

# A Review on the Vanillin derivatives showing various Biological activities

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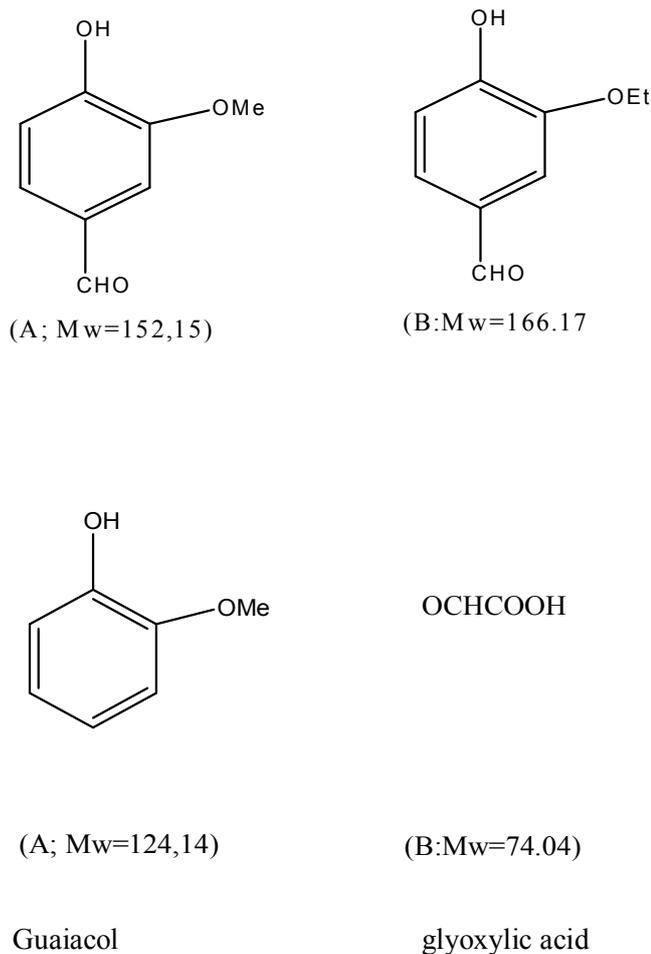
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**Abstract:** The present review summarizes the physicochemical properties, various synthetic procedures and the various pharmacological activities of vanillin derivatives. Thus by studying all the vanillin derivatives showing different biological activities

**Key word:** Vanillin, various synthetic procedures of vanillin, physicochemical properties, various biological activities.

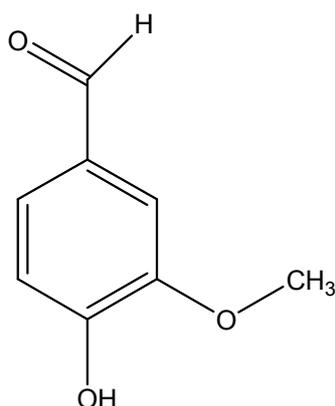
## Introduction:

Vanillin is the primary chemical component of the extract of vanilla bean. Natural vanilla extract is a mixture of several hundred compounds in addition to vanillin. Artificial vanilla flavoring solution of pure vanillin, usually of synthetic origin. Synthetic vanillin and ethyl vanillin are used as flavoring agents in foods, beverages, and pharmaceuticals. Ethyl vanillin is more expensive and has a stronger flavor. Compared to vanillin, ethyl vanillin has an ethoxy group (-O-CH<sub>2</sub>CH<sub>3</sub>) rather than a methoxy group (-O-CH<sub>3</sub>). The largest single use of vanillin is for flavoring. Vanillin was first synthesized from eugenol found in oil of clove and afterward synthesized from lignin-containing sulfite liquor, a by product of wood pulp processing in paper manufacture. While some vanillin is still made from lignin waste, today most synthetic vanillin is synthesized in a two-step process from the petrochemical precursors: *vanillin*, ethyl vanillin, and guaiacol and, glyoxylic acid. Vanillin (4-hydroxy-3-methoxybenzaldehyde), a pleasant smelling aromatic compound, occurs naturally in vanilla beans. It is used widely as a flavoring additive for beverages, cooking, and as an aromatic additive for candles, incense, potpourri, fragrances, perfumes, and air fresheners. It may be isolated from the vanilla bean, and is often obtained as a by product of the pulp and paper industry by the oxidative breakdown of lignin[1].

**Fig.1**

Vanillin is a phenolic aldehyde an organic compound with the molecular formula  $C_8H_8O_3$ . Its functional groups include aldehyde, ether and phenol. It is the primary component of the extract of the vanilla bean. It is also found in *Leptotes bicolor* [2] roasted coffee [3] and the Chinese red pine. Synthetic vanillin, instead of natural vanilla extract, is sometimes used as a flavoring agent in foods, beverages, and pharmaceuticals. Vanillin as well as ethyl vanillin is used by the food industry. It differs from vanillin by having an ethoxy group ( $-O-CH_2CH_3$ ) instead of a methoxy group ( $-O-CH_3$ ).

Natural "vanilla extract" is a mixture of several hundred different compounds in addition to vanillin. Artificial vanilla flavoring is a solution of pure vanillin, usually of synthetic origin. Because of the scarcity and expense of natural vanilla extract, there has long been interest in the synthetic preparation of its predominant component. The first commercial synthesis of vanillin start with the more readily available natural compound eugenol today, artificial vanillin is made from either guaiacol or from lignin, a constituent of wood which is a byproduct of the pulp industry, Lignin-based artificial vanilla flavoring is alleged to have a richer flavor profile than oil-based flavoring; the difference is due to the presence of acetovanillone in the lignin-derived product[4].



