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Synthesis and antibacterial Activity of (±)-trans-2-[-methoxy-4-(4-chlorophenylthioethoxy)-5-(*N*-methyl-*N*-hydroxyureidyl) methylphenyl]-5-(3,4,5-trimethoxyphenyl) tetrahydrofuran and its intermediates

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ABSTRACT

*The 2,5-diaryl tetrahydrofuran class of compounds are extensively studied PAF receptor antagonists. On the other hand, hydroxamic acids and hydroxyl ureas are the most potent 5-lipoxygenase inhibitors known. A number of monofunctional and dual functional 5-lipoxy-genase (5-LO) inhibitors and PAF receptor antagonist have been reported. A number of hydroxyureidyl derivatives of diaryl tetrhydrofurans have been synthesized previously, which show dual 5-LO inhibitors and PAF receptor antagonistic activities. The present paper describes the synthesis of title compound, applying green methodologies, from commercially available 5-iodovanillin and 3,4,5-trimethoxy benzaldehyde as starting materials (Scheme 1). The title compound and its intermediates have been screened against five bacterial strains such as three Gram positive, Staphylococcus aureus, Bacillus sphaericus, Bacillus megaterium and two Gram negative, Pseudomonas putida, Enterobacter aerogenes. Compound **13** i.e., the title compound displayed excellent activity against Gram-positive bacteria: Staphylococcus aureus, Bacillus sphaericus, Bacillus megaterium and Gram-negative bacteria: Enterobacter aerogenes.*

Keywords: PAF, 2,5-trans diaryl tetrahydrofuran, 5-iodo vanillin, 3,4,5-trimethoxy benzaldehyde, Gram positive and Gram negative bacteria.

INTRODUCTION

Leukotrienes (LTs) are potent lipid mediators produced by the oxidation of arachidonic acid by 5-lipoxygenase (5-LO) [1]. LTB_4, C_4, D_4 and E_4 play major roles in inflammatory and allergic responses [2,3]. For example LTB_4, a potent chemotactic agent for neutrophils and esinophilis, is an important mediator of inflammation [4]. LTB_4, C_4, D_4 and E_4 are potent branchoconstrictors, as well as the slow reacting substance of anaphylaxis [5]. Platelet activating factor (PAF) generated and released by many inflammatory cells, as well as by renal and cardiac tissues under appropriate immunological and non immunological stimulation. This unknown substance was termed platelet activating factor. Investigations in to the pharmacology of PAF accelerated when synthetic preparations became available. Systemic effects of intravenous injections of PAF vary according to species and include bronchoconstriction (guinea pigs), increased vascular permeability (rats and guinea pigs) and pulmonary hypertension (rabbits). And Leukotrienes (LTs) are potent lipid mediators produced by the oxidation of arachidonic acid by 5-lipoxy-genase (5-LO) [5]. LTB_4, C_4, D_4, and E_4 were played major roles in inflammatory and allergic responses [6, 7].

Platelet-activating factor (PAF) is a potent inflammatory phospholipid mediator with a wide variety of biological activities [6, 7]. It is generated and released by many inflammatory cells, as well as by renal and cardiac tissues under appropriate immunological and non-immunological stimulation [8] and it appears to play a pathological role during immune and inflammatory responses in a number of disorders [9]. Since both PAF and leukotrienes are

released simultaneously from leukocytes and upon cellular activation, act synergistically in many biological models, a single compound which effectively inhibits the actions of both PAF and leukotrienes may offer certain therapeutic advantages in terms of efficacy and pharmacodynamics over agents which inhibits either mediator alone [10]. The 2,5-diaryl tetrahydrofuran class of compounds are extensively studied PAF receptor antagonists [11]. On the other hand, hydroxamic acids and hydroxyl ureas are the most potent 5-lipoxygenase inhibitors known [12]. A number of monofunctional and dual functional 5-LO inhibitors and PAF receptor antagonist have been reported [13-15]. A number of hydroxyureidyl derivatives of diaryl tetrhydrofurans have been synthesized previously, which show dual 5-LO inhibitors and PAF receptor antagonistic activities [15-20]. We report here the synthesis and anti-bacterial activity of the title compound and its intermediates from commercially available 5-iodovanillin and 3, 4, 5-trimethoxy benzaldehyde (**Scheme1**) utilizing green methodologies.

