend
EXPNO 461
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220310
Time 13.13 h
INSTRUM spect
PROBHD Z119470_0291 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 162
DS 4
SWH 29761.304 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 192.83
CW 16.800 usec
DE 6.50 usec
TE 295.7 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1
SFO1 125.8304669 MHz
NUC1 13C
P1 10.00 usec
PLW1 115.01000214 W
SFO2 500.3710015 MHz
NUC2 1H
PCPGP2 waltz16
PCPD2 80.00 usec
PLW2 25.23100090 W
PLW12 0.36236999 W
PLW13 0.18257999 W

F2 - Processing parameters
SI 32768
SF 125.8179171 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

AB-3-87-1-4 Br



Current Data Parameters

NAME AB-500
EXPNO 316
PROCNO 1

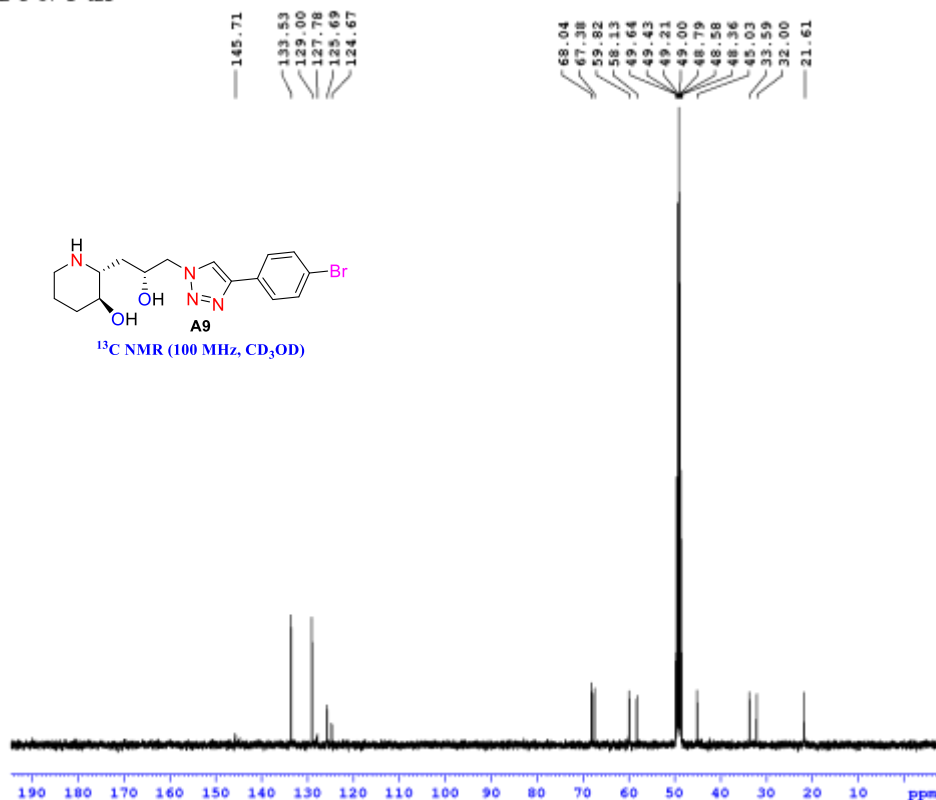
F2 - Acquisition Parameters

Date_ 20220418
Time 16.17 h
INSTRUM spect
PROBHD z109128_0042 {
PULPROG zg30
TD 65536
SOLVENT MeOD
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 161
SW 50.000 usec
DE 13.04 usec
TE 297.7 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W

F2 - Processing parameters

SI 65536
SF 500.1800000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

AB-3-87-1-4Br



Current Data Parameters

NAME AB-400
EXPNO 165
PROCNO 1

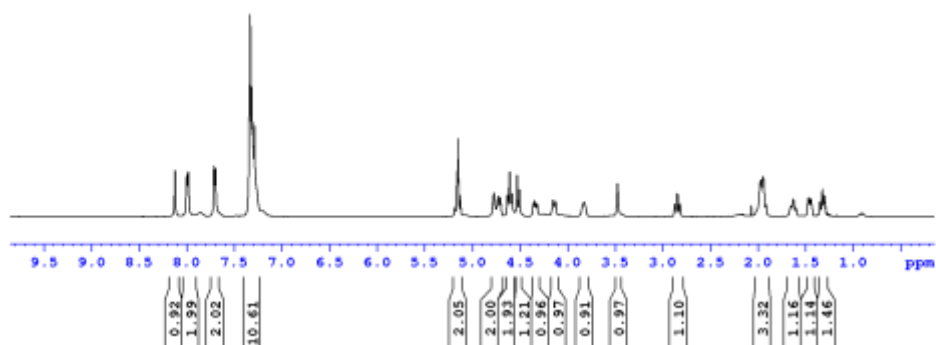
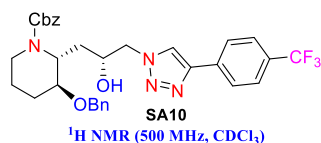
F2 - Acquisition Parameters

Date_ 20220331
Time 14.28 h
INSTRUM spect
PROBHD z108618_0098 {
PULPROG zgpg30
TD 65536
SOLVENT MeOD
NS 1202
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 203
SW 20.800 usec
DE 6.50 usec
TE 457.5 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6130223 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLM1 49.43999863 W
SFO2 400.0924004 MHz
NUC2 1H
PCPD2 waltz65
PCPD2 90.00 usec
PLM2 15.1859987 W
PLM12 0.41622999 W
PLM13 0.20936000 W

F2 - Processing parameters

SI 32768
SF 100.6028302 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

AB-3-74-1-CF3

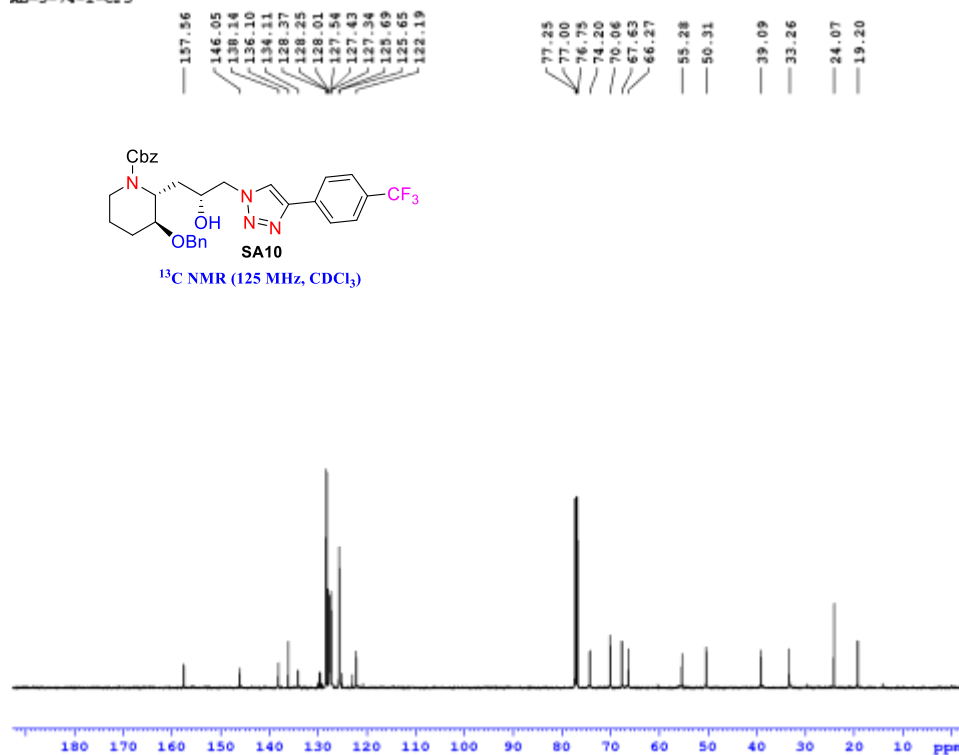
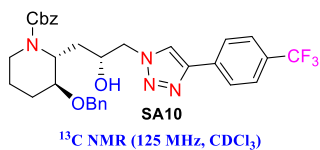


Current Data Parameters
NAME AB-500 Ascend
EXPNO 462
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220311
Time 13.11 h
INSTRUM spect
PROBHD E119470_0291 (1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 18.03
DM 50.000 usec
DE 6.50 usec
TE 300.2 K
D1 1.00000000 sec
TDO 1
SFO1 500.3720898 MHz
NUC1 1H
P1 10.00 usec
PLW1 23.23100090 W

F2 - Processing parameters
SI 65536
SF 500.3690000 MHz
WDW EM
SBB 0
LB 0.30 Hz
GB 0
PC 1.00

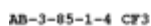
AB-3-74-1-CF3



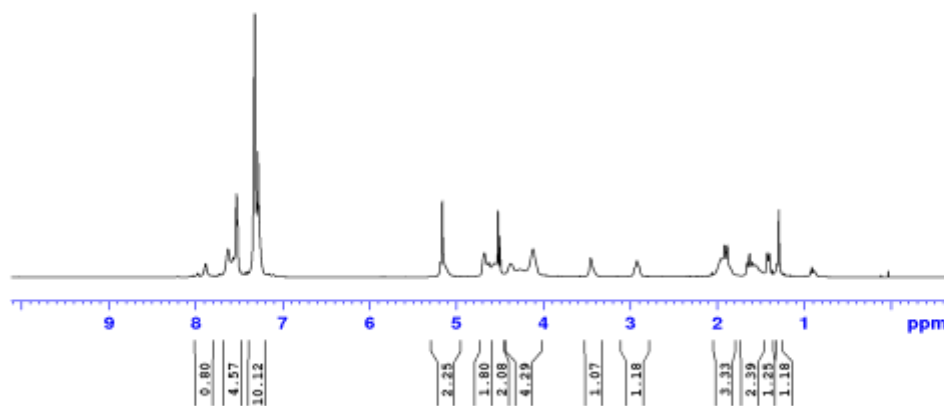
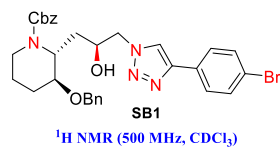
Current Data Parameters
NAME AB-500 Ascend
EXPNO 464
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220311
Time 14.19 h
INSTRUM spect
PROBHD E119470_0291 (1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 192.83
DM 16.800 usec
DE 6.50 usec
TE 295.5 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1
SFO1 125.8304669 MHz
NUC1 13C
P1 10.00 usec
PLW1 115.01000214 W
SFO2 500.3710015 MHz
NUC2 1H
CPDPRG12 waltz16
PCPD2 80.00 usec
PLW2 23.23100090 W
PLW12 0.36298999 W
PLW13 0.19257999 W

F2 - Processing parameters
SI 32768
SF 125.8179050 MHz
WDW EM
SBB 0
LB 1.00 Hz
GB 0
PC 1.40



AB-3-78-2-Bx

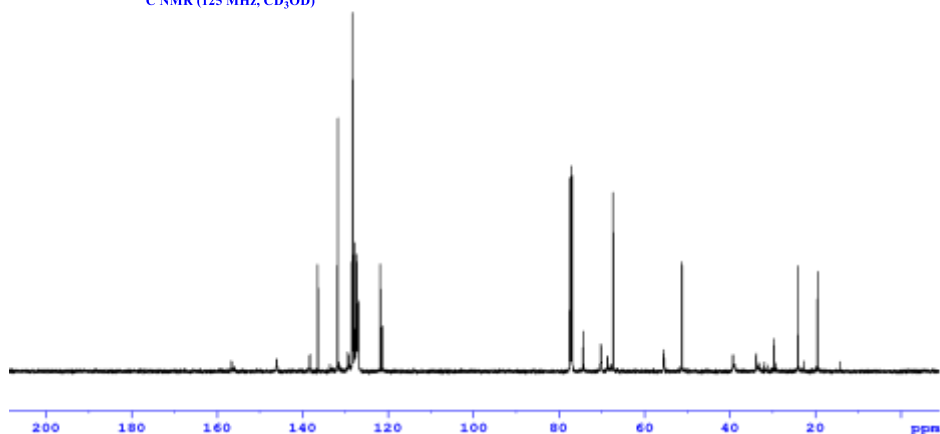
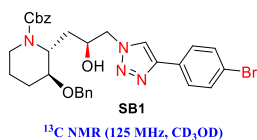


Current Data Parameters
 NAME AB-500
 EXPNO 254
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220315
 Time 14.56 h
 INSTRUM spect
 PROBRD Z109128_0042
 PULPROG zg30
 TD 65536
 SOLVENT CDCl3
 NS 16
 DS 2
 SWH 10000.000 Hz
 FIDRES 0.305176 Hz
 Aq 3.2767999 sec
 RG 57
 DW 50.000 usec
 DE 13.04 usec
 TE 298.0 K
 D1 1.00000000 sec
 TDO 1
 SFO1 500.1830886 MHz
 NUC1 1H
 P0 5.00 usec
 P1 15.00 usec
 PLW1 4.84679985 W

F2 - Processing parameters
 SI 65536
 SF 500.1800000 MHz
 NDN EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

AB-3-78-2-BR

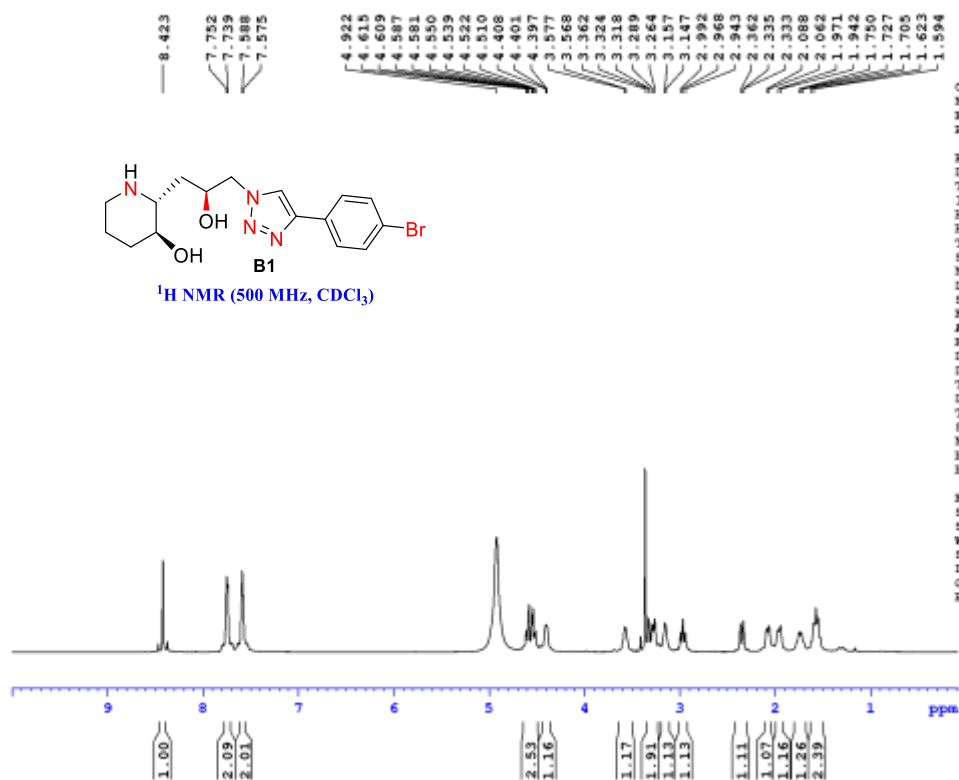


Current Data Parameters
 NAME AB-500 Ascend
 EXPNO 475
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220323
 Time 13.57 h
 INSTRUM spect
 PROBRD Z125331_0034
 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 1572
 DS 4
 SWH 23761.904 Hz
 FIDRES 0.908261 Hz
 Aq 1.1010048 sec
 RG 19.51
 DW 16.800 usec
 DE 6.50 usec
 TE 298.2 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TDO 1
 SFO1 125.9304669 MHz
 NUC1 13C
 P1 12.00 usec
 PLW1 172.66999817 W
 SFO2 500.3710015 MHz
 NUC2 1H
 CPDPRG2 waltz16
 PCPD2 80.00 usec
 PLW2 12.18000031 W
 PLW12 0.12180000 W
 PLW13 0.06126500 W

