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Stereoselective Total Synthesis of Vilanterol

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Abstract

A total synthesis of Vilanterol, a potent molecule for asthma and chronic obstructive pulmonary disease and a long-acting β_2-adrenoceptor agonist, is carried out effectively using a multistep manner. A key intermediate tert-butyl-(R)- dimethyl benzo dioxin 2-hydroxy ethyl carbamate **8** was synthesized using C1- Wittig on aromatic aldehyde, Sharpless asymmetric dihydroxylation, selective tosyl protection of primary alcohol. Additionally, another key intermediate **9** was synthesized using alcohol and dibromo hexane compound via substitution reactions. Combining of the two synthetic fragments to create an acceptable amount of Vilanterol.

Introduction

Pulmonary infections are caused by inflammatory responses are becoming a prominent cause of obstructive lung disease characterized by long-term difficulty breathing problems and poor air flow [1] across the globe. Global prevalence of COPD was 10.3% in 2019, accounting for 391.9 million cases worldwide among people aged 30–79 years.[2] Asthma and chronic obstructive pulmonary disease (COPD) are traditionally thought to be two different respiratory illnesses.[2] β_2-Adrenoceptor (β_2-AR) agonists are indeed the main class of drugs used to treat both asthma and COPD by enhancing airflow into the lungs through regulating the airways.[3] This class is further sub divided into long-acting and short-acting β_2-AR agonists depending on the length of time and effect.[4] All these β_2-AR agonists show bronchodilating properties.[5,6]

Vilanterol 1 (Figure-1) is a potent, ultra-long acting β_2-adrenoreceptor agonist used as a first-line treatment for asthma and chronic obstructive pulmonary disease (COPD). Vilanterol is more active as a β-agonist, showing no side effects. It has a greater intrinsic efficacy than salmeterol and a greater potency than indacaterol and salbutamol. In addition, it has been shown using human recombinant $\beta_{1/2/3}$-AR cAMP assays that **vilanterol 1** has significantly

greater β_2-AR selectivity than formoterol, indacaterol and Salbutamol.[7,8] **(Figure-2)**

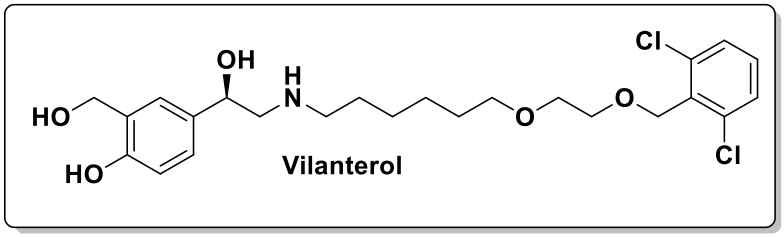


Figure-1: Vilanterol structure

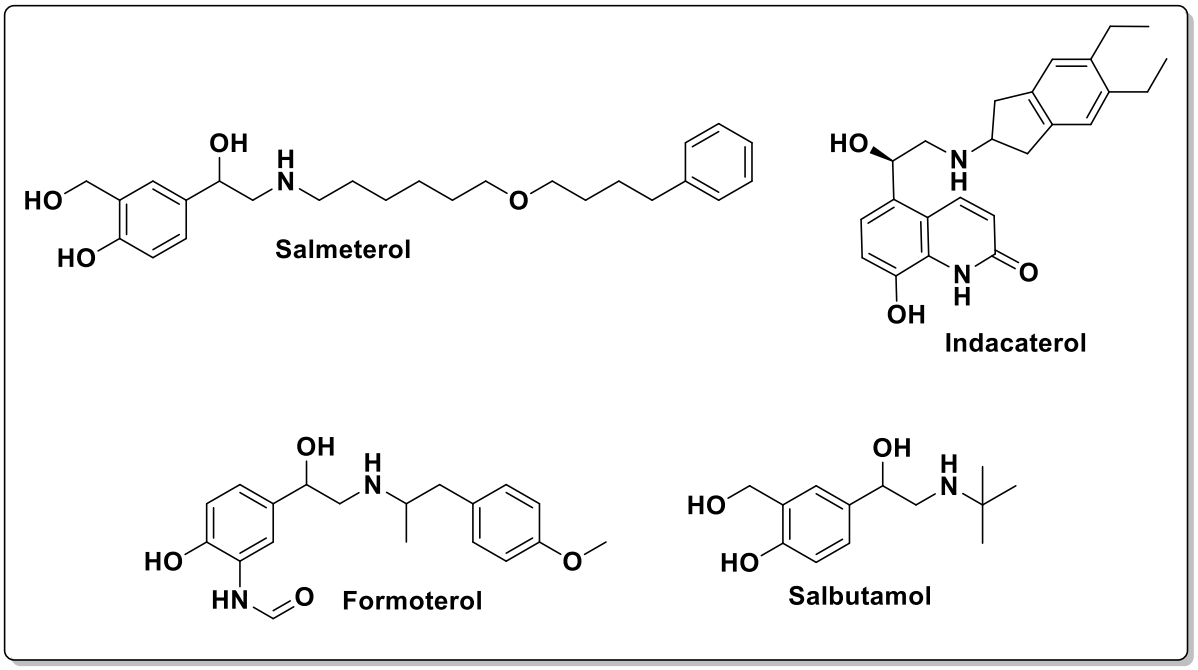


Figure-2: Some of Chronic obstructive pulmonary disease (COPD) drugs

COPD patient's bronchodilator therapy

Treatment for COPD attempts to reduce the fast loss in lung function, treat difficulty breathing and cough and increase daily lung function, minimize exacerbations, and enhance efficiency of life. There are currently many kinds of bronchodilators available in the market. Drugs that may be employed include β_2-AR agonists, anti cholinergics and methyl xanthines with oral steroids or alone. The inhaled route is now used in order to minimize systemic effects. For long-term treatment, long-acting pharmaceuticals are preferable over fast-acting and short-acting treatments. All recommendations indicate to long-acting bronchodilator treatment subsist considered when patients are with COPD symptomatic. Despite this, it is not mentioned that which type of drugs must be

evaluated first in the first evaluation.[9, 10] The cost, consequence profile, with availability of an agent may all play a role in the selection process. Novel β_2-agonists, Novel antimuscarinic agents, and Novel bronchodilator combinations are some of the drugs now under research (below tables).

Table-1: Novel β_2-agonists developments

Drug	The Characteristics	progress	Working company
Vilanterol	Compared to salmeterol, indacaterol and salbutamol in terms of intrinsic effectiveness, it is more potent. It has a rapid beginning of action and a long-lasting bronchodilation effect that lasts for 24 hours.	Phase III information on these drugs is scarce.	GlaxoSmithKline, London, United Kingdom/Theravance, South San Francisco, California, United States
Olodaterol	It is a partial 2-agonist that retain s β_2-agonists signaling capability even after prolonged preincubation True 24-hour bronchodilation. Phase II trials showed 24-hour bronchodilation after 4 weeks of once-daily dosing.	The results of Phase III clinical trials are not yet released.	Germany
Indacaterol	It acts as a near-complete 2-agonist. It has a quick beginning of act and provides full 24-hour bronchodilation. Indacaterol 150 and/or 300 mg once day has been shown to be more efficient than formoterol/ salmeterol and at least as efficient as astiotropium in massive Phase III studies. It is well tolerated and has an excellent safety profile in both the general and cardiovascular systems.	Currently launched in a number of countries	Novartis, Basle, Switzerland

Table-2: New antimuscarinic drugs in the works.

Drug	The Characteristics	progress	Working company
Glycopyrronium bromide	In vitro, it has a period of activity among tiotropium and ipratropium. Everyday use of glycopyrronium50 mg results in persistent 24-hour bronchodilator.	III-phase	Basle, Novartis, Switzerland.
Aclidinium bromide	In human isolated lungs, ipratropium had a quicker start and longer duration of effect than tiotropium. The ACCLAIM/COPD studies had mixed effectiveness findings, though aclidinium 400 mg daily twice offered equivalent bronchodilation to tiotropium 18 mg per a day.	III-phase	Almirall Prodesfarma, Spain, Barcelona.
GSK573719	Daily one bronchodilator for COPD, it is supported by its lengthy time of action when delivered through inhalation within animal model.	III-phase No clinical data were released.	GlaxoSmithKline, London, UK

Table-3: Novel bronchodilator combinations in development

a) β_2-agonist/antimuscarinic agent combinations.

Drug	The Characteristics	progress	Working company
Indacaterol/ Glycopyrronium bromide (QVA149)	It is once in a day, extra potent than indacaterol when administered by supra maximal doses	Phase-III available data is limited	Switzerland, Basle, Novartis.

Olodaterol or Tiotropium	daily once and more effect	Phase-III available data is limited	Boehringer Ingelheim, Germany.
Vilanterol	Combination of Once in a day	No phase-III data	GlaxoSmithKline, London.
Formoterol/ aclidinium	Twice in a day	2 nd Phase data not available.	Almirall Prodesfarma, Spain.
Formoterol/ glycopyrronium	Twice in a day	No data for 2nd Phase II	Pearl Therapeutics,USA.

b) β_2-agonist/inhaled corticosteroid combinations.

Drug	The Characteristics	progress	Working ompany
Vilanterol/ fluticasone furoate	Combination of Once in a day	Limited data available.	GlaxoSmithKline, UK.
Indacaterol/ mometasone	Combination of Once in a day	No Clinical data	Novartis, Switzerland.
Formoterol/ mometasone	Twice in a day combination	III- Phase Clinical data not disclosed	Merck & Co., White house Station, USA
fluticasone propionate / Formoterol	Daily twice	Limited data obtainable on phase-III.	Mundipharma Research Ltd, United Kingdom.

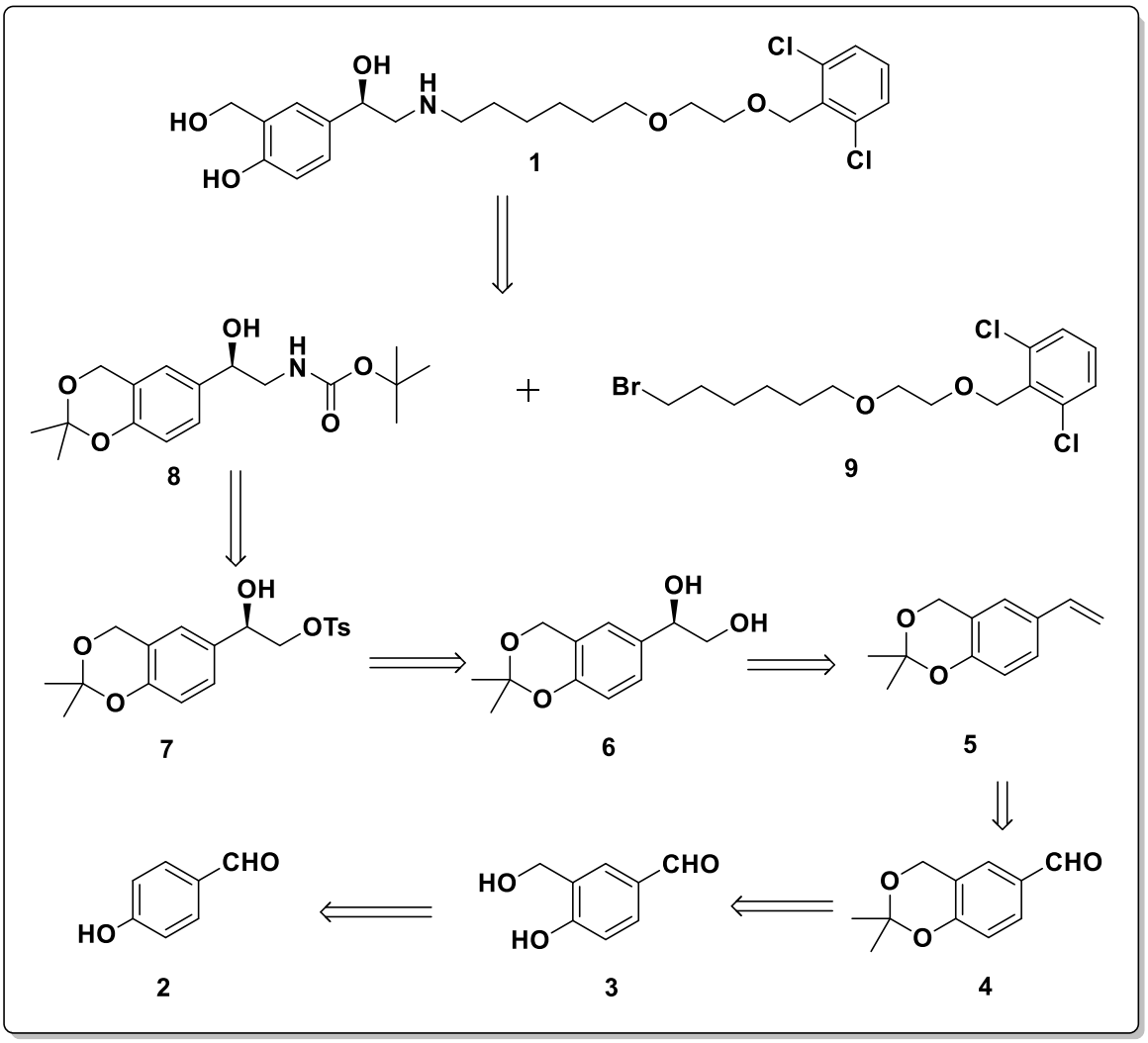
Present work

We choose the **Vilanterol 1 (Figure-1)** molecule Based on its significant biological potential, the molecule was synthesized via a non-infringing manner using commercially accessible and inexpensive 4-hydroxybenzaldehyde as a starting **compound 2**.