Vanillin

4-Hydroxy-3-methoxybenzaldehyde

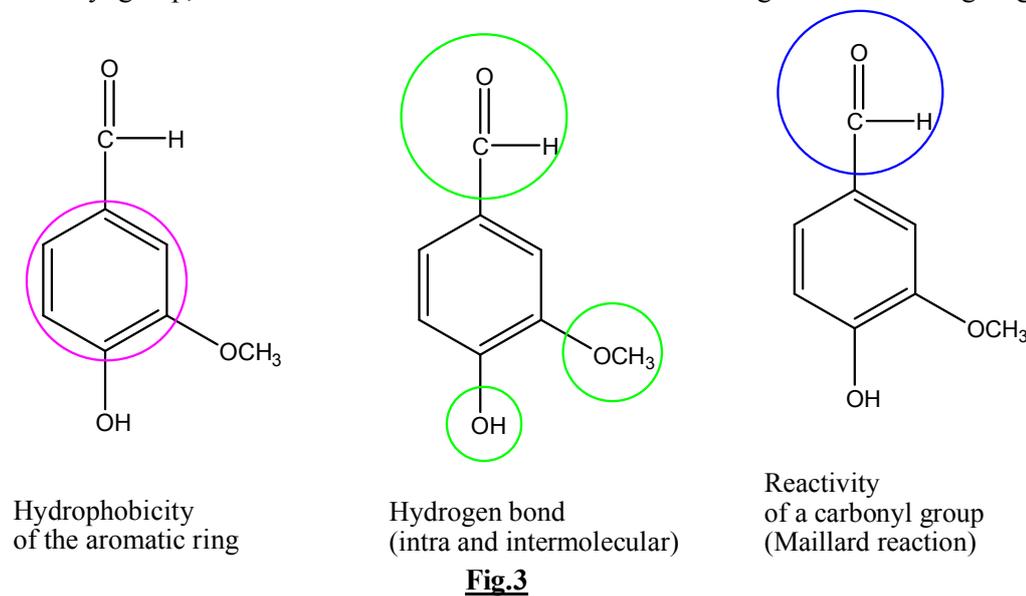
**Fig.2****Physical properties:****Characteristic/Property****Data**

Molecular Formula:	C <sub>8</sub> H <sub>8</sub> O <sub>3</sub>
Common Synonyms	4-hydroxy-3-methoxybenzaldehyde; methyl-B Protocatechuic aldehyde; vanillic Aldehydes; 3-Methoxy-4-hydroxybenzaldehyde
Chemical Structure	(CH <sub>3</sub> O) C <sub>6</sub> H <sub>3</sub> (OH) CHO
Physical State	white or slightly yellow nee
Melting Point:	178-181 ° F
Vapor Density:	data unavailable
Specific Gravity:	1.056 at 68.0 ° F.
Boiling Point:	545.0 ° F at 760 mm Hg.
Molar mass	152.15 g mol <sup>-1</sup>
Exact mass	152.047344122 g mol <sup>-1</sup>
Odor	Floral, pleasant
Acidity	(pKa) 7.781
Basicity	(pKb) 6.216
Crystal structure	Monoclinic
Water Solubility	1 g/100 ml
Density	1.056 g/mL
Vapor Density	(air = 1) 5.2
KOC	not found
Log KOW	not found
Vapor Pressure	2.2 x 10 <sup>-3</sup> mm Hg
Reactivity	can react violently with bromine, potassium Tert-butoxide, tert-chlorobenzene + NaOH, Formic acid + Tl (NO <sub>3</sub> ) <sub>3</sub> and perchloric acid
Flammability	not found
Flash Point	not found
Dissociation Constant	pKa1 7.40, pKa2 11.4 (25°C)

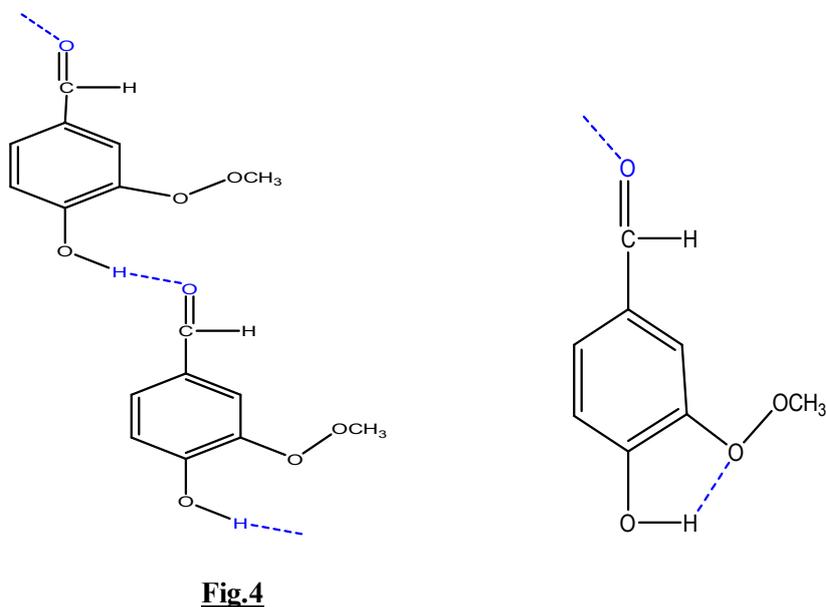
Henry's Law Constant	2.15 E-090(atm-3/molat25C)
Molecular Diffusivity Coefficient	not found
Air Diffusivity Coefficient	not found
Fish Bioconcentration Factor	not found
Odor Threshold	2 x 10 <sup>-1</sup> ppm, water; 1.10 x 10 <sup>-8</sup> ppb
Conversion Factors	1 ppm = 6.2 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.161 ppm
Solvent solubility	ether, chloroform, acetic acid
These are all the physical properties of vanillin. [5]	

### Chemical property of vanillin:

The molecular features of vanillin, including hydrophobicity, efficacy for forming hydrogen bonds and reactive carbonyl group, which could influence the fate of vanillin during various handling stag.

