

**SYNTHESIS OF NOVEL *DECYL* DERIVATIVE OF ETHYL  
VANILLATE**

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**ABSTRACT:**

Vanillic acid (4-hydroxy-3-methoxybenzoic acid) is a dihydroxybenzoic acid derivative used as a flavoring agent. It is used in the synthesis of various active pharmaceutical ingredients such as Etamivan, Modecainide, Brovanexine, Vanitilide, Vanyldisulfamide etc. In this paper, novel ester / hybrid derivative of vanillic acid was synthesized. This combinatorial synthesis of novel vanillic ester / hybrid derivative can be a useful approach to generate potent chemotherapeutic agents in developing new drug candidates.

**KEYWORDS:** Vanillic acid, IR, <sup>1</sup>HNMR, TOF MS, DCC, DMAP *etc.*

**INTRODUCTION**

Phenolic phytochemicals are known to exhibit anti-inflammatory, antioxidant, anticarcinogenic, antidiabetic, antiatherosclerosis and immunomodulatory activities in animals<sup>1,2</sup>. These are mostly polyphenols known as secondary plant metabolites<sup>3</sup>, present in plants and trees. Polyphenols are commonly divided into flavonoids and the hydroxyl

cinnamic acids. Vanillic acid is a naturally occurring active compound having antimicrobial, anti-inflammatory and antioxidant / anticancer properties<sup>4-9</sup>. In continuation to our earlier work<sup>10-13</sup>, we thought of synthesizing compound with novel ether, ester and hybrid derivative of Vanillic acid wherein Vanillic acid would be first esterified, etherified, hydrolysed and finally hybridized with various other compounds and to check whether these compounds possess above biological activities. 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

### A. Materials

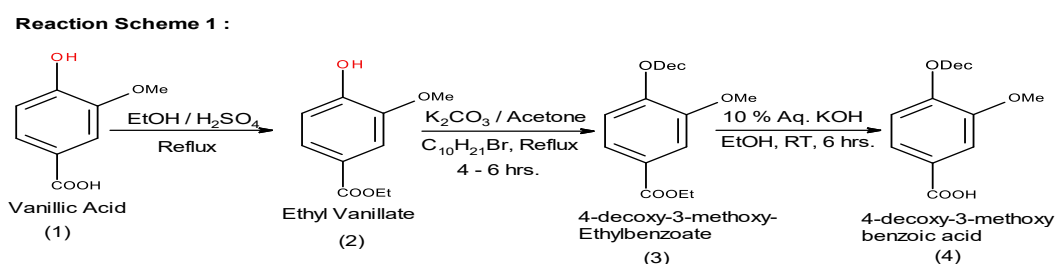
Chemicals used were of a laboratory grade. The reactions were monitored by TLC on aluminium-backed silica plate visualized by UV-light.

### B. 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. <sup>1</sup>H NMR spectra were recorded on a Varian 400 MHz spectrometer in CDCl<sub>3</sub>. 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

Preparation of 3,4-dialkoxy benzoic acids :- Vanillic acid was subjected to esterification (EtOH / Conc. H<sub>2</sub>SO<sub>4</sub>) followed by etherification (K<sub>2</sub>CO<sub>3</sub> / Acetone / C<sub>10</sub>H<sub>21</sub>Br) to yield crude 4-decoxy-3-methoxyethylbenzoate which was purified by column chromatography. This purified ether derivative was subjected to hydrolysis (Aq. KOH / EtOH and then Conc. HCl) to yield 4-decoxy-3-methoxy-benzoic acid respectively.