F2 - Processing parameters
 SI 32768
 SF 125.0179101 MHz
 NDN EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

AB-3-94-2-4 Bz

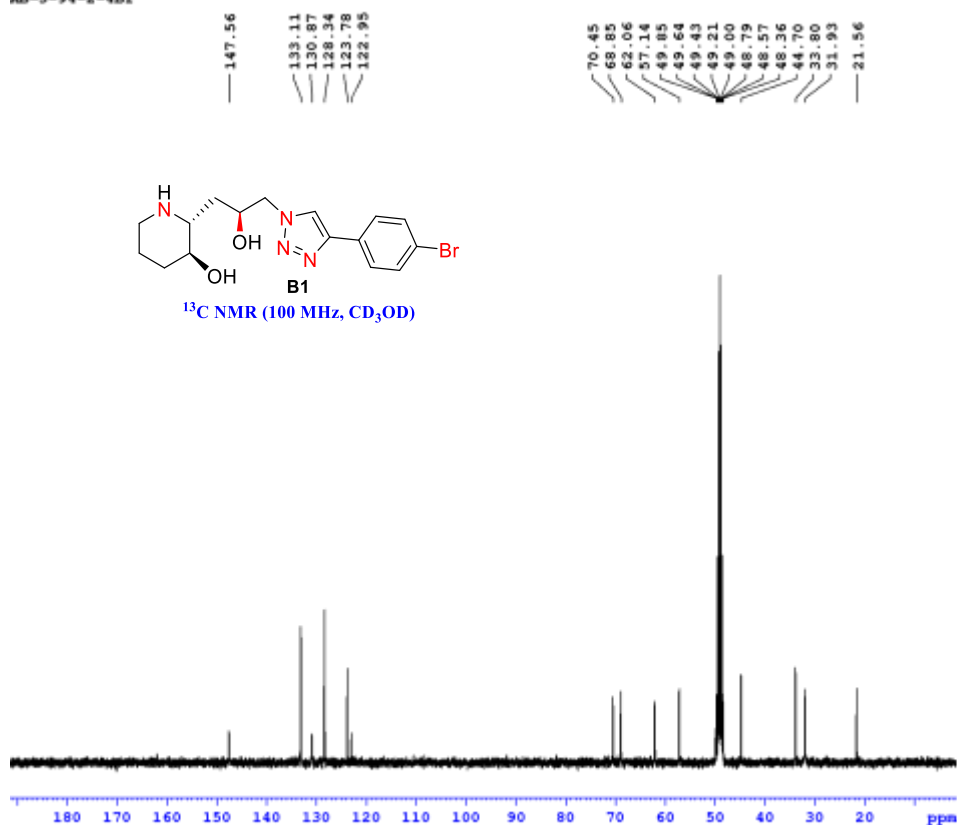


Current Data Parameters
 NAME AB-500 Ascend
 EXPNO 515
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220428
 Time 17.40 h
 INSTRUM spect
 PROBHD S119470_0291 (zg30)
 PULPROG 65536
 TD 16
 SOLVENT MeOD
 NS 2
 DS 10000.000 Hz
 FIDRES 0.305176 Hz
 AQ 3.2767999 sec
 RG 31.25
 DW 50.000 usec
 DE 6.50 usec
 TE 297.6 K
 D1 1.00000000 sec
 TDO 1
 SFO1 500.3720698 MHz
 NUC1 1H
 P1 10.00 usec
 PLW1 23.23100090 W

F2 - Processing parameters
 SI 65536
 SF 500.3690000 MHz
 WDW EM
 SSB 0
 LB 0.50 Hz
 GB 0
 PC 1.00

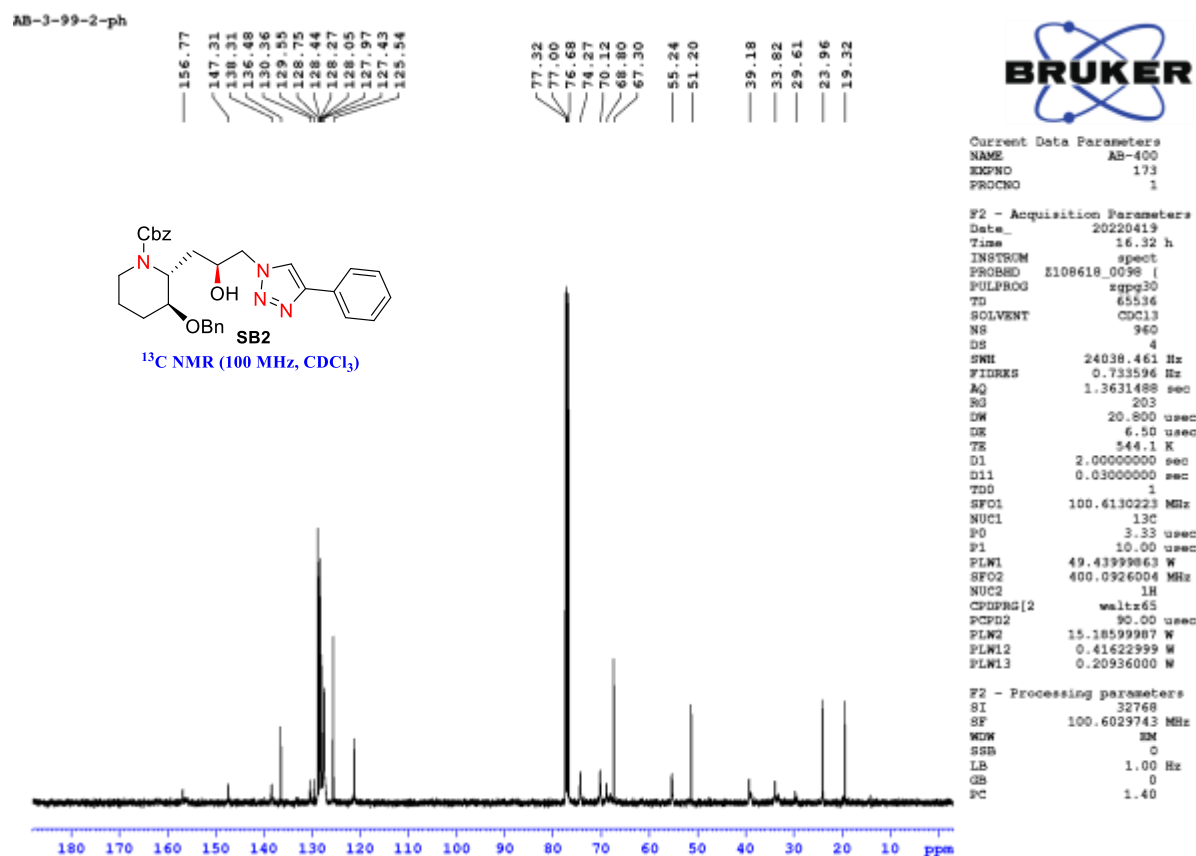
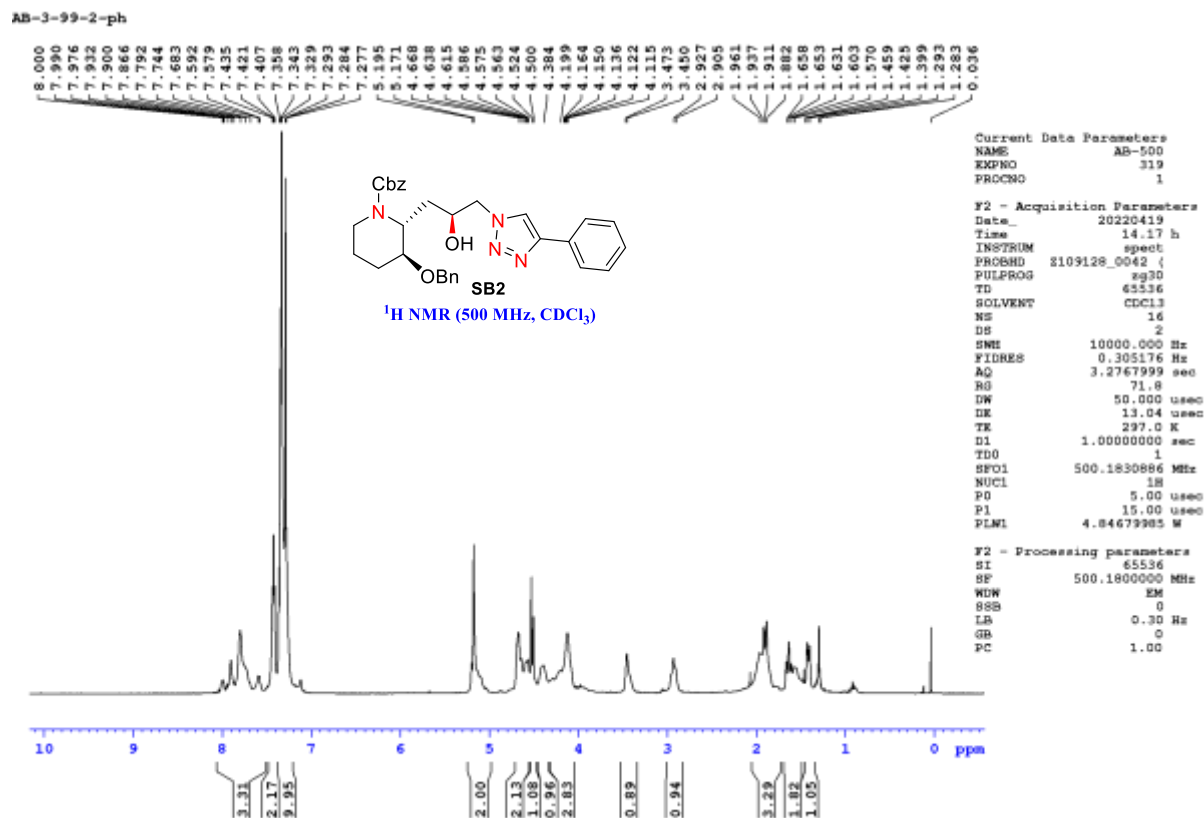
AB-3-94-2-4Bz



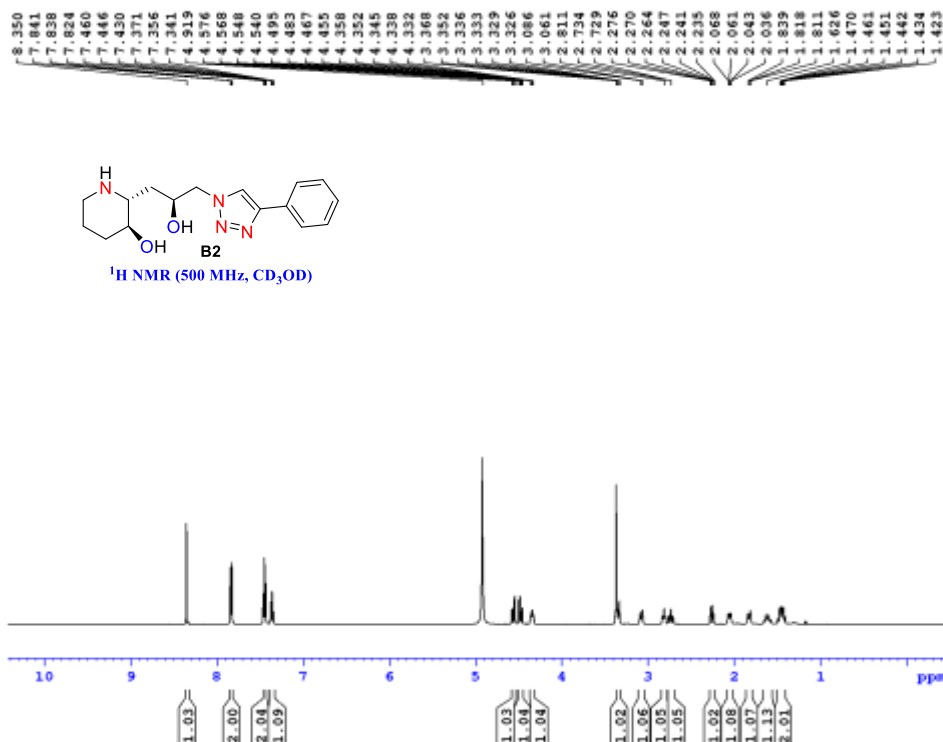
Current Data Parameters
 NAME AB-400
 EXPNO 180
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220429
 Time 12.32 h
 INSTRUM spect
 PROBHD Z108610_0098 (zgpg30)
 PULPROG 65536
 TD 1024
 SOLVENT MeOD
 NS 4
 DS 24038.461 Hz
 FIDRES 0.733596 Hz
 AQ 1.3631488 sec
 RG 203
 DW 20.800 usec
 DE 6.50 usec
 TE 462.2 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TDO 1
 SFO1 100.6130223 MHz
 NUC1 13C
 P0 3.33 usec
 P1 10.00 usec
 PLW1 49.43999863 W
 SFO2 400.0926004 MHz
 NUC2 1H
 CPDPRG2 waltz65
 PCPD2 90.00 usec
 PLW2 15.18599987 W
 PLW12 0.41622999 W
 PLW13 0.20936000 W

F2 - Processing parameters
 SI 32768
 SF 100.6028348 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40



AB-3-100-2-Ph

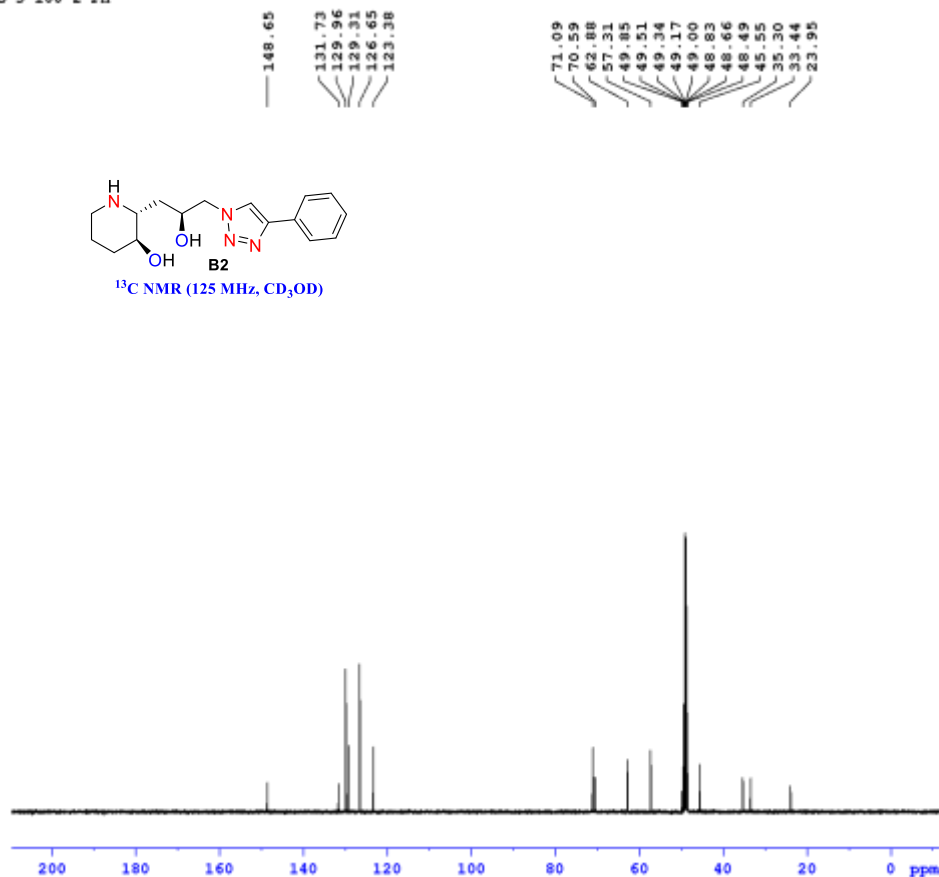


Current Data Parameters
 NAME AB-500
 EXPNO 336
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220429
 Time 17.02 h
 INSTRUM spect
 PROBRD X109128.0042 (
 PULPROG zg30
 TD 65536
 SOLVENT MeOD
 NS 16
 DS 2
 SWH 10000.000 Hz
 FIDRES 0.305176 Hz
 AQ 3.2767999 sec
 RG 71.8
 DW 50.000 usec
 DE 13.04 usec
 TE 298.0 K
 D1 1.00000000 sec
 TD0 1
 SFO1 500.1830886 MHz
 NUC1 1H
 P0 5.00 usec
 P1 15.00 usec
 PLW1 4.84679985 W

