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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF ISOEUGENOL ETHER DERIVATIVES

Vijay D. Gangan[a]*, Deepak A. Tupare[b], Pradip S. Shelar[c], Sharad G. Shilkande[d], Preetha Achary[a], Namrata A. Ringe[e], Shreya Shukla[e] and Om Prakash Yadav[a]

a. Department of Chemistry, Reena Mehta College of Arts, Commerce, Science and Management Studies, Bhayandar (W), Thane – 401101.

b. Department of Chemistry, S. G. Arts, Science & G. P. Commerce College, Shivle Murbad.

c. Department of Chemistry, K. J. Somaiya college of Arts, Science and Commerce, Mohinirajnagar, Kopargaon - 423601, Dist. Ahemadnagar.

d. Department of Chemistry, Sheth J. N. Paliwala College of Arts, Science and Commerece, Pali-Sudhagad, Dist. Raigad – 410205.

e. Department of Chemistry, Kalyani Patil Degree College of Arts, Commerce and Science, Nallasopara East.

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***Corresponding Author: Vijay D. Gangan**

Department of Chemistry, Reena Mehta College of Arts, Commerce, Science and Management Studies, Bhayandar (W), Thane – 401101.

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ABSTRACT

Isoeugenol is a major constituent from the essential oil of *Cananga odorata* (ylang-ylang) and is also common in other spice oils. Contrary to eugenol, the physical appearance of isoeugenol varies from white crystalline (*trans*-isoeugenol) to a pale yellow liquid (*cis*-isoeugenol). Plants synthesize isoeugenol like other VPs as a defence compound against animals and micro-organisms, as well as attracting pollinators. Isoeugenol is one of several structurally similar phenylpropenoid compounds produced by plants. As a fragrance with a spicy, carnation-like odour, isoeugenol is incorporated into numerous household and personal hygiene products due to the pleasant spicy, carnation-like fragrance. As a flavouring agent, it is used in drinks, baked foods and chewing gums. Isoeugenol is known for its anti-infective properties and has been found to possess high antibacterial and antifungal activities. For these reasons, this phenylpropene molecule has been used as a preservative and a medicinal agent (EFSA, 2012; Nazzaro et al., 2013). Even though isoeugenol has been the least studied of all

the VPs, noteworthy efficacies against *Mycobacterium smegmatis* (25 µg/mL), and the fungi *Laetiporus sulphureus* at 27.6 µg/mL, have certainly shown promising activity. It is thus, recommended that the anti-infective properties against other micro-organisms be given more attention against this lesser studied molecule. Its analogues also show many biological activities which prompted us to synthesize few more analogues for their future application as bioactive molecules. All these analogues were extensively purified by chromatographic techniques and unambiguously characterized by ^{1}H NMR, IR, elemental analysis and Mass spectral data. These molecules were screened for their potential antibacterial activity against certain Gram positive and Gram negative cultures. Few of them posses promising antibacterial activity.

KEYWORDS: medical preparations, perfumery, antiseptic and analgesic, ^{1}H NMR, IR, spectroscopic techniques, Gram + ve and Gram - ve cultures *etc*.

INTRODUCTION

Phenolic compounds exist in most plant tissues as secondary metabolites *i.e.* they are not essential for growth, development or reproduction but may play roles as antioxidants and in interactions between the plant and its biological environment. Phenolics are also important components of the human diet due to their potential antioxidant activity[1], their capacity to diminish oxidative stress induced tissue damage resulted from chronic diseases[2], and their potentially important properties such as anticancer activities[3-5]. One of such compound is Isoeugenol which is a phenylpropene, a propenyl substituted guaiacol. It occurs in the essential oils of plants such as ylang–ylang. It can be synthesized from eugenol and had been used in the manufacture of vanillin. It may occur as either the cis (*Z*) or trans (*E*) isomer. Trans (*E*) isoeugenol is crystalline while cis (*Z*) isoeugenol is a liquid[6]. It also possess various Medical and Pharmacological Applications such as in Neuroprotective and Alzheimer's Treatment, as Anti-Diabetic and Metabolic Regulation, as Anti-inflammatory and Analgesic, as Antimicrobial and Antifungal agent, having an Anticancer Potential, in Skin Care / Photoaging, having Dental Applications and as Veterinary Use. It also possess various industrial applications such as flavoring agent, fragrance component and as preservative. In the present study in continuation to our earlier work[7-10], we are diversifying isoeugenol to its ether derivatives using conventional method. 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 biological activity.

