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Facile Synthesis, Isolation and Characterization of 1-(4-Hydroxy-3-methoxyphenyl)ethanone (Acetovanillone) and its Isomeric Related Substances as Key Starting Materials for an Antipsychotic Drug: Iloperidone

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Three isomeric and one process related substances of acetovanillone 1-(4-hydroxy-3-methoxyphenyl)ethanone (**I**) were isolated and characterized while developing a laboratory process and pilot scale synthesis of acetovanillone. These impurities namely, 1-(3-hydroxy-4-methoxyphenyl)ethanone (**Imp 1**) (isoacetovanillone impurity), 1-(4-hydroxy-3-methoxyphenyl)-propan-1-one) (**Imp 2**) (propiovanillone impurity), 1-(3-hydroxy-2-methoxyphenyl)ethanone (**Imp 3**) (O-acetoisovanillone impurity-1), 1-(2-hydroxy-3-methoxyphenyl)ethanone (**Imp 4**) (O-acetoisovanillone impurity-2) have been synthesized and reported for the first time. The spectral characteristics of the synthesized impurities were confirmed with FTIR, ^{1}H NMR and mass spectrometry.

Keywords: Antipsychotic drug, Iloperidone, Isoacetovanillone, Acetoisovanillone.

INTRODUCTION

Acetovanillone is belongs to class of alkyl-phenyl ketones compounds known as acetoguaiacone. These aromatic compounds consist of ketone substituted by one alkyl and phenyl group. Acetovanillone is faint, sweet and vanillin tasting compound found in corn and garden onion, which makes it a potential biomarker in consumption of food products.

Acetovanillone, 1-(4-hydroxy-3-methoxyphenyl)ethanone (**I**) (Fig. 1) is commercially known as Apocynin. It is an aromatic ketone, which is 1-phenylethanone substituted by a hydroxyl group at position 4 and a methoxy group at position 3. It has a structural relation with vanillin, which can be isolated from a variety of plant sources. It is a promising compound due to its wide range of pharmacological properties and conventionally used as antiarthritic, antiasthmatic, atherosclerosis natural drug and also for treatment of bowel disease [1]. Acetovanillone (**I**) has ability to inhibit the activity of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase [2,3]. The release of superoxide by NADPH oxidase enzyme is especially important in the modulation of redox-sensitive signaling pathways, implication in neuronal dysfunction, degeneration and neuro-

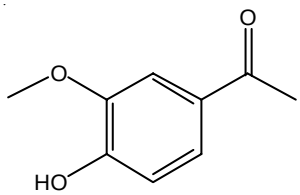


Fig. 1. Chemical structure of acetovanillone (**I**)

inflammation. This leads to CNS disorders such as Alzheimer's, schizophrenia and Parkinson's diseases. Apocynin is also proved as prototype novel series of non-steroidal anti-inflammatory drugs (NSAID) [4].

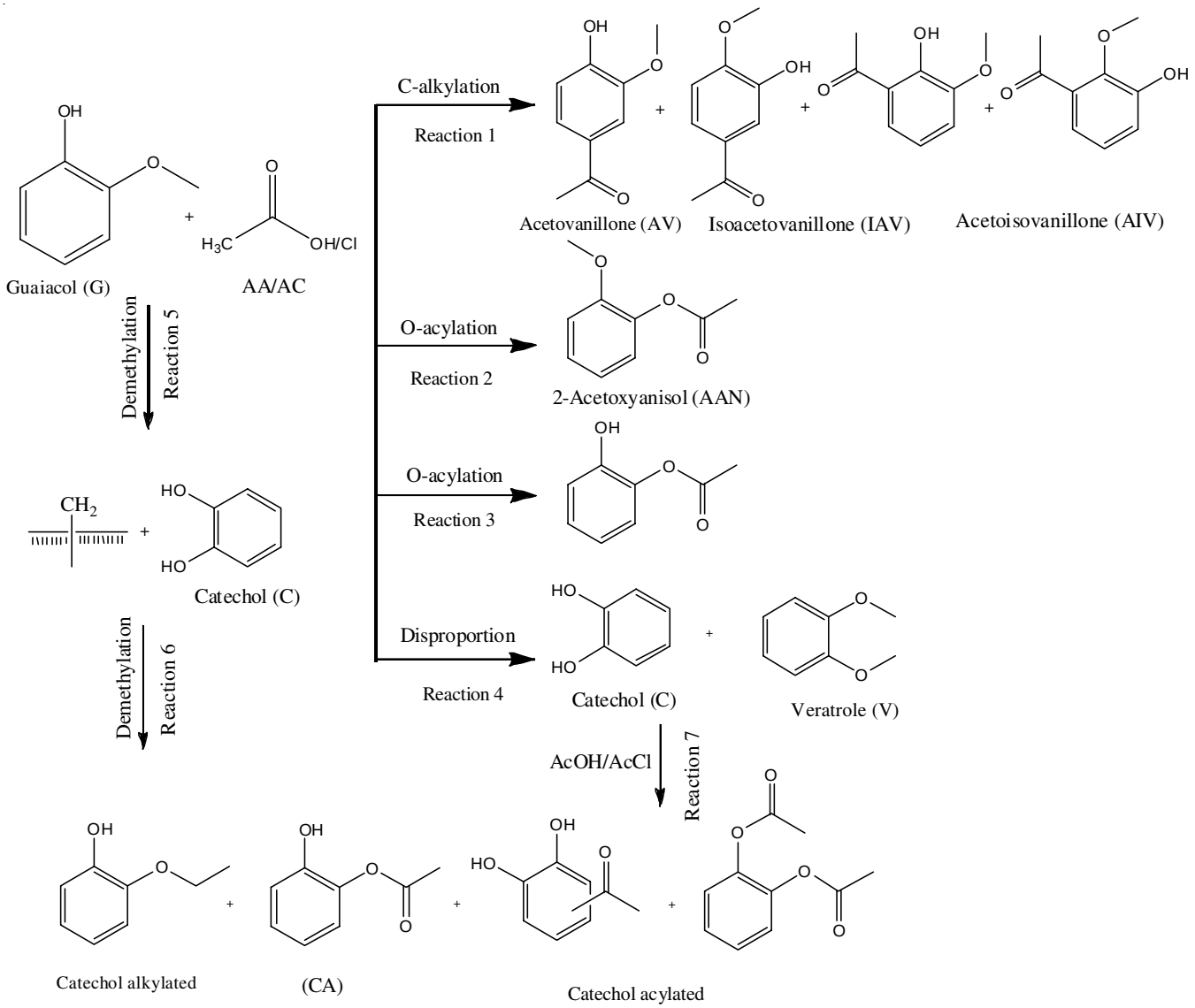
Acetovanillone and its metabolic derivative are effective natural drugs. Generally, acetovanillone (**I**) is synthesized by Friedel-Crafts acylation of guaiacol with acetic acid or acetyl chloride in presence of $AlCl_3$ or $ZnCl_2$. Conventional synthetic processes [5-7] involves the Friedel-Crafts catalysts ($AlCl_3$, $ZnCl_2$ and $TiCl_4$) and Brønsted acids (HF, H_2SO_4 and HCl). Literature provides detailed account of variety of catalysts and reagents used for the synthesis of apocynin. Coulthard *et al.* [8] have reported the acylation of guaiacol using acetic acid as acylation agent in presence of $ZnCl_2$ and $AlCl_3$. Selective

demethylation of 3,4-dimethoxy acetophenone was achieved using NaSEt [9].

