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Graphical Abstract

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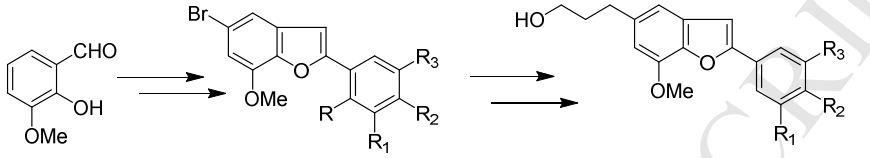

An alternate method for the synthesis of 2-aryl/alkyl-5-bromo-7-methoxy benzofurans; Application to the synthesis of Egonol, Homoegonol and Analogs via Heck reaction

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Abstract:

We herein report the general, versatile and convenient method for the synthesis of 2-arly/alkyl-5-bromo-7-methoxy benzofurans from easily available *o*-Vanillin in five steps. These benzofurans was successfully converted into biological active natural products Egonol, Homoegonol and analogous on applying Heck reaction using ethyl/methyl acrylate in the presence of palladium catalyst.

Key Words:

2-aryl/alkyl-5-bromo-7-methoxy benzofurans

Egonol

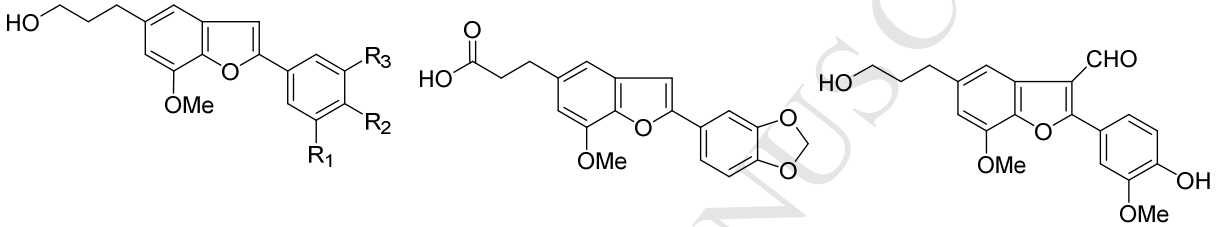
Homoegonol

Heck reaction

Synthesis

1. Introduction

2-aryl/alkylbenzofurans constitute an important subclass of naturally occurring Lignans and Neolignans. These compounds have attracted much attention in medicinal chemistry for their remarkable and diverse biological activities.[1-4] Egonol (**I**) and Homoegonol (**II**) are among the most recognized benzofurans which possess hydroxypropyl side chain at C-5 position. They have isolated from the Styracaceae family such as *S. japonicum, S. formosanus, S. Obassia, S. macranthus*, and *S. officinalis*.[5, 6] Egonoic acid (**III**), an acid analog of Egonol was isolated from the wood of *Anaxagorea clavata*.[7] These compounds were found to exhibit broad range of biological activities including cytotoxicity, antimicrobial, fungicidal, anti-inflammatory, anti-asthama and anti-oxidant properties.[8-11] Lignans like (**IV**) possess formyl group at C-3 position along with the 3-hydroxypropyl side chain at C-5 position has also been reported for its adenosine A1 receptor activities.[12]



Egonol (I), R_3=H, R_1-R_2=-OCH_2O-
Homoegonol (II), R_1=R_2=OMe, R_3=H

Egonoic acid (III)

(IV)

In view of this broad spectrum of biological activity and therapeutic applications associated with these compounds, number of approaches has been developed for the efficient synthesis of their basic skeleton.[13] Several methods have been reported for the synthesis of 2-aryl/alkyl-5-carboxyaldehyde/allyl benzofurans and their usefulness in the preparation of above bioactive natural products. Many researchers have employed conventional coupling reactions for the synthesis of such compounds.[14] Major drawbacks of those approaches are complexity and low yield. In designing an alternate and simple synthesis of Egonol, Homoegonol and analogous compounds we decided to use Heck reaction as this reaction is well known to generate vinylic compounds from the aromatic halides.[15] To achieve the desired synthetic application of Heck reaction in the preparation of Egonol and analogous, we first developed a general, versatile and convenient method for the synthesis of 2-aryl/alkyl-5-bromo benzofurans (**A**) from easily available *o*-Vanillin in five steps. Heck reaction was performed on these benzofurans using ethyl/methyl acrylate in the presence of palladium catalyst to afford 5-(2-(ethoxy/methoxycarbonyl)-E-ethenyl)-7-methoxy benzofurans (**B**) which on reduction with lithium aluminium hydride successfully produced (**I**) and (**II**). We herein report for the first time the synthesis of 2-arly/alkyl-5-bromo-7-methoxy benzofurans and their application in the synthesis of Egonol, Homoegonol and analogous via Heck reaction (**Fig. 1**).

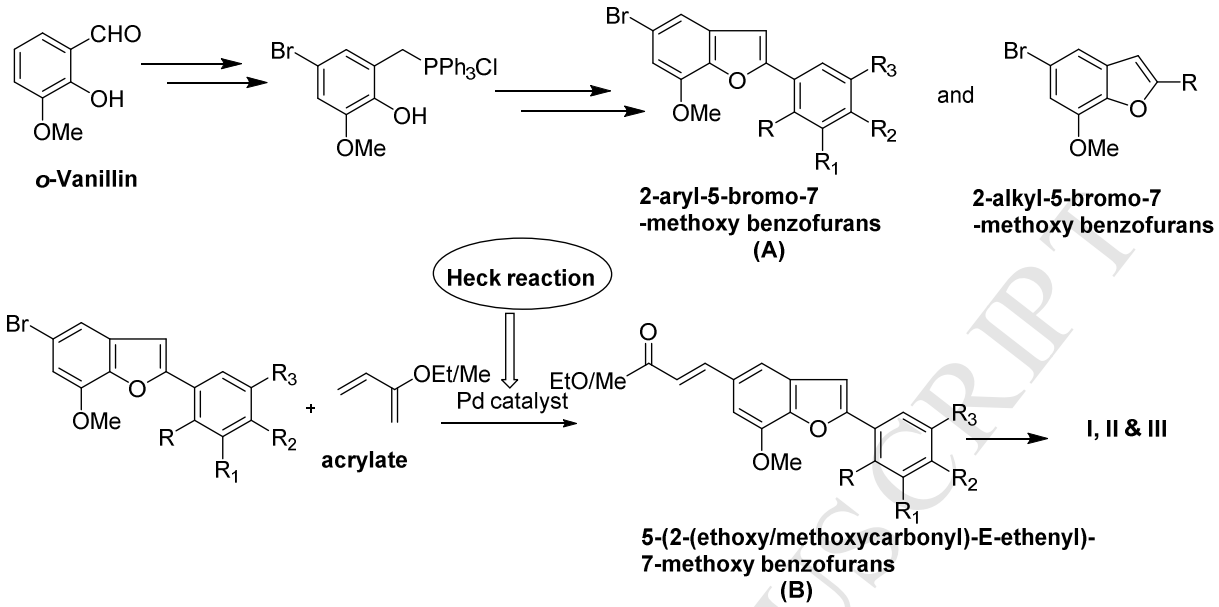
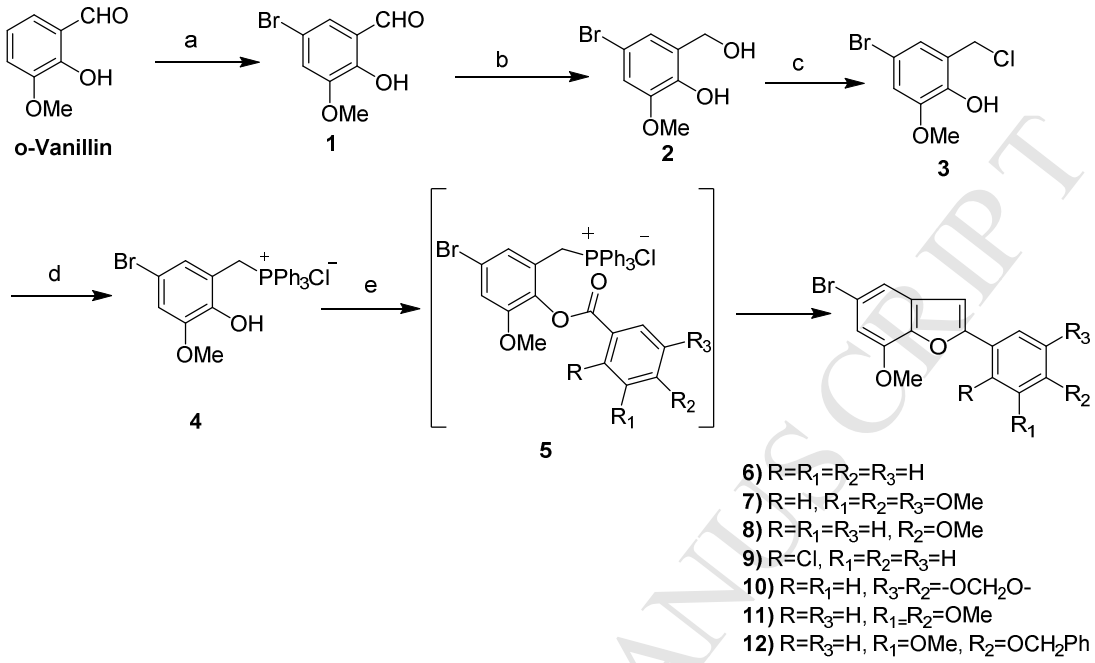


Fig. 1. Novel approach to the synthesis of 2-aryl-5-bromo-7-methoxybenzofurans and its application in the synthesis of natural products

