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Synthesis and Antibacterial Activity of Novel Dehydrodiisoeugenol Derivatives

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Abstract: Dehydrodiisoeugenol constitute a new group of antimitotic and potential anti-cancer agents that inhibit tubulin polymerization. It is a dihydrobenzofuranoid type neolignan have been synthesized and diversified to its respective ether using conventional method (K_2CO_3/R-Br/acetone; R = alkyl, aralkyl) and characterized by ^{1}H NMR, IR, elemental analysis and mass spectral data. These synthesized compounds were screened for their potential antibacterial activity against Gram-positive and Gram-negative bacteria. Few of them displayed promising antibacterial activity. All these compounds were new and confirmed by Scifinder search.

Keywords: Dehydrodiisoeugenol, ^{1}H NMR, TOF MS, IR, Gram-positive and Gram-negative bacteria, antibacterial *etc*.

1. Introduction

Due to the presence of heterocyclic skeleton[1] in large number of natural products and bio-active heterocycles, the development of new and user friendly strategies for accessing various heterocycles scaffold[2] has become important area in organic synthesis. The 2,3-dihydrobenzofuran (2,3-DHB) skeleton is present in large number of bio-active natural products. Due to the better thermodynamic stability, 2,3-

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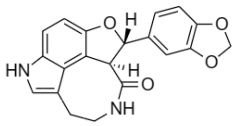
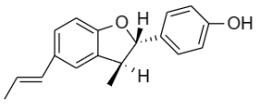
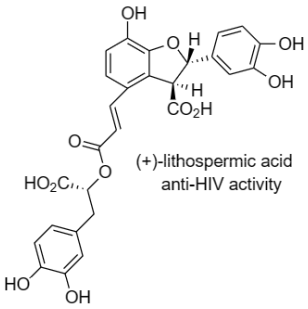
dihydrobenzofurans with *trans* geometry are found to be present in most of the bio-active natural products such as (+)-decursivine, (+)-lithospermic acid, (+)-conocarpan, haliannuol G *etc*.



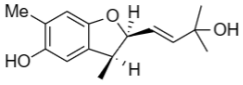
(+)-decursivine
antimalarial activity



(+)-conocarpan



(+)-lithospermic acid
anti-HIV activity



heliannuol G

Heterocyclic synthesis has emerged as powerful technique for generating new molecules useful for drug discovery[1]. Heterocyclic compounds provide scaffolds on which pharmacophores can arrange to yield potent and selective drugs[2]. Benzofuran nucleus may be combined with nitrogen heterocycles in different ways. Several benzofuran compounds are reported to possess antibacterial[3], antifungal[4], anti-inflammatory[5], antidepressant[6], analgesic[7] and hypoglycemic activities[8]. It has been pointed out that: benzofuran nucleus is very rarely associated with a nitrogen hetrocycle. Since dehydrodiisoeugenol displayed pronounced antileishmanial, antiplasmodial activities it was of interest to make a library of dehydrodiisoeugenol to establish the structure-activity relationship. To this end, dehydrodiisoeugenol was used as a starting material which was synthesized by oxidative coupling of isoeugenol with diacetoxy iodobenzene (IDA) as oxidant[9]. To this end, in addition to our earlier work[10], seven different ethers of the phenolic moiety of dehydrodiisoeugenol was synthesized by classical way (K_2CO_3/R-Br) from dehydrodiisoeugenol.

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The objective of this study is to condense two molecules of the same disease domain to produce more potent candidate in the same disease domain or to condense two molecules of different disease domain to produce mixed variety of those disease domain or to have drug candidate with entirely different disease domain.

2. Experimental

2.1 Materials and Methods: Chemicals used were of a laboratory grade. The reactions were monitored by TLC on aluminium-backed silica plate visualized by UV-light. Melting points were determined on a Thomas Hoover capillary melting point apparatus using digital thermometer. ^{1}H NMR spectra were recorded on a Varian 400 MHz spectrometer in $CDCl_3$. Chemical shifts were recorded in parts per million down field from tetramethyl silane. Mass spectra were recorded on a TOF MS ES mass spectrometer. Elemental analysis were carried out as a percentage on a Thermo finnigan, Flash EA 1112 series, Italy.

