ISSN PRINT 2319 1775 Online 2320 7876

3.3.2 (22-23)

Research paper

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 10, 2022

10

ESTER DERIVATIVES OF EUGENOL AS POTENTIAL ANTIBACTERIAL AGENT

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ABSTRACT

Eugenol (4-allyl-2-methoxyphenol), belonging to phenylpropanoid class of naturally occurring phenols, is well known material for its wide use in dentistry. Beside this, it displayed a wide variety of biological activities including antipyretic, antioxidant, antifungal, analgesic and neuroprotective properties. However, its mechanism of biological action is yet to be discovered and several derivatives of eugenol have been synthesized earlier to augment their valuable bioactive properties. We felt to exploit the presence of hydroxy group in eugenol in making ester derivatives to compare their biological action with eugenol. Accordingly, six ester derivatives of eugenol were synthesized with aromatic acids using DCC/DMAP/pyridine methodology in moderate to good yields and used them in the study of antibacterial activity against Gram-positive and Gram-negative cultures. Few of them displayed promising antibacterial activity.

Keywords: Eugenol, antibacterial, fungicidal, ^{1}HNMR, hybrid molecules, TOFMS ES, elemental analysis, Gram + ve, Gram – ve etc.

INTRODUCTION

Eugenol, an allyl substituted guaicol, is present in variety of naturally occurring essential oils extracted from several plants belonging to the Lamiaceae, Lauraceae, Myrtaceae, and Myristicaceae families. It is also one of the major constituents of clove oil and is largely used in both foods and cosmetics as a flavoring agent. A large number of reports disclosed its beneficial effects on human health.

The aim of this review is to analyze scientific data from the main published studies describing the antibacterial and antifungal activities of eugenol targeting different kind of microorganisms, such as those responsible for human infectious diseases, diseases of the oral cavity, and food-borne pathogens. This article also reports the effects of eugenol on multi-drug resistant microorganisms. On the basis of this collected data, eugenol represents a very interesting bioactive compound with broad spectrum antimicrobial activity against both planktonic and sessile cells belonging to food-decaying microorganisms and human pathogens.

Eugenol is a member of the phenylpropanoids class of phenolic natural product. It is a clear to pale yellow oil extracted from certain essential oils especially from clove oil, nutmeg, cinnamon, basil and bay leaf. Eugenol is responsible for the aroma of cloves. It is the main component in the essential oil extracted from cloves, comprising 72 – 90 % of the total. It is partially soluble in water and soluble in most of the common organic solvents.

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. Phenolic compounds are also important components of the human diet due to their potential antioxidant activity[1]. Eugenol has been used as anticancer agent to diminish the oxidative stress induced tissue damage which is the root cause of chronic diseases such cancer[2-5]. It has also been used as ingradient in perfumeries, flavorings, essential oils and in medicine as a local antiseptic and anesthetic[6]. It was used in the production of isoeugenol for the manufacture of vanillin, though most vanillin is now produced from phenol or from lignin. Eugenol can be combined with zinc

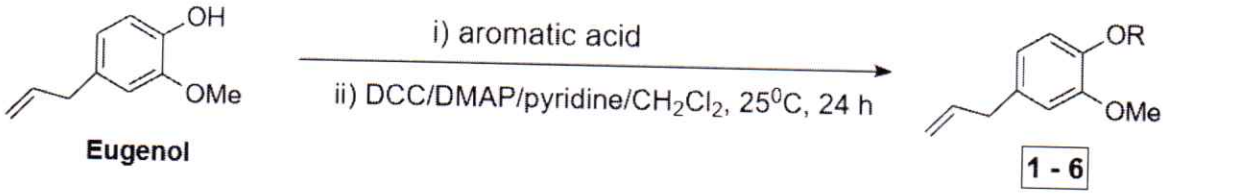
ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 10, 2022