2. Results and Discussions

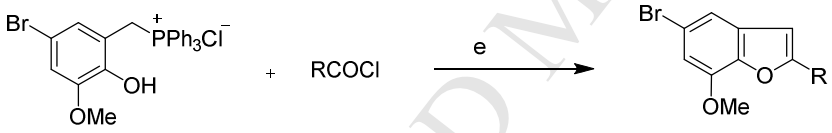
Synthesis of 2-arly/alkyl-5-bromo-7-methoxy benzofurans was carried from *o*-Vanillin as described in **Scheme-1**. 5-Bromo-o-vanillin **1** was synthesized by doing bromination on vanillin using bromine in ethylene dichloride as per reported literature.[16] Conversion of 5-bromo-o-vanillin into benzyl alcohol **2** was achieved using sodium borohydride in THF at 0 °C in 82% yield. The completion of reaction was confirmed by doing 2,4-DNP test. After 2 h, the negative 2, 4-DNP test indicates the absence of formyl group, hence completion of the reaction. To improve the yield we tried the solvent monoglyme under same reaction conditions and successfully obtained **2** in 94% yield. This benzyl alcohol was then reacted with thionyl chloride in dry MDC to afford 2-hydroxy-3-methoxy-5-bromobenzylchloride **3** as a brown solid. In IR (KBr) spectrum presence of band at 3491cm^{-1} confirmed the presence of OH group. The next step was the formation of phosphonium salt **4** by the reaction of **3** with triphenylphosphine in dry benzene under refluxing condition for 5 h. The soild separated out was filtered, washed with benzene and dried to afford phosphonium salt **4**, m.p. 244-245 °C (decomp.). It exhibited an affirmative $FeCl_3$ test and in IR (KBr) spectrum, band at 3428 cm^{-1} confirmed the presence of phenolic-OH group. These phosphonium salts on reaction with different benzoyl chloride (**Scheme 1a**) and methyl/formyl chloride (**Scheme 1b**) in toluene under reflux conditions in the presence of base triethylamine afforded corresponding 2-arly/alkyl-5-bromo-7-methoxy benzofurans (**6-14**) in good to moderate yield.

Scheme 1a:



6) R=R_1=R_2=R_3=H
7) R=H, R_1=R_2=R_3=OMe
8) R=R_1=R_3=H, R_2=OMe
9) R=Cl, R_1=R_2=R_3=H
10) R=R_1=H, R_3-R_2=-OCH_2O-
11) R=R_3=H, R_1=R_2=OMe
12) R=R_3=H, R_1=OMe, R_2=OCH_2Ph

Scheme 1b:

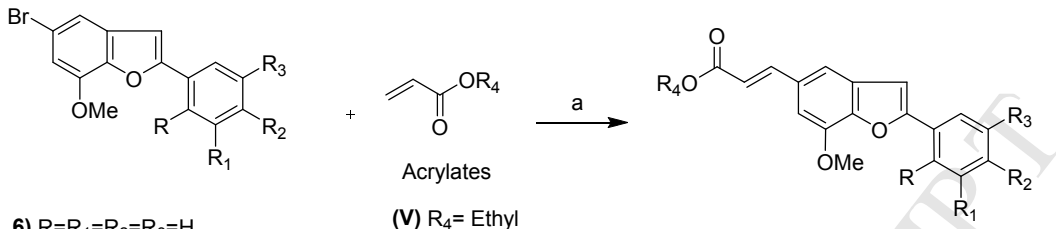


13) R= H
14) R= Me

Reagents and Conditions: a) MDC, liq. Br_2,rt, (82%); b) $NaBH_4$, monoglyme, 0 °C, (94%); c) $SOCl_2$, MDC, 0 °C, (93%); e) Acid chloride, Et_3N, toluene, 110 °C, (60-70%)

Preparation of 5-(2-(ethoxy/methoxycarbonyl)-E-ethenyl)-7-methoxy-2-arylbenzofurans from 2-arly-5-bromo-7-methoxy benzofurans have been carried out as described in **Scheme 2**. The main challenge in the projected synthesis was the formation of α, β unsaturated esters (**15a-22b**) from these 5-bromobenzofurans. This was overcome by the application of Heck reaction. Reaction conditions were optimized and the best results achieved when mixture of 5-bromobenzofurans **6-12,** (1 mmol), ethyl acrylate (2 mmol), triphenylphoshine (0.2 mmol), potassium carbonate (2 mmol) and palladium acetate (0.1 mmol) was heated under reflux for 6 h in the solvent acetonitrile under argon atmosphere. Yield of corresponding 5-(2-(ethoxycarbonyl)-E-ethenyl)-benzofurans (**15a-22b**) obtained was around 65-70% yield.

Scheme 2:



6) R=R_1=R_2=R_3=H
7) R=H, R_1=R_2=R_3=OMe
10) R=R_3=H, R_1-R_2=-OCH_2O-
11) R=R_3=H, $R_{1=}R_2$=OMe
12) R=R_3=H, $R_{1=}$OMe, R_2=OCh_2Ph

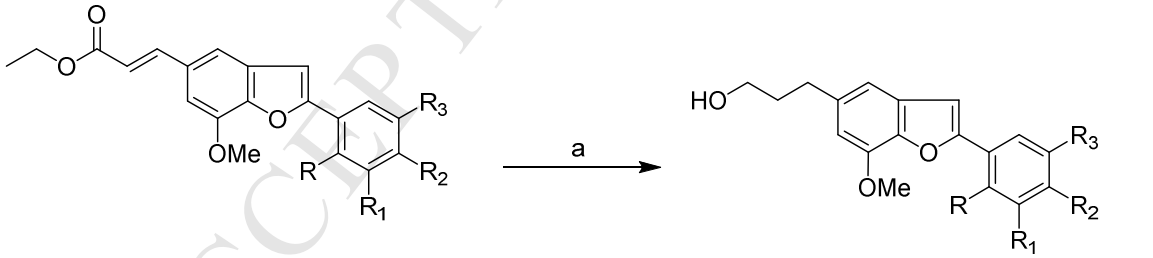
(V) R_4= Ethyl
(VI) R_4= Methyl

15a) R_4= Et, R=R=R_2=R_3=H
16a) R_4=Et, R=H, R_1=R_2=R_3=OMe
17a) R_4=Et, R=R_3=H, R_1-R_2=-OCH_2O-
18a) R_4=Et, R=R_3=H, $R_{1=}R_2$=OMe
19a) R_4=Et, R=R_3=H, R_1=OMe, R_2=OCH_2Ph
20b) R_4=Me, R=R_3=H, R_1-R_2=-OCH_2O-
21b) R_4=Me, R=R_3=H, $R_{1=}R_2$=OMe
22b) R_4=Me, R=R_3=H, R_1=OMe, R_2=OCH_2Ph

Reagents and Conditions: a) PPh_3, K_2CO_3, $Pd(OAc)_2$, ACN, 80 °C, (65-85%)

Last section of our proposed synthesis was the conversion of above obtained 5-(2-(ethoxycarbonyl)-E-ethenyl)-benzofurans (**15a-22b**) into the required natural products and analogs. Egonol (**I**) and Homoegonol (**II**) was successfully achieved by the conversion of corresponding α, β unsaturated esters (**16a, 17a, 18a, 20b**) into alcohols via reduction with lithium aluminium hydride (LAH) in THF (**Scheme 3**). 3 moles of LAH have been used for complete reduction of unsaturated esters into alcohols. Initial the addition was done at 0 °C and then reaction was continued at room temperature for 4-5 h. All these, β unsaturated esters was successfully converted into required products in around 70% yield.

Scheme 3:



16a) R_4=Et, R=H, $R_{1=}R_2$=R_3=OMe
17a) R_4=Et, R=R_3=H, R_1-R_2=-OCH_2O-
18a) R_4 =Et, R=R_3=H, $R_{1=}R_2$=OMe
20b) R_4=Me, R=R_3=H, R_1-R_2=-OCH_2O-
21b) R_4 =Me, R=R_3=H, $R_{1=}R_2$=OMe

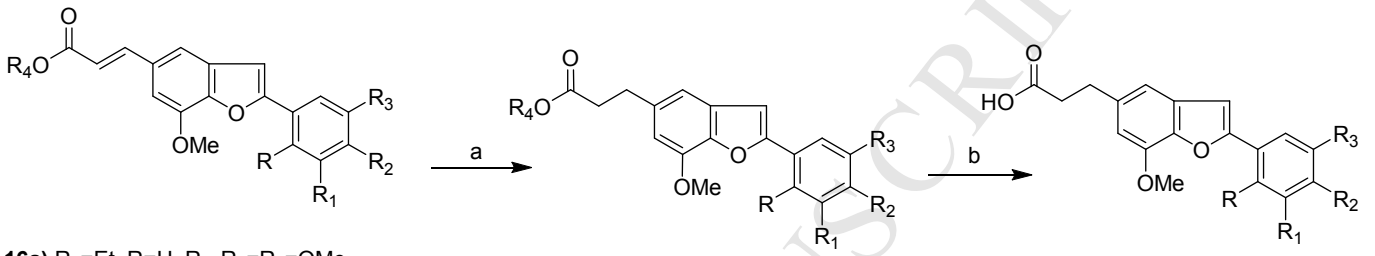
Egonol (I), R=R_3=H, R_1-R_2=-OCH_2O-
Homoegonol (II), R=R_3=H, $R_{1=}R_2$=OMe
23) R=H, $R_{1=}R_2$=R_3=OMe

Reagents and Conditions: a) LAH, THF, 0 °C - rt, (70%)

Till date only one method has been reported for the conversion of Egonol into Egonoic acid (**III**) which involves the oxidation with chromium oxide in pyridine.[17] We have developed a simple two step synthesis starting from 5-(2-(ethoxy/methoxycarbonyl)-E-ethenyl)-7-methoxy-2-(3,4-

dimethoxyphenyl) benzofuran (**Scheme 4**). First step is the conversion of α, β unsaturated esters (**16a-19a and 20b-22b**) into dihydroesters (**24-31**) in the presence of 5% Pd/C in THF at room temperature. Then these dihydroesters were hydrolyzed in the presence of NaOH and methanol to give corresponding acids (**32-34**). Compound **19a** and **22b** reacts with 5% Pd/C in THF at hydrogen pressure of 44 psi and results into the formation of corresponding dihydroester (**27 & 30**). While on increasing the pressure to 60 psi it gets converted into dihydroester (**28 & 31**) along with the removal of O-benzyl group.