Guaiacol (2-methoxyphenol) is the most abundant product obtained by thermal decomposition/de-polymerization of lignin [10,11] usually; the presence of oxygen in lignin-derived aromatic compounds is considered as unfavourable, which requires an additional hydroxy treatment step. However, these functional groups activate the aromatic ring and makes suitable for C-C and C-O bond formation involving in reactions like alkylation or acylation [12]. Acetic acid can also be derived from lignocellulosic materials [13,14] by pyrolysis. Thus, the use of renewable feed stock as acylation agent is to be attractive.

The impurities form during the acylation of renewable resources such as guaiacol and acetyl chloride/acetic acid to produce valuable substances and the facile synthetic routes for the possible isomeric impurities is reported. The current work delineates the process development and network aspects of selective acylation of guaiacol with acetyl chloride as new acylation agent. The acylation products of guaiacol and acetic acid includes acetovanillone (AV) and its isomers acetoisovanillone (AIV), 2-acetoxyanisole (AAN), which results through acylation of a C-atom of aromatic ring and O-acylation (or esterification) of AAN, respectively.

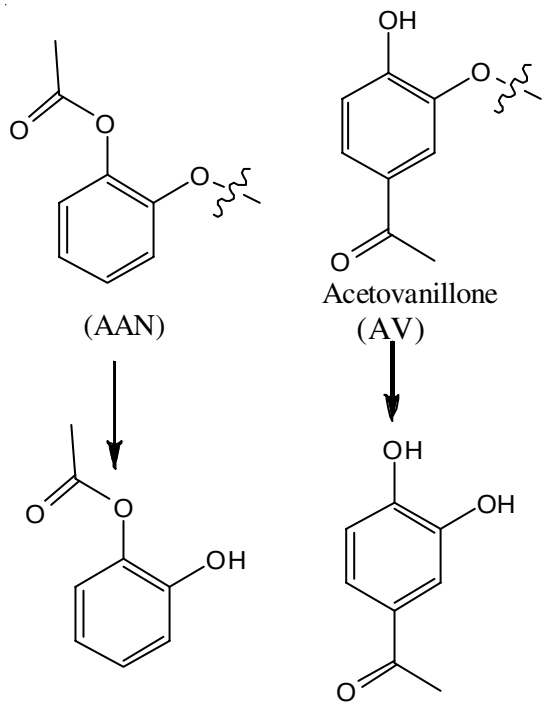
The acylation of guaiacol (G) with acetic acid (AA) can proceed through two main routes shown in **Scheme-I** and reported in literature [15]. The C-acylation of aromatic ring (reaction 1) results the acetovanillone (AV), isoacetovanillone (IAV) and its isomers acetoisovanillone (AIV) as acylation products. O-Acylation at the hydroxyl (OH) group of guaiacol (reaction 2) gives 2-acetoxyanisole (AAN) as acylation product. O-Acylation at methoxy (OCH_3) group of guaiacol would also be possible during acylation which results the catechol acetate. The formation catechol acetate is also shown in **Scheme-I**. In addition to this, two parallel reactions are expected to take place when guaiacol adsorbs on the surface of the catalysts. The disproportionation reaction (reaction 4) of guaiacol to give catechol (C) and veratrole (V) and demethylation of guaiacol (reaction 5) to produce catechol and olefins. The formed catechol may combine with methylene species adsorbed on catalyst surface (reaction 6) or acetic acid molecule (reaction 7) results



Scheme-I: Reaction network for acylation of guaiacol with acetic acid/acetyl chloride

the acylatedcatechol compounds *viz*. (2-hydroxyphenyl-acetate, 1,2-diacetoxybenzene and alkylated (2-ethoxyphenol, 2-propoxyphenol).

The maximum yield of C-acylated guaiacol (*i.e.* AV and AIV) and O-acylated guaiacol (*i.e.* AAN) can be attributed to the formation of acylated catechol molecules *via* demethylation mechanism as shown in the **Scheme-II**. The possible Fries rearrangement of AAN to C-acylated AV and AIV should also be considered which was reported earlier [16]. This rearrangement reaction may take place through either an intramolecular or *via* an intermolecular mechanism involving a guaiacol molecule and solid catalysts.



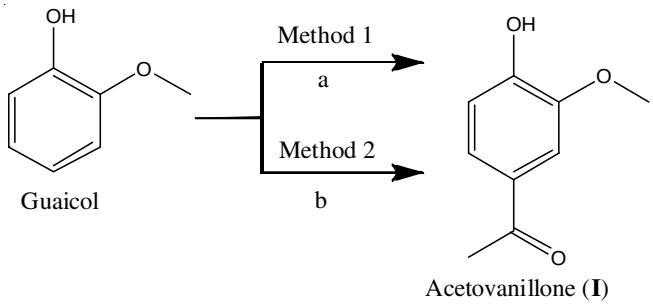
Scheme-II: Proposed mechanism for demethylation of acylation products to form catechol

Literature reveals that few studies are focused on the acylation of guaiacol. Coulthard *et al.* [8] reported the acetovanillone with a yield of 4% by reacting guaiacol with glacial acetic acid under reflux conditions in the presence of $ZnCl_2$, whereas Nakazawa [17] obtained 36% of yield using phosphoric acid, instead of $ZnCl_2$. Acetovanillone was obtained from Fries rearrangement of 2-acetoxyanisole using $AlCl_3$ as catalyst at 273-278 K [16,17]. A similar synthesis route has been patented using phosphorus pentoxide as catalyst and methane sulfonic acid as a solvent [18]. Synthesis of 1-(4-hydroxy-3-methoxyphenyl)ethanone was achieved from guaiacol with acetic acid or acetyl chloride in presence of $ZnCl_2$ at ambient conditions with low yields [19]. However, the yield can be improved under vigorous conditions. The HPLC chromatogram of 1-(4-hydroxy-3-methoxyphenyl)ethanone shows the four impurity peaks in the range of 0.05-0.15% levels along with the desired molecule peak. As per the guidelines recommended by ICH, the acceptable level for a known or unknown related impurity should be in between 0.15 and 0.10% [20].

Following compounds were identified as related substances during the synthetic process of 1-(4-hydroxy-3-methoxyacetophenone) (**I**) *e.g*. 1-(3-hydroxy-4-methoxyphenyl)ethanone (**Imp 1**), 1-(4-hydroxy-3-methoxyphenyl)propan-1-one (**Imp 2**), 1-(2-hydroxy-3-methoxyphenyl)ethanone (**Imp 3**) and 1-(3-hydroxy-2-methoxyphenyl)ethanone (**Imp 4**).

To have a thorough understanding about the impurity profile of an antipsychotic agent iloperidone, it is very much essential to know its key starting material acetovanillone and its process related substances (raw material contaminations of acetovanillone and its isomers) and mechanism of formation of acetovanillone and its potential impurities. The isoacetovanillone, acetoisovanillone and propiovanillone (Ksms) related substances of iloperidone close related derivatives (structurally similar) are proved to be promising candidates for further efficacy evaluation on the basis of their structure activity relationship studies, very useful for toxicological and validation studies and have regulatory importance. These compounds are regarded as viable leads for the studies in various aspects of CNS drug candidates in the future. Present efforts to synthesis and characterize them effectively prove to be valuable.