oxide to form a material - known as zinc oxide eugenol - which has restorative and prosthodontic applications in dentistry[7]. Eugenol derivatives or methoxyphenol derivatives in wider classification are used in perfumery and flavoring. They are used in formulating insect attractants and UV absorbers, analgesics, biocides, and antiseptics. It can be used to reduce the presence of *Listeria monocytogenes* and *Lactobacillus sakei* in food[8]. They are also used in manufacturing stabilizers and antioxidants for plastics and rubbers. Attempts have been made to develop eugenol derivatives for intravenous injection, such as propanidid and G.29.505. The latter produced unacceptable side effects around the site of injection in many patients[9]. It is one of many compounds that is attractive to males of various species of orchid bees, who apparently gather the chemical to synthesize pheromones; it is commonly used as bait to attract and collect these bees for study[10]. It also attracts female cucumber beetles[11]. Clove oil is growing in popularity as an anaesthetic for use on aquarium fish as well as on wild fish when sampled for research and management purposes[12,13] where, readily available over-the-counter from pharmacies, it may be a humane method to euthanise sick and diseased fish either by direct over-dose or to induce sleep before an overdose of ethanol.[14]. It is also used in some mousetraps[15] and kills certain human colon cancer cell lines *in vitro*[16]. In the present study, we are diversifying eugenol to its ester 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 disease domain.

RESULTS AND DISCUSSION

Plant derived phenolic secondary metabolites are well known to display various interesting antioxidant activities such as resveratrol and flavonoids. Preliminary study on biological activity of eugenol revealed its potential as antioxidant and anti-inflammatory agents. Recent report disclosed its activity against fungi and a wide range of gram-negative and gram-positive bacteria. The mechanism of their biological action is yet to be established and needs further detailed investigation. Keeping this in view we felt that ester derivative (devoid of phenolic OH group) of eugenol may be used as interesting candidates to compare their potential against bacteria as compared with that of eugenol itself. Accordingly, several aromatic esters of eugenol were prepared following a classical methodology (DCC/DMAP/pyridine) using aromatic acid. The synthesized ester derivatives of eugenol were used in the study on antibacterial activity against gram-positive and gram-negative bacteria.

Scheme 1



Eugenol

1 - 6

Ester derivatives of eugenol

Table 1: Synthesized ester derivatives of eugenol.

ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 10, 2022

Compound No.	R
1	3,4-dimethoxybenzoyl
2	3-methoxy-4-ethoxybenzoyl
3	4-nitrobenzoyl
4	3,4,5-trimethoxybenzoyl
5	4-methoxy cinnamoyl
6	3,5-bis(trifluoromethyl)benzoyl

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.

MATERIALS AND METHODS

Chemicals used were of laboratory grade. The progress of the reactions were monitored by TLC on aluminium-backed silica plate visualized by UV-light. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz and 100 MHz spectrometer respectively in $CDCl_3$. Chemical shifts were recorded in parts per million down field from tetramethylsilane (TMS). Mass spectra were recorded on a TOF MS-ES mass spectrometer. Elemental analysis was carried out on a Thermo finnigan, Flash EA 1112 series, Italy.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 400 MHz & ^{13}C NMR spectra were recorded at 100 MHz on a Varian spectrometer and Mass spectra on TOF MS ES mode. Elemental analysis was carried out on a Thermo finnigan, Flash EA 1112 series, Italy.

Chromatographic Procedure

Column Chromatography : For column chromatography 100 – 200 mesh Acme grade silica gel was used. The crude reaction mixture was concentrated under reduced pressure to yield thick mass which was preadsorbed on silica gel and purified by column chromatography with gradient elution with ethyl acetate-petroleum ether mixture. The fractions having similar "R_f" values were pooled together, concentrated and finally characterized 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 distilled water (105 ml). For elution, gradually gradient elution with EtOAc- pet ether mixture was used.

ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 10, 2022

General procedure for the synthesis of eugenol esters* (1-6) *on 0.006090 mol scale:

To a solution of eugenol (1 g, 0.006090 mol, 1.0 eq) in dichloromethane (30 mL) was added pyridine (0.25 mL, 0.003045 mol, 0.5 eq.), DMAP (0.037 g, 0.0003045 mol, 0.05 eq.), DCC (1.5 g, 0.007308 mol, 1.3 eq.) and aromatic acid (1.33 g, 0.007308 mol, 1.3 eq.) and the mixture was stirred at ambient temperature (**Scheme 1**) (insoluble by product dicyclohexylurea precipitated out of the reaction mixture and floats on the solvent surface as the reaction progressed). After 24 h, tlc showed complete consumption of eugenol when the reaction mixture was filtered through a Buchner funnel to get rid of dicylohexylurea. The mother liquor was then concentrated under reduced pressure to a minimum, pre-adsorbed on silica gel and purified by column chromatography (SiO_2, 100 – 200 mesh) with gradient elution with ethyl acetate - petroleum ether mixture to yield pure compounds in 75 – 80 % yield. The purified compounds (**1-6**) were unambiguously characterized by ^1H, ^{13}C NMR, elemental analysis and mass spectral data.