2.2 Synthesis of dehydrodiisoeugenol: To a stirred solution of isoeugenol (4.0 g, 24.35 mmol) in dichloromethane (75 ml) was added dropwise a solution of $PhI(OAc)_2$ (2.5 g, 7.76 mmol) in dichloromethane (100 ml) at room temperature within 4h and stirring was continued at room temperature for 48h. Subsequently the same amount of IDA in dichloromethane (100 ml) was added within 4 h. After stirring, the reaction mixture at room temperature for 2 h, solid $NaHCO_3$ (3 g) was added and the stirring was continued for 5 h. Subsequently, $NaHCO_3$ was filtered off, and the solvent was evaporated to give a yellow oil, which was purified by flash chromatography on silica gel (n-hexane:ethyl acetate, 6:1) to yield dehydrodiisoeugenol (1.4 g, 38 %) as white needles

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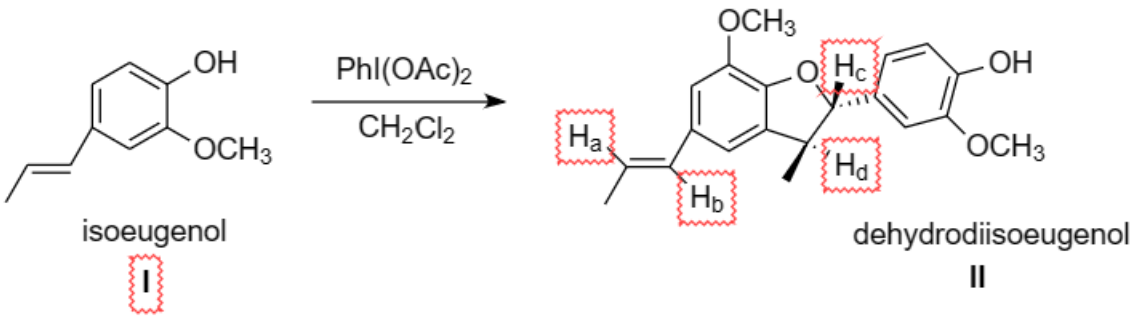
with m.p. 132-133^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$)∂_{ppm} :1.38 (d, J = 6.8 Hz, 3H, -CH_3), 1.86 (d, J = 6.6 Hz, 3H, -terminal –CH_3 of propenyl moiety), 3.4-3.5 (m, 1H, H_d), 3.87 (s, 3H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 5.10 (d, J = 9.2 Hz, 1H, H_c), 5.64 (s, 1H, -OH, D_2O exchangeable), 6.0-6.2 (m, 1H, H_a), 6.36 (d, J = 15.8 Hz, 1H, H_b), 6-7-7.1 (m, 5H, ArH).



2.3 Diversification of Dehydrodiisoeugenol to its ether derivatives :- Compounds (1) to (7) [Table 1] were synthesized by following general method.

To a stirred solution of [A] (1 eq.) in 30 ml acetone was added [B] (2.5 eq.) and stirring continued at 40^{0}C for next 30 min. for complete formation of K-salt. To this compound [C] (2 eq.) was added and stirring continued at 45 – 50^{0}C for next 8 h. The progress of the reaction is monitored by TLC for the completion of the reaction.

Work up :- The reaction mixture filtered through buchner funnel, wash the cake with 25 ml acetone. The total organic layer was concentrated to minimum, preadsorbed on silica gel and purified by silica gel (100 – 200 mesh) column chromatography with increase in concentration of ethyl acetate in petroleum ether. The general yields ranges between 60 – 70 %.