Scheme 4:



16a) R_4=Et, R=H, R_1=R_2=R_3=OMe
17a) R_4=Et, R=R_3=H, R_1=R_2=-OCH_2O-
18a) R_4=Et, R=R_3=H, R_1=R_2=-OMe
19a) R_4=Et, R=R_3=H, R_1=OMe, R_2=-OCH2Ph
20b) R_4=Me, R=R_3=H, R_1-R_2=-OCH_2O-
21b) R_4=Me, R=R_3=H, R_1=R_2=-OMe
22b) R_4=Me, R=R_3=H, R_1=OMe, R_2=-OCH2Ph

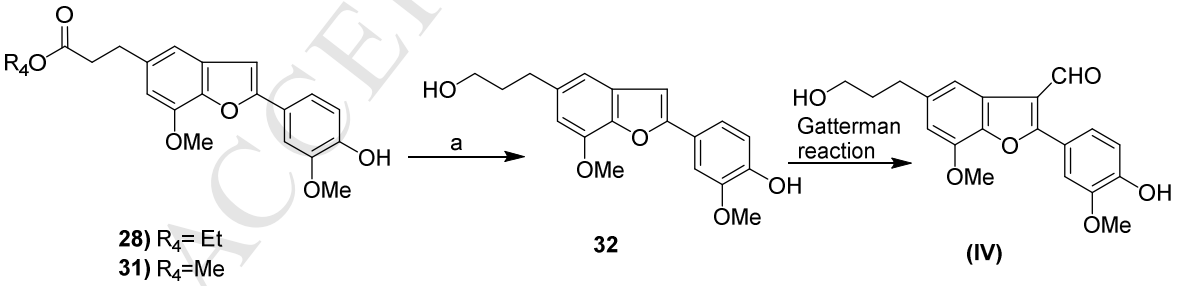
24) R_4=Et, R=H, R_1=R_2=R_3=OMe
25) R_4=Et, R=R_3=H, R_1=R_2=-OCH_2O-
26) R_4=Et, R=R_3=H, R_1=R_2=-OMe
27) R_4=Et, R=R_3=H, R_1=OMe, R_2=-OCH2Ph, p=44 psi
28) R_4= Et, R=R_3=H, R_1=OMe, R_2=OH,p=60 psi
29) R_4=Me, R=R_3=H, R_1=R_2=-OMe
30) R_4=Me, R=R_3=H, R_1=OMe, R_2=-OCH2Ph
31) R_4=Me, R=R_3=H, R_1=OMe, R_2=OH
32) R_4=Me, R=R_3=H, R_1-R_2=-OCH_2O-

33)R=H, R_1=R_2=R_3=OMe
Egonoic acid (III), R=R_3=H, R_1-R_2=-OCH_2O-
34) R=R_3=H, R_1=R_2=OMe
35) R=R_3=H, R_1=OMe, R_2=OH

Reagents and Conditions: a) 5% Pd/C, THF, rt, (65-85%); b) 1N NaOH, MeOH, 60 °C, 1N HCl, (60-90%)

As described in Scheme 5, compound **28** and **31** react with lithium aluminium hydride (2.8 mmol) in THF at 0 °C to give alcohol (**32**) in ~80% yield. The C-3 formylation of its acetylated derivative using Gatterman reaction have already been reported in literature.[18, 19] In this way we successfully achieved the formal synthesis of Lignans (**IV**).

Scheme 5:



28) R_4= Et
31) R_4=Me

32

(IV)

Reagnets and Conditions: $LiAlH_4$, THF, 0 °C - rt, 80%

3. Conclusions

We have devised an efficient method for the synthesis of 5-bromo-7-methoxy-2-aryl-/2-alkylbenzofurans from easily available *o*-vanillin and their application in the synthesis of Egonol, Homoegonol and related compounds using Heck reaction.

4. Experimental

4.1 General

All melting points recorded are uncorrected and are measured in degree Celsius with a Thomas Hoover Capillary melting point apparatus. NMR spectra were recorded on Joel FX 90Q (90 MHz) and Varian Mercury 300 (300 MHz) spectrometers using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on FT IR-Perkin Elmer 1600 instrument. Elemental analysis was obtained using Hoslis's and Perkin Elmer 2400 carbon-hydrogen analyzer. All studies were done at Department of Chemistry, University of Pune.

4.2 2-hydroxy-3-methoxy-5-bromobenzaldehyde (1)

To a well stirred mixture of *o*-vanillin (20 g, 130 mmol) in dichloroethane (75 mL), liquid bromine (23.2 g, 140 mmol) was added over a period of 0.5 hr., at room temperature. The reaction was completed in 1 hr. (monitored by TLC). Ice cold water (50 mL) was added to the reaction mixture. The organic layer was separated and washed with water. It was dried over anhydrous Na_2SO_4. Dichloroethane was removed under reduced pressure to give a crude solid product. Which was recrystallized from dichloromethane: methanol (1:1) to give a pure 5-bromo-o-vanilin **5** (25 g, 82%), m.p. 132-32 °C, (lit. [16] 127-29 °C).

4.3 Preparation of 2-hydroxy-3-methoxy-5-bromobenzyl alcohol (2)

Sodium borohydride (0.83 g, 20 mmol) was added in lots to a well cooled solution of 5-bromo-o-vanillin **1** (10 g, 43 mmol) in monoglyme (60 mL). The reaction mixture was stirred at 0 °C for 15 min and decomposed with ice cold water (25 mL). The mixture was saturated with sodium chloride and extracted with dichloromethane (2 × 50 mL). The organic layer was washed with water and dried over anhydrous Na_2SO_4. Evaporation of solvent gave a crude solid product, which was recrystallized from hexane to furnish benzylalcohol **2** (9.5 g, 94%), m.p. 90-91 °C (lit.[20] 91-92 °C). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.04(d, J= 1.8Hz, 1H), 6.94(d, J= 1.8Hz, 1H), 4.71(s, 2H, CH_2OH), 3.89(s, 3H, OCH_3) 1.76(bs, 2H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ150.2, 145.6, 128.0, 131.2, 119.5, 108.9, 59.0, 54.2.

4.4 Preparation of 2-hydroxy-3-methoxy-5-bromobenzyl chloride (3)

Thionyl chloride (2.0 g, 17 mmol) was added dropwise to a well stirred solution of benzyl alcohol **2** (2.0 g, 8.6 mmol) in dry dichloromethane (60 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hr. (monitored by TLC). Ice cold water (50 mL) was added, separated the organic layer and aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layer was washed with water and dried (Na_2SO_4). The solvent was evaporated to give a solid which on crystallization from dichloromethane: hexane (2: 8) afforded **7** (2 g, 93%) as a brown colour solid m.p. 73-75 °C. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.10(bs, 1H), 6.94(bs, 1H), 5.82(s, 1H, OH), 4.61(s, 2H, CH_2Cl), 3.89(s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 146.0, 117.0, 134.2, 121.5, 106.5, 55.7, 51.3.

4.5 Preparation of 2-hydroxy-3-methoxy-5-bromobenzyltriphenyl-phosphonium chloride (4)

Dry benzene (50 mL) was added to a mixture of triphenylphosphine (2.5 g, 9.4 mmol) and benzyl chloride **3** (2.0 g, 7.6 mmol) and the reaction mixture was refluxed for 5 h. The solid product separated out was filtered, washed with warm benzene and dried to furnish the phosphonium salt **4** (3.5 g, 88%) as a white crystalline solid, m.p. 244-45 °C (decomp.).

4.6 Preparation of 5-bromo-7methoxy-2-phenylbenzofuran (6)

A solution of benzoic acid (0.30 g, 2.4 mmol) and thionyl chloride (0.43 g, 3.6 mmol) in toluene (10 mL) was heated under reflux for 4 hr. Excess of toluene and thionyl chloride was removed under reduced pressure to furnish benzoyl chloride (0.19 g) which was used further without purification. A mixture of phosphonium salt **4** (0.2 g, 0.39 mmol), benzoyl chloride (0.065 g, 0.46 mmol) and triethylamine (0.09 g, 0.89 mmol) in toluene (30 mL) was heated under reflux for 6 hr. The reaction mixture was allowed to cool to room temperature. Water (25 mL) was added to it. The organic layer was separated, washed with water (25 mL × 2) and dried (Na_2SO_4). Toluene from the organic layer layer was distilled off under reduced pressure to give a gummy mass which was purified by passing it through a column of silica gel using ethyl acetate: hexane (1:9) as an eluent. The initial fraction on evaporation gave a solid which on recrystallization from dichloromethane: hexane (8:2) furnished the 5-bromobenzofuran **6** (0.075 g, 64%) as a white solid m.p. 115-116 °C. [Found: C, 59.98; H, 3.40. $C_{15}H_{11}BrO_2$ requires C, 59.59; H, 3.65%]; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.86-7.88(m, 2H, Ar-H), 7.36-7.48(m, 3H, Ar-H), 7.32(d, J= 1.2Hz, 1H), 6.95(s, 1H), 6.91(d, J= 1.2Hz, 1H), 4.04(s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 145.6, 143.3, 125.0, 124.2, 119.7, 117.3, 114.2, 115.0, 109.6, 109.1, 108.0, 107.8, 99.8, 55.6; IR(cm^{-1},KBr): 1616, 1586, 1493, 1472, 1247, 1154.