3.3.1. Retro synthetic analysis of Vilanterol

The retrosynthesis of Vilanterol 1 showed in **Scheme-1.** Its structure has one

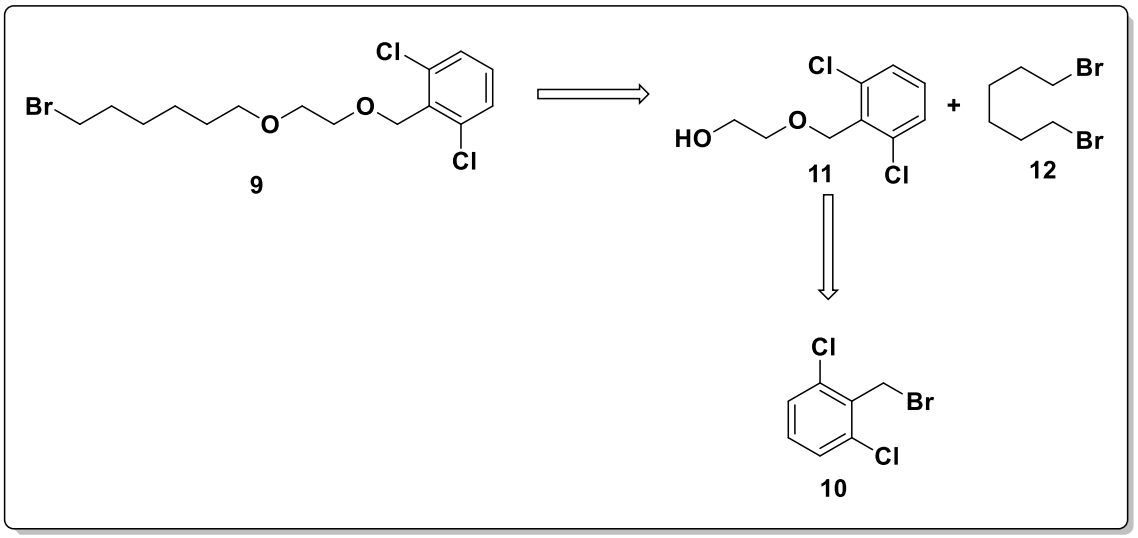
chiral center, a secondary amine linkage, two ether linkages, aromatic phenol, and aromatic dichloro moieties. **Vilanterol 1** can be synthesized by the two key fragments: *N*-protected fragment compound **8** and alkyl bromide fragment **9**. In which *N*-protected amine fragment **8** could be accessed from commercially available, 4-hydroxybenzaldehyde **2**, and alkyl bromide fragment **9** could be synthesized from 2,6-dichloro benzyl bromide **10 (Scheme-1 & 2).**



Scheme-1: Retrosynthesis of Vilanterol

The pharmacophoric key precursor *N*-protected compound **8** can be synthesized from 4-hydroxy benzaldehyde **2**. In this synthetic process the main diol compound **6** can be achieved from compound **2** through phenolic Aldol condensation[11], followed by diol acetonide protection compound **4** and olefination with C_1-wittig salt in presence of *t*-BuOK affords, 2,2-dimethyl-6-vinyl-4*H*-benzo[d][1,3]dioxine **5** as shown in the **Scheme-1**[12-14] followed by Sharpless asymmetric dihydroxylation[15,16]

using AD-mix-β, to produce the key intermediate-chiral diol **6**, The diol further can be converted to compound **7** selective tosyl protection of alcohol [17,18] and obtained tosyl compound **7** could be converted in to compound **8** through nucleophilic substitution with tert-butyl carbamate [19] by using base. This compound formation was the crucial step in this synthesis.

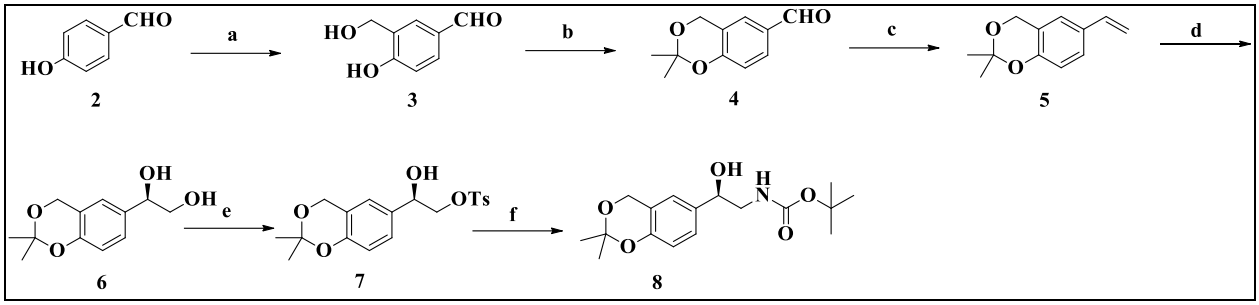


Scheme-2: Retro synthesis of Fragment 9

Then fragment **9** could be resulted from 2,6-di chloro benzyl bromide **10**, on substitution using ethylene glycol to produce **11** followed by coupling with 1,6-dibromohexane **12** develops alkyl bromide fragment [20] **9**. Further the target molecule can be easily obtained by combining the two fragments **8** and **9** through *N*-alkylation followed by deprotection.

Results and Discussion

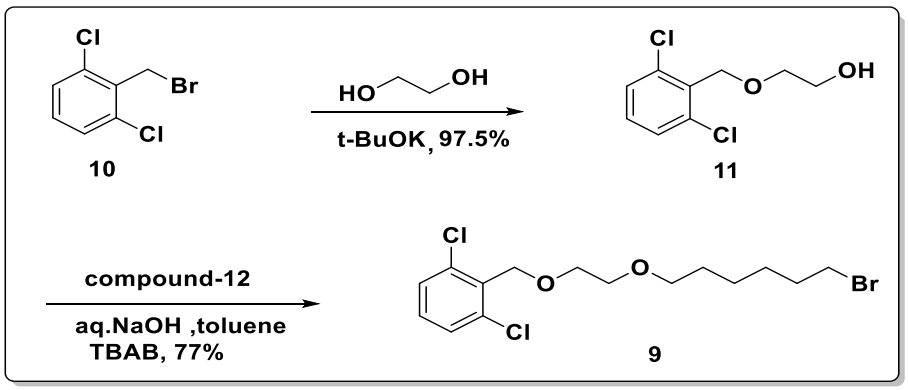
As part of our regular research program, in synthesis of biologically active natural and synthetic molecules [21-23] herein we report the enantioselective synthesis of bronchilo dilating agent **Vilanterol 1.** As mentioned in the proposed retro synthetic sequence, we have proceeded with compound **2** to synthesize the fragment **8** (**scheme-3**) with compound 10 to synthesize fragment 9 **(scheme-4)**



Scheme-3: Synthesis of fragment 8

Reagents & Conditions: *(a) HCHO, H_2O, $Na_2B_4O_7$, 1M, NaOH, reflux, 83%. (b) 2,2-DMP, DCM, CSA, 2h, 65%. (c) C_1 Wittig, ^{t}BuOK, THF, 2h, 80%. (d) AD-mix-β, ^{t}BuOH: H_2O, 0 ^{o}C, 24h, 94%. (e) TsCl, Bu_2SnO, Et_3N, DCM. 1h, 79 %. (f) tert-butyl carbamate, DIPEA, THF, 6 hr 80 %.*

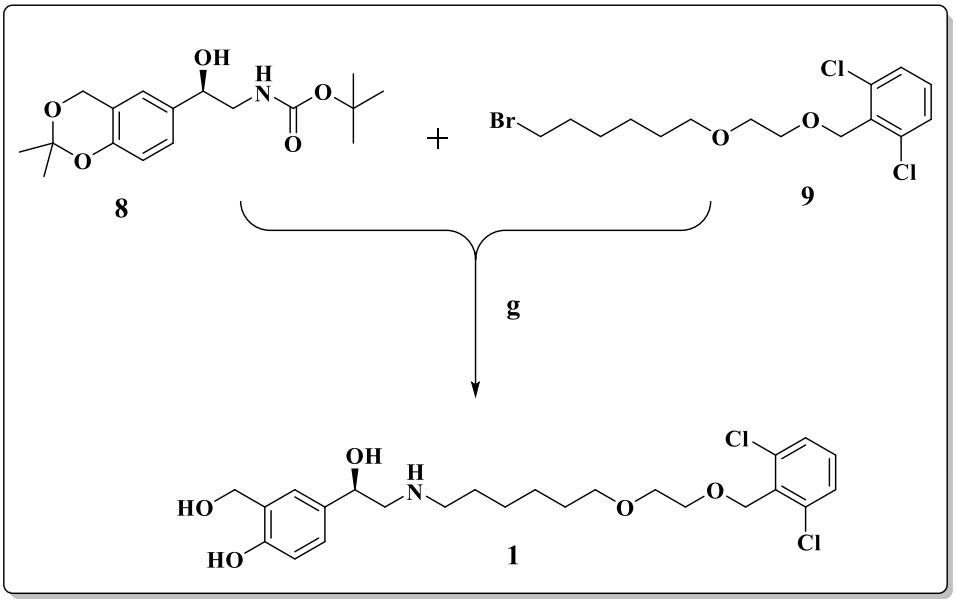
The synthesis of *N*-protected compound **8 (Scheme-4)** was achieved from 4-hydroxy benzaldehyde **2.** The compound **2** was subjected to phenolic Aldol condensation using HCHO, $Na_2B_4O_7$, 1-molar NaOH under reflux condition to produce diol compound **3** with 83% of yield. Further diol compound was subsequently protected as an acetonide protected by using 2,2-DMP and CSA catalyst to produce compound **4** with 65% of promising yield. This protected compound subjected to Wittig olefination with C_1-wittig salt in presence of ^{t}BuOK affords to produce compound **5,** these obtained alkene compound under Sharpless asymmetric dihydroxylation using AD-mix-*β*, to produce chiral diol **6** further it was converted to selective tosyl protected compound presents of TsCl, Bu_2SnO, Et_3N with 79 % of good yield. Thus obtained tosyl compound **7** was converted in to compound **8** using *tert*-butyl carbamate and DIPEA as base to produce nucleophilic substituted compound **8**



Scheme-4: Synthesis of fragment 9

Reagents & Conditions: *(g) excess ethylene glycol, t-BuOK, 97.5% (h) 1,6-dibromohexane, aq. NaOH, TBAB, toluene,77%.*

Further staring with 2,6-di chloro benzyl bromide **10**, substitution with excess ethylene glycol under the alkalinity of *t*-BuOK afforded the corresponding intermediate **11**, which was then subjected to etherification with excess 1,6-dibromohexane **12** in aqueous solution of NaOH to give the halo hydrocarbon [20] **9**.



Scheme-4: Synthesis of Vilanterol (fragments 8 and 9 coupling)

Reagents & Conditions: CH_3CN, K_2CO_3, KI, 80 ^oC, reflux, 24h, followed by AcOH, H_2O,
70 ^0C, 1h, 88%

As mentioned in the retro synthetic analysis (**scheme-1**), the molecule was assembled *via* coupling of two important building blocks, an amine fragment **8** and halo fragment **9 (scheme-4)** coupling in presence of CH_3CN, K_2CO_3, KI, under reflux conditions for 24h. This newly developed method of alkylation, BOC deprotection followed by the acetonide deprotection was achieved smoothly in presence of acetic acid-water mixture in a single pot reaction, to give the target molecule, **(*R*)-Vilanterol 1** in excellent yield and selectivity.

