Original Article

Synthesis, Physicochemical And Spectral Characterization Of Novel Cannabidiol Derivatives As Anti-Epileptic Agents

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Abstract

Epilepsy is the second most common chronic neurological condition characterized by recurrent seizures affecting more than 60 million people world-wide. Since currently available antiepileptic drugs have been associated with several side effects and fail to control seizures in about 30% of epileptic patients, there is a substantial need for development of new, more effective and less toxic antiepileptic drugs. The present study aim to generate pharmacophore and to design the structure of lead molecule from which a series of analogues of the lead molecule is to be synthesized and screen them for anticonvulsant activity. Preliminary anticonvulsant evaluation of all the newly synthesized cannabidiol derivative of heterocyclic compounds were done against seizure models, Chemical test subcutaneous pentylenetetrazole (scPTZ). Synthesized compounds were characterized by spectral analysis (FT-IR, 1 H-NMR). In the present series of compounds, cannabidiol derivatives were designed and synthesized to meet structural requirements essential for anticonvulsant activity. The anticonvulsant data revealed that newly synthesized compounds Compound-1, Compound-4, Compound-10, Compound-12, afforded significant protection at 10mg/kg; i.p. in sc PTZ test. The anticonvulsant activity of the other tested compounds was found to be much moderately effective then phenytoin used as standard anticonvulsant

Keywords: Epilepsy, Seizures, Anti-convulsant, Pharmacophore, Cannabidiol.

INTRODUCTION

According to WHO 'epileptic seizure' is the result of transient dysfunction of part or all of the brain due to excessive discharge of a hyper-excitable population of neurons, causing sudden and transitory phenomena of motor, sensory, autonomic or psychic nature. Epilepsy affects 3-14 individuals per 1000 people in children and 5-19 people per 1000 people in adults, making it one of the most frequent brain illnesses. It's a chronic central nervous system illness characterized by recurrent seizure episodes caused by a variety of factors. Seizures are becoming better recognized as co-morbidity with other prevalent illnesses in adults and children, such as Alzheimer's disease and autism [1, 2].

Currently, many antiepileptic drugs [AEDs] are available such as Phenytoin, Carbamazepin, Phenobarbitone, Valproic acid, Lamotrigine, Vigabatin, Gabapentine, Flabamates, Denzimol, loreclazole, Nafimidone alcohol, Nafimimidone and Benzodiazepines are synthetic molecules. But only about 50% of the patients can have complete control of the seizures with AEDs. Apart from this the side effects associated with chronic therapy of epilepsy with AED's like CNS depression, psychiatric disturbances, osteomalacia, leucopenia, megaloblastic and aplastic anemia, hepatic failure, allergic reactions, teratogenic effects and withdrawal emergent disorders are the other disadvantages of the therapy [3].

The basic models used are maximal electroshock (MES) test (electrical method), subcutaneous Pentylenetetrazole (scPTZ) test and Isoniazide induced convulsion test (chemical method). Anticonvulsant activity against MES predicts the ability of the testing material / compound in preventing the spread of seizures discharge and effectiveness in the treatment of the grandmal seizures, while activity in scPTZ predicts the ability to evaluate seizure threshold and effectiveness in myoclonic seizures. Further screening test are directed to detect activity against Bicuculline, Picrotoxin (GABA receptor antagonist) and strychnine (glycine receptor antagonist) induced convulsions [4].

The present research involves to generate pharmacophore and to design the structure of lead molecule from which a series of analogues of the lead molecule is to be synthesized and screen them for anticonvulsant activity.
A survey of literature reveals that cannabinoids moiety constitutes an important structural feature in several anticonvulsant, antimicrobial, anxiolytic activities.

- To provide such anticonvulsant agents which are effective under mild or physiological conditions.
- To carry out literature survey and review on substituted cannabinoids derivative.
- To establish the method of synthesis for the proposed cannabinoids derivative compounds.

- To carry out preliminary test such physical constant determination, melting point, TLC and chemical test.
- To confirm the structure of synthesized compounds by IR, ^{1}HNMR and element analysis.

To evaluate the newly synthesized cannabinoids derivative of heterocyclic compounds for their anticonvulsant activity.

MATERIALS AND METHODS

Sketching of Ligands

The structures were first developed in the 2Dfile using Chemdraw® Ultra 8.0 software as a ".cdx" format, and then converted to ".sdf" format [7-9].

METHODS

1. Determination of melting point range

Melting point ranges of newly synthesized compounds were determined by open glass capillary tube using Visual melting point apparatus and were uncorrected. The temperature at which compound starts melting to the temperature at which it completely melts was taken as the melting point range.

2. Thin layer chromatography of compounds

Thin layer chromatographic analyses of the compounds were performed on silica gel G coated plates. The adsorbents silica gel G was coated to a thickness of about 1 mm on previously cleaned TLC plates 20×5 cm using conventional spreader. The plates were placed in hot air oven at 110ºC for 30 min. Chloroform: Methanol (9:1), Ethyl Acetate: Hexane (9:1) and Benzene: Ethylacetate: Methanol (8.5: 1.4: 1) were used as mobile phase. The spots were visualized by exposure to iodine vapours and by placing it in UV Cabinet.

3. Solubility studies

Various solvents such as water, ethanol, chloroform, benzene, methanol, dimethylsulphoxide and dichloromethane were taken for solubility studies of the intermediate compounds and final compounds.

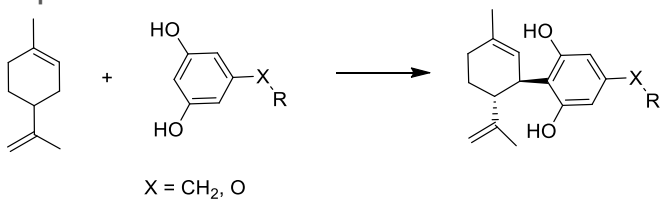
4. IR spectral analysis

IR spectrum of compounds in KBr pellets were recorded on a FT-IR spectrophotometer (Nicolet).

5. ^{1}H NMR spectral analysis

^{1}H NMR spectra of the compounds were recorded on Bruker NMR spectrophotometer in DMSO-d_6 using TMS as internal standard (chemical shift in δ ppm).

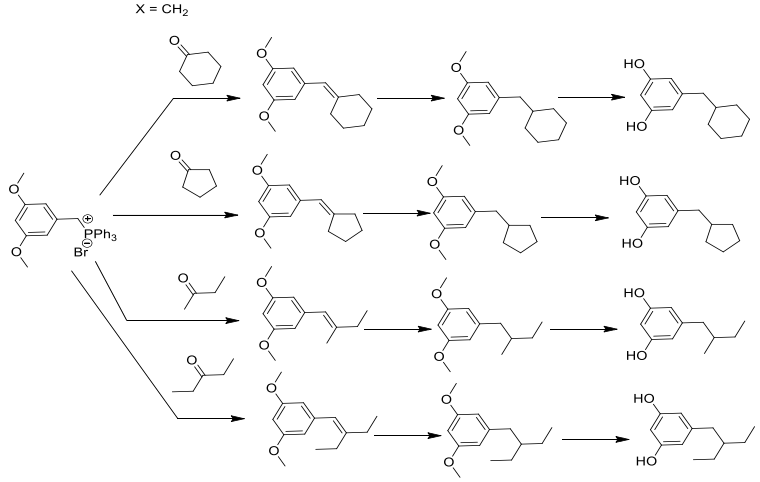
Scheme of synthesis of Compounds 1-16:

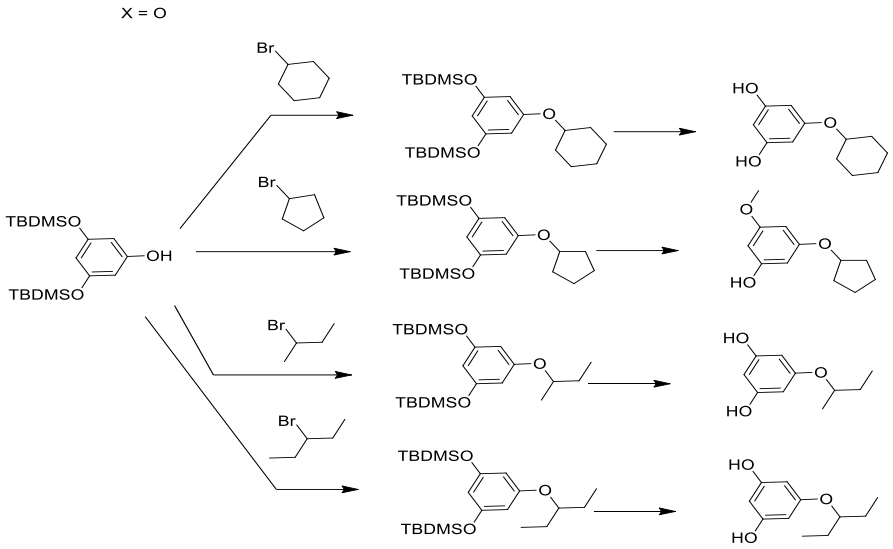


Cycloalkyl fragment Aryl Fragment Product

Scheme for the synthesis of Cannabidiol derivatives

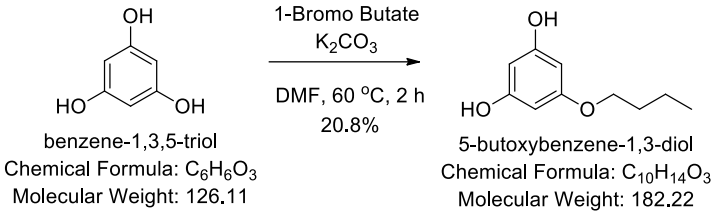
Synthesis of Aryl Fragments





METHODS OF SYNTHESIS

Synthesis of Intermediate-1:



benzene-1,3,5-triol
Chemical Formula: $C_6H_6O_3$
Molecular Weight: 126.11

5-butoxybenzene-1,3-diol
Chemical Formula: $C_{10}H_{14}O_3$
Molecular Weight: 182.22

Procedure:

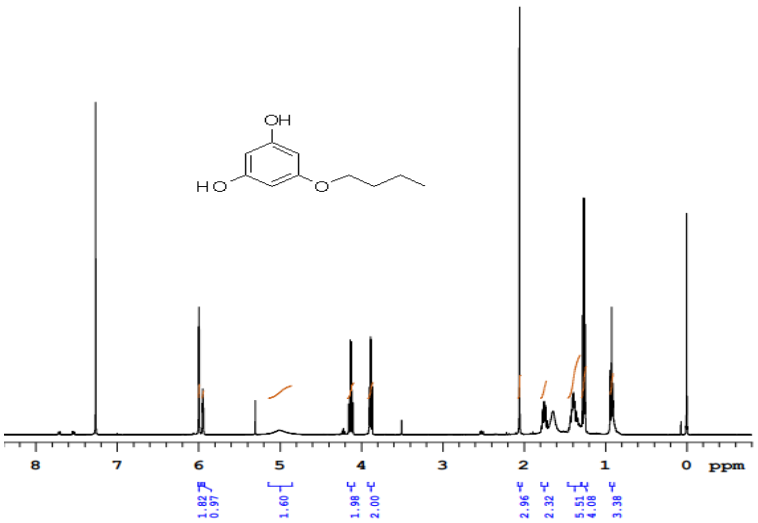
To a solution of Benzne-1,3,5-triol (2.1 g, 16.6 mmol) in DMF (16.6 ml, 1ml/mmol), anhydrous K_2CO_3 (1.5 g, 10.7 mmol) and 1-Bromobutane (0.87 ml, 8.1 mmol) were added. The resulting solution was heated at 60°C for 2 h. Water (150 ml) was added and extracted with ethylacetae (2 x 100 ml). Solvent was removed after drying over anhydrous sodium sulphate and the residue obtained was passed through silica gel column in Ethylacetate: Pet.ether to get 600 mg (20.8%) of product.

TLC:

Mobile Phase: 1:4:: Ethylacetate: Hexane
Rf Vlaue: 0.2
Visualization: UV, $KMnO_4$

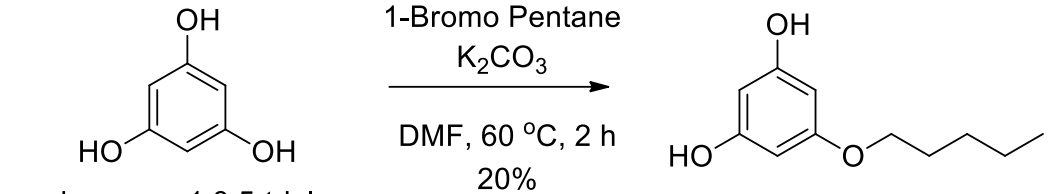
Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 5.60-5.99 (m, 2H), 5. 95 (t, J = 2.0 Hz, 1H), 5.00 (bs, 2H), 3.90-3.87 (m, 2H), 1.77-1.72 (m, 2H), 1.42-1.34 (m, 2H), 0.94-0.89 (m, 3H).



^{1}H NMR of Intermediate- 1

Synthesis of Intermediate-2:



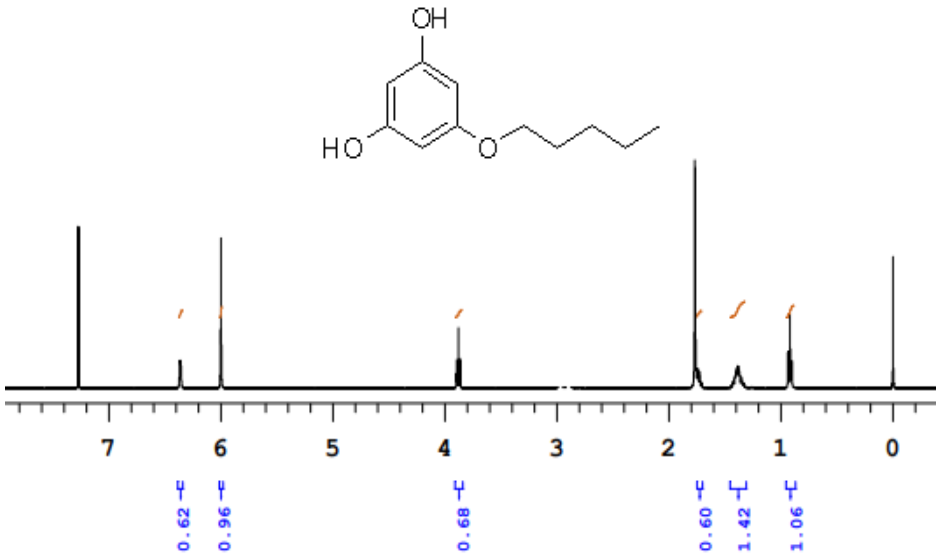
benzene-1,3,5-triol
Chemical Formula: $C_6H_6O_3$
Molecular Weight: 126.11

5-(pentyloxy)benzene-1,3-diol
Chemical Formula: $C_{11}H_{16}O_3$
Molecular Weight: 196.24

Procedure:
To a solution of Benzne-1,3,5-triol (4.0 g, 31 mmol) in DMF (31 ml, 1ml/mmol), anhydrous K_2CO_3 (2.7 g, 20.1 mmol) and 1-Bromopentane (1.7 ml, 15 mmol) were added. The resulting solution was heated at 60°C for 2 h. Water (300 ml) was added and extracted with ethylacetae (2 x 200 ml). Solvent was removed after drying over anhydrous sodium sulphate and the residue obtained was passed through silica gel column in Ethylacetate: Pet.ether to get 1.2 g (20%) of product.

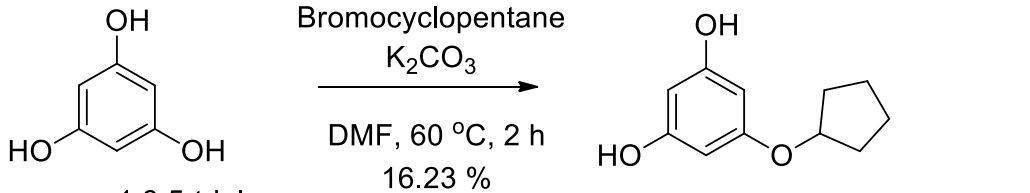
TLC:
Mobile Phase: 3:2:: Ethylacetate: Hexane
Rf Vlaue: 0.7
Visualization: UV, $KMnO_4$

Analytical data:
^{1} H NMR (400 MHz, $CDCl_3$): δ 6.36 (bs, 2H), 5.99 (s, 3H), 3.88 (t, J = 6.4 Hz, 2H), 1.77-1.74 (m, 2H), 1.40-1.37 (m, 4H), 0.92 (t, J = 8 Hz, 3H)



^{1}H NMR of Intermediate- 2

Synthesis of Intermediate-3:



benzene-1,3,5-triol
Chemical Formula: $C_6H_6O_3$
Molecular Weight: 126.11

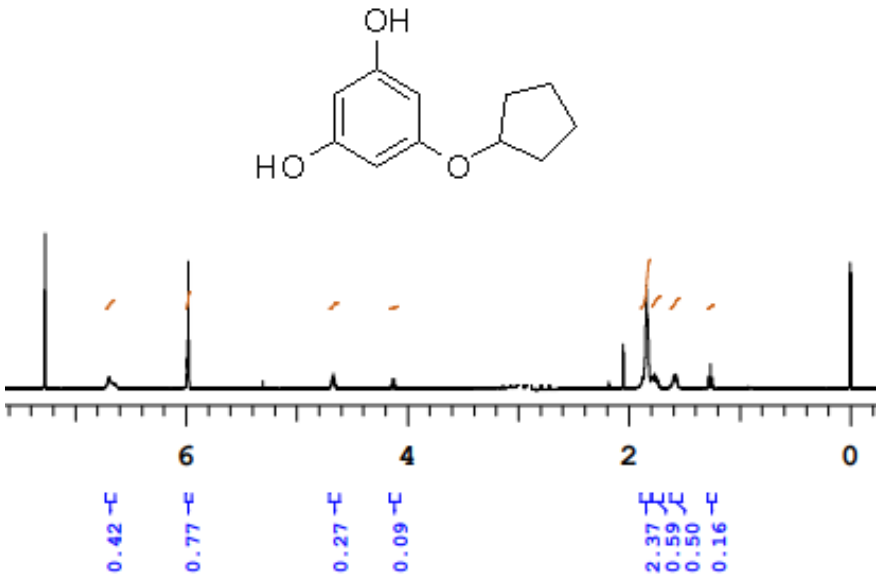
5-(cyclopentyloxy)benzene-1,3-diol
Chemical Formula: $C_{11}H_{14}O_3$
Molecular Weight: 194.23

Procedure:
To a solution of Benzne-1,3,5-triol (4.0 g, 31 mmol) in DMF (31 ml, 1ml/mmol), anhydrous K_2CO_3 (2.7 g, 20.1 mmol) and Bromocyclopentane (1.5 ml, 15 mmol) were added. The resulting solution was heated at 60°C for 2 h. Water (300 ml) was added and extracted with ethylacetae (2 x 200 ml). Solvent was removed after drying over anhydrous sodium sulphate

and the residue obtained was passed through silica gel column in Ethylacetate: Pet.ether to get 1.0 g (16.23 %) of product.

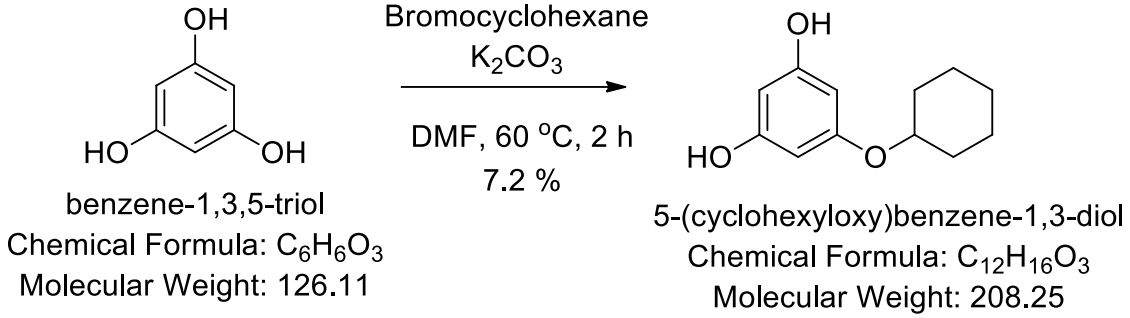
TLC:
Mobile Phase: 3:2:: Ethylacetate: Hexane
Rf Vlaue: 0.7
Visualization: UV, $KMnO_4$

Analytical data:
^{1} H NMR (400 MHz, $CDCl_3$): δ 6.69 (bs, 2H), 5.99-5.97 (m, 3H), 4.62-4.69 (m, 1H), 1.85-1.52 (m, 8H)



^{1}H NMR of Intermediate- 3

Synthesis of Intermediate-4:



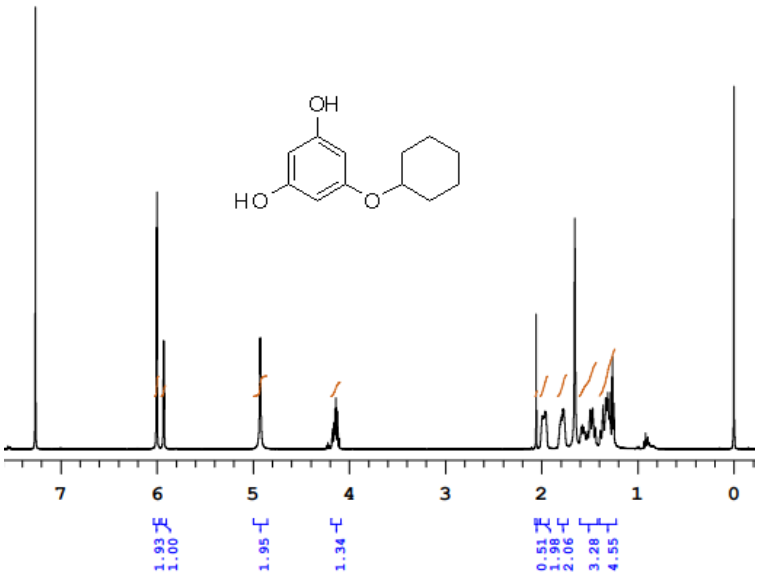
benzene-1,3,5-triol
Chemical Formula: $C_6H_6O_3$
Molecular Weight: 126.11

5-(cyclohexyloxy)benzene-1,3-diol
Chemical Formula: $C_{12}H_{16}O_3$
Molecular Weight: 208.25

Procedure:
To a solution of Benzne-1,3,5-triol (4.0 g, 31 mmol) in DMF (31 ml, 1ml/mmol), anhydrous K_2CO_3 (2.7 g, 20.1 mmol) and Bromocyclohexane (1.9 ml, 15 mmol) were added. The resulting solution was heated at 60°C for 2 h. Water (300 ml) was added and extracted with ethylacetae (2 x 200 ml). Solvent was removed after drying over anhydrous sodium sulphate and the residue obtained was passed through silica gel column in Ethylacetate: Pet.ether to get .48 g (7.2 %) of product.

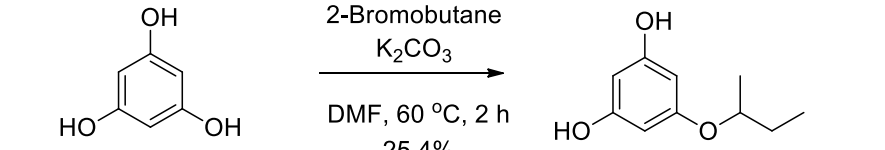
TLC:
Mobile Phase: 3:2:: Ethylacetate: Hexane
Rf Vlaue: 0.7
Visualization: UV, $KMnO_4$

Analytical data:
^{1} H NMR (400 MHz, $CDCl_3$): δ 6.01-6.00 (m, 2H), 5.93 (t, 1.6 Hz, 1H), 4.93 (bs, 2H), 4.18-4.10 (m, 2H), 1.98-1.96 (m, 2H), 1.79-1.65 (m, 2H), 1.55-1.25 (m, 6H).



^{1}H NMR of Intermediate- 4

Synthesis of Intermediate-5:



benzene-1,3,5-triol
Chemical Formula: $C_6H_6O_3$
Molecular Weight: 126.11

5-(*sec*-butoxy)benzene-1,3-diol
Chemical Formula: $C_{10}H_{14}O_3$
Molecular Weight: 182.22

Procedure:

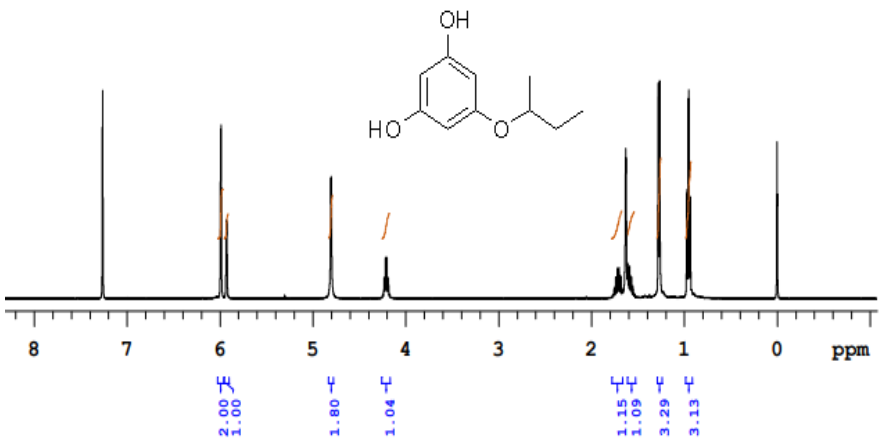
To a solution of Benzne-1,3,5-triol (3.0 g, 23.7 mmol) in DMF (23.7 ml, 1ml/mmol), anhydrous K_2CO_3 (2.3 g, 16.5 mmol) and 2-Bromobutane (1.3 ml, 11.8 mmol) were added. The resulting solution was heated at 60°C for 2 h. Water (200 ml) was added and extracted with ethylacetae (2 x 150 ml). Solvent was removed after drying over anhydrous sodium sulphate and the residue obtained was passed through silica gel column in Ethylacetate: Pet.ether to get 1.1 g (25.4 %) of product.

TLC:

Mobile Phase: 3:2:: Ethylacetate: Hexane
Rf Vlaue: 0.5
Visualization: UV, $KMnO_4$

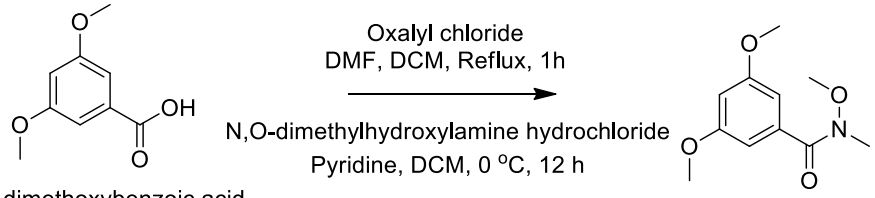
Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 5.99 (s, 2H), 5.93 (s, 1H), 4.80 (s, 2H), 4.23-4.19 (m, 2H), 1.74-1.68 (m, 1H), 1.63-1.57 (m, 1H), 1.27 (d, J = 6.0 Hz, 3H), 0.95 (t, J = 7.6 Hz, 3H).