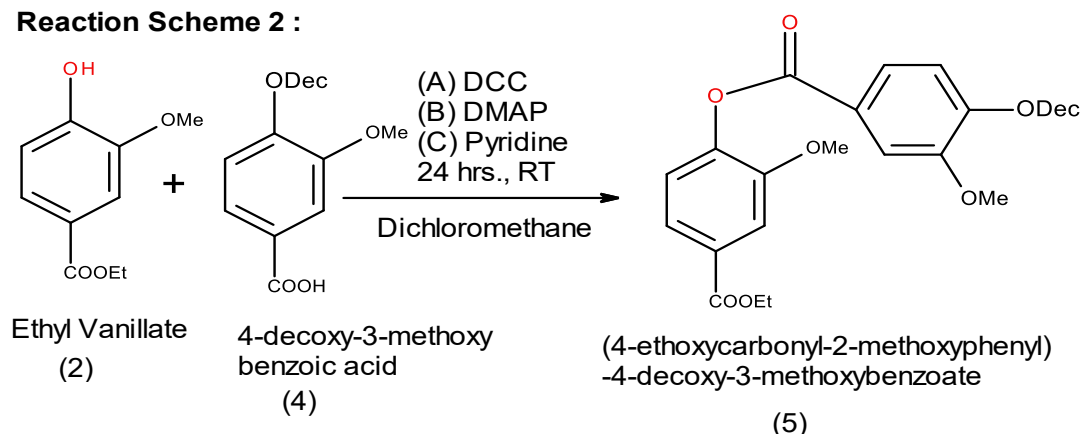
Above 4-decoxy-3-methoxybenzoic acid was then condensed with ethyl vanillate under DCC/DMAP/Pyridine condition to yield hybrid derivative whose structure was unambiguously confirmed by IR,  $^1\text{H}$  NMR, Mass spectroscopy and elemental analysis.

**Synthesis of Hybrid Molecule using compound (2) and (4) :-** It was prepared by following general method as depicted below.

To a stirred solution of ethyl vanillate [A] (1 eq.) in 40 ml dichloromethane was added DCC [A] (1.4 eq.), DMAP [B] (0.05 eq.), pyridine [C] (0.5 eq., 4 drops) and the reaction mixture stirred at room temperature for 5 min. Clear solution of reaction mixture was obtained. To this, compound [B] aromatic / substituted aromatic acid (1.4 eq.) was added and stirring continued at room temperature for next 24 hrs. As the reaction proceeds, urea derivative precipitates out as by product. The progress of the reaction was monitored by TLC for completion of reaction.

Work up :-The reaction mixture filtered through celite bed which get rids of by product urea derivative, wash the cake with 10 ml of DCM. The filtrate was concentrated to minimum, preadsorbed on silica gel (100 – 200 mesh) and purified by column chromatography with increase in concentration of ethyl acetate in petroleum ether. The general yields of these reactions ranges between 70 – 80 %. This is another method of preparing ester derivative and follows green chemistry parameters.

**Reaction Scheme 2 :**



**Compound 1 : (4-ethoxycarbonyl-2-methoxyphenyl)-4-decoxy-3-methoxybenzoate**

Sr. No.	2	4	Synthetic Derivative (5)
1	Ethyl vanillate	4-decoxy-3-methoxybenzoic acid	(4-ethoxycarbonyl-2-methoxyphenyl)-4-decoxy-3-methoxybenzoate

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm : 1.12 (t,  $J = 7.2$  Hz, 3H, terminal methyl from decyl bromide moiety), 1.41 (t,  $J = 7.0$  Hz, 3H, -CH<sub>3</sub> from -COOCH<sub>2</sub>CH<sub>3</sub> group), 1.5 - 2.3 (m, 16H, 8 x -CH<sub>2</sub> from decyl bromide moiety), 3.93 (s, 6H, 2 x Ar-OCH<sub>3</sub> group), 4.06 (t,  $J = 6.9$  Hz, 2H, 1 x -OCH<sub>2</sub> from decyl bromide moiety), 4.36 (q,  $J = 7.0$  Hz, 14 Hz, 2H, -CH<sub>2</sub> from -COOCH<sub>2</sub>CH<sub>3</sub> group), 6.8 – 8.0 (m, 6H, ArH); TOF MS ES: 509 (M + Na); IR (KBr)  $\text{cm}^{-1}$ :- 2930, 2855, 2830 (methyl, methylenes, methines), 1732 – 1725 (2 x ester carbonyl), 1597 (aromatic); Molecular Formula C<sub>28</sub>H<sub>38</sub>O<sub>7</sub>; Off white solid; Melting range 131 – 132<sup>0</sup>C; Elemental Analysis, Calcd.: C 68.60 %, H 7.70 %, O 23.70 %. Found C 68.58 %, H 7.68 %, O 23.73 %;

