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Methyl Vanillate Ether Derivatives as Future Potential Drug

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ABSTRACT

Vanillic acid (4-hydroxy-3-methoxybenzoic acid) is a dihydroxybenzoic acid derivative used as a flavouring agent. It is used in the synthesis of various active pharmaceutical ingredients such as Etamivan, Modecainide, Brovanexine, Vanitiolide, Vanyldisulfamide etc. In this paper, novel ether derivatives of vanillic acid were synthesized and tested for potential antibacterial activity. This combinatorial synthesis of novel vanillic acid ether derivatives can be a useful approach to generate potent chemotherapeutic agents in developing new drug candidates.

Keywords : Vanillic Acid, IR, [1]HNMR, TOF MS, DCC, DMAP, Antibacterial, Ditch-Plate Method.

I. INTRODUCTION

Phenolic phytochemicals are known to exhibit anti-inflammatory, antioxidant, anticarcinogenic, antidiabetic, antiatherosclerosis and immunomodulatory activities in animals[1,2]. These are mostly polyphenols known as secondary plant metabolites, present in plants and trees. Polyphenols are commonly divided into flavonoids and the hydroxyl cinnamic acids[3-5]. Vanillic acid is a naturally occurring active compound having antimicrobial, anti-inflammatory and antioxidant / anticancer properties, we thought of synthesizing compounds with novel ether, ester and hybrid derivatives of Vanillic acid wherein Vanillic acid would be etherified, esterified and hybridized with various other compounds and to check whether these compounds possess above biological activities[6-19]. 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.

II. METHODS AND MATERIAL

Materials: Chemicals used were of a laboratory grade. The reactions were monitored by TLC on aluminium-backed silica plate visualized by UV-light.

Experimental

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. [1]H NMR spectra were recorded on a Varian 200 MHz

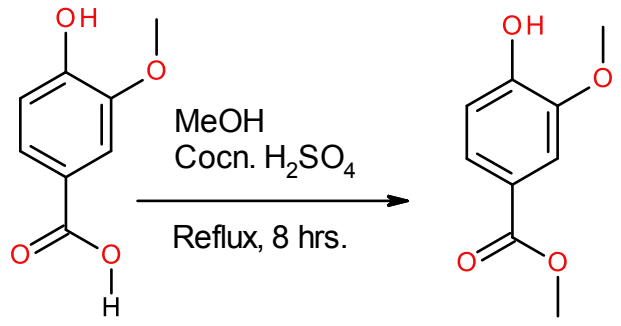
spectrometer in $CDCl_3$. Chemical shifts were recorded in parts per million down fields from tetramethyl silane. Mass spectra were recorded on a TOF MS ES mass spectrometer. Elemental analyses were carried out as a percentage on a Thermo finnigan, Flash EA 1112 series, Italy.

III. RESULTS AND DISCUSSION

Preparation of methyl vanillate: - It was prepared by refluxing 50 gms of vanillic acid with 500 ml of LR methanol using 2 ml of conc. sulphuric acid as a catalyst for 8 hrs. The progress of the reaction was monitored by TLC for the completion of reaction.

Work up:- The reaction mixture concentrated under reduced pressure to minimum and to that 400 ml of dichloromethane + 400 ml of water was added. The aqueous layer was extracted successively with dichloromethane (2 x 200 ml). The total organic layer was washed with water (2 X 200 ml), brine (200 ml) and concentrated to yield52.54 gms of methyl vanillate quantitatively (97 % yield).

Reaction Scheme 1:



(1)
Vanillic acid

(2)
Methyl vanillate

The above procedure can be scaled up to get more quantities of methylvanillate.

Methyl-4-hydroxybenzoate (2)

1H NMR (200 MHz, $CDCl_3$) δppm : 3.89 (s, 3H, Ar x-OCH3),3.92 (s, 3H, Ar x–$COOCH_3$ group), 6.26 (brs, 1H, -OH, D2O exchangeable), 6.93 (d, J = 8.4 Hz, 1H, ArH, ortho coupling), 7.53 (d, J = 1.8 Hz, 1H, ArH, meta coupling), 7.63 (dd, J = 8.2 Hz, 1.8 Hz, ArH, 1H, ortho as well as meta coupling).TOF MS ES : 205 (M + Na); Molecular formula $C_9H_{10}O_4$;Off white solid (52.54 gms, 97.0 %);Melting range 64 – 670C; Anal. Calcd. for $C9H_{10}O_4$: C 59.30 %, H 5.50 %, O 35.11%. Found C 59.28 %, H 5.52 %, O 35.10 %;

The methyl vanillate was then subsequently converted to their ether derivatives as mentioned below.