Conclusion

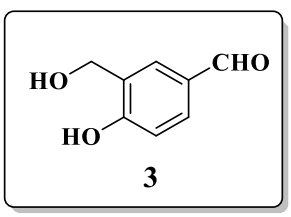
We keep our efforts to develop the convenient and effective total synthesis of β2-adrenoreceptor agonist drug **(R)-vilanterol 1**, which has a more potent drug for COPD & asthma. This synthetic route has advantages like commercially available starting materials, reagents and broadly used reactions are used. Hence overall

synthesis of target compound is achieved in **7** steps with satisfactory yield.

Experimental procedure

All the air and moisture sensitive reactions were carried out under nitrogen atmosphere. Oven-dried glass apparatus were used to perform all the reaction. Freshly distilled anhydrous solvents were used for air and moisture sensitive reactions. Commercially available reagents were used as such. Purification of compounds was carried out *via* column chromatography by using silica gel (60-120 mesh) packed in glass columns. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on 400 MHz and 500 MHz spectrometer, using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FT-RT 240-c Spectrophotometer using KBr / Thin Film optics. Mass spectra were recorded on a Finnegan MAT 1020 mass spectrometer operating at 70 eV. Optical rotation values were recorded on Horiba sepa300 polarimeter. High resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer.

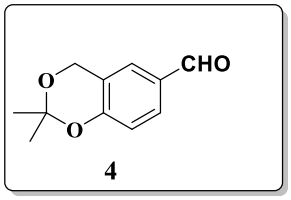
4-Hydroxy-3-(hydroxymethyl)benzaldehyde (3).



3

To a stirred solution of 4-hydroxy benzaldehyde (10 g, 89.3 mmol), in water (80 mL) was added borax (25 g) and NaOH solution (1M, 60 mL) and stirred for 30 minutes at room temperature, then aqueous formaldehyde (10 mL) was added in one portion. The reaction was stirred at 40 ^{o}C for 5 days. After completion of the reaction (monitored by TLC) cooled and mixture was acidified with HCl (3M) up to pH-2 then extracted with ethyl acetate (3 x 50 mL). The combined organic portions were washed brine, dried over Na_2SO_4 and solvent removed under vacuum concentration under reduced pressure, the residue was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (3:7) mixture to gives a compound 3 as white solid, in 11.2 g (85%) yield. Mp: 142 - 143 ^{0}C. **^{1}H NMR (400 MHz, $CDCl_3$) :** δ 9.85 (s, 1H), 7.80 - 7.72 (m, 1H), 7.68 (d, 1H, *J* = 1.9 Hz), 7.60 (d, 1H, *J* = 1.8 Hz), 7.01 (dd, 1H, *J* = 8.3, 3.6 Hz), 4.99 (brs, 1H), 4.87 (s, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 190.7, 161.1, 132.6, 130.8, 122.8, 117.2, 67.6. **HRMS-ESI :** $[M-H]^+$ Calcd for $C_8H_9O_3^+$: 151.0475, Found: 151.0489.

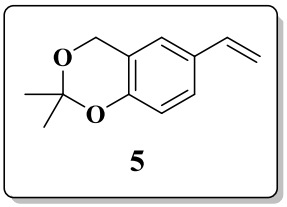
2, 2 - Dimethyl-4*H*-benzo[*d*][1,3]dioxine-6-carbaldehyde (4).



4

To a stirred solution of compound **3** (5 g, 32.9 mmol) in dry acetone was added 2,2-DMP (4.4 g, 42.8 mmol) and a catalytical amount of *P*-TSA, continued to stir for 1hr at room temperature. After completion of the reaction,(monitored by TLC) extracted with ethyl acetate (3x20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, the crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:9) mixture to obtain compound **4** as yellow oil, in 3.90 g (65%), yield. **^{1}H NMR (400 MHz, $CDCl_3$)** : δ 9.86 (s, 1H), 7.71 (d, 1H, *J* = 10.3 Hz), 7.55 (s, 1H), 6.93 (d, 1H, *J* = 8.4 Hz), 4.91 (s, 2H), 1.58 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 190.7, 156.8, 130.5, 129.5, 126.9, 119.7, 117.7, 100.8 ,60.6, 24.8. **IR (neat) :** υmax 3146, 2924, 2853, 1742, 1444 cm.$^{-1}$; **HRMS-ESI** : $[M+H]^+$ Calcd for $C_{11}H_{13}O_3$: 193.0872; Found: 193.0927.

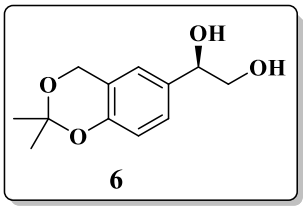
2,2-Dimethyl-6-vinyl-4*H*-benzo[*d*][1,3]dioxine (5).



5

To a stirred suspension of compound **4** (2 g, 10.4 mmol) in dry THF, was added the C_1-witting salt (21.1 g, 52.1 mmol), and ^{t}BuOK (5.8 g, 10.4 mmol) at 0 ºC and continued stirring for 2h at room temperature. After completion of the reaction (monitored by TLC) was quenched with cold water, then removed THF under vacuum and extracted with ethyl acetate (3x20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (2:8) mixture to give the compound **5** as yellow liquid, in 1.59 g (83%) yield. **^{1}H NMR (400 MHz, $CDCl_3$) :** δ 7.23 (d, 1H, *J* = 8.4 Hz), 7.01 (s, 1H), 6.78 (d, 1H, *J* = 8.4 Hz), 6.62 (dd, 1H, *J* =17.3, 10.9 Hz), 5.59 (d, 1H, *J* = 17.3 Hz), 5.12 (d, 1H, *J* = 10.9 Hz), 4.84 (s, 2H), 1.54 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$) :** δ 151.0, 136.1, 130.1, 125.9, 122.4, 119.2, 117.1, 111.7, 99.6, 60.9, 24.7.; **IR (neat):** υmax 2991, 2923, 1728, 1614, 1499, 1257 cm.$^{-1}$.; **HRMS-ESI:** $[M+H]^+$ Calcd for $C_{12}H_{15}O_2$: 191.0995; Found: 191.1009.

(*R*)-1-(2,2-Dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)ethane-1,2-diol (6).



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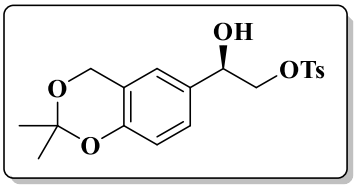
To a stirred mixture of ^{t}BuOH**:** H_2O (1:1, 63 mL) was added compound **5** (1.2 g, 6.3 mmol), than added AD-mix-*β* (8.8 g) followed by methyl sulfonamide (0.6 g) at 0 °C and stirred continuously for 24h at same temperature. After the completion of reaction indicated by TLC, sodium sulphite (7.5 g) was added. The suspension was dissolved in cold water, extract with ethyl acetate (3x20mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (3:7) mixture to give compound **6** as a white solid, in 1.3 g (95%) yield. Mp: 80 - 81 °C, Optical rotation: $[\alpha]_D^{25}$ -11 (c 1, $CHCl_3$) **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.14 (dd, 1H, *J* = 8.4, 1.8 Hz), 7.02 (s, 1H), 6.81 (d, 1H, *J* = 8.43 Hz), 4.84 (s, 2H), 4.77-4.72 (m, 1H), 3.78 - 3.69 (m, 1H), 3.68 - 3.60 (m, 1H), 1.54 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 151.0, 132.3, 125.9, 122.4, 119.4, 117.1, 99.6, 74.2, 68.0, 60.9, 24.7, 24.6.; **IR (neat):** υmax 3351, 2923, 1731, 1500, 1458, 1142 cm.$^{-1}$; **HRMS-ESI:** $[M-H]^+$ Calcd for $C_{12}H_{15}O_4$: 224.1047; Found: 224.1063.

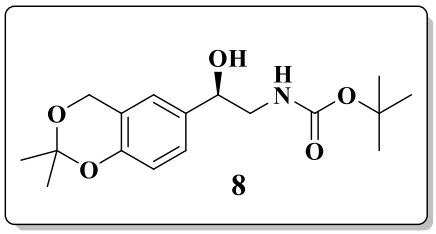
(*R*)-1-(2,2-Dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2-hydroxyethyl-4-methylbenzene-sulfonate(7).



To a stirred mixture of **6** (1 g, 4.5 mmol) in dry DCM (10 mL) at 0 °C was added Bu_2SnO (0.2 g, 0.9 mmol), TsCl (0.85 g, 4.5 mmol) and Et_3N (0.67 g, 6.7 mmol) and stirring continued for 1h. After completion of the reaction (monitored by TLC), quenched with cold water and extracted with DCM (3x10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, thus obtained crude compound **7**, as yellow liquid, in 1.68 g (81%) %) yield. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.77 (d, 2H, *J* = 8.6 Hz), 7.34 (d, 2H, *J* = 8.6 Hz), 7.07 (dd, 1H, *J* = 8.0, 1.8 Hz), 6.95 (d, 1H, *J* = 1.4 Hz), 6.77 (d, 1H, *J* = 8.4 Hz), 4.92 - 4.87 (m, 1H), 4.80 (s, 2H), 4.14 - 4.09 (m, 1H), 4.05 - 3.99 (m,

1H), 2.45 (s, 3H).1.52 (s, 6H).; **^{13}C NMR (101 MHz, $CDCl_3$) :** δ 151.4, 145.0, 132.6, 130.0, 129.9, 127.9, 126.0, 122.6, 119.6, 117.2, 99.7, 74.2, 71.5, 60.7, 24.8, 24.5, 21.6.; **IR (neat):** υmax 3428, 2924, 1725, 1597, 1452, 1174 cm.$^{-1}$.**HRMS-ESI :** $[M+Na]^+$ Calcd for $C_{19}H_{22}NaO_6S$: 401.1037; Found: 401.1045.

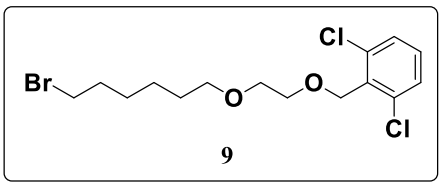
***tert*-butyl(R)-(2-(2,2-dimethyl-4H-benzo[d][1,3]dioxin-6-yl)-2-hydroxyethyl)carbamate (8) .**



8

To a stirred solution of compound **7** (1 g, 2.6 mmol) in DMF was added tertiary-butyl carbamate (0.68 g, 5.2 m mol), DIPEA (0.68 g, 5.2 m mol) and stirred continuously at 70 °C for 12 h after completion of the reaction, extracted with ethyl acetate (3x20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography, yield (.25 g, 80%) as a white solid. **^{1}H NMR (300 MHz, CDCl3):** 7.11 (d, J 8.3 Hz, 1H), 6.98 (s, 1H), 6.78 (d, J 8.4 Hz, 1H), 5.02 (s, 1H), 4.81 (s, 2H), 4.74-4.65 (m, 1H), 3.41-3.16 (m, 2H), 1.53 (s, 6H), 1.44 (s, 9H).**^{13}C NMR (101 MHz, CDCl3):** 156.9, 150.8, 133.8, 125.7, 122.2, 119.3, 117.0, 99.62, 79.8, 73.5, 60.9, 48.4, 28.3, 24.6.; **IR(KBr):** υmax 3359, 3299, 3021, 2991, 2942, 2822, 2608, 2515, 1886, 1596, 1434, 1379, 746cm^{-1}.**ESI-MS :** $[M+H]^+$ calculated for $C_{17}H_{25}NO_5$: 324.1805, Found: 324.1719.

2-((2-((6-bromohexyl)oxy)ethoxy)methyl)-1,3-dichlorobenzene (9).

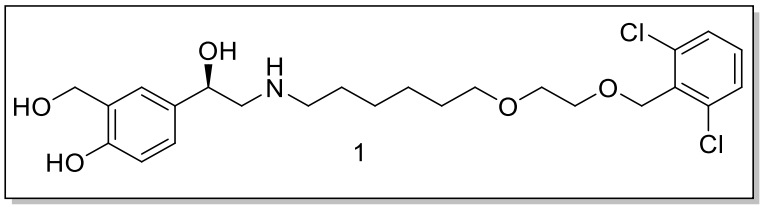


9

A 50 mL round bottom flask was charged with **11** (25 g, 113.1 mol, 1.0 equiv.), 1,6-dibromohexane (27.3 g, 113.5 mol, 5.0 eq.), toluene (20mL). CH_3ONa (1.24g, 24.9 mol, 1.1 eq.) was added to the mixture over the period of 3h at below 50 ^{0}C, then the mixture warmed to 80 ^{0}C and stirred for 1.5h. After reaction completion, the mixture was cooled to room temperature, filtered to remove the inorganic salts. The fractions were separated using fractional distillation. The 1,6-dibromohexane was collected between 130–135 ^{0}C and then the pure produced **9** was collected at 155–160 ◦C (7.64g, 88% yield, 99.2% purity) as colorless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.31 (d, J = 8.0 Hz, 2H), 7.17 (t, J = 8.0 Hz, 1H), 4.83 (s,

2H), 3.72–3.67 (m, 2H), 3.61 (t, J = 4.9 Hz, 2H), 3.46 (t, J = 6.6 Hz, 2H), 3.39 (t, J = 6.8 Hz, 2H), 1.89-1.81 (m, 2H), 1.61-1.54 (m, 2H), 1.44 (dt, J = 14.5, 7.3 Hz, 2H), 1.40–1.33 (m, 2H).**^{13}C NMR (126 MHz, CDCl3):** δ 136.9, 133.4, 129.8, 128.3, 71.1, 71.0, 69.1, 67.5, 33.9, 32.7, 29.5, 28.0, 25.3.;**HRMS (ESI):** $[M+H]^+$ calculated for $C_{15}H_{22}BrCl_2O_2$: 383.0174, Found: 383.0199.