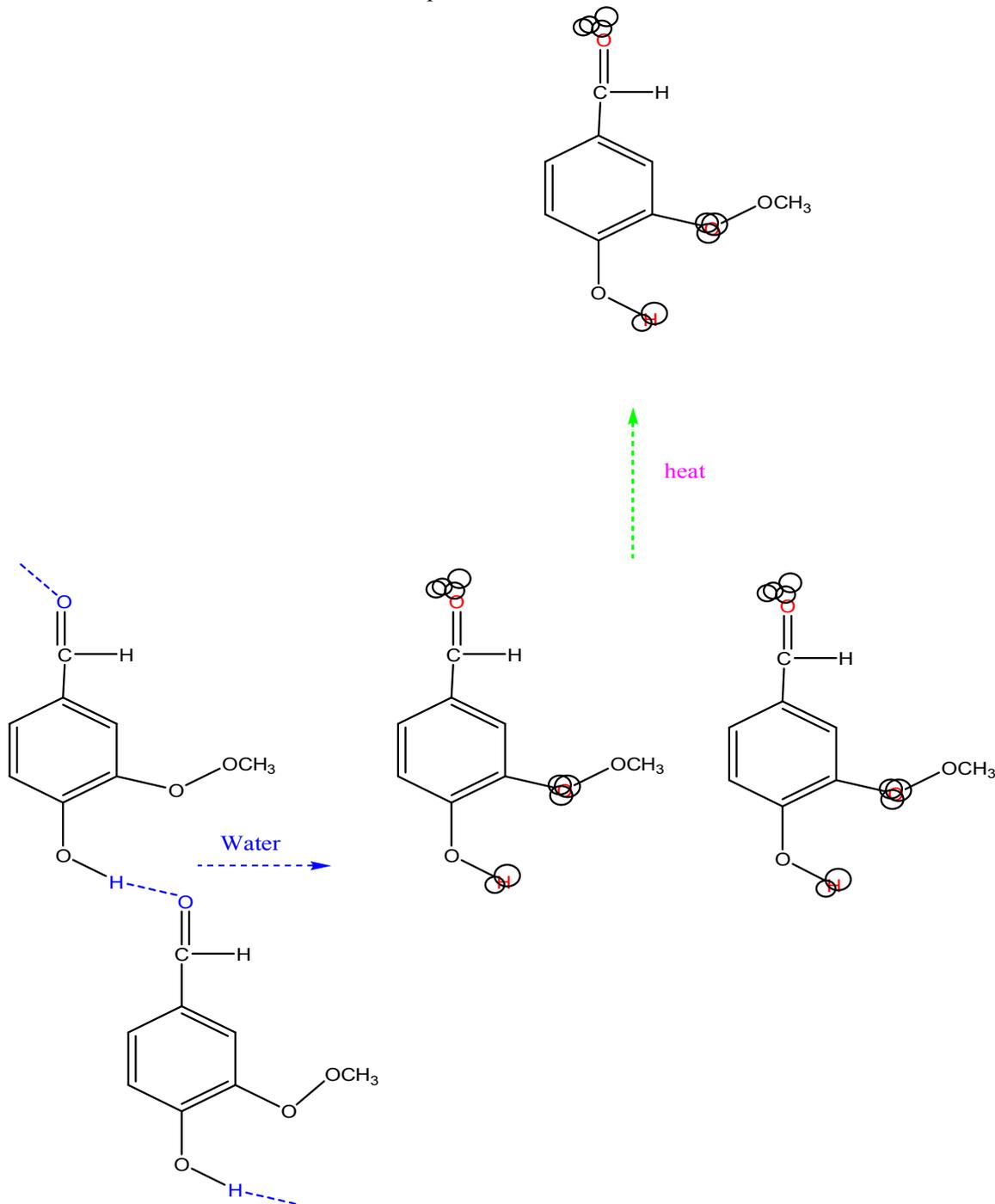


$\pi$ -  $\pi$  stacking of aromatic rings. This phenomenon, stemming from the hydrophobicity of aromatic compounds contributes to the tendency of vanillin to form aggregates.



**Hydration of vanillin:**

A hypothetical scheme indicating that hydration of vanillin, due to vanillin-water hydrogen bonding, leads to the volatilization of vanillin-water complex.