4.7 General procedure for preparation of 5-bromo-7-methoxy-2arylbenzofurans (7-12)

A solution of substituted benzoic acids (1 mmol) in thionyl chloride (1.5 mmol) in toluene was heated under reflux for 4 hr. Excess of toluene and thionyl chloride was removed under reduced pressure to furnish benzoyl chlorides which were used further without purification.

A mixture of phosphonium salt **4** (1 mmol), benzoyl chlorides (1.1 mmol) and triethylamine (2.3 mmol) in toluene was heated under reflux for 3-6 h. Once the reaction completed, usual work up was done as mentioned above. Solid products obtained were purified through silica gel column using hexane: ethyl acetate (9.5: 0.5) as an eluent to give the desired derivatives (**7-12**) in 60-70% yield range.

4.7.1 5-bromo-7-methoxy-2-(3,4,5-trimethoxyphenyl)benzofuran (7)

White solid, Yield 59%; m.p. 187-188 °C; Rf (5% EtOAc/hexane) 0.45; [Found: C, 54.80; H, 4.10. $C_{18}H_{17}BrO_5$ requires C, 54.98; H, 4.35%]; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.33(bs, 1H), 7.28(s, 2H, Ar-H), 6.93(bs, 1H), 6.90(s, 1H), 4.05(s, 3H, OCH_3), 3.98(s, 6H, 2-OCH_3), 3.92(s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 149, 147.3, 145.5, 144.0, 142.9, 131, 126.9, 124, 117.3, 114.6, 102, 56.7, 56.5, 55, 53.2 ; IR(cm^{-1},KBr): 1589, 1507, 1472, 1243, 1131.

4.7.2 5-bromo-7-methoxy-2-(4-methoxyphenyl)benzofuran (8)

White crystalline solid, Yield 66%; m.p. 130-131 °C; Rf (5% EtOAc/hexane) 0.65; [Found: C, 57.70; H, 4.00. $C_{16}H_{13}BrO_3$ requires C, 57.67; H, 3.93%]; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.79(d, J=8.7Hz, 2H), 7.29(d, J= 1.8Hz, 1H), 6.97(d, J= 8.7Hz, 2H), 6.88(d, J=1.8Hz, 1H), 6.80(s, 1H), 4.02(s, 3H, OCH_3), 3.86(s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156, 151.6, 149, 143.4, 128.9, 128, 127.5, 118, 114.1, 111, 108, 105.7, 101.3, 54.5, 51.8; IR(cm^{-1},KBr): 1612, 1505, 1472, 1254, 1174.

4.6.3 5-bromo-7-methoxy-2-(2-chlorophenyl)benzofuran (9)

White solid, Yield 65%; m.p. 105-106 °C; Rf (5% EtOAc/hexane) 0.71; [Found: C, 53.60; H, 2.69. $C_{15}H_{10}BrClO_2$ requires C, 53.36; H, 2.98%]; ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.06(bs, 1H), 7.51(d, J=1.8Hz, 1H), 7.48(d, J=1.8Hz, 1H), 7.35(m, 1H), 7.31(m, 1H), 7.26(bs, 1H), 6.94(s, 1H), 4.03(s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154, 152.5, 141, 139.6, 127.7, 127, 126.3, 116, 111.8, 109, 105.6, 105, 99.8, 56; IR(cm^{-1},KBr): 1588, 1481, 1469, 1250, 1185.

4.6.4 5-bromo-7-methoxy-2-(3,4,-methylenedioxyphenyl)benzofuran (10)

White solid, Yield 53%; m.p. 167-169 °C; Rf (5% EtOAc/hexane) 0.55; [Found: C, 55.50; H, 3.42. $C_{16}H_{11}BrO_4$ requires C, 55.35; H, 3.19%]; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.43(dd, J= 8.1Hz, J= 1.84Hz), 7.31(d, J=1.8Hz, 1H), 7.29(d, J=1.2Hz, 1H), 6.89(d, J= 1.2Hz, 1H), 6.86(d, J= 8.1Hz, 1H), 6.79(s, 1H), 6.02(s, 2H), 4.02(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DMSO-d_6) δ 153, 143.6, 142, 140.9, 131.4, 124.5, 124, 122.2, 119.7, 111.3, 104.6, 107, 102.4, 55.4; IR(cm^{-1},KBr):1585, 1501, 1476, 1248, 1169.

4.6.5 5-bromo-7-methoxy-2-(3,4-dimethoxyphenyl)benzofuran (11)

White solid, Yield 53%; m.p. 201-202 °C; Rf (5% EtOAc/hexane) 0.61; [Found: C, 56.20; H, 3.90. $C_{17}H_{15}BrO_4$ requires C, 56.20; H, 4.16%]; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.47(dd, J= 8.1Hz,1.8Hz, 1H), 7.37(d, J=1.8Hz), 7.31(d, J=1.2Hz, 1H), 6.95(d, J=8.1Hz, 1H), 6.91(d, J=1.2Hz, 1H), 6.83(s, 1H), 4.05(s, 3H, OCH_3), 4.01(s, 3H, OCH_3), 3.96(s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151, 150.7, 149, 139, 127.1, 124.5, 123, 115, 109.7, 108, 106.3, 104.5, 55.8, 56.3, 56.8; IR(cm^{-1},KBr): 1584, 1511, 1470, 1125, 1137.

4.6.6 5-bromo-7-methoxy-2-(3-methoxy-4-benzyloxyphenyl)benzofuran (12)

White solid, Yield 67%; m.p. 156-158 °C; Rf (5% EtOAc/hexane) 0.42; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.45(d, J=8.1Hz, 1H), 7.4-7.3(m, 6H), 6.97(bs, 1H), 6.93(d, J= 8.1Hz, 1H), 6.82(s, 1H), 6.63(bs, 1H), 5.20(s, 2H), 4.02(s, 3H), 3.99(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152, 151.7, 150, 142, 141.2, 137, 129, 124, 122.5, 116, 109.7, 109, 108.6, 105.7, 104, 103.2, 101.5, 71.3, 56.7, 55.5; IR(cm^{-1},KBr): 1580, 1507, 1475, 1120, 1131.

4.7 Preparation of 5-bromo-7-methoxybenzofuran (13)

A solution of formic acid (0.5 g, 10 mmol) and thionyl chloride (1.3 g, 1.1 mmol) in toluene (10 mL) was stirred at room temperature for 8 h. Phosphonium salt **4** (4.5 g, 0.009 mol), triethylamine (2.5 g, 210 mmol) and toluene (100 mL) were added to it and refluxed for 5 h. On usual workup as mentioned above, a gummy mass was obtained which was chromatographed on a silica gel using hexane: ethyl acetate (9:1) as an eluent to afford **13** as yellow oil (0.8 g, 40%). [Found: C, 47.40; H, 3.05. $C_9H_7BrO_2$ requires C, 47.61; H, 3.11%]; Rf (10% EtOAc/hexane) 0.56; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.61(d, J=1.8Hz, 1H), 7.34(d, J=1.8Hz, 1H), 6.91(d, J=1.8Hz, 1H), 6.71(d, J=1.8Hz, 1H), 3.99(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 147, 142.4, 133, 126.3, 123.1, 115, 106, 57; IR(cm^{-1},KBr): 1590, 1500, 1475, 1130

4.8 Preparation of 5-bromo-7-methoxy-2-methylbenzofuran (14)

A mixture of phosphonium salt **4** (0.5 g, 0.97 mmol), acetyl chloride (0.9 g, 1.14 mmol) and triethylamine in toluene (20 mL) was refluxed for 3 h. On usual workup as mentioned above, a thick liquid was obtained which was chromatographed on a silica gel using hexane as an eluent to furnish **14** as yellow oil (0.19 g, 81%). Rf (100% hexane) 0.74; [Found: C, 49.48; H, 3.91. $C_{10}H_9BrO_2$ requires C, 49.82; H, 3.76%]; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.21(d, J=1.8Hz, 1H), 6.84(d, J=1.8Hz, 1H), 6.31(s, 1H), 3.98(s, 3H), 2.46(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157, 155.5, 141, 133.4, 126.8, 122.9, 117.3, 113, 54.3, 14.6; IR(cm^{-1} ,KBr): 1629, 1475, 1436, 1207, 1116.

4.9 Preparation of 5-(2-(ethoxycarbonyl) – E –ethenyl)-7-methoxy-2-(3, 4-methylenedioxyphenyl) benzofuran (17a)

A mixture of 5-bromobenzofuran **10** (0.05 g 0.144 mmol), ethyl acrylate (0.028 g, 0.28 mmol), triphenylphodphine (0.075 g, 0.29 mmol), potassium carbonate (0.04 g, 0.29 mmol) and palladium acetate (0.003 g) in acetonitrile (5 mL) was heated under reflux for 6 hr. in argon atmosphere (monitored by TLC). The reaction mixture was cooled to room temperature and filtered. The solvent from the filtrate was recovered under reduced pressure to give a solid product which was chromatographed over silica gel using hexane: ethyl acetate (9.5:0.5) as an eluent to give (E)-ethyl cinnamate **17a** as white solid (0.033 g, 63%) m.p. 170-171 °C. [Found: C, 68.90; H, 4.89. $C_{21}H_{18}O_6$ requires C, 68.84; H, 4.95%]; Rf (5% EtOAc/hexane) 0.35; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.78(d, J=16Hz, 1H), 7.42(d, J= 1.2Hz, 1H), 7.4(d, J=1.2Hz, 1H), 7.33(d, J=1.2Hz, 1H), 6.88(bd, J=7.8Hz, 1H), 6.86(d, J=7.8Hz, 1H), 6.85(s, 1H), 6.41(d, J=16Hz, 1H), 6.02(s, 2H, OCH_2O), 4.28(q, J= 6.5Hz, 2H, OCH_2CH_3), 4.06(s, 3H, OCH_3), 1.35(t, J=6.5Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167, 158.3, 149.7, 148, 147.3, 144, 142.5, 121.8, 120, 116.5, 115.1, 112.5, 105, 103.7, 98.9, 61.2, 57, 14.8; IR(cm^{-1}, KBr): 1703, 1580, 1500, 1465, 1156.