F2 - Processing parameters
 SI 65536
 SF 500.1800000 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

AB-3-100-2-Ph

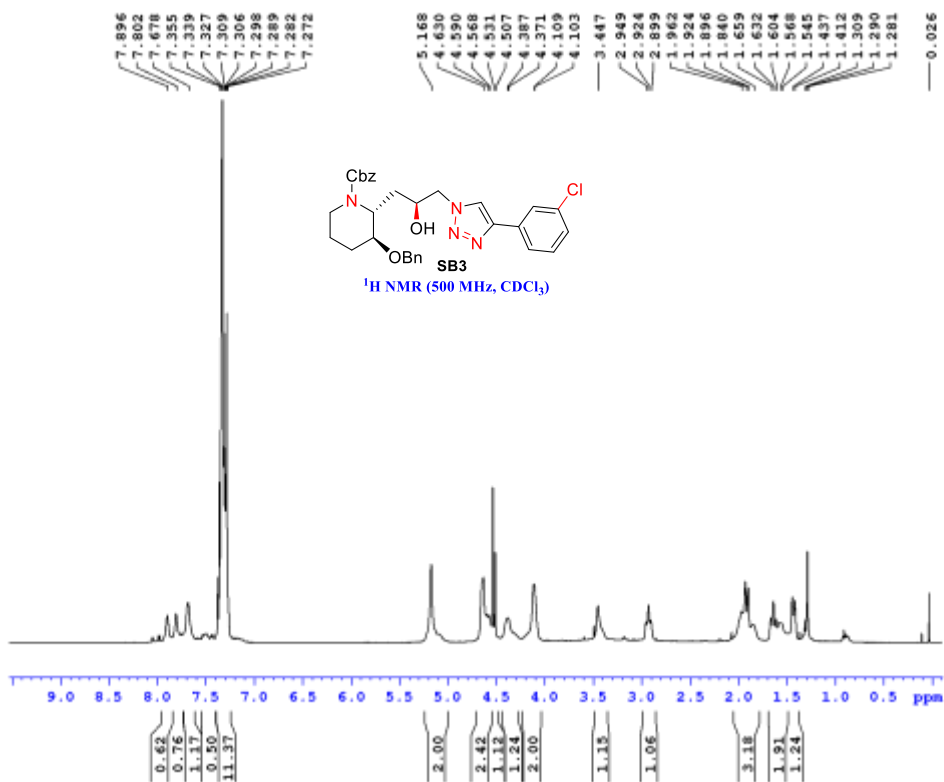


Current Data Parameters
 NAME AB-500
 EXPNO 338
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220429
 Time 17.24 h
 INSTRUM spect
 PROBRD X109128.0042 (
 PULPROG zgpg30
 TD 65536
 SOLVENT MeOD
 NS 248
 DS 4
 SWH 29761.904 Hz
 FIDRES 0.908261 Hz
 AQ 1.1010048 sec
 RG 203
 DW 16.800 usec
 DE 6.50 usec
 TE 298.4 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1
 SFO1 125.7829381 MHz
 NUC1 13C
 P0 3.33 usec
 P1 10.00 usec
 PLW1 64.00399780 W
 SFO2 500.1820007 MHz
 NUC2 1H
 CPDPRG2 waltz65
 PCPD2 80.00 usec
 PLW2 4.84679985 W
 PLW12 0.17039999 W
 PLW13 0.08570800 W

F2 - Processing parameters
 SI 32768
 SF 125.7701902 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

AB-3-79-2-3c1

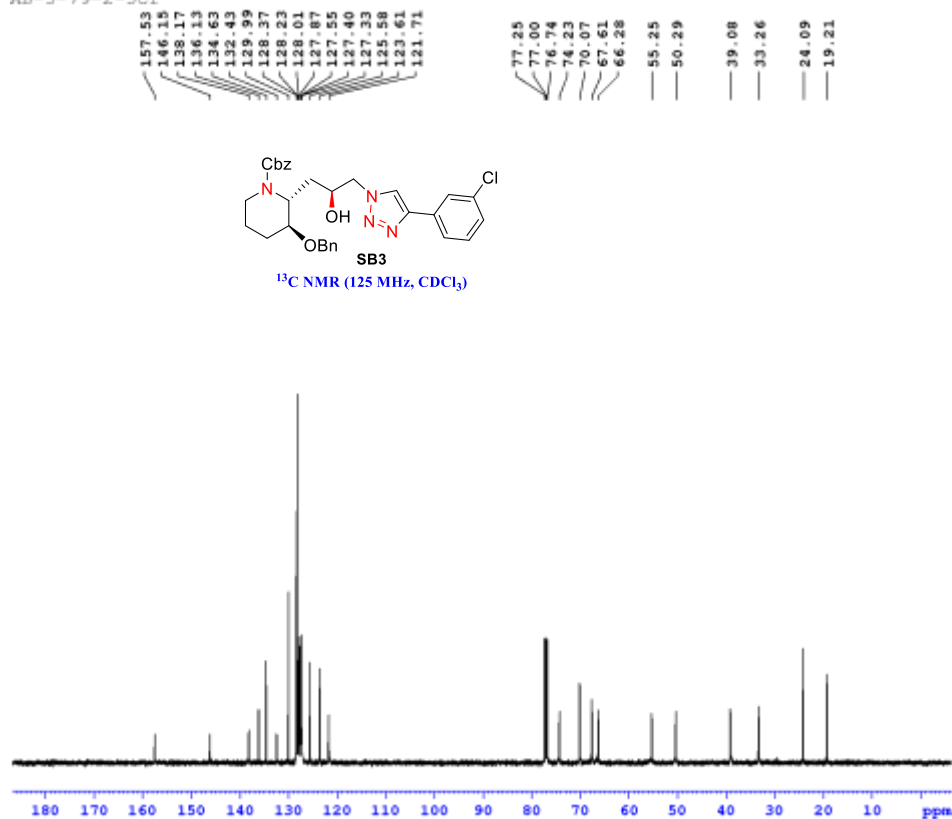


Current Data Parameters
NAME AB-500
EXPNO 296
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220321
Time 15.19 h
INSTRUM spect
PROBHD E109128.0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 114
DW 50.000 usec
DE 13.04 usec
TE 296.8 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W

F2 - Processing parameters
SI 65536
SF 500.1800000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

AB-3-79-2-3C1

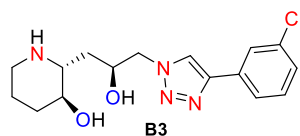
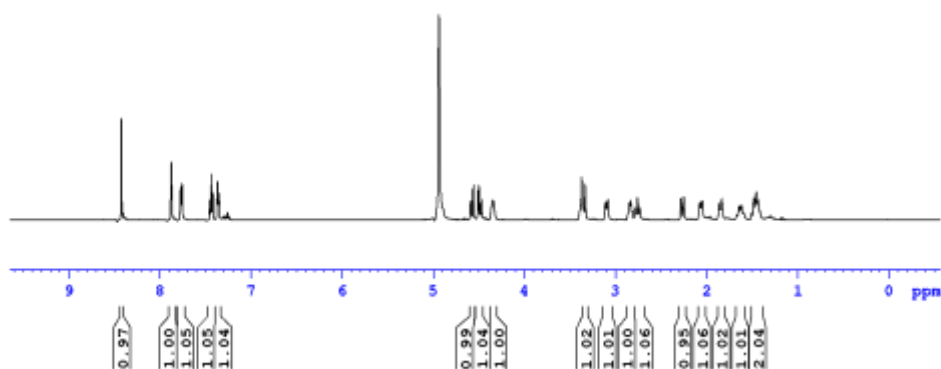


Current Data Parameters
NAME AB-500
EXPNO 278
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220310
Time 13.27 h
INSTRUM spect
PROBHD E109128.0042 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 29761.904 Hz
FIDRES 0.968261 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 297.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.7829381 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 64.00399780 W
SFO2 500.1820007 MHz
NUC2 1H
CPDPRG2 waltz165
PCPD2 80.00 usec
PLW2 4.84679985 W
PLW12 0.17039999 W
PLW13 0.08570800 W

F2 - Processing parameters
SI 32768
SF 125.7703813 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

AB-3-92-2-3Cl

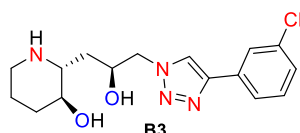
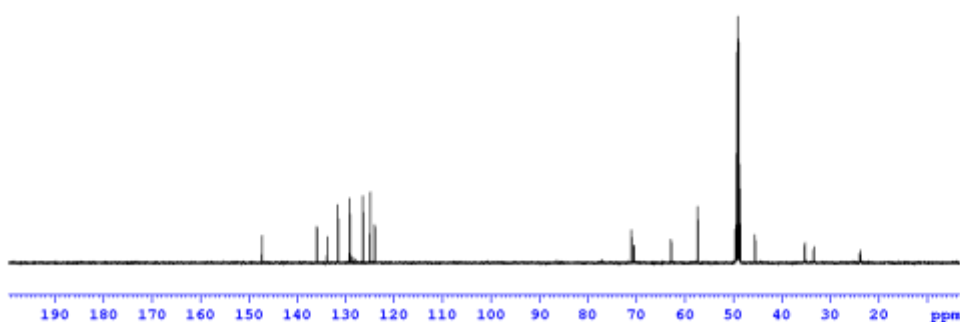
¹H NMR (500 MHz, CD₃OD)

Current Data Parameters
 NAME AB-500
 EXPNO 332
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220428
 Time 12.15 h
 INSTRUM spect
 PROBHD Z109128_0042 ()
 PULPROG zg30
 TD 65536
 SOLVENT MeOD
 NS 16
 DS 2
 SWH 10000.000 Hz
 FIDRES 0.305176 Hz
 AQ 3.2767999 sec
 RG 90.5
 DW 50.000 usec
 DE 13.04 usec
 TE 295.9 K
 D1 1.00000000 sec
 TDO 1
 SFO1 500.1830886 MHz
 NUC1 1H
 P0 5.00 usec
 P1 15.00 usec
 PLW1 4.84673985 W

F2 - Processing parameters
 SI 65536
 SF 500.1800000 MHz
 NCH EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

AB-3-92-2-3Cl

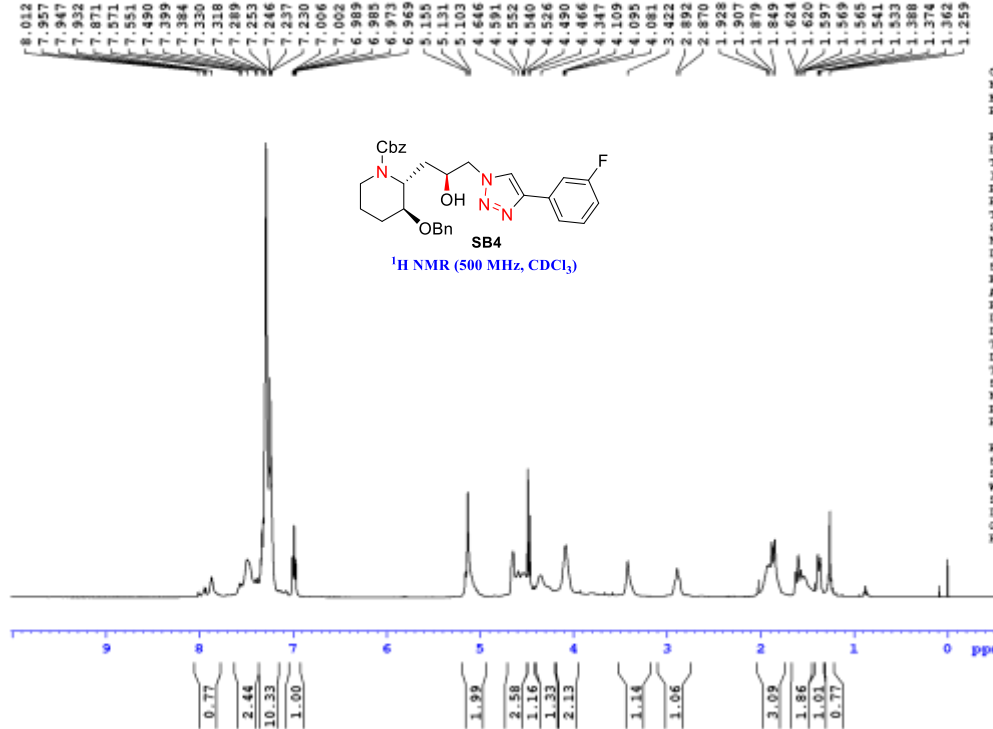
¹³C NMR (125 MHz, CD₃OD)

Current Data Parameters
 NAME AB-500
 EXPNO 334
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220428
 Time 12.58 h
 INSTRUM spect
 PROBHD Z109128_0042 ()
 PULPROG zgpg30
 TD 65536
 SOLVENT MeOD
 NS 548
 DS 4
 SWH 29761.904 Hz
 FIDRES 0.908261 Hz
 AQ 1.1010048 sec
 RG 203
 DW 16.800 usec
 DE 6.50 usec
 TE 296.4 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TDO 1
 SFO1 125.7829381 MHz
 NUC1 13C
 P0 3.33 usec
 P1 10.00 usec
 PLW1 64.00399780 W
 SFO2 500.1820007 MHz
 NUC2 1H
 CPDPRG2 waitz65
 PCPD2 80.00 usec
 PLW2 4.84673985 W
 PLW12 0.17039999 W
 PLW13 0.08570800 W

F2 - Processing parameters
 SI 32768
 SF 125.7701897 MHz
 NCH EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

AB-3-46-2-3F

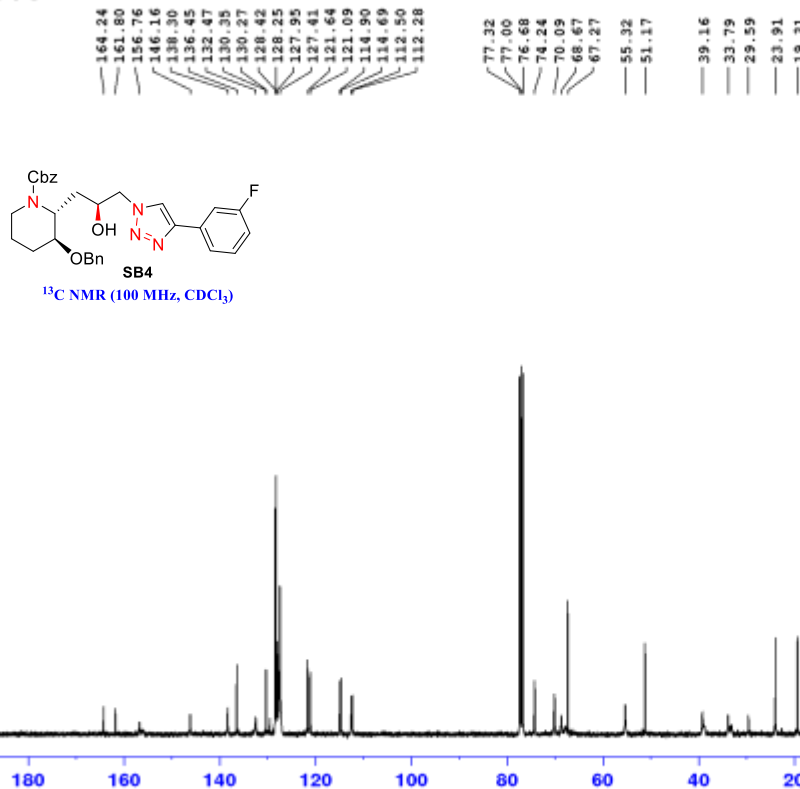


Current Data Parameters
NAME Ascend-500
EXPNO 451
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220202
Time 12.08 h
INSTRUM spect
PROBHD z119470_0291 1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 31.25
DM 50.000 usec
DE 6.50 usec
TE 300.3 K
D1 1.00000000 sec
TDO 1
SFO1 500.3720898 MHz
NUC1 1H
P1 10.00 usec
PLM1 23.23100090 W