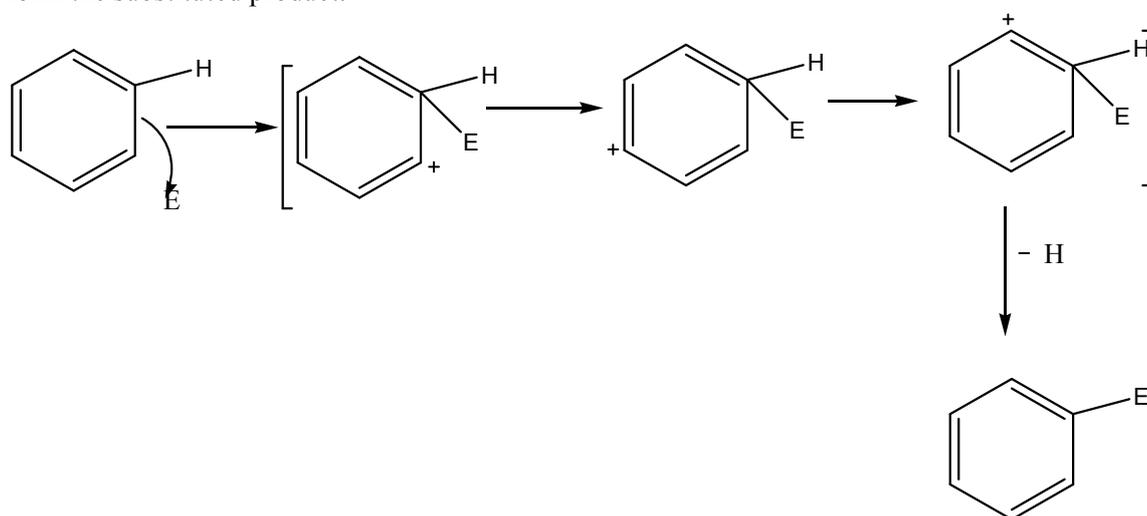
**Fig.5**

Some ions, which enhance or diminish the structure of water. Water structure-breaking ions are presumed to enhance the solubility and, thereby, the chemical reactivity of vanillin. [6]

## Electrophilic Aromatic Iodination of Vanillin:

### Mechanism of vanillin:

These reactions occur two-step addition/elimination mechanism, in which the electrophilic reagent first adds to the aromatic ring by attacking the  $\pi$  electrons, forming a cationic intermediate which then eliminates a leaving group to form the substituted product.



**Fig.6**

The electron-releasing substituents accelerate the reaction and preferentially drive the incoming substituent into *ortho* and *Para* positions, where resonance stabilization of the positive charge is optimized. Halogenations of aromatic compounds are typically carried out from side to side the reaction of the aromatic compound with  $\text{Cl}_2$ ,  $\text{Br}_2$ , or  $\text{I}_2$ , with a catalyst typically required to mediate the reaction.[7]

### Air & Water Reactions

Slowly oxidizes on exposure to air .it is the slightly water soluble.

### Transformation/Persistence

1. Air — Vanillin oxidizes to some extent when exposed to moist air and is "affect" by Light Vanillin absorbs UV light at wavelengths of 308 and 278 nm suggesting that photo transformation is possible. Decomposition of vanillin under strict anaerobic conditions has been observed.
2. Water — Information was not found about the vanillin in the aquatic environment. Based on its absorption of UV light at Wavelengths of 308 and 278 nm, vanillin in surface water could undergo some Photo transformation.
3. Biota — now present time no information was found in the searched regarding the bioaccumulation of vanillin.

### Sensitivity of vanillin

Vanillin also sensitive to sunlight.

### On Heating

Vanillin on heating gives CO and  $\text{CO}_2$  and it is give also antimicrobial activity against pathogenic micro organisms such as *E.coli*. Santeria .

### Reactivity Profile

Vanillin can react violently with  $\text{Br}_2$ ,  $\text{HClO}_4$ , potassium-tert-butoxide, (tert-chloro-benzene + NaOH), (formic acid +  $\text{Ti}(\text{NO}_3)_3$ ) (NTP, 1992). Vanillin is Aldehydes. Aldehydes are readily oxidized to give carboxylic acids.

Flammable and/or toxic gases are generated by the combination of Aldehydes with azo, diazo compounds, dithiocarbamates, nitrides, and strong reducing agents. Aldehydes can react with air to give first peroxy acids, and ultimately carboxylic acids. These autoxidation reactions are activated by light, catalyzed by salts of transition metals, and are autocatalytic (catalyzed by the products of the reaction).

### Environmental Release

No information found about the Environmental release of vanillin. The chemical occurs naturally in vanilla, potato Parings and Siam benzoin.

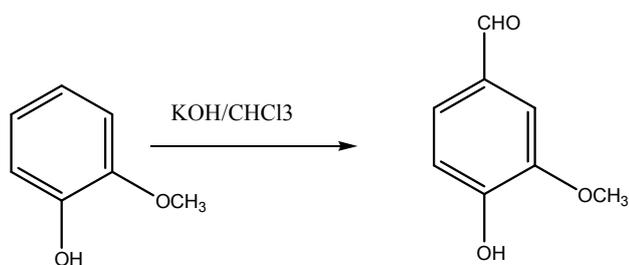
### Transport

Environmental transport of vanillin is not information found the vapor pressure ( $2.2 \times 10^{-3}$  mm Hg) for the chemical indicates that little volatilization from soil or water could occur. Vanillin is soluble in water (1 g/100 mL) and may move through the soil, possibly to groundwater. [8]

### Different Synthetic procedure of vanillin:

#### Synthesis of Vanillin by eugenol

Karl Reimer et al synthesized in (1876) vanillin from guaiacol. More dramatic is the Reimer-Tiemer method (1876). It is obtained from the eugenol react with the potassium hydroxide and last product found out the vanillin when it refluxed with an alkaline solution of chloroform. [9]