The most significant features of this methodology are (a) good accessibility of the reagents and its stability (b) a stoichiometric amount of reagent can be used by direct weighing, avoiding

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excess (c) no evolution of hazardous vapors during the reaction (d) the total elimination of the use of toxic organic solvents (e) a simple experimental procedure (g) good control over the outcome of the reaction by varying the amount of reagent. The aforesaid protocol thus provides an improved procedure for the synthesis of useful benzofuran derivatives having important pharmaceutical, agricultural and other physicochemical properties.

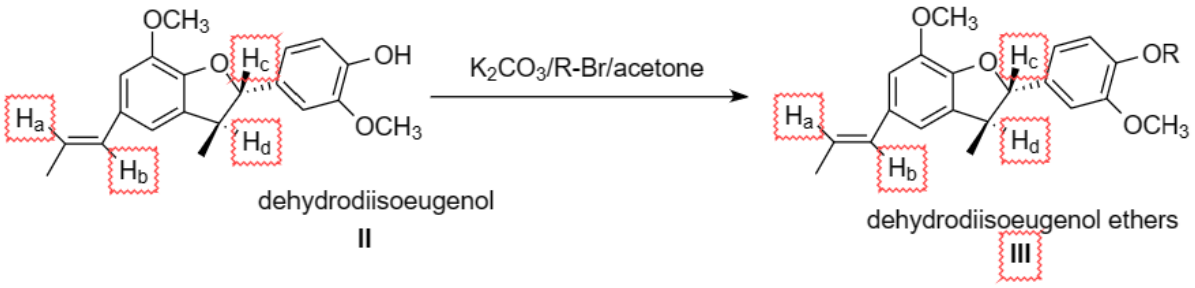

Table 1: Dehydrodiisoeugenol ether derivatives.

Compound No.	R
1	pentyl
2	hexyl
3	octyl
4	nonyl
5	decyl
6	dodecyl
7	benzyl

2.4 : Characterization of compounds (1-7):

(±) 7-Methoxy-2-(3-methoxy-4-pentoxyphenyl)-3-methyl-5-[(*E*)-prop-1-enyl]-2,3-dihydro benzofuran (1) : colorless solid; Molecular Formula $C_{25}H_{32}O_4$; M.P.: 89-91^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$)∂_{ppm}: 0.97 (t, J = 7.4 Hz, 3H, -CH_3 from n-penyl moiety), 1.38 (d, J = 6.8 Hz, 3H), 1.4-1.7 (m, 4H, -CH_2 of n-pentyl moiety), 1.75-1.85 (m, 2H, -CH_2 of n-pentyl moiety), 1.86 (d, J =

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6.6 Hz, 3H, terminal CH_3 of propenyl moiety), 3.4-3.5 (m, 1H, H_d), 3.85 (s, 3H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.02 (t, J = 6.4 Hz, 2H, -OCH_2 of n-pentyl moiety), 5.10 (d, J = 9.2 Hz, 1H, H_c), 6.0-6.2 (m, 1H, H_a), 6.36 (d, J = 15.8 Hz, 1H, H_b), 6-7-7.0 (m, 5H, ArH); IR (KBr) cm^{-1}: 1600 (aromatic), 1380 (C-O); TOFMS-ES: 397 (M + H); Elemental analysis, Required C 75.70, H 8.10 %; Found C 75.67, H 8.13 %.