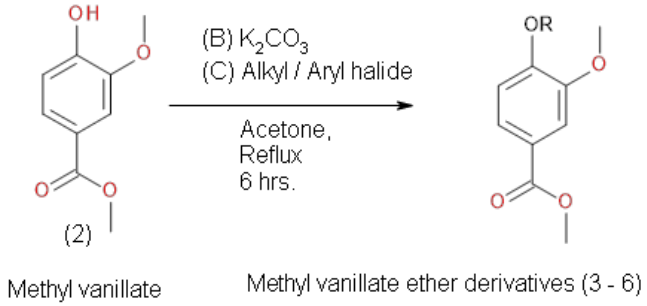
Diversification of methyl vanillate to its ether derivatives (3 - 6) :- These were prepared by following general method as depicted below.

To a stirred solution of [A] (1 eq.) in 50 ml acetone was added [B] (2.5 eq.) and stirring continued at 500 C for the next 30 min. for complete formation of K-salt. To this compound [C] (2 eq.) was added drop wise and stirring continued at reflux temperature for next 6 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 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 - 80 %.

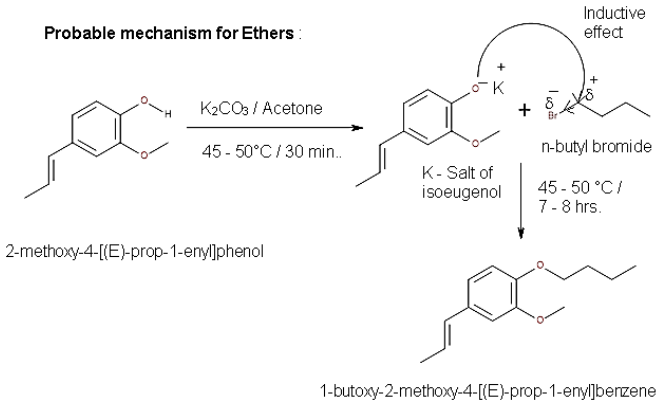
Reaction Scheme 2 :



Methyl vanillate — Methyl vanillate ether derivatives (3 - 6)

Compound No.	R
3	Methyl
4	Propyl
5	Pentyl
6	Hexyl

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



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. The aforesaid protocol thus provides an improved procedure for the synthesis of useful ether derivatives having important pharmaceutical, agricultural and other physicochemical properties.

Characterization of compounds (3 – 6):

methyl 3,4-dimethoxybenzoate (3)

^{1}HNMR($CDCl_3$, 200 MHz) δ ppm :- 3.85 (s, 3H, Ar x –**OCH$_3$**), 3.89 (s, 3H, Ar x –**OCH$_3$**), 3.89 (s, 3H, Ar x –CO**OCH$_3$**), 6.84 (d, J = 8.4 Hz, 1H, ArH), 7.5 (d, J = 1.8 Hz, 1H, ArH, meta coupling), 7.62 (dd, J = 8.2 Hz, 1.8 Hz, ArH, 1H, meta coupling); TOFMS ES : 219 (M + Na); Molecular Formula $C_{10}H_{12}O_4$;Off white solid; Melting Range 59 – 62^{0}C;Elemental Analysis, Calcd: C 61.20 %, H 6.20 %, O 32.6 % Found C 61.23 %, H 6.17 %, O 32.58 %;

methyl 3-methoxy-4-propoxy-benzoate(4)

^{1}HNMR($CDCl_3$, 200 MHz) δ ppm- 1.02 (t, J= 7.8 Hz, 3H, terminal -CH_3 from propyl bromide moiety), 1.83 – 1.94 (m, 2H, 1 x –CH_2 from propyl bromide moiety), 3.88 (s, 3H, AR x -**OCH$_3$**), 3.91 (s, 3H, Ar x -CO**OCH$_3$**), 4.05(t, J= 7.0 Hz, 2H, 1 x -O**CH$_2$** group), 6.87 (d, J = 8.6 Hz, 1H, ArH, ortho coupling), 7.537 (d, J = 2.0 Hz, 1H, ArH, meta coupling), 7.65 (dd, J = 8.4 Hz, 2.0 Hz, 1H, ArH, ortho as well as meta coupling); TOF MS ES: 247 (M + Na); Molecular Formula $C_{12}H_{16}O_4$; Pure viscous mass;Elemental Analysis, Calcd : C 64.30 %, H 7.20 %, O 28.50 % Found C 64.28 %, H 7.21 %, O28.48 %;

methyl 3-methoxy-4-pentoxy-benzoate (5)