(R)-4-(2-((6-(2-((2,6-dichlorobenzyl)oxy)ethoxy)hexyl)amino)-1-hydroxyethyl)-2-(hydro -xy methyl)phenol (1).



To a stirred mixture of compound **8** (0.4 g, 1.23 m mol) and K_2CO_3 (340 mg, 2.46 mmol) in dry acetonitrile (10 mL) at room temperature was added compound **9** (0.25 g, 0.6 mmol) and continued to stir for 48h at 80 °C. TLC confirmed the consumption of starting materials, to was acetic acid (4 mL) and water (2 mL) and then the reaction mixture was stirred at 70°C for another 1h. After the completion of the reaction (by TLC), neutralized with sat. $NaHCO_3$. Then reaction mixture extracted with EtOAc (3×20 mL), the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, to obtain the crude product, which was recrystallized with ethyl acetate to yield 40 mg (55%) of pure solid product. **^{1}H NMR (400 MHz, DMSO):** δ 9.44 (s, 1H), 8.70 (s, 1H), 7.52-7.47 (m, 3H), 7.42- 7.38 (m, 1H), 7.37 (s, 1H), 7.32 (d, *J* = 2.0 Hz, 1H), 7.05 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.94 (s, 1H), 5.03 (t, *J* = 5.1 Hz, 1H), 4.84 (d, *J* = 9.9 Hz, 1H), 4.69 (s, 3H), 4.48 (d, *J* = 4.3 Hz, 3H), 3.61 (d, *J* = 9.5 Hz, 3H), 3.55-3.47 (m, 3H), 3.37 (d, *J* = 6.5 Hz, 4H), 2.99 (d, *J* = 9.7 Hz, 1H), 2.89 (t, *J* = 6.7 Hz, 4H), 1.63 (d, *J* = 5.9 Hz, 2H), 1.54-1.43 (m, 3H), 1.29 (t, *J* = 5.1 Hz, 6H **^{13}C NMR (126 MHz, CDCl3):** 154.4, 135.8, 132.2, 130.1, 128.9, 127.3, 125.9, 114.8, 70.1, 68.9, 67.7, 66.4, 53.2, 46.9, 28.4, 25.5, 25.2, 24.6, 22.7.;).; **IR (KBr) :** υmax 3444, 2936, 2876, 1629, 1563, 1423, 1262, 1110, 769, 608 cm $^{-1}$.; **HRMS (ESI):** $[M+H]^+$ calculated for $C_{24}H_{34}Cl_2NO_5$: 486.1814, Found: 486.1899.

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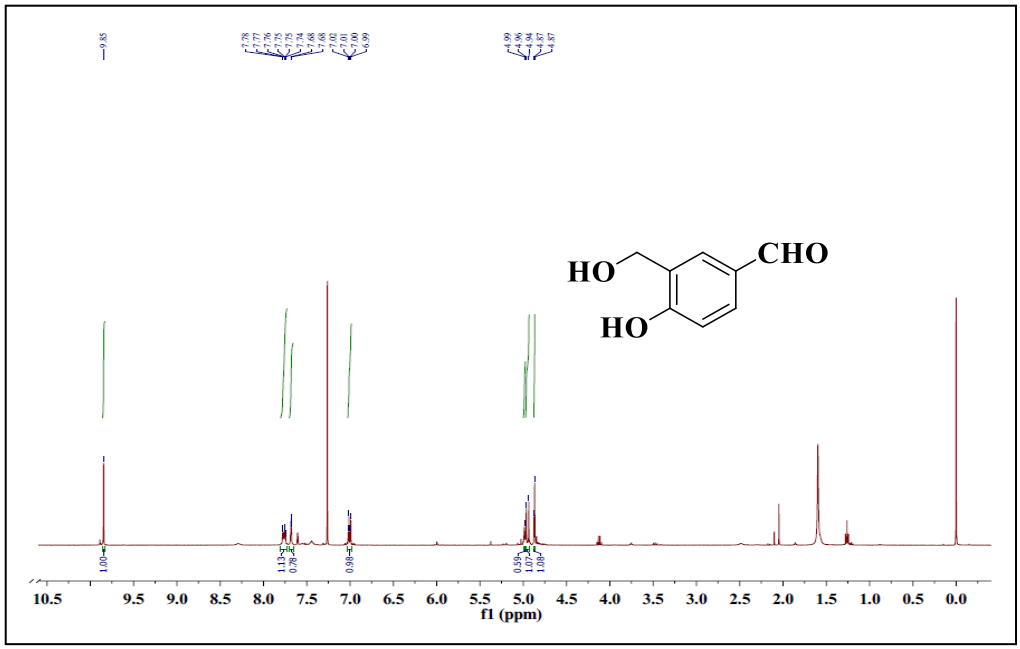
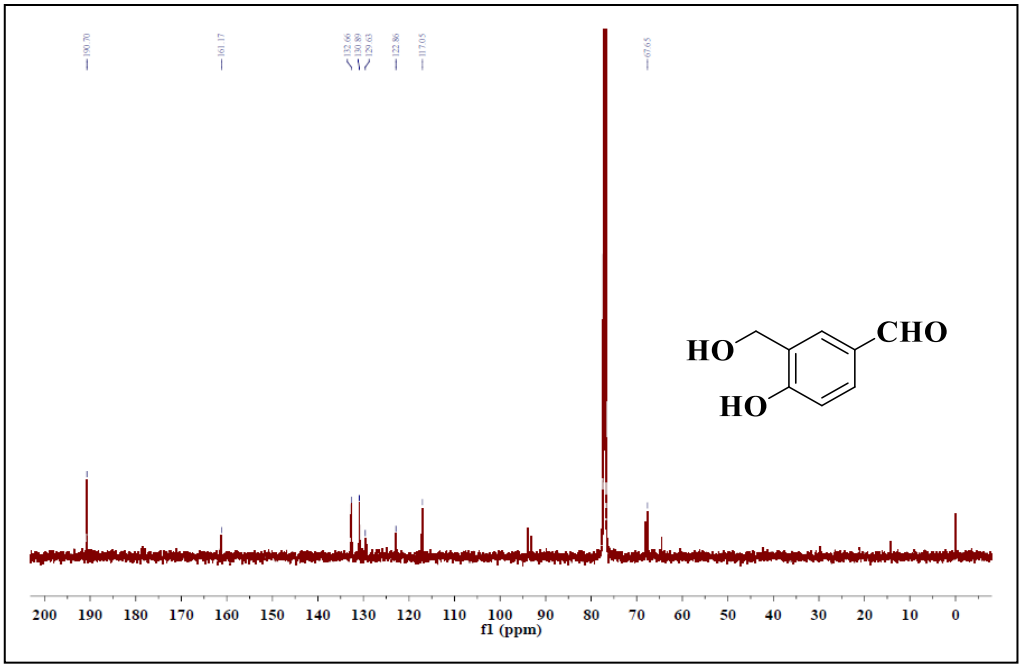
SPECTRAL DATA

4-hydroxy-3-(hydroxymethyl)benzaldehyde (3).

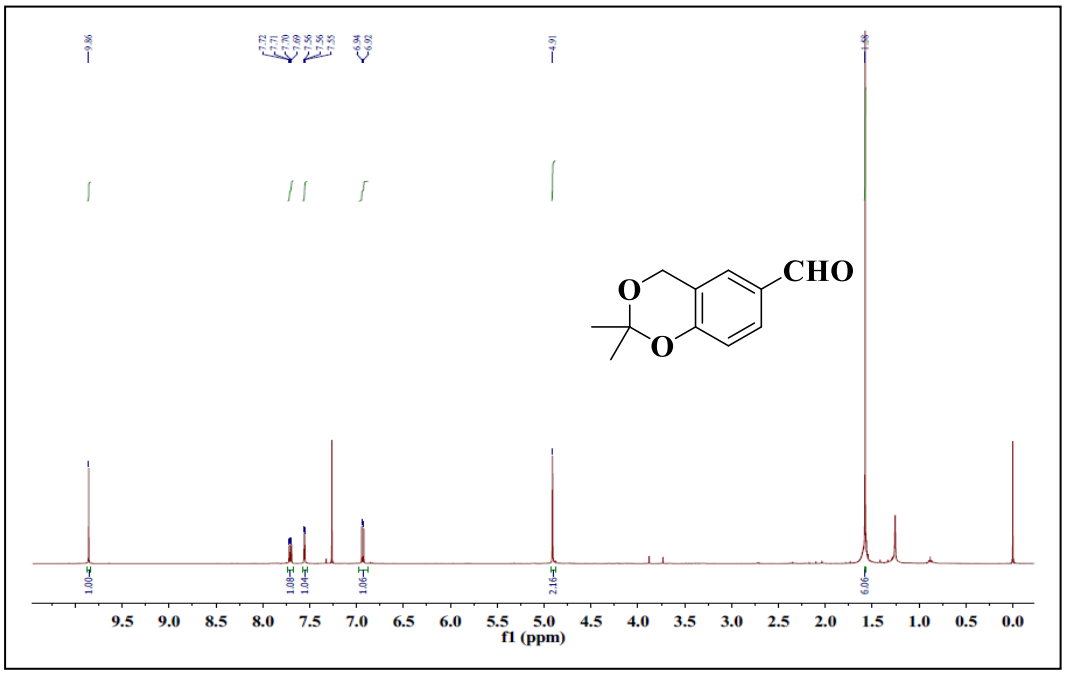


^{1}H NMR spectrum of 4 (400 MHz, $CDCl_3$)

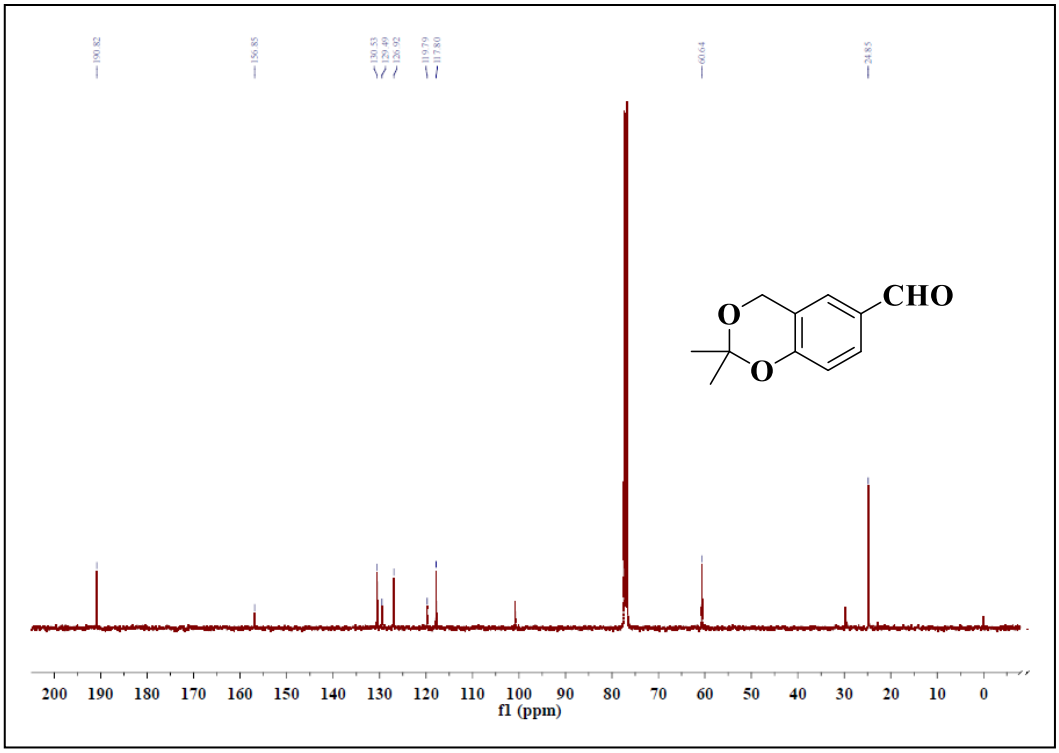


^{13}C NMR spectrum of compound 3 (101 MHz, $CDCl_3$)