^{1}H NMR of Intermediate- 5

Synthesis of Intermediate-6:



3,5-dimethoxybenzoic acid
Chemical Formula: $C_9H_{10}O_4$
Molecular Weight: 182.17

N,3,5-trimethoxy-*N*-methylbenzamide
Chemical Formula: $C_{11}H_{15}NO_4$
Molecular Weight: 225.24

Procedure:

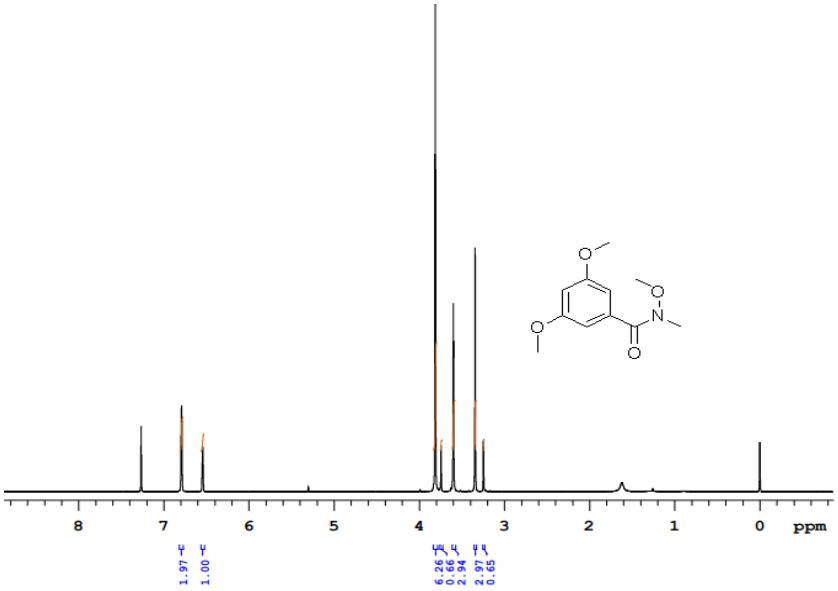
To a suspension of 3,5-dimethoxybenzoic acid (10.0 g, 54.9 mmol) in Dichloromethane (30ml, 3ml/mmol) at room temperature was added DMF (2 drops) followed by oxalyl chloride (16.0 mL, 183 mmol). The reaction mixture was heated to reflux for 1 h, and the excess oxalyl chloride and solvent were removed by distilled off. The crude acid chloride was dissolved Dichloromethane (10 ml, 1ml/mmol) and added via cannula to a solution of N,O-dimethylhydroxylamine hydrochloride (6.49 g, 66.5 mmol) and pyridine (10.0 mL, 124 mmol) in Dichloromethane (20ml, 2 ml/mmol) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 12 h. The organic phase was washed with Saturated bicarbonate solution (3 x 10 ml), water (10 ml) and brine (10 ml). Volatiles were evaporated after drying over anhydrous sodium sulphate. The residue was submitted to the next reaction as such without further purification.

TLC:

Mobile Phase: 1:1:: Ethylacetate: Hexane
Rf Vlaue: 0.5
Visualization: UV, $KMnO_4$

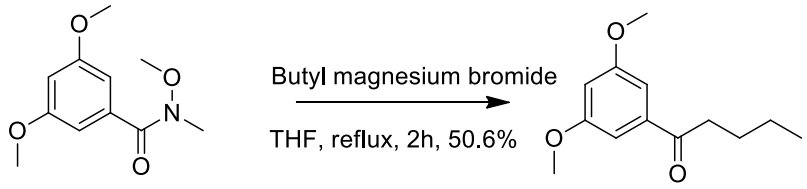
Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 6.79 (s, 2H), 6.54 (s, 1H), 3.81 (s, 6H), 3.60 (s, 3H), 3.34 (s, 3H).



^{1}H NMR of Intermediate- 6

Synthesis of Intermediate-7:



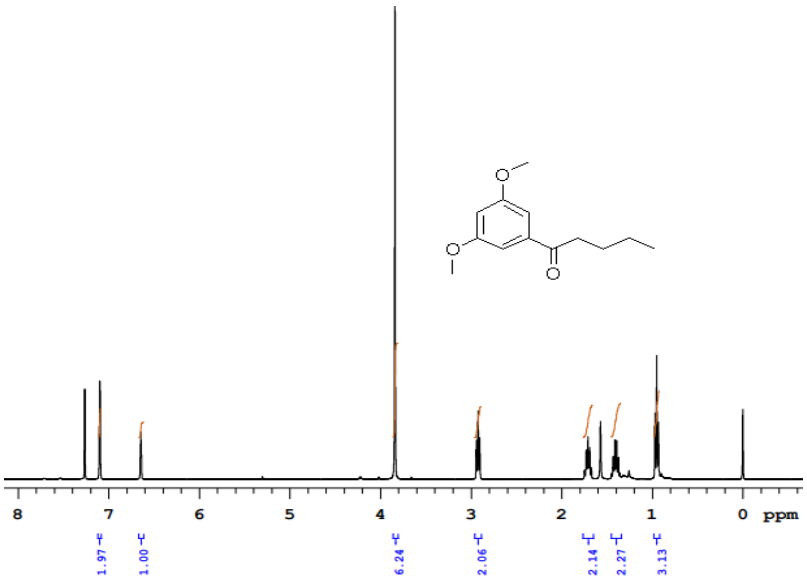
N,3,5-trimethoxy-*N*-methylbenzamide
Chemical Formula: $C_{11}H_{15}NO_4$
Molecular Weight: 225.24

1-(3,5-dimethoxyphenyl)pentan-1-one
Chemical Formula: $C_{13}H_{18}O_3$
Molecular Weight: 222.28

Procedure:
A solution of N,3,4,5-tetramethoxy-N-methylbenzamide (4 g, 17.76 mmol) in dry THF (35.5 mL, 2 ml/mmol) was added dropwise via a syringe to this solution of the Grignard reagent (35.52 mmol) and refluxed for 2h. The reaction mixture was poured onto ice (200 g) and aqueous HCl (100 mL, 2 M) and the organic layers separated. The aqueous layer was extracted with ethyl acetate (3 X 100 mL) and the combined organic phases were washed with water (3 X 50 mL), dried (anhy. Na_2SO_4) and volatiles were evaporated to afford the crude product. It was purified by silicagel column purification in Ethylacetate: Pet.ether to get 2 g (50.6%) of product.

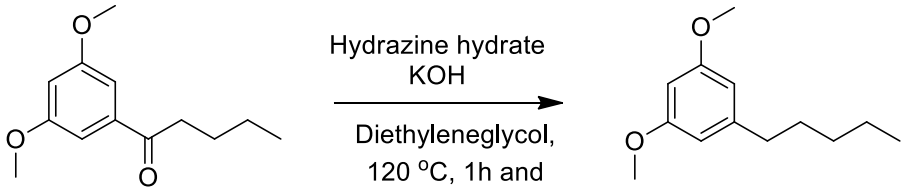
TLC:
Mobile Phase: 1:4:: Ethylacetate: Hexane
Rf Vlaue: 0.8
Visualization: UV, $KMnO_4$

Analytical data:
^{1} H NMR (400 MHz, $CDCl_3$): δ 7.09 (s, 2H), 6.64 (s, 1H), 3.84 (s, 6H), 2.92 (t, J = 8.0 Hz, 2H), 1.73-1.69 (m, 2H), 1.43-1.38 (m, 2H), 0.95 (t, J = 7.6 Hz, 3H).



^{1}H NMR of Intermediate- 7

Synthesis of Intermediate-8:



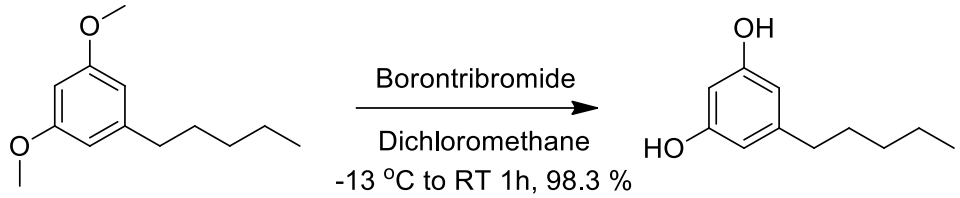
1-(3,5-dimethoxyphenyl)pentan-1-one
Chemical Formula: $C_{13}H_{18}O_3$
Molecular Weight: 222.28

1,3-dimethoxy-5-pentylbenzene
Chemical Formula: $C_{13}H_{20}O_2$
Molecular Weight: 208.30

Procedure:
A solution of 1-(3,5dimethoxyphenyl) pentanone (2.5 g, 11.25 mmol) in diethyleneglycol (112.5 ml, 10 ml/ mmol), KOH (11.4 g, 203.4 mmol) and hydrazine hydrate (85%) (14.3 ml, 1.27 ml/ mmol) were added. The resulting solution was heated at 120 °C for 1 h and 195 °C for 4 h. After the formed water was removed, the mixture was heated at 195°C for an ad- ditional 4 h. After cooling, the solution was diluted with water (200ml) and extracted with ethyl acetate (2 x 100 ml). The combined ethylacetate layers were dried over anhy. Na_2SO_4 and volatiles were evaporated. The residue was used in the next step as such without further purification.

TLC:
Mobile Phase: 1:9:: Ethylacetate: Hexane
Rf Vlaue: 0.7
Visualization: UV, $KMnO_4$

Synthesis of Intermediate-9:



1,3-dimethoxy-5-pentylbenzene
Chemical Formula: $C_{13}H_{20}O_2$
Molecular Weight: 208.30

5-pentylbenzene-1,3-diol
Chemical Formula: $C_{11}H_{16}O_2$
Molecular Weight: 180.24

Procedure:

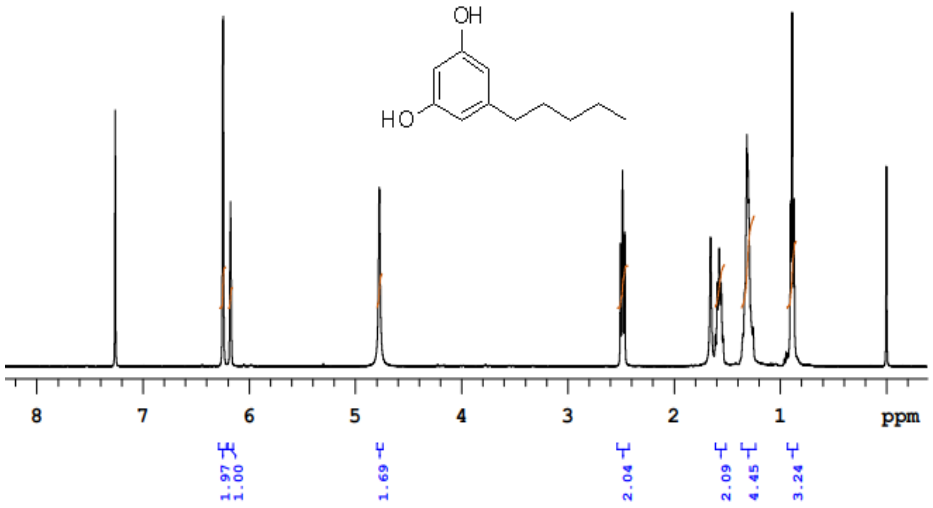
To a solution of 1,3-diemthoxy-5-pentylbenzene (1 g, 4.8 mmol) in Dichloromethane (24 ml, 5ml/ mmol), Borontribromide (0.9 ml, 10.3 mmol) was added at -13 4.8 mmol) -13 °C drop wise. The resulting mixture was stirred at RT for 1 h. pH of the reaction mixture was adjusted to 7 with saturated sodium bicarbonate solution and it was extracted with Dichloromethane (3 x 50 ml). Combined dichloromethane layer was washed with brine, dried over anhy. Na_2SO_4 and volatiles were evaporated. The residue obtained was purified by silicagel column chromatography to obtain (850 mg, 98.3%) of product.

TLC:

Mobile Phase: 1:4:: Ethylacetate: Hexane
Rf Vlaue: 0.2
Visualization: UV, $KMnO_4$

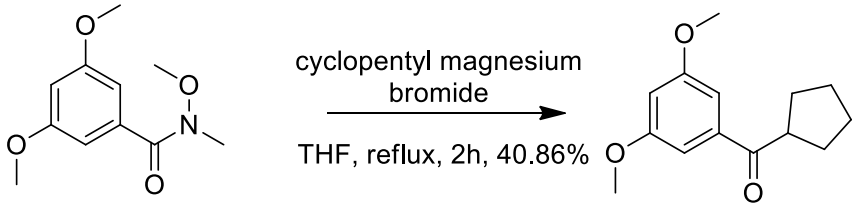
Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 6.24 (s, 2H), 6.18 (s, 1H), 4.77 (s, 2H), 2.48 (t, J = 7,6 Hz, 2H), 1.61-1.54 (m, 2H), 1.35-1.26 (m, 4H), 0.89 (t, J = 6.4 Hz, 3H)



^{1}H NMR of Intermediate- 9

Synthesis of Intermediate-10:



N,3,5-trimethoxy-*N*-methylbenzamide
Chemical Formula: $C_{11}H_{15}NO_4$
Molecular Weight: 225.24

cyclopentyl(3,5-dimethoxyphenyl)methanone
Chemical Formula: $C_{14}H_{18}O_3$
Molecular Weight: 234.29

Procedure:

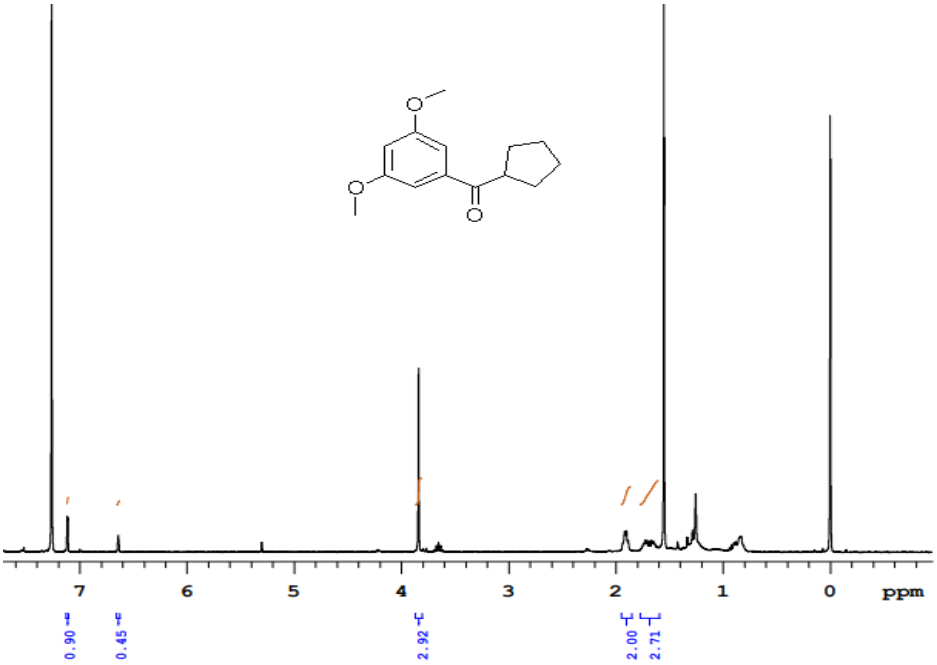
A solution of N,3,4,5-tetramethoxy-N-methylbenzamide (4 g, 17.76 mmol) in dry THF (35.5 mL, 2 ml/mmol) was added dropwise via a syringe to this solution of the cyclopentyl Grignard reagent (35.52 mmol) and refluxed for 2h. The reaction mixture was poured onto ice (200 g) and aqueous HCl (100 mL, 2 M) and the organic layers separated. The aqueous layer was extracted with ethyl acetate (3 X 100 mL) and the combined organic phases were washed with water (3 X 50 mL), dried (anhy. Na_2SO_4) and volatiles were evaporated to afford the crude product. It was purified by silicagel column purification in Ethylacetate: Pet.ether to get 2 g (40.86%) of product.

TLC:

Mobile Phase: 1:4:: Ethylacetate: Hexane
Rf Vlaue: 0.7
Visualization: UV, $KMnO_4$

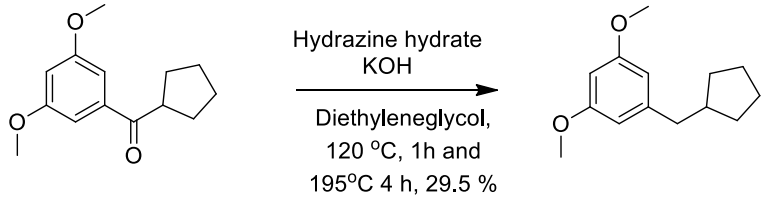
Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 7.11 (s, 2H), 6.64 (s, 1H), 3.84 (s, 6H), 1.92-1.90 (m, 4H), 1.80-1.60 (m, 5H)



^{1}H NMR of Intermediate- 10

Synthesis of Intermediate-11:



cyclopentyl(3,5-dimethoxyphenyl)methanone
Chemical Formula: $C_{14}H_{18}O_3$
Molecular Weight: 234.29

1-(cyclopentylmethyl)-3,5-dimethoxybenzene
Chemical Formula: $C_{14}H_{20}O_2$
Molecular Weight: 220.31

Procedure:

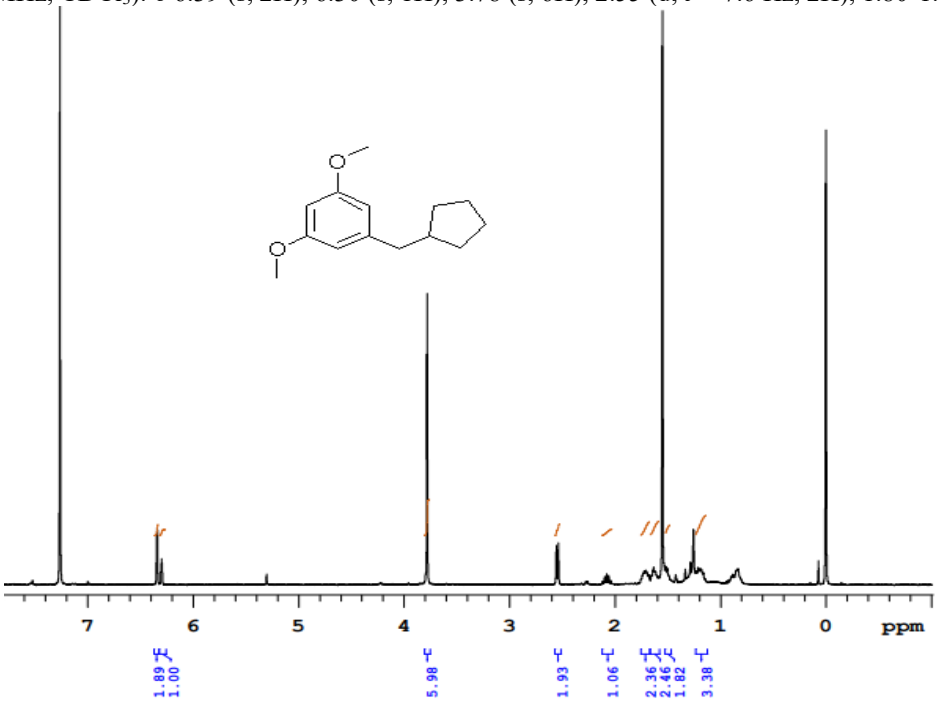
A solution of cyclopentyl (3,5-dimethoxyphenyl)methanone (1.7 g, 7.26 mmol) in diethyleneglycol (72.6 ml, 10 ml/ mmol), KOH (9.5 g, 169.3 mmol) and hydrazine hydrate (85%) (9.22 ml, 1.27 ml/ mmol) were added. The resulting solution was heated at 120 °C for 1 h and 195 °C for 4 h. After the formed water was removed, the mixture was heated at 195°C for an ad- ditional 4 h. After cooling, the solution was diluted with water (200ml) and extracted with ethyl acetate (2 x 100 ml). The combined ethylacetate layers were dried over anhy. Na_2SO_4 and volatiles were evaporated. The residue was purified on silica gel column in Ethylacetate: Pet.ether to obtaine 470 mg (29.5 %) of product.

TLC:

Mobile Phase: 1:9:: Ethylacetate: Hexane
Rf Vlaue: 0.7
Visualization: UV, $KMnO_4$

Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 6.39 (s, 2H), 6.30 (s, 1H), 3.78 (s, 6H), 2.55 (d, J = 7.6 Hz, 2H), 1.80-1.50 (m, 5H)



^{1}H NMR of Intermediate- 11

Procedure:

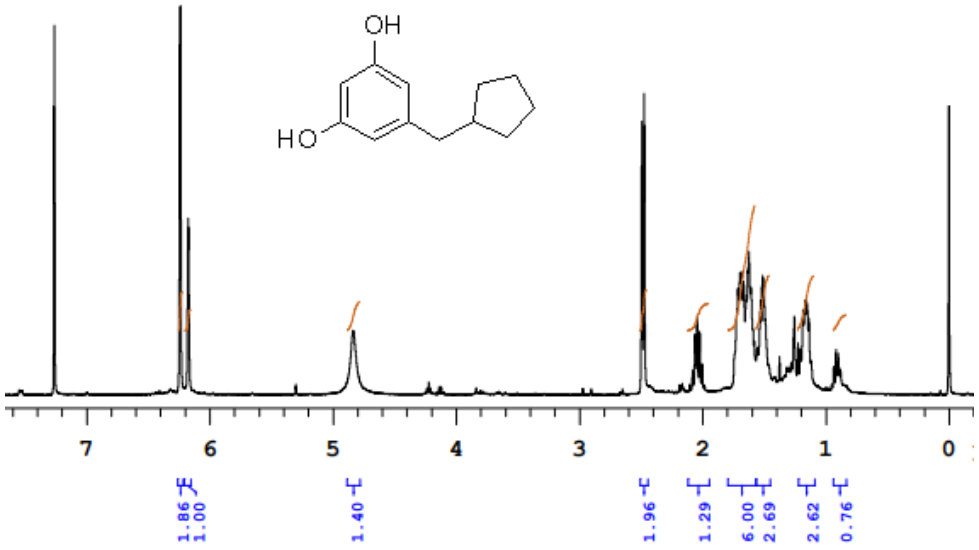
To a solution of 1-(cyclopentylmethyl)-3,5-diemthoxybenzene (470 mg, 2.133 mmol) in Dichloromethane (10.5 ml, 5ml/mmol), Borontribromide (0.4 ml, 4.2 mmol) was added at -13 ºC drop wise. The resulting mixture was stirred at RT for 1 h. pH of the reaction mixture was adjusted to 7 with saturated sodium bicarbonate solution and it was extracted with Dichloromethane (3 x 50 ml). Combined dichloromethane layer was washed with brine, dried over anhy. Na_2SO_4 and volatiles were evaporated. The residue obtained was purified by silicagel column chromatography to obtain (370 mg, 90.2 %) of product.

TLC:

Mobile Phase: 1:4:: Ethylacetate: Hexane
Rf Vlaue: 0.2
Visualization: UV, $KMnO_4$

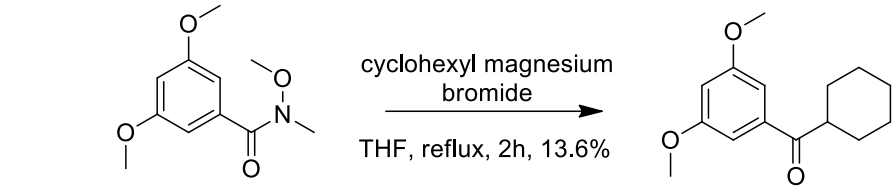
Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 6.24 (s, 2H), 6.17 (s, 1H), 4.84 (s, 2H), 2.48 (d, J = 7.6 Hz, 2H), 2.08-2.00 (m, 1H), 1.70-1.16 (m, 8H).



^{1}H NMR of Intermediate- 12

Synthesis of Intermediate-13:



N,3,5-trimethoxy-*N*-methylbenzamide
Chemical Formula: $C_{11}H_{15}NO_4$
Molecular Weight: 225.24

cyclohexyl(3,5-dimethoxyphenyl)methanone
Chemical Formula: $C_{15}H_{20}O_3$
Molecular Weight: 248.32

Procedure:

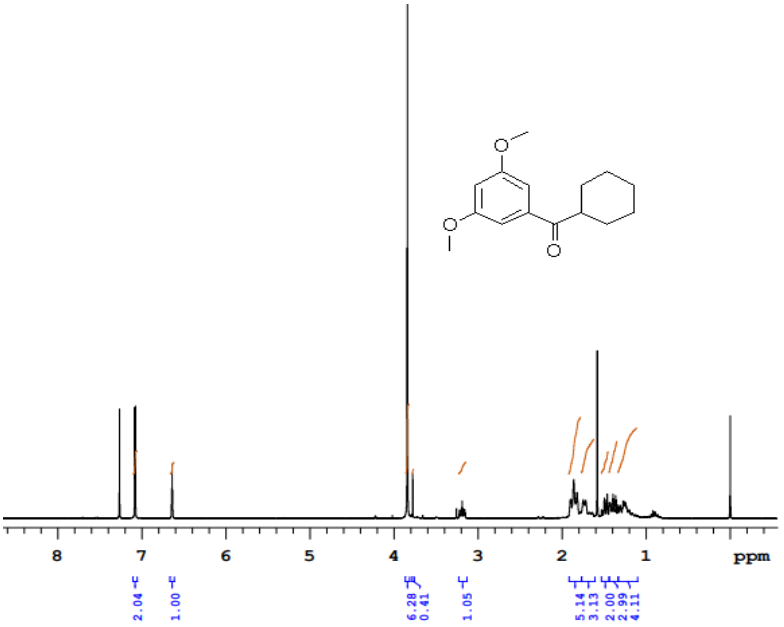
A solution of N,3,4,5-tetramethoxy-N-methylbenzamide (4 g, 17.76 mmol) in dry THF (35.5 mL, 2 ml/mmol) was added dropwise via a syringe to this solution of the cyclohexyl Grignard reagent (35.52 mmol) and refluxed for 2h. The reaction mixture was poured onto ice (200 g) and aqueous HCl (100 mL, 2 M) and the organic layers separated. The aqueous layer was extracted with ethyl acetate (3 X 100 mL) and the combined organic phases were washed with water (3 X 50 mL), dried (anhy. Na_2SO_4) and volatiles were evaporated to afford the crude product. It was purified by silicagel column purification in Ethylacetate: Pet.ether to get 0.6 g (13.6 %) of product.