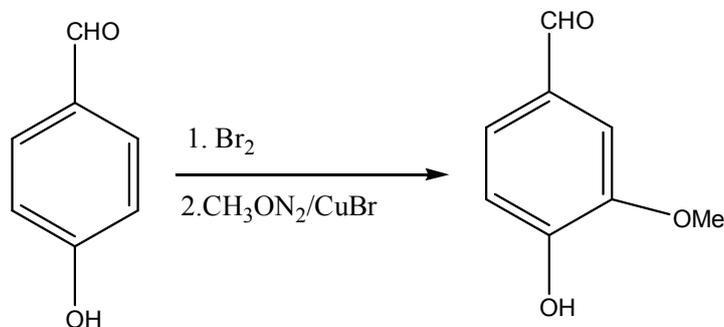
**Fig.7**

#### Vanillin synthesized from cow dung:

In October 2007 Mayo Yamamoto of the International Medical Center of Japan won an Ig Nobel Prize for developing a way to extract vanillin from cow dung. [10]

#### Vanillin synthesis from 4-hydroxybenzaldehyde:

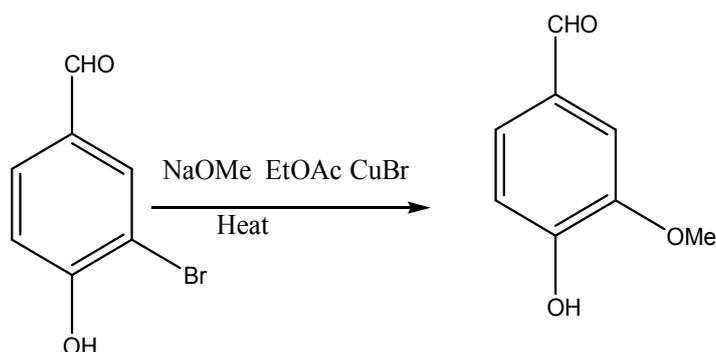
The developed a convenient two step synthesis of vanillin using electrophilic aromatic substitution, followed by an organometallic methoxylation procedure using copper bromide and sodium methoxide. [11]



**Fig.8**

**From 3-Bromo 4-Hydroxybenzaldehyde preparation 4-Hydroxy-3-Methoxybenzaldehyde (Vanillin):**  
(Microscale preparation):

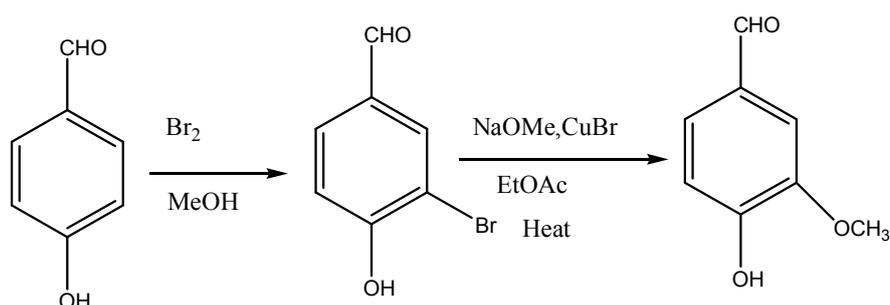
Weigh 200 mg of the crude 3-bromo-4-hydroxybenzaldehyde, and transfer it to a 5 mL reaction vial. Add 2.3 mL of the prepared sodium methoxide solution. And sodium methoxide in methanol solution, 4.4 mL of ethyl acetate, and 2.2 g of (CuBr). Seal the reaction vial, and heat in the oil bath at 100°C for 1 hour. Cool to room temperature, transfer the contents to a separatory funnel then acidify with 3 M aqueous HCl until all solids dissolve and then sodium methoxide solution and ethyl acetate in presence of copper bromide and yield the vanillin. [12]



**Fig.9**

**Vanillin Synthesis from 4-Hydroxybenzaldehyde**

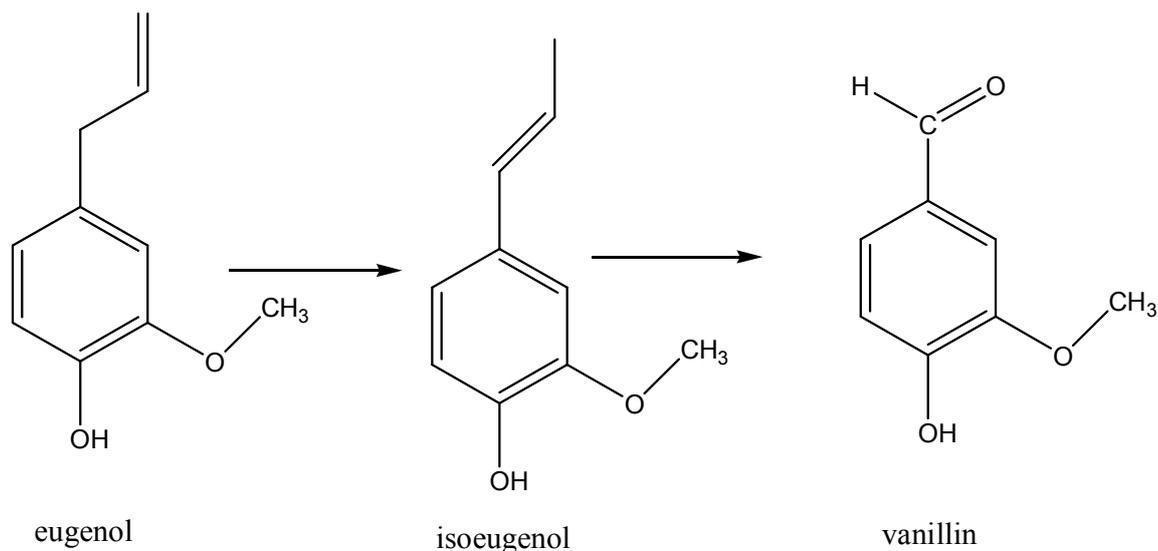
This synthesis has involving electrophilic bromination of 4-hydroxybenzaldehyde, and copper-catalyzed methoxylation, given the vanilla fragrance. This method involving in two steps the bromination of 4-hydroxybenzaldehyde to give 3-bromo-4-hydroxybenzaldehyde and Cu-mediated coupling of with methoxide to give the regioselectivity. The initial monobromo product disproportionates easily to starting material and 3, 5-dibromo-4 hydroxybenzaldehyde. Hence, the bromination is complete 30 seconds and the reaction mixture is then carrying directly on to the next step. The Br is replaced with OCH<sub>3</sub> in the presence of Cu- catalyst a pathway that probably involves oxidative addition and reductive elimination. Reaction. [13]