(±) 2-(4-Hexoxy-3-methoxyphenyl)-7-methoxy-3-methyl-5-[(*E*)-prop-1-enyl]-2,3-dihydro benzofuran (2) : colorless solid; Molecular Formula $C_{26}H_{34}O_4$; M.P.: 97-98^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$)∂_{ppm}: 0.92 (t, J = 7.0 Hz, 3H , -CH_3 of n-hexyl moiety), 1.2-1.6 (m, 6H, 3 x –CH_2 of n-hexyl moiety), 1.38 (d, J = 6.8 Hz, 3H, -CH_3), 1.78-1.90 (m, 2H, -CH_2 of n-hexyl moiety), 1.86 (d, J = 6.6 Hz, 3H, terminal –CH_3 of propenyl moiety), 3.4-3.6 (m, 1H, H_d), 3.86 (s, 3H, Ar-OCH_3), 3.90 (s, 3H, Ar-OCH_3), 4.0 (t, J = 6.4 Hz, 2H, OCH_2 of n-hexyl moiety), 5.10 (d, J = 9.2 Hz, 1H, H_c), 6.0-6.2 (m, 1H, H_a), 6.36 (d, J = 15.8 Hz, 1H, H_b), 6.7-7.0 (m, 5H, ArH); IR (KBr) cm^{-1}: 1596 (aromatic), 1378 (C-O); TOFMS-ES: 411 (M + H); Elemental analysis, Required C 76.12, H 8.28 %; Found C 76.15, H 8.31 %.

(±) 7-Methoxy-2-(3-methoxy-4-octoxyphenyl)-3-methyl-5-[(*E*)-prop-1-enyl]-2,3-dihydrobe nzofuran (3) : colorless solid: Molecular Formula $C_{28}H_{38}O_4$; M.P.: 110-112^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$)∂_{ppm}: 0.88 (t, J = 7.3 Hz, 3H, CH_3 of n-octyl moiety), 1.2-1.6 (m, 8H, 4 x –CH_2 of n-octyl moiety), 1.38 (d, J = 6.8 Hz, 3H, CH_3), 1.75-1.85 (m, 4H, 2 x -CH_2 of n-octyl moiety), 1.86 (d, J = 6.6 Hz, 3H, terminal CH_3 of propenyl moiety), 3.3-3.5 (m, 1H, H_d), 3.85 (s, 3H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.08 (t, J = 7.4 Hz, 2H, -OCH_2 of n-octyl moiety), 5.12 (d, J = 9.4 Hz, 1H, H_c), 6.0-6.2 (m, 1H, H_a), 6.36 (d, J = 15.9 Hz, 1H, H_b), 6.7-7.2 (m, 5H, ArH); IR (KBr) cm^{-}

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^{1}:1599 (aromatic), 1379 (C-O); TOFMS-ES: 439 (M + H); Elemental analysis, Required C 76.68, H 8.71 %; Found C 76.66, H 8.73 %.

(±) 7-Methoxy-2-(3-methoxy-4-nonoxyphenyl)-3-methyl-5-[(*E*)-prop-1-enyl]-2,3-dihydrobenzofuran (4) : colorless solid; Molecular Formula $C_{29}H_{40}O_4$; M.P.: 118-120^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$)∂_{ppm}: 0.90 (t, *J* = 7.2 Hz, 3H, terminal CH_3 of n-nonyl moiety), 1.2-1.6 (m, 10H, 5 x $-CH_2$ of n-nonyl moiety), 1.36 (d, *J* = 6.8 Hz, 3H, -CH_3), 1.75-1.85 (m, 4H, 2 x -CH_2 of n-nonyl moiety), 1.84 (d, *J* = 6.8 Hz, 3H, terminal CH_3 of propenyl moiety), 3.4-3.5 (m, 1H, H_d), 3.87 (s, 3H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.08 (s, 2H, -OCH_2 of n-nonyl moiety), 5.10 (d, *J* = 9.2 Hz, 1H, H_c), 6.0-6.2 (m, 1H, H_a), 6.35 (d, *J* = 15.7 Hz, 1H, H_b), 6.7-7.1 (m, 5H, ArH); IR (KBr) cm^{-1}: 1600 (aromatic), 1380 (C-O); TOFMS-ES: 453 (M + H); Elemental analysis: Required C 77.13, H 8.92 %; Found C 77.11, H 8.95 %.