TLC:

Mobile Phase: 1:4:: Ethylacetate: Hexane
Rf Vlaue: 0.8
Visualization: UV, $KMnO_4$

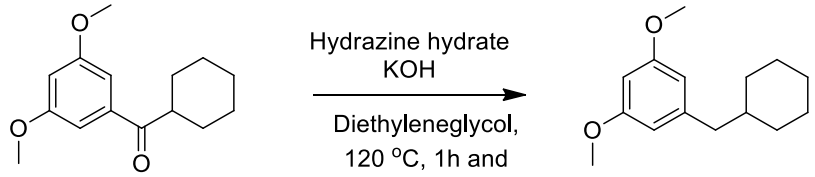
Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 7.07 (d, J = 2.4 Hz, 2H), 6.64 (t, J = J = 2.4 Hz, 1H), 3.84 (s, 6H), 3.22-3.16 (m, 1H), 1.90-1.19 (m, 10H).



^{1}H NMR of Intermediate- 13

Synthesis of Intermediate-14:



cyclohexyl(3,5-dimethoxyphenyl)methanone
Chemical Formula: $C_{15}H_{20}O_3$
Molecular Weight: 248.32

1-(cyclohexylmethyl)-3,5-dimethoxybenzene
Chemical Formula: $C_{15}H_{22}O_2$
Molecular Weight: 234.33

Procedure:

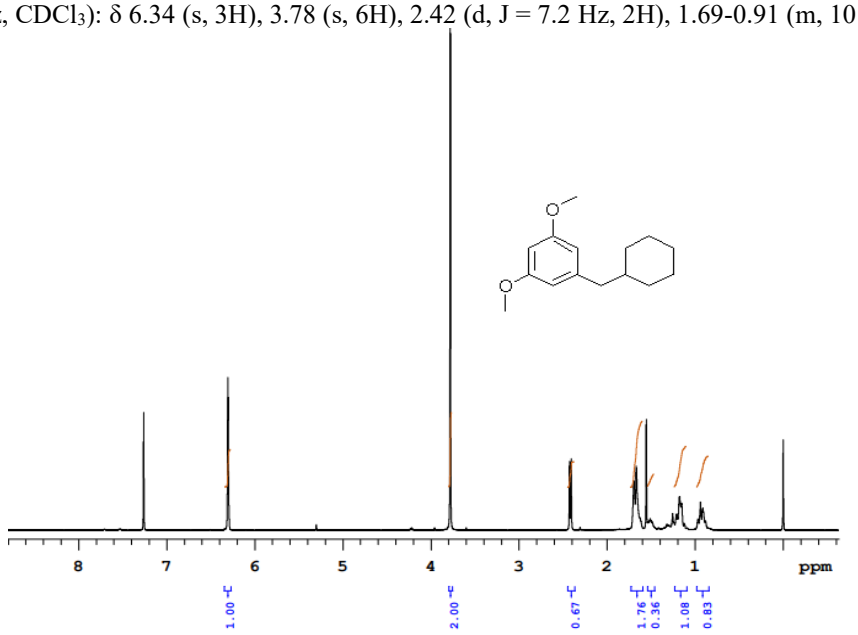
A solution of cyclohexyl (3,5-dimethoxyphenyl)methanone (600 mg, 2.42 mmol) in diethyleneglycol (24.2 ml, 10 ml/ mmol), KOH (3.4 g, 60.6 mmol) and hydrazine hydrate (85%) (3.07 ml, 1.27 ml/ mmol) were added. The resulting solution was heated at 120 °C for 1 h and 195 °C for 4 h. After the formed water was removed, the mixture was heated at 195°C for an ad- ditional 4 h. After cooling, the solution was diluted with water (100ml) and extracted with ethyl acetate (2 x 50 ml). The combined ethylacetate layers were dried over anhy. Na_2SO_4 and volatiles were evaporated. The residue was purified on silica gel column in Ethylacetate: Pet.ether to obtaine 330 mg (58.3 %) of product.

TLC:

Mobile Phase: 1:4:: Ethylacetate: Hexane
Rf Vlaue: 0.8
Visualization: UV, $KMnO_4$

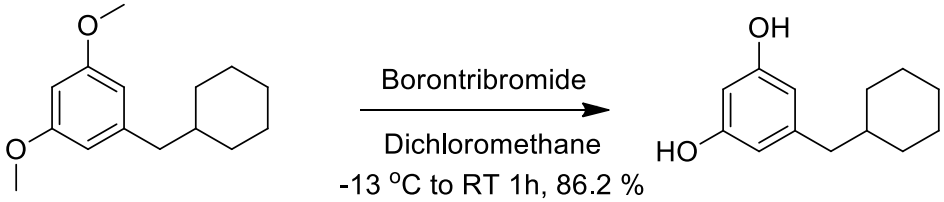
Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 6.34 (s, 3H), 3.78 (s, 6H), 2.42 (d, J = 7.2 Hz, 2H), 1.69-0.91 (m, 10 H).



^{1}H NMR of Intermediate- 14

Synthesis of Intermediate-15:



1-(cyclohexylmethyl)-3,5-dimethoxybenzene
Chemical Formula: $C_{15}H_{22}O_2$
Molecular Weight: 234.33

5-(cyclohexylmethyl)benzene-1,3-diol
Chemical Formula: $C_{13}H_{18}O_2$
Molecular Weight: 206.28

Procedure:

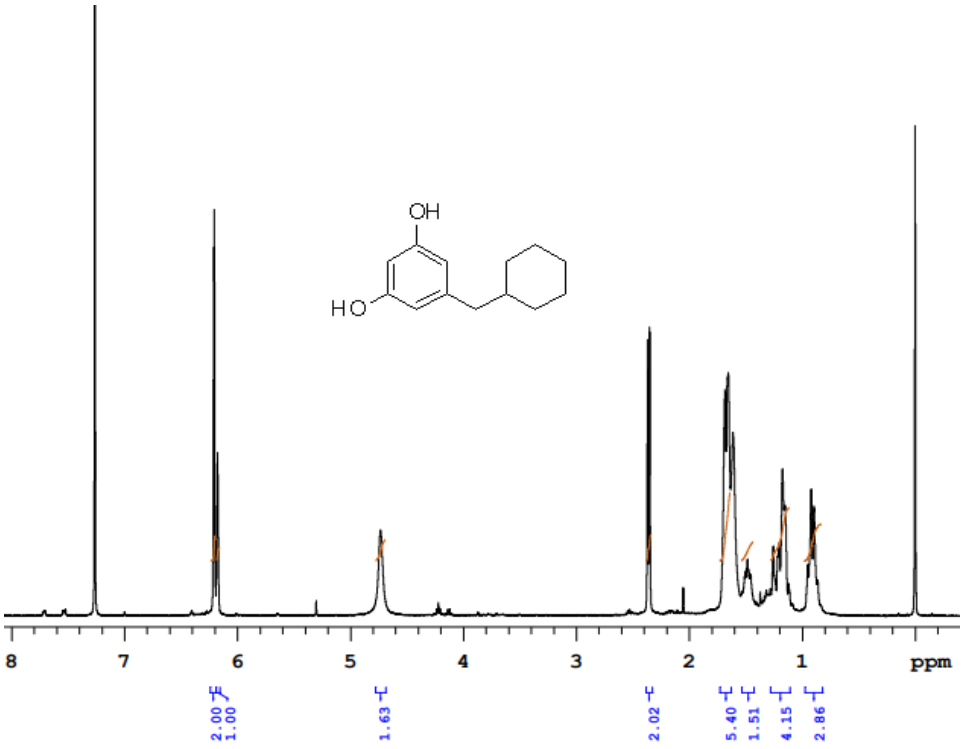
To a solution of 1-(cyclohexylmethyl)-3,5-diemthoxybenzene (330 mg, 1.41 mmol) in Dichloromethane (7 ml, 5ml/ mmol), Borontribromide (0.2 ml, 2.1 mmol) was added at -13 ºC drop wise. The resulting mixture was stirred at RT for 1 h. pH of the reaction mixture was adjusted to 7 with saturated sodium bicarbonate solution and it was extracted with Dichloromethane (3 x 50 ml). Combined dichloromethane layer was washed with brine, dried over anhy. Na_2SO_4 and volatiles were evaporated. The residue obtained was purified by silicagel column chromatography to obtain (250 mg, 86.2 %) of product.

TLC:

Mobile Phase: 1:4:: Ethylacetate: Hexane
Rf Vlaue: 0.2
Visualization: UV, $KMnO_4$

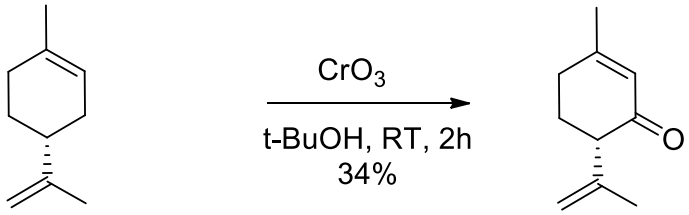
Analytical data:

[1] H NMR (400 MHz, $CDCl_3$): δ 6.21 (s, 2H), 6.18 (s, 1H), 4.73 (s, 2H), 2.36 (d, J = 7.2 Hz, 2H), 1.68-0.86 (m, 11 H).



^{1}H NMR of Intermediate- 15

Synthesis of Intermediate-16:



(+)-limonene
Chemical Formula: $C_{10}H_{16}$
Molecular Weight: 136.23

(*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enone
Chemical Formula: $C_{10}H_{14}O$
Molecular Weight: 150.22

Procedure:

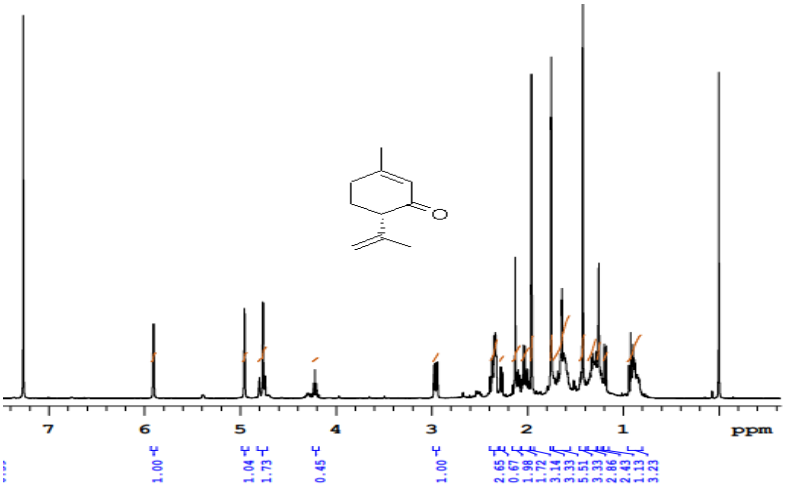
To a magnetically stirred solution of tertiary butyl alcohol (120 mL) was added chromium trioxide (48 g, 480.0 mmol) in small portions and stirred for 15 min. To this R-(+)-Limonene (16 g, 117.44 mmol) was added and stirred at room temperature for 2 h. Then reaction mixture was diluted with water (500 ml) extracted with Dichloromethane (3 x 500 ml). Total Dichloromethane layer was dried over anhy. Sodium sulphate and the volatiles were evaporated under vacuum. The residue obtained was passed through a silica gel column using EtOAc-hexane to obtain the product (6 g, 34%) as yellow liquid.

TLC:

Mobile Phase: 1:9:: Ethylacetate: Hexane
Rf Vlaue: 0.5
Visualization: UV, $KMnO_4$

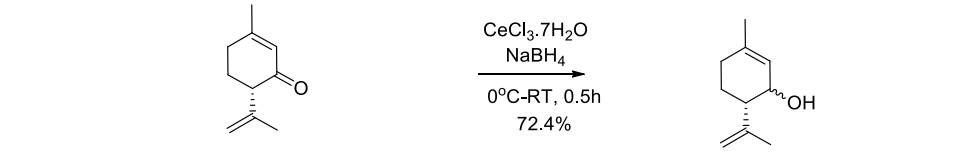
Analytical data:

[1] H NMR (400 MHz, $CDCl_3$): δ 5.90 (s, 1H), 4.87 (s, 1H), 4.78 (s, 1H), 2.90-2.95 (m, 1H), 2.40-1.20 (m, 10H)



^{1}H NMR of Intermediate- 16

Synthesis of Intermediate-17:



(*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enone
Chemical Formula: $C_{10}H_{14}O$
Molecular Weight: 150.22

(6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enol
Chemical Formula: $C_{10}H_{16}O$
Molecular Weight: 152.23

Procedure:

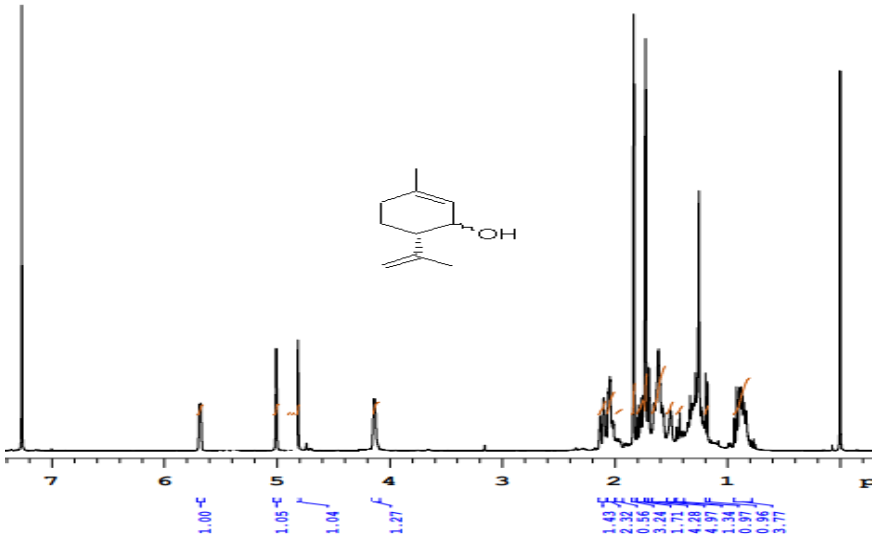
To a magnetically stirred solution of (S)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enone (4 g, 26.63 mmol) in anhydrous MeOH (133 mL, 5ml/mmol) was added CeCl3.7H2O (5 g, 13.3 mmol) at rt and stirred for 10 min. Then NaBH4 (1.2 g, 31.3 mmol) was added portion wise at 0 °C. The reaction mixture was stirred for 30 min. at rt and quenched with water. Then the reaction mixture was extracted with DCM (1L) and dried over Na_2SO_4. The solvent was evaporated and the residue obtained was purified on silica gel column using EtOAc: hexane to furnish the compound (2.2 g, 72.4%) as pale yellow liquid.

TLC:

Mobile Phase: 1:4:: Ethylacetate: Hexane
Rf Vlaue: 0.5
Visualization: UV, $KMnO_4$

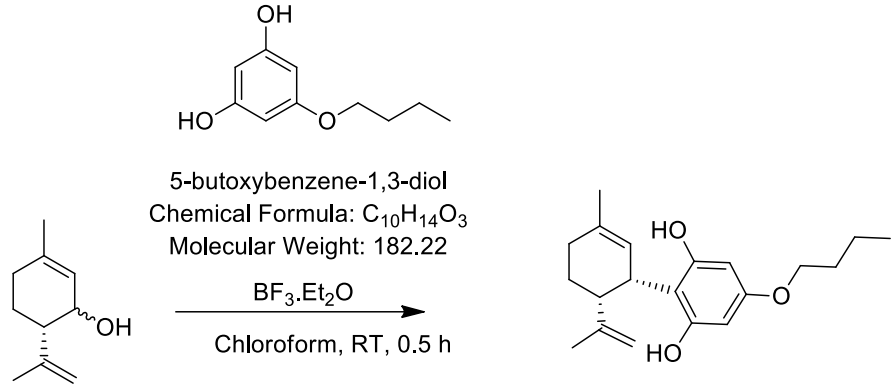
Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 5.64 (s, 1H), 5.01 (s, 1H), 4.82 (s, 1H), 4.18 (s, 1H), 2.18-2.00 (m, 2H), 1.80-1.20 (m, 10H).



^{1}H NMR of Intermediate- 17

Synthesis of Compound-1:



(6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enol
Chemical Formula: $C_{10}H_{16}O$
Molecular Weight: 152.23

(1'*S*,2'*R*)-4-butoxy-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol
Chemical Formula: $C_{20}H_{28}O_3$
Molecular Weight: 316.43 13.7 %

+ Minute quanity of 1' R-isomer is obtained

Procedure:

To a solution of (6S)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enol (600 mg, 3.94 mmol) and 5-butoxybenzene-1,3-diol (720 mg, 3.94 mmol) in chloroform (39.4 ml, 10 ml/ mmol), Borontrifluoride etherate (56 mg, 0.394 mmol) was added and the resulting solution was stirred for 30 min at room temperature. The volatiles were evaporated and the residue obtained was purified by silicagel column chromatography in ethylacetate: Pet.ether to get 170 mg (13.7%) and minute quantity of 1'R-isomer were obtained.

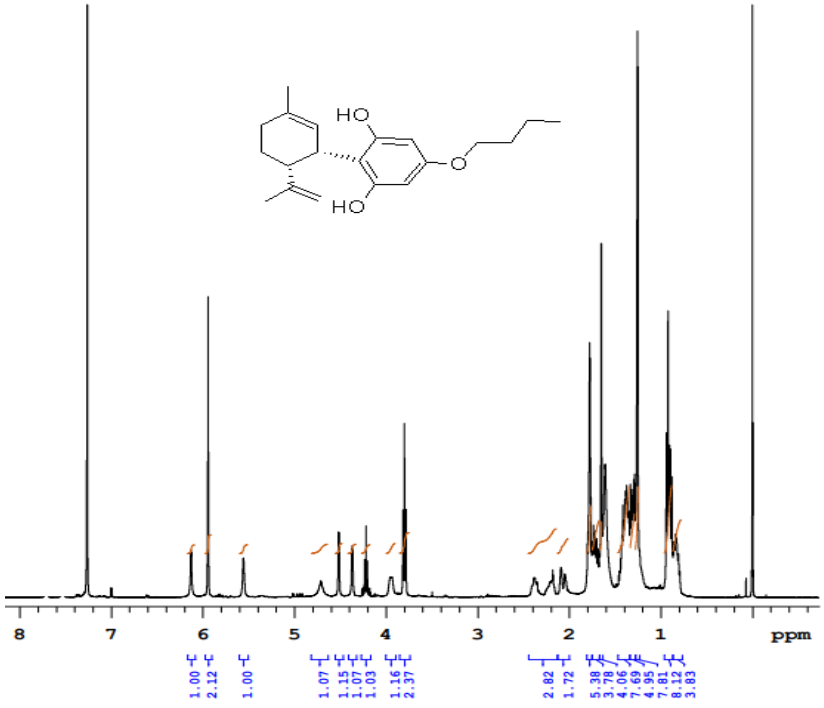
TLC:

Mobile Phase: 1:4:: Ethylacetate: Hexane
Rf Vlaue: 0.25
Visualization: UV, $KMnO_4$

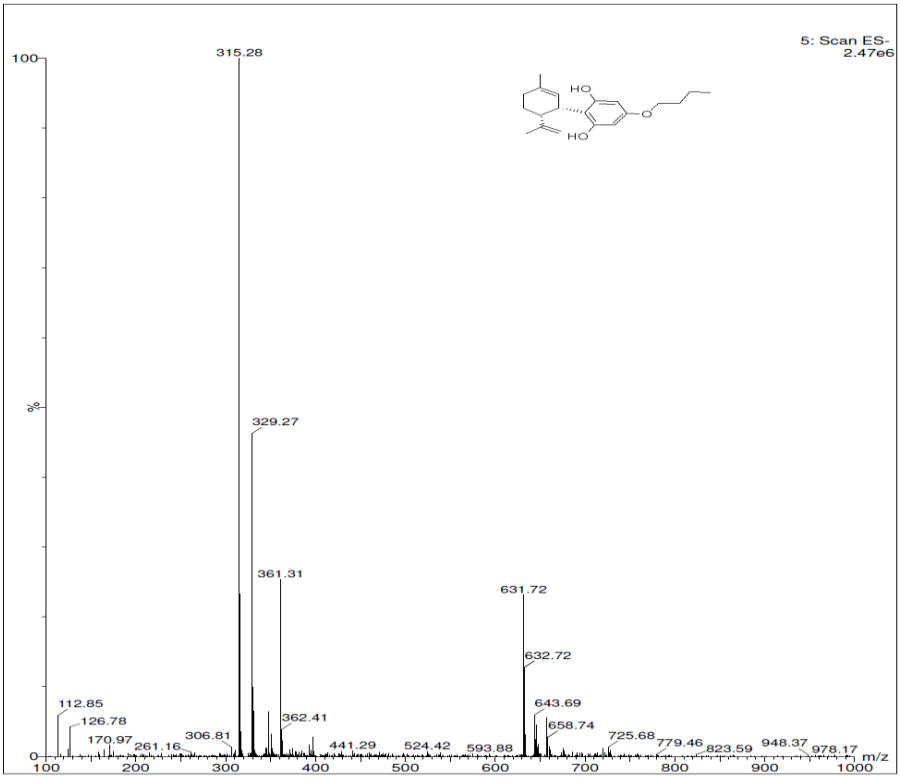
Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 6.13 (s, 1H), 5.94 (s, 2H), 5.56 (s, 1H), 4.71 (bs, 1H), 4.52 (s, 1H), 4.37 (s, 1H), 4.26-4.18 (m, 1H), 3.94 (bs, 1H), 3.80 (t, J = 6.8 Hz, 2H), 2.42-2.40 (4H), 1.80-1.20 (m, 10 H), 0.94-0.79 (m, 3H).

MS (ESI) m/z: calculated, $C_{20}H_{28}O_3$, 316.43 $[M]^+$; found, 315.28 $[M-H]^-$

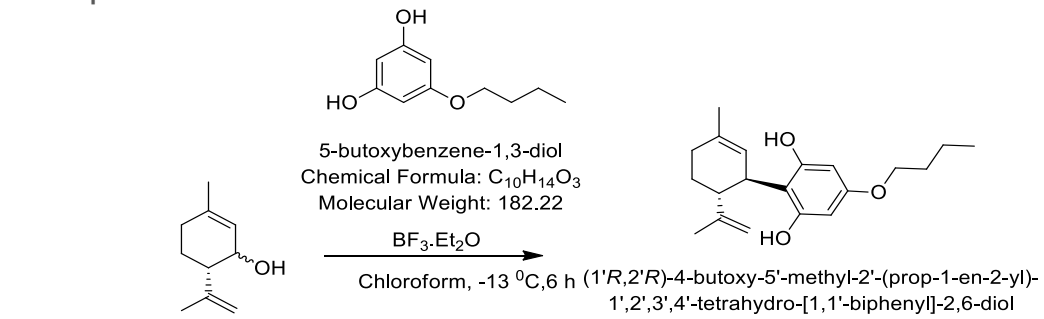


^{1}H NMR of Compound – 1



ESI-MS (-Ve mode) of Compound-1

Synthesis of Compound-2:



Procedure:

To a solution of (6S)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enol (600 mg, 3.94 mmol) and 5-butoxybenzene-1,3-diol (720 mg, 3.94 mmol) in chloroform (39.4 ml, 10 ml/ mmol), Borontrifluoride etherate (56 mg, 0.394 mmol) was added at -13 ^{0}C and the resulting solution was stirred for 6 h. The volatiles were evaporated and the residue obtained was purified by silicagel column chromatography in ethylacetate: Pet.ether to get 200 mg (16.12%) of products and minute quantity of 1'S isomer were obtained.

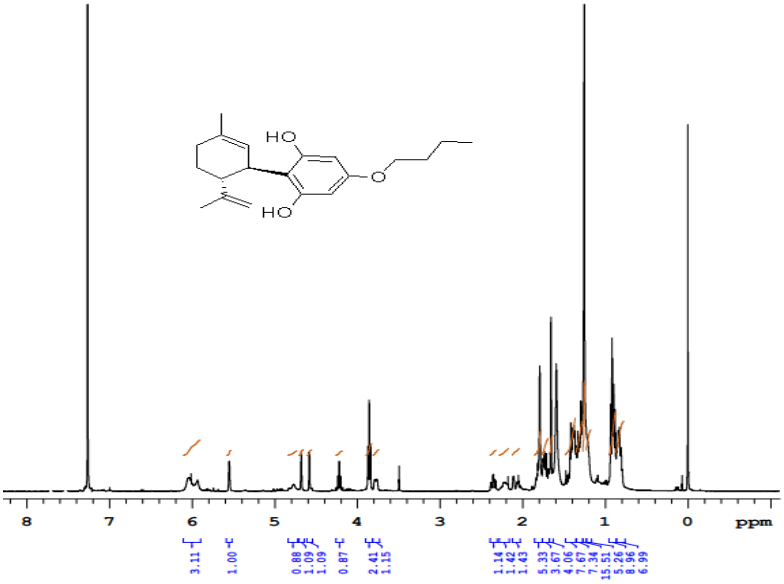
TLC:

Mobile Phase: 1:4:: Ethylacetate: Hexane
Rf Vlaue: 0.75
Visualization: UV, $KMnO_4$

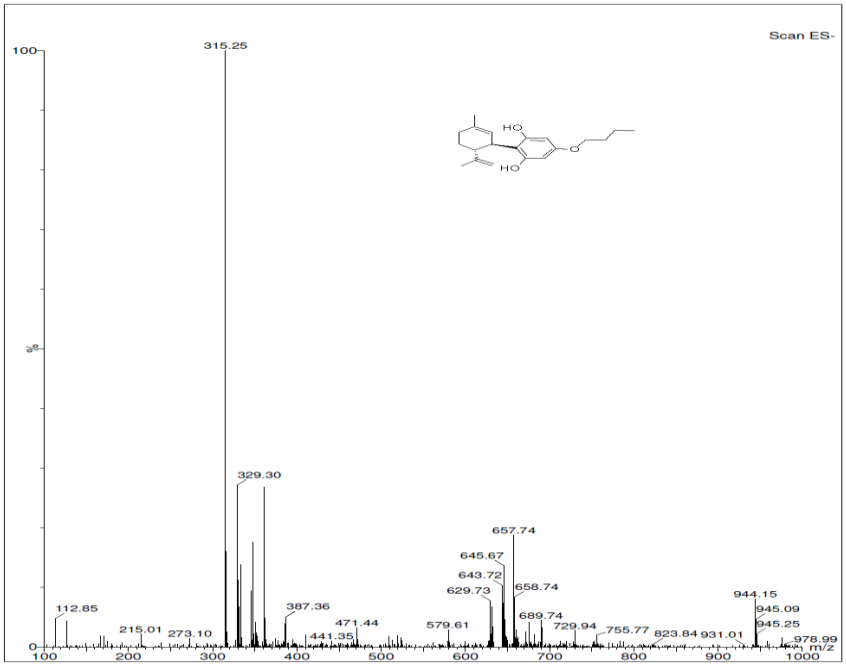
Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 6.04-5.93 (m, 3H), 5.55 (s, 1H), 4.77 (bs, 1H), 4.68 (s, 1H), 4.58 (s, 1H), 4.23-4.20 (m, 1H), 3.86 (t, J = 6.4 Hz, 2H), 3.79-3.76 (m, 1H), 2.39-2.33 (m, 1H), 2.30-2.00 (m, 2H), 1.80-1.20 (m, 11 H), 1.00-0.88 (m, 3H)

MS (ESI) m/z: calculated, $C_{20}H_{28}O_3$, 316.43 $[M]^+$; found, 315.28 $[M-H]^-$

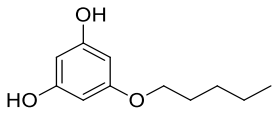


^{1}H NMR of Compound – 2

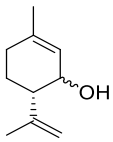


ESI-MS (-Ve mode) of Compound-2

Synthesis of Compound-3:



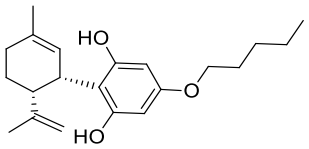
5-(pentyloxy)benzene-1,3-diol
Chemical Formula: $C_{11}H_{16}O_3$
Molecular Weight: 196.24



(6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enol
Chemical Formula: $C_{10}H_{16}O$
Molecular Weight: 152.23

$BF_3.Et_2O$

Chloroform, RT, 0.5 h



(1'*S*,2'*R*)-5'-methyl-4-(pentyloxy)-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol
Chemical Formula: $C_{21}H_{30}O_3$
Molecular Weight: 330.46

12.44 %

+ Minute quantities of 1' R isomer is obtained

Procedure:

To a solution of (6S)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enol (800 mg, 5.2 mmol) and 5-pentyloxybenzene-1,3-diol (1.03 mg, 5.2 mmol) in chloroform (52 ml, 10 ml/ mmol), Borontrifluoride etherate (73.8 mg, 0.52 mmol) was added and the resulting solution was stirred for 30 min at room temperature. The volatiles were evaporated and the residue obtained was purified by silicagel column chromatography in ethylacetate: Pet.ether to get 216 mg (12.44 %) and minor isomer of 1' R isomer were obtained.