**Fig.10**

**From eugenol to vanillin:**

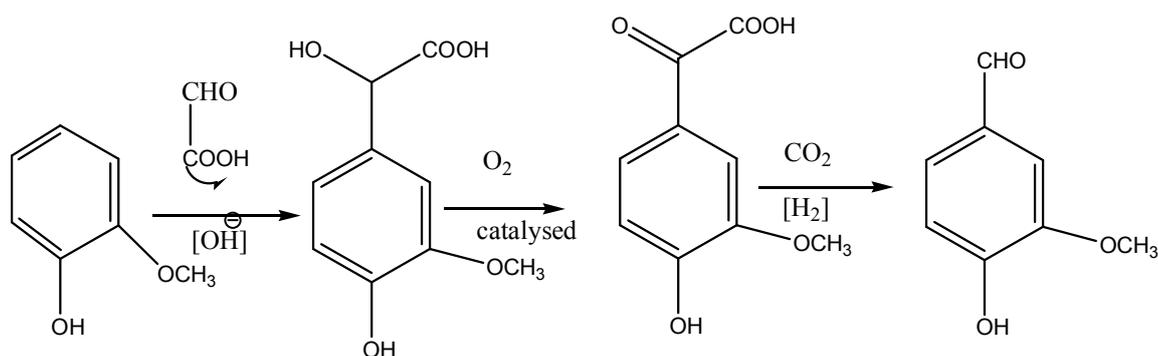
As far as large-scale industrial syntheses go to, a classic early method starts from eugenol, which occurs naturally in cloves, nutmeg and cinnamon. This isomerizes to isoeugenol in alkaline solution, and this in turn can be oxidized (by nitrobenzene) to vanillin.

**Fig.11**

Other oxidizing agents like acidified potassium dichromate can be used, but then the OH group has to be protected by acetylation prior to oxidation. The double bond was isomerized, and then oxidized and cleaved to form vanillin. [14]

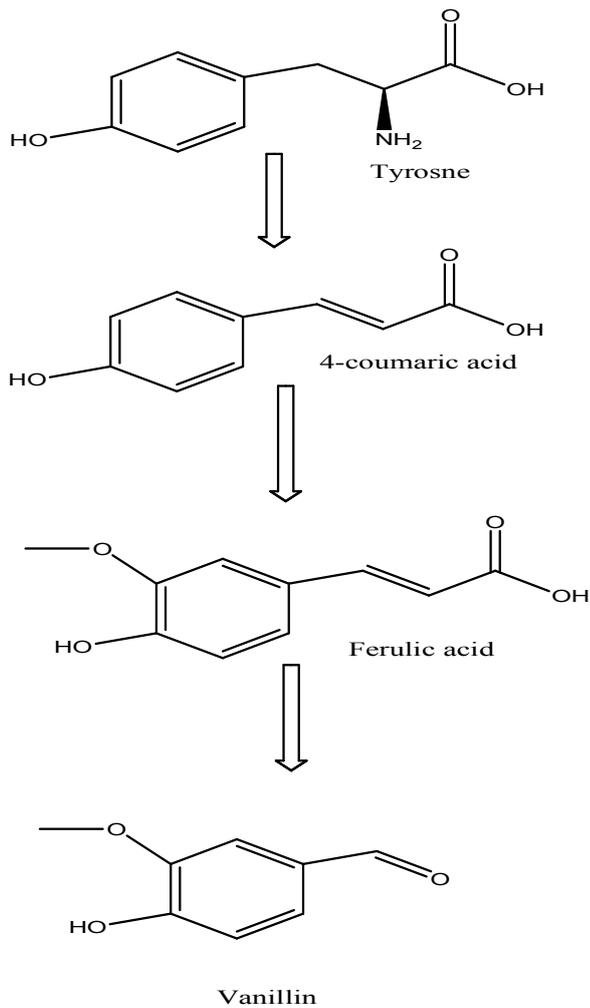
#### Synthesis of vanillin from guaiacol:

A more modern method reacts guaiacol, obtained from catechol, with glyoxylic acid, and that is how a lot of vanillin is produced today. At the present time, the most significant of these is the two-step process practiced by Rhoda since the (1970), in which guaiacol reacts with glyoxylic acid by electrophilic aromatic substitution. The resulting vanillylmandelic acid is then converted 4-Hydroxy-3-methoxyphenylglyoxylic acid to vanillin by oxidative decarboxylation and last in last product become found out is vanillin. [15]