F2 - Processing parameters
SI 65536
SF 500.3690188 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

AB-3-46-2-3-F



Current Data Parameters
NAME 400
EXPNO 151
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220203
Time 14.47 h
INSTRUM spect
PROBHD z108618_0098 1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1379
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 203
DM 20.800 usec
DE 6.50 usec
TE 588.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1
SFO1 100.6130223 MHz
NUC1 13C
PC 3.33 usec
P1 10.00 usec
PLM1 49.43999863 W
SFO2 400.0926004 MHz
NUC2 1H
CPCPRG[2] waltz65
PCPD2 90.00 usec
PLW2 15.18599987 W
PLW12 0.41622999 W
PLW13 0.20936000 W

F2 - Processing parameters
SI 32768
SF 100.6029778 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



```

Current Data Parameters
NAME                500
EXPNO               280
PROCNO              1

F2 - Acquisition Parameters
Date_              20220311
Time                14:30 h
INSTRUM             spect
PROBHD              zgpg30
PULPROG             zg30
TD                  65536
SOLVENT             H2O
NS                   16
DS                   2
SWH                  10000.000 Hz
FIDRES              0.305176 Hz
AQ                   3.2767999 sec
RG                   228
DNW                  50.000 usec
DE                   13.04 usec
TE                   296.3 K
D1                   1.00000000 sec
TDC
SFOCAL              500.1830886 MHz
NUC1                 1H
P0                   5.00 usec
P1                   15.00 usec
PLW1                4.84679985 W

F2 - Processing parameters
SI                   65536
SF                   500.1800000 MHz
WDM                  EM
SSB                  0
LB                   0.30 Hz
GB                   0
PC                   1.00

```

AB-3-64-2-3F final compd



```

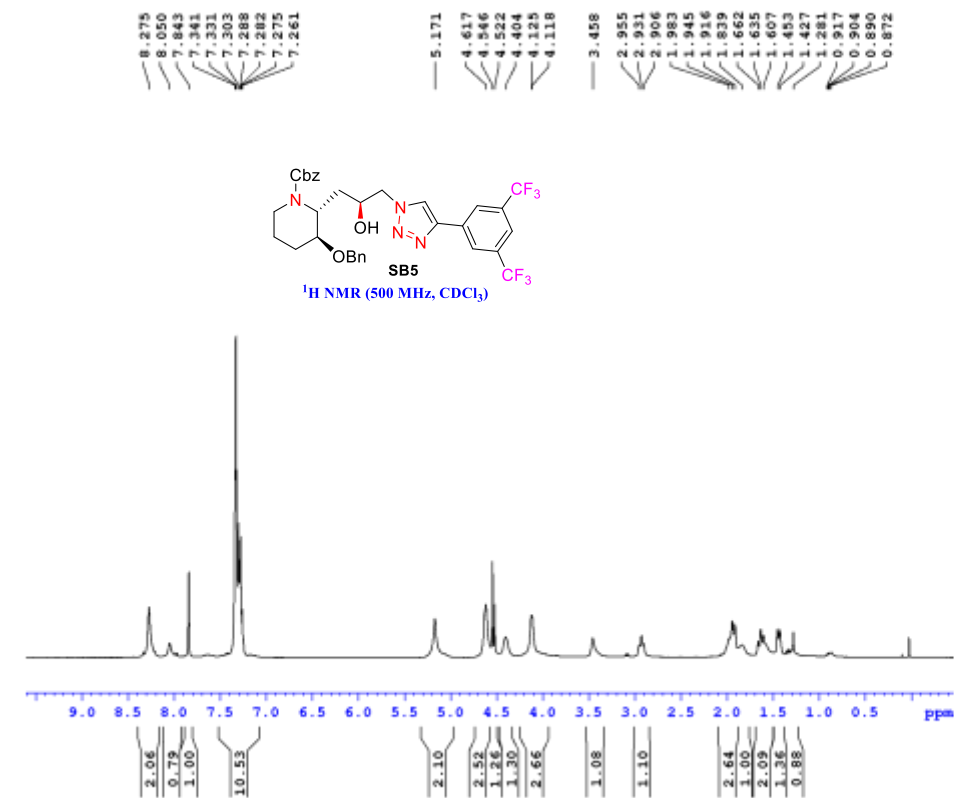
Current Data Parameters
NAME                AB-500
EXPNO                283
PROCNO               1

F2 - Acquisition Parameters
Date_                20220312
Time                 12.12 h
INSTRUM              spect
PROBHD               E109128_0042
PULPROG              zgpg30
TD                   65536
SOLVENT              MeOD
NS                   1032
DS                   4
SWH                  29761.904 Hz
FIDRES              0.908261 Hz
AQ                  1.1010048 sec
RG                   203
DX                   16.800 used
DE                   6.50 used
TE                   295.8 K
D1                   2.0000000 sec
D11                  0.0300000 sec
TDO                  1
SFO1                 125.7829381 MHz
NUC1                 13C
P0                   3.33 used
T0                   10.00
PLW1                 64.00399780 W
SFO2                 500.1820007 MHz
NUC2                 1H
CPCPDPRG2           waltz65
PCPD2                80.00 used
PLW2                 4.84675985 W
PLW12                0.17039990 W
PLW13                0.08570800 W

F2 - Processing parameters
SI                   32768
SF                   125.7703610 MHz
WDM                  KM
SR                   1
LB                   1.00 Hz
GB                   0
PC                   1.40

```

AB-3-81-2-Bis-CF₃

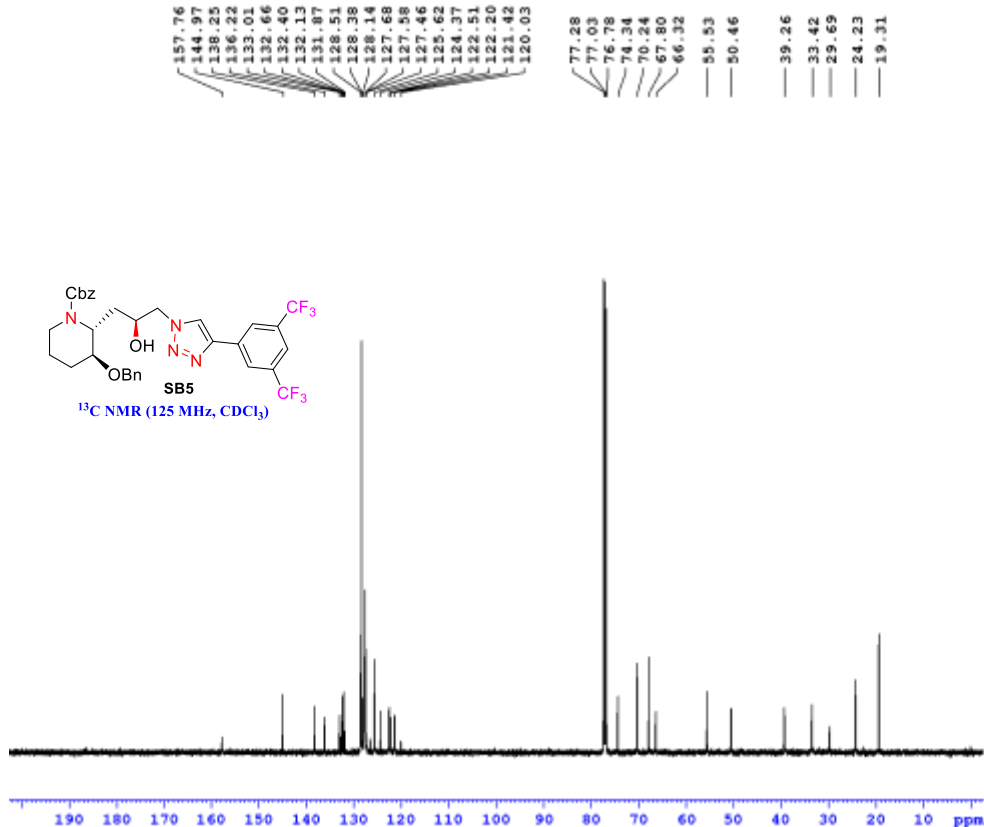


Current Data Parameters
NAME 500
EXPNO 295
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220321
Time 15.15 h
INSTRUM spect
PROBHD E109128_0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.276799 sec
RG 114
DM 50.000 usec
DE 13.04 usec
TE 296.9 K
D1 1.00000000 sec
TD0 1
SFO1 500.183086 MHz
NUC1 1H
PO 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W

F2 - Processing parameters
SI 65536
SF 500.1800000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

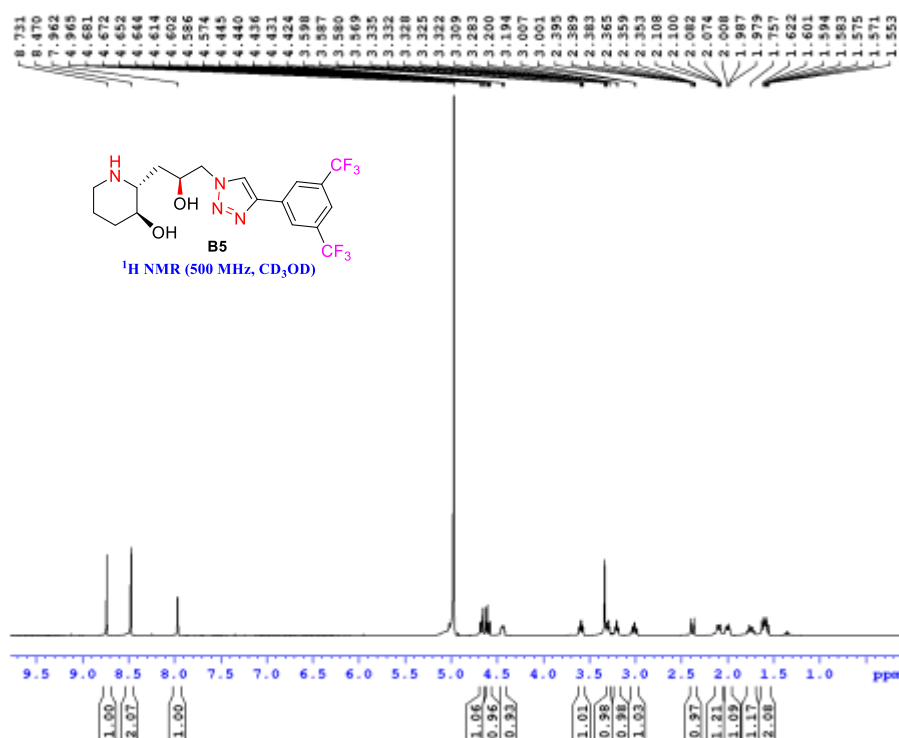
AB-3-73-1-2CF₃



Current Data Parameters
NAME AB-500
EXPNO 273
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220308
Time 14.23 h
INSTRUM spect
PROBHD E109128_0042 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 858
DS 4
SWH 29761.904 Hz
FIDRES 0.308261 Hz
AQ 1.1010048 sec
RG 203
DM 14.800 usec
DE 6.50 usec
TE 299.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.7829381 MHz
NUC1 13C
PO 3.33 usec
P1 10.00 usec
PLW1 64.00399780 W
SFO2 500.1820007 MHz
NUC2 1H
CPDPRG2 waltz65
PCPD2 80.00 usec
PLW2 4.84679985 W
PLW12 0.17039999 W
PLW13 0.08570800 W

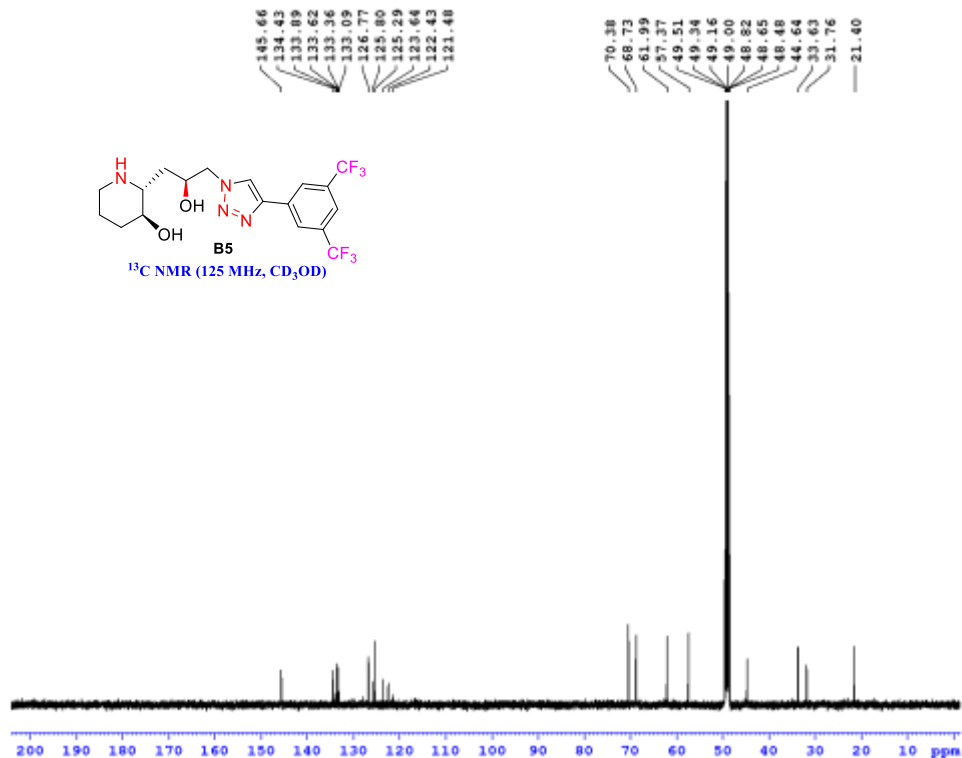
F2 - Processing parameters
SI 32768
SF 125.7703610 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

AB-3-81-2-Bis-CF₃

Current Data Parameters
NAME: 500
EXPNO: 303
PROCNO: 1

F2 - Acquisition Parameters
Date_: 20220404
Time: 16.45 h
INSTRUM: spect
PROBHD: E109128_0042 (
PULPROG: zg30
TD: 65536
SOLVENT: MeOD
NS: 16
DS: 2
SWH: 10000.000 Hz
FIDRES: 0.305176 Hz
AQ: 3.2767999 sec
RG: 163
DW: 50.000 usec
DE: 13.04 usec
TE: 298.6 K
D1: 1.00000000 sec
TDO: 1
SFO1: 500.1830886 MHz
NUC1: 1H
P0: 5.00 usec
P1: 15.00 usec
PLW1: 4.84679985 W

F2 - Processing parameters
SI: 65536
SF: 500.1800000 MHz
WDW: EM
SSB: 0
LA: 0.30 Hz
GB: 0
PC: 1.00