Characterization of compounds 1 – 6 :-

(2-Methoxy-4-prop-2-enylphenyl)-3,4-dimethoxybenzoate (**1**)

Viscous oil (0.88 g). ^1H NMR (400 MHz, $CDCl_3$): δ 3.41 (d, J = 6.6 Hz, 2H, benzylic –CH_2), 3.81 (s, 3H, Ar–OCH_3), 3.96 (s, 3H, Ar–OCH_3), 3.97 (s, 3H, Ar–OCH_3), 5.0 – 5.2 (m, 2H, =CH_2 , olefinic protons H_a), 5.9 – 6.1 (m, 1H, =C*H*-, olefinic proton H_b), 6.6 – 8.0 (m, 6H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.36 (benzylic –CH_2), 56.18 (1 x Ar-OCH_3), 56.24 (1 x Ar-OCH_3), 56.37 (1 x Ar-OCH_3), 110.54 (=CH_2), 112.71 (=C*H*-), 113.1 (*ArC*), 116.36 (*ArC*), 120.97 (*ArC*), 122.13 (Ar*C*), 122.90 (Ar*C*), 124.77 (ArC), 137.32 (quaternary, >C<), 138.51 (quaternary, >C<), 139.17 (quaternary, ArC-O), 148.93 (quaternary, ArC-O), 151.40 (quaternary, ArC-O), 153.63 (quaternary, ArC-O), 164.88 (quaternary, >C=O); IR (NaCl) cm^{-1} : 1728 (ester >C=O), 1602 (aromatic); TOF MS-ES: 351 (M + Na). Analysis: Calculated C 69.50, H 6.14 %; Found C 69.54, H 6.10 %.

(2-Methoxy-4-prop-2-enylphenyl)-4-ethoxy-3-methoxybenzoate (**2**)

Viscous oil (0.86 g). ^1H NMR (400 MHz, $CDCl_3$): δ 1.51 (t, J = 7.0 Hz, 3H, terminal CH_3 of –OCH_2CH_3), 3.41 (d, J = 6.6 Hz, 2H, benzylic –CH_2), 3.81 (s, 3H, Ar–OCH_3 of eugenol), 3.95 (s, 3H, Ar x –OCH_3 of vanillic acid), 4.19 (q, J = 2.0, 13.9 Hz, 2H of –OCH_2CH$_3$ group), 5.0 – 5.2 (m, 2H, =CH_2, olefinic protons H_a), 5.9 – 6.1 (m, 1H, =CH-, olefinic proton H_b), 6.8 – 7.2 (m, 3H, Ar*H* of eugenol), 6.7 – 8.0 (m, 6H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.88 (s, 3H, -CH_3, terminal –CH_3 from –OCH_2CH_3 group), 40.36 (benzylic –CH_2), 56.07 (-OCH_2), 56.26 (Ar-OCH_3), 64.69 (Ar-OCH_3), 111.47 (=CH_2), 112.99 (=C*H*-), 113.06 (Ar*C*), 116.35 (quaternary, >*C*<), 120.96 (Ar*C*), 121.86 (Ar*C*), 122.91 (Ar*C*), 124.68 (Ar*C*), 137.30 (quaternary, >*C*<), 138.52 (Ar*C*), 139.15 (q, Ar*C*-O), 149.05 (quaternary, Ar*C*-O), 151.41 (quaternary, Ar*C*-O), 153.03 (quaternary, Ar*C*-O), 164.93 (quaternary, >*C*=O); IR (NaCl) cm^{-1} : 1730 (ester >C=O), 1604 (aromatic); TOF MS-ES: 365 (M + Na); Analysis: Calculated C 70.16, H 6.48 %; Found C 70.20, H 6.51 %.