**Fig.12**

#### Synthesis of Vanillin from Tyrosine:

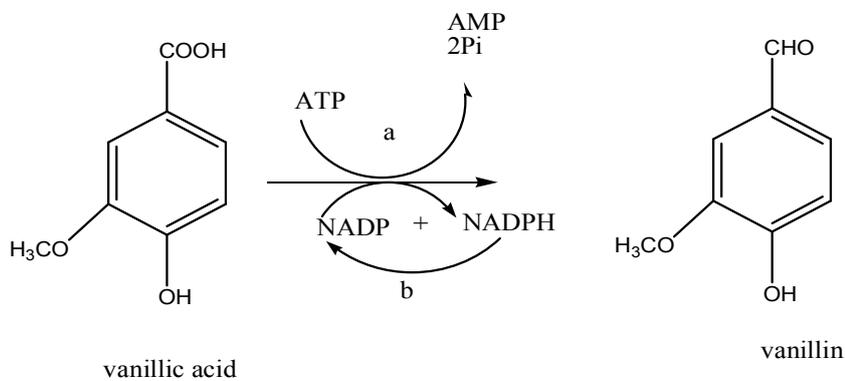
The synthesis of vanillin is achieved by the conversion of tyrosine into 4-coumaric acid then into ferulic acid and finally into vanillin. Vanillin is then converted into its corresponding glucose ester. His conversion of ferulic acid into vanillin is achieved by conversion of the carboxylic acid into a thioester with acetyl-CoA. The feruloyl CoA is then hydrated into 4-hydroxy-3-methoxyphenyl- $\beta$ -hydroxyprppionyl CoA (HMPHP CoA). At this point, two different pathways have been purposed for the conversion of HMPHP CoA into vanillin. One pathway is similar to the  $\beta$ -oxidation of fatty acid, beginning with the oxidation of the hydroxyl group, cleavage to release acetyl-CoA to form a shortened thioester and then cleavage of the thioester into an aldehyde. The other pathway contains one enzyme that would simultaneously oxidize the hydroxyl group along with the release of acetyl-CoA. [16]



**Fig.13**

**Synthesis vanillin from vanillic acid:**

The production vanillin from a carbon source is provided. Bioconversion method of the present invention comprise the step of microbe-catalyzed conversion of a carbon source to vanillic acid followed by enzyme catalyzed reduction of the vanillic acid to produce vanillin [17]

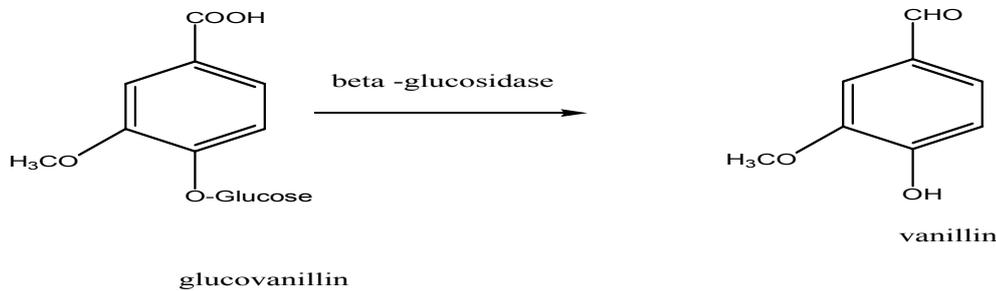


a= aryl-aldehyde dehydrogenase  
 b=D-glucose 6-phosphate dehydrogenase

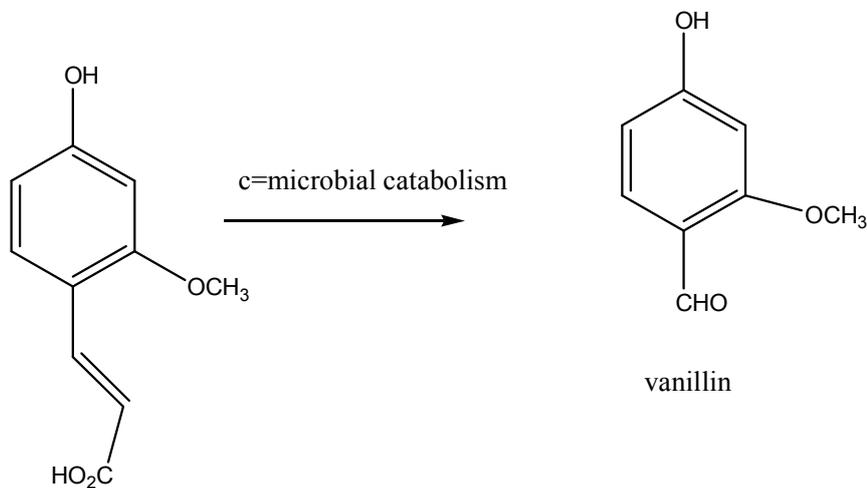
**Fig.14**

**Vanillin synthesis from glucose:**

Vanillin synthesis from the conversion of glucovanillin by beta -glucosidase enzyme and produced the vanillin. [18]