4.10 General procedure for preparation of 5-(2-(ethoxycarbonyl) – E –ethenyl)-7-methoxy-2-arylbenzofuran (15a-22b)

A mixture of 5-bromobenzofurans **6-12,** (1 mmol), ethyl acrylate (2 mmol), triphenylphodphine (0.2 mmol), potassium carbonate (2 mmol) and palladium acetate (0.1 mmol) in acetonitrile was heated under reflux for 6 h. in argon atmosphere (monitored by TLC). The reaction mixture was cooled to room temperature and filtered. The solvent from the filtrate was recovered under reduced pressure to give a crude product which was chromatographed over silica gel using hexane: ethyl acetate (9:1) as an eluent to furnish corresponding α, β unsaturated esters.

4.10.1 5-(2-(ethoxycarbonyl) – E –ethenyl)-7-methoxy-2-phenylbenzofuran (15a)

Yield 73%, m.p. 165-166 °C. [Found: C, 74.46; H, 5.58. $C_{20}H_{18}O_4$ requires C, 74.52; H, 5.63%]; Rf (10% EtOAc/hexane) 0.38; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.88(m, 2H), 7.76(d, J= 15.9Hz, 1H, **CH**=CHCO), 7.38-7.5(m, 3H), 7.35(d, J= 1.2Hz, 1H), 7.01(s, 1H), 6.98(d, J=1.2Hz, 1H), 6.42(d, J=15.9Hz, 1H, CH=**CH**CO), 4.28(q, J= 7.2Hz, 2H, OCH_2CH_3), 4.07(s, 3H, OCH_3), 1.35(t, J=7.2Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166, 157.9, 145, 144.7, 144.1, 121.3, 120.2, 116, 113.8, 112.7, 112.3, 109, 103.6, 103, 60.6, 56, 14.3; IR(cm^{-1},KBr): 1715, 1576, 1502, 1457, 1140.

4.10.2 5-(2-(ethoxycarbonyl) – E –ethenyl)-7-methoxy-2-(3,4,5-trimethoxyphenyl)benzofuran (16a)

Yield 72.5%, m.p. 140-142 °C. [Found: C, 67.10; H, 5.90. $C_{23}H_{24}O_7$ requires C, 66.98; H, 5.86%]; Rf (10% EtOAc/hexane) 0.32; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.76(d, J= 15.9Hz, 1H, **CH**=CHCO), 7.34(d, J= 1.2Hz, 1H), 7.09(s, 2H), 6.99(d, J=1.2Hz, 1H), 6.96(s, 1H), 6.42(d, J=15.9Hz, 1H, CH=**CH**CO), 4.28(q, J= 7.2Hz, 2H, OCH_2CH_3), 4.07(s, 3H, OCH_3), 3.97(s, 6H, 2-OCH_3), 3.9(s, 3H, OCH_3), 1.34(t, J=7.2Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166, 157.9, 151, 149.3, 145.7, 145, 144.7, 144.1, 121.3, 120.2, 116, 113.8, 112.7, 112.3, 105.7, 59.1, 55.4, 56.8, 56.4, 56, 14.8; IR(cm^{-1}, KBr): 1718, 1570, 1500, 1455, 1166.

4.10.3 5-(2-(ethoxycarbonyl) – E –ethenyl)-7-methoxy-2-(3,4, dimethoxyphenyl)benzofuran (18a)

Yield 72.5%, m.p. 140-142 °C. [Found: C, 68.96; H, 5.39. $C_{22}H_{22}O_6$ requires C, 69.10; H, 5.79%]; Rf (10% EtOAc/hexane) 0.33; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.77(d, J= 15.9Hz, 1H, **CH**=CHCO), 7.48(dd, J= 8.4Hz, 2.0Hz, 1H), 7.37(d, J=2.0Hz, 1H), 7.34(d, J=1.8Hz, 1H), 6.98(d, J=1.8Hz, 1H), 6.95(d, J=8.4Hz, 1H), 6.91(s, 1H), 6.43(d, J= 15.9Hz, 1H, CH=**CH**CO), 4.29(q, J= 6.9Hz, 2H, OCH_2CH_3), 4.08(s, 3H, OCH_3), 4(s, 3H, OCH_3), 3.95(s, 3H, OCH_3), 1.37(t, J=6.9Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 157.8, 151.3, 150.8, 144.2, 144, 132.5, 131.7, 122.4, 119, 116.5, 114.3, 112.5, 112.1, 112, 109.6, 105, 104.6, 58.8, 55.5, 56.1, 56, 18.2; IR(cm^{-1}, KBr): 1710, 1580, 1507, 1450, 1160.

4.10.4 5-(2-(ethoxycarbonyl)–E–ethenyl)-7-methoxy-2-(3-methoxy-4-benzyloxyphenyl)benzofuran (19a)

Yield 87%, m.p. 117-119 °C. [Found: C, 73.45; H, 5.75. $C_{28}H_{26}O_6$ requires C, 73.34; H, 5.71%]; Rf (10% EtOAc/hexane) 0.30; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.76(d, J=15.9Hz, 1H, **CH**=CHCO), 7.3-7.5(m, 7H), 6.96(s, 1H), 6.93(m, 2H), 6.88(s, 1H), 6.42(d, J=15.9Hz, 1H, CH=**CH**CO), 5.21(s, 2H, OCH_2Ph), 4.28(q, J=6.9Hz, 2H, OCH_2CH_3), 4.07(s, 3H, OCH_3), 4.00(s, 3H, OCH_3), 1.36(t, J=6.9Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166, 155.6, 153, 147.2, 145.3, 144.9, 143, 121.3, 120, 116.4, 112.5, 112.4, 112, 110.3, 109.6, 109.2, 105, 103.8, 75, 60, 55.5, 56.1, 15; IR(cm^{-1},KBr): 1716, 1589, 1506, 1450, 1159.

4.10.5 5-(2-(methoxycarbonyl)–E–ethenyl)-7-methoxy-2-(3,4-methylenedioxyphenyl)benzofuran (20b)

Yield 61%, m.p. 184-185 °C. [Found: C, 66.80; H, 4.43. $C_{20}H_{16}O_6$ requires C, 68.17; H, 4.58%]; Rf (10% EtOAc/hexane) 0.34; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.76(d, J=16Hz, 1H), 7.42(d, J=7.5 Hz, 1.2Hz, 1H), 7.32(bs, 1H), 6.96(bs, 1H), 6.88(d, J=7.5Hz, 1H), 6.85(bs, 2H), 6.41(d, J= 16Hz, 1H, CO**CH**=CH), 6.02(s, 2H, OCH_2O), 4.06(s, 3H, OCH_3), 3.82(s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 158, 148.7, 148, 147.1, 143, 142.8, 121, 120.1, 115.8, 115, 112.4, 103, 1023, 97.5, 60.8, 53; IR(cm^{-1}, KBr): 1724, 1585, 1500, 1458, 1169.

4.10.6 5-(2-(methoxycarbonyl)–E–ethenyl)-7-methoxy-2-(3,4-dimethoxyphenyl)benzofuran (21b)

Yield 57%, m.p. 172-173 °C. [Found: C, 68.60; H, 5.50. $C_{21}H_{20}O_6$ requires C, 68.47; H, 5.47%]; Rf (10% EtOAc/hexane) 0.36; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.80(d, J=16Hz, 1H, **CH**=CHCO), 7.67(d, J=1.5Hz, 1H), 7.64(d, J=1.5Hz, 1H), 7.36(d, J=8.4Hz, 1H), 7.32(d, J=8.4Hz, 1H), 7.28(bs, 1H), 7.26(s, 1H), 6.43(d, J=16Hz, 1H, CH=**CH**CO), 4.07(s, 3H, OCH_3), 3.99(s, 3H, OCH_3), 3.94(s, 3H, OCH_3), 3.82(s, 3H, OCH_3); δ 168.9, 150, 148.7, 146.5, 144, 142.1, 140, 133.3, 121.7, 118, 117.3, 115.9, 112, 111.3, 109.2, 105, 56.5, 56, 54.3, 51.7; IR(cm^{-1}, KBr): 1720, 1582, 1515, 1459, 1155.

4.10.7 5-(2-(methoxycarbonyl)–E–ethenyl)-7-methoxy-2-(3-methoxy-4-benzyloxyphenyl) benzofuran (22b)

Yield 50%, m.p. 155-156 °C. [Found: C, 72.83; H, 5.38. $C_{27}H_{24}O_6$ requires C, 72.96; H, 5.44%]; Rf (10% EtOAc/hexane) 0.28; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.77(d, J=15.9Hz, 1H, **CH**=CHCO), 7.46(d, J= 8.0Hz, 1H), 7.32-7.42(m, 7H), 6.98(s, 1H), 6.95(d, J=8.0Hz, 1H), 6.89(s, 1H), 6.42(d, J=15.9Hz, 1H, CH=**CH**CO), 5.22(s, 2H, OCH_2Ph), 4.07(s, 3H, OCH_3), 4.00(s, 3H, OCH_3), 3.83(s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 154, 152.9, 146.5, 145.1, 144, 142.8, 121.3, 120.7, 116.5, 112.9, 112.4, 112.2, 113, 109.3, 109, 106.8, 104.1, 75.4, 59, 55.4, 56.1, 52.4; IR(cm^{-1}, KBr): 1702, 1581, 1510, 1455, 1158.