(±) 2-(4-Decoxy-3-methoxyphenyl)-7-methoxy-3-methyl-5-[(*E*)-prop-1-enyl]-2,3-dihydrobenzofuran (5) : colorless solid: Molecular Formula $C_{30}H_{42}O_4$; M.P.: 126-128^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$)∂_{ppm}: 0.91 (t, *J* = 7.4 Hz, 3H, -CH_3 of n-decyl moiety), 1.1-1.7 (m, 10H, 5 x $-CH_2$ of n-decyl moiety), 1.36 (d, *J* = 6.8 Hz, 3H, -CH_3), 1.75-1.85 (m, 6H, 3 x -CH_2 of n-decyl moiety), 1.86 (d, *J* = 6.8 Hz, 3H, terminal CH_3 of propenyl moiety), 3.4-3.5 (m, 1H, H_d), 3.87 (s, 3H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.10 (s, 2H, -OCH_2 of n-decyl moiety), 5.11 (d, *J* = 9.2 Hz, 1H, H_c), 6.0-6.2 (m, 1H, H_a), 6.36 (d, *J* = 15.7 Hz, 1H, H_b), 6.7-7.1 (m, 5H, ArH); IR (KBr) cm^{-1}: 1600 (aromatic), 1380 (C-O); TOFMS-ES: 467 (M + H); Elemental analysis, Required C 77.18, H 9.08 %; Found C 77.21 %, H 9.20 %.

(±) 2-(4-Dodecoxy-3-methoxyphenyl)-7-methoxy-3-methyl-5-[(*E*)-prop-1-enyl]-2,3-dihydrobenzofuran(6) : colorless solid: Molecular Formula

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$C_{32}H_{46}O_4$; M.P.: 127-129^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$)∂_{ppm}: 0.88 (t, *J* = 7.3 Hz, 3H, -CH_3 of n-dodecyl moiety), 1.2-1.6 (m, 16H, 8 x –CH_2 of n-dodecyl moiety), 1.38 (d, *J* = 6.8 Hz, 3H, -CH_3), 1.75 – 1.85 (m, 2H, -CH_2 of n-dodecyl moiety), 1.86 (d, *J* = 6.6 Hz, 3H, terminal CH_3 of propenyl moiety), 3.41 (t, *J* = 7.3 Hz, 2H, -CH_2 of n-dodecyl moiety), 3.3-3.5 (m, 1H, H_d), 3.85 (s, 3H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.0 (t, *J* = 7.3 Hz, 2H, -OCH_2 of n-dodecyl moiety), 5.10 (d, *J* = 9.7 Hz, 1H, H_c), 6.0-6.2 (m, 1H, H_a), 6.36 (d, *J* = 15.9 Hz, 1H, H_b), 6-7-7.0 (m, 5H, ArH); TOFMS-ES : 495 (M + H); Elemental analysis, Required C77.69, H 9.37 %; Found C 77.66, H 9.33 %.

(±) 2-(4-Benzyloxy-3-methoxyphenyl)-7-methoxy-3-methyl-5-[(*E*)-prop-1-enyl]-2,3-dihydrobenzofuran (7) : colorless solid: Molecular Formula $C_{27}H_{28}O_4$; M.P.: 118 – 120^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$)∂_{ppm}: 1.37 (d, *J* = 6.7 Hz, 3H, -CH_3), 1.86 (d, *J* = 6.5 Hz, 3H, -terminal –CH_3 of isoeugenol moiety), 3.4-3.5 (m, 1H, H_d), 3.87 (s, 3H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 5.10 (d, *J* = 9.2 Hz, 1H, H_c), 5.15 (s, 2H, -O**CH_2**Ph), 6.0 – 6.2 (m, 1H, H_a), 6.36 (d, *J* = 15.8 Hz, 1H, H_b), 6.7-7.0 (m, 5H, ArH), 7.2-7.5 (m, 5H, ArH -OCH_2C_6**H_5**); IR (KBr) cm^{-1}: 1600 (aromatic), 1380 (C-O); TOFMS-ES: 416 (M + H); Elemental Analysis, Required C 77.86, H 6.78 %; Found C 77.83, H 6.80 %.