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.IR spectra were recorded on a Shimadzu FTIR Prestige model as KBr pellet. 1H NMR spectra were recorded on a Varian 400 MHz spectrometer in CDCl3. 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.

RESULTS AND DISCUSSION:

Isoeugenol is treated with potassium carbonate in acetone at 50^0C for 30 mins. to have complete formation of K-salt which in turn reacted with suitable alkyl / aryl halide at ambient temperature for 4 hrs. to yield respective ether derivatives. The crude reaction mixture filtered through buchner funnel, wash the cake with acetone. The total organic layer was concentrated to minimum and purified by column, radial and preparative thin layer chromatographic techniques and unambiguously characterized by ^{1}H NMR, IR, Mass spectroscopy and elemental analysis techniques.

Research Methodology

K_2CO_3 is chosen over Na_2CO_3 because it has a larger atomic radius, which allows its outermost valence electron to be lost more easily. As a larger atom, potassium has a lower ionization energy and weaker nuclear attraction on its electrons compared to sodium, making its compounds and reactions more aggressive. Reactions with Na_2CO_3 are slow, sluggish, time consuming and also yields were poor as compared to K_2CO_3.

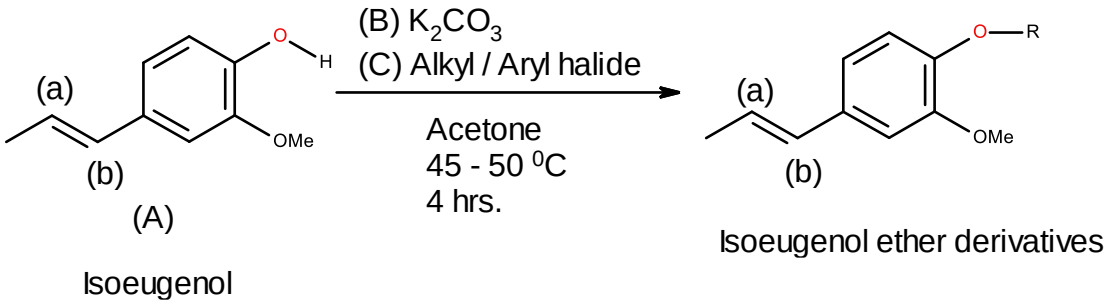
General method for the preparation of compounds (I - V):- These were prepared by following general method as depicted below.

In a single necked 100 ml RB, fitted with magnetic stirrer, $CaCl_2$ guard tube charge - 1 gm of Isoeuegnol + 2.0 eq. of K_2CO_3 in 30 ml acetone and stirred at 50^0C for 30 mins to have complete formation of K-salt. To this charge 1.3 eq. of alkyl / aryl halide dropwise through

dropping funnel and the reaction mixture stirred at 50^0C for next 4 hrs. The progress of the reaction was monitored by TLC for the completion of the reaction.

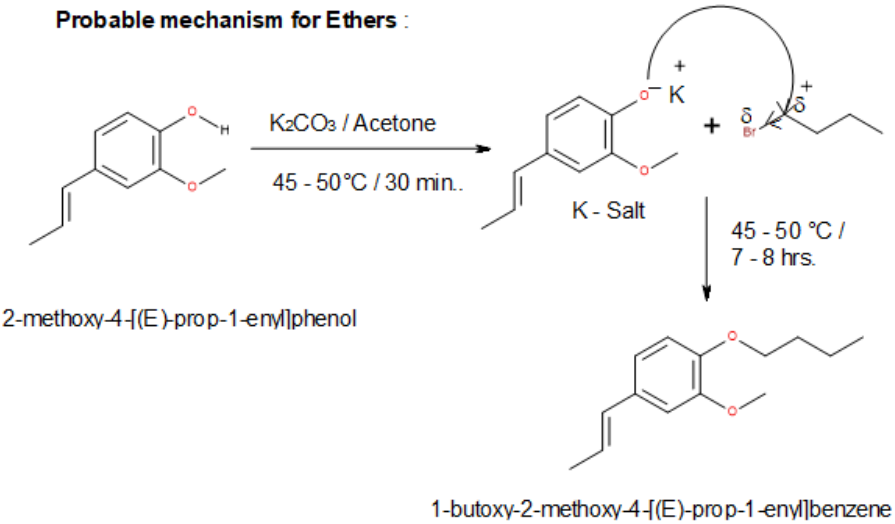
Work up:- The reaction mixture filtered through buchner funnel, wash the cake with 10 ml acetone. The total organic layer was concentrated to minimum, preadsorbed on silica gel and purified by silica gel (100 – 200 mesh) column chromatography with increase in concentration of ethyl acetate in petroleum ether. The general yields ranges between 70 – 80 %.