4.11 Preparation of Egonol (I)

Lithium aluminium hydride (0.025 g, 0.65 mmol) was added to a solution of compound **17a** (0.025 g, 0.068 mmol) in THF (4.0 mL) at room temperature. Reaction mixture was

refluxed for 10 h and then cooled to room temperature. It was then decomposed slowly with ice-cooled water followed by 5% H_2SO_4 and extracted with ether (3×15 mL). The combined organic layer was washed with water and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue obtained was chromatographed over silica gel using hexane: ethyl acetate (8:2) as an eluent to afford Egonol (**I**, 0.015 g, 69%), m.p. 112-113 °C, as a white solid. [Found: C, 68.70; H, 5.38. $C_{21}H_{20}O_6$ requires C, 68.47; H, 5.47%]; Rf (20% EtOAc/hexane) 0.23; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.40(d, J=8.4Hz, 1H), 7.33(bs, 1H), 6.98(bs, 1H), 6.88(d, J=8.4Hz, 1H), 6.80(s, 1H), 6.44(bs, 1H), 6.01(s, 2H, OCH_2O), 4.03(s, 3H, OCH_3), 3.71(t, J=7.5Hz, 2H, γ-CH_2), 2.78(t, J=7.5Hz, 2H, α-CH_2), 1.92-1.97(m, 2H, β-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 148.4, 148.2, 145, 142.6, 137.5, 131.2, 125.9, 119.7, 115.0, 108.8, 107.4, 105.3, 101.2, 101, 69.2, 62.3, 59.7, 54.1, 53.1, 37.6, 36; IR(cm^{-1}, KBr): 3357, 1520, 1445, 1151

4.12 Preparation of Homoegonol (II)

Lithium aluminium hydride (0.15 g, 3.9 mmol) was added to a solution of compound **18a** (0.16 g, 0.418 mmol) in THF (15 mL) at room temperature. Reaction mixture was refluxed for 10 h and then cooled to room temperature. It was then decomposed slowly with ice-cooled water followed by 5% H_2SO_4 and extracted with ether (3×20 mL). The combined organic layer was washed with water and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue obtained was chromatographed over silica gel using hexane: ethyl acetate (8:2) as an eluent to afford Homoegonol (**II**, 0.1 g, 70%), m.p. 123-125 °C, as a white solid. [Found: C, 70.03; H, 6.37. $C_{20}H_{22}O_5$ requires C, 70.15; H, 6.47%]; Rf (20% EtOAc/hexane) 0.28; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.46(dd, J=1.8Hz, 8.7Hz, 1H), 7.37(d, J=1.8Hz, 1H), 6.99(bs, 1H), 6.93(d, J=8.7Hz, 1H), 6.84(s, 1H), 6.64(bs, 1H), 4.05(s, 3H, OCH_3), 4.04(s, 3H, OCH_3), 3.93(s, 3H, OCH_3), 3.72(t, J=7.5Hz, 2H, γ-CH_2), 2.79(t, J=7.5Hz, 2H, α-CH_2), 1.93-1.98(m, 2H, β-CH_2), 1.74(bs, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 147.4, 146.3, 144.2, 141.5, 133.2, 119.7, 119.5, 112.5, 111.8, 111.1, 109.8, 108.9, 62.3, 56.7, 55.5, 32.5, 34.1, 33.4, 30.6; IR(cm^{-1}, KBr): 3374, 1515, 1450, 1161.

4.13 Preparation of 5-(3-hydroxypropyl)-7-methoxy-2-(3,4,5-trimethoxyphenyl) benzofuran (23)

Lithium aluminium hydride (0.106 g, 2.8 mmol) was added to a solution of compound **16a** (0.412 g, 1 mmol) in THF (5 mL) at 0 °C and the reaction mixture was stirred at room temperature for 4-5 h. Reaction mixture was then cooled to room temperature. It was then decomposed slowly with ice-cooled water followed by 5% H_2SO_4 and extracted with ether (2×10 mL). The combined organic layer was washed with water and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue obtained was chromatographed over silica gel using hexane: ethyl acetate (9:1) as an eluent to afford compound (**23**, 0.25 g, 67%), as a thick liquid. [Found: C, 67.80; H, 6.50. $C_{21}H_{24}O_6$ requires C, 67.72; H, 6.49%]; Rf (10% EtOAc/hexane) 0.25; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.08(s, 2H), 6.99(bs, 1H), 6.89(s, 1H), 6.66(d, J=1.2Hz, 1H), 4.04(s, 3H, OCH_3), 3.96(s, 6H, 2-OCH_3), 3.89(s, 3H, OCH_3), 3.72(t, J=7.2Hz, 2H, γ-CH_2), 2.79(t, J=7.2Hz, 2H, α-CH_2), 1.95(m, 2H, β-CH_2), 1.64(bs, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ^{13}C NMR (100 MHz,

$CDCl_3$) δ 160.2, 147.3, 145.2, 144.8, 142.8, 135.6, 119, 112.8, 111.7, 109.8, 107.9, 65.3, 57.5, 56, 52.9, 32.8, 33.7, 33, 31.4; IR(cm^{-1}, KBr): 3361, 1512, 1446, 1160.

4.14 Preparation of 5-(2-ethoxycarbonly)ethyl)-7-methoxy-2-(3,4,5-trimethoxyphenyl) benzofuran (24)

A solution of **16a** (0.04 g, 0.1 mmol) in THF (6mL) containing 5% Pd/C (100 mg) was stirred under H2 pressure (44 psi) at room temperature for 10-12 h. The reaction mixture was filtered through a short column of silica gel to remove the catalyst. The solvent from the filtrate was removed under reduced pressure. The residue obtained was purified by chromatography on a silica gel using hexane: ethyl acetate (8:2) as an eluent to give compound **24** (0.034 g, 85%), m.p. 58-59 °C as a solid. [Found: C, 66.50; H, 6.40. $C_{23}H_{26}O_7$ requires C, 66.65; H, 6.32%]; Rf (20% EtOAc/hexane) 0.47; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.07(s, 2H), 6.9(d, J=1.5Hz, 1H), 6.88(s, 1H), 6.65(d, J=1.5Hz, 1H), 4.14(q, J=7.5Hz, 2H, OCH_2CH_3), 4.03(s, 3H, OCH_3), 3.95(s, 6H, 2× OCH_3), 3.88(s, 3H, OCH_3), 3.02(t, J= 7.8Hz, 2H, $\mathbf{CH_2}CH_2CO$), 2.67(t, J=7.8Hz, 2H, $CH_2\mathbf{CH_2}CO$), 1.24(t, J=7.5Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 150.7, 148.4, 146.0, 144.6, 142.3, 140, 133.2, 121.5, 118.7, 117, 116.5, 112.4, 111, 109.8, 105.6, 61.5, 56.7, 56.1, 54.2, 36.4, 29.8, 14.7; IR(cm^{-1}, KBr): 1728, 1515, 1440, 1156.

4.15 General procedure for preparation of 5-(2-ethoxycarbonly)ethyl)-7-methoxy-2-aryl benzofurans (25-31)

A solution of α, β unsaturated esters (0.1 mmol) in THF (6 mL) containing 5% Pd/C (100 mg) was stirred under H2 pressure (44 psi) at room temperature for 10-12h. The reaction mixture was filtered through a short column of silica gel to remove the catalyst. The solvent from the filtrate was removed under reduced pressure. The residue obtained was purified by chromatography on a silica gel using hexane: ethyl acetate (9:1) as an eluent to give corresponding dihydroesters except compound 28.

4.15.1 5-(2-ethoxycarbonly)ethyl)-7-methoxy-2-(3,4 methylenedioxyphenyl)benzofuran(25)

Thick liquid, Yield 82%; [Found: C, 68.70; H, 5.38. $C_{21}H_{20}O_6$ requires C, 68.47; H, 5.47%]; Rf (10% EtOAc/hexane) 0.45; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.39(bd, J=7.8Hz, 1H), 7.32(bs, 1H), 6.97(bs, 1H), 6.87(d, J=7.8Hz, 1H), 6.79(s, 1H), 6.36(bs, 1H), 6.0(s, 2H, OCH_2O), 4.02(s, 3H, OCH_3), 3.01(t, J= 7.5 Hz, 2H, $CO\mathbf{CH_2}CH_2$-Ar), 2.66(t, J=7.5 Hz, 2H, $COCH_2\mathbf{CH_2}$-Ar), 4.14(q, J=7.2Hz, 2H, OCH_2CH_3), 1.25(t, J=7.2Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168, 150.2, 148, 147.4, 146.5, 142.6, 142.3, 140, 133.2, 120.7, 119.2, 116.8, 116, 113.4, 111.6, 109.9, 105, 98.5, 62.5, 57.7, 34.8, 30.2, 15.4; IR(KBr): 1726, 1510, 1441, 1150.