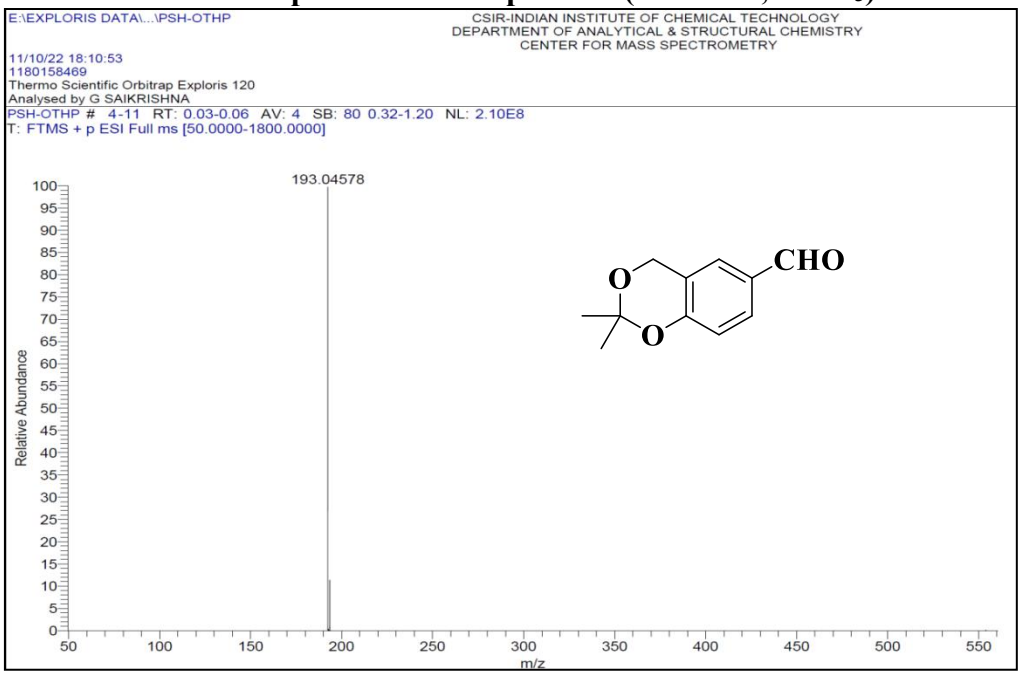
2,2-dimethyl-4H-benzo[d][1,3]dioxine-6-carbaldehyde(4).



^{1}H NMR spectrum of 4 (400 MHz, $CDCl_3$)

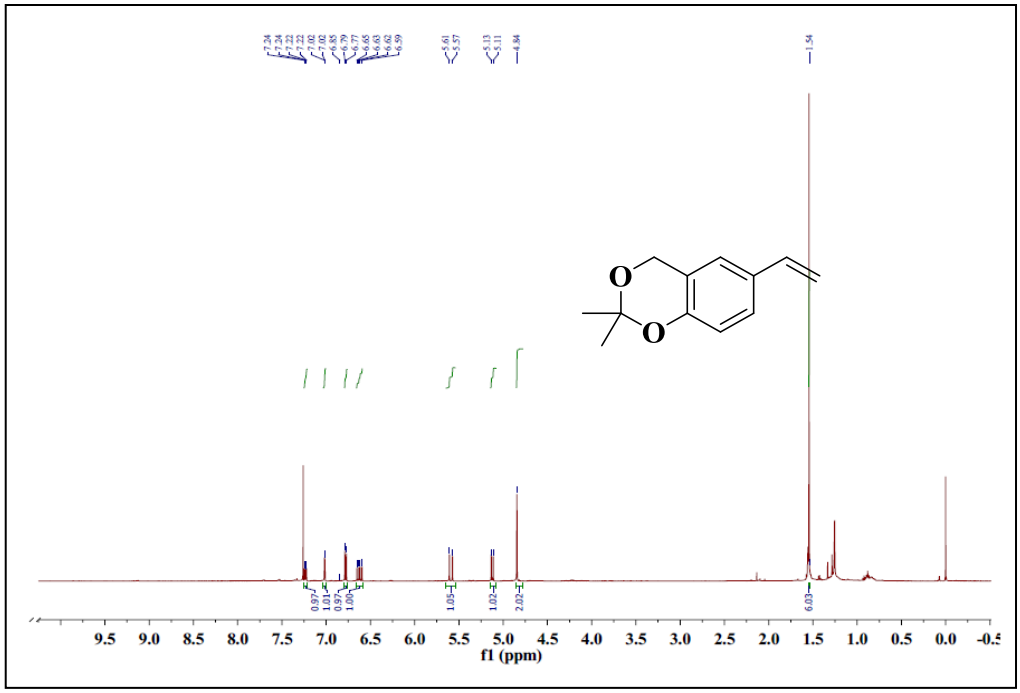


^{13}C NMR spectrum of compound 4 (101 MHz, $CDCl_3$)

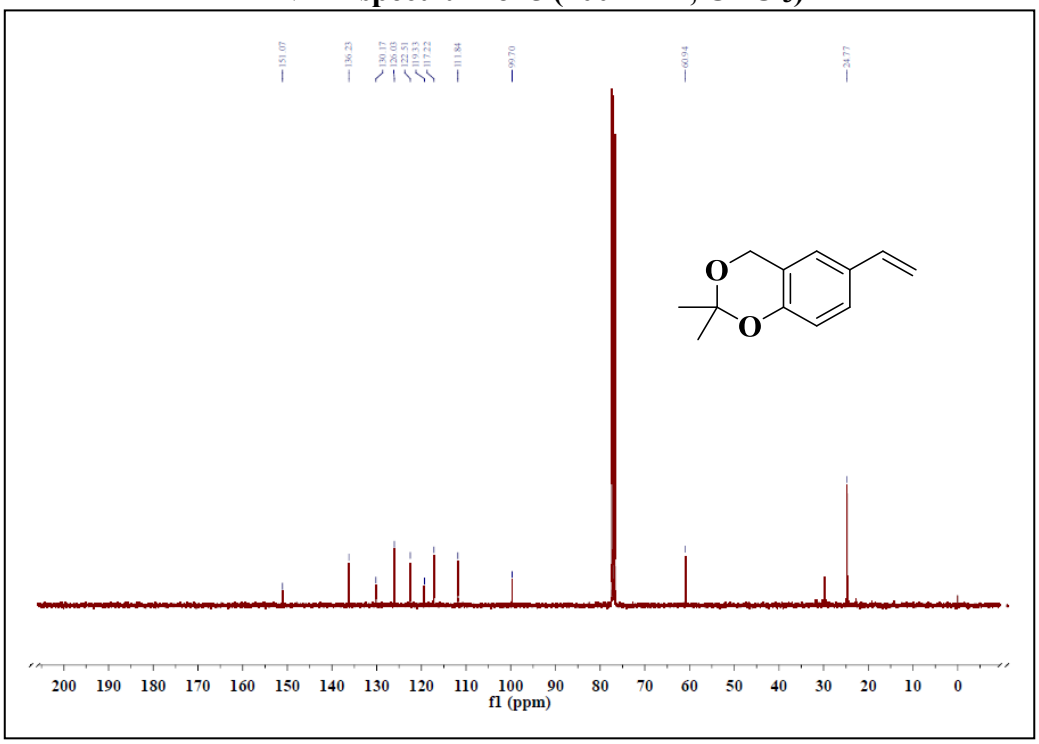


HRMS spectrum of compound 4

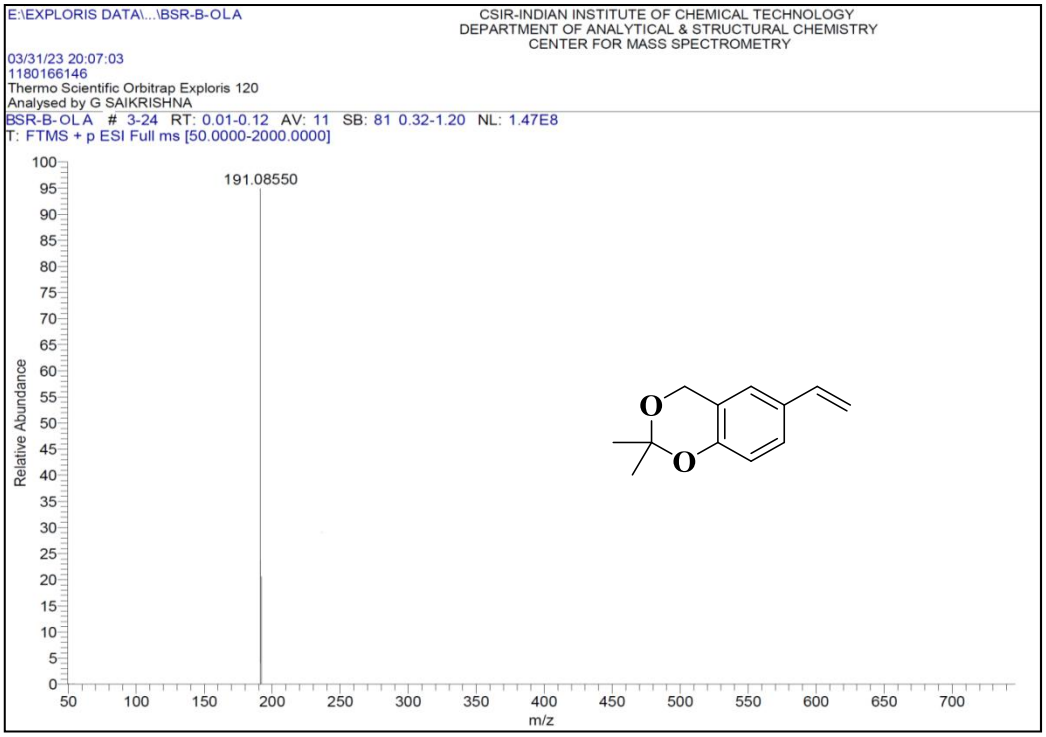
2,2-dimethyl-6-vinyl-4H-benzo[d][1,3]dioxine (5).



^{1}H NMR spectrum of 5 (400 MHz, $CDCl_3$)

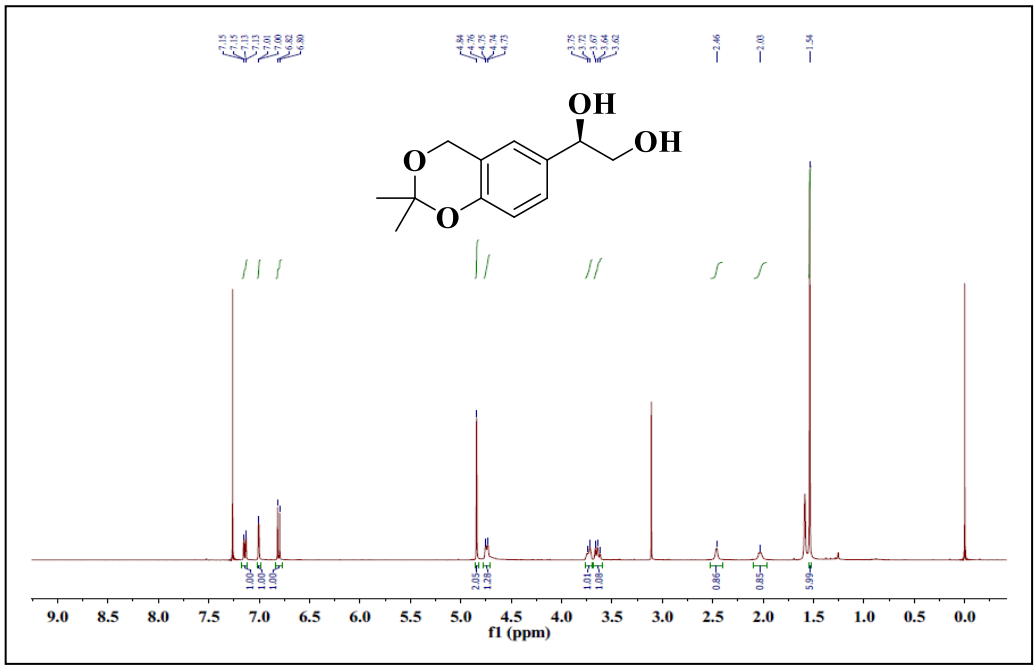


^{13}C NMR spectrum of compound 5 (101 MHz, $CDCl_3$)