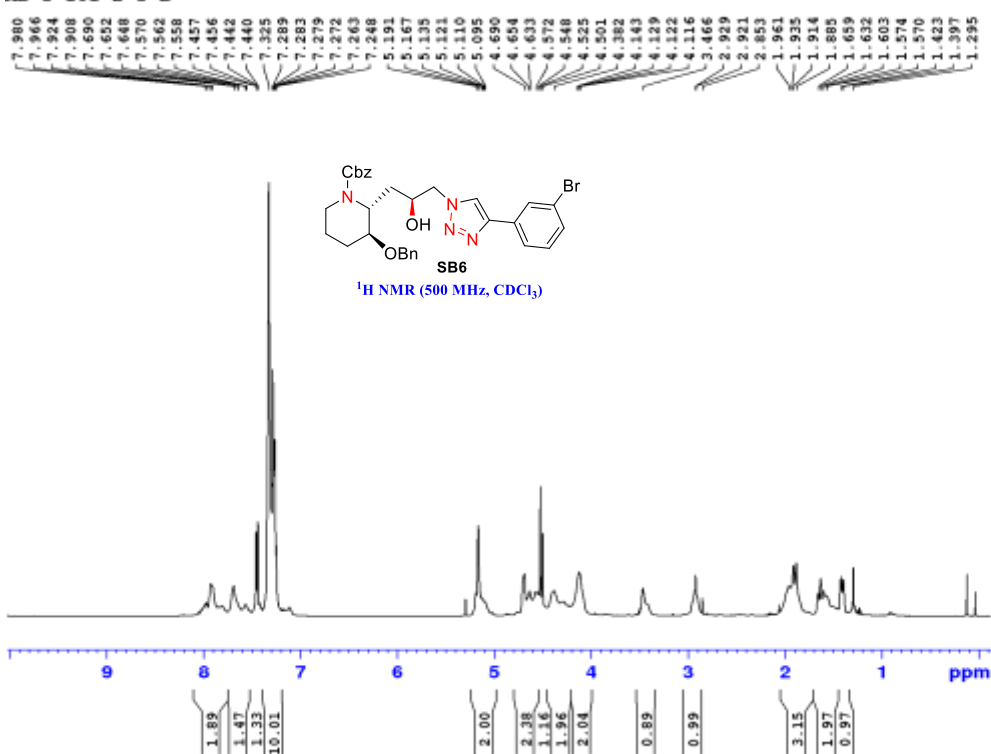
AB-3-81-2-BIS-CF₃

Current Data Parameters
NAME: Ascend-500
EXPNO: 494
PROCNO: 1

F2 - Acquisition Parameters
Date_: 20220405
Time: 16.56 h
INSTRUM: spect
PROBHD: E125331_0034 (
PULPROG: zgpg30
TD: 65536
SOLVENT: MeOD
NS: 1024
DS: 4
SWH: 29761.904 Hz
FIDRES: 0.308261 Hz
AQ: 1.1010048 sec
RG: 27.53
DW: 16.000 usec
DE: 6.50 usec
TE: 298.1 K
D1: 2.00000000 sec
D11: 0.03000000 sec
TDO: 1
SFO1: 125.8304669 MHz
NUC1: 13C
P1: 12.00 usec
PLW1: 172.66999817 W
SFO2: 500.3710015 MHz
NUC2: 1H
CPDPRG2: waltz16
PCPD2: 80.00 usec
PLW2: 12.18000031 W
PLW12: 0.12180000 W
PLW13: 0.06126500 W

F2 - Processing parameters
SI: 32768
SF: 125.8177115 MHz
WDW: EM
SSB: 0
LA: 1.00 Hz
GB: 0
PC: 1.40

AB-3-101-2-3 B

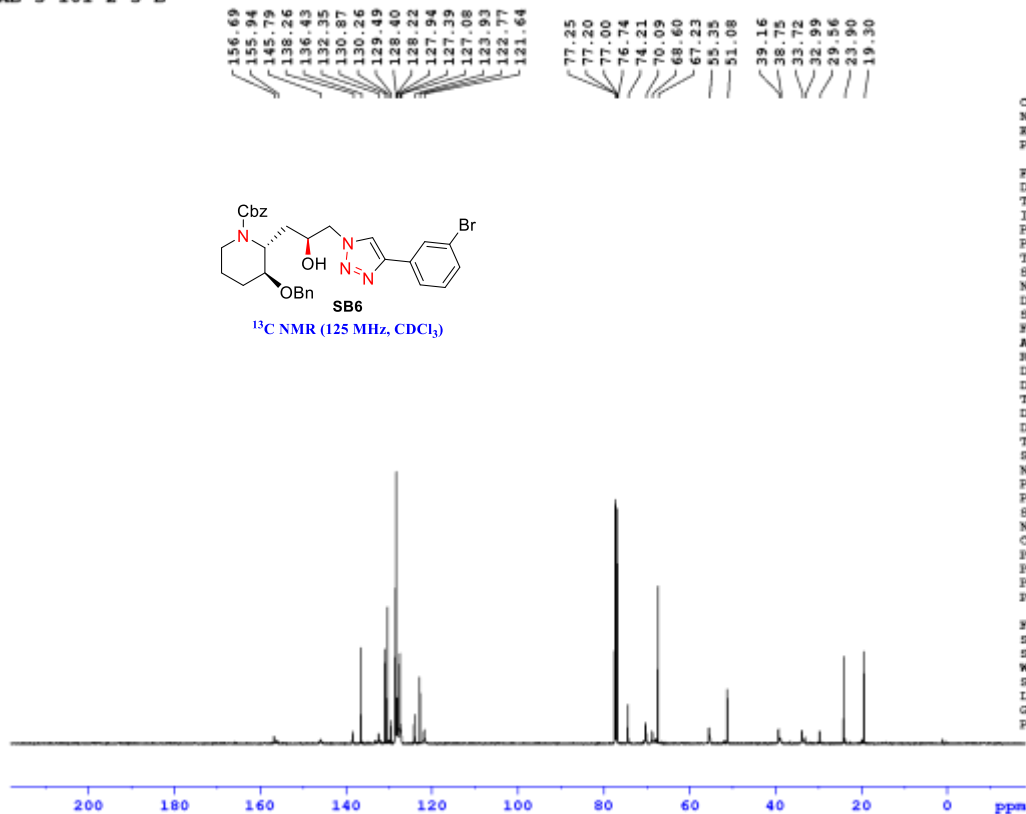


Current Data Parameters
NAME Ascend-500
EXPNO 516
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220504
Time 15.11 h
INSTRUM spect
PROBHD E119470_0291 (1H)
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 31.25
DW 50.000 usec
DE 6.50 usec
TE 296.4 K
D1 1.00000000 sec
TDO 1
SFO1 500.3720898 MHz
NUC1
P1 10.00 usec
PLW1 23.23100090 W

F2 - Processing parameters
SI 65536
SF 500.3690000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

AB-3-101-2-3 B

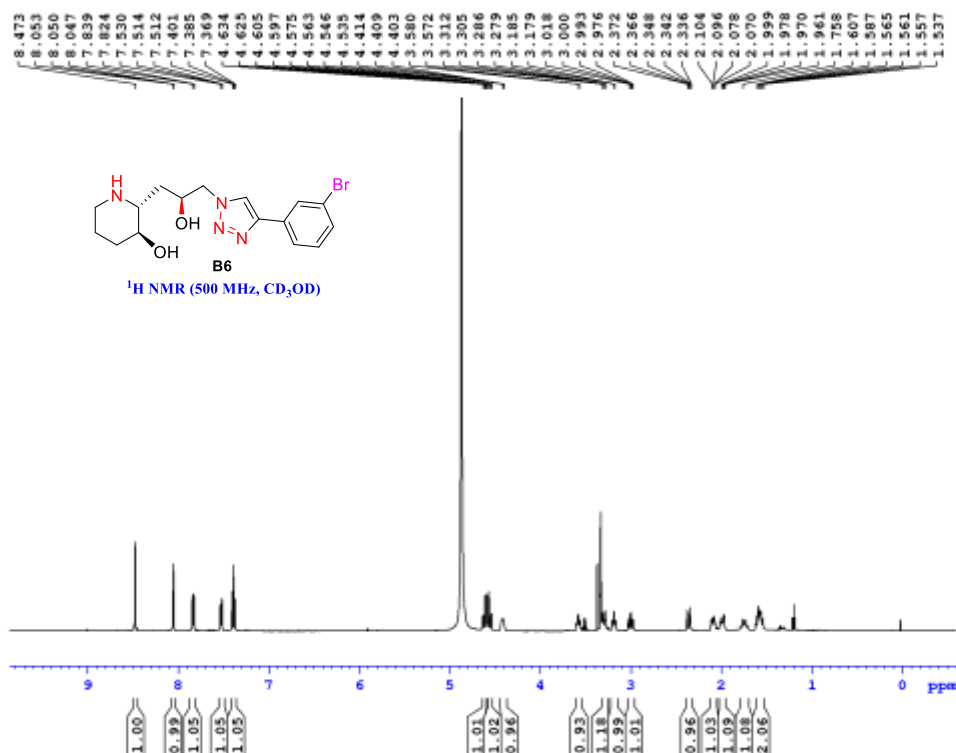


Current Data Parameters
NAME Ascend-500
EXPNO 518
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220504
Time 16.28 h
INSTRUM spect
PROBHD E119470_0291 (1H)
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1206
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 192.83
DW 16.800 usec
DE 6.50 usec
TE 296.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1
SFO1 125.8304669 MHz
NUC1 13C
P1 10.00 usec
PLW1 115.01000214 W
SFO2 500.3710015 MHz
NUC2 1H
CPOPRG2 waltz16
PCPD2 80.00 usec
PLW2 23.23100090 W
PLW12 0.36298999 W
PLW13 0.18257999 W

F2 - Processing parameters
SI 32768
SF 125.8179056 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

AB-3-106-2-3Br

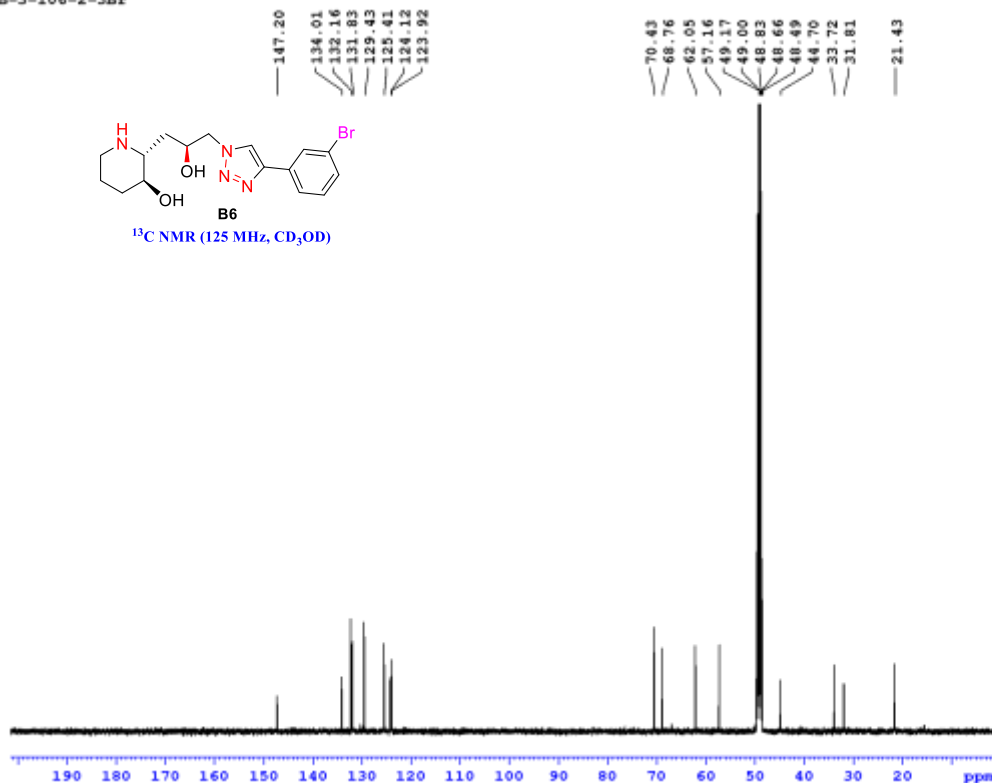


Current Data Parameters
 NAME AB-500
 EXPNO 344
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220509
 Time 12.33 h
 INSTRUM spect
 PROBHD Z109128_0042 (
 PULPROG zg30
 TD 65536
 SOLVENT MeOD
 NS 16
 DS 2
 SWSH 10000.000 Hz
 FIDRES 0.305176 Hz
 AQ 3.2767399 sec
 RG 144
 DW 50.000 usec
 DE 13.04 usec
 TE 300.7 K
 D1 1.00000000 sec
 TDC 1
 SFO1 500.1830886 MHz
 NUC1 1H
 P0 5.00 usec
 P1 15.00 usec
 PLW1 4.04679985 W

F2 - Processing parameters
 SI 65536
 SF 500.1800000 MHz
 NCM 32768
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

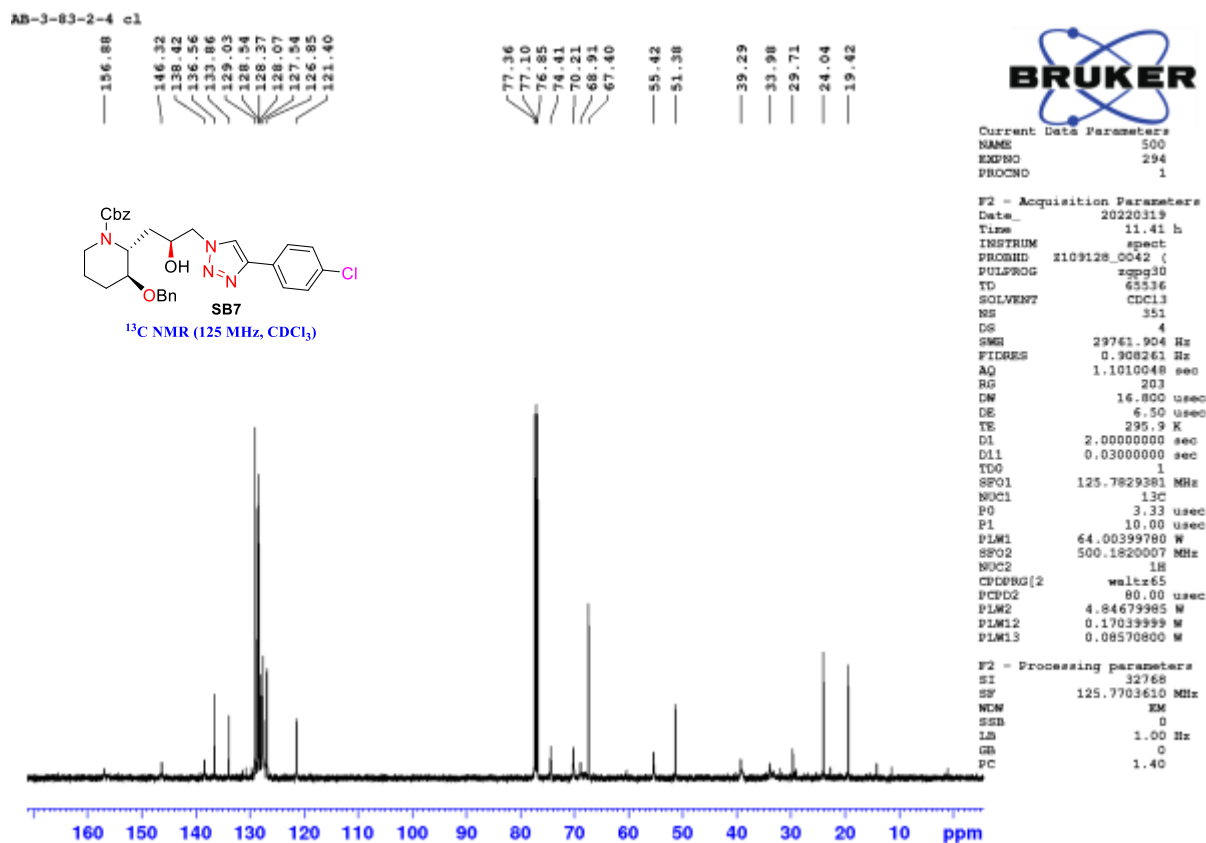
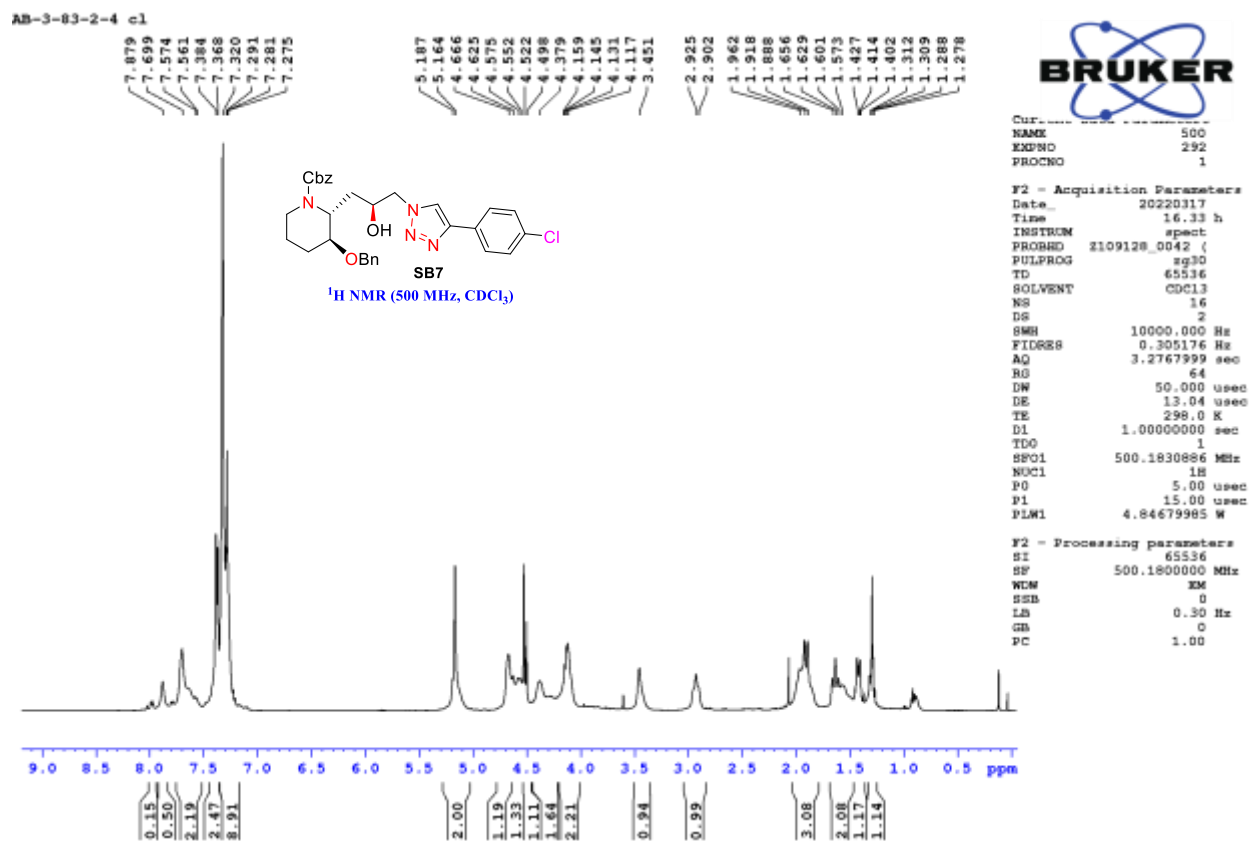
AB-3-106-2-3Br