MATERIALS AND METHODS

The uncorrected melting points of compounds were taken in an open capillary in a paraffin bath. All reagents used were commercial and laboratory grade, melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on potassium bromide disks on a Perkin-Elmer 383 spectrophotometer. ^{1}H NMR spectra were obtained on Varian 500 MHz instrument and Varian 200 MHz, with TMS as internal Standard and chemical shifts are expressed in δ ppm solvent used in $CDCl_3$ & DMSO-d_6 and Mass spectrum on a Hewelett Packard mass spectrometer operating at 70 ev, purity of the compounds were checked by TLC, which is performed with E. Merck pre coated silica gel plates (60 F-254) with iodine as a developing agent. Acme, India silica gel, 60-120 mesh for column chromatography is used. All compounds were purified by column chromatography using ethyl acetate in hexane.

Experimental methods

*Synthesis of 4-benzyloxy-3-iodo-5-methoxy-benzaladehyde **2:***

To a stirred mixture of 5-iodovanillin (83 g, 0.298 mol) and potassium carbonate (206 g, 1.5 mol) in dimethyl formamide (800 mL), cooled to 5-10°C, was added benzyl bromide (40 ml, 0.328 mol) over a period of 20 min. The reaction mixture was stirred at room temperature for 90 min. The reaction mixture was diluted with water (2.5 L) and extracted with isopropyl acetate (1.5 L). Organic layer was separated and washed with water (3 x 200 mL) followed by brine solution, dried over $MgSO_4$, filtered and concentrated in *vacuo* to give crude compound, which was purified by flash chromatography eluting with hexane-ethyl acetate (90:10) to afford compound **2** as a white solid. Yield 84%; m.p. 57–58°C; ^{1}H NMR ($CDCl_3$, 200 MHz, δ ppm): 3.93 (s, 3 H), 5.14 (s, 2 H), 7.26 – 7.86 (m, 7 H), 9.83 (s, 1H).

Green procedure: NaOH (17.90 mmol) in water (9.0 mL) was added to a vigorously stirred solution of benzyl bromide (1.2 eq.) and 5-iodovanillin (0.83g, 2.985 mmol) in [bmim][PF_6] (4.15 mL) at room temperature for 10 h in sealed tube. The course of the reaction was followed by TLC (eluent: n-hexane/ethyl acetate, 90:10). The reaction mixture was extracted with cyclopentyl methyl ether-CPME (5 x 3 mL) and the combined organic phases were dried over $MgSO_4$, filtered and evaporated in *vacuo* and the residue was passed through a small flash chromatography. After partial evaporation of the solvent, the compound **2** precipitated from the CPME solution. Yield: 82%.

*Synthesis of 1-(4-benzyloxy-3-iodo-5-methoxy-phenyl)-prop-2-en-1-ol **3:***

To a solution of vinyl magnesium bromide (1 M in THF) (305 mL, 305.7 mmol), cooled to 0-5°C, was added a premixed solution of compound **2** (50 g, 135.8 mmol) in dichloromethane (400 mL) over a period of 30 min and allowed to attain room temperature and stirred for 1 h. The reaction mixture was cooled to 0 °C and quenched with 15% aq.NH_4Cl solution. The reaction mixture was concentrated in *vacuo* and the obtained residue was extracted with isopropyl acetate (2 x 250 mL). The organic layer was washed with water (2 x 150 mL) and brine solution (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo* to get crude compound **3,** which was purified by flash column chromatography eluting with hexanes-ethyl acetate (85:15to afford compound **3** as a white solid. Yield: 77%; m.p. 77-79°C; ^{1}H NMR ($CDCl_3$, 200 MHz, δ ppm): 3.87 (s, 3 H), 4.99 (s, 2 H), 5.10 (br.t, *J* = 5.4 Hz, 1 H), 5.41 – 5.21 (m, 2 H), 6.04 – 5.93 (m, 1 H), 6.95 (d, *J* = 3.6 Hz, 1 H), 7.43 - 7.32 (m, 4 H), 7.59 (d, *J* = 5.6 Hz, 2 H).