^{1}HNMR($CDCl_3$, 200 MHz) δ ppm- 0.89 (t, J= 8.2 Hz, 3H, terminal -CH_3 from pentyl bromide moiety), 1.33 – 1.36 (m, 4H, 2 x –CH_2 from pentyl bromide moiety), 1.7 – 2.0 (m, 4H, 2 x –CH_2 from pentyl bromide moiety), 3.89 (s, 3H, Ar x -**OCH_3**), 3.91 (s, 3H, Ar x -CO**OCH_3**), 4.05 (t, J= 7.0 Hz, 2H, 1 x -O**CH_2** group), 6.87 (d, J = 8.4Hz, 1H, ArH, ortho coupling), 7.54 (d, J = 1.4 Hz, 1H, ArH, meta coupling), 7.64 (dd, J = 8.2 Hz, 1.8 Hz, 1H, ArH, ortho as well as meta coupling); TOF MS ES: 275 (M + Na); Molecular Formula $C_{14}H_{20}O_4$; Pure viscous mass;Elemental Analysis, Calcd : C 66.60 %, H 8.00 %, O 25.40 % Found C 66.58 %, H 8.02 %, O25.38 %;

methyl 4-hexoxy-3-methoxy-benzoate (6)

^{1}HNMR($CDCl_3$,200 MHz) δ ppm- 0.84 (t, J= 8.4 Hz, 3H, terminal -CH_3 from hexyl bromide moiety), 1.2 – 1.6 (m, 6H, 3 x –CH_2 from hexyl bromide moiety), 1.7 – 2.0 (m, 2H, 1 x –CH_2 from hexyl bromide moiety), 3.80 (s, 3H, Ar x -**OCH_3**group), 3.84 (s, 3H, Ar x –CO**OCH_3** group), 4.04(t, J= 7.0 Hz, 2H, 1 x -O**CH_2** group), 6.86 (d, J = 8.6 Hz, 2H, ArH, ortho coupling),7.32 (d, J = 2.0 Hz, 1H, ArH, meta coupling), 7.60 (dd, J = 8.4 Hz, 2.0 Hz, 1H, ArH, ortho as well as meta coupling); TOF MS ES: 289 (M + Na); Molecular Formula $C_{15}H_{22}O_4$; Pure viscous mass;Elemental Analysis, Calcd : C 67.60 %, H 8.30 %, O 24.0 % Found C 67.63 %, H 8.27 %, O23.98 %;

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz on a Varian spectrometer and Mass spectra on TOF MS ES mode. Elemental analysis was carried out as a percentage on a Thermo finnigan, Flash EA 1112 series, Italy.

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

BIOLOGICAL ACTIVITY:

Antibacterial Activity using ditch platemethod[20] :- Conc. 100 µg/ml

The synthesized molecules were screened for their antibacterial activity using ditch plate method at 100 µg/ml concentration against Gram positive (Staphylococcus aureus, *Corynebacterium diphtheria*) and Gram negative (Escherichia coli, *Salmonellatyphi*, *Klebsiellapneumoniae*) 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-microbial. 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 10mm 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 following Table.

SAMPLE NO.	ACTIVE AGAINST
2	*Staphylococcusaureus*[Gram positive] *Salmonellatyphi*[Gram negative] *Klebsiellapneumoniae*[Gram negative] *Corynebacteriumdiphtheriae* [Gram positive] *Escherichiacoli* [Gram negative]
4	*Staphylococcusaureus* [Gram Positive] *Proteusvulgaris* [Gram negative]
5	*Staphylococcusaureus* [Gram positive] *Escherichiacoli* [Gram negative]
6	*Staphylococcusaureus* [Gram positive] *Escherichiacoli* [Gram negative]

The novel ether derivatives of vanillic acid were synthesized by cost effective industry viable process following the principle of green chemistry. The probable mechanism for the formation of ether derivative was also discussed.

The biological activity suggests that the base molecule methyl vanillate have anti-bacterial activity against both the bacterial cultures. Its derivatives *viz.* 4, 5 and 6 were also active against certain Gram + ve and Gram – ve cultures. Thus, ether derivatives of methyl vanillate (4, 5 & 6) having long alkyl side chain 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.

IV.CONCLUSION

The structural diversity and the pronounced biological activities encountered in the vanillicacidether 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 vanillic acid ether derivatives develop new

therapeutic molecules that might result in candidates having better activity.

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