Thus, the present work is aimed to synthesize acetovanillone (**I**) (**Scheme-III**), which is key intermediate of antipsychotic drug; iloperidone and its process impurities. Four impurities are found during the process development and pilot scale preparation of acetovanillone (**I**) in the laboratory. Syntheses of these impurities are not reported so far. Herein, origin, an alternative synthetic route, characterization and control synthesis of acetovanillone (**I**) and its process related impurities (1-4) are shown in Table-1.

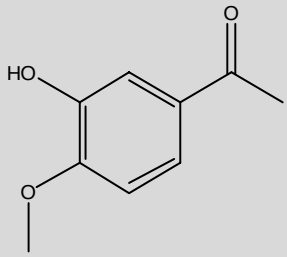
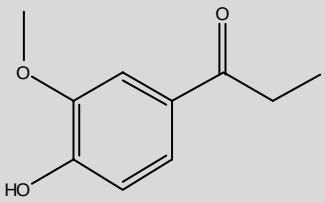
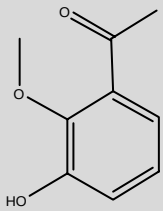
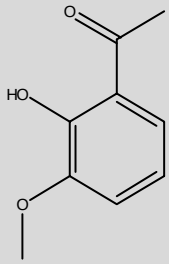


Scheme-III: Synthetic route of acetovanillone (**I**)

EXPERIMENTAL

All the reagents and chemicals used were of reagent grade. Infrared spectra were recorded in KBr disc using Perkin-Elmer model 1600 FTIR spectrophotometer (Perkin-Elmer, Norwalk, USA). Electrospray ionization mass spectra were recorded on API 4000 triple quadruple instrument (MDSSCIEX, Concord, Ontario, Canada). LC-mass spectra were recorded on Agilent-1100 series LC-MSD-TRAP-SL system mass spectrometer. Elemental analysis was performed on Hosli CH-Analyzer and the results were within ± 0.35% of the calculated values. ^{1}H NMR spectra were obtained on a Bruker proton NMR spectrometer (Fallanden, Switzerland) at 400 MHz using deuterated reagents as solvents. Melting points were determined by Polman

TABLE-1
NAME, SYNONYM AND SOURCE OF 1-(4-HYDROXY-3-METHOXYPHENYL)ETHANONE (**I**) AND ITS PROCESS RELATED IMPURITIES

Impurity name	Synonym	Structure	Source
Imp 1	1-(3-Hydroxy-4-methoxy-phenyl)-ethanone (isoacetovanillone impurity)		Process
Imp 2	1-(4-Hydroxy-3-methoxy-phenyl)-propan-1-one (propiovanillone impurity)		Process/Degraded
Imp 3	1-(3-Hydroxy-2-methoxy-phenyl)-ethanone (O-acetoisovanillone impurity-1)		Process
Imp 4	1-(2-Hydroxy-3-methoxy-phenyl)-ethanone (O-acetoisovanillone impurity-2)		Process

melting point apparatus (Model No.: MP-96) and are uncorrected. Chromatography refers to column chromatography performed using 100-200 mesh silica gel and executed under nitrogen pressure (flash chromatography) conditions.

Synthesis of 1-(4-hydroxy-3-methoxyphenyl)ethanone (acetovanillone) (I)

Method 1: To a solution of guaiacol (2-methoxyphenol) (124.14 g, 0.1 mmol) and anhydrous $ZnCl_2$ (170.32 g, 0.125 mmol) in acetic acid (125 mL), acetic anhydride (112.29 g, 0.11 mmol) was added dropwise at room temperature for 0.5 h. The reaction mixture was heated to 90-95 ºC and maintained at the same temperature for 5 h. The progress of the reaction was monitored by TLC. The reaction mass was allowed to cool down to room temperature and the solvent acetic acid was removed under reduced pressure at below 80 ºC to obtain residue and quenched with water (300 mL). The desired product was extracted twice using CH_2Cl_2 (500 mL) and filtered the inorganics by high-flow bed Büchner funnel filtration assembly. Finally, the combined organic layer was washed with water (400 mL) and neutralized with 10% $NaHCO_3$ solution (400 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and then concentrated by rotary evaporator at below 40 ºC under reduced pressure to obtain crude product. The crude was treated with of *n*-hexane (2 × 200 mL), decanted the solvent and dried under reduced pressure to afford off white solid 126.5 g of the target product **I** with 76.0% yield (98.9% purity by HPLC).

Method 2: Anhydrous $AlCl_3$ (73.34 g, 0.055 mmol) was cooled to below 0-5 ºC and then added guaiacol (2-methoxyphenol) (62.07 g, 0.05 mmol) dropwise with stirring for 0.5 h and maintained at the same temperature for 1 h. Then acetyl chloride (43 g, 0.055 mmol) was added dropwise with the duration of 40 min at below 0-5 ºC under inert atmosphere. The reaction mass was allowed to cool slowly to room temperature. Then, the reaction temperature was increased to 50-55 ºC and maintained at the same temperature for 5 h. Reaction was monitored with TLC. After completion of the reaction, contents were cooled to room temperature and quenched in 300 g of crushed ice, 100 mL of water and 30 mL of conc. HCl, stirred well for 0.5 h. The desired product was extracted with chloroform (2 × 250 mL), filtered the inorganics and emulations by high-flow bed Büchner funnel filtration assembly. Finally, the combined chloroform layers were washed with

brine solution (200 mL) and neutralized with 10% $NaHCO_3$ solution (200 mL). The chloroform was removed and concentrated by rotary evaporator at below 45 ºC under reduced pressure to obtain a residue. The residue was further purified by column chromatography using eluent system *n*-hexane:ethyl acetate in 4:2 ratio to obtain compound **I** as off-white crystalline solid (54 g, yield, 65.06%) (99.12% purity by HPLC). m.p.: 114.4-115.2 ºC; FTIR (KBr, ν_{max}, cm^{-1}): 3384, 2934, 2850, 2719, 1682, 1583, 1469, 1359, 1280, 792, 557; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.53 (s, 3H, COC**H**$_3$), 3.94 (s, 3H, OC**H**$_3$), 6.15 (s, broad 1H, Ar-O**H**), 6.86-6.89 (dd, 1H, AR-**H**), 7.53-7.54 & 7.57-7.59 (m, 2H, *J* = 4.0 & 8.0 Hz, Ar-**H**); ESI-MS (*m/z*): 167.2 $[M+H]^+$; Anal. calcd. (found) % for $C_9H_{10}O_3$ (*m.w.* 166.17): C, 67.08 (67.05); H, 6.33 (5.65).

Synthesis of 1-(3,4-dihydroxyphenyl)ethanone (1)

Method-1: To a stirred solution of 1-(4-hydroxy-3-methoxyphenyl)ethanone **(I)** (50 g, 0.030 mmol) in acetic acid (100 mL) was charged with 48% aqueous HBr (40.92 g, 0.051 mmol) at 25-30 ºC. The reaction contents were stirred at ambient temperature for 15 min and then slowly raised the temperature up to 130-135 ºC and maintained for 10 h. The reaction progress was monitored by TLC (chloroform:methanol, 4:1), then it was cooled to room temperature. The solvent acetic acid was distilled off on under reduced pressure at below 80 ºC to obtain residue, which was quenched into water (200 mL). The desired product was extracted with ethyl acetate (2 × 200 mL), the combined ethyl acetate layer was washed with water (100 mL). The ethyl acetate was removed by rotary evaporator at below 65 ºC under reduced pressure to obtain a residue and recrystallized from isopropyl alcohol (150 mL) under reflux and cooled to below 2 ºC. The desired product was obtained as a white crystalline wet solid. The wet product was dried in vacuum at 50-55 ºC for 1-2 h. Dry weight of compound **1** was 39.5 g, yield: 86.37%.