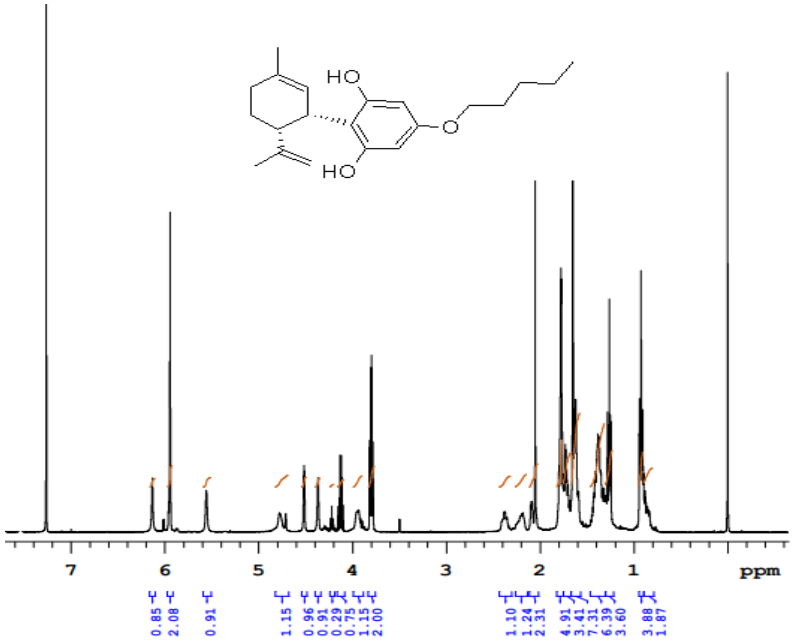
TLC:

Mobile Phase: 1:4:: Ethylacetate: Hexane
Rf Vlaue: 0.25
Visualization: UV, $KMnO_4$

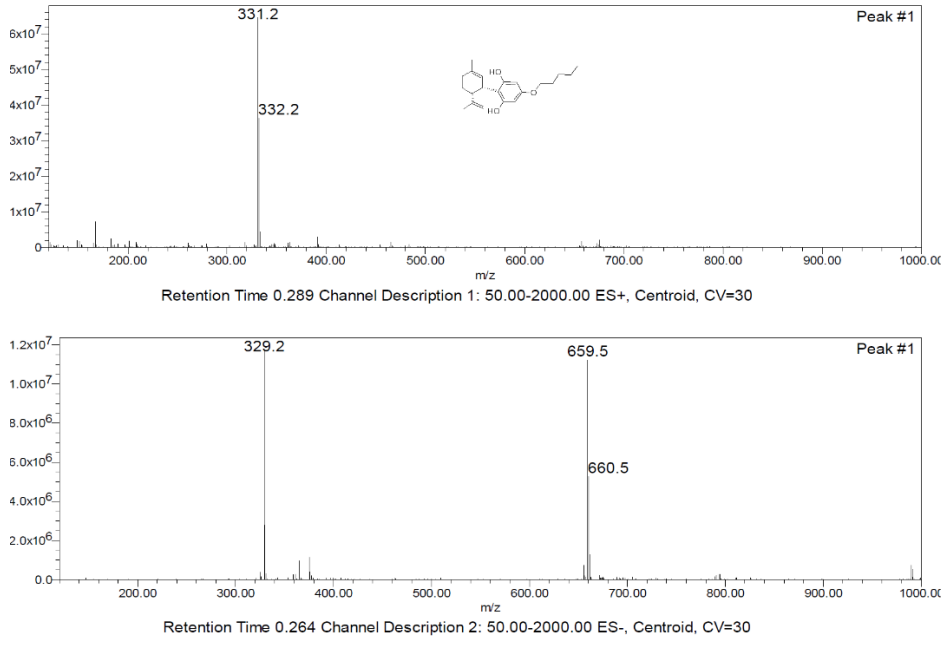
Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 6.13 (s, 1H), 5.94 (s, 2H), 5.57 (s, 1H), 4.71 (bs, 1H), 4.52 (s, 1H), 4.37 (s, 1H), 3.94 (bs, 1H), 3.80 (t, J = 6.8 Hz, 2H), 2.44-2.30 (m, 1H), 2.18 (bs, 1H), 2.09-2.02 (m, 1H), 0.90-0.88 (m, 3H)

MS (ESI) m/z: calculated, $C_{21}H_{30}O_3$, 330.46 $[M]^+$; found, 331.2 $[M+H]^+$, 329.2 $[M-H]^-$

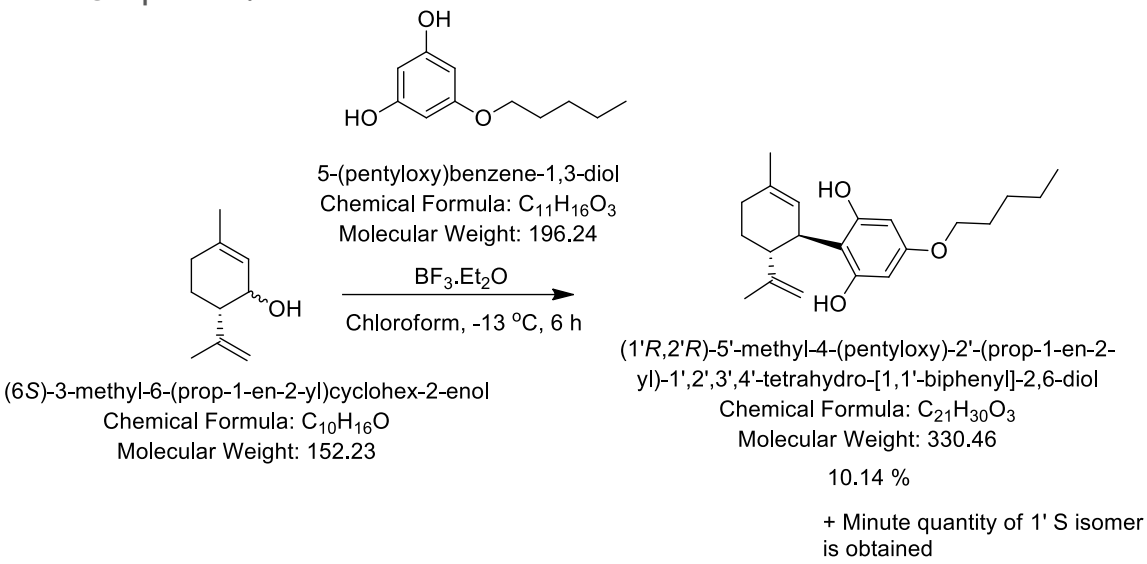


^{1}H NMR of Compound - 3



ESI-MS (+Ve & -Ve mode) of Compound-3

Synthesis of Compound-4:



Procedure:

To a solution of (6S)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enol (800 mg, 5.2 mmol) and 5-pentyloxybenzene-1,3-diol (1.03 mg, 5.2 mmol) in chloroform (52 ml, 10 ml/ mmol), Borontrifluoride etherate (73.8 mg, 0.52 mmol) was added at -13 ^{0}C and the resulting solution was stirred for 6 h. The volatiles were evaporated and the residue obtained was purified by silicagel column chromatography in ethylacetate: Pet.ether to get 176 mg (10.14%) of product and minor isomer of 1' S isomer were obtained.

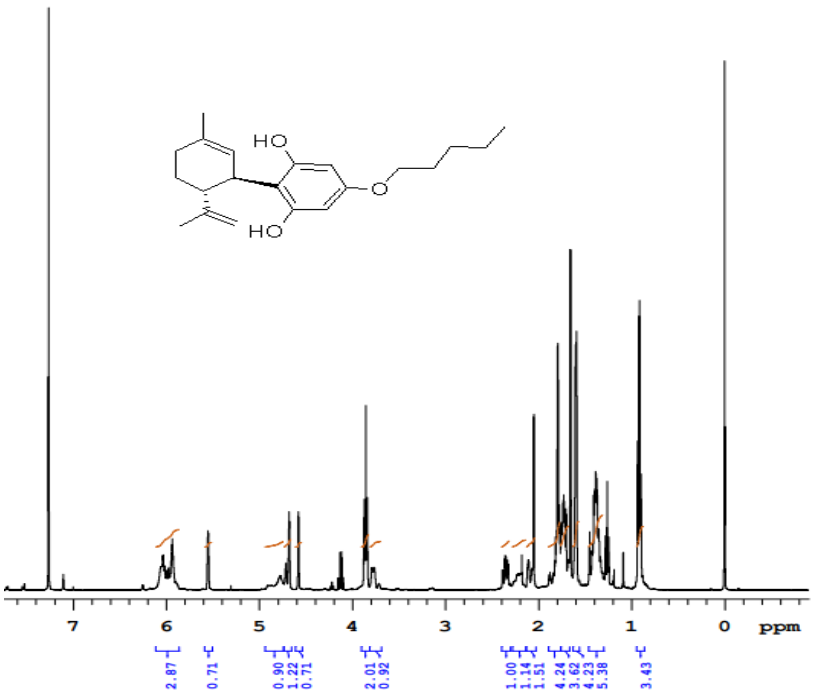
TLC:

Mobile Phase: 1:4:: Ethylacetate: Hexane
Rf Vlaue: 0.75
Visualization: UV, $KMnO_4$

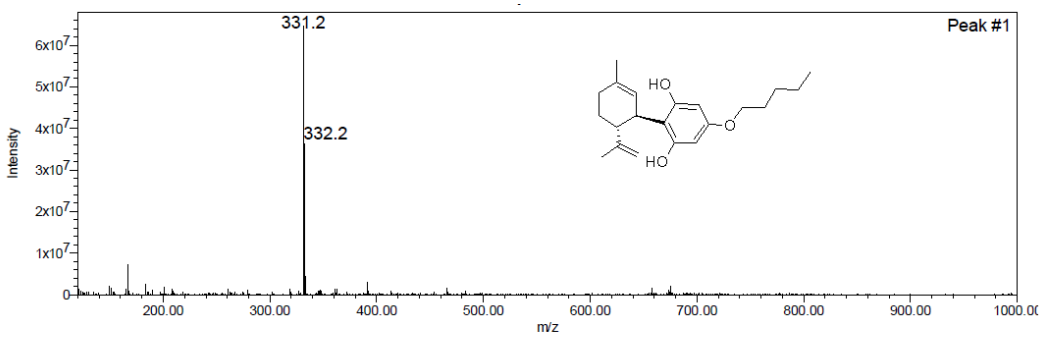
Analytical data:

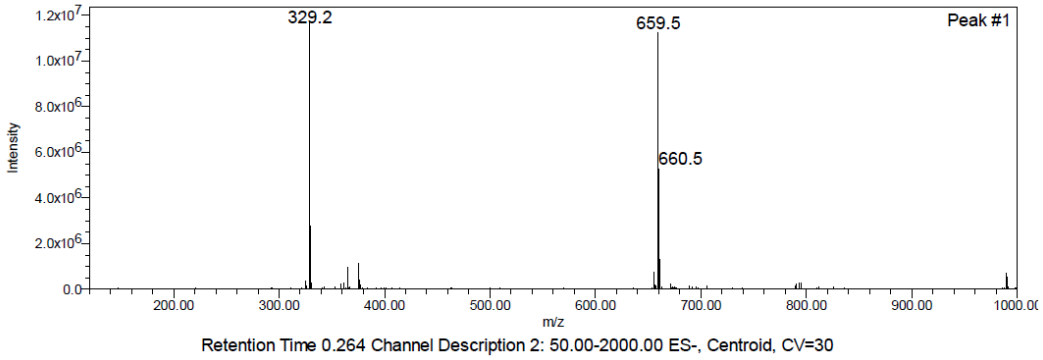
^{1} H NMR (400 MHz, $CDCl_3$): δ 6.06-5.90 (m, 3H), 5.55 (s, 1H), 4.77 (bs, 1H), 4.68 (s, 1H), 4.58 (s, 1H), 3.88-3.84 (m, 2H), 3.79-3.76 (m, 1H), 2.39-2.05 (m, 3H), 1.90-1.20 (m, 14H), 0.92 (t, J = 7.1 Hz, 3H)

MS (ESI) m/z: calculated, $C_{21}H_{30}O_3$, 330.46 $[M]^+$; found, 331.2 $[M+H]^+$, 329.2 $[M-H]^-$



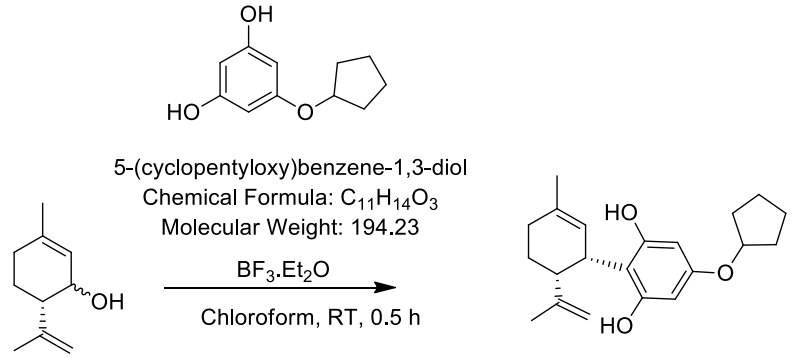
^{1}H NMR of Compound -4





ESI-MS (+Ve & -Ve mode) of Compound-4

Synthesis of Compound-5:



+ monor quantity of 1' R isomer was obtained

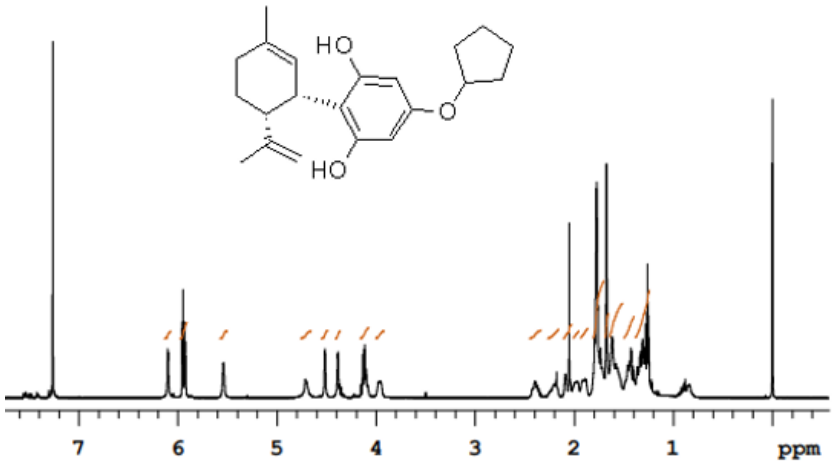
Procedure:

To a solution of (6S)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enol (400 mg, 2.6 mmol) and 5-(cyclopentyloxy)-benzene-1,3-diol (510 mg, 2.6 mmol) in chloroform (26 ml, 10 ml/ mmol), Borontrifluoride etherate (36.9 mg, 0.26 mmol) was added and the resulting solution was stirred for 30 min at room temperature. The volatiles were evaporated and the residue obtained was purified by silicagel column chromatography in ethylacetate: Pet.ether to get 150 mg (17.4 %) and minor quantity of 1'R isomer was obtained.

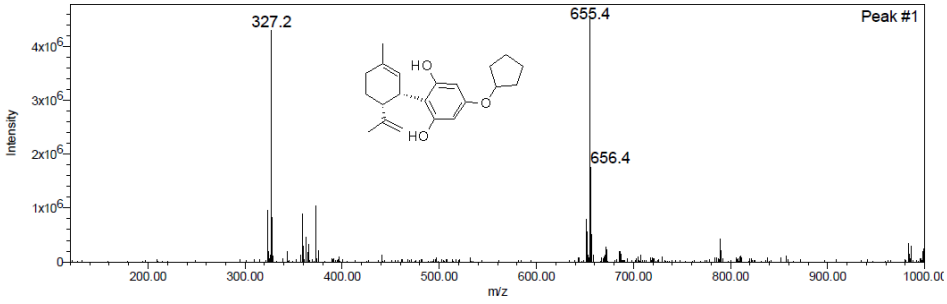
TLC:

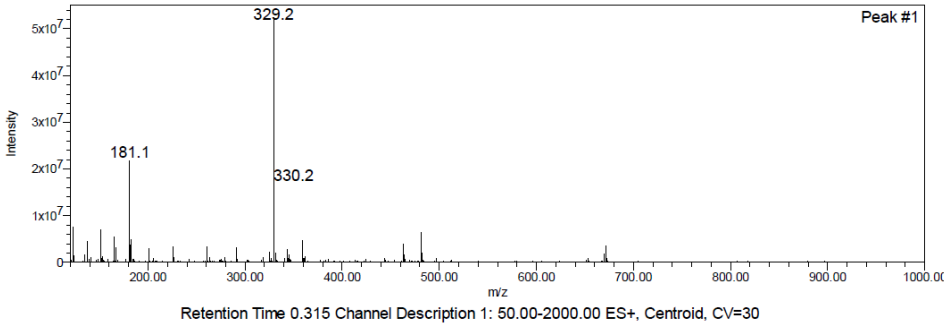
Mobile Phase: 1:4::Ethylacetate: Hexane
Rf Vlaue: 0.25
Visualization: UV, $KMnO_4$

Analytical data:



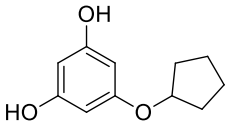
^{1}H NMR of Compound -5



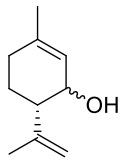


ESI-MS (-Ve mode) of Compound-5

Synthesis of Compound-6:

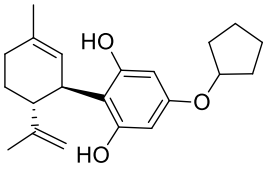


5-(cyclopentyloxy)benzene-1,3-diol
Chemical Formula: $C_{11}H_{14}O_3$
Molecular Weight: 194.23



$BF_3.Et_2O$

Chloroform, -13 ^oC, 6 h



(6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enol
Chemical Formula: $C_{10}H_{16}O$
Molecular Weight: 152.23

(1'*R*,2'*R*)-4-(cyclopentyloxy)-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol
Chemical Formula: $C_{21}H_{28}O_3$
Molecular Weight: 328.45

13.9 %

+ Minor quantity of 1' S isomer was obtained.

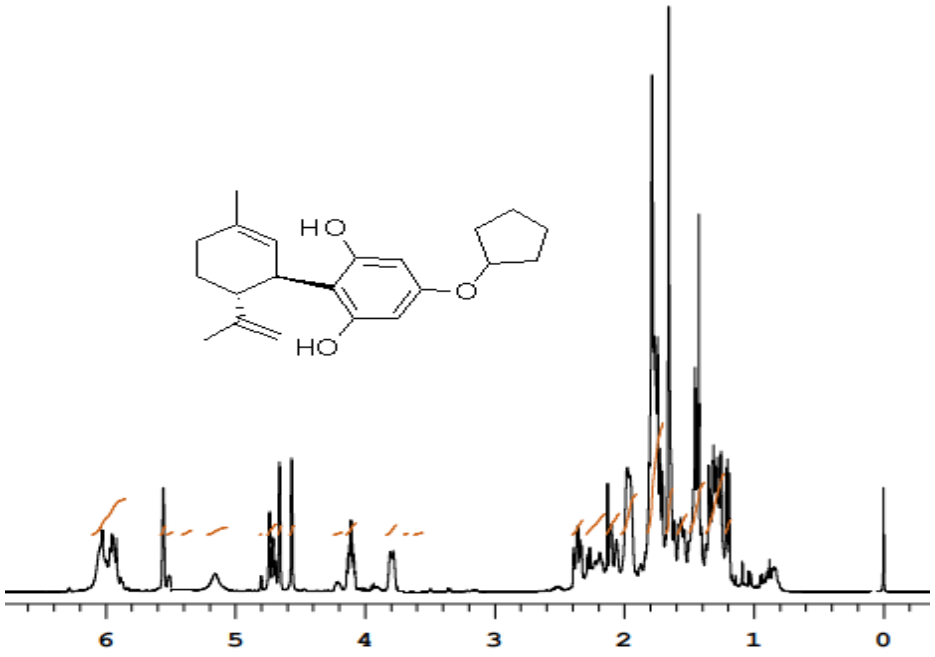
Procedure:

To a solution of (6S)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enol (400 mg, 2.6 mmol) and 5-(cyclopentyloxy)-benzene-1,3-diol (510 mg, 2.6 mmol) in chloroform (26 ml, 10 ml/ mmol), Borontrifluoride etherate (36.9 mg, 0.26 mmol) was added at -13 ^{0}C and the resulting solution was stirred for 6 h. The volatiles were evaporated and the residue obtained was purified by silicagel column chromatography in ethylacetate: Pet.ether to get 120 mg (13.9 %) of product and minor quantity of 1'S isomer was obtained.

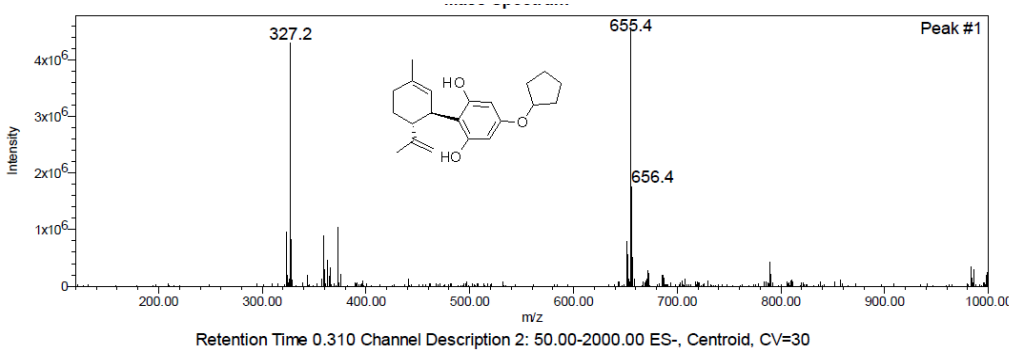
TLC:

Mobile Phase: 1:4:: Ethylacetate: Hexane
Rf Vlaue: 0.75
Visualization: UV, $KMnO_4$

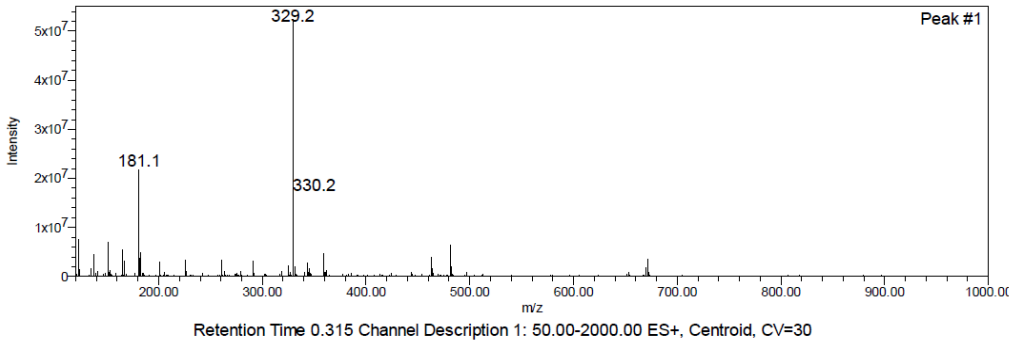
Analytical data:



^{1}H NMR of Compound – 6



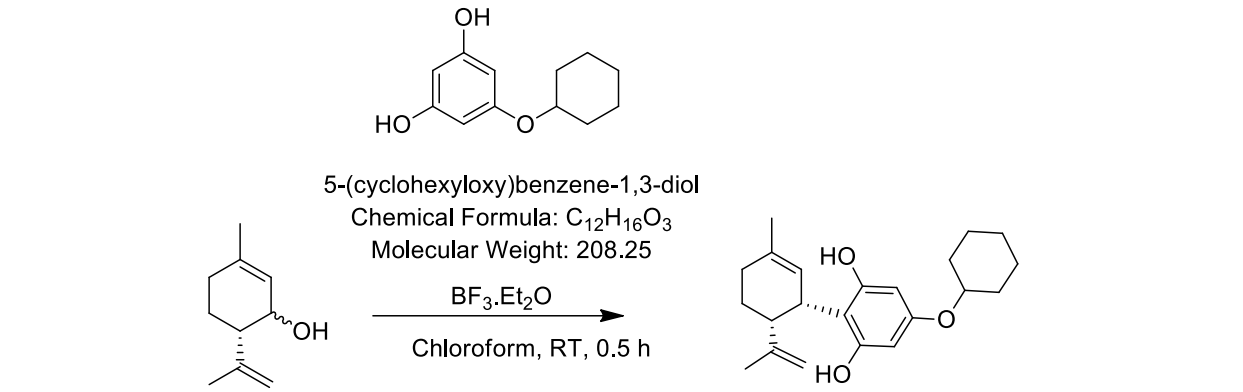
Retention Time 0.310 Channel Description 2: 50.00-2000.00 ES-, Centroid, CV=30



Retention Time 0.315 Channel Description 1: 50.00-2000.00 ES+, Centroid, CV=30

ESI-MS (-Ve mode) of Compound-

Synthesis of Compound-7:



5-(cyclohexyloxy)benzene-1,3-diol
Chemical Formula: $C_{12}H_{16}O_3$
Molecular Weight: 208.25

$BF_3.Et_2O$

Chloroform, RT, 0.5 h

(6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enol
Chemical Formula: $C_{10}H_{16}O$
Molecular Weight: 152.23

(1'*S*,2'*R*)-4-(cyclohexyloxy)-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol
Chemical Formula: $C_{22}H_{30}O_3$
Molecular Weight: 342.47 16.7 %

+ Minor quantity of 1'R isomer is obtained.