(2-Methoxy-4-prop-2-enylphenyl)-4-nitrobenzoate (**3**)

Viscous oil (0.90 gms); ^1H NMR (400 MHz, $CDCl_3$): δ 3.41 (d, J = 6.6 Hz, 2H, benzylic –CH_2), 3.81 (s, 3H, Ar x –OCH_3), 5.0 – 5.2 (m, 2H, =CH_2, olefinic protons H_a), 5.9 – 6.1 (m, 1H, =C*H*-, olefinic proton H_b), 6.8 – 7.2 (m, 3H, Ar*H* of eugenol), 8.2 – 8.4 (m, 4H, Ar*H* of 4-nitro benzoic acid); ^{13}C NMR (100 MHz,

ISSN PRINT 2319 1775 Online 2320 7876
Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 10, 2022

$CDCl_3$): δ 40.34 (benzylic $-CH_2$), 56.01 (1 x Ar-OCH_3), 113.08 ($=CH_2$), 116.57 (=CH-), 121.0 (2 x Ar*C*), 122.56 (quaternary, >*C*<), 123.87 (2 x Ar*C*), 131.62 (Ar*C*), 135.15 (Ar*C*), 137.09 (quaternary, >*C*<), 137.23 (quaternary, >*C*<), 137.97 (Ar*C*), 139.90 (quaternary, Ar*C*-O), 151.02 (quaternary, Ar*C*-O), 163.27 (quaternary, >*C*=O); IR (NaCl) cm^{-1} : 1729 (ester >C=O), 1600 (aromatic); TOF MS-ES: 336 (M + Na). Analysis: Calculated C 65.17, H 4.83, N 4.47 %; Found C 65.14, H 4.80, N 4.50 %.

(2-Methoxy-4-prop-2-enylphenyl)-3,4,5-trimethoxybenzoate (**4**)

Viscous oil (0.83 gms); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.41 (d, *J* = 6.6 Hz, 2H, benzylic $-CH_2$), 3.81 (s, 3H, Ar x $-OCH_3$ from eugenol moiety), 3.94 (s, 9H, 3 x Ar-OCH_3 of gallic acid), 5.0 – 5.2 (m, 2H, $=CH_2$, olefinic protons H_a), 5.9 – 6.1 (m, 1H, =C*H*-, olefinic proton H_b), 6.8 – 7.1 (m, 3H, Ar*H* of eugenol), 7.47 (s, 2H, Ar*H* of gallic acid); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.36 (benzylic $-CH_2$), 56.17 (1 x Ar-OCH_3), 56.46 (1 x Ar-OCH_3), 56.58 (1 x Ar-OCH_3), 61.25 (1 x Ar-OCH_3 of eugenol), 107.76 ($=CH_2$), 113.08 (=*C*H-), 116.41 (quaternary, >*C*<), 120.99 (>CH-, Ar*C*), 122.84 (>CH-, Ar*C*), 124.63 (>CH-, Ar*C*), 137.29 (q, >*C*<), 138.40 (>CH-, Ar*C*), 139.34 (>CH-, Ar*C*), 142.81 (quaternary, Ar*C*-O), 151.32 (quaternary, Ar*C*-O), 153.23 (quaternary, 3 x Ar*C*-O), 164.72 (quaternary, >*C*=O); IR (NaCl) cm^{-1} : 1727 (ester >C=O), 1605 (aromatic); TOF MS-ES: 381 (M + Na); Analysis: Calculated C 63.03, H 6.19 %; Found C 63.07, H 6.22 %.

(2-Methoxy-4-prop-2-enylphenyl)-(*E*)-3-(4-methoxyphenyl)prop-2-enoate (**5**)

Viscous oil (0.85 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.39 (d, *J* = 6.8 Hz, 2H, benzylic $-CH_2$), 3.82 (s, 3H, Ar–OCH_3), 3.85 (s, 3H, Ar–OCH_3), 5.0 – 5.2 (m, 2H, $=CH_2$, olefinic protons H_a), 5.9 – 6.1 (m, 1H, =CH-, olefinic proton H_b), 6.53 (d, *J* = 16.0 Hz, 1H, *trans* coupling), 6.7 – 7.6 (m, 7H, ArH), 7.82 (d, *J* = 16.0 Hz, 1H, *trans* coupling). ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.37 (benzylic $-CH_2$), 56.1 (Ar-OCH_3), 56.19 (Ar-OCH_3), 112.98 ($=CH_2$), 114.60 (Ar*C*), 114.65 (Ar*C*), 116.39 (=*C*H-), 120.95 (>*C*H-, Ar*C*), 122.91 (=*C*H-), 127.28 (=*C*H-), 130.21 (>*C*H-, Ar*C*), 130.30 (Ar*C*), 137.31 (quaternary, >*C*<), 138.30 (quaternary, >*C*<), 139.12 (>*C*H-, Ar*C*), 146.39 (>*C*H-, Ar*C*), 146.43 (quaternary, Ar*C*-O), 151.30 (quaternary, Ar*C*-O), 161.86 (quaternary, Ar*C*-O), 165.73 (quaternary, >*C*=O); IR (NaCl) cm^{-1} : 1726 (ester >C=O), 1601 (aromatic); TOF MS-ES: 357 (M + Na). Analysis: Calculated C 74.06, H 6.21 %; Found C 74.10, H 6.25 %.