Method 2: Anhydrous $AlCl_3$ (40.12 g, 0.03 mmol) was cooled to below 0-5 ºC and then added 1-(4-hydroxy-3-methoxyphenyl)ethanone **(I)** (50 g, 0.030 mmol) in portion under stirring condition for 0.5 h and maintained at same temperature for another 0.5 h. Pyridine (23.8 g, 0.030 mmol) was added dropwise in the interval of 20 min at below 0-5 ºC under inert atmosphere carefully. The reaction temperature was brought to room temperature slowly and then was heated to 60-65 ºC and maintained at same temperature for 4 h. After completion of the reaction, it was cooled to room temperature and quenched in 400 g of crushed ice, 100 mL of water and 50 mL of conc. HCl; stirred well for 0.5 h. The desired product was extracted with chloroform (2 × 400 mL), filtered the inorganics and emulsions by high-flow bed Büchner funnel filtration assembly. Finally, the combined chloroform layers were washed with brine solution (300 mL). The chloroform layer was dried over anhydrous sodium sulphate, filtered and then concentrated by rotary evaporator at below 45 ºC under reduced pressure to obtain residue. The residue was further purified by column chromatography with an eluent of *n*-hexane:ethyl acetate, (4:2) to obtain 1 as off-white crystalline solid (29 g, yield 63.4%). FTIR (KBr, ν_{max}, cm^{-1}): 3394, 3382, 2934, 2850, 2719, 1695, 1571, 1440, 1371, 1253, 748; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.55 (s, 3H, COC**H**$_3$), 3.97 (s, 3H, OC**H**$_3$), 5.76 (s, broad 1H, Ar-O**H**), 6.15 (s, broad 1H, Ar-O**H**), 6.86-6.89 (dd, 1H, Ar-**H**), 7.53-7.55 & 7.54-7.55 (m, 2H, *J* = 8.0 & 4.0 Hz, Ar-**H**). 9.38 (s, broad 1H, Ar-O**H**), 12.0 (s, broad 1H, Ar-O**H**); ESI-MS (*m/z*): 151.1 $[M-H]^+$; Anal. calcd. (found)% for $C_8H_8O_3$ (*m.w.* 152.15): C, 67.08 (67.06); H, 6.33 (5.75).

Synthesis of 1-(3-hydroxy-4-methoxyphenyl)ethanone (isoacetovanillone) (Imp 1): To a stirred solution of powder anhydrous Ce_2CO_3 (107.94 g, 0.033 mmol) in DMF (80 mL), was cooled to below 0-5 ºC and then added 1-(3,4-dihydroxyphenyl)ethanone (**1**) (40 g, 0.026 mmol) in portion under stirring for 20 min and maintained at the same temperature for 0.5 h. Then, dimethyl sulphate (36.5 g, 0.028 mmol) was added dropwise for about 20 min at below 0-5 ºC under inert conditions carefully. The reaction mass was maintained at 20-25 ºC for 15 h. After completion of the reaction, it was quenched in 300 mL of water and stirred for 0.5 h. The desired product was extracted twice using ethyl acetate (300 mL), filtered the inorganics and emulsions by high-flow bed Büchner funnel filtration assembly. Finally, the combined ethyl acetate layer was washed with brine solution (300 mL). The ethyl acetate layer was dried over anhydrous sodium sulphate, filtered and then concentrated by rotary evaporator at below 45 °C under reduced pressure to obtain a residue. The residue was further purified by column chromatography eluent system (*n*-hexane: ethyl acetate, 4:2) to obtain **Imp 1** as off-white crystalline solid (25.5 g yield: 58.37%) (1.0 g of 3, 4-methoxy acetophenone compound was isolated) purity by HPLC was 99.12%. m.p.: 88-92 ºC; FTIR (KBr, ν_{max}, cm^{-1}): 3398.92, 2934, 1682, 1583.7, 1459, 1359, 1283, 752; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.54 (s, 3H, COC**H**$_3$), 3.95 (s, 3H, OC**H**$_3$), 6.16 (s, broad 1H, Ar-O**H**), 6.88-6.91 (dd, 1H, Ar-**H**), 7.53-7.54 & 7.57-7.59 (m, 2H, *J* = 4.0 & 8.0 Hz, Ar-**H**), ESI-MS (*m/z*): 167.1 $[M+H]^+$; Anal. calcd. (found) % for $C_9H_{10}O_3$ (*m.w.* 166.17): C, 67.08 (67.03); H, 6.33 (5.95).

Synthesis of 1-(4-hydroxy-3-methoxyphenyl)propanone (propiovanillone) (Imp 2): Anhydrous $AlCl_3$ (73.34 g, 0.055 mmol) was cooled to below 0-5 ºC and then guaiacol (2-methoxyphenol) (62.07 g, 0.05 mmol) was added dropwise with stirring for 0.5 h and maintained at the same temperature for 1 h. Propionyl chloride (50.88 g, 0.055 mmol) was added in portion in a period of 40 min below 0-5 ºC under inert conditions. The reaction mass was kept at room temperature and gradually raised temperature up to 55-60 ºC and maintained at the same temperature for 5 h. After completion of the reaction, it was cooled to room temperature and quenched in 300 g of crushed ice, 100 mL of water and 30 mL of conc. HCl. Stirred well for 0.5 h, the product was extracted twice using chloroform (250 mL), filtered the inorganics and emulsions by high-flow bed Büchner funnel filtration assembly. Lastly, combined chloroform layer was washed with brine solution (200 mL) and neutralized with 10% $NaHCO_3$ solution (200 mL). The chloroform layer was dried over anhydrous sodium sulphate, filtered and then concentrated by rotary evaporator at below 45 ºC under reduced pressure to obtain a residue. The residue was further purified by column chromatography eluent system

(*n*-hexane:ethyl acetate, 4:2) to obtain **Imp 2** as off-white crystalline solid (54 g, yield: 65.06%) (99.22% purity by HPLC). FTIR (KBr, ν_{max}, cm^{-1}): 3398, 2932, 2845, 2740, 1685, 1591, 1440, 1371, 1253, 748' ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18-1.22 (t, 3H,-C**H**$_2$-CH$_3$), 2.91-2.96 (qt, 2H, CO-CH$_2$-C**H**$_3$), 3.92 (s, 3H, OC**H**$_3$), 6.25 (s, broad 1H, Ar-O**H**), 6.91-6.94 (dd, 1H, Ar-**H**), 7.51-7.52 & 7.52-7.54 (m, 2H, *J* = 4.0 & 8.0 Hz, Ar-**H**); ESI-MS (*m/z*): 181.2 $[M+H]^+$; Anal. calcd. (found) % for $C_{10}H_{12}O_3$ (*m.w.* 180.20) C, 67.08 (67.04); H, 6.33 (5.79).