Synthetic Scheme :



Compound No.	R
1	Methyl
2	Ethyl
3	n-Propyl
4	Allyl
5	n-Butyl

Probable mechanism for Ethers :



Compound 1:- 1,2-dimethoxy-4-[(1*E*)-prop-1-en-1-yl]benzene.

^{1}H NMR (400 MHz, $CDCl_3$) δppm : 1.84 (d, 3H, *J* = 7.6 Hz, terminal methyl from isoeugenol moiety), 3.84 (s, 3H, Ar x –OCH_3), 3.86 (s, 3H, Ar x –OCH_3), 6.0 – 6.25 (m, 1H, olefinic proton 'a'), 6.32 (d, *J* = 15.8 Hz, 1H, olefinic proton "b'), 6.7 – 7.0 (m, 3H, ArH). TOF MS ES: 179 (M + H). IR(KBr) cm^{-1} : 3000 - 2800 (methyl, methylenes and methines), 1634 (>C=C<),1600(ArH), 1250 - 1060 (C-O stretch, ether linkage); Molecular formula $C_{11}H_{14}O_2$. Pure viscous mass (0.89 gms, 82 %). Anal. Calcd. for $C_{11}H_{14}O_2$: C 74.13; H 7.92; O 17.95. Found C 74.05; H 7.88; O 18.10;

^{1}H NMR Analysis (ppm) : It gives information regarding structure of a molecule.The signal resonating at 1.84 ppm appearing as a doublet with *J* = 7.6 Hz integrating for 3 protons accounting for terminal methyl from isoeugenol moiety. Peak at 3.84 ppm appearing as a singlet integrating for 3 protons accounting for -OCH_3 group. Such deshielding is due to attachment of methyl group to hetero atom, in this case it is oxygen. The signal resonating at 3.86 ppm appearing as a singlet integrating for 3 protons accunting for -OCH_3 from isoeugenol moiety. The signal resonating between 6.00 - 6.25 ppm apearing as a multiplet integrating for single proton accounts for olefinic proton 'a' from isoeugenol moiety. The peak at 6.32 ppm appeared as a doublet with *J* = 15.8 Hz integrating for single proton accounts for olefinic proton. This deshielding wrt former is due to anisotropic effect of benzene ring (ring current) as well as attached to elecronegativity of the double bond.The signal resonating between 6.7 - 7.0 ppm appearing as a multiplet integrating for 3 protons accounts for aromatic protons.

TOF MSES : refers to Time-of-Flight Mass Spectrometry (TOF-MS) with an Electrospray Ionization (ESI) source, a powerful analytical technique that separates ions based on their mass-to-charge ratio (m/z) by measuring their flight time, allowing for rapid and accurate identification of molecules, commonly used in proteomics, metabolomics, and drug discovery, with the 'ES' indicating the ESI interface for producing ions from liquids.
It gives molecular ion peak at 179 (M + H) indicating molecular weight to be 178.

IR Analysis (cm-1) : It is a vibrational spectroscopy gives information regarding functional group present in a molecule.
The signals between 3000 - 2800 cm-1 indicating the presence of methyls, methylenes and methines in a compound. The signal at 1634 cm-1indicating the presence of tetrasubstituted

double bond The signal at 1600 cm-1 appeared as a sharp peak indicating the presence of aromatic ring. The signal between 1250 - 1060 cm-1 accounts for C-O stretch indicating the presence of ether linkage.