### 3-methoxy-4-nonoxybenzoic acid(4)

Off white solid; Molecular Formula C<sub>18</sub>H<sub>28</sub>O<sub>4</sub>;  $^1\text{H}$  NMR (DMSO-d<sub>6</sub>, 400 MHz)  $\delta$  ppm : 1.11 (t,  $J = 8.0$  Hz, 3H, terminal methyl from decyl bromide moiety), 1.5 - 2.3 (m, 16H, 8 x -CH<sub>2</sub> from decyl bromide moiety), 3.92 (s, 3H, 1 x Ar-OCH<sub>3</sub> group), 4.07 (t,  $J = 6.8$  Hz, 2H, 1 x -OCH<sub>2</sub> from decyl bromide moiety), 6.8 – 8.0 (m, 3H, ArH), 10.12 (brs, 1H, -OH from -COOH group, D<sub>2</sub>O exchangeable); TOF MS ES: 331 (M + Na); IR (KBr)  $\text{cm}^{-1}$ :- 2929, 2854, 2873 (methyl, methylene, methines), 2600 - 2800 (-OH stretching due to -COOH group), 1690 (acid carbonyl), 1598 (aromatic);

**$^1\text{H}$  NMR Analysis** : The peak resonating at 1.12 ppm appeared as a triplet integrating for three protons corresponding to terminal methyl from decyl bromide moiety. The peak resonating at 1.41 ppm appeared as a triplet integrating for three protons corresponding to methyl group from ethyl vanillate moiety. The signals at 1.5 - 2.3 ppm appeared as a multiplet integrating for sixteen protons from decyl bromide moiety. The signal at 3.93 ppm appeared as a singlet integrating for six protons corresponding to 2 x -OCH<sub>3</sub> group from ethyl vanillate and 4-decoxy vanillic acid moiety. The signal resonating at 4.06 ppm integrating for two protons from decyl bromide moiety. This deshielding can be explained as -CH<sub>2</sub> group from decyl bromide moiety is bonded to electronegative oxygen atom from vanillic acid moiety. The signal at 4.36 ppm appeared as a quartet integrating for two protons from ethyl vanillate moiety. This deshielding is also due to attachment of -CH<sub>2</sub> group to two electronegative oxygen atom from ester group. The region 6 – 8 ppm integrating for six protons corresponding to aromatic protons from ethyl vanillate and 4-decoxy vanillic acid respectively.

**IR Analysis** : In original ethyl vanillate, tertiary phenolic -OH group appears at 3307  $\text{cm}^{-1}$ . Similarly, in original 4-decoxy vanillic acid, the acid carbonyl appears at 1690  $\text{cm}^{-1}$  as sharp peak. However, when condensation reaction is carried out between ethyl vanillate and 4-

decoxy vanillic acid using DCC as a dehydrating agent, the peak at  $3307\text{ cm}^{-1}$  corresponding to tertiary phenolic  $-\text{OH}$  and acid carbonyl peak at  $1690\text{ cm}^{-1}$  disappears and peak due to ester carbonyl at  $1732\text{ cm}^{-1}$  appears with the elimination of water molecule suggesting that reaction takes place at this position resulting in the formation of desired ester / hybrid molecule. The peaks appearing at  $2929 - 2873\text{ cm}^{-1}$  corresponding to methyls, methylenes and methines from both the aromatic moieties. The peak at  $1597\text{ cm}^{-1}$  accounts for the presence of aromatic moiety.

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 vapours 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:**

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 'rf' 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 (95 : 5) was used as the solvent system.

**CONCLUSION:** The novel derivative of ethyl vanillate was prepared by cost effective industry viable method using DCC as a dehydrating agent. In depth analysis of this compound through structure activity relationship studies would provide further insight and can be an interesting topic of future studies.

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