(2-Methoxy-4-prop-2-enylphenyl)-3,5-bis(trifluoromethyl)benzoate (**6**)

Viscous oil (0.85 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.43 (d, *J* = 6.6 Hz, 2H, benzylic $-CH_2$ group), 3.82 (s, 3H, Ar x $-OCH_3$), 5.10 – 5.2 (m, 2H, $=CH_2$, olefinic protons H_a), 5.9 – 6.1 (m, 1H, =C*H*-, olefinic proton H_b), 6.83 (d, *J* = 1.1.Hz, 1H, Ar*H*, of eugenol), 6.85 (d, *J* = 2.8 Hz, 1H, Ar*H*), 7.08 (d, *J* = 8.0 Hz, 1H, Ar*H*), 8.13 (s, 1H, Ar*H* of 3,5-bis-[trifluoromethyl] benzoic acid moiety), 8.66 (s, 2H, Ar*H*, of 3,5-bis-[trifluoromethyl] benzoic acid moiety). ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.35 (benzylic $-CH_2$), 56.1 (Ar-OCH_3), 113.064 (=*C*H-), 116.59 (=*C*H-), 121.04 (>*C*H-, ArC), 121.74 (>*C*H-, ArC), 122.44 (>*C*H-, ArC), 124.45 (>*C*H-, ArC), 126.96 (>*C*H-, ArC), 130.59 (quaternary, ArC), 131.98 (>*C*H-, ArC), 132.39 (quaternary, 2 x CF_3), 137.16 (quaternary, Ar*C*), 137.77 (quaternary, 2 x Ar-CF_3), 140.03 (quaternary, Ar*C*-O), 150.95 (quaternary, Ar*C*-O), 162.47 (quaternary,

ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 10, 2022

>C=O); IR (NaCl) cm^{-1} : 1725 (ester >C=O), 1600 (aromatic); MS-ES: 427 (M + Na). Analysis: Calculated C 56.44, H 3.49 %; Found C 56.47, H 3.53 %.

Biological Activity:

Antibacterial Activity using ditch plate method.[17]

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 technique to screen/test compounds/drugs for their potential as anti-microbial agents. 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 h. 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 following Table 3.

Table 2: Antibacterial Activity Results.

SAMPLE NO.	ACTIVE AGAINST
Eugenol	*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]
3	*Staphylococcus .aureus* [Gram Positive] *Proteus vulgaris* [Gram negative] *Salmonella typhi* [Gram negative] *Escherichia coli* [Gram negative]
6	*Staphylococcus aureus* [Gram positive] *Salmonella typhi* [Gram negative] *Klebsiella pneumoniae* [Gram negative] *Corynebacterium diphtheriae* [Gram positive] *Escherichia coli* [Gram negative]

All the synthesized 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

ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 10, 2022

activity was determined using cup plate agar diffusion method[17] 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** showed moderate antibacterial activity against all bacterial cultures where as its derivatives *viz.* **3** and **6** showed moderate activity against *S. aureus*, *S. typhi*, *P. vulgaris* and *E. coli*. Thus 3, 6 derivatives having electron withdrawing groups such as nitro, fluoro 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.

CONCLUSION

The structural diversity and the pronounced antibacterial activities encountered with the ester derivatives of eugenol as hybrid material suggests that a library synthesis of these hybrid molecules may help in the development of more potent therapeutic drug using combinatorial chemistry approach.

ACKNOWLEDGEMENT

One of the authors Ms. Anamika Singh thanks Dr. Vijay D. Gangan, Research Guide and Head of the Division, Reena Mehta College of Arts, Science, Commerce and Management studies for suggesting the problem and providing constant valuable guidance throughout the course of the research work and allowing to avail laboratory facilities.

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