In original isoeugenol, tertiary phenolic –OH group appears at 3307 cm^{-1}. When etherification is carried out using K_2CO_3 as a base and CH_3I as methylating agent the peak due to tertiary -OH appearing at 3307 disappears and peak between 1250 - 1060 appears for C-O stretch indicating for the presence of ether linkage.

Compound 2 :- 1-ethoxy-2-methoxy-4-[(1*E*)-prop-1-en-1-yl]benzene

^{1}H NMR (400 MHz, $CDCl_3$) δppm : 1.45 (t, *J* = 7.0 Hz, 3H, from $–OCH_2CH_3$ ethyl bromide moiety), 1.86 (d, 3H, *J* = 6.7 Hz, terminal methyl from isoeugenol moiety), 3.88 (s, 3H, Ar x $–OCH_3$), 4.025 (q, *J* = 6.8 Hz, 14Hz, 2H, from $–OCH_2CH_3$ ethyl bromide moiety), 6.0 – 6.2 (m, 1H, olefinic proton 'a'), 6.33 (d, *J* = 15.6 Hz, 1H, olefinic proton 'b'), 6.7 – 7.0 (m, 3H, ArH). IR(KBr) cm-1 : 3000 - 2800 (methyl, methylenes and methines), 1633 (>C=C<), 1598(ArH), 1250 - 1060 (C-O stretch, ether linkage); TOF MS ES: 193 (M + H). Molecular formula $C_{12}H_{16}O_2$. Pure viscous mass (0.913 gms, 78 %). Anal. Calcd. for $C_{12}H_{16}O_2$: C 74.97; H 8.39; O 16.64. Found C 74.90; H 8.35; O 16.76;

Compound 3 :- 2-methoxy-4-[(1*E*)-prop-1-en-1-yl]-1-propoxybenzene

^{1}H NMR (400 MHz, $CDCl_3$) δppm : 1.03 (t, *J* = 7.3 Hz, 3H, terminal methyl from n-propylbromide moiety), 1.7 – 2.0 (m, 2H, $-CH_2$ from n-propylbromide moiety), 1.86 (d, *J* = 8.6 Hz, 3H, terminal methyl from isoeugenol moiety), 3.87 (s, 3H, Ar x $–OCH_3$), 3.96 (t, *J* = 7.9 Hz, 2H, $–OCH_2$ from n-propyl bromide moiety), 6.0 – 6.25 (m, 1H, olefinic proton 'a'), 6.33 (d, *J* = 15.8 Hz, 1H, olefinic proton 'b'), 6.7 – 7.0 (m, 3H, ArH). IR(KBr) cm-1 : 3000 - 2800 (methyl, methylenes and methines), 1634 (>C=C<), 1600 (ArH), 1250 - 1060 (C-O stretch, ether linkage); TOF MS ES: 207 (M + H). Molecular formula $C_{13}H_{18}O_2$. Anal. Calcd. for $C_{13}H_{18}O_2$: C 75.69; H 8.80; O 15.51. Found C 75.60; H 8.35; O 16.76;

Compound 4 :- 2-methoxy-4-[(1*E*)-prop-1-en-1-yl]-1-(prop-2-en-1-yloxy)benzene

^{1}H NMR (400 MHz, $CDCl_3$) δppm : 1.85 (d, *J* = 7.8 Hz, 3H, terminal methyl from isoeugenol moiety), 3.86 (s, 3H, Ar x $–OCH_3$), 4.58 (d, *J* = 7.5 Hz, 2H, $-OCH_2$ from allyl bromide moiety), 5.32 (dd, *J* = 15.0 Hz, 2H, $=CH_2$ from allyl bromide moiety), 5.9 – 6.2 (m, 1H, olefinic proton 'a'), 6.32 (d, *J* = 15.6 Hz, 1H, olefinic proton 'b'), 6.7 – 7.0 (m, 3H, ArH). IR(KBr) cm-1 : 3000 - 2800 (methyl, methylenes and methines), 1634 (>C=C<),1600 (ArH), 1250 - 1060 (C-O stretch, ether linkage); TOF MS ES : 205 (M + H).