Procedure:

To a solution of (6S)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enol (500 mg, 3.2 mmol) and 5-(cyclohexyloxy)-benzene-1,3-diol (683 mg, 3.2 mmol) in chloroform (32 ml, 10 ml/ mmol), Borontrifluoride etherate (45.4 mg, 0.32 mmol) was added and the resulting solution was stirred for 30 min at room temperature. The volatiles were evaporated and the residue obtained was purified by silicagel column chromatography in ethylacetate: Pet.ether to get 180 mg (16.7 %) and Minor quantity of 1'R isomer is obtained.

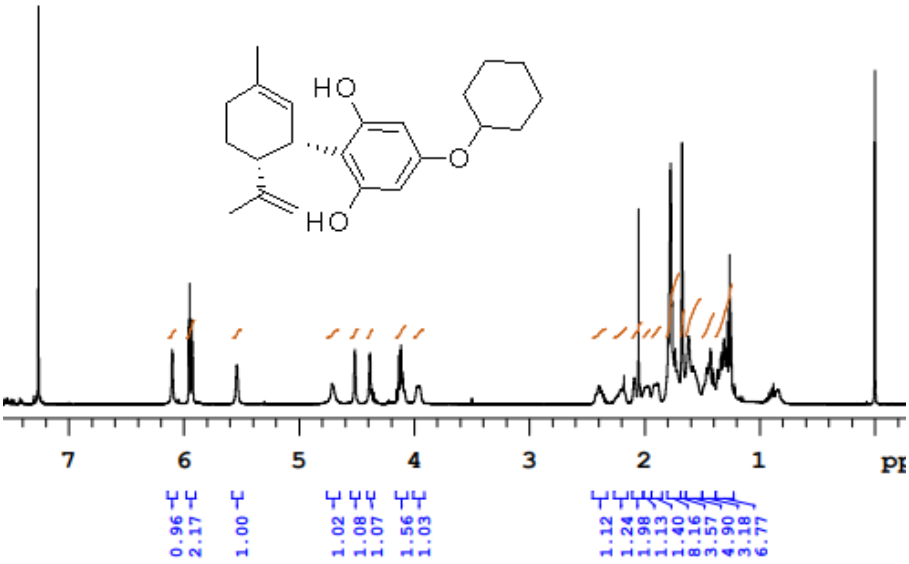
TLC:

Mobile Phase: 1:4:: Ethylacetate: Hexane
Rf Vlaue: 0.3
Visualization: UV, $KMnO_4$

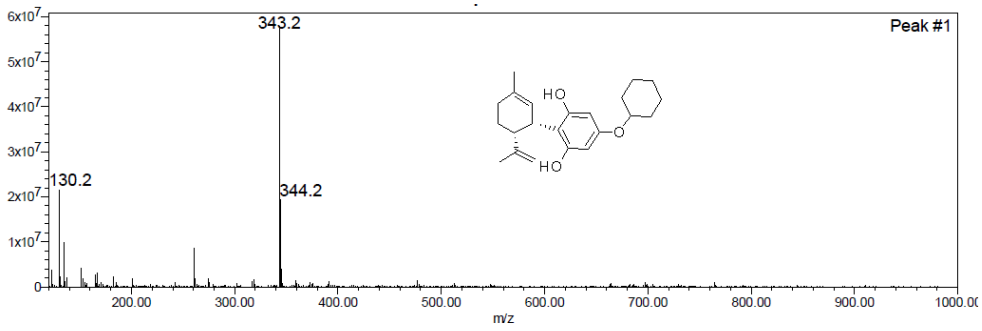
Analytical data:

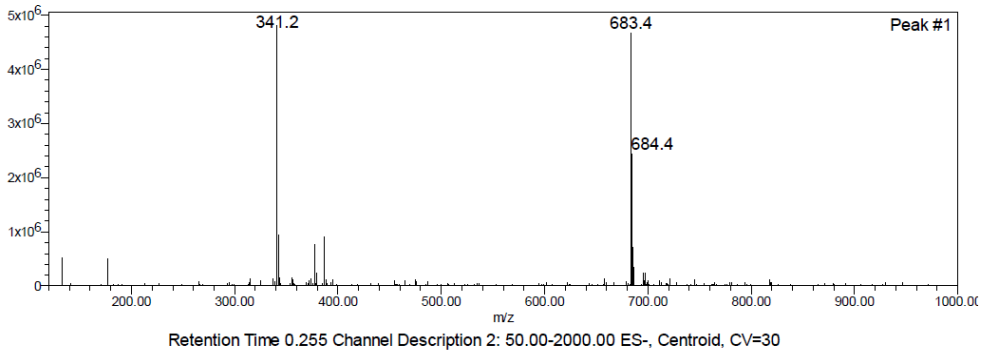
^{1} H NMR (400 MHz, $CDCl_3$): δ 6.10 (s, 1H), 5.96-5.92 (m, 2H), 5.54 (s, 1H), 4.71 (bs, 1H), 4.52 (s, 1H), 4.15-4.08 (m, 1H), 3.97-3.95 (m, 1H), 2.44-2.14 (m, 2H), 2.12-1.85 (m, 4H), 1.80-1.24 (16H)

MS (ESI) m/z: calculated, $C_{22}H_{30}O_3$, 342.47 $[M]^+$; found, 343.2 $[M+H]^+$, 341.2 $[M-H]^-$



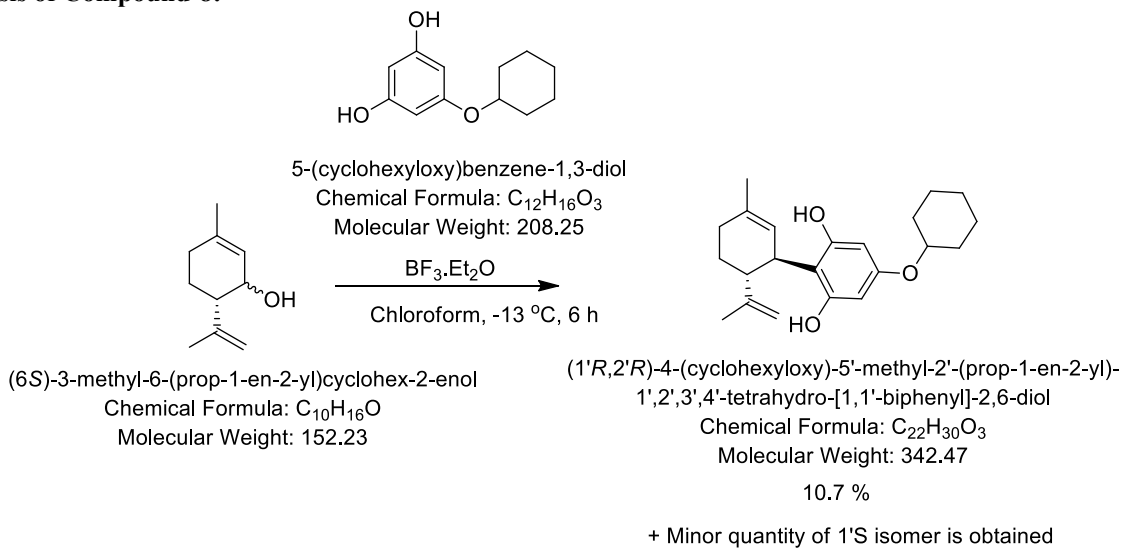
^{1}H NMR of Compound – 7





ESI-MS (+Ve & -Ve mode) of Compound-

Synthesis of Compound-8:



Procedure:

To a solution of (6S)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enol (500 mg, 3.2 mmol) and 5-(cyclohexyloxy)-benzene-1,3-diol (683 mg, 3.2 mmol) in chloroform (32 ml, 10 ml/ mmol), Borontrifluoride etherate (45.4 mg, 0.32 mmol) was added at -13 ^{0}C and the resulting solution was stirred for 6h. The volatiles were evaporated and the residue obtained was purified by silicagel column chromatography in ethylacetate: Pet.ether to get 120 mg (10.7 %) of product and minor quantity of 1'S isomer was obtained.

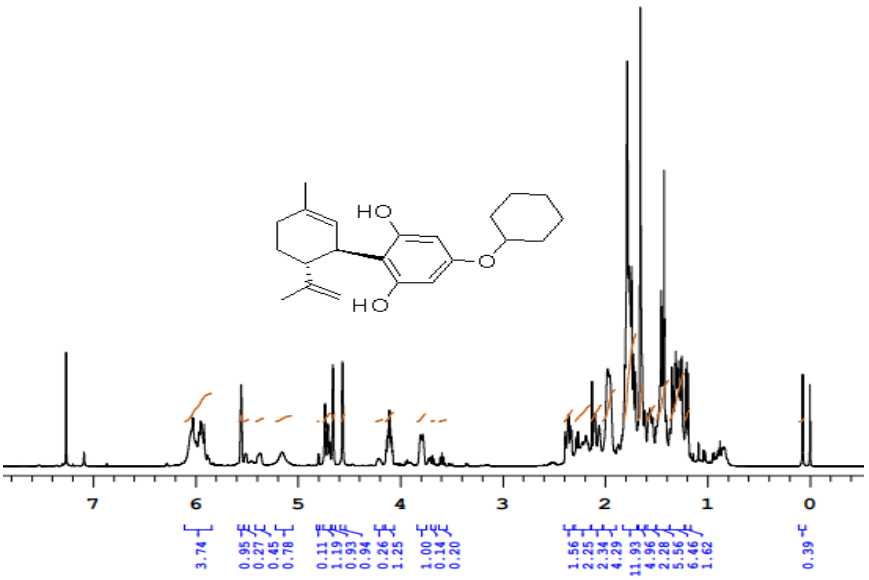
TLC:

Mobile Phase: 1:4:: Ethylacetate: Hexane
Rf Vlaue: 0.8
Visualization: UV, $KMnO_4$

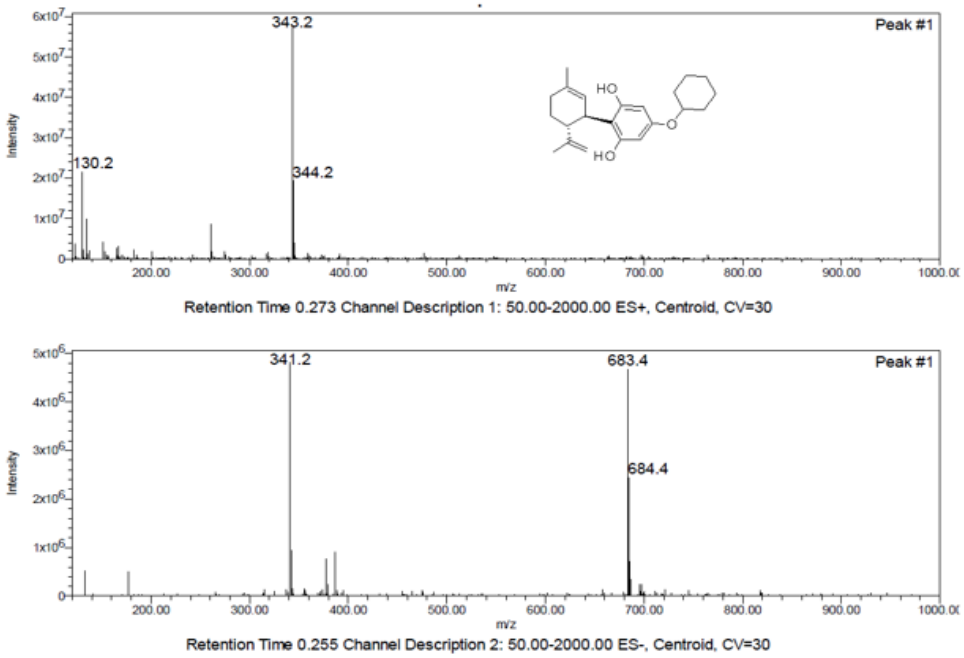
Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 6.28-5.83 (m, 3H), 5.51 (s, 1H), 5.16 (s, 1H), 4.69 (s, 1H), 4.22 (s, 1H), 4.14-4.08 (m, 1H), 3.81-3.78 (m ,1H), 2.30-1.06 (21 H)

MS (ESI) m/z: calculated, $C_{22}H_{30}O_3$, 342.47 $[M]^+$; found, 343.2 $[M+H]^+$, 341.2 $[M-H]^-$

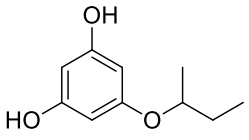


^{1}H NMR of Compound – 8

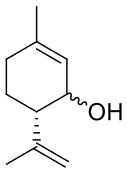


ESI-MS (+Ve & -Ve mode) of Compound-8

Synthesis of Compound-9:



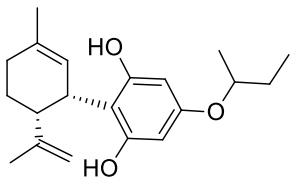
5-(*sec*-butoxy)benzene-1,3-diol
Chemical Formula: $C_{10}H_{14}O_3$
Molecular Weight: 182.22



(6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enol
Chemical Formula: $C_{10}H_{16}O$
Molecular Weight: 152.23

$BF_3.Et_2O$

Chloroform, RT, 0.5 h



(1'*S*,2'*R*)-4-(*sec*-butoxy)-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol
Chemical Formula: $C_{20}H_{28}O_3$
Molecular Weight: 316.43 17.88 %

Procedure:

To a solution of (6S)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enol (350 mg, 2.3 mmol) and 5-(sec butoxy)-benzene-1,3-diol (418 mg, 2.3 mmol) in chloroform (23 ml, 10 ml/ mmol), Borontrifluoride etherate (32.6 mg, 0.23 mmol) was added and the resulting solution was stirred for 30 min at room temperature. The volatiles were evaporated and the residue obtained was purified by silicagel column chromatography in ethylacetate: Pet.ether to get 130 mg (17.88 %) of product and minor quantity of 1' R isomer is obtained.

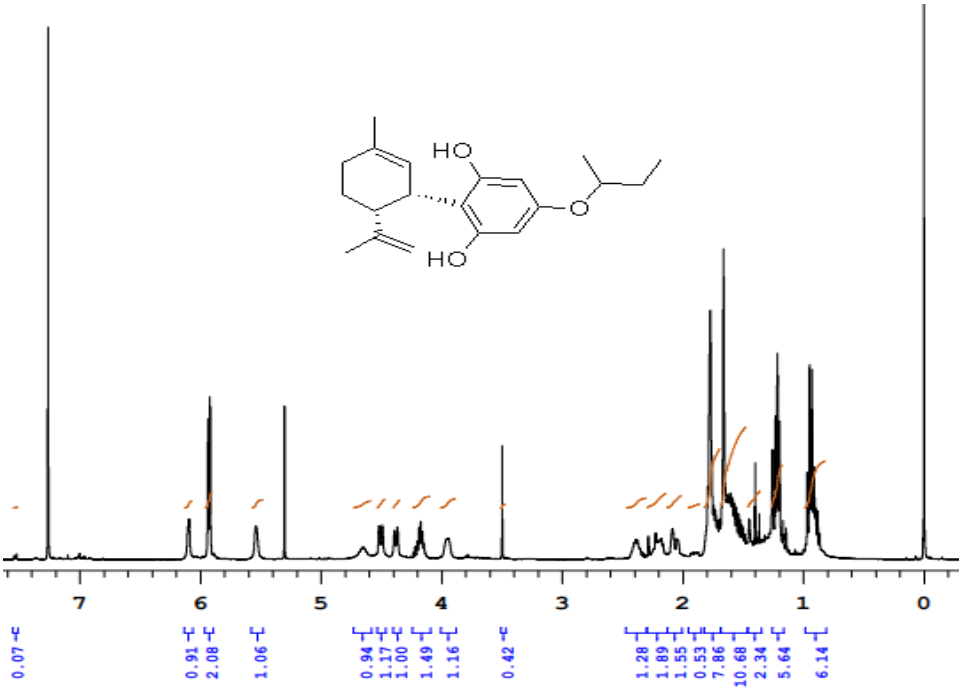
TLC:

Mobile Phase: 1:4::Ethylacetate: Hexane
Rf Vlaue: 0.4
Visualization: UV, $KMnO_4$

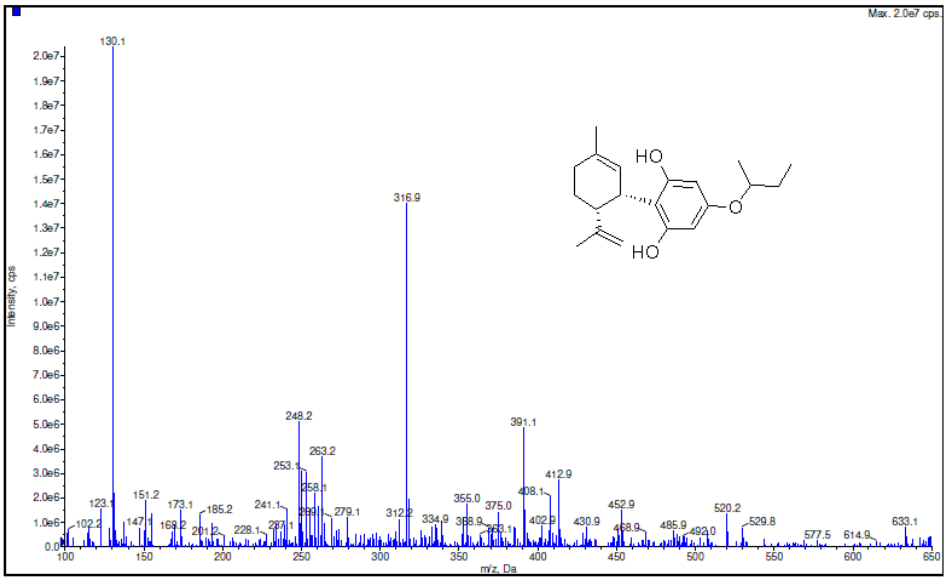
Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 6.10 (s, 1H), 5.94 (s, 1H), 5.92 (s, 1H), 5.54 (s, 1H), 4.65 (bs, 1H), 4.51 (d, J = 10.6 Hz, 1H), 4.38 (d, J = 9.2 Hz, 1H), 4.23-4.15 (m, 1H), 3.94 (bs, 1H), 2.44-2.00 (m, 4H), 1.80-0.90 (m, 15 H)

MS (ESI) m/z: calculated, $C_{20}H_{28}O_3$, 316.43 $[M]^+$; found, 316.9 $[M]^+$

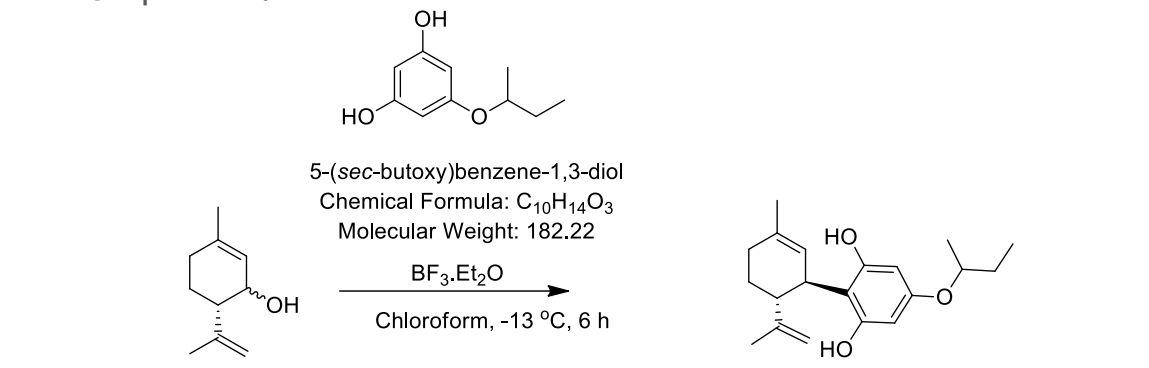


^{1}H NMR of Compound – 9



ESI-MS (+Ve mode) of Compound-9

Synthesis of Compound-10:



Procedure:

To a solution of (6S)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enol (350 mg, 2.3 mmol) and 5-(sec butoxy)-benzene-1,3-diol (418 mg, 2.3 mmol) in chloroform (23 ml, 10 ml/ mmol), Borontrifluoride etherate (32.6 mg, 0.23 mmol) was added and at -13 ^{0}C the resulting solution was stirred for 6 h. The volatiles were evaporated and the residue obtained was purified by silicagel column chromatography in ethylacetate: Pet.ether to get 160 mg (22.0 %) of product and minor quantity of 1'S isomer is obtained.

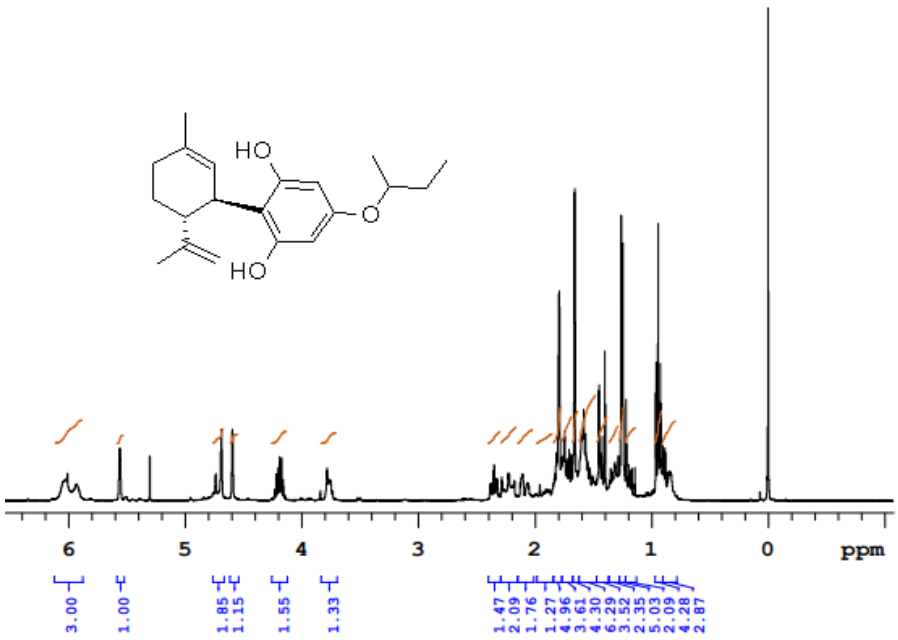
TLC:

Mobile Phase: 1:4::Ethylacetate: Hexane
Rf Vlaue: 0.6
Visualization: UV, $KMnO_4$

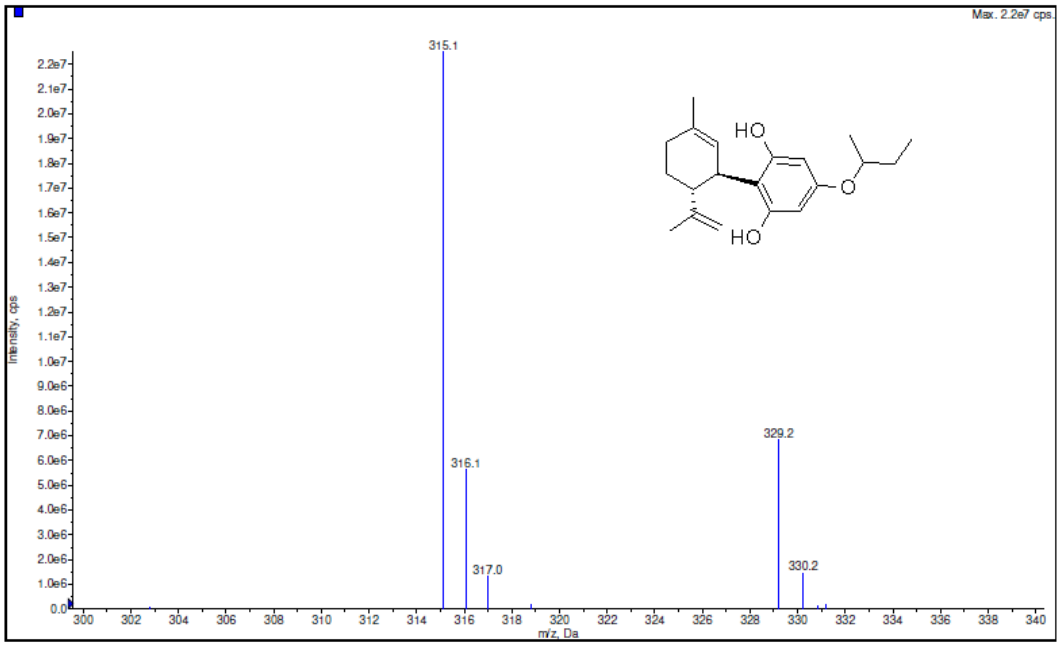
Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 6.02-5.93 (m, 3H), 5.56 (s, 1H), 4.73 (bs, 1H), 4.69 (s, 1H), 4.60 (s, 1H), 4.23-4.16 (m, 1H), 3.79-3.73 (m, 1H), 2.40-2.24 (m, 4H), 1.80-0.80 (m, 15H)

MS (ESI) m/z: calculated, $C_{20}H_{28}O_3$, 316.43 $[M]^+$; found, 315.9 $[M-H]^-$

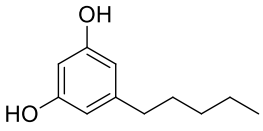


^{1}H NMR of Compound – 10

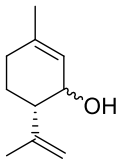


ESI-MS (-Ve mode) of Compound- 10

Synthesis of Compound-11:

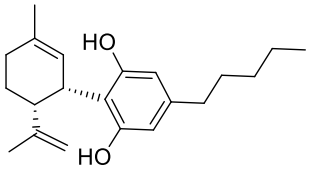


5-pentylbenzene-1,3-diol
Chemical Formula: $C_{11}H_{16}O_2$
Molecular Weight: 180.24



$BF_3.Et_2O$

Chloroform, RT, 0.5 h



(6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enol
Chemical Formula: $C_{10}H_{16}O$
Molecular Weight: 152.23

(1'*S*,2'*R*)-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol
Chemical Formula: $C_{21}H_{30}O_2$
Molecular Weight: 314.46 29.12 %

+ Minor quantity of 1'R isomer is obtained

Procedure:

To a solution of (6S)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enol (500 mg, 3.2 mmol) and 5-(pentyl)-benzene-1,3-diol (545 mg, 3.2 mmol) in chloroform (32 ml, 10 ml/ mmol), Borontrifluoride etherate (45.2 mg, 0.32 mmol) was added and the resulting solution was stirred for 30 min at room temperature. The volatiles were evaporated and the residue obtained was purified by silicagel column chromatography in ethylacetate: Pet.ether to get 300 mg (29.12 %) of product and minor quantity of 1'R isomer is obtained.