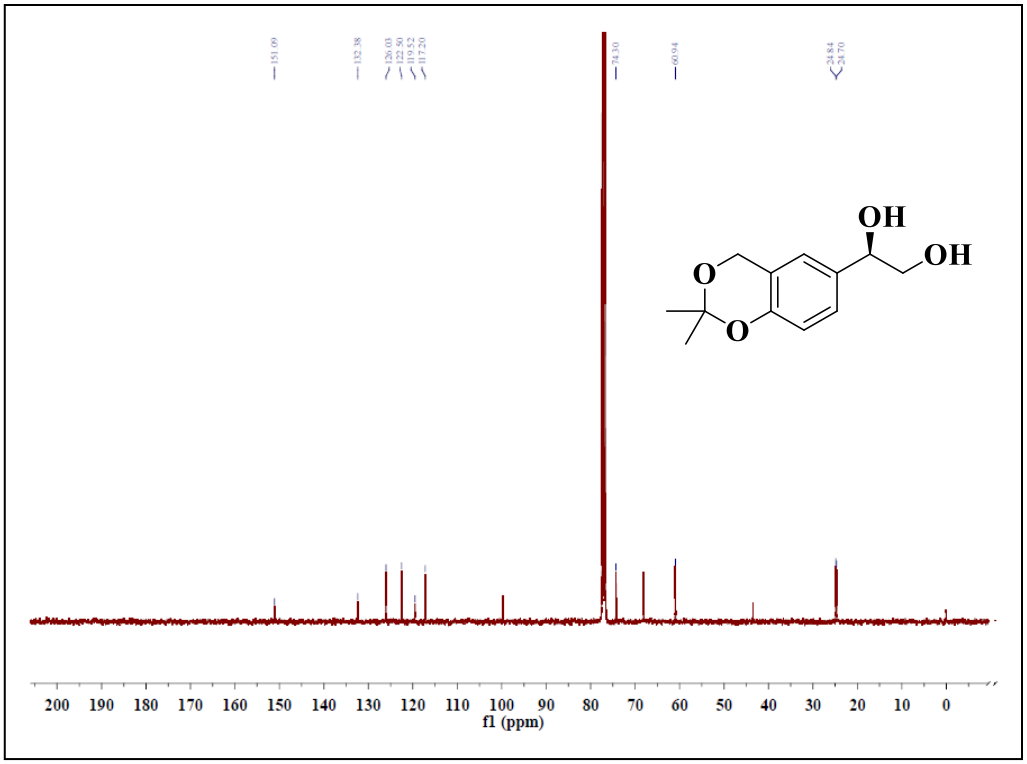


HRMS spectrum of compound 5

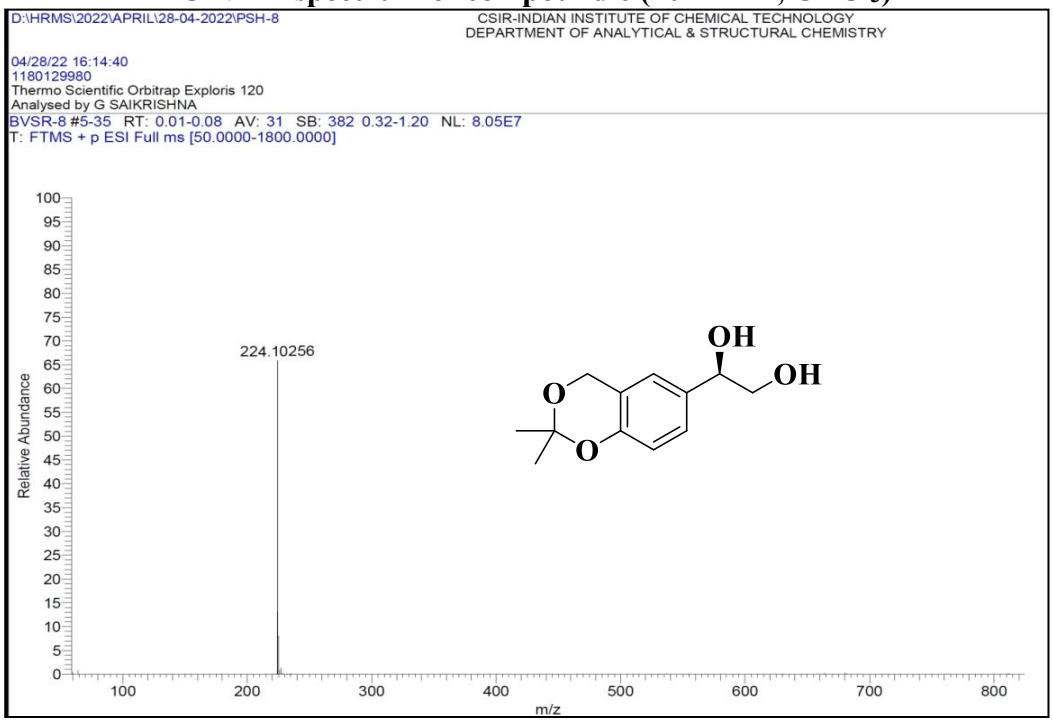
(R)-1-(2,2-dimethyl-4H-benzo[d][1,3]dioxin-6-yl)ethane-1,2-diol (6).



^{1}H NMR spectrum of 6 (400 MHz, $CDCl_3$)

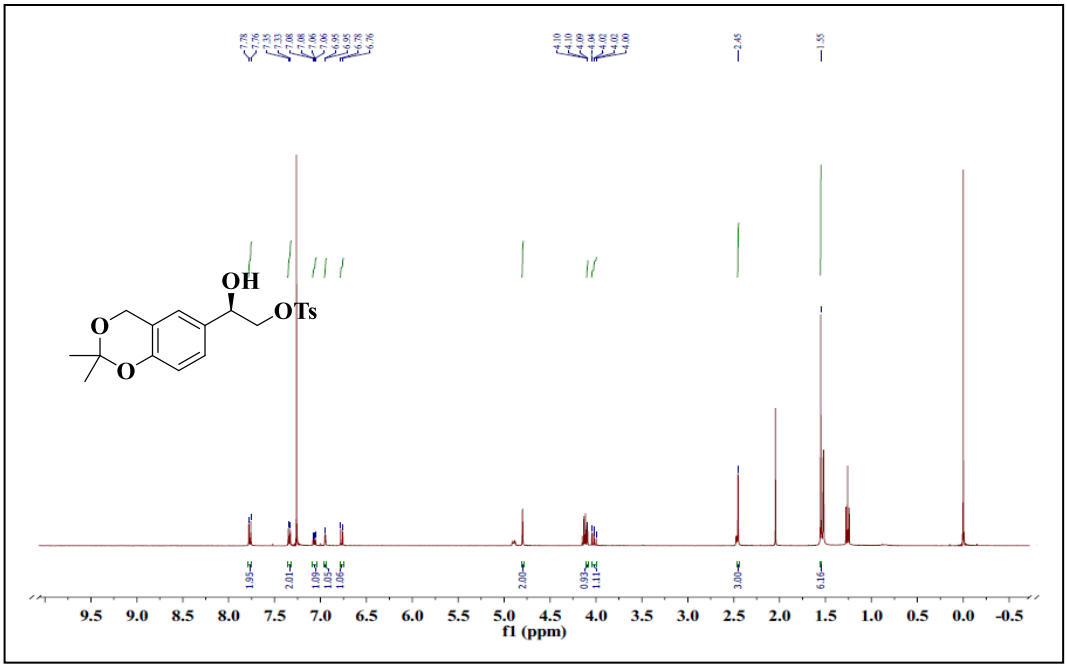


^{13}C NMR spectrum of compound 6 (101 MHz, $CDCl_3$)

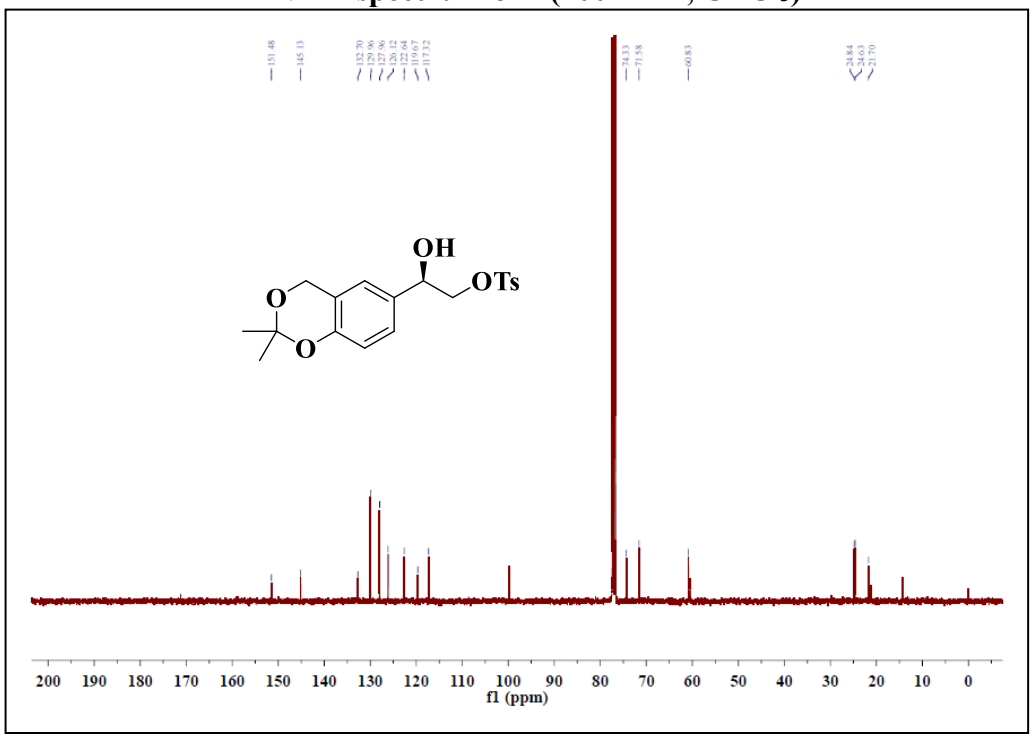


HRMS spectrum of compound 6

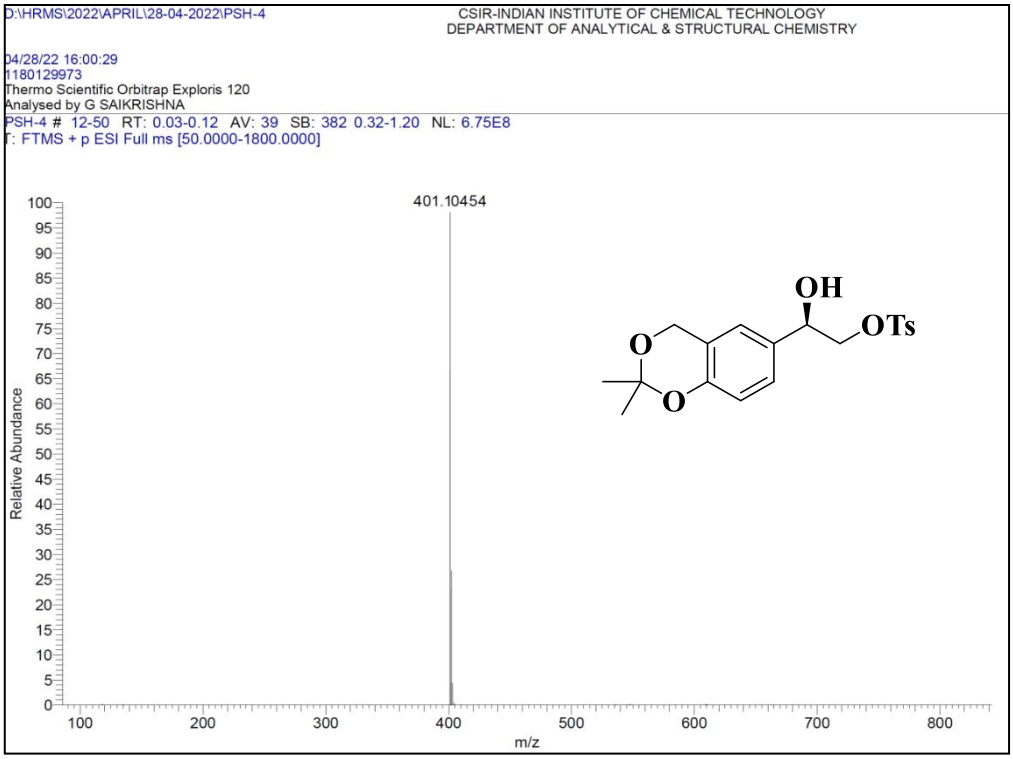
(R)-2-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2-hydroxyethyl-4-methylbenzene sulfonate (7).