4.15.2 5-(2-ethoxycarbonly)ethyl)-7-methoxy-2-(3,4-dimethoxyphenyl)benzofuran(26)

White solid, Yield 71%, m.p. 110-112 °C; [Found: C, 68.78; H, 6.21. $C_{22}H_{24}O_6$ requires C, 68.73; H, 6.29%]; Rf (10% EtOAc/hexane) 0.42; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.45(dd,

J=1.8Hz, 8.7Hz, 1H), 7.36(d, J=1.8Hz, 1H), 6.98(d, J=1.2Hz, 1H), 6.92(d, J=8.7Hz, 1H), 6.83(s, 1H), 6.64(d, J=1.2Hz, 1H), 4.14(q, J=6.9Hz, 2H, OCH_2CH_3), 4.03(s, 3H, OCH_3), 3.94(s, 3H, OCH_3), 3.93(s, 3H, OCH_3), 3.02(t, J=7.5Hz, 2H, $CH_2\mathbf{CH_2}CO$), 2.67(t, J=7.5Hz, 2H, $\mathbf{CH_2}CH_2CO$), 1.25(t, J=6.9Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 150.1, 148, 146.6, 145.2, 142.6, 139.2, 134, 122.6, 118.3, 117.6, 115.8, 113.2, 110.9, 109.3, 106.5, 62.5, 56.5, 56.1, 33, 32.7, 14.9; IR(KBr): 1729, 1505, 1447, 1158

4.15.3 5-(2-ethoxycarbonly)ethyl)-7-methoxy-2-(3-methoxy-4-benzyloxyphenyl)benzofuran(27)

White solid, Yield 75%, m.p. 111-112 °C; [Found: C, 66.50; H, 6.40. $C_{23}H_{26}O_7$ requires C, 66.65; H, 6.32%]; Rf (10% EtOAc/hexane) 0.40; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.45(d, J=8.1Hz, 1H), 7.3-7.4(m, 6H), 6.97(bs, 1H), 6.93(d, J=8.1Hz, 1H), 6.82(s, 1H), 6.63(bs, 1H), 5.20(s, 2H, OCH_2Ph), 4.14(q, J=7.2Hz, 2H, OCH_2CH_3), 4.02(s, 3H, OCH_3), 3.99(s, 3H, OCH_3), 3.01(t, J=7.5Hz, 2H, $\mathbf{CH_2}CH_2CO$), 2.66(t, J=7.5Hz, 2H, $CH_2\mathbf{CH_2}CO$), 1.25(t, J=7.2Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 158.5, 149.4, 148.3, 137.5, 136.9, 132.2, 128.4, 125.9, 123.9, 123.1, 119.7, 116.1, 115.0, 100.9, 100.2, 72.5, 60.3, 58.7, 58.1, 57.3, 39.6, 38.5, 32.2, 16.2; IR(cm^{-1}, KBr): 1726, 1500, 1445, 1150.

4.15.4 Preparation of 5-(2-ethoxycarbonly)ethyl)-7-methoxy-2-(3-methoxy-4-hydroxyphenyl) benzofuran (28)

A solution of **19a** (0.1 g, 0.22 mmol) in THF (4 mL) containing 5% Pd/C (25 mg) was stirred under H2 pressure (60 psi) at room temperature for 12 h. The reaction mixture was filtered through a short column of silica gel to remove the catalyst. The solvent from the filtrate was removed under reduced pressure. The residue obtained was purified by chromatography on a silica gel using hexane: ethyl acetate (7:3) as an eluent to give compound **28** (0.065 g, 80%) as a thick liquid. [Found: C, 68.10; H, 6.10. $C_{21}H_{22}O_6$ requires C, 68.09; H, 5.98%]; Rf (30% EtOAc/hexane) 0.32; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.38(dd, J=1.8 Hz, 8.1Hz, 1H), 7.36(bs, 1H), 6.98(bs, 1H), 6.96(d, J=8.1Hz, 1H), 6.80(s, 1H), 6.63(bs, 1H), 5.84(s, 1H, OH), 4.14(q, J=7.2Hz, 2H, OCH_2CH_3), 4.02(s, 3H, OCH_3), 3.99(s, 3H, OCH_3), 3.01(t, J=7.5Hz, 2H, $\mathbf{CH_2}CH_2CO$), 2.66(t, J=7.5Hz, 2H, $CH_2\mathbf{CH_2}CO$), 1.24(t, J=7.2Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 152.1, 147.5, 146, 145.8, 143.4, 139.3, 133.9, 122.5, 117.4, 117.1, 116.2, 113.7, 109.9, 109.1, 105.8, 64, 56.6, 55.4, 35.5, 30.5, 16.2; IR(cm^{-1}, KBr): 3424, 1725, 1510, 1444, 1156.

4.15.5 5-(2-methoxycarbonly)ethyl)-7-methoxy-2-(3,4-dimethoxyphenyl) benzofuran (29)

Yield 60%, m.p. 120-122 °C; [Found: C, 67.64; H, 5.72. $C_{21}H_{22}O_6$ requires C, 68.09; H, 5.98%]; Rf (30% EtOAc/hexane) 0.43; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.40(dd, J=1.8Hz, 8.1Hz, 1H), 7.38(d, J=1.8z, 1H), 7.00(bs, 1H), 6.95(d, J=8.1Hz, 1H), 6.86(s, 1H), 6.66(bs, 1H), 4.06(s, 3H, OCH_3), 4.01(s, 3H, OCH_3), 3.95(s, 3H, OCH_3), 3.71(s, 3H, OCH_3), 3.05(t, J=7.5Hz, 2H, $\mathbf{CH_2}CH_2CO$), 2.71(t, J=7.5Hz, 2H, $CH_2\mathbf{CH_2}CO$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 150.6, 149.2, 146.6, 145.8, 143.5, 138.6, 134.5, 123.7, 118, 117.9, 116.3,

112.2, 110.3, 109.1, 108.5, 57.2, 56.5, 54.3, 51.1, 35.4, 29.8; IR(cm^{-1}, KBr): 1729, 1515, 1440, 1155.

4.15.6 5-(2-methoxycarbonly)ethyl)-7-methoxy-2-(3-methoxy-4-benzyloxyphenyl) benzofuran (30)

Yield 75%, m.p. 121-123 °C; [Found: C, 72.31; H, 5.45. $C_{27}H_{26}O_6$ requires C, 72.63; H, 5.86%]; Rf (30% EtOAc/hexane) 0.39; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.30-7.48(m, 7H), 6.98(d, J=1.8Hz, 1H), 6.93(d, J=8.7Hz, 1H), 6.82(s, 1H), 6.62(d, J=1.8Hz, 1H), 5.20(s, 2H), 4.03(s, 3H), 3.98(s, 3H), 3.68(s, 3H), 3.01(t, J=7.8Hz, 2H), 2.68(t, J=7.8Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 155.5, 147.4, 146, 137.8, 136.5, 131.7, 128.2, 126.8, 123.3, 123, 118.2, 116.5, 115.6, 115.0, 109.7, 109.2, 100.5, 72.6, 51.7, 58, 55.8, 35.2, 31.4; IR(cm^{-1}, KBr): 1726, 1515, 1448, 1149.

4.15.7 5-(2-methoxycarbonly)ethyl)-7-methoxy-2-(3-methoxy-4-hydroxyphenyl) benzofuran (31)

White solid, Yield 77%, m.p. 71-73 °C; [Found: C, 67.15; H, 5.48. $C_{20}H_{20}O_6$ requires C, 67.40; H, 5.66%]; Rf (30% EtOAc/hexane) 0.33; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.38(dd, J=1.8Hz, J=8.4Hz, 1H), 7.36(d, J=1.8Hz, 1H), 6.98(d, J=1.5Hz, 1H), 6.97*d, J=8.4Hz, 1H), 6.80(s, 1H), 6.62(d, J=1.5Hz, 1H), 5.82(s, 1H, OH), 4.03(s, 3H, OCH_3), 3.99(s, 3H, OCH_3), 3.68(s, 3H, OCH_3), 3.02(t, J=7.5Hz, 2H, $\mathbf{CH_2}CH_2CO$), 2.68(t, J=7.5Hz, 2H, $CH_2\mathbf{CH_2}CO$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 155, 148.4, 146.6, 138.9, 135.4, 131.2, 127.9, 127.8, 124.3, 123.5, 119.2, 116.4, 115.6, 109.2, 100.8, 52.7, 57.3, 55, 35, 32.3; IR(cm^{-1}, KBr): 1715, 1510, 1445, 1140.

4.15.7 5-(2-methoxycarbonly)ethyl)-7-methoxy-2-(3,4-methylenedioxyphenyl) benzofuran (32)

White solid, Yield 80%, m.p. 114-115 °C; [Found: C, 67.65; H, 5.25. $C_{20}H_{18}O_6$ requires C, 67.80; H, 5.10%]; Rf (30% EtOAc/hexane) 0.46; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.36(d, J=1.8Hz, 1H), 6.97(bs, 1H), 7.39(dd, J=8.4Hz, 1.8Hz, 1H), 6.87(d, J=8.4Hz, 1H), 6.79(s, 1H), 6.62(d, J=1.2Hz, 1H), 6.01(s, 2H, OCH_2O), 4.02(s, 3H, OCH_3), 3.86(s, 3H, OCH_3), 3.01(t, J=7.5Hz, 2H, OCH_2CH_2Ar), 2.68(t, J=7.5Hz, 2H, OCH_2CH_2Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 151.3, 148.2, 147.3, 145.5, 142.3, 142, 139.8, 133.5, 121.6, 119.8, 115.7, 114.5, 112.3, 111.5, 109.1, 104.2, 97.6, 62.5, 51.7, 35.8, 31.4; IR(cm^{-1}, KBr): 1734, 1513, 1456, 1148.

4.16 Preparation of Egonoic acid (III)

Sodium hydroxide (1N, 0.2 mL, 0.2 mmol) was added to a solution of compound **25** (0.05 g, 0.13 mmol) in methanol (3 mL) and refluxed for 30 min. Methanol was removed under reduced pressure and water(4 mL) was added and cooled to 10 °C. It was then acidified with HCl (1N, 2mL) and the precipitate obtained was extracted with ether (1×20 mL). The combined organic layer was washed with water (2×20 mL), dried over sodium sulfate and evaporated to give a solid. This crude mass was chromatographed on silica gel using hexane: ethyl acetate (1:1) as an eluent and afforded **Egonoic acid** (0.027 g, 58%),

m.p. 180-182 °C, as a white crystalline solid. [Found: C, 67.34; H, 4.50. $C_{19}H_{16}O_6$ requires C, 67.05; H, 4.74 %]; Rf (50% EtOAc/hexane) 0.61; ^{1}HNMR (400 MHz, $CDCl_3$, DMSO-d_6) δ 7.40(dd, J=8.1Hz, 1.8Hz, 1H), 7.32(d, J=1.8Hz, 1H), 6.97(bs, 1H), 6.87(d, J=8.1Hz, 1H), 6.79(s, 1H), 6.64(bs, 1H), 6.01(s, 2H, OCH_2O), 4.03(s, 3H, OCH_3), 3.03(t, J=7.5Hz, 2H, **CH_2**CH_2CO), 2.73(t, J=7.5Hz, 2H, CH_2**CH_2**CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 152.4, 147.9, 146.3, 145.8, 142, 141.3, 138.8, 134.5, 122.5, 119.2, 116.7, 114.5, 112.7, 110.5, 109, 104.8, 96.9, 56.7, 34.8, 32.5; IR(cm^{-1}, KBr): 3424, 1725, 1510, 1444, 1156.