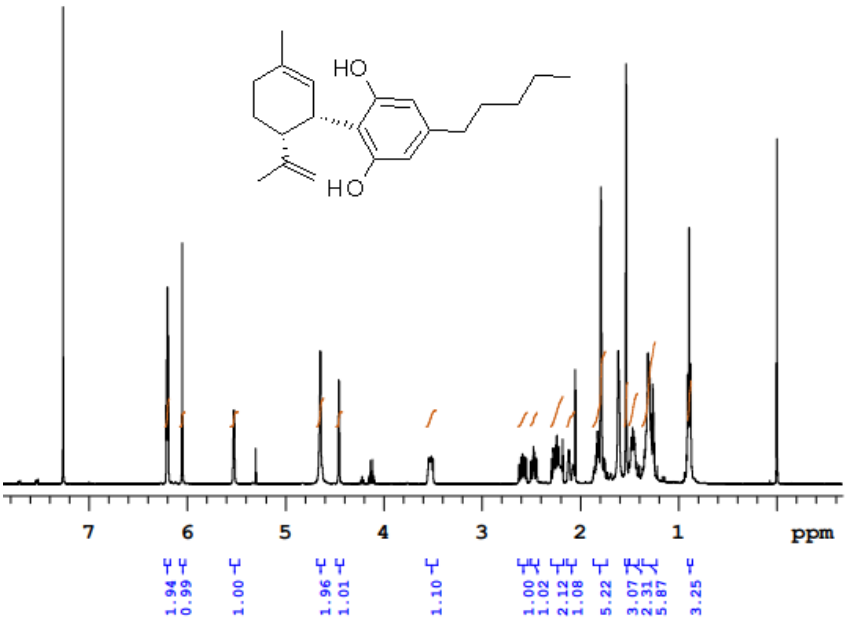
TLC:

Mobile Phase: 1:4:: Ethylacetate: Hexane
Rf Vlaue: 0.35
Visualization: UV, $KMnO_4$

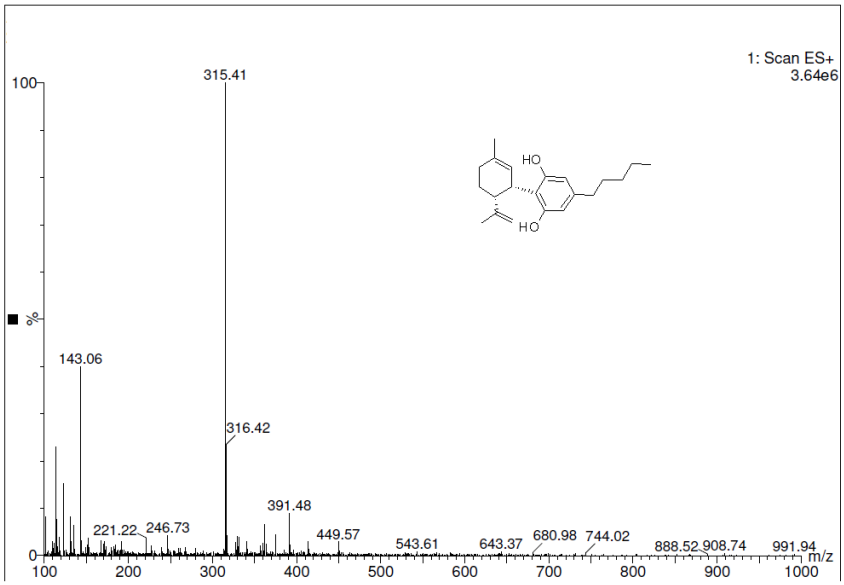
Analytical data:

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.21 (m, 2H), 6.05 (s, 1H), 5.52 (s, 1H), 4.65-4.64 (m, 2H), 4.46 (s, 1H), 3.54-3.50 (m, 1H), 2.64-2.44 (m, 2H), 2.29-2.18 (m, 2H), 2.10-2.05 (m, 1H), 1.88-1.24 (m, 14H), 0.92-0.86 (m, 3H).

MS (ESI) m/z: calculated, $C_{21}H_{30}O_2$, 314.46 $[M]^+$; found, 315.4 $[M+H]^+$

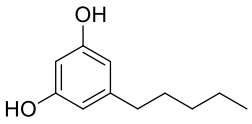


^{1}H NMR of Compound – 11

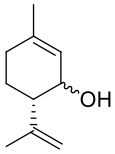


ESI-MS (-Ve mode) of Compound-11

Synthesis of Compound-12:



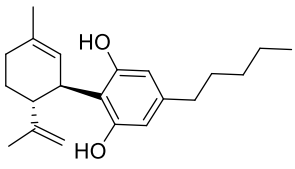
5-pentylbenzene-1,3-diol
Chemical Formula: $C_{11}H_{16}O_2$
Molecular Weight: 180.24



(6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enol
Chemical Formula: $C_{10}H_{16}O$
Molecular Weight: 152.23

$BF_3.Et_2O$

Chloroform, -13 ^{o}C, 6 h



(1'*R*,2'*R*)-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol
Chemical Formula: $C_{21}H_{30}O_2$
Molecular Weight: 314.46

27.18 %

+ Minor quantity of 1'S isomer is obtained

Procedure:

To a solution of (6S)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enol (500 mg, 3.2 mmol) and 5-(pentyl)-benzene-1,3-diol (545 mg, 3.2 mmol) in chloroform (32 ml, 10 ml/ mmol), Borontrifluoride etherate (45.2 mg, 0.32 mmol) was added at -13 ^{0}C and the resulting solution was stirred for 6 h. The volatiles were evaporated and the residue obtained was purified by silicagel column chromatography in ethylacetate: Pet.ether to get 160 mg (27.18 %) of product and minor quantity of 1'S isomer is obtained.

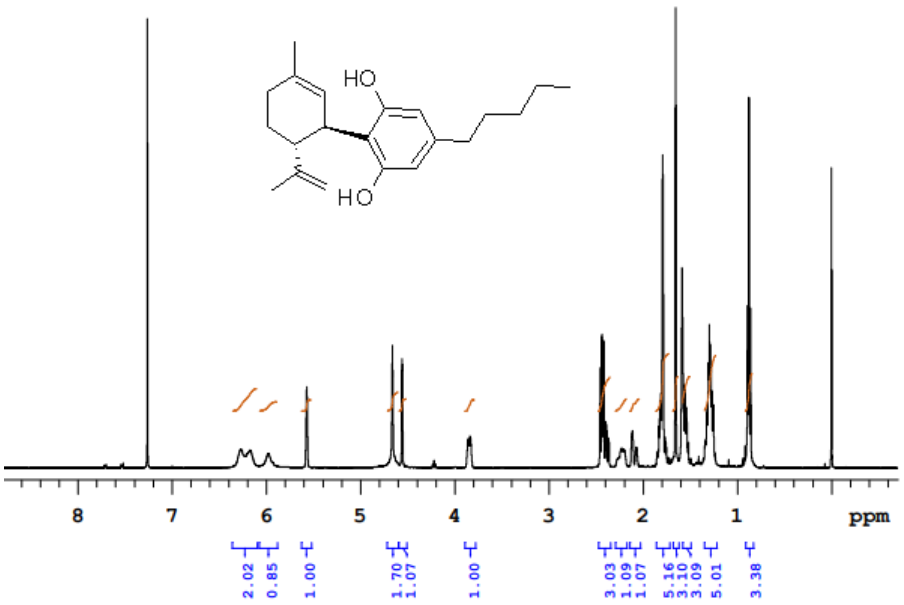
TLC:

Mobile Phase: 1:4::Ethylacetate: Hexane
Rf Vlaue: 0.65
Visualization: UV, $KMnO_4$

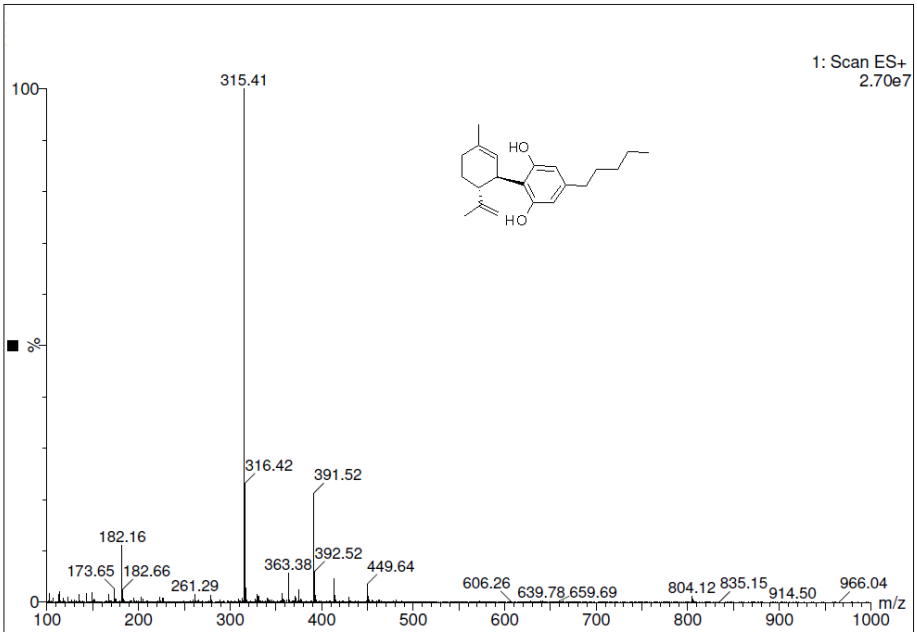
Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 6.27-6.17 (m, 2H), 5.98 (bs, 1H), 5.57 (s, 1H), 4.67-4.66 (m, 2H), 4.59 (s, 1H), 3.87-3.83 (m, 1H), 2.46-2.36 (m, 3H), 2.23-2.20 (m, 1H), 2.12-2.07 (m, 1H), 1.85-1.76 (m, 5H), 1.65 (s, 3H), 1.59-1.52 (m, 3H), 1.35-1.24 (m, 5H), 0.92-0.86 (m, 3H).

MS (ESI) m/z: calculated, $C_{21}H_{30}O_2$, 314.46 $[M]^+$; found, 315.4 $[M+H]^+$

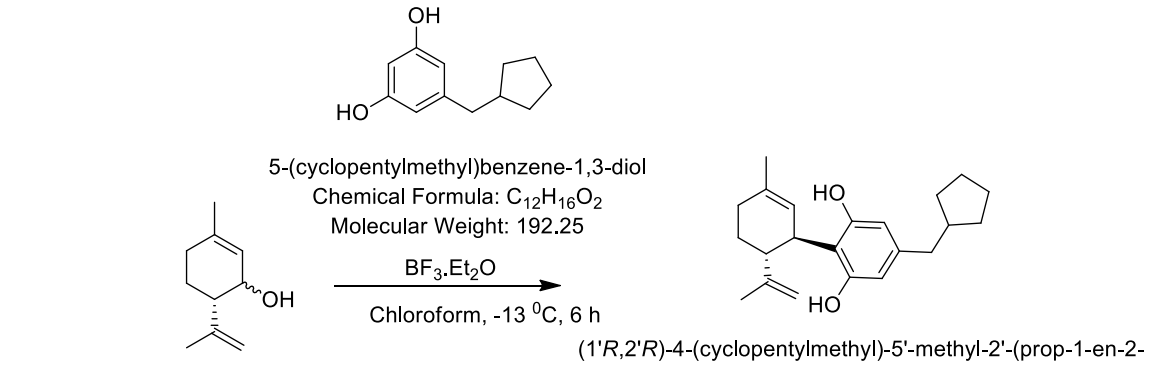


^{1}H NMR of Compound – 12



ESI-MS (-Ve mode) of Compound- 12

Synthesis of Compound-13:



Procedure:

To a solution of (6S)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enol (300 mg, 1.9 mmol) and 5-(cyclopentylmethyl)-benzene-1,3-diol (370nmg, 1.9 mmol) in chloroform (19 ml, 10 ml/ mmol), Borontrifluoride etherate (27 mg, 0.19 mmol) was added at -13 ^{0}C and the resulting solution was stirred for 6 h. The volatiles were evaporated and the residue obtained was purified by silicagel column chromatography in ethylacetate: Pet.ether to get 180 mg (28 %) of product and minor quantity of 1'S isomer is obtained.

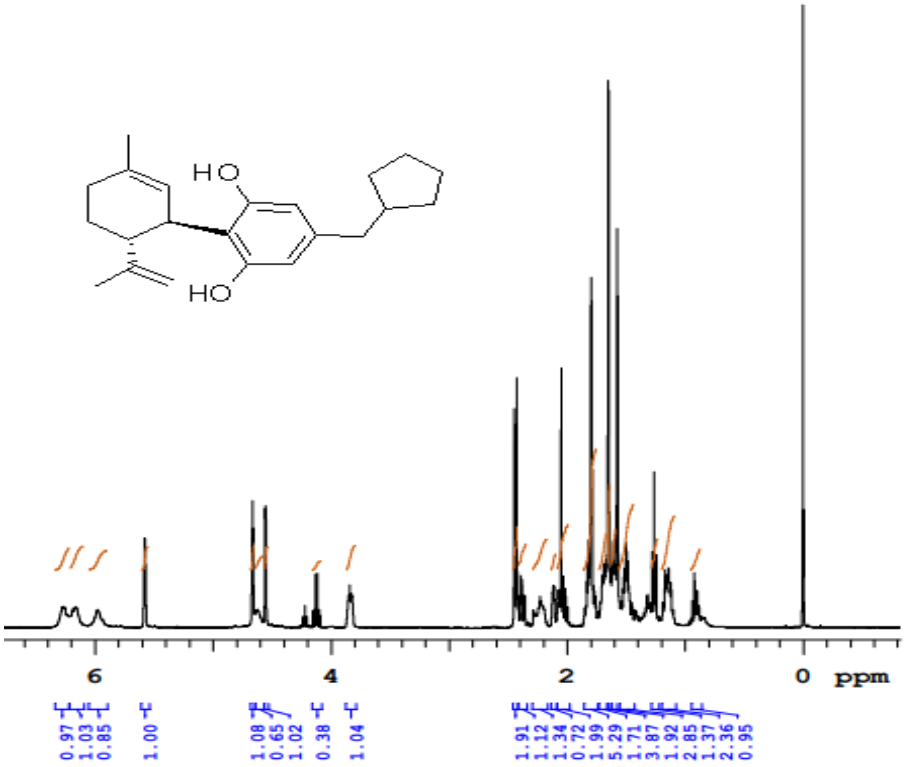
TLC:

Mobile Phase: 1:4::Ethylacetate: Hexane
Rf Vlaue: 0.65
Visualization: UV, $KMnO_4$

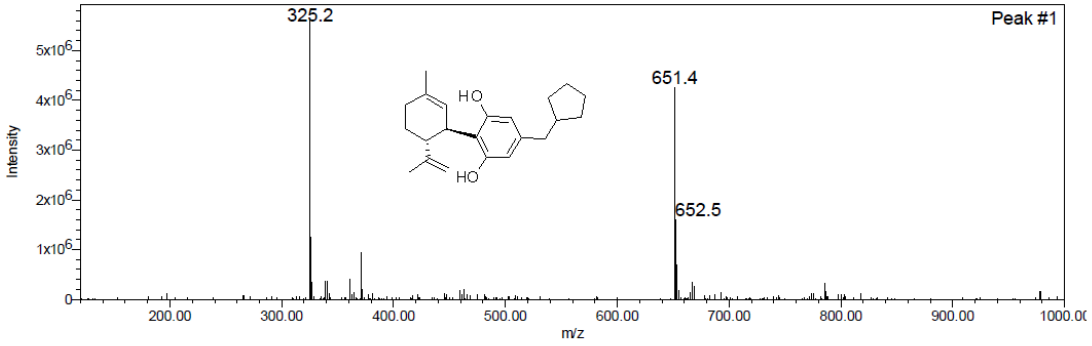
Analytical data:

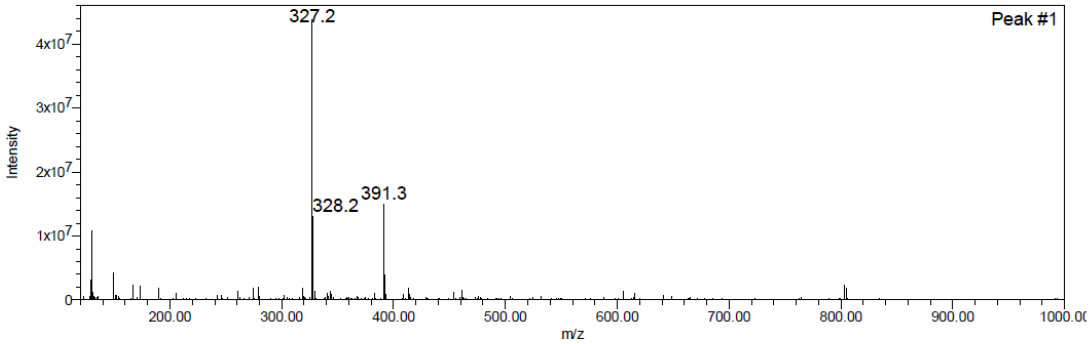
^{1} H NMR (400 MHz, $CDCl_3$): δ 6.27-6.16 (m, 2H), 5.98 (bs, 1H), 5.58 (s, 1H), 4.67-4.66 (m, 2H), 4.56 (s, 1H), 3.86-3.82 (m, 1H), 2.46-0.86 (m, 22H).

MS (ESI) m/z: calculated, $C_{22}H_{30}O_2$, 326.47 $[M]^+$; found, 327.2 $[M+H]^+$, 325.2 $[M-1]^-$



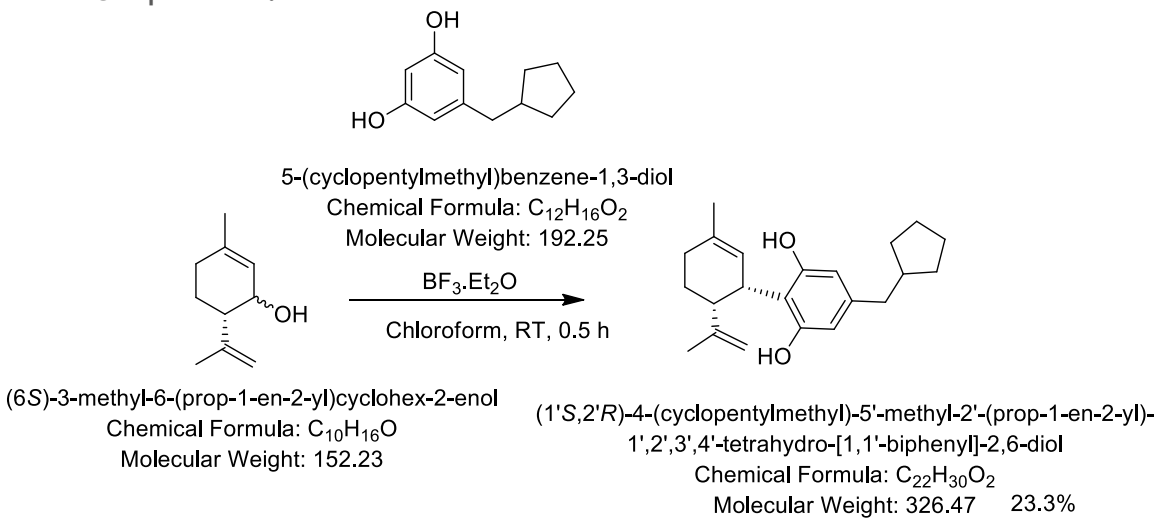
^{1}H NMR of Compound – 13





ESI-MS (-Ve mode) of Compound-13

Synthesis of Compound-14:



Procedure:

To a solution of (6S)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enol (300 mg, 1.9 mmol) and 5-(cyclopentylmethyl)-benzene-1,3-diol (370nmg, 1.9 mmol) in chloroform (19 ml, 10 ml/ mmol), Borontrifluoride etherate (27 mg, 0.19 mmol) was added and the resulting solution was stirred for 30 min at room temperature. The volatiles were evaporated and the residue obtained was purified by silicagel column chromatography in ethylacetate: Pet.ether to get 151 mg (23.3 %) of product and minor quantity of 1'R isomer is obtained.

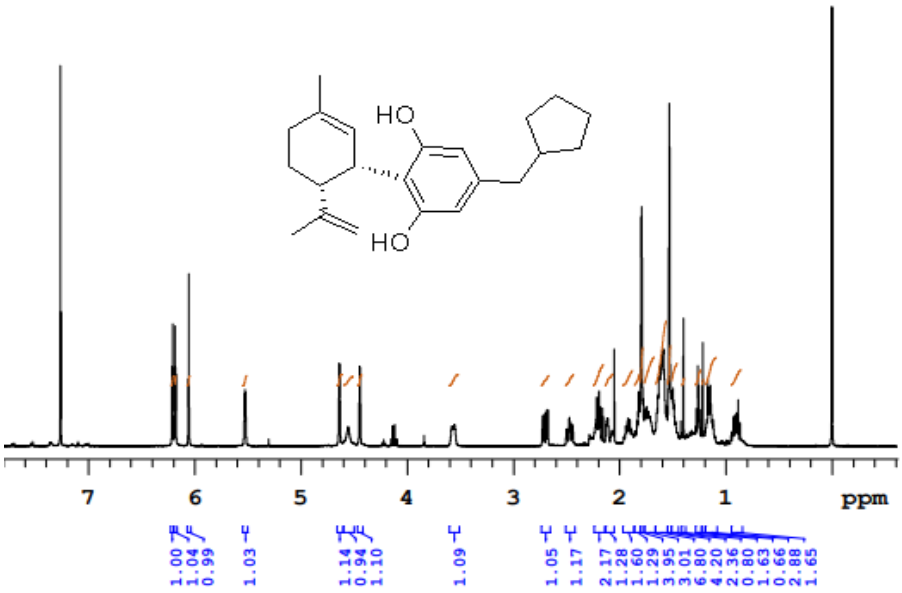
TLC:

Mobile Phase: 1:4::Ethylacetate: Hexane
Rf Vlaue: 0.35
Visualization: UV, $KMnO_4$

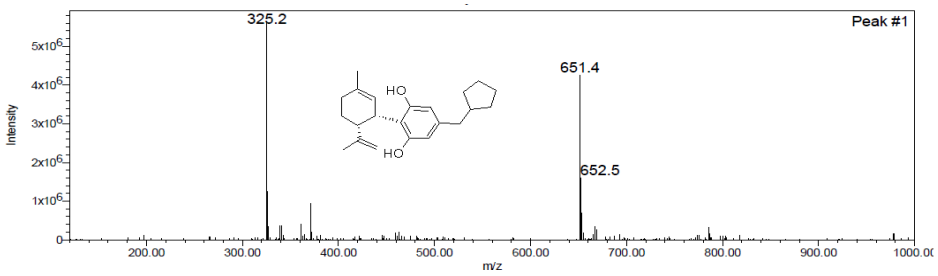
Analytical data:

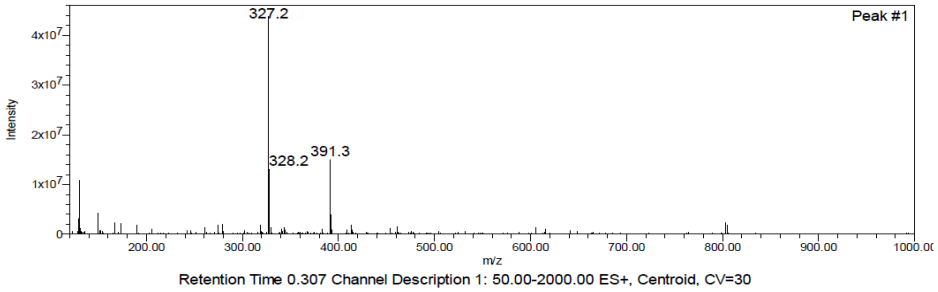
^{1} H NMR (400 MHz, $CDCl_3$): δ 6.21-6.18 (m, 2H), 6.06 (s, 1H), 5.52 (s, 1H), 4.64-4.63 (m, 1H), 4.56 (bs, 1H), 4.45 (s, 1H), 3.58-3.56 (m, 1H), 2.73-2.68 (m, 1H), 2.47-2.44 (m, 1H)2.29-0.86 (m, 20H).

MS (ESI) m/z: calculated, $C_{22}H_{30}O_2$, 326.47 $[M]^+$; found, 327.2 $[M+H]^+$, 325.2 $[M-1]^-$



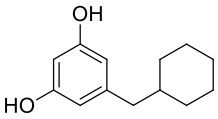
^{1}H NMR of Compound – 14



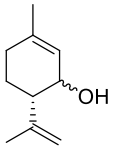


ESI-MS (-Ve mode) of Compound-14

Synthesis of Compound-15:

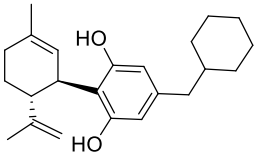


5-(cyclohexylmethyl)benzene-1,3-diol
Chemical Formula: $C_{13}H_{18}O_2$
Molecular Weight: 206.28



$BF_3.Et_2O$

Chloroform, -13 ^{o}C, 6 h



(6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enol
Chemical Formula: $C_{10}H_{16}O$
Molecular Weight: 152.23

(1'*R*,2'*R*)-4-(cyclohexylmethyl)-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol
Chemical Formula: $C_{23}H_{32}O_2$
Molecular Weight: 340.50

20 %

+ Minor quantity of 1'S isomer is obtained

Procedure:

To a solution of (6S)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enol (450 mg, 3.0 mmol) and 5-(cyclohexylmethyl)-benzene-1,3-diol (590 mg, 3.0 mmol) in chloroform (30 ml, 10 ml/ mmol), Borontrifluoride etherate (42.5 mg, 0.19 mmol) was added at -13 ^{0}C and the resulting solution was stirred for 6 h. The volatiles were evaporated and the residue obtained was purified by silicagel column chromatography in ethylacetate: Pet.ether 200 mg (20 %) of product and minor quantity of 1'S isomer is obtained.