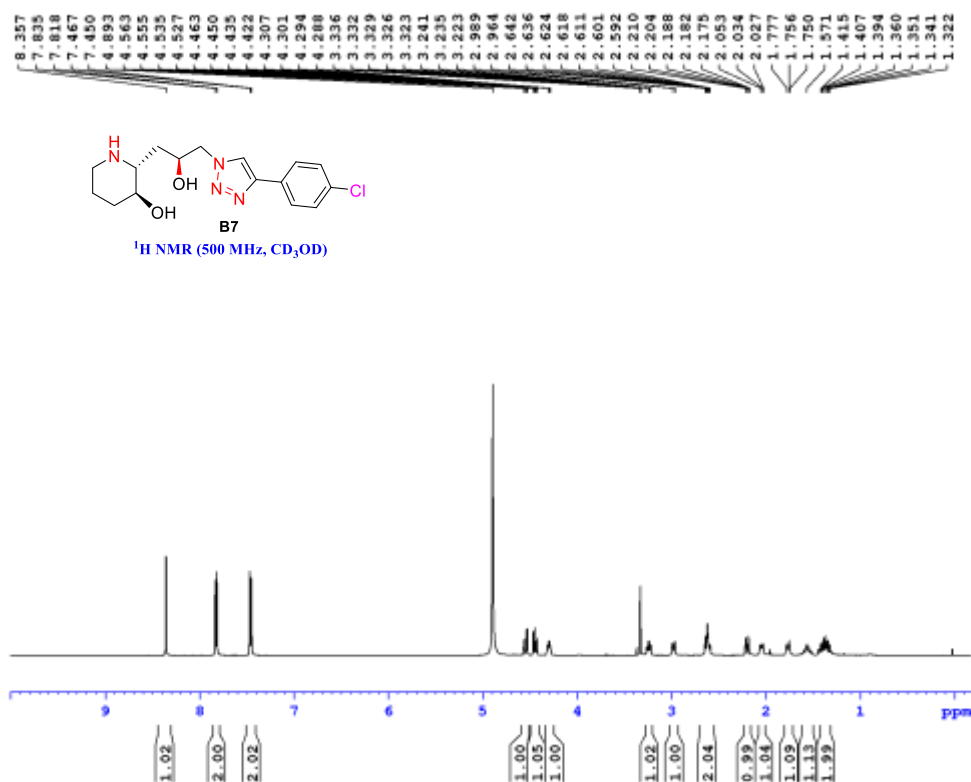
Current Data Parameters
 NAME AB-500
 EXPNO 343
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220507
 Time 11.43 h
 INSTRUM spect
 PROBHD Z109128_0042 (
 PULPROG zgpg30
 TD 65536
 SOLVENT MeOD
 NS 4327
 DS 4
 SWSH 29761.904 Hz
 FIDRES 0.908261 Hz
 AQ 1.1010048 sec
 RG 2050
 DW 16.800 usec
 DE 6.50 usec
 TE 300.7 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TDC 1
 SFO1 125.7829381 MHz
 NUC1 13C
 P0 3.33 usec
 P1 10.00 usec
 PLW1 64.00399780 W
 SFO2 500.1820007 MHz
 NUC2 1H
 CPDPRG2 waltz65
 PCPD2 80.00 usec
 PLW2 4.04679985 W
 PLW3 0.17039999 W
 PLW13 0.08570800 W

F2 - Processing parameters
 SI 32768
 SF 125.7701875 MHz
 NCM 32768
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40



AB-3-93-2-4C1

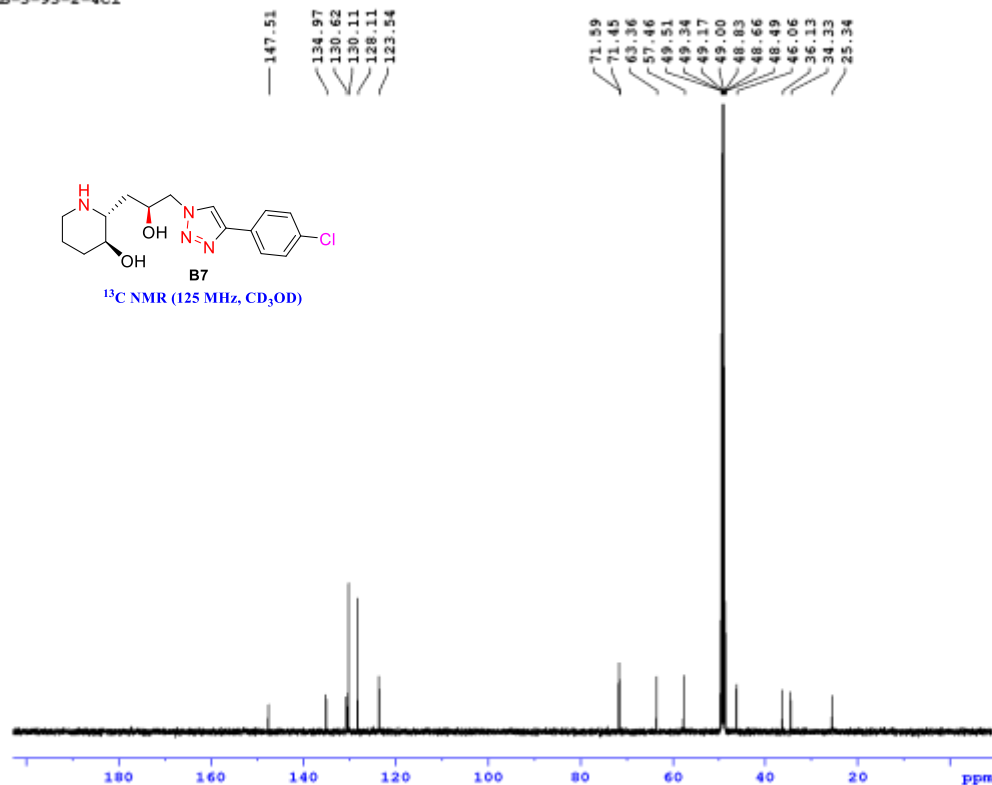


Current Data Parameters
 NAME AB-500
 EXPNO 329
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220427
 Time 14.54 h
 INSTRUM spect
 PROBNM X109128_0042 (
 PULPROG zg30
 TD 65536
 SOLVENT MeOD
 NS 16
 DS 2
 SWH 10000.000 Hz
 FIDRES 0.305176 Hz
 AQ 3.2767999 sec
 RG 161
 DW 50.000 usec
 DE 13.04 usec
 TE 297.7 K
 D1 1.0000000 sec
 TDO 1
 SFO1 500.1830886 MHz
 NUC1 1H
 P0 5.00 usec
 P1 15.00 usec
 PLM1 4.84679985 W

F2 - Processing parameters
 SI 65536
 SF 500.1800000 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

AB-3-93-2-4C1

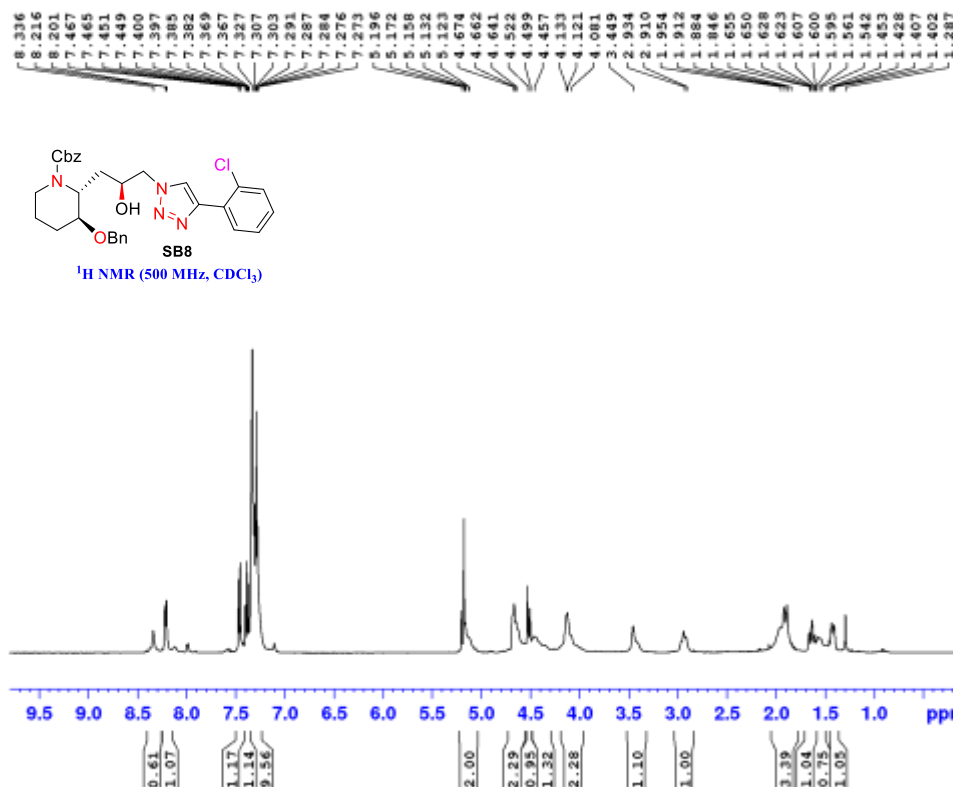


Current Data Parameters
 NAME AB-500
 EXPNO 331
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220427
 Time 15.38 h
 INSTRUM spect
 PROBNM X109128_0042 (
 PULPROG zgpg30
 TD 65536
 SOLVENT MeOD
 NS 451
 DS 4
 SWH 29761.304 Hz
 FIDRES 0.908261 Hz
 AQ 1.1010048 sec
 RG 203
 DW 16.800 usec
 DE 6.50 usec
 TE 298.8 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TDO 1
 SFO1 125.7629361 MHz
 NUC1 13C
 P0 3.33 usec
 P1 10.00 usec
 PLM1 64.00399780 W
 SFO2 500.1820007 MHz
 NUC2 1H
 CPDPRG2 waltz165
 PCPD2 80.00 usec
 PLM2 4.84679985 W
 PLM12 0.17039999 W
 PLM13 0.08570800 W

F2 - Processing parameters
 SI 32768
 SF 125.7701854 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

AB-3-104-2-2C1



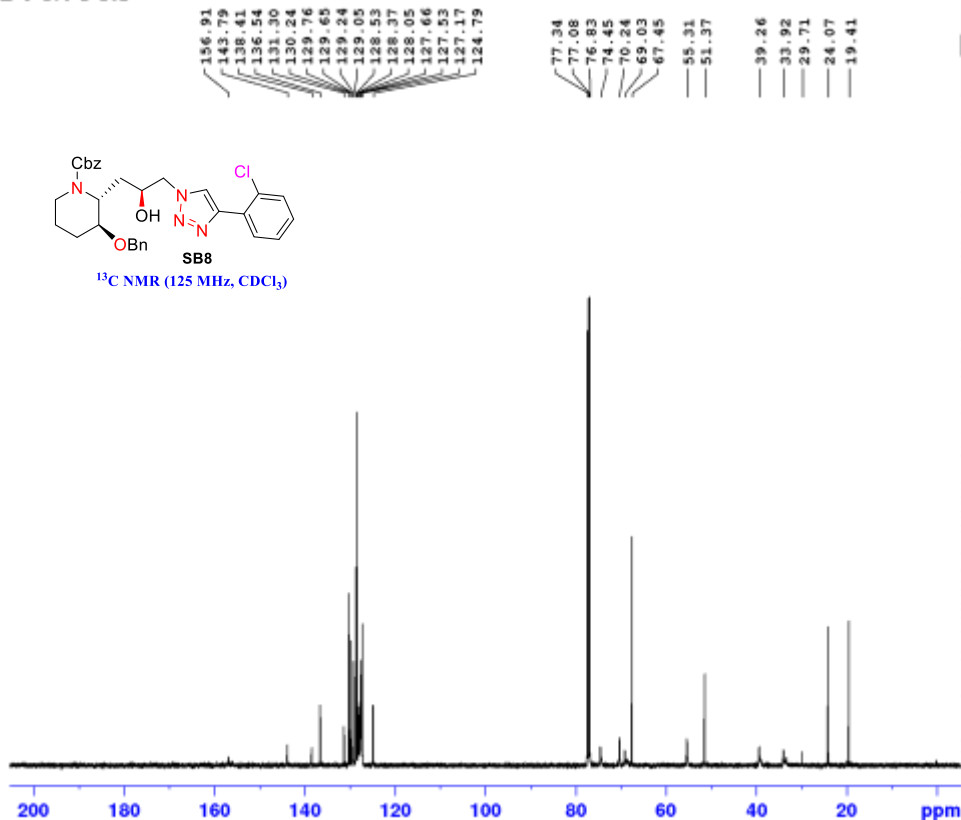
BRUKER

Current Data Parameters
NAME 500
EXPNO 339
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220504
Time 13.11 h
INSTRUM spect
PROBHD x109128_0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 71.8
DW 50.000 usec
DE 13.04 usec
TE 2668.1 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W

F2 - Processing parameters
SI 65536
SF 500.1800000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