Green procedure: Vinyl bromide (1.358 mmol) in 2-MeTHF (3.5 mL) was added to a stirred mixture of Zinc (1.358 mmol) in 2-MeTHF (2.5 mL) and after stirring for 1 h, compound **2** (0.5 g, 1.358 mmol) in 2-MeTHF (2.5 mL) was added. The mixture was stirred at room temperature for 5 hours, and then saturated aqueous NH_4Cl solution (5 mL) was added. After 0.5 h the reaction mixture was filtered to remove the remaining zinc, 10% methane sulphonic acid (10 mL) was added and organic layer was separated. The aqueous layer was extracted with small portions of 2-MeTHF; the combined organic extracts were dried over $MgSO_4$ and concentrated in *vacuo* to afford compound **3.** Yield: 81%;

*Synthesis of 1-(4-benzyloxy-3-iodo-5-methoxy-phenyl)-propenone **4:***
To a stirred solution of compound **3** (26 g, 0.065 mol) in dichloromethane (300 mL) was added manganese dioxide (228 g, 2.62 mol) portion wise for 1 h. The reaction mixture was stirred over night at room temperature under nitrogen atmosphere. The reaction mixture was filtered through celite and the filtrate was concentrated in *vacuo* to obtain crude compound **4** (28 g). Purification by flash chromatography, eluting with hexanes-ethyl acetate (95:5) gave the compound **4** as a white solid. Yield 85%; m.p. 83-84°C; IR (KBr): 3079, 3001, 2936, 1746, 1663, 1554, 1459, 1405, 1273, 1164, 1023,787, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz, δ ppm): 3.93 (s, 3 H), 5.12 (s, 2 H), 5.96 (dd, *J* = 1.4,10.6 Hz, 1 H), 6.45 (dd, *J* = 1.4,16.8 Hz, 1 H,), 7.19 – 7.05 (m, 1 H), 7.42-7.36 (m, 3 H), 7.54 (d, *J* = 1.6 Hz, 1 H), 7.58-757 (m, 2 H), 7.95 (d, *J* = 1.8 Hz, 1H), ; ^{13}C NMR ($CDCl_3$, 200 MHz, δ ppm): 56.01, 74.58, 92.29, 112.45, 128.22, 128.44, 130.2, 131.89, 134.63, 152.50, 188.05; HRMS: $C_{17}H_{15}O_3NaI$ Calculated m/z is 416.9963 (M +Na).

Green procedure: Under air, a reaction tube was charged with CsOH (20 mol %), compound **3** (0.26 g, 0.656 mmol) and toluene (4 mL). The mixture was heated under air at 110 °C for 10 h, and then cooled to room temperature. The mixture was concentrated in *vacuo* and the residue was purified by flash column chromatography on a silica gel to give the desired product compound **4**. Yield: 94%.

*Synthesis of 1-(4-benzyloxy-3-iodo-5-methoxy-phenyl)-4-(3,4,5-trimethoxy-phenyl)-butane-1,4-dione **5:***
To a stirred solution of 3, 4, 5-trimethoxy benzaldehyde (9.2 g, 47 mmol) and 3-benzyl-5 (2-hydroxy ethyl)-4-methyl-thiazolium chloride (2.16 g, 8.17 mmol) in DMF (48 mL), under nitrogen atmosphere, was added a pre-mixed solution of compound **4** (16.1 g, 40.86 mmol) in DMF (30 mL) followed by the addition of triethylamine (8.4 mL, 61.29 mmol). The reaction mixture was heated to 70 °C for 3 h. Reaction mixture was cooled to room temperature and diluted with water (150 mL) and adjusted the pH to 2 - 3 with 5% aq. HCl solution, stirred for 30 minutes and extracted with dichloromethane (100 mL). The organic layer was washed with 5% aq. HCl, water followed by brine solution, dried over $MgSO_4$, filtered and concentrated in *vacuo* to get the crude compound. The crude compound was purified by flash chromatography eluting with hexane-ethyl acetate (80:20–75:25) to afford compound **5** as a pale yellow solid. Yield 81%; m.p. 140-141°C; IR (KBr): IR: 3433, 2943, 1692, 1681, 1584, 1463, 1414, 1352, 1275, 1129, 994, 856, 731 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz, δ ppm): 3.40 (br.s, 4 H), 3.92 (s, 12 H), 5.12 (s, 2 H), 7.26-7.57 (m, 8 H), 8.08 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz, δ ppm): 32.38, 56.06, 56.29, 60.9, 74.66, 76.73, 76.99, 105.65, 111.94, 128.24, 128.33, 128.58, 131.63, 131.91, 134.3, 152.52, 153.07, 196.47, 197.23. HRMS: $C_{27}H_{27}O_7NaI$ Calculated m/z 613.0699 (M+Na).