Synthesis of 2-hydroxy-3-methoxybenzoic acid (2): Potassium hydroxide (85%, 412.45 mmol) in water (35 mL) was stirred at ambient temperature for 20 min and heated to 155-160 ºC and then 2-hydroxy-3-methoxybenzaldehyde was added (114.10 g, 74.99 mmol) dropwise carefully for 1 h. The reaction mass temperature was raised up to 180-190 ºC and maintained the temperature at 155-160 ºC for 2 h. The reaction progress was monitored by TLC (chloroform:methanol; 4:1), after completion of reaction, mixture was allowed to cool with stirring and one liter water was added, stirred until all the fusion mixture is dissolved. Later, it was cooled to below 50 ºC and diluted with 300 mL of water; aqueous layer was extracted twice using toluene (600 mL). Finally, the aqueous layer was cooled to below 0-10 ºC and then acidified with 800 mL of 6N HCl under stirring (pH 1-2), maintained the cooling for further 1 h. The formed solid was filtered, washed with water twice (300 mL) to get wet crude compound. The crude compound was recrystallized from 1:1 w/v of water under reflux and cooled to below 10 ºC and obtained as a white crystalline wet solid. The wet product was dried under vacuum for 1 h. Yield: 84.06 (106 g). m.p. range: 148-150 ºC; ESI-MS (*m/z*): 167.2 $[M-H]^+$, 191.2 $[M+Na]^+$; Anal. calcd. (found) % for $C_8H_8O_4$ (*m.w.* 168.15): C, 67.08 (67.07); H, 6.33 (6.26).

Synthesis of 1-(2-hydroxy-3-methoxyphenyl)ethanone (O-acetoisovanillone-1) (Imp 3): 2-Hydroxy-3-methoxybenzoic acid (**2**) (55.0 g, 32.70 mmol) was suspended in diethyl ether (200 mL) containing few drops of DMF. Thionyl chloride (42.81 g, 35.97 mmol) in 50 mL of diethyl ether was added slowly over a period of 15 min at 5-8 ºC and stirred for 2 h under nitrogen atmosphere. After the completion of reaction, the reaction contents were kept aside under cold conditions. Sodium metal (11.28 g, 49.06 mmol) was added to 300 mL of absolute ethyl alcohol through a funnel with stirring over a period of 40 min under cold conditions using 1 L dry round-bottomed flask was equipped with a reflux condenser. The stirring was continued to till solution attains room temperature and then, mixture of ethyl acetoacetate (46.81 g, 35.97 mol) in 100 mL absolute ethyl alcohol was added slowly in the duration of 2 h. Initially, formation of white precipitate was observed which turns into yellow precipitate. As the reaction proceeds this precipitate becomes dark and later turns into yellow again. The reaction temperature rose to 40 ºC. At the end, the reaction mixture becomes highly viscous liquid and difficult to stirr. Then the reaction mixture was cooled to below 5 ºC, acid chloride compound (part 1) was added dropwise carefully under nitrogen atmosphere for 40 min. The reaction temperature gradually increased to 40-45 ºC and then the solvent diethyl ether was evaporated under reduced pressure. Later, reaction temperature was raised to 75-80 ºC and then maintained at the same temperature for 4 h. After confirming the reaction completion with TLC, it was cooled to room temperature and quenched in 300 g of crushed ice and 100 mL of water. To this, cold sulfuric acid solution (70 mL) was added rapidly to prevent melting of ice and stirred well for 0.5 h. The reaction mass was then refluxed for 4 h and progress of the reaction was monitored with TLC. After completion of the reaction and the solvent ethanol was distilled under reduced pressure at below 60 ºC to obtain residue and quenched with water (300 mL). The desired product was extracted twice using ethyl acetate (300 mL). Finally, the combined ethyl acetate layer was washed with brine water (300 mL) and neutralized with 10% $NaHCO_3$ solution (300 mL) and dried over anhydrous sodium sulphate. Then filtered and concentrated by rotary evaporator at below 45 ºC under reduced pressure to obtain residue. The residue was further purified by column chromatography eluent system being (*n*-hexane:ethyl acetate, 4:2) to obtain **Imp 3** as off-white crystalline solid (43 g, yield: 79.11%) (98.9% purity by HPLC). m.p.: 53.4-54.1 ºC; FTIR (KBr, ν_{max}, cm^{-1}): 3385, 2932, 1689, 1556, 1440, 1366, 1253, 748; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H, COC**H**$_3$), 3.90 (s, 3H, OC**H**$_3$), 6.81-6.84 (dd, Ar-H), 7.05-7.07(m, 1H, *J* = 8.0 Hz, Ar-**H**), 7.33-7.35 (m, 1H, *J* = 8.0 Hz, Ar-**H**), 12.57 (s, broad 1H, Ar-O**H**), ESI-MS (*m/z*): 167.1 $[M+H]^+$; Anal. calcd. (found) % for $C_9H_{10}O_3$ (*m.w.* 166.17): C, 67.08 (67.04); H, 6.33 (5.93).

Synthesis of 1-(2,3-dihydroxyphenyl)ethanone (3): To a stirred solution of 1-(2-hydroxy-3-methoxyphenyl)ethanone (O-acetoisovanillone-1) (**Imp 3**) (35 g, 0.021 mmol) in acetic acid (80 mL) was charged with 48% aq. HBr (28.64 g, 0.035 mmol) at 25-30 ºC. The reaction mixture was stirred at ambient temperature for 15 min and then slowly raised the reaction temperature up to 130-135 ºC and maintained at the same temperature for 10 h. The reaction progress was monitored by TLC (chloroform:methanol, 4:1), after completion of the reaction, it was cooled to room temperature and then the solvent acetic acid was distilled off under reduced pressure at below 80 ºC to obtain residue and quenched with water (150 mL). The desired product was extracted twice using ethyl acetate (150 mL) and combined ethyl acetate layer was washed with water (100 mL). The ethyl acetate layer was then concentrated by rotary evaporator at below 65 ºC under reduced pressure to obtain residue. This residue was further purified by column chromatography using eluent system of *n*-hexane:ethyl acetate (4:2) to obtain compound **3** as off-white crystalline solid (27.5 g, yield: 85.83%) (99.4% purity by HPLC). m.p.: 97-98 ºC; FTIR (KBr, ν_{max}, cm^{-1}): 3387, 3382, 1685, 1566, 1440, 1351, 1117, 746; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.61 (s, 3H, COC**H**$_3$), 6.76-6.78 (dd, 1H, Ar-**H**),7.05-7.07 (m, 1H, *J* = 8.0 Hz, Ar-**H**), 7.33-7.35 (m, 1H, *J* = 8.0 Hz, Ar-**H**), 9.39 (s, broad 1H, Ar-O**H**), 12.01 (s, broad 1H, AR-O**H**); ESI-MS (*m/z*): 151.1 $[M-H]^+$; Anal. calcd. (found) % for $C_8H_8O_3$ (*m.w.* 152.15): C, 67.08 (67.02); H, 6.33 (5.96).

Synthesis of acetic acid 3-acetyl-2-hydroxyphenyl ester (4): To a stirred solution of 1-(2,3-dihydroxyphenyl)ethanone (**3**) (27.5 g, 0.018 mmol) in 100 mL CH_2Cl_2 and pyridine (29.98

g, 0.037 mmol) were cooled to below 0-5 ºC and then added acetyl chloride (15.6 g, 0.0198 mmol) in 50 mL of CH_2Cl_2 dropwise in 0.5 h under inert atmosphere carefully. The reaction was maintained at the temperature for about 1 h. Then, the temperature was brought to room temperature gradually, with the monitoring of the reaction progress by TLC. After completion of the reaction, it was quenched in 200 mL of water, stirred well for 0.5 h. The desired product was extracted twice using CH_2Cl_2 (100 mL), filtered the inorganics and emulsions by high-flow bed Büchner funnel filtration assembly. Finally, the combined CH_2Cl_2 layer was washed with brine solution (200 mL). The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4, filtered and then concentrated by rotary evaporator at below 40 ºC under reduced pressure to obtain crude product. The crude was further purified by column chromatography eluent system being (*n*-hexane:ethyl acetate, 4:2) to obtain compound **4** as brown oily mass (24.3 g, yield: 69.2%) (2 g of diacetyl protected 2; 3-dihydroxy acetophenone compound was isolated). FTIR (KBr, ν_{max}, cm^{-1}): 3392, 2840, 1875, 1685, 1566, 1440, 1351, 1243, 745; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H, **O**COC**H**$_3$), 2.51(s, 3H, COC**H**$_3$), 7.43-7.45 (dd, 1H, Ar-**H**), 7.50-7.52 (m, 1H, *J* = 8.0 Hz, Ar-**H**), 7.79-7.81 (m, 1H, *J* = 8.0 Hz, AR-**H**), 9.52 (s, broad 1H, Ar-O**H**); ESI-MS (*m/z*): 151.1 $[M-43]^+$; Anal. calcd. (found) (%) for $C_{10}H_{10}O_4$ (*m.w.* 194.18): C, 67.08 (67.07); H, 6.33 (5.71).