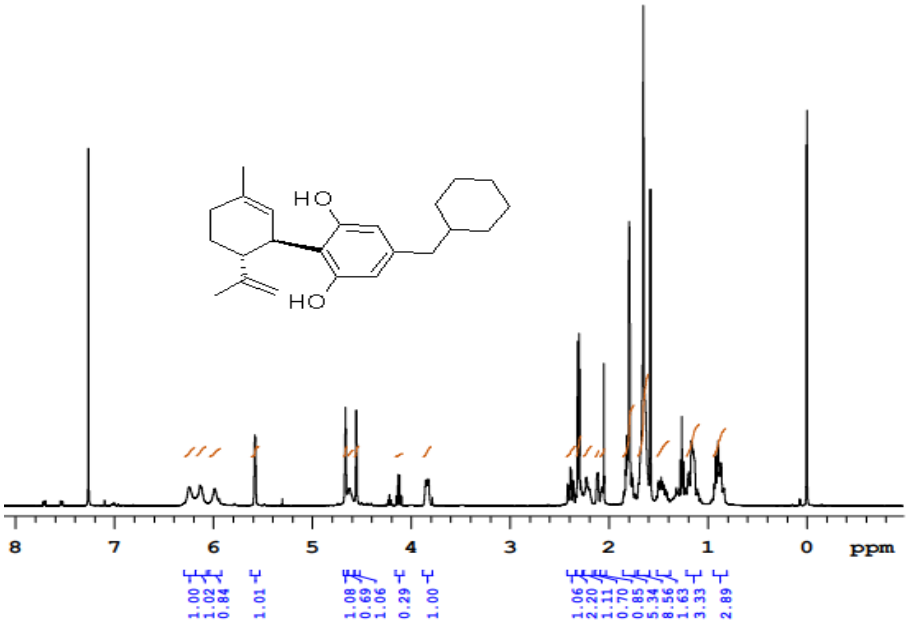
TLC:

Mobile Phase: 1:4::Ethylacetate: Hexane
Rf Vlaue: 0.65
Visualization: UV, $KMnO_4$

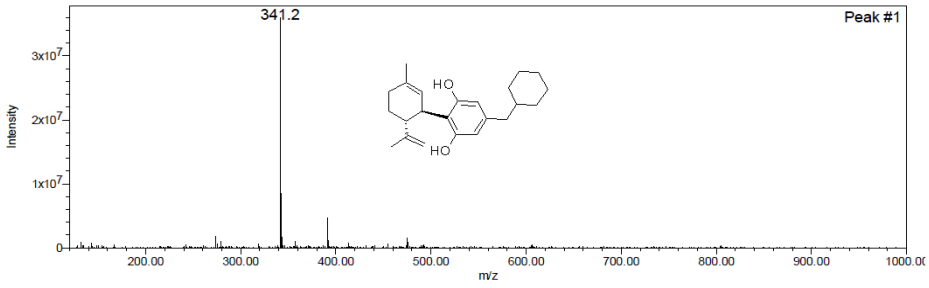
Analytical data:

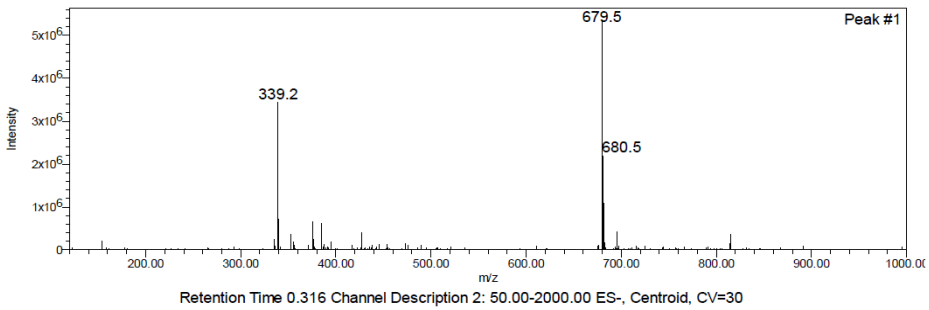
^{1} H NMR (400 MHz, $CDCl_3$): δ 6.27-6.16 (m, 2H), 5.98 (bs, 1H), 5.58 (s, 1H), 4.67-4.66 (m, 2H), 4.56 (s, 1H), 3.86-3.82 (m, 1H), 2.46-0.86 (m, 24H).

MS (ESI) m/z: calculated, $C_{23}H_{32}O_2$, 340.50 $[M]^+$; found, 341.2 $[M+H]^+$, 339.2 $[M-1]^-$



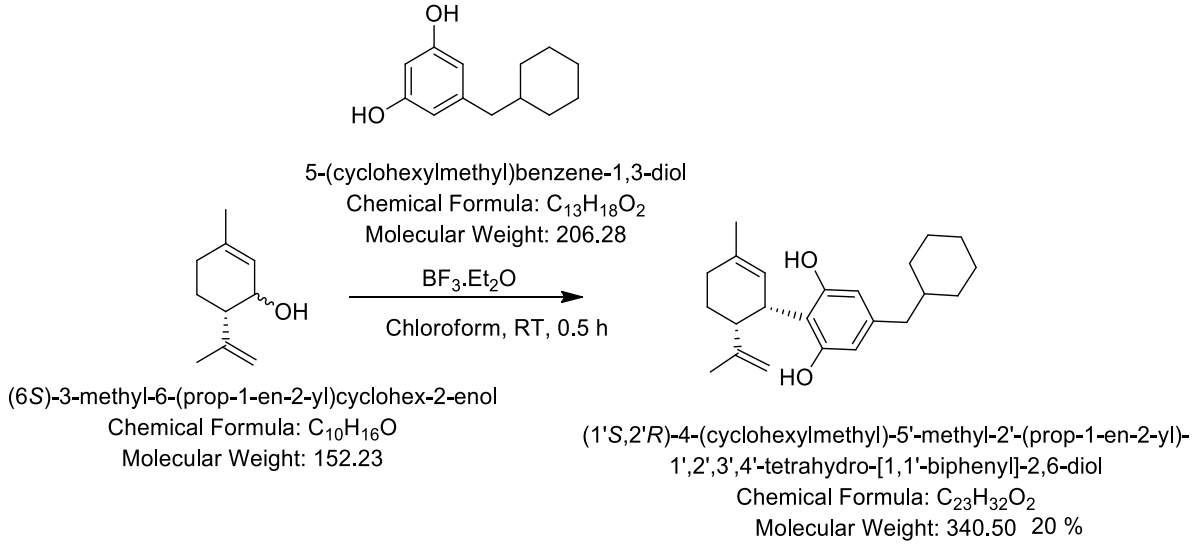
^{1}H NMR of Compound – 15





ESI-MS (-Ve mode) of Compound-15

Synthesis of Compound-16:



Procedure:

To a solution of (6S)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enol (450 mg, 3.0 mmol) and 5-(cyclohexylmethyl)-benzene-1,3-diol (590 mg, 3.0 mmol) in chloroform (30 ml, 10 ml/ mmol), Borontrifluoride etherate (42.5 mg, 0.19 mmol) was added and the resulting solution was stirred for 30 min at room temperature. The volatiles were evaporated and the residue obtained was purified by silicagel column chromatography in ethylacetate: Pet.ether to get 200 mg (20 %) of product and minor amount of 1'R isomer is obtained.

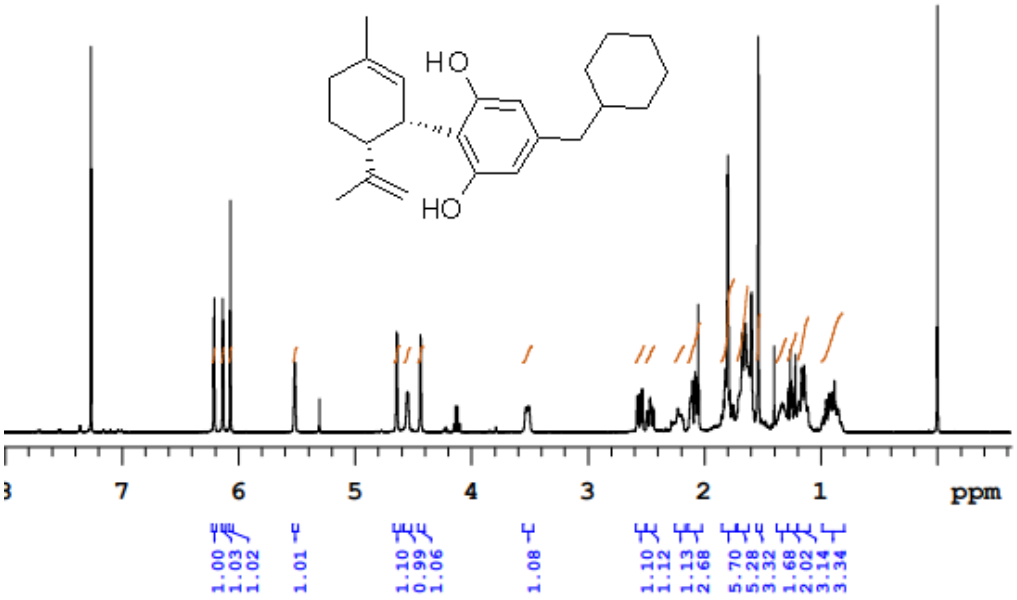
TLC:

Mobile Phase: 1:4::Ethylacetate: Hexane
Rf Vlaue: 0.35
Visualization: UV, $KMnO_4$

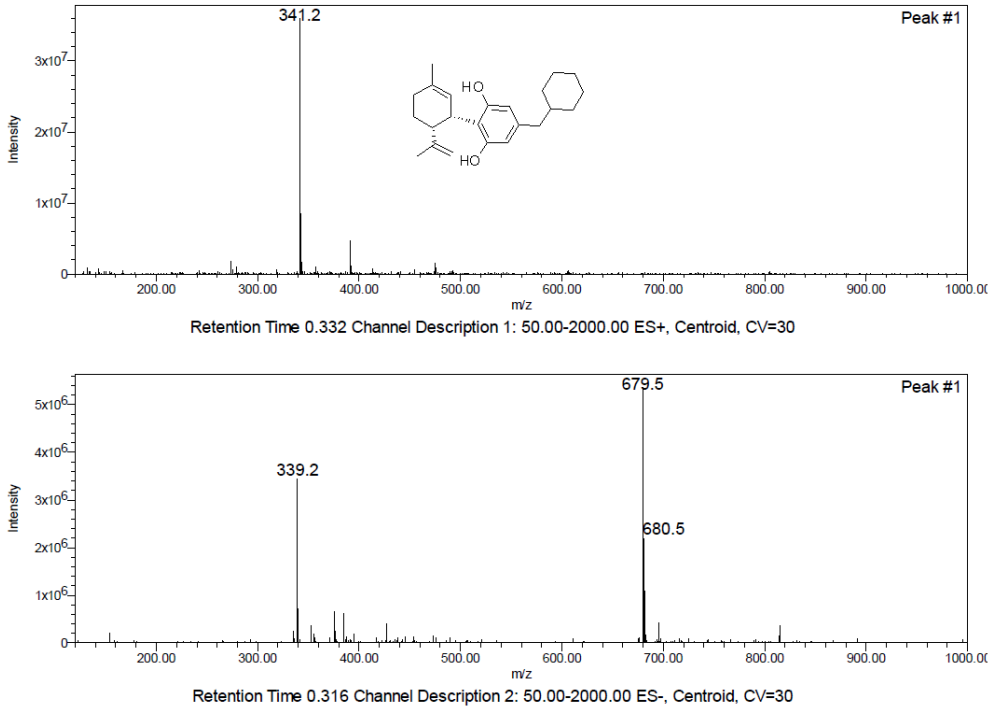
Analytical data:

^{1} H NMR (400 MHz, $CDCl_3$): δ 6.21 (d, J = 2.4 Hz, 1H), 6.13 (d, J = 2.4 Hz, 1H), 6.07 (s, 1H), 5.52 (s, 1H), 4.64-4.63 (m, 1H), 4.54 (bs, 1H), 4.44 (s, 1H), 3.53-3.51 (m, 1H), 2.58-2.44 (m, 2H), 2.43-0.82 (m, 22H).

MS (ESI) m/z: calculated, $C_{23}H_{32}O_2$, 340.50 $[M]^+$; found, 341.2 $[M+H]^+$, 339.2 $[M-1]^-$



^{1}H NMR of Compound – 16



ESI-MS (-Ve mode) of Compound-16

PHARMACOLOGICAL EVALUATION

BIOLOGICAL STUDY:

1. Animals and management:

Adult male albino mice, weighing 25-30g were chosen. During the experiment, the animals were housed in big, spacious, and sanitary cages. The animals were housed in a well-kept environment with a 12-hour day and night schedule and a temperature of [64-79°F] maintained at standard experimental conditions. The animals were fed conventional rodent pellet diet and given free access to water. The animals were fasted for 12 hours before the experiment, with only water available to them. The experimental procedure was approved by IAEC (Institutional animal ethical committee of Deshpande Laboratories – CCP).

1.1 ACUTE TOXICITY STUDY:

Prior to medication treatment, mice were fasted overnight. A total of six animals were employed, each of which received a single oral dosage of drug. Food was withheld for another 3–4 hours after the test extract was administered. Individual animals were monitored at least once during the first 30 minutes after treatment, on a regular basis for the next 24 hours (with specific focus during the first 4 hours), and daily for the next 14 days. Changes in skin and fur, eyes, and mucous membranes (nasal), as well as respiratory rate, circulatory (heart rate and blood pressure), autonomic (salivation, lacrimation, perspiration, piloerection, urinary incontinence, and defecation), and central nervous system (ptosis, drowsiness, gait, tremors, and convulsion) changes, were observed once daily in the cage Over the course of two weeks, any mortality was determined. The LD50 was calculated according to OECD 423 criteria for determining the dosage for biological assessment.

1.2 EVALUATION OF ANTIEPILEPTIC ACTIVITY OF CANNABIDIOL DERIVETIVES:

A. Maximal electroshock seizure [MES] model

Experimental design:

Albino mice weighed around 25-30g were used for the study. Mice were divided into four groups of 6 animals each.

Table-1: Maximal electroshock seizure model

Model I: Maximal electroshock seizure [MES] Model	
Group 1:	*Vehicle control* [Equivalent normal saline i.p]
Group 2:	*Standard* [Phenytoin 20 mg/Kg BW i.p]
Group 3:	*Compound-6 ,10& 16* low dose (6.25 mg/kg) i.p
Group 4:	*Compound-6 ,10 &16* high dose (12.5 mg/kg) i.p

Procedure: The control group [Group 1] will receive an equivalent amount of normal saline / CMC via the intraperitoneal method. The usual medicine Phenytoin was given to the animals in Group 2. Compound-6,10 & 16 low and high doses were given through i.p in 1 percent carboxy methyl cellulose solution in Groups 3 and 4, respectively. After 30 minutes of treatment with the aforesaid medicines, all mice were electroshocked for 0.2 seconds using an electro convulsiometer through ear electrodes [after moistening the animals' ears with a drop of normal saline] at intensity of 50

mA, 60Hz. Following that, a variety of parameters were recorded.

B. Pentylenetetrazol [PTZ] model

Experimental design:

Swiss albino mice weighed around 25-30g were used for the study. Mice were divided into four groups of 6 animals each.

Table-2: Pentylenetetrazole model

Model II: **Pentylenetetrazole Model**	
Group 1:	*Vehicle control* [Equivalent normal saline i.p]
Group 2:	*Standard* Phenytoin (20 mg/Kg BW i.p)
Group 3:	*Compound-6,10&16* low dose (6.25 mg/kg) i.p
Group 4:	*Compound-6,10&16*high dose (12.5 mg/kg) i.p

Procedure:

The control group [Group 1] will receive an equivalent amount of 1% CMC via the intraperitoneal method. The usual medicine Phenytoin was given to the animals in Group 2. Compound 6,10&16 low and high doses were given through intraperitoneal route in 1 percent carboxy methyl cellulose solution in Groups 3 and 4, respectively. All of the animals were administered Pentylenetetrazol [PTZ] after 30 minutes after receiving the aforesaid medicines, and the relevant parameters were recorded.

2. RESULT:

2.1 Acute toxicity study:

The substance was tested at dosages of 2000 mg/kg, 1000 mg/kg, 500 mg/kg, 250 mg/kg, 100 mg/kg, and 50 mg/kg in the acute toxicity test. As a result, the test animal received 2000 mg/kg orally. In addition, three animals perished. Following the observation of mortality following the injection of 2gm/kg body weight, a lower dosage of 1000 mg/kg and 500 mg/kg was administered. For both dosages, mortality was found in all animals. As a result, a reduced dosage of 100, 50 & 25 mg/kg was administered. After receiving 25 mg/kg, two animals died and one animal survived. As a result, a reduced dosage of 12.5 mg/kg was administered. For 12.5 mg/kg, two animals survived and one died. Then a 6.25 mg/kg dosage was administered. Following treatment of 6.25 mg/kg, all animals survived and no symptoms of toxicity were seen. As a result, at 6.25 mg/kg, the compound 6,10 &16 was confirmed to be safe.

Table-3: Acute toxicity study of compound-6

No. of animals used	Dose (mg/kg)	No. of animals survived
3	2000	0
3	1000	0
3	500	0
3	100	0
3	50	0
3	25	1
3	12.5	2
3	6.25	3

Table-4: Acute toxicity study of compound-10

No. of animals used	Dose (mg/kg)	No. of animals survived
3	2000	0
3	1000	0
3	500	0
3	100	0
3	50	1
3	25	2
3	12.5	3

Table-5: Acute toxicity study of compound-16

No. of animals used	Dose (mg/kg)	No. of animals survived
3	2000	0
3	1000	0
3	500	0
3	100	0
3	50	1
3	25	2
3	10	3

2.2 EVALUATION OF ANTIEPILEPTIC ACTIVITY

Table-6: Effect of Compound-6 in MES induced seizures models

1. Control group

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	28.9	CMC	2	3	2	154	Recovery
2.	29.5		2	2	2	152	Recovery
3.	28.2		3	2	3	158	Recovery
4.	26.8		2	1	2	140	Recovery
5.	29.9		1	1	1	138	Recovery
6.	30		3	3	3	146	Recovery
Mean							

2. Standard group

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	28.6	Phenytoin	2	2	1	32	Recovery
2.	27.4		2	1	1	44	Recovery
3.	29.6		2	1	2	30	Recovery
4.	29.2		1	1	1	28	Recovery
5.	30		1	1	1	26	Recovery
6.	28.8		2	2	2	24	Recovery
Mean							

3. Test group with low dose

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	28.5	Compound-6(low dose-3.25mg/kg)	2	3	2	50	Recovery
2.	29.5		2	1	2	42	Recovery
3.	30		1	1	1	28	Recovery
4.	29.2		3	1	1	32	Recovery
5.	27.5		2	2	2	38	Recovery
6.	28.6		2	2	2	40	Recovery
Mean							

4. Test group with high dose

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	27.6	Compound-6(high dose-6.5 mg/kg)	2	3	2	48	Recovery
2.	29		2	1	2	42	Recovery
3.	29.5		1	1	1	28	Recovery
4.	30		2	1	1	32	Recovery
5.	27.9		2	2	2	38	Recovery
6.	28.5		4	0	4	32	Death
Mean							

Table-7: Effect of compound-6 in PTZ induced seizures models

1. Control group

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	30	CMC	2	1	2	154	Recovery
2.	28.3		1	1	1	152	Recovery
3.	28.5		3	3	1	158	Recovery
4.	27.2		2	2	2	140	Recovery
5.	28		3	2	3	138	Recovery
6.	29.5		3	3	3	146	Recovery
Mean							

2. Standard group

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	29	Phenytoin	1	1	1	32	Recovery
2.	30		2	1	2	44	Recovery
3.	28.5		1	1	1	30	Recovery
4.	29		2	1	2	28	Recovery
5.	30.5		1	2	1	26	Recovery
6.	30		2	2	2	24	Recovery
Mean							

3. Test group with low dose

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	27.6	Compound-6(low dose-3.25mg/kg)	2	1	2	50	Recovery
2.	28.6		2	1	2	42	Recovery
3.	29		1	1	1	28	Recovery
4.	30		1	1	1	32	Recovery
5.	28.8		1	2	2	38	Recovery
6.	29.5		2	2	2	42	Recovery
Mean							

4. Test group with high dose

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	29.2	Compound-6 (high dose-6.5 mg/kg)	1	2	2	48	Recovery
2.	28.9		2	1	2	42	Recovery
3.	29.2		1	1	1	28	Recovery
4.	28.8		1	1	1	32	Recovery
5.	28.7		2	2	2	38	Recovery
6.	28.2		2	1	2	40	Recovery
Mean							

Table-8: Effect of Compound-10 in MES induced seizures models

1. Control Group

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	28.9	CMC	2	3	2	154	Recovery
2.	29.5		2	2	2	152	Recovery
3.	28.2		3	2	3	158	Recovery
4.	26.8		2	1	2	140	Recovery
5.	29.9		1	1	1	138	Recovery
6.	30		3	3	3	146	Recovery
Mean							

2. Standard group

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	28.6	Phenytoin	2	2	1	32	Recovery
2.	27.4		2	1	1	44	Recovery
3.	29.6		2	1	2	30	Recovery
4.	29.2		1	1	1	28	Recovery
5.	30		1	1	1	26	Recovery
6.	28.8		2	2	2	24	Recovery
Mean							

3. Test group with low dose

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	28.5	Compound-10(low dose-6.25mg/kg)	2	3	2	40	Recovery
2.	29.5		2	1	2	28	Recovery
3.	30		1	1	1	26	Recovery
4.	29.2		3	1	1	32	Recovery
5.	27.5		2	2	2	35	Recovery
6.	28.6		2	2	2	30	Recovery
Mean							

4. Test Group with high dose

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	27.6	Compound-10(high dose-12.5 mg/kg)	2	3	2	38	Recovery
2.	29		2	1	2	28	Recovery
3.	29.5		1	1	1	26	Recovery
4.	30		2	1	1	32	Recovery
5.	27.9		2	2	2	31	Recovery
6.	28.5		4	0	4	30	Death
Mean							

Table-9: Effect of compound-10 in PTZ induced seizures models

Control group

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	30	CMC	2	1	2	154	Recovery
2.	28.3		1	1	1	152	Recovery
3.	28.5		3	3	1	158	Recovery
4.	27.2		2	2	2	140	Recovery
5.	28		3	2	3	138	Recovery
6.	29.5		3	3	3	146	Recovery
Mean							

Standard group

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	29	Phenytoin	1	1	1	32	Recovery
2.	30		2	1	2	44	Recovery
3.	28.5		1	1	1	30	Recovery
4.	29		2	1	2	28	Recovery
5.	30.5		1	2	1	26	Recovery
6.	30		2	2	2	24	Recovery
Mean							

3. Test group with low dose

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	28.5	Compound-10(low dose-6.5mg/kg)	2	3	2	40	Recovery
2.	29.5		2	1	2	28	Recovery
3.	30		1	1	1	26	Recovery
4.	29.2		3	1	1	32	Recovery
5.	27.5		2	2	2	35	Recovery
6.	28.6		2	2	2	30	Recovery
Mean							

4. Test Group with high dose

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	27.6	Compound-10(high dose-12.5 mg/kg)	2	3	2	38	Recovery
2.	29		2	1	2	28	Recovery
3.	29.5		1	1	1	26	Recovery
4.	30		2	1	1	32	Recovery
5.	27.9		2	2	2	30	Recovery
6.	28.5		4	0	4	32	Death
Mean							

Table-10: Effect of Compound16 on MES induced seizures models

1. Control group

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	29.6	CMC	2	2	3	154	Recovery
2.	28.5		2	1	2	152	Recovery
3.	29.4		1	1	1	158	Recovery
4.	28.8		2	2	2	140	Recovery
5.	28.7		3	2	3	138	Recovery
6.	29.7		2	3	3	146	Recovery
Mean							

2. Standard group

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	29.8	Phenytoin	1	3	2	32	Recovery
2.	28.9		2	1	2	44	Recovery
3.	30.1		1	1	1	30	Recovery
4.	28.8		2	1	1	28	Recovery
5.	28.7		1	1	2	26	Recovery
6.	28.8		2	2	2	24	Recovery
Mean							

3. Test group with low dose

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	30	Compound-16(low dose-5mg/kg)	2	1	2	50	Recovery
2.	28.9		2	1	2	42	Recovery
3.	29.4		1	1	1	52	Recovery
4.	28.8		1	1	1	50	Recovery
5.	28.7		1	1	1	54	Recovery
6.	28.8		2	2	2	74	Recovery
Mean							

4. Test group with high dose

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	30	Compound-16(high dose-10mg/kg)	1	1	2	48	Recovery
2.	29.9		1	1	1	42	Recovery
3.	29.2		2	1	2	48	Recovery
4.	28.8		1	1	1	50	Recovery
5.	28.8		2	2	1	54	Recovery
6.	28.7		2	1	1	70	Recovery
Mean							

Table-11: Effect of Compound-16 on PTZ induced seizures models

1. Control group

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	29.4	CMC	2	1	2	154	Recovery
2.	28.9		1	1	1	152	Recovery
3.	29.2		3	3	1	158	Recovery
4.	30		2	2	2	140	Recovery
5.	28.7		2	3	2	138	Recovery
6.	30.1		3	3	3	146	Recovery
Mean							

2. Standard group

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convuision				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	29.6	Phenytoin	1	2	1	32	Recovery
2.	28.9		2	1	2	44	Recovery
3.	29.2		1	1	1	30	Recovery
4.	28.8		2	1	2	28	Recovery
5.	29.7		1	2	1	26	Recovery
6.	30		2	2	2	24	Recovery
Mean							

3. Test group with low dose

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	29.6	Compound-16(low dose-5mg/kg)	2	1	2	50	Recovery
2.	28.7		1	1	1	42	Recovery
3.	29.2		2	1	2	52	Recovery
4.	28.3		1	1	1	50	Recovery
5.	29.7		1	2	1	54	Recovery
6.	28.8		2	2	2	74	Recovery
Mean							

4. Test group with high dose

Sr. No.	Body weight (g)	Treatment	Time (Sec) in various phases of convulsion				
			Flexion	Extensor	Clonus	Stupor	Recovery/death
1.	29.6	Compound-16 (high dose-10mg/kg)	2	2	2	48	Recovery
2.	28.7		1	2	1	42	Recovery
3.	29.2		2	3	2	48	Recovery
4.	28.3		3	2	1	50	Recovery
5.	29.7		2	2	2	54	Recovery
6.	28.8		2	1	2	70	Recovery
Mean							

Statistical Analysis

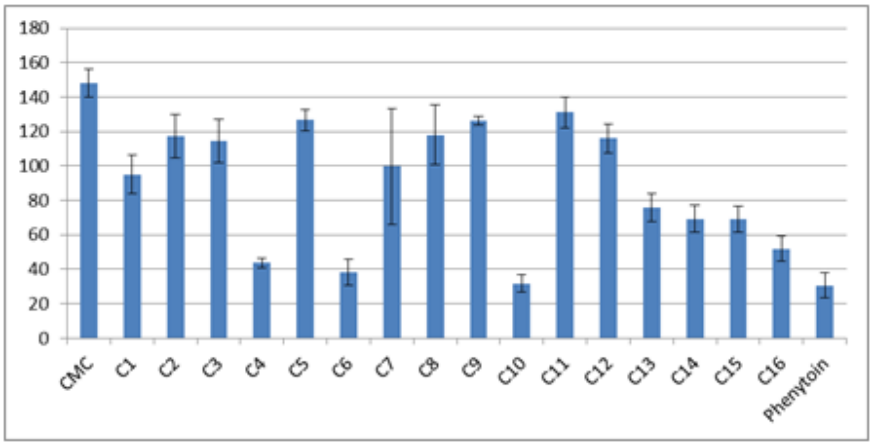
All the compounds exhibited mild to moderate activities. The data expressed as mean±SEM and statistical assessed by one way analysis of variance (ANOVA). The data was analyzed using Student's t-test followed by Dunnett's test. In all tests, the criterion for statistical significance was $p < 0.05$. Biological activity data of synthesized compounds is summarized in Table:-

Table: 12- Anti-convulsant activity of synthesized compounds

Group	Compound	Onset time of convulsion (sec)	Recovery/death
1	Control (1% CMC)	148±8	Recovery
2	Standard (Phenytoin)	30.6±7	Recovery
3	Compound 1	95±11	Recovery
4	Compound 2	117.3±12	Recovery
5	Compound 3	114.6±12.5	Recovery
6	Compound 4	43.6±2.5*	Recovery
7	Compound 5	126.6±6	Recovery
8	Compound 6	38.3±7.7*	Recovery
9	Compound 7	99.6±33	Recovery
10	Compound 8	118±17	Recovery
11	Compound 9	126.3±2.4	Recovery
12	Compound 10	31.8±5*	Recovery
13	Compound 11	131±8.8	Recovery
14	Compound 12	116±8.4	Recovery
15	Compound 13	76±8.1	Recovery
16	Compound 14	69.3±7.8	Recovery
17	Compound 15	69.3±7.5	Recovery
18	Compound 16	52±7.3*	Recovery

Phenytoin was used as standard drug. Values are expressed as Mean ± SEM.