Green procedure: To a stirred suspension of catalyst (0.21 g, 0.81 mmol) in [bmim] [PF_6] (0.5 mL) was added Et_3N (0.61 mmol), compound **4** (0.16 g, 0.41 mmol) and compound **4a** (0.92 g, 0.47 mmol) at room temperature. The temperature was raised to 80 °C and stirred for 6 h. After completion of the reaction, as indicated by TLC, the product was extracted with cyclopentyl methyl ether CPME (4 x 5 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica-gel (60 – 120 mesh) to afford compound **5**. Yield: 95%;

*Synthesis of 1-(4-benzyloxy-3-iodo-5-methoxy-phenyl)-4-(3,4,5-trimethoxy-phenyl)-butane-1,4-diol **6:***
To a stirred solution of compound **5** (23 g, 38.95 mmol) in tetrahydrofuran (200 mL): methanol (8 mL), cooled to 5-10 °C, was added $NaBH_4$ (1.62 g, 42.85 mmol) in four portions. The reaction mixture was allowed to reach room temperature and stirred for 30 min. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to 10 °C and quenched with cold water (3 mL) and stirred for 20 minutes. The reaction mixture was evaporated under reduced pressure to obtain brown residue which was dissolved in isopropyl acetate. The organic layer was washed with water (2 x 50 mL) followed by brine solution, dried over $MgSO_4$, filtered and concentrated in *vacuo* at 30°C to afford compound **6** as yellow oily liquid. Yield 95%; ^1H NMR ($CDCl_3$, 200 MHz, δ ppm): 1.85 (br.s, 4 H), 3.83 (s, 3 H), 3.86 (s, 9 H), 4.68 (br.s, 2 H), 4.98 (s, 2 H), 6.56 (s, 2 H), 6.91 (s, 1 H), 7.32 – 7.38 (m, 4 H), 7.57 (d, *J* = 7.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 200 MHz, δ ppm): 35.06, 35.22, 55.94, 56.08, 60.77, 73.10, 74.48, 92.66, 102.6, 110.31, 127.73, 128.04, 128.26, 128.5, 136.96, 140.38, 142.87, 152.67, 153.13; EI-MS (m/z, %): 616.6 (M+Na).

Green procedure: Compound **5** (0.23 g, 0.389 mol) was dissolved in [bmim]PF_6 (1.25 mL), Sodium borohydride (0.162 g, 0.428 mmol) was added slowly, with stirring, over a period of 0.5 h. The reaction was left to stir for 1 h and then ice cold water was added (3 mL). After 10 min the [bmim]PF_6 layer was separated from the aqueous layer and extracted with cyclopentyl methyl ether (2 x 5 mL). The combined extracts were dried over $MgSO_4$, filtered, and evaporated in *vacuo*, to yield the crude compound **6** as a yellow oily liquid. Yield: 92%.

*Synthesis of 2-(4-benzyloxy-3-iodo-5-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-tetrahydro-furan **7:***
To a stirred solution of compound **6** (22 g, 37.02 mmol) in toluene (220 mL) was added ortho -phosphoric acid (10.7 mL, 185 mmol) slowly at room temperature. The reaction mixture was heated to 80-85 ^{o}C for 6 h. The reaction mixture was cooled to room temperature and diluted with water (60 mL). The organic layer was washed with water (3 x 50 mL), 10% aqueous sodium bicarbonate (3 x 25 mL) followed by brine solution. The organic layer was dried over $MgSO_4$, filtered and concentrated in *vacuo* to obtain crude compound, which was purified by flash chromatography eluting with hexane-ethyl acetate (85:15) to obtain compound **7** (trans) as a white solid. Yield 53%; m.p. 104-105 ^{o}C; IR (KBr): 3434, 2936, 2840, 1590, 1562, 1505, 1462, 1412, 1231, 1125, 1075, 1039, 1012, 902, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz, δ ppm): 1.98 (m, 2 H), 2.46 (m, 2 H), 3.84 (s, 3 H), 3.88 (s, 9 H), 4.99 (s, 2 H), 5.18 (m, 2 H), 6.62 (s, 2 H), 6.96 (s, 1 H), 7.35 – 7.39 (m, 4 H), 7.58 (d, *J* = 6.2 Hz, 2 H). ^{13}C NMR($CDCl_3$, 200 MHz, δ ppm): 35.42, 55.97, 56.04, 60.68, 74.35, 76.36, 77.0, 77.63, 80.15, 81.33, 92.72, 102.36, 110.18, 127.27, 127.83, 128.09, 128.34, 136.97, 138.77, 141.50, 146.63, 152.56, 153.11; EI-MS (m/z, %): 576.6 (M +1); HRMS: $C_{27}H_{29}O_6NaI$ Calculated m/z is 599. 0906 (M+Na).