AB-3-104-2-2C1



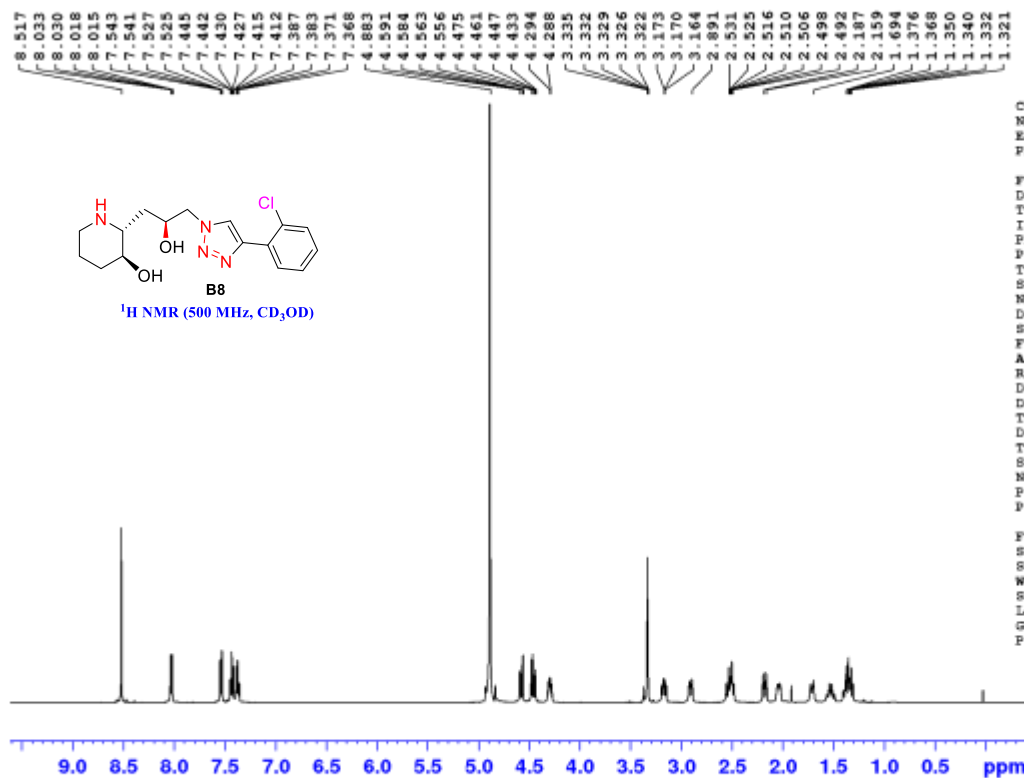
BRUKER

Current Data Parameters
NAME 500
EXPNO 341
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220504
Time 14.20 h
INSTRUM spect
PROBHD x109128_0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 1039
DS 4
SWH 29761.904 Hz
FIDRES 0.308261 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 2833.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.7829381 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 64.00399780 W
SFO2 500.1820007 MHz
NUC2 1H
CPDPRG2 waltz65
PCPD2 80.00 usec
PLW2 4.84679985 W
PLW12 0.17039999 W
PLW13 0.08570800 W

F2 - Processing parameters
SI 32768
SF 125.7703610 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

AB-3-105-2-2 C1

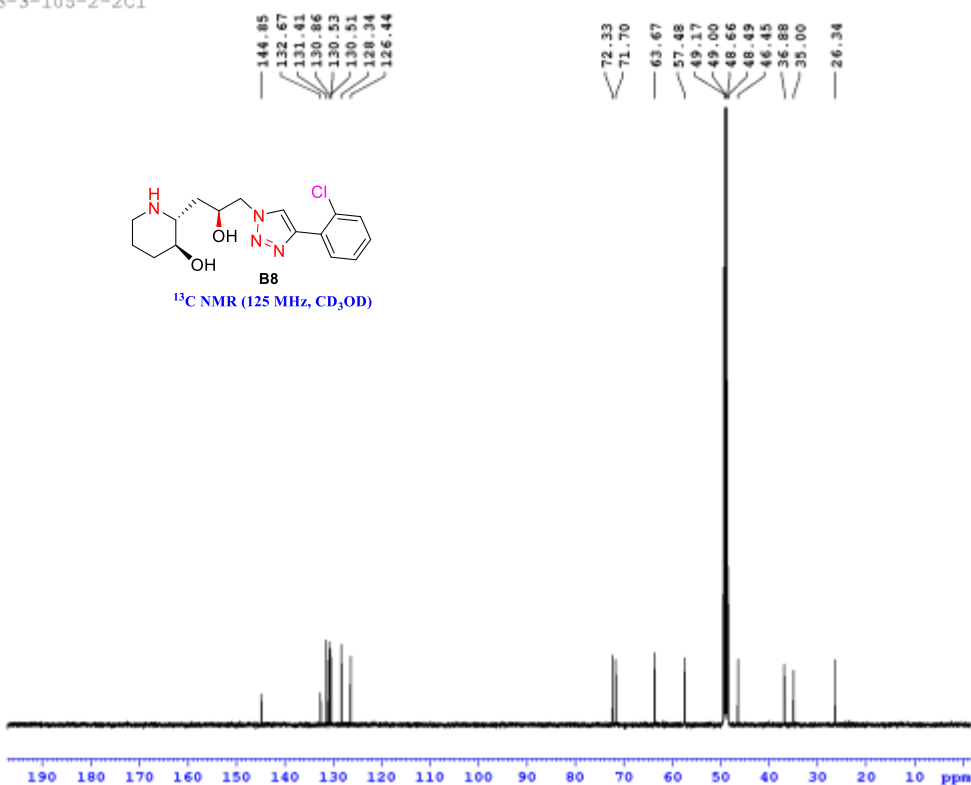


Current Data Parameters
NAME AB-500 Ascend
EXPNO 524
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220509
Time 16.03 h
INSTRUM spect
PROBHD E119470_0291 (4
PULPROG zg30
TD 65536
SOLVENT MeOD
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 87.13
DM 50.000 usec
DE 6.50 usec
TE 298.5 K
D1 1.00000000 sec
TD0 1
SFO1 500.3720898 MHz
NUC1 1H
P1 10.00 usec
PLW1 23.23100090 W

F2 - Processing parameters
SI 65536
SF 500.3690000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

AB-3-105-2-2C1

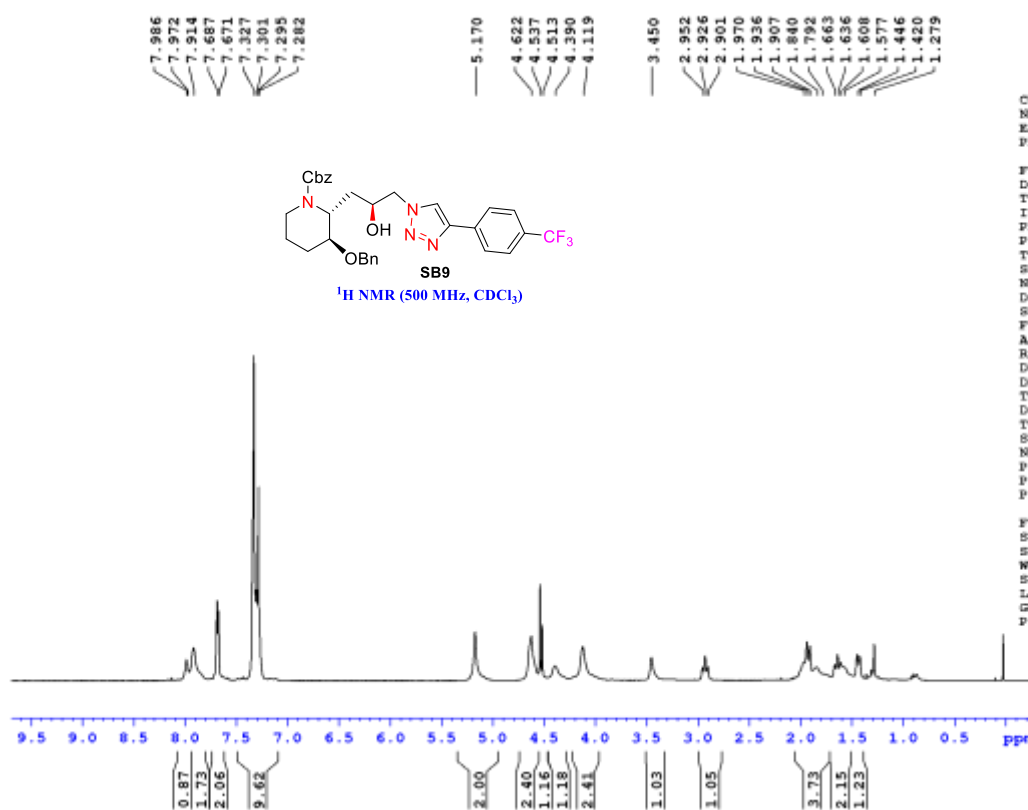


Current Data Parameters
NAME AB-500 Ascend
EXPNO 527
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220510
Time 12.32 h
INSTRUM spect
PROBHD E119470_0291 (4
PULPROG zgpg30
TD 65536
SOLVENT MeOD
NS 701
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 192.83
DM 16.000 usec
DE 6.50 usec
TE 300.4 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8304669 MHz
NUC1 13C
P1 10.00 usec
PLW1 115.01000214 W
SFO2 500.3710015 MHz
NUC2 1H
PCPDPRG2 waltz16
PCPD2 80.00 usec
PLW2 23.23100090 W
PLW12 0.36298999 W
PLW13 0.18257999 W

F2 - Processing parameters
SI 32768
SF 125.8177090 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

AB-3-80-2-4CF3

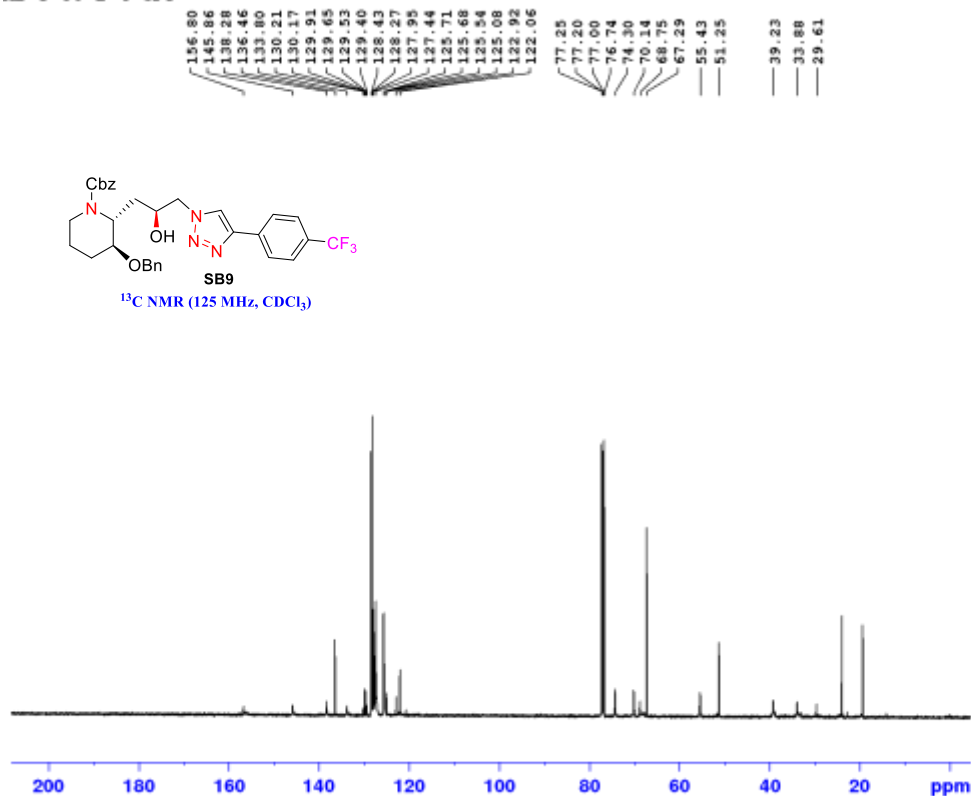


Current Data Parameters
NAME 500
EXPNO 297
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220321
Time 15.24 h
INSTRUM spect
PROBHD Z109128_0042
PULPROG zg30
TD 65536
SOLVENT CDC13
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 144
DM 50.000 usec
DE 13.04 usec
TE 296.8 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W

F2 - Processing parameters
SI 65536
SF 500.1800000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

AB-3-80-2-4 CF3

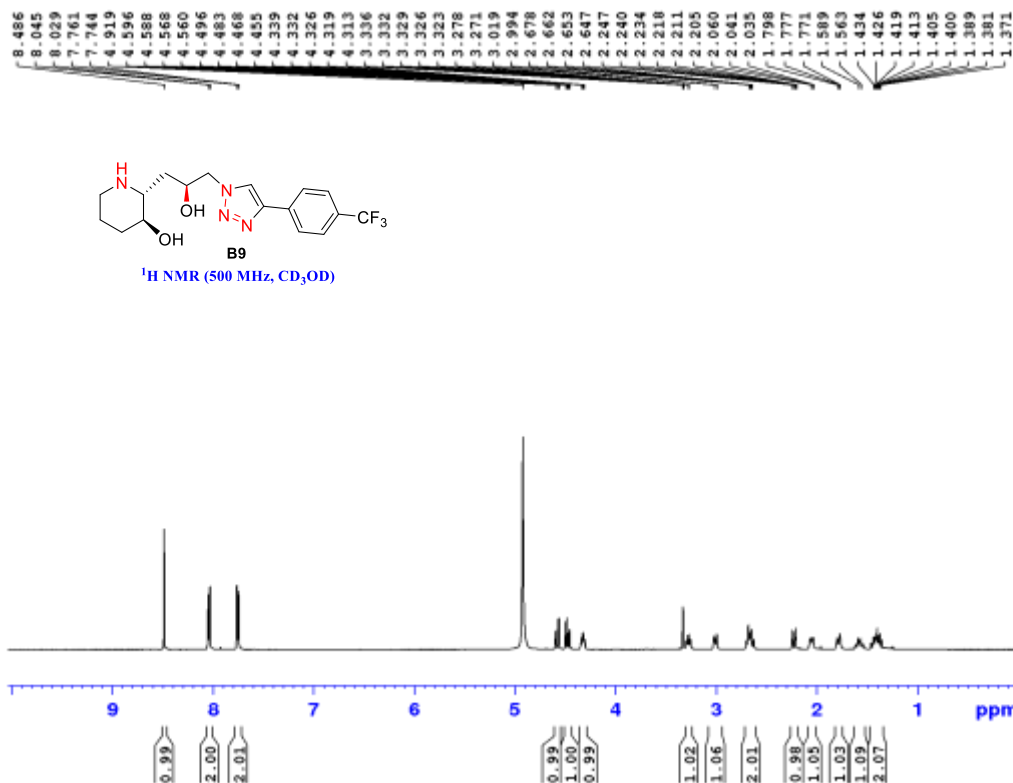


Current Data Parameters
NAME Ascend-500
EXPNO 469
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220315
Time 9.47 h
INSTRUM spect
PROBHD Z119470_0231
PULPROG zgpg30
TD 65536
SOLVENT CDC13
NS 1024
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 192.83
DM 16.800 usec
DE 6.50 usec
TE 297.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8304669 MHz
NUC1 13C
P1 10.00 usec
P1M1 115.01000214 W
SFO2 500.3710015 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 80.00 usec
P1M2 23.23100090 W
P1M12 0.36230899 W
P1M13 0.18257999 W

F2 - Processing parameters
SI 32768
SF 125.8178989 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