^{1}H NMR spectrum of 7 (400 MHz, $CDCl_3$)

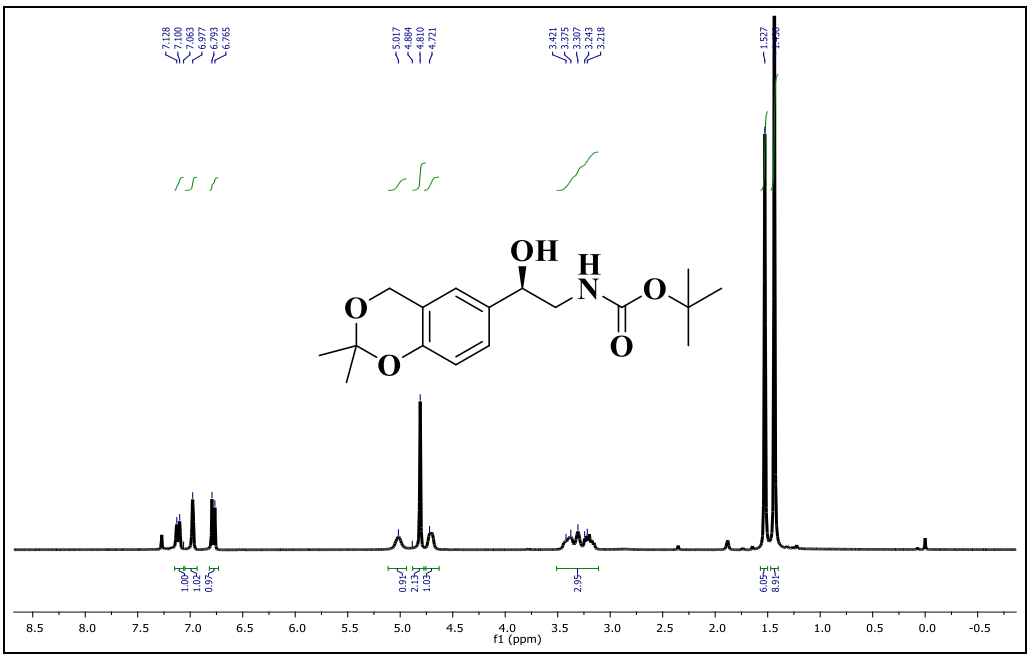


^{13}C NMR spectrum of compound 7 (101 MHz, $CDCl_3$)

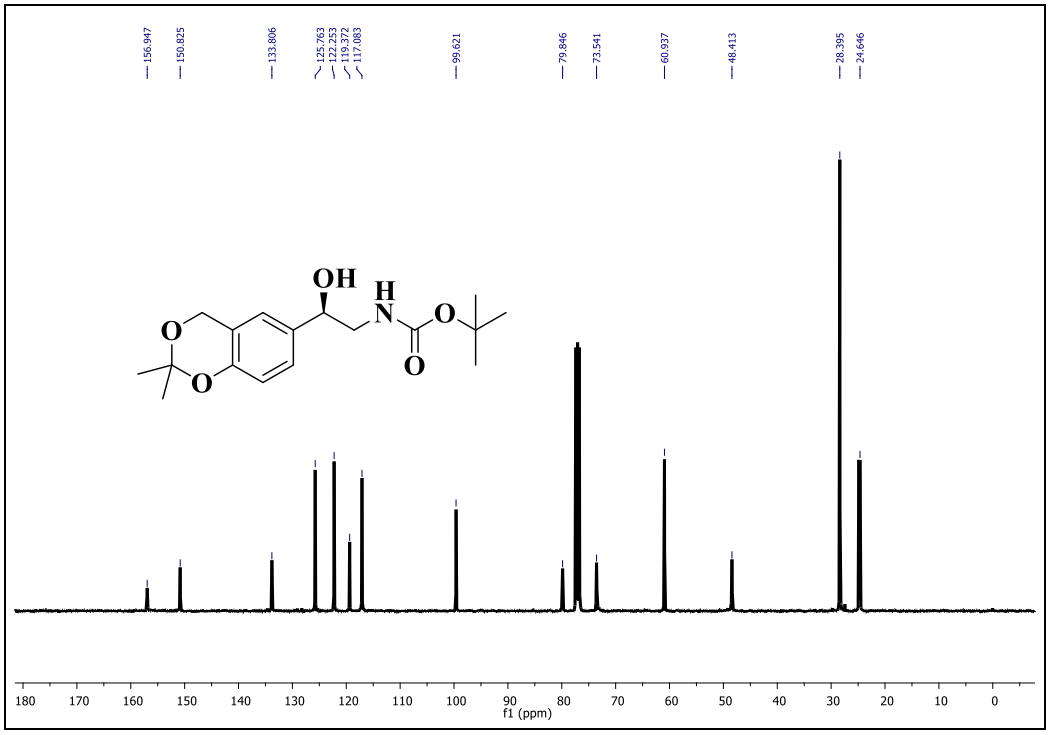


HRMS spectrum of compound 7

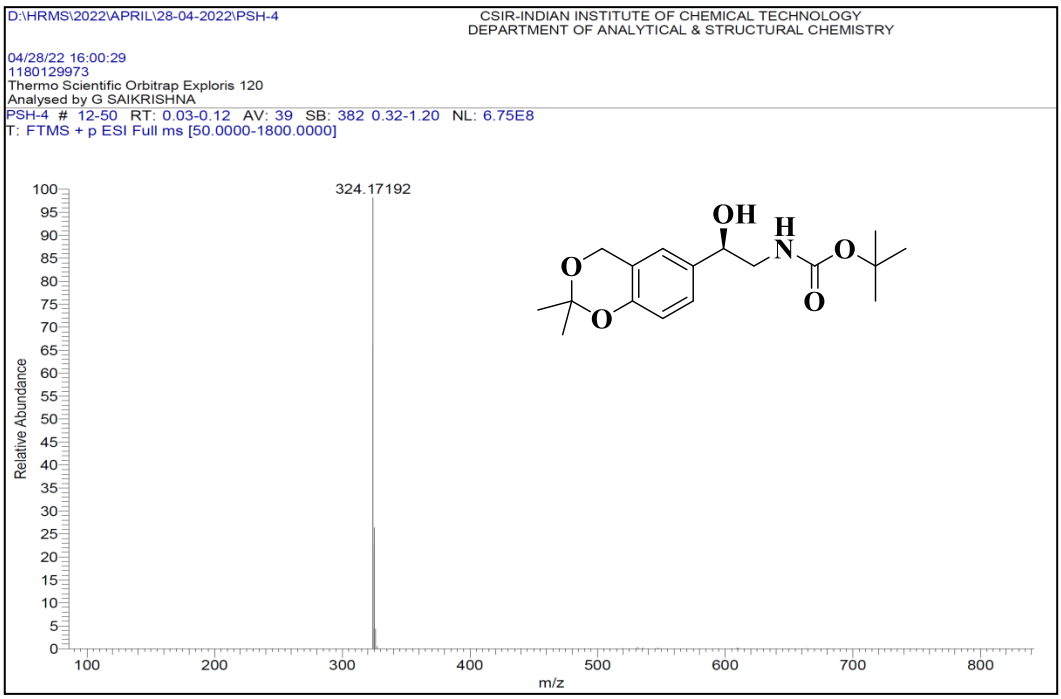
***tert*-butyl (R)-(2-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2-hydroxyethyl) carbamate (8).**



^{1}H NMR spectrum of 8 (300 MHz, $CDCl_3$)

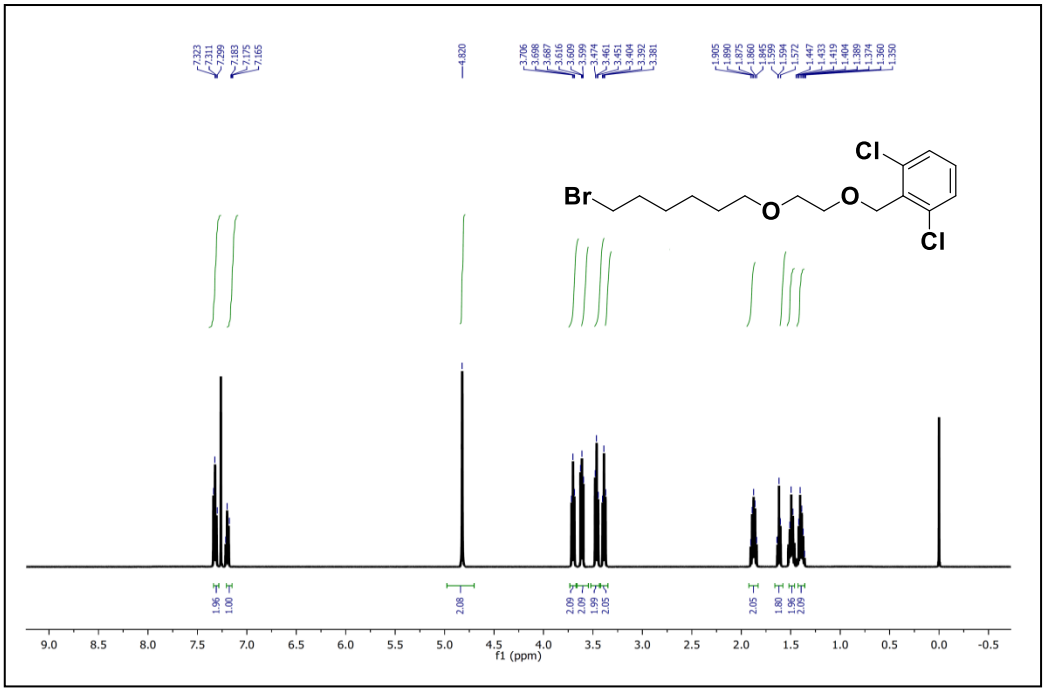


^{13}C NMR spectrum of compound 8 (101 MHz, $CDCl_3$)

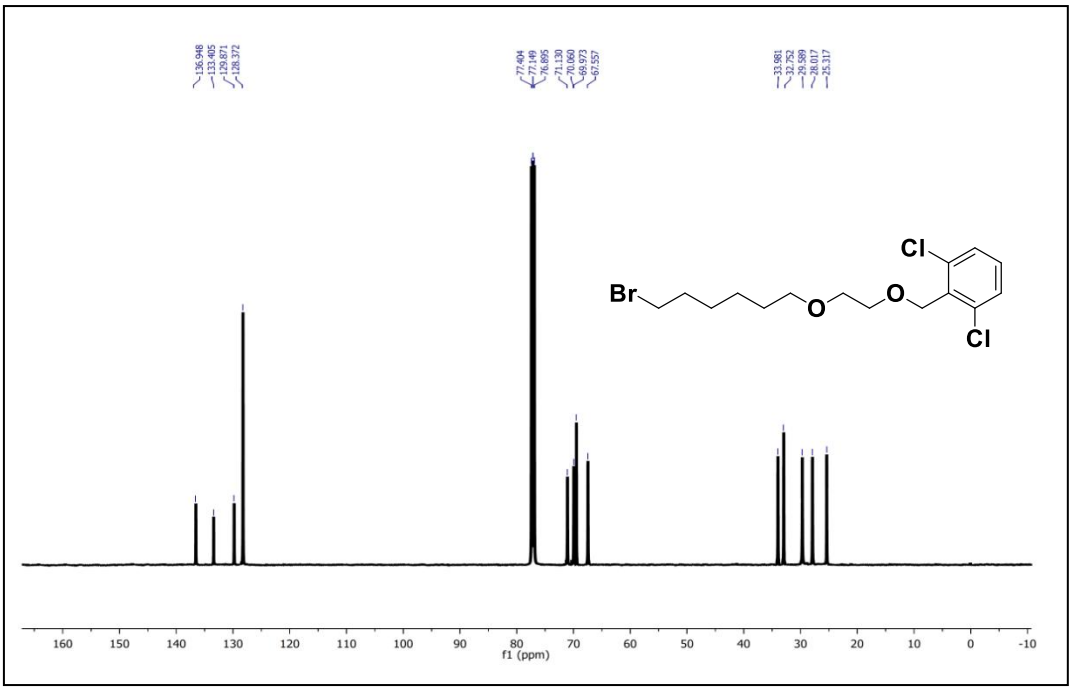


HRMS spectrum of compound 8

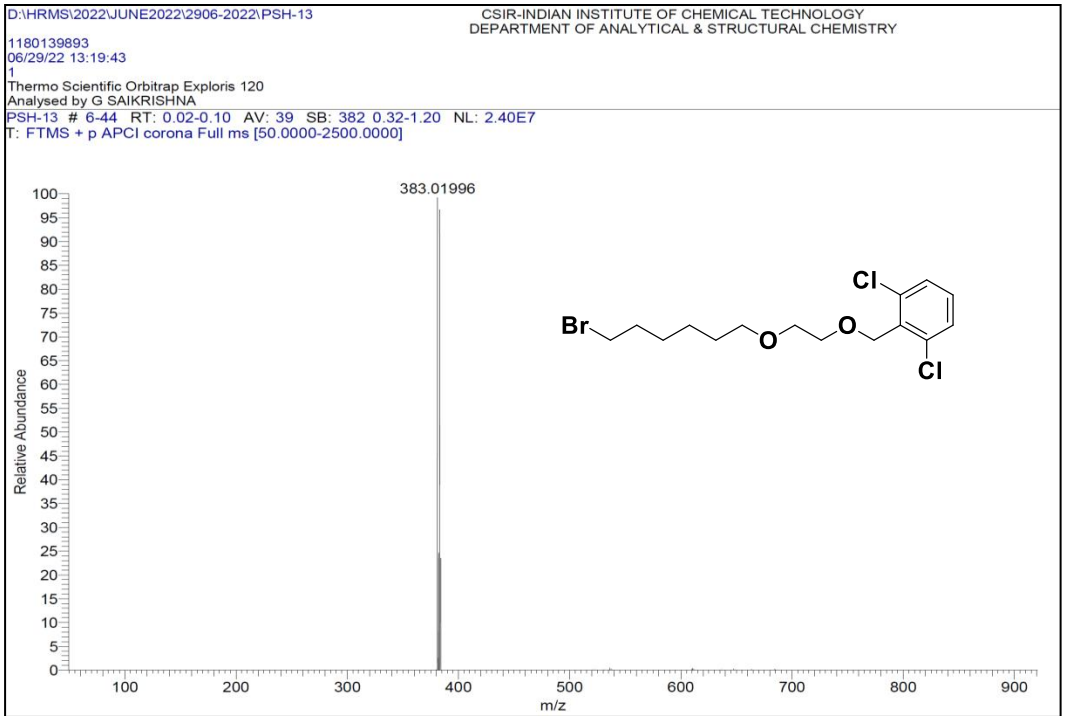
2-((2-((6-bromohexyl)oxy)ethoxy)methyl)-1,3-dichlorobenzene(9).