Green procedure: A mixture of compound **6** (0.22 g, 0.37 mmol), catalytic amount of methane sulphonic acid (10 mol %) in acetic acid was subjected to reflux for 1 h. Workup with water afforded compound **7** (trans) as solid which was filtered off and purified by column chromatography using ethyl acetate: petroleum ether (9:1) as eluent to get pure product. Yield: 50 %

*Synthesis of 2-benzyloxy-3-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-tetrahydro-furan-2-yl]-benzonitrile **8:***
To a solution of compound **7** (5 g, 8.68 mmol) in dimethyl formamide (50 mL) was added cuprous cyanide (1.165 g, 13.02 mmol) and heated to 130–135 ^{o}C for 3 h. The reaction mixture was cooled to room temperature and diluted with isopropyl acetate (150 mL) followed by water (200 mL). The organic layer was washed with water (3 x 100 mL) followed by brine solution, dried over $MgSO_4$, filtered and concentrated in *vacuo* to obtain crude compound **8** which was further purified by flash chromatography eluting with hexanes-ethyl acetate (75:25) to afford compound **8** as pale yellow solid. Yield 94%; m.p. 148-150°C; IR (KBr): 3459, 2926, 2225, 1739, 1590, 1499, 1464, 1423, 1324, 1233, 1121, 1060, 1002, 856, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz, δ ppm): 1.97 (m, 2 H), 2.46 (m, 2 H), 3.84 (s, 3 H), 3.88 (s, 6 H), 3.92 (s, 3 H), 5.13-5.23 (m, 4 H), 6.61 (s, 2 H), 7.15 (d, *J* = 7.8 Hz, 2 H), 7.35 – 7.39 (m, 3 H), 7.6 (d, *J* = 6.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 200 MHz, δ ppm): 35.39, 56.04, 60.71, 75.62, 80.08, 81.56, 102.36, 107.53, 114.12, 116.31, 120.89, 128.25, 128.46, 136.15, 138.44, 140.54, 152.71, 153.17; EI-MS (m/z, %): 476 (M+1).

Green procedure: A mixture of CuCN (1.736 mmol), compound **7** (0.5 g, 0.868 mmol) in 1.0 mL of 1-*n*-butyl-3-methylimidazolium iodide (bmiI) in sealed tube was heated at 100°C with stirring for 19 h. A complete conversion of compound **7** was observed. Product was extracted using cyclopentyl methyl ether (CPME) as solvent, further purification afforded compound **8**. Yield: 79%.

*Synthesis of 2-hydroxy-3-methoxy-5- [5-(3,4,5-trimethoxy-phenyl) -tetrahydro-furan-2-yl]-benzonitrile **9:***
To a solution of compound **8** (4 g, 8.42 mmol) in methanol (40 mL) under nitrogen atmosphere, was added 10% palladium carbon (3 g) and hydrogenated under balloon pressure at room temperature for 6 h. After completion of the reaction (monitored by TLC), reaction mixture was filtered through celite bed and the filtrate was concentrated in *vacuo* to obtain compound **9** as pale yellow solid**.** Yield; 92%; m.p. 149-151°C; IR (KBr): 3254, 2940, 2842, 2226, 1593, 1505, 1462, 1416, 1342, 1293, 1237, 1129, 1068, 1005, 917, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz, δ ppm): 1.92–2.06 (m, 2 H), 2.41 – 2.53 (m, 2 H), 3.84 (s, 3 H), 3.88 (s, 6 H), 3.95 (s, 3 H), 5.17 (m, 2 H), 6.10 (br.s, 1 H), 6.61 (s, 2 H), 7.11 (s, 2 H); ^{13}C NMR ($CDCl_3$, 200 MHz, δ ppm): 35.32, 56.01, 56.14, 60.64, 80.21, 81.43, 98.21, 102.37, 112.14, 115.84, 120.4, 136.02, 138.53, 146.78, 148.07, 153.07; EI-MS (m/z, %): 386.1 (M+1).