AB-3-90-2-CF3

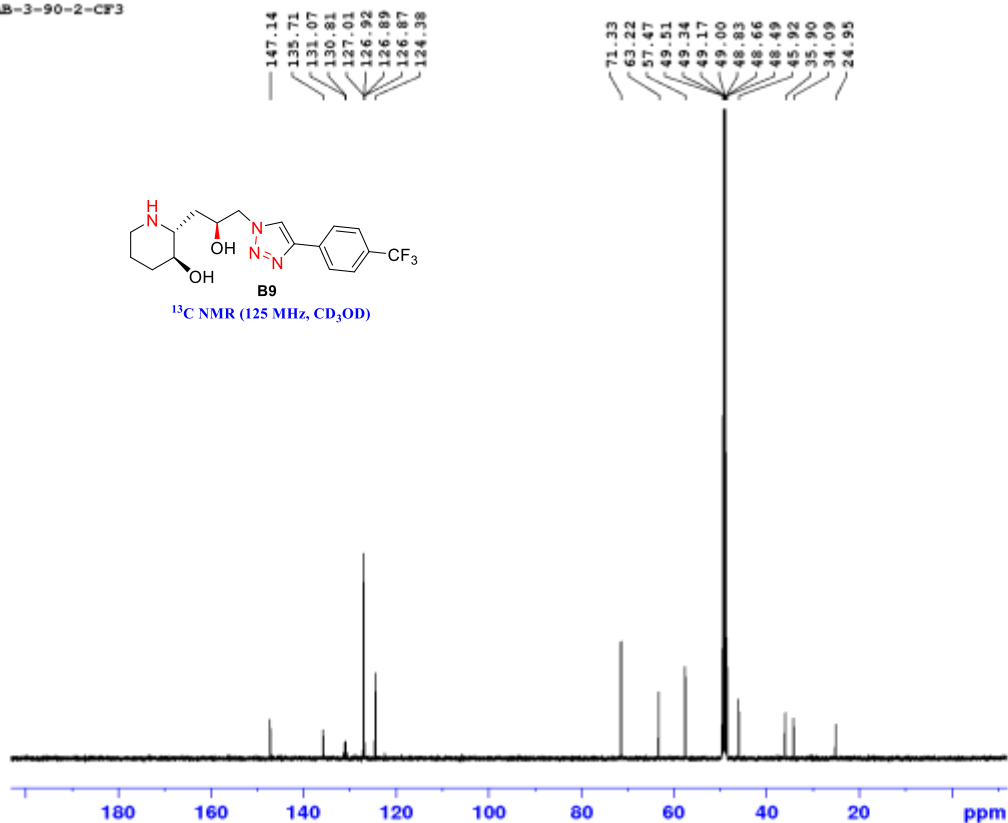


Current Data Parameters
 NAME AB-500
 EXPNO 326
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220427
 Time 12.00 h
 INSTRUM spect
 PROBHD Z109128_0042 (1
 PULPROG zg30
 TD 65536
 SOLVENT MeOD
 NS 16
 DS 2
 SWH 10000.000 Hz
 FIDRES 0.305176 Hz
 AQ 3.2767999 sec
 RG 114
 DW 50.000 usec
 DE 13.04 usec
 TE 295.9 K
 D1 1.00000000 sec
 TDO 1
 SFO1 500.1830886 MHz
 NUC1 1H
 P0 5.00 usec
 P1 15.00 usec
 PLW1 4.84679985 W

F2 - Processing parameters
 SI 65536
 SF 500.1800000 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

AB-3-90-2-CF3

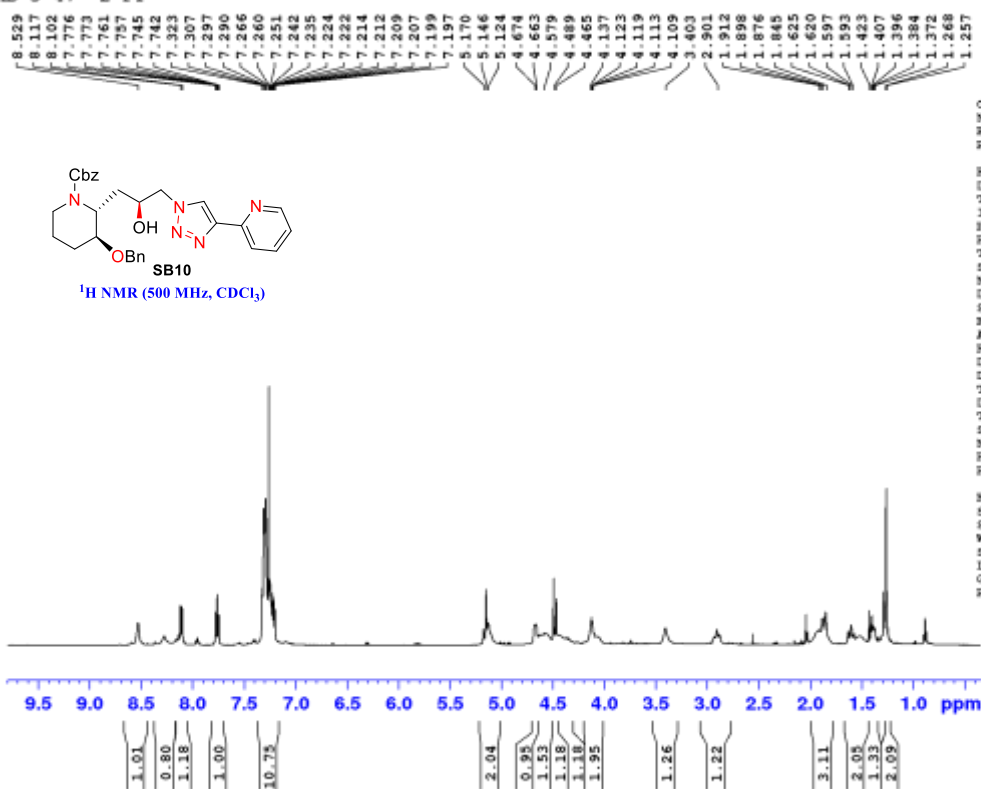


Current Data Parameters
 NAME AB-500
 EXPNO 328
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20220427
 Time 12.50 h
 INSTRUM spect
 PROBHD Z109128_0042 (1
 PULPROG zgpg30
 TD 65536
 SOLVENT MeOD
 NS 806
 DS 4
 SWH 29761.904 Hz
 FIDRES 0.908261 Hz
 AQ 1.1010048 sec
 RG 203
 DW 16.800 usec
 DE 6.50 usec
 TE 296.4 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TDO 1
 SFO1 125.7829381 MHz
 NUC1 13C
 P0 3.33 usec
 P1 10.00 usec
 PLW1 64.00399780 W
 SFO2 500.1820007 MHz
 NUC2 1H
 CPDPRG2 waltz16
 PCPD2 80.00 usec
 PLW2 4.84679985 W
 PLW12 0.17039939 W
 PLW13 0.08570800 W

F2 - Processing parameters
 SI 32768
 SF 125.7701861 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

AB-3-47- 2-PY

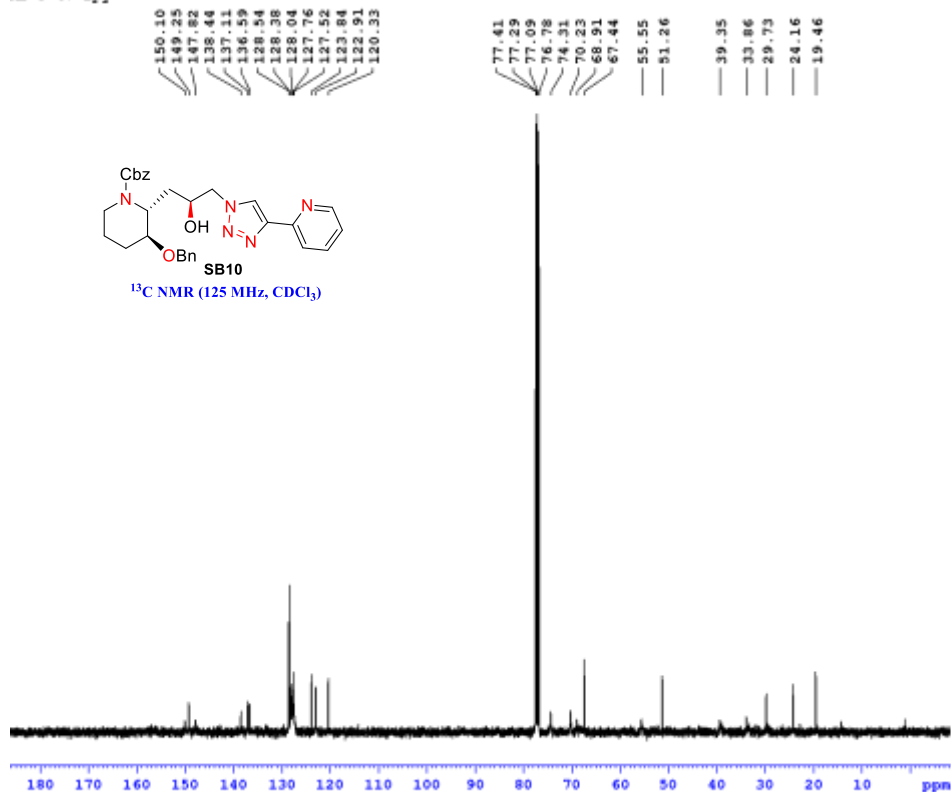


Current Data Parameters
NAME Ascend-500
EXPNO 450
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220121
Time 16.17 h
INSTRUM spect
PROBHD Z125331_0034 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 69.79
CW 50.000 usec
DE 6.50 usec
TE 299.9 K
D1 1.00000000 sec
TD0 1
SFO1 500.1320898 MHz
NUC1 1H
P1 8.00 usec
PLW 12.18000031 W

F2 - Processing parameters
SI 65536
SF 500.13690114 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

AB-3-47-2py

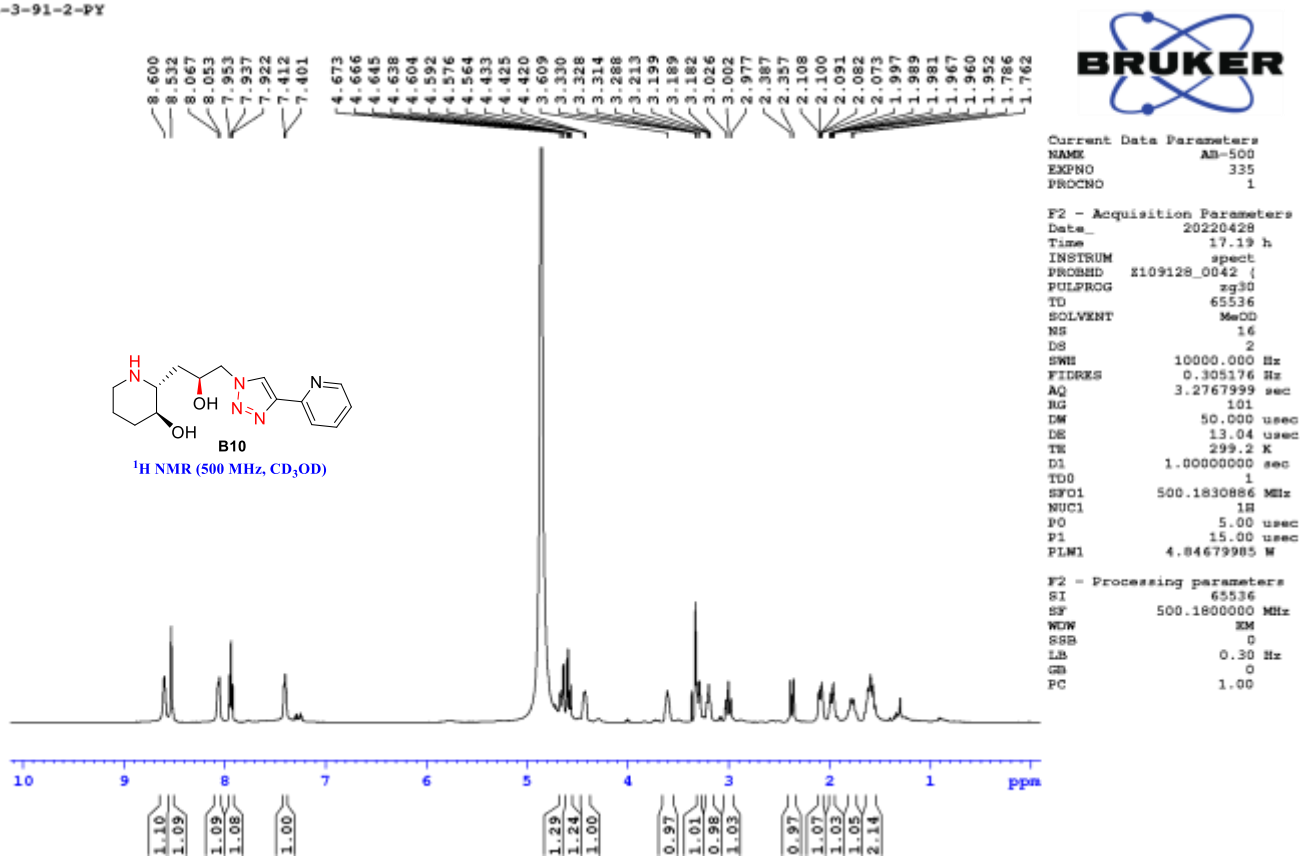


Current Data Parameters
NAME 400
EXPNO 147
PROCNO 1

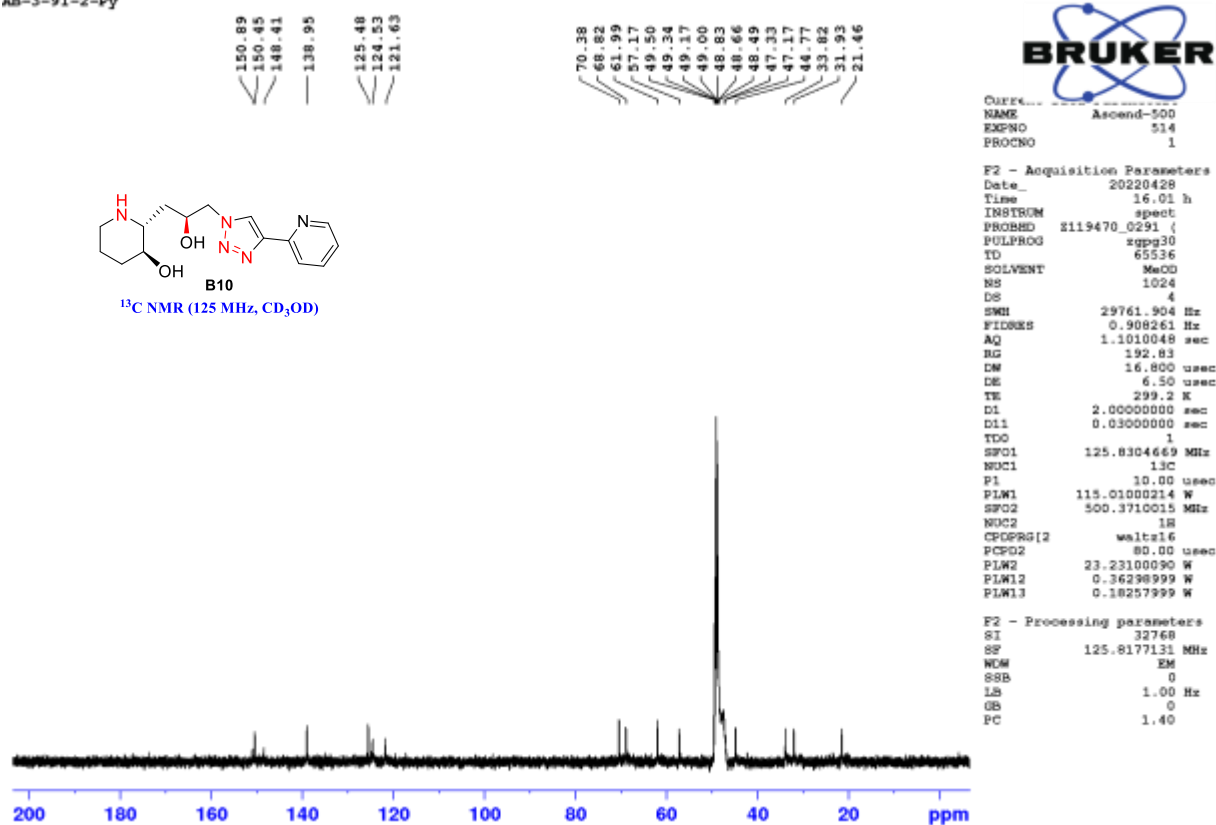
F2 - Acquisition Parameters
Date_ 20220124
Time 15.16 h
INSTRUM spect
PROBHD Z108618_0098 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 203
CW 20.800 usec
DE 6.50 usec
TE 405.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6130223 MHz
NUC1 13C
P1 3.13 usec
P1 10.00 usec
PLW1 49.43999863 W
SFO2 400.0924004 MHz
NUC2 1H
CPDPRG2 waltz65
PCPD2 90.00 usec
PLW2 15.18599807 W
PLW12 0.41622999 W
PLW13 0.20936000 W

F2 - Processing parameters
SI 32768
SF 100.6029620 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

AB-3-91-2-PY



AB-3-91-2-Py



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by Anjaneyulu Bandi

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