^{1}H NMR spectrum of 9 (500 MHz, $CDCl_3$)

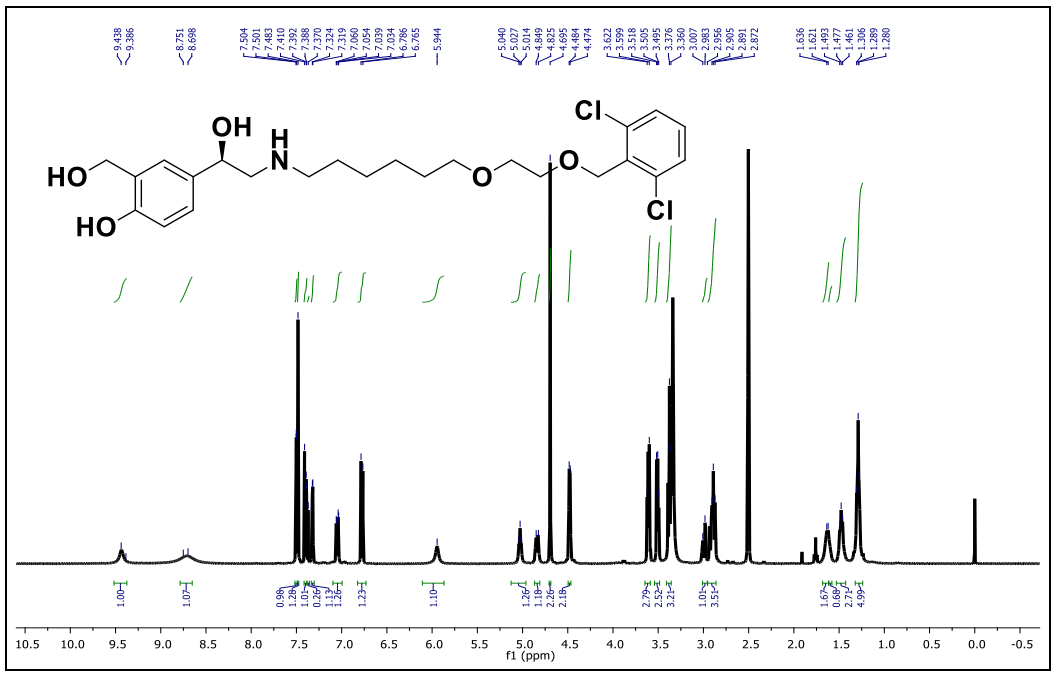


^{13}C NMR spectrum of compound 9 (126 MHz, $CDCl_3$)

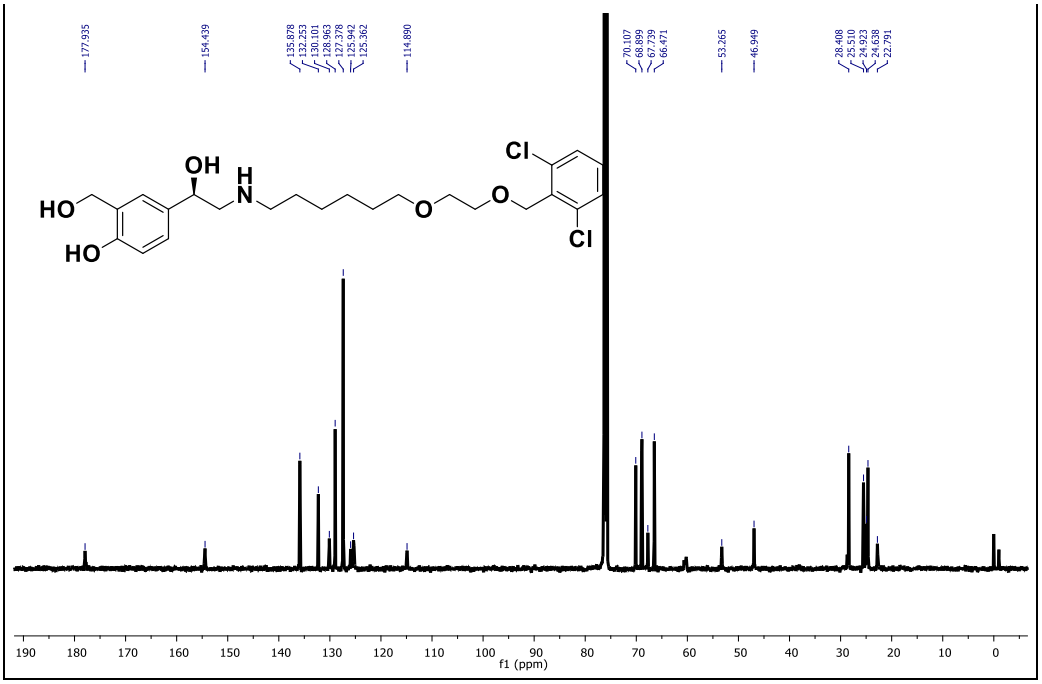


HRMS spectrum of compound 9

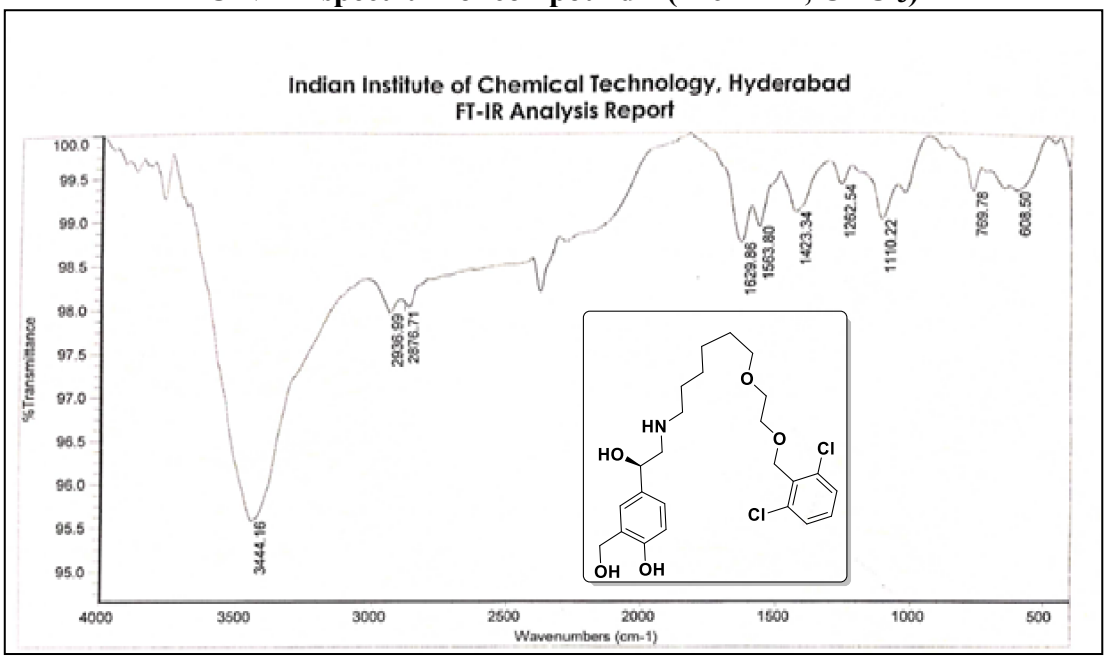
(1R)-2-((1-bromo-6-(2-((2,6-dichlorobenzyl)oxy)ethoxy)hexyl)amino)-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)ethan-1-ol (1).



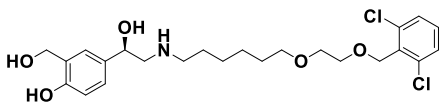
^{1}H NMR spectrum of 1 (400 MHz, DMSO-d$_6$)

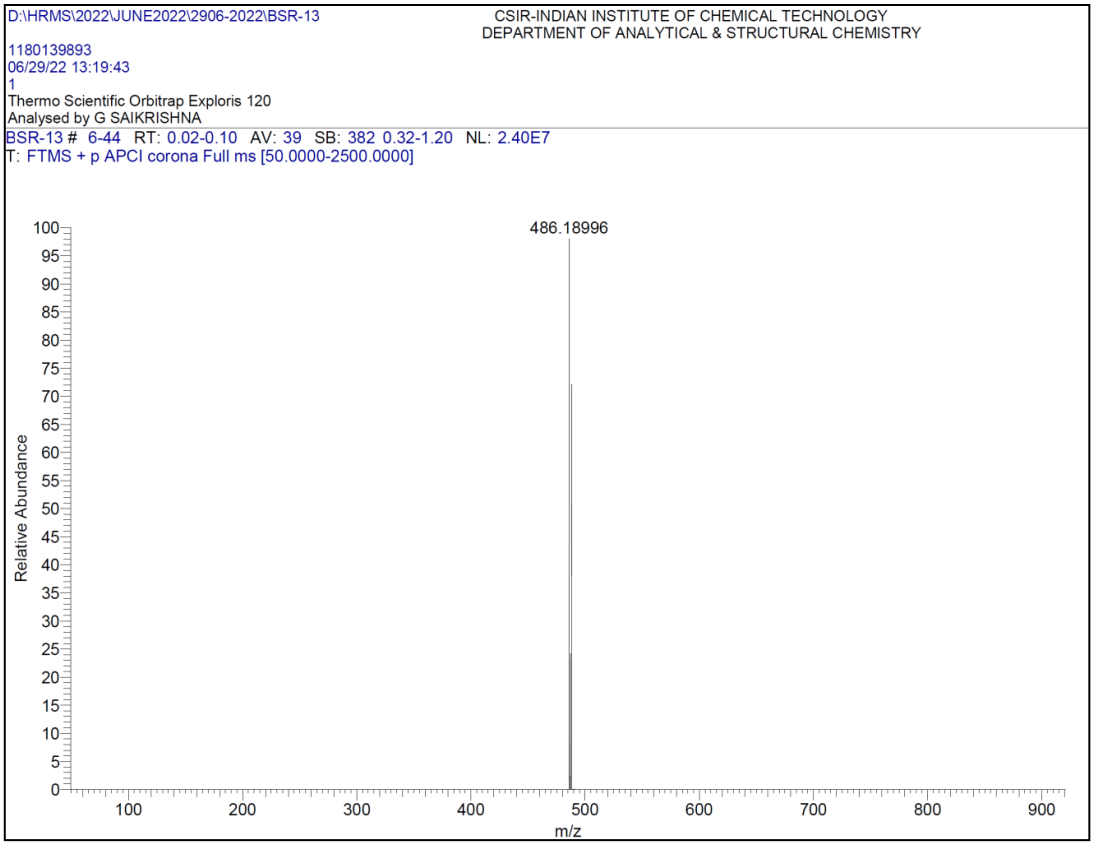


^{13}C NMR spectrum of compound 1 (126 MHz, $CDCl_3$)



1 IR spectra of Compound-1





HRMS spectrum of Compound-1