Green procedure: Ether (0.4 g, 0.84 mmol) and concentrated hydrobromic acid (47%, 1.68 mmol) in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (4.0 mL) were stirred at 115 °C for 6 h. The reaction time was determined by TLC analysis. The reaction mixture was extracted with diethyl ether (4 x 5 mL). The combined ether extracts were concentrated under reduced pressure to obtain compound **9.** Yield: 87%.

*Synthesis of 2-(2-bromo-ethoxy)-3-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-tetrahydro-furan-2-yl]-benzonitrile **10:***
To a mixture of compound **9** (5.2 g, 13.5 mmol) and potassium carbonate (2.24 g, 16.2 mmol) in dimethyl formamide (36 mL) at room temperature was add 1,2-dibromoethane (3.5 mL, 40.51 mmol) over a period of 30 min. The reaction mixture was heated to 70–75^{o}C for 2 h and cooled to room temperature, diluted with water (180 mL) and extracted with isopropyl acetate (75 mL). The organic layer was washed with water (3 x 25 mL) followed by brine solution, dried over $MgSO_4$, filtered and concentrated in *vacuo* to obtain crude compound **10** which was purified by flash column chromatography eluting with hexane-dichloromethane (1:1) to afford compound **10** as white solid. Yield 88%; m.p. 145-146°C; IR (KBr): 3434, 2944, 2228, 1590, 1462, 1423, 1351, 1327, 1280, 1234,

1126, 1059, 1011, 860, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz, δ ppm): 1.88 – 2.08 (m, 2 H), 2.41–2.56 (m, 2 H), 3.65 (t, *J* = 6.7 Hz, 2 H), 3.84 (s, 3 H), 3.88 (br.s, 9 H), 4.44 (t, *J* = 7.0 Hz, 2 H), 5.14 – 5.24 (m, 2 H), 6.61 (s, 2 H), 7.17 (s, 2 H). ^{13}C NMR ($CDCl_3$, 200 MHz, δ ppm): 29.02, 35.35, 56.03, 60.67, 73.15, 79.96, 81.54, 102.33, 107.14, 114.16, 115.94, 120.80, 137.08, 138.36, 140.94, 148.52, 152.15, 153.13; EI-MS (m/z, %): 493.6 (M+1).

Green method: To a stirred mixture of K_2CO_3 (2.24 g, 16.2 mmol) in 2-MeTHF (25 mL) was added drop wise a solution of compound **9** (5.2 g, 13.5 mmol) in 2-MeTHF (5 mL) at room temperature. The reaction mixture was stirred for 15 min and then 1,2-dibromoethane (3.5 mL, 40.51 mmol) was added. The reaction mixture was stirred at 80 ^oC for 6 hours, quenched with water and extracted with isopropyl acetate. The organic layer was washed with water (2 x 50 mL) followed by brine solution (2 x 50 mL), dried over $MgSO_4$, filtered and evaporated in *vacuo* to obtain crude compound **10** which was purified by flash column chromatography eluting with hexane-dichloromethane (1:1) to afford compound **10** as white solid. Yield: 84%.