**Fig.15**

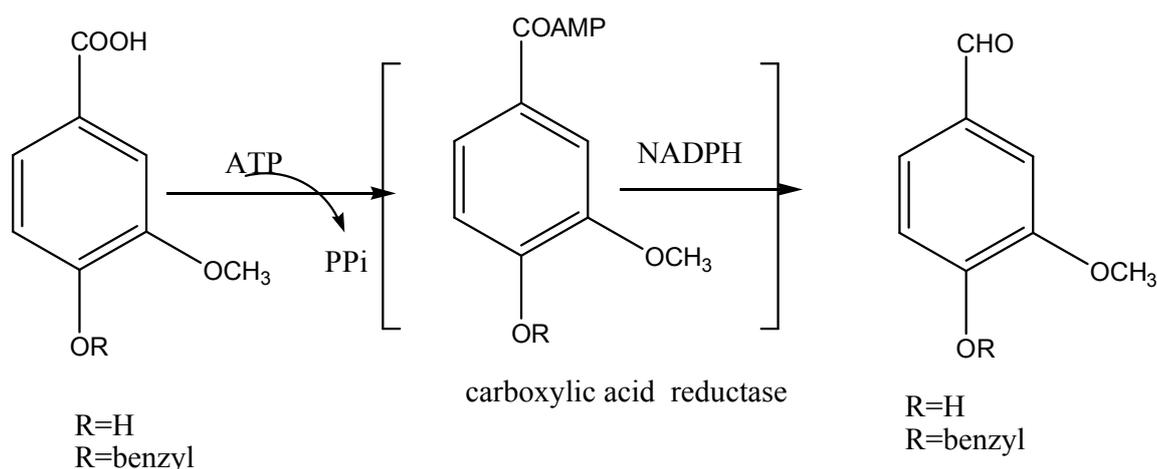
**Vanillin synthesis from ferulic:** vanillin synthesis in the one steps by microbial catabolism and give vanillin. [19]



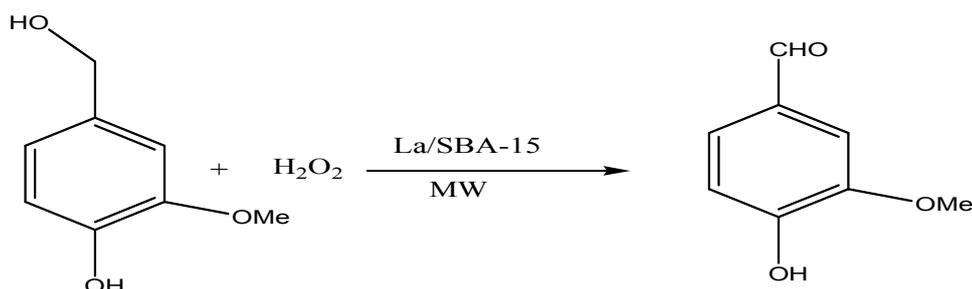
ferulic

**Fig.16****Vanillin synthesis from the *O*-benzylvanillic:**

The conversions of *O*-benzylvanillic and vanillin were examined by using whole cells and enzyme preparations of *Nocardia* sp. strain NRRL 5646. With growing cultures, decarboxylated (69% yield. In resting *Nocardia* cells in buffer, 4-*O*-benzylvanillic acid was converted to the corresponding alcohol product without decarboxylation. Purified *Nocardia* carboxylic acid reductase, an ATP and NADPH-dependent enzyme, quantitatively reduced *O*-benzylvanillic to vanillin. [20]

**Fig.17****Vanillin synthesis from 3-methoxy-4-hydroxybenzyl alcohol:**

The oxidation of 3-methoxy-4-hydroxybenzyl alcohol using La/SBA-15 at different times with changeable temperature (<423K) under microwave irradiation. Only traces of detectable low molecular weight products such as vanillin were observed at short times of reaction (<5min). About 68% of substrate conversion was observed with an optimum yield to vanillin within 30 min of reaction. Complete oxidation of 3-methoxy-4-hydroxybenzyl alcohol was observed after 40 min with high molecular weight compounds. [21].

**Fig. 18**

**Biological screening of vanillin:** these derivatives showing various biological activities

**Antioxidant activity:**

We systematically evaluated the antioxidant activity of vanillin using multiple assay systems given below:

- (a) DPPH free radical scavenging method
- (b) Galvinoxyl radical
- (c) ABTS (+)-scavenging assays
- (d) ORAC assay and an
- (e) Oxidative hemolysis inhibition assay (OxHLIA) was used for determining the antioxidant activity. [22]

**Antimicrobial activity:**

- (a) Cup-plate diffusion method [23]
- (b) Agar Diffusion method. [24]

**Anti-diabetic activity:**

- (a) Streptozotocin (STZ) induced diabetic Rats method [25]

**Anti-inflammatory activity:**

- (b) Carrageenan-induced air pouch models in mice [26]

**Analgesic activity**

(a) Acetic acid-induced permeability method [27]

**Anticancer activity**

Vanillin showing by semicarbazone (VSC) has been evaluated as anticancer

(a) compound VSC at Methods: The three doses m (5, i c7e.5 t oa nodb sl e0r vmeg i/tksg e if.fpic) iewnacsy a b dym sintuisdtyeirnegd tihnet oc ethlle g irnotwrathp eirmihtoibeitaol nc, arevdiuyc otifo tnh eo f EtAumC oiunro cwueliagthetd, seunchha npcaermamenett eorfs swuerrveiv aalls oti msteu daise dw ewlilt ha sa thken ocwhna nsgtaens dianr dd edprluegte bdl ehoemmyactionl oagti thale pdaorsaem oeft e0r.3s. mAgl. [28]

**Acknowledgement:**

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**Conclusion:**

In the present work, an attempt has been made to discuss various aspects such as physicochemical properties, chemical properties and varies type synthetic method of vanillin preparation. and discovering for potent drugs. The present review highlighted that although a number of methods are available for the synthesis of vanillin. In past years and is still used for future development of new drugs against many more pathological conditions.

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