Synthesis of acetic acid 3-acetyl-2-methoxyphenyl ester (5): To a stirred solution of an anhydrous K_2CO_3 (25.58 g, 0.018 mmol) in DMF (80 mL), was cooled to below 0-5 ºC and then added acetic acid 3-acetyl-2-hydroxyphenyl ester (**4**) (24 g, 0.012 mmol) in portion under stirring for 10 min and maintained at the same temperature for 0.5 h. To this, methyl iodide (19.3 g, 0.0135 mmol) was added dropwise in 10 min at below 0-5 °C under inert atmosphere carefully. Then, the reaction mass was maintained at 20-25 ºC for 4 h. After confirming the completion of reaction by TLC, it was quenched in 200 mL of water and stirred well for 0.5 h. The desired product was extracted twice using ethyl acetate (150 mL), filtered the inorganics and emulsions by high-flow bed Büchner funnel filtration assembly. Finally, the combined ethyl acetate layer was washed with brine solution (200 mL). The ethyl acetate layer was dried over anhydrous sodium sulphate, filtered and then concentrated by rotary evaporator at below 45 ºC under reduced pressure to obtain a residue. The residue was further purified by column chromatography eluent system being (*n*-hexane:ethyl acetate, 4:2) to obtain compound **5** as thick mass (20 g, yield: 77.73%) [2.0 g of (2,3-dimethoxy acetophenone) was isolated]. FTIR (KBr, ν_{max}, cm^{-1}): 3398.92, 2934, 2885, 1885, 1682, 1583.7, 1459, 1359, 1283, 752; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.21 (s, 3H, OCOC**H**$_3$), 2.55(s, 3H, COC**H**$_3$), 3.98 (s, 3H, OC**H**$_3$), 6.89-6.91 (dd, 1H, Ar-**H**), 7.54-7.56 & 7.79-7.81 (m, 2H, *J* = 8.0 Hz, Ar-**H**), ESI-MS (*m/z*): 209.21 $[M+H]^+$; Anal. calcd. (found) % for $C_{11}H_{12}O_4$ (*m.w.* 208.21): C, 67.08 (67.07); H, 6.33 (5.99).

Synthesis of 1-(3-hydroxy-2-methoxyphenyl)ethanone (O-acetoisovanillone-2) (Imp 4): To a stirred solution of powder of an anhydrous K_2CO_3 (27.83 g, 201.71 mmol) in methanol (100 mL) was cooled to below 20 ºC and then acetic acid 3-acetyl-2-methoxyphenyl ester (**5**) (20 g, 96.05 mmol) in 50 mL of methanol was added drop wise during the period of 15 min at below 20 ºC under inert atmosphere. The reaction was maintained at 20-25 ºC for 3 h and monitored the reaction progress by TLC. After completion of the reaction, then the methanol was distilled under reduced pressure at below 55 ºC to obtain residue, which was quenched in 100 mL of water and stirred well for 0.5 h. The reaction mixture was cooled to below 0-10 ºC and then acidified with 40 mL of 6N HCl under stirring (pH 2-3) and continued cooling for an additional 10 min. The desired product was extracted twice using ethyl acetate (150 mL), filtered the inorganics and emulsions by high-flow bed Büchner funnel filtration assembly. Finally, the combined ethyl acetate layer was washed with brine solution (150 mL). The ethyl acetate layer was dried over anhydrous sodium sulphate, filtered and then concentrated by rotary evaporator at below 45 ºC under reduced pressure to obtain a residue. The residue was further purified by column chromatography eluent system being (*n*-hexane:ethyl acetate, 4:2) to obtain **Imp 4** as tawny brown liquid (9.0 g, yield: 56.39%). FTIR (KBr, ν_{max}, cm^{-1}): 3398.92, 2934, 1682, 1583.7, 1459, 1359, 1283, 752, 557; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.52 (s, 3H, COC**H**$_3$), 3.79 (s, 3H, OC**H**$_3$), 6.96-6.98 (dd, 1H, *J* = 8.0 Hz, Ar-**H**), 7.02-7.04 (m, 2H, *J* = 8.0 Hz, Ar-**H**), 9.73 (s, broad 1H, Ar-O**H**); ESI-MS (*m/z*): 167.1 $[M+H]^+$; Anal. calcd. (found) % for $C_9H_{10}O_3$ (*m.w.* 166.17): C, 67.08 (67.22); H, 6.33 (5.85).

RESULTS AND DISCUSSION

Synthesis of commercially important procedures for the synthesis of acetovanillone (**I**) are reported in the literature [5-19] shown in **Scheme-III**. Although, we wish to report an alternative synthetic protocol for the synthesis of acetovanillone (**I**) with improved yield under mild conditions and facile synthetic protocols for the synthesis of process related impurities of **I**. The impurities; isoacetovanillone and isomers of acetoisovanillone may originate from corresponding starting material of 1-(4-hydroxy-3-methoxyphenyl)ethanone (acetovanillone), which can be controlled with raw material specification. Synthetic methods of acetovanillone by acylation of guaiacol with acetic acid or acetyl chloride in the presence of $ZnCl_2$ at ambient conditions in low yield are reported in the literature [17-19]. However, we have successfully demonstrated two different methods for the synthesis of acetovanillone at little energetic conditions with high yield. In the first method, acetovanillone (**I**) is prepared by acylation of guaiacol with acetic anhydride in presence of anhydrous $ZnCl_2$ and acetic acid as solvent medium under inert conditions. The obtained crude is recrystalized in *n*-hexane to afford desired product (**Scheme-III**, method 1) with HPLC purity of 98.91%.