4.17 General procedure for preparation of 5-(2-carboxyethyl)-7-methoxy-2-arylbenzofurans (33-35)

Sodium hydroxide (1N, 0.25 mL, 0.25 mmol) was added to a solution of dihydroesters (**24, 26** & **28,** 0.2 mmol) in methanol (5 mL) and refluxed for 30 min. Methanol was removed under reduced pressure and water (5 mL) was added and cooled to 10 °C. It was then acidified with HCl (1N, 2.5 mL) and the precipitate obtained was extracted with ether (2×20 mL). The combined organic layer was washed with water (2×20 mL), dried over sodium sulfate and evaporated to give a solid. Solid mass was chromatographed on silica gel using hexane: ethyl acetate (8.5:1.5) as an eluent to afford corresponding acids in 75-90% yield.

4.17.1 5-(2-carboxyethyl)-7-methoxy-2-(3,4,5-trimethoxybenzyl)benzofuran(33)

Yield 86%, m.p. 121-122 °C; [Found: C, 65.50; H, 5.80. $C_{21}H_{22}O_7$ requires C, 65.27; H, 5.74 %]; Rf (15% EtOAc/hexane) 0.65; ^{1}HNMR (400 MHz, $CDCl_3$, DMSO-d_6) δ 7.14(s, 2H), 7.07(bs, 1H), 6.96(s, 1H), 6.72(bs, 1H), 4.09(s, 3H, OCH_3), 4.02(s, 6H, 2×OCH_3), 3.95(s, 3H, OCH_3), 3.10(t, J=7.5Hz, 2H, **CH_2**CH_2CO), 2.81(t, J=7.5Hz, 2H, CH_2**CH_2**CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162, 152.8, 148.5, 147.2, 145.6, 142.5, 142.1, 139.6, 134.7, 123.2, 118.9, 116.5, 114, 112.3, 110.1, 108.6, 104.1, 57.2, 56.8, 56.7, 55.4, 34.5, 32.8; IR(cm^{-1}, KBr): 3435, 1714, 1510, 1438, 1150.

4.17.2 5-(2-carboxyethyl)-7-methoxy-2-(3,4-dimethoxybenzyl)benzofuran(34)

Yield 75%, m.p. 156-157 °C; [Found: C, 67.80; H, 5.50. $C_{20}H_{20}O_6$ requires C, 67.40; H, 5.65 %]; Rf (15% EtOAc/hexane) 0.57; ^{1}HNMR (400 MHz, $CDCl_3$, DMSO-d_6) δ 7.45(dd, J=1.8Hz, J=8.4Hz, 1H), 7.36(d, J=1.8Hz, 1H), 6.99(d, J=1.2Hz, 1H), 6.92(d, J-8.4Hz, 1H), 6.84(s, 1H), 6.64(d, J=1.2Hz, 1H), 4.03(s, 3H, OCH_3), 3.98(s, 3H, OCH_3), 3.92(s, 3H, OCH_3), 3.03(t, J=7.2Hz, 2H, **CH_2**CH_2CO), 2.47(t, J=7.2Hz, 2H, CH_2**CH_2**CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162, 153.2, 148.6, 147, 145.3, 141.9, 141.7, 139, 135.3, 122.9, 118.2, 115.9, 114.5, 113.6, 110.5, 108.7, 103.9, 56.7, 55.8, 54.6, 35.5, 31.7; IR(cm^{-1}, KBr): 3523, 1704, 1510, 1439, 1144.

4.17.3 5-(2-carboxyethyl)-7-methoxy-2-(3-methoxy-4-hydroxybenzyl)benzofuran(35)

Yield 90%, m.p. 158-159 °C; [Found: C, 66.70; H, 5.30. $C_{19}H_{18}O_6$ requires C, 66.66; H, 5.23 %]; Rf (15% EtOAc/hexane) 0.42; ^{1}HNMR (400 MHz, $CDCl_3$, DMSO-d_6) δ 7.39(dd, J=1.8Hz, J=8.1Hz, 1H), 7.37(d, J=1.8Hz, 1H), 6.99(s, 1H), 6.98(d, J-8.1Hz, 1H), 6.81(s, 1H), 6.64(bs, 1H), 5.88(s, 1H, OH), 4.03(s, 3H, OCH_3), 3.99(s, 3H, OCH_3), 3.04(t, J=7.2Hz,

2H, **CH_2**CH_2CO), 2.74(t, J=7.2Hz, 2H, CH_2**CH_2**CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165, 155.6, 150.6, 149.3, 145, 144.7, 142.5, 138.7, 135.2, 123.8, 117.9, 115, 114.8, 113.7, 111.5, 109.7, 104.2, 58.2, 55.9, 34.5, 30.6; IR(cm^{-1}, KBr): 3523, 1704, 1510, 1439, 1144.

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Supplementary data

^{1}H NMR, ^{13}C NMR

References and Notes:

1. Tsai, I.L.; Hsieh, C. F.; Duh, C. Y. *Phytochemistry*, **1998**, *48*, 1371-1375.
2. Honson, S. W.; Crowford, M.; Thanasingh, D. P. J. *Phytochemistry*, **1981**, *20*, 1162-1164.
3. Ward, R. S. *Nat. Prod. Rep*. **1999**, *16*, 75-96.
4. Forbes, M.; Zilliken, F.; Roberts, C.; Gyorgy, P. J. Am. Chem. Soc., **1958**, *80*, 385-389.
5. Okada, H. *J. Pharm. Soc. Jpn*. **1915**, 657.
6. Segal, R.; Milo-Goldzweig, I.; Sokoloff, S.; Zaitschek, D.V. *J. Chem. Soc. (C)*, **1967**, 2402-2404.
7. De Diaz, A. M. P. *Phytochemistry*, **1997**, *44*, 345-346.
8. Talapatra, B.; Ray, T.; Talapatra, S. K. *Indian J. Chem*. **1976**, *14B*, 613.
9. Hirano, T.; Goto, M.; Oka, K. *Life Sci.* **1994**, *55*, 1061-1069.
10. Shin, I. S.; Ahn, K. S.; Shin, N. R.; Jeon, C. M.; Kwon, O. K.; Chin, Y. W.; Lee, K.; Oh, S. R. *Arch Pharm. Res*. **2014**, *37*, 1201-10.
11. Pollyanna, F.O.; Jaqueline, L. D.; Camila, S. B.; Alba, R. B. A.; Patrícia, M. P.; Denise, C. T. *Cytotechnology*, **2015**, *67*, 1-6.
12. Yang, Z.; Hon, P. M.; Chui, K. Y.; Xu, Z. L.; Chang, H. M. *Tetrahedron Lett*. **1991**, *32*, 2061-2064.
13. a) Seemuth, P.D.; Zimmer, H. *J. Org. Chem*. **1978**, *43*, 3063-3065. (b) Watanabe, M.; Kawanishi, K.; Furukawa, S. *Chem. Pharm. Bull*. **1991**, *39*, 579-583. (c) Guy, A.; Guette, J. P. *Synthesis*, **1980**, 222-223. (d) Duffley, R. P.; Stevenson, R. *J. Chem. Soc. Perkin Trans. I*, **1977**, 802-804. (e) Villemin, D.; Goussu, D. *Heterocycles*, **1989**, *29*, 1255-1261.
14. (a) Kumar, A.; Gangwar, M.; Prakasham, A. P.; Mhatre, D.; Kalita, A. C.; Ghosh, P. *Inorg. Chem.* **2016**, *55*, 2882–2893. (b) Naveen, M.; Reddy, Ch. U.; Hussain, M.; Chaitanya, M.; Narayanaswamy, G. *J. Heterocyclic Chem*. **2013,** *50*, 1064-66. (c) Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1969**, *22*, 1329-30. (d) Mali, R. S.; Massey, A. P. *J. Chem. Res*. **1998,** *5*, 1109-1120. (e) Choi, D. H.; Hwang, J. W.; Lee, H. S.; Yang, D. M.; Jun, J.-G. *Bull. Korean Chem. Soc*. **2008**, *29*, 1594-1596.
15. (a) Iyer, S.; Ramesh, C. *Tetrahedron Lett*. **1999,** *40*, 4719-4720. (b) Villemin, D.; Nechab,B. *J. Chem. Res. (S)*, **2000**, *9*, 429-431. (c) Larhed, M.; Hallberg, A. *J. Org. Chem*. **1996**, *61*, 9582-9584. (d) Jeffery, T. *Tetrahedron lett*. **1994**, *35*, 3051-3054.

16. Henry, T. A.; Sharp, T.M. *J. Chem. Soc*. **1930**, 2088.
17. Hopkins, C. Y.; Ewing, D. F.; Chisholm, M. J. *Can. J. Chem*. **1967**, *45*, 1425-1429.
18. Yang, Z.; Liu, H. B.; Lee, C. M.; Chang, H. M.; Wong, H. N. C. *J. Org. Chem*. **1992**, 57, 7248-7257.
19. Hutchinson, S. A.; Luetjens, H.; Scammells, P. J. *Bioorg. Med. Chem. Lett*. **1997**, 7, 3081-3084.
20. Deya, P. M.; Dopico, M.; Morey, A. C. R. J.; Saa, J. M. *Tetrahedron*, **1987**, *43*, 3523-3532.