Molecular formula $C_{13}H_{16}O_2$. Anal. Calcd. for $C_{13}H_{16}O_2$: C 76.44; H 7.90; O 15.67. Found C 76.40; H 7.84; O 15.70;

Compound 5 :- 1-butoxy-2-methoxy-4-[(1*E*)-prop-1-en-1-yl]benzene

^{1}H NMR (400 MHz, $CDCl_3$) δppm : 0.97 (t, *J* = 7.9 Hz, 3H, terminal methyl from n-butyl bromide moiety), 1.4 – 1.6 (m, 2H, -CH_2 from n-butyl bromide moiety), 1.7 – 2.0 (m, 2H, -CH_2 from n-butyl bromide moiety), 1.90 (d, *J* = 7.3 Hz, 3H, terminal methyl from isoeugenol moiety), 3.87 (s, 3H, Ar x –OCH_3), 4.0 (t, *J* = 7.3 Hz, 2H, –OCH_2 from n-butyl bromude moiety), 6.0 – 6.2 (m, 1H, olefinic proton 'a'), 6.33 (d, *J* = 15.8 Hz, 1H, olefinic proton "b'), 6.7 – 7.0 (m, 3H, ArH); IR(KBr) cm-1 : 3000 - 2800 (methyl, methylenes and methines), 1634 (>C=C<), 1600 (ArH), 1250 - 1060 (C-O stretch, ether linkage); TOF MS ES : 221 (M + H). Molecular formula $C_{14}H_{20}O_2$. Anal. Calcd. for $C_{14}H_{20}O_2$: C 76.33; H 9.15; O 14.52. Found C 76.28; H 9.12; O 14.60;

The most significant features of this methodology are (a) good accessibility of the reagent and its stability (b) a stoichiometric amount of reagent can be used by direct weighing, avoiding 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 (h) less expensive and (i) very simple reaction work up with avoidance of by-product. The aforesaid protocol thus provides an improved procedure for the synthesis of useful hybrid derivatives having important pharmaceutical, agricultural and other physicochemical properties.

Chromatographic system : The crude reaction mixtures were purified by extensive column, radial and preparative thin layer chromatography techniques to get desired ether derivatives which were unambiguously characterized by ^{1}H NMR, IR, mass and elemental analysis.

BIOLOGICAL ACTIVITY:

Antibacterial Activity using agar diffusion method[10,11] :- Conc 100 µm

The synthesized molecules were screened for their antibacterial activity using agar diffusion method at 100 µm concentration against Gram positive (*Staphylococcus aureus*) and Gram negative (*Escherichia coli*) bacterial species qualitatively. The results of the antibacterial activities are summarized in Table 1.

Table 1: Antibacterial Activity Results.

Sr. No	Compound No.	Antibacterial Activity	
		Against Gram - ve bacteria species (*Escherichia coli*)	**Against Gram + ve bacterial species (*Staphylococcus aureus*)**
1	Isoeugenol	+	+
2	Standard Drug Ampicillin	+	+
3	I	-	-
4	II	-	-
5	III	-	-
6	IV	+	-
7	V	-	+

CONCLUSION:

The ether derivatives of isoeugenol were prepared by cost effective industry viable method using the principles of Green chemistry. This is the cheapest way to prepare ether derivatives as raw maerials were very cheap, easily available and work procedures were simple for scale up purpose unlike $NaNH_2$ / NaH / nBuLi which requires absolutely dry conditions and special attention.

The above results shows that the base molecule, isoeugenol has antibacterial activity against both the bacterial cultures. Its ether derivatives *viz.* IV and V were active against *Escherichia coli* (Gram negative bacteria) and *Staphylococcus aureus* (Gram positive bacteria) respectively. Thus, unsaturated side chain and long side chain ether derivatives (IV and V) 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.

Future Path:

1. Few more NCE's having unsaturated side chain and long carbon side chain were going to be prepared.
2. Dose dependent study of selected candidates
3. Screen these pure NCE's for different biological assays having better understanding of structure activity relationship.

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