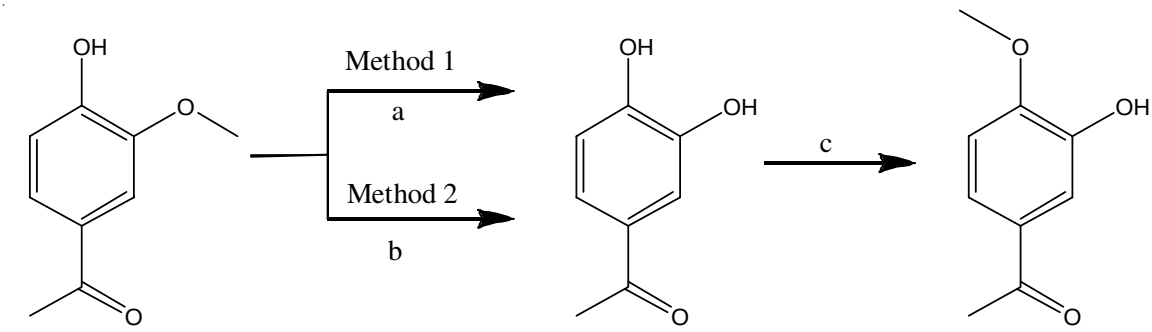
In the other method, acetovanillone (**I**) was synthesized by Friedel-Crafts acylation of guaiacol with acetyl chloride in presence of $AlCl_3$ under solvent free conditions. The obtained crude is purified by column chromatography to get target compound (**Scheme-III**, method 2) with HPLC purity of 99.12%. The product is confirmed by spectral analysis. FTIR spectrum of acetovanillone shows C=O stretching frequency of carbonyl

group of acetophenone at 1682.2 cm^{-1}, corresponding protons signal at δ 2.53 ppm as singlet in the ^1H NMR and peak at *m/z* 167.2 $[M+H]^+$value in mass spectrum.

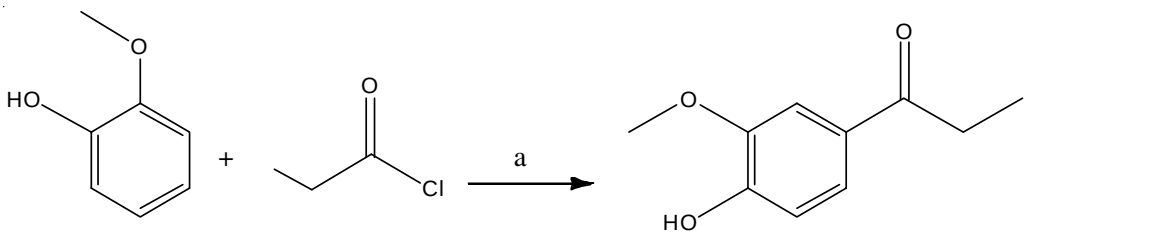
Process impurity (**Imp 1**) is an isomer of acetovanillone (**I**) known as isoacetovanillone. It is formed by C-acylation take place towards the methoxy group of guaiacol at *p*-position during the synthesis of acetovanillone. This impurity can be synthesized from acetovanillone (**I**) directly. The first step of synthetic methods involves the demethylation of **I** using 48% aq. HBr in acetic acid under reflux conditions (**Scheme-IV**, method 1) or $AlCl_3$ in pyridine under thermal conditions (**Scheme-IV**, method 2) to provide 1-(3,4-dihydroxyphenyl)ethanone (**1**). The obtained product was recrystallized from isopropyl alcohol or purified by column chromatography to afford compound **1** with HPLC purity more than 98%. The structure was confirmed by spectral analysis. FTIR spectrum of compound **1** confirms the absence of C-O stretching frequency of methoxy group at 1283.2 cm^{-1}. ^1H NMR shows the two protons of hydroxyl group as singlet at δ 9.38 ppm and δ 12.0 ppm, respectively and no signal related to methoxy protons of **I** at δ 3.94 ppm. A peak is observed at *m/z* 151.1 $[M-H]^+$ in the mass spectrum. Selective O-methylation of compound **1** is achieved with dimethyl sulphate in the presence of Cs_2CO_3 as mild base and DMF as solvent under ambient conditions to get impurity **1**. This is further purified by column chromatography to obtain desired product with good yield and HPLC purity 99.12%. FTIR spectrum of **Imp 1** shows C-O stretching frequency of methoxy group of **Imp 1** at 1283.2 cm^{-1}. In ^1H NMR, it is observed that methoxy protons as singlet at δ 3.97 ppm and a peak at *m/z* 167.2 $[M+H]^+$ in mass spectrum. Isoacetovanillone (**1**) was spiked with acetovanillone (**Imp 1**) sample and confirmed related as substance.

1-(4-Hydroxy-3-methoxyphenyl)propanone (**Imp 2**) is known as propiovanillone and referred as related substances of acetovanillone (**I**). This impurity is synthesized by performing Friedel-Crafts acylation on guaiacol with propionyl chloride in presence of $AlCl_3$ under solvent free conditions (**Scheme-V**). The obtained product was purified by column chromatography to get target compund with good yield and purity 99.22%. The impurity structure is confirmed by spectral analysis. FTIR spectrum displayed at C=O stretching frequency of carbonyl group of propiophenone at 1685.2 cm^{-1}. ^1H NMR confirms the presence of methylene protons propiophenone as quartet at δ 1.18-1.22 ppm and triplet of methyl protons at δ 2.91-2.96 ppm respectively. Mass spectrum showed mass peak at *m/z* 181.2 $[M+H]^+$.

1-(2-Hydroxy-3-methoxyphenyl)ethanone (**Imp 3**) is known as acetoisovanillone (**1**) is regarded as the isomeric impurity of acetovanillone (**I**). This compound may form during the synthesis of acetovanillone (**I**) from guaiacol, if C-acylation occurs at *ortho*-position towards to hydroxyl group during the synthesis of acetovanillone (**I**). The synthesis of **Imp 3** (**Scheme-VI**) starts from the commercially available 2-hydroxy-3-methoxy-benzaldehyde, which is converted to 2-hydroxy-3-methoxybenzoic acid (**2**) using KOH in caustic fusion method at higher temperature with good yield reported in the literature [21]. Product is confirmed by mass spectrum, which shows peak value at *m/z* 167.2 $[M-H]^+$ amu and its sodium adduct at *m/z* 191.2 amu $[(M+H+Na)^+]$. Compound **2** was transformed to acid chloride by treating with $SOCl_2$ in ether under cold



Scheme-IV: Synthetic route of 1-(3-hydroxy-4-methoxyphenyl)ethanone (**Imp 1**); Reagents and conditions: (a) 48% Aq. HBr, AcOH, D 130-135 °C, 10 h, 86%, (b) $AlCl_3$, pyridine, D 55-60 °C, 4 h, 63.4%, (c) Cs_2CO_3, DMF, dimethyl sulfate, 0-20 °C, 15 h, 67%

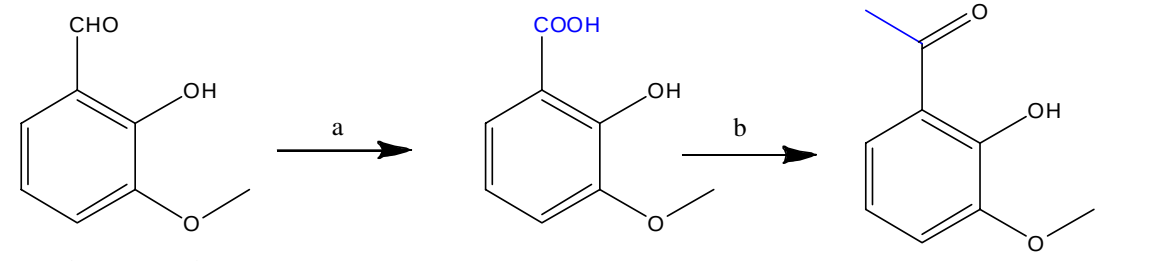


Scheme-V: Synthetic route of1-(4-hydroxy-3-methoxyphenyl)propan-1-one (propiovanillone) (**Imp 2**); Reagents and conditions: (a) $AlCl_3$, neat, D 55-60 °C, 5 h, 69 %