Taking Isoeugenol as general example, the probable mechanism for ethers can be given as follows.

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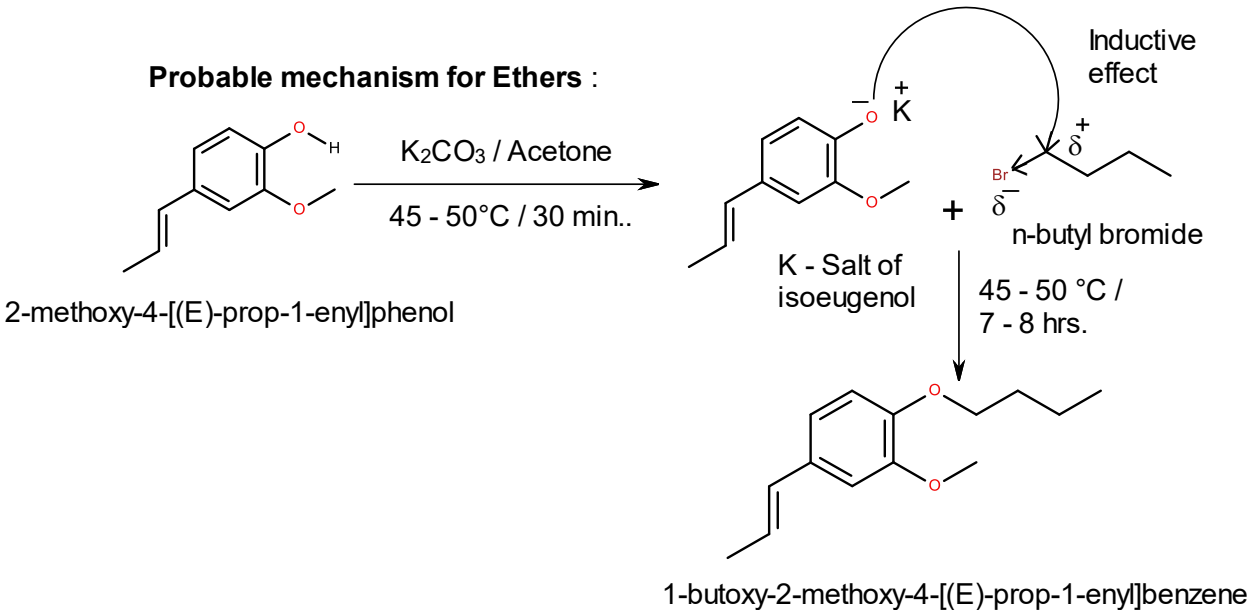

3. Chromatographic System:

Column chromatography: For column chromatography 100-200 mesh Acme grade silica gel is used. The crude reaction mixture is concentrated under reduced pressure to yield crude mass which is preadsorbed on silica gel and purified by column chromatography with gradual elution with ethyl acetate-petroleum ether mixture. The fractions having similar 'R_f" values were pooled together, concentrated and subjected for characterization using various spectroscopic techniques.

Thin layer chromatography: TLC plates were prepared using silica gel G (ACME, Bombay). Pet. ether: EtOAc (85:15) was used as the solvent system.

Radial chromatography: The circular glass plates of thickness 1 mm, were prepared by using silica gel (PF254, E. MERCK, 50 g) in cold

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distilled water (105 ml). For elution, gradually increasing concentrations of EtOAc in pet ether were employed

4. Biological Activity :

Antibacterial Activity using ditch plate method[11,12] :-

The synthesized molecules were screened for their antibacterial activity using ditch plate method at 100 µg/ml concentration against Gram positive (*Staphylococcus aureus, Corynebacterium diphtheriae*) and Gram negative (*Escherichia coli*, *Salmonella typhi, Klebsiella pneumoniae*) bacterial species qualitatively. The results of the antibacterial activities are summarized in Table 1.