* p < 0.05 in comparison to control (n=6).



Comparision between Synthesized compound and Phenytoin

RESULTS AND DISCUSSION

CHEMICAL STUDIES

1. A series of compounds of **Compound1 to Compound16** has been synthesized.
2. The structure, IUPAC name, physiochemical characteristics and spectral view of synthesized derivatives are given in the Table 2, Table 3 and Table 4.
3. Compounds were synthesized in moderate to good yield. Purity of the compounds was determined by TLC on silica gel G plates. The spots were detected by exposure to iodine vapours.
4. Synthesized compounds were characterized by spectral analysis (FT-IR, ^{1}H-NMR). The spectra were found to be in agreement with the assigned molecular structure.

BIOLOGICAL STUDIES

1. Preliminary anticonvulsant evaluation of all the newly synthesized cannabinoids derivative of hetero cyclic compounds were done against seizure models, Chemical test subcutaneous pentylenetetrazole (scPTZ).
2. Compounds affording protection in the chemical test employed was subcutaneous pentylenetetrazole (scPTZ) seizure threshold test is claimed to denote agents of value in treating absence seizures. All the experiment protocols were carried out with the permission from Institutional Animal Ethics Committee (IAEC).

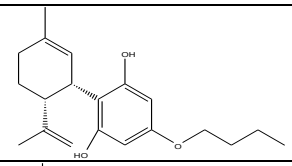
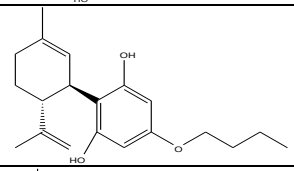
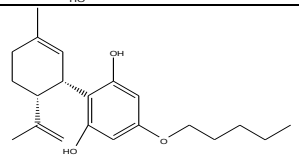
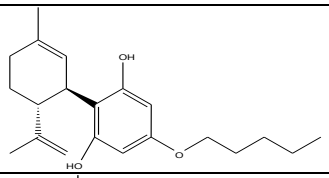
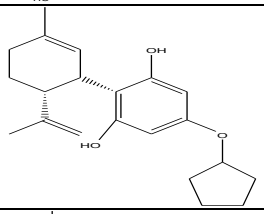
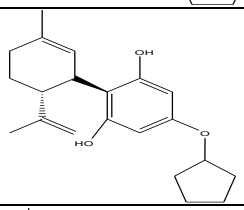
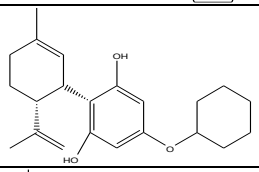
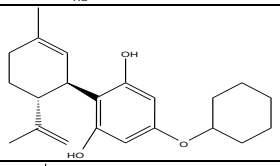
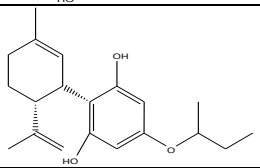
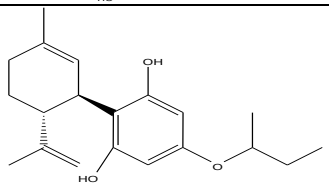
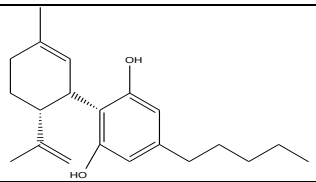
In the present series of compounds, cannabinoids derivatives were designed and synthesized to meet structural requirements essential for anticonvulsant activity. The anticonvulsant data revealed that newly synthesized compounds **Compound1, Compound4, Compound10, Compound12,** afforded significant protection at 10mg/kg; i.p. in sc PTZ test. The anticonvulsant activity of the other tested compounds was found to be much moderately effective then phenytoin used as standard anticonvulsant.

Table: 1- Anti-convulsant activity of synthesized compounds

Group	Compound	Onset time of convulsion (sec)	Recovery/death
1	Control (1% CMC)	39.3±0.8	Recovery
2	Compound 1	148.8±2.4*	Recovery
3	Compound 2	124.8±10	Recovery
4	Compound 3	43.7±2.5	Recovery
5	Compound 4	123.1±1.1*	Recovery
6	Compound 5	126.6±6.0*	Recovery
7	Compound 6	133.5±4.3	Recovery
8	Compound 7	39.0±4.6	Recovery
9	Compound 8	134.8±2.0*	Recovery
10	Compound 9	126.3±2.4*	Recovery
11	Compound 10	131±4.9	Recovery
12	Compound 11	131±4.9	Recovery
13	Compound 12	143.5±2.8*	Recovery
14	Compound 13	140.5±2.8*	Recovery
15	Compound 14	142.5±2.8*	Recovery
16	Compound 15	145.5±2.8*	Recovery
17	Compound 16	148.5±2.8*	Recovery
18	Standard (Phenytoin)	152.5±1.5	Recovery

Phenytoin was used as standard drug. Values are expressed as Mean ± SEM.
*p<0.05 in comparison to control (n=6).

Table: 2- Nomenclature of newly synthesized compounds

S. No.	Chemical Structure	I.U.P.A.C. Name
Compound 1		5-butoxy-2-((1S,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)benzene-1,3-diol
Compound 2		5-butoxy-2-((1R,6R)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enyl)benzene-1,3-diol
Compound 3		2-((1S,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)-5-(pentyloxy)benzene-1,3-diol
Compound 4		2-((1R,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)-5-(pentyloxy)benzene-1,3-diol
Compound 5		5-(cyclopentyloxy)-2-((1S,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)benzene-1,3-diol
Compound 6		5-(cyclopentyloxy)-2-((1R,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)benzene-1,3-diol
Compound 7		5-(cyclohexyloxy)-2-((1S,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex2-enyl)-1,3-diol
Compound8		5-(cyclohexyloxy)-2-((1R,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex2-enyl)-1,3-diol
Compound 9		5-sec-butoxy-2-((1S,6R)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enyl)benzene-1,3-diol
Compound 10		5-sec-butoxy-2-((1R,6R)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enyl)benzene-1,3-diol
Compound 11		2-((1S,6R)-3-methyl-6-(prop-1en-2-yl)cyclohex-2-enyl)-5-pentylbenzene-1,3-diol

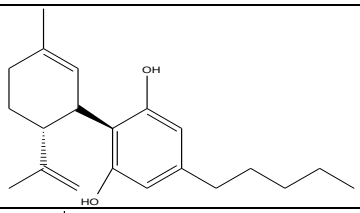
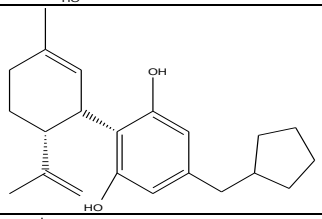
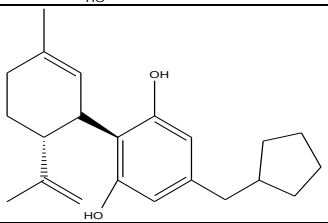
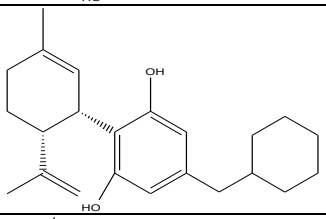
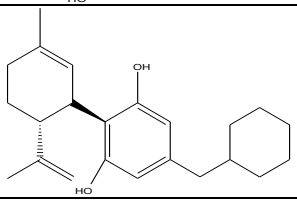
Compound 12		2-((1R,6R)-3-methyl-6-(prop-1en-2-yl)cyclohex-2-enyl)-5-pentylbenzene-1,3-diol
Compound 13		5-(cyclopentylmethyl)-2-(1S,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)benzene-1,3-diol
Compound 14		5-(cyclopentylmethyl)-2-(1S,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)benzene-1,3-diol
Compound 15		5-(cyclohxylmethyl)-2-(1R,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)benzene-1,3-diol
Compound 16		5-(cyclohxylmethyl)-2-(1S,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)benzene-1,3-diol

Table: 3- Physicochemical parameters of the synthesized compounds

Compound	I.U.P.A.C. Name	Molecular Formula	Molecular Weight	Melting Point (°C)	Yield (%)
Compound 1	5-butoxy-2-((1S,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)benzene-1,3-diol	$C_{20}H_{28}O_3$	316.4	326-328	84
Compound 2	5-butoxy-2-((1R,6R)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enyl)benzene-1,3-diol	$C_{20}H_{28}O_3$	316.4	327-329	85
Compound 3	2-((1S,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)-5-(pentyloxy)benzene-1,3-diol	$C_{21}H_{30}O_3$	330.4	227-228	82
Compound 4	2-((1R,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)-5-(pentyloxy)benzene-1,3-diol	$C_{21}H_{30}O_3$	330.4	80-82	86
Compound 5	5-(cyclopentyloxy)-2-((1S,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)benzene-1,3-diol	$C_{21}H_{28}O_3$	328.2	80-82	82
Compound 6	5-(cyclopentyloxy)-2-((1R,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)benzene-1,3-diol	$C_{21}H_{28}O_3$	328.2	80-82	84
Compound 7	5-(cyclohexyloxy)-2-((1S,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex2-enyl)-1,3-diol	$C_{22}H_{30}O_3$	342.2	357-58	88
Compound 8	5-(cyclohexyloxy)-2-((1R,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex2-enyl)-1,3-diol	$C_{22}H_{30}O_3$	342.2	357-58	82
Compound 9	5-sec-butoxy-2-((1S,6R)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enyl)benzene-1,3-diol	$C_{20}H_{28}O_3$	316.4	312-14	88
Compound 10	5-sec-butoxy-2-((1R,6R)-3-methyl-6-(prop-1-en-2yl)cyclohex-2-enyl)benzene-1,3-diol	$C_{20}H_{28}O_3$	316.4	312-14	86
Compound 11	2-((1S,6R)-3-methyl-6-(prop-1en-2-yl)cyclohex-2-enyl)-5-pentylbenzene-1,3-diol	$C_{21}H_{30}O_2$	314.2	316-18	82
Compound 12	2-((1R,6R)-3-methyl-6-(prop-1en-2-yl)cyclohex-2-enyl)-5-pentylbenzene-1,3-diol	$C_{21}H_{30}O_2$	314.2	316-17	86
Compound 13	5-(cyclopentylmethyl)-2-(1S,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)benzene-1,3-diol	$C_{22}H_{30}O_2$	326.2	338-340	82
Compound 14	5-(cyclopentylmethyl)-2-(1R,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)benzene-1,3-diol	$C_{22}H_{30}O_2$	326.2	338-340	88
Compound 15	5-(cyclohxylmethyl)-2-(1R,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)benzene-1,3-diol	$C_{23}H_{32}O_2$	340.2	346-348	80
Compound 16	5-(cyclohxylmethyl)-2-(1S,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)benzene-1,3-diol	$C_{23}H_{32}O_2$	340.2	346-348	84

Table: 4 - IR and NMR Spectra Details

Compound	MS spectra	NMR spectra
Compound 1	MS (ESI) m/z: calculated, $C_{20}H_{28}O_3$, 316.43 $[M]^+$; found, 315.28 $[M-H]^-$	^{1}H NMR (400 MHz, $CDCl_3$): δ 6.13 (s, 1H), 5.94 (s, 2H), 5.56 (s, 1H), 4.71 (bs, 1H), 4.52 (s, 1H), 4.37 (s, 1H), 4.26-4.18 (m, 1H), 3.94 (bs, 1H), 3.80 (t, J = 6.8 Hz, 2H), 2.42-2.40 (4H), 1.80-1.20 (m, 10 H), 0.94-0.79 (m, 3H).
Compound 2	MS (ESI) m/z: calculated, $C_{20}H_{28}O_3$, 316.43 $[M]^+$; found, 315.28 $[M-H]^-$	^{1}H NMR (400 MHz, $CDCl_3$): δ 6.04-5.93 (m, 3H), 5.55 (s, 1H), 4.77 (bs, 1H), 4.68 (s, 1H), 4.58 (s, 1H), 4.23-4.20 (m, 1H), 3.86 (t, J = 6.4 Hz, 2H), 3.79-3.76 (m, 1H), 2.39-2.33 (m, 1H), 2.30-2.00 (m, 2H), 1.80-1.20 (m, 11 H), 1.00-0.88 (m, 3H)
Compound 3	MS (ESI) m/z: calculated, $C_{21}H_{30}O_3$, 330.46 $[M]^+$; found, 331.2 $[M+H]^+$, 329.2 $[M-H]^-$	^{1}H NMR (400 MHz, $CDCl_3$): δ 6.13 (s, 1H), 5.94 (s, 2H), 5.57 (s, 1H), 4.71 (bs, 1H), 4.52 (s, 1H), 4.37 (s, 1H), 3.94 (bs, 1H), 3.80 (t, J = 6.8 Hz, 2H), 2.44-2.30 (m, 1H), 2.18 (bs, 1H), 2.09-2.02 (m, 1H), 0.90-0.88 (m, 3H)
Compound 4	MS (ESI) m/z: calculated, $C_{21}H_{30}O_3$, 330.46 $[M]^+$; found, 331.2 $[M+H]^+$, 329.2 $[M-H]^-$	^{1}H NMR (400 MHz, $CDCl_3$): δ 6.06-5.90 (m, 3H), 5.55 (s, 1H), 4.77 (bs, 1H), 4.68 (s, 1H), 4.58 (s, 1H), 3.88-3.84 (m, 2H), 3.79-3.76 (m, 1H), 2.39-2.05 (m, 3H), 1.90-1.20 (m, 14H), 0.92 (t, J = 7.1 Hz, 3H)
Compound 6		
Compound 7	MS (ESI) m/z: calculated, $C_{22}H_{30}O_3$, 342.47 $[M]^+$; found, 343.2 $[M+H]^+$, 341.2 $[M-H]^-$	^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (s, 1H), 5.96-5.92 (m, 2H), 5.54 (s, 1H), 4.71 (bs, 1H), 4.52 (s, 1H), 4.15-4.08 (m, 1H), 3.97-3.95 (m, 1H), 2.44-2.14 (m, 2H), 2.12-1.85 (m, 4H), 1.80-1.24 (16H)
Compound 8	MS (ESI) m/z: calculated, $C_{22}H_{30}O_3$, 342.47 $[M]^+$; found, 343.2 $[M+H]^+$, 341.2 $[M-H]^-$	^{1}H NMR (400 MHz, $CDCl_3$): δ 6.28-5.83 (m, 3H), 5.51 (s, 1H), 5.16 (s, 1H), 4.69 (s, 1H), 4.22 (s, 1H), 4.14-4.08 (m, 1H), 3.81-3.78 (m ,1H), 2.30-1.06 (21 H)
Compound 9	MS (ESI) m/z: calculated, $C_{20}H_{28}O_3$, 316.43 $[M]^+$; found, 316.9 $[M]^+$	^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (s, 1H), 5.94 (s, 1H), 5.92 (s, 1H), 5.54 (s, 1H), 4.65 (bs, 1H), 4.51 (d, J = 10.6 Hz, 1H), 4.38 (d, J = 9.2 Hz, 1H), 4.23-4.15 (m, 1H), 3.94 (bs, 1H), 2.44-2.00 (m, 4H), 1.80-0.90 (m, 15 H)
Compound 10	MS (ESI) m/z: calculated, $C_{20}H_{28}O_3$, 316.43 $[M]^+$; found, 315.9 $[M-H]^-$	^{1}H NMR (400 MHz, $CDCl_3$): δ 6.02-5.93 (m, 3H), 5.56 (s, 1H), 4.73 (bs, 1H), 4.69 (s, 1H), 4.60 (s, 1H), 4.23-4.16 (m, 1H), 3.79-3.73 (m, 1H), 2.40-2.24 (m, 4H), 1.80-0.80 (m, 15H)
Compound 11	MS (ESI) m/z: calculated, $C_{21}H_{30}O_2$, 314.46 $[M]^+$; found, 315.4 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$): δ 6.21 (m, 2H), 6.05 (s, 1H), 5.52 (s, 1H), 4.65-4.64 (m, 2H), 4.46 (s, 1H), 3.54-3.50 (m, 1H), 2.64-2.44 (m, 2H), 2.29-2.18 (m, 2H), 2.10-2.05 (m, 1H), 1.88-1.24 (m, 14H), 0.92-0.86 (m, 3H).
Compound 12	MS (ESI) m/z: calculated, $C_{21}H_{30}O_2$, 314.46 $[M]^+$; found, 315.4 $[M+H]^+$	^{1}H NMR (400 MHz, $CDCl_3$): δ 6.27-6.17 (m, 2H), 5.98 (bs, 1H), 5.57 (s, 1H), 4.67-4.66 (m, 2H), 4.59 (s, 1H), 3.87-3.83 (m, 1H), 2.46-2.36 (m, 3H), 2.23-2.20 (m, 1H), 2.12-2.07 (m, 1H), 1.85-1.76 (m, 5H), 1.65 (s, 3H), 1.59-1.52 (m, 3H), 1.35-1.24 (m, 5H), 0.92-0.86 (m, 3H).
Compound 13	MS (ESI) m/z: calculated, $C_{22}H_{30}O_2$, 326.47 $[M]^+$; found, 327.2 $[M+H]^+$, 325.2 $[M-1]^-$	^{1}H NMR (400 MHz, $CDCl_3$): δ 6.27-6.16 (m, 2H), 5.98 (bs, 1H), 5.58 (s, 1H), 4.67-4.66 (m, 2H), 4.56 (s, 1H), 3.86-3.82 (m, 1H), 2.46-0.86 (m, 22H).
Compound 14	MS (ESI) m/z: calculated, $C_{22}H_{30}O_2$, 326.47 $[M]^+$; found, 327.2 $[M+H]^+$, 325.2 $[M-1]^-$	^{1}H NMR (400 MHz, $CDCl_3$): δ 6.21-6.18 (m, 2H), 6.06 (s, 1H), 5.52 (s, 1H), 4.64-4.63 (m, 1H), 4.56 (bs, 1H), 4.45 (s, 1H), 3.58-3.56 (m, 1H), 2.73-2.68 (m, 1H), 2.47-2.44 (m, 1H)2.29-0.86 (m, 20H).
Compound 15	MS (ESI) m/z: calculated, $C_{23}H_{32}O_2$, 340.50 $[M]^+$; found, 341.2 $[M+H]^+$, 339.2 $[M-1]^-$	^{1}H NMR (400 MHz, $CDCl_3$): δ 6.27-6.16 (m, 2H), 5.98 (bs, 1H), 5.58 (s, 1H), 4.67-4.66 (m, 2H), 4.56 (s, 1H), 3.86-3.82 (m, 1H), 2.46-0.86 (m, 24H).
Compound 16	MS (ESI) m/z: calculated, $C_{23}H_{32}O_2$, 340.50 $[M]^+$; found, 341.2 $[M+H]^+$, 339.2 $[M-1]^-$	^{1}H NMR (400 MHz, $CDCl_3$): δ 6.21 (d, J = 2.4 Hz, 1H), 6.13 (d, J = 2.4 Hz, 1H), 6.07 (s, 1H), 5.52 (s, 1H), 4.64-4.63 (m, 1H), 4.54 (bs, 1H), 4.44 (s, 1H), 3.53-3.51 (m, 1H), 2.58-2.44 (m, 2H), 2.43-0.82 (m, 22H).

DISCUSSION

1. A series of cannabidiol derivatives were synthesized.
2. The structure, IUPAC name, physiochemical characteristics and spectral view of synthesized derivatives are given in the Table 7, Table 8 and Table 9.
3. Compounds were synthesized in moderate to good yield. Purity of the compounds was determined by TLC on silica gel G plates. The spots were detected by exposure to iodine vapours.
4. Synthesized compounds were characterized by spectral analysis (FT-IR, ^{1}H-NMR). The spectra were found to be in agreement with the assigned molecular structure.

ABBREVIATIONS

Please explain all the abbreviations included in the manuscript in alphabetical order. For example,

Ar	Aromatic
B. pumilus	bacillus pumilus
B .subtilis	Bacillus subtilis
C. albicans	Candida albicans
CDCl3	Deuterated chloroform
DMF	Dimethyl formamide
E.coli	Escherichia coli
DMSO	Dimethyl sulphoxide
IR	Infra Red
m	Multiplates
M	Mole
M.F.	Molecular Formula
m.p.	Melting Point

MDR	Multidrug resistant
MHz	Mega Hertz
MRSA	Methicillin-resistant staphylococcus aureus
NMR	Nuclear magnetic resonance
P.aeruginosa	Pseudomonas aeruginosa
PPM	Parts per million
PDR	Pandrug-resistant
RT	Room Temperature
S	Singlet
T:E:F	Toluene :Ethyl acetate :Formic acid
TLC	Thin Layer Chromatography
TMS	Tetra methyl silane
VRSA	Vancomycin-resistant staphylococcus aureus
XDR	Extensively drug-resistant
δ	Chemical shift

DECLARATIONS

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Author contributions
"The author contributed solely to the work."

Conflicts of interest
The authors declare that they have no conflicts of interest.

Ethical approval
Animal study was approved Institutional Animal Ethics committee of KRMU with protocol No. KRMU/ CPCSEA/RES/IAEC-2021-I (5)

Consent to participate
"Not applicable."

Consent to publication
"Not applicable."

Availability of data and materials
"Not applicable."

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REFERENCES

1. Mahapatra DK, Bharti SK, 2019. Medicinal Chemistry with Pharmaceutical Product Development. New Jersey: Apple Academic Press.
2. Mohan C, Kumar V, Kumari S, 2018. Synthesis, characterization, and antibacterial activity of the schiff bases derived from thiosemicarbazide, 2-acetyl thiophene and thiophene-2 aldehyde. International Research Journal of Pharmacy 9(7), 153-158.
3. Tescarollo FC, Rombo DM, DeLiberto LK, Fedele DE, Alharfoush E, Tomé ÂR, Cunha RA, Sebastião AM, Boison D, 2020. Role of adenosine in epilepsy and seizures. J Caffeine Adenosine Res. 10(2), 45-60, DOI: 10.1089/caff.2019.0022.
4. Boison D, 2005. Adenosine and epilepsy: from therapeutic rationale to new therapeutic strategies. Neuroscientist. 11(1), 25-36, DOI: 10.1177/1073858404269112.
5. Masino SA, Kawamura Jr M, Ruskin DN, 2014. Adenosine receptors and epilepsy: current evidence and future potential. Int Rev Neurobiol. 119, 233-55, DOI: 10.1016/B978-0-12-801022-8.00011-8.
6. Aryati WD, Salamah NN, Syahdi RR, Yanuar A, 2019. The Role and Development of the Antagonist of Adenosine A2A in Parkinson's Disease. In: Neuroprotection. London: IntechOpen.
7. Deb PK, Kokaz SF, Abed SN, Chandrasekaran B, Hourani W, Jaber AY, Mailavaram RP, Kumar P, Venugopala KN, 2020. Pharmacology of Adenosine Receptors. In: Frontiers in Pharmacology of Neurotransmitters. Singapore: Springer.
8. Joseph TM, Mahapatra DK, 2018. Bacterial DNA Gyrase (Topoisomerase) Inhibitory Potentials of Heterocyclic Natural Products: Investigations through Induced-Fit Molecular Docking Approach. Research and Reviews: J Drug Design Discov. 5(2), 7-9.
9. Mohan C, Kumar V, Kumari N, Kumari S, Yadav J, Gandass T, Yadav S, 2020. Synthesis, characterization and antibacterial studies of semicarbazide based Schiff bases and their Pb(II), Zr(IV) and U(VI) complexes. Advanced Journal of Chemistry -Section B 2(4), 187-196, DOI: 10.33945/SAMI/AJCB.2020.4.3.
10. Arya H, Mohan C, Pandey P, Verama M, Kumar V, 2021. Phytochemical screening of Basella alba leaves extracts and evaluate its efficacy on sun burn (Sun Protection Factor). European Journal of Molecular & Clinical Medicine, 8(1), 417-423, DOI: 10.31838/ejmcm.
11. Silky S, Neerupma D, Arun G, 2021. Inhibitory Perspective of New Synthesized Compounds against Angiotensin Receptor: Schrodinger-based Induced-Fit Molecular Docking. J Pharm Res Int. 33(32A), 79-87, DOI: 10.9734/jpri/2021/v33i32A31718.

12. Mahapatra DK, Bharti SK, 2017. Handbook of Research on Medicinal Chemistry: Innovations and Methodologies. New Jersey: Apple Academic Press.
13. Mahapatra DK, Bharti SK, 2016. Drug Design. New Delhi: Tara Publications Private Limited.