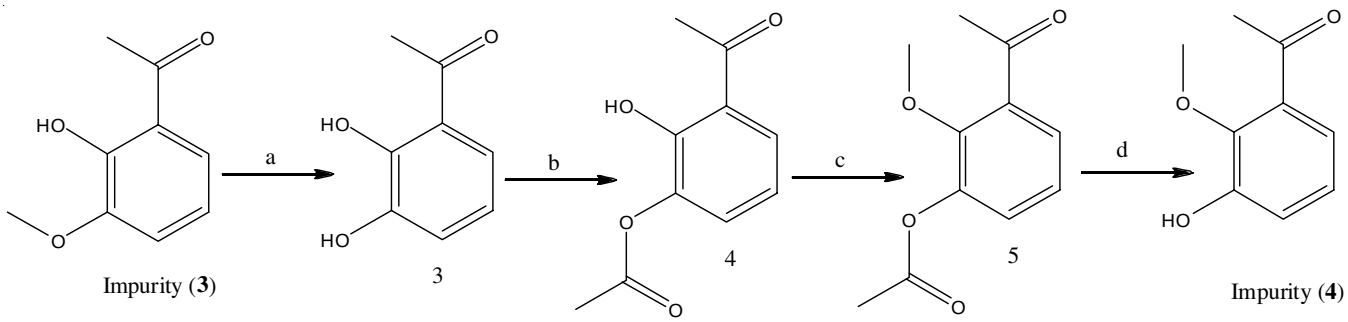
conditions (**Scheme-VI**). This acid chloride was further treated with ethyl acetoacetate (EAA) in the presence of sodium ethoxide in ethanol at ambient temperature to get condensation adduct product. Then, the obtained compound was subjected for acidic hydrolysis with dil. H_2SO_4 and followed by decarboxylation at thermal conditions to provide crude compound of 1-(2-hydroxy-3-methoxyphenyl)ethanone (**Imp 3**) with good yields and HPLC purity reported in literature [22]. The structure was confirmed by spectral analysis. FTIR spectrum displayed at C=O stretching frequency of carbonyl group of acetophenone at 1689.2 cm^{-1}. ^1H NMR indicates the three protons acetophenone protons at δ 2.63 ppm as singlet. Mass spectrum showed mass peak at *m/z* 167.2 $[M+H]^+$. This compound was spiked with acetovanillone (**I**) sample containing O-acetoisovanillone-1 (**Imp 3**), which confirmed as related substance.

1-(3-Hydroxy-2-methoxyphenyl)ethanone (**Imp 4**) is also known as O-acetoisovanillone-2 and originates from guaiacol, if C-acylation reaction takes place towards the *ortho*-position of methoxy group during the synthesis of acetovanillone (**I**). The synthetic protocol (**Scheme-VII**) involves the O-demethylation of 1-(2-hydroxy-3-methoxyphenyl)ethanone (**Imp 3**) with 48% aq. HBr in AcOH under reflux conditions to yield 1-(2,3-dihydroxyphenyl)ethanone (**3**). FTIR spectrum displays at O-H stretching frequency of phenol at 3387 cm^{-1}. ^1H NMR depicts the three alkyl protons of carbonyl functional group as singlet at δ 2.61 ppm and two phenolic hydroxyl groups of singlet proton at δ 9.39 ppm and δ 12.01 ppm respectively. Mass spectrum showed mass at *m/z* 151.1 $[M-H]^+$. Selective O-acetylation has been carried out with acetyl chloride (1 mol equivalent) in presence of pyridine as mild base and dichloromethane as solvent under ambient conditions to afford compound **4** with good yield. The structure was confirmed by spectral analysis. Mass spectrum showed mass value at *m/z* 151.1 $[M-43]^+$. Then, compound **4** was subjected for O-methylation with methyl iodide in presence of K_2CO_3 as mild base and DMF as solvent under ambient conditions to give ester compound **5**. ^1H NMR shows the Ar-OCH_3 protons as singlet at δ 3.98 ppm. Mass spectrum showed mass value at *m/z* 209.21 $[M+H]^+$. In final step, ester compound **5** was hydrolyzed in basic conditions with K_2CO_3 in methanol at ambient conditions to provide corresponding salt which was neutralized with dil. HCl in cold water to give crude compound of 1-(3-hydroxy-2-methoxyphenyl)-ethanone **(Imp 4**). This final product was further purified by column chromatography to obtain desired product in good yield with HPLC purity of 99.35%. All the intermediate products are purified by column chromatography and its structures were confirmed by spectral analysis. The C=O stretching frequency of carbonyl group of acetophenone observed at 1689.2 cm^{-1} and stretching frequency of phenolic O-H at 3398 cm^{-1} in the FTIR spectrum of **Imp 4**. ^1H NMR indicates the three protons of acetophenone, three protons of Ar-OCH_3 and one proton of phenolic OH as singlet at δ 2.52 ppm, δ 3.79 ppm and δ 9.73 ppm, respectively. Mass spectrum showed mass value at *m/z* 167.2 $[M+H]^+$. O-Acetoisovanillone impurity **(Imp 4)** was spiked with acetovanillone (**I**) sample containing O-acetoisovanillone (**Imp 4**) and confirmed related substance.

Acetovanillone related compounds (**Imp 1, 2** and **3**) were originating from the corresponding impure raw materials. These are controlled by raw material specification. Further, any traces of these impurities can be removed during the isolation aceto-



Scheme-VI: Synthetic scheme of 1-(2-hydroxy-3-methoxyphenyl)ethanone (O-acetoisovanillone-1) (**Imp 3**); Reagents and conditions: (a) Aq. KOH, D 155-160 °C, 4 h, 84%; (b) Thionyl chloride, DEE; EAA, NaOEt/EtOH, D 75-80 °C, 5 h, dil. sulfuric acid, heat, 79%



Scheme-VII: Synthetic scheme of1-(3-hydroxy-2-methoxy-phenyl)-ethanone (**Imp 4**); Reagents and conditions: (a) 48% Aq. HBr, AcOH, D 130-135 °C, 10 h, 85%; (b) Acetyl chloride, pyridine, MDC, 0-5 °C, 3 h, 69%; (c) K_2CO_3, DMF, methyl iodide, 10-15 °C, 2 h, 77%; (d) K_2CO_3, Me OH, 20-25 °C, 2 h, 56%

vanillone. Acetovanillone related substance (**Imp 3** and **4)** were removed by the purification of acetovanillone during recrystallization from acetone. These can be controlled by carrying out reaction using lower volume of reaction solvent, solvent free conditions and appropriate Lewis acid, optimization of mole ratio, reaction time and temperature. Further, these impurities can be removed from acetovanillone by additional purification in acetone.

Conclusion

It is demonstrated that the synthesis of acetovanillone (**I**), which is key intermediate of antipsychotic drug; iloperidone and its potential process impurities and one close related substances; namely, 1-(3-hydroxy-4-methoxyphenyl)ethanone (**Imp 1**) (isoacetovanillone impurity), 1-(4-hydroxy-3-methoxyphenyl)-propan-1-one) (**Imp 2**), (propiovanillone impurity), 1-(3-hydroxy-2-methoxyphenyl)ethanone (**Imp 3)** (O-acetoisovanillone impurity-1), 1-(2-hydroxy-3-methoxyphenyl)-ethanone (**Imp 4**) (O-acetoisovanillone impurity-2) while developing a laboratory process and pilot scale synthesis of acetovanillone (**I**). All the synthesized compounds (impurities) were characterized successfully by FTIR, ^{1}H NMR and mass spectrometry.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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