Theory: One of the many ways to test the anti-bacterial activity of compounds/drugs is ditch plate method. Ditch plate method is a preliminary method to screen the test compounds/drugs for their potential as anti-microbials. In this method, the compound to be tested for antimicrobial activity is seeded in the agar plate and the test organisms are streaked across.

Procedure: A ditch 10 mm wide is cut into sterile MH agar plate. The test drug / compound is added to 5 ml molten MH agar butt at 40^0C and this mixture is poured into the ditch and allowed to solidify. The ditch should be made in level with the rest of the agar by pouring the mixture. The different bacterial cultures are streaked perpendicular to the ditch using nichrome wire loop. The plate is then incubated at 37^0 C for 24 hours.

The results are observed as inhibition of bacterial growth on the ditch as well as adjacent to the ditch .

RESULTS: The following test samples showed anti-bacterial activity against the organisms mentioned in the follo2.

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Table 2 : Antibacterial Activity Results

SAMPLE NO.	ACTIVE AGAINST
Isoeugenol	*Staphylococcus aureus* [Gram positive] *Corynebacterium diphtheriae* [Gram positive] *Salmonella typhi* [Gram negative] *Klebsiella pneumoniae* [Gram negative] *Escherichia coli* [Gram negative]
Dehydrodiisoeugenol	*Staphylococcus aureus* [Gram positive] *Salmonella typhi* [Gram negative] *Klebsiella pneumoniae* [Gram negative] *Corynebacterium diphtheriae* [Gram positive] *Escherichia coli* [Gram negative]
Ampicillin (Standard Drug	*Staphylococcus aureus* [Gram positive] *Salmonella typhi* [Gram negative] *Klebsiella pneumoniae* [Gram negative] *Corynebacterium diphtheriae* [Gram positive] *Escherichia coli* [Gram negative]
5	*Staphylococcus .aureus* [Gram Positive] *Proteus vulgaris* [Gram negative] *Salmonella typhi* [Gram negative]
6	*Staphylococcus aureus* [Gram positive] *Escherichia coli* [Gram negative]
7	*Staphylococcus aureus* [Gram positive] *Salmonella typhi* [Gram negative] *Klebsiella pneumoniae* [Gram negative] *Corynebacterium diphtheriae* [Gram positive]

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	Escherichia coli [Gram negative]

All the compounds were screened for their antibacterial activity against bacterial strains such as *Staphylococcus aureus*, *Corynebacterium diphtheria* [Gram positive] and *Salmonella typhi*, *Klebsiella pneumonia*, *Escherichia coli* [Gram negative] using ampicillin as standard drugs. The activity was determined using cup plate agar diffusion method[13] by measuring the inhibition zone in millimeters. Nutrient agar was used as a culture medium. A µg/ml solution in dimethylformamide was used. The agar medium was inoculated with bacterial cultures tested. After 24 hr. of incubation at 37^0C, the diameter of inhibition zone in millimeters was measured. Among the compounds screened, the base molecule **1** and **2** showed moderate antibacterial activity against all bacterial cultures where as its derivatives *viz.* **5**, **6, 7** showed moderate activity against *S. aureus*, *S. typhi*, *P. vulgaris* and *E. coli*. Thus **5, 6, 7** derivatives having long alkyl side chain (hydrophobic nature) and aromatic ring were potential antibacterial candidates. In depth analysis of these compounds through structure activity relationship studies would provide further insight and can be an interesting topic of future studies.

5. Conclusion : The structural diversity and the pronounced biological activities encountered in the benzofuran ether derivatives suggests that this class of compounds is worthy for further studies that may lead to derivatives by using combinatorial chemistry approach is an alternative strategy to new therapeutic discovery. In other words the generation of diverse benzofuran ether derivatives develop new therapeutic molecules that might result in candidates having better activity.

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