Synthesis of 2-[2-(4-chloro-phenyl)-ethoxy]-3-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-tetrahydro-furan-2-yl]-benzonitrile ***11:***

To a stirred mixture of *p*-chloro thiophenol (367 mg, 2.53 mmol) in dimethyl formamide (1 mL) was added sodium methoxide (165 mg, 3.04 mmol) and stirred at room temperature for 5-10 min. To the above reaction mixture a pre-mixed solution of compound **10** (1 g, 2.03 mmol) in DMF (10 mL) was added slowly for 20 min and stirred at room temperature for 1 h. The reaction mixture was quenched with cold water (20 mL) and extracted with isopropyl acetate. The organic layer was washed with water (25 mL), brine and dried over $MgSO_4$, filtered and evaporated in *vacuo* at 35^oC to obtain crude compound **11** which was purified by flash column chromatography eluting with hexane-ethyl acetate (65:35) to afford compound **11** as yellow solid. Yield 89%; m.p. 84-86$^\circ C$; IR (KBr): 3421, 2940, 2222, 1717, 1590, 1462, 1421, 1327, 1278, 1234, 1129, 1006, 855, 704. ^1H NMR ($CDCl_3$, 200 MHz, δ ppm): 1.98 (m, 2 H), 2.48 (m, 2 H), 3.35 (t, *J* = 7.3 Hz, 2 H), 3.84 (s, 6 H), 3.88 (s, 6 H), 4.26 (t, *J* = 7.3 Hz, 2H), 5.2 (m, 2 H), 6.61 (s, 2 H),7.15 (s, 2 H), 7.27 (d, *J* = 9.2 Hz, 2 H), 7.32 (d, *J* = 8.8 Hz, 2 H); EI-MS (m/z, %): 555.9 (M+1); HRMS: $C_{29}H_{30}NO_6NaSCl$ Calculated m/z: 578.1380 (M+Na).

Green Method: To a mixture of compound **10** (1 g, 2.03 mmol) and p-chloro thiophenol (367 mg, 2.53 mmol) in water (10 mL) was added K_2CO_3 (2.43 mmol) and stirred at room temperature for 12 h. The reaction mixture was quenched with cold water (20 mL) and extracted with isopropyl acetate. The organic layer was washed with water (15 mL), brine and dried over $MgSO_4$, filtered and evaporated in *vacuo* at 35$^\circ C$ to obtain crude compound **11** which was purified by flash column chromatography eluting with hexane-ethyl acetate (65:35) to afford compound **11** as yellow solid. Yield; 77%.

Synthesis of 2-[2-(4-chloro-phenyl)-ethoxy]-3-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-tetrahydro-furan-2-yl]-benzylamine ***12:***

To a stirred mixture of aluminium chloride (193 mg, 1.44 mmol) in cyclopentyl methylether (10 mL), cooled to 10 ^oC, was added lithium aluminum hydride (72 mg, 1.89 mmol) followed by slow addition of a pre-mixed solution of compound **11** (700 mg, 1.25 mmol) in 2-MeTHF (3 mL) for 10 min. After being stirred for 4 h at room temperature, the reaction mixture was cooled to 0-5 ^oC, quenched with cold water and then with 10% hydrochloric acid (~10 mL) and extracted with cyclopentyl methyl ether (CPME) twice (5 x 3 mL). The aqueous layer was made alkaline to pH ~9.0 utilizing 10% aq. sodium hydroxide solution and extracted with iso propyl acetate, dried over $MgSO_4$, filtered and evaporated in *vacuo* to obtain crude compound **12**, which was purified by flash column chromatography eluting with dichloromethane-methanol (96:4) to afford compound **12** as viscous liquid. Yield 55%; m.p. 84-86$^\circ C$; IR (KBr): 3368, 2937, 1592, 1462, 1418, 1377, 1328, 1233, 1127, 1064, 1008, 825, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz, δ ppm): 1.98 (m, 2 H), 2.45 (m, 2 H), 3.28 (t, *J* = 6.6 Hz, 2 H), 3.83 (s, 6 H), 3.87 (s, 6 H), 3.88 (m, 2 H), 4.17 (t, *J* = 6.8 Hz, 2 H), 5.18 (m, 2 H), 6.62 (s, 2 H), 6.90 (s, 2 H), 7.23 (d, *J* = 8.6 Hz, 2 H), 7.32 (d, *J* = 8.6 Hz, 2 H); EI-MS (m/z, %): 559.9 (M+1).

Synthesis of (±)-trans-2-[-Methoxy-4-(4-chlorophenylthioethoxy)-5-(N-methyl-N-hydroxyur-eidyl) methylphenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran ***(13):***

To a stirred solution of compound **12** (385 mg, 0.68 mmol) in 2-Me-THF (5 mL) was added triphosgene (71 mg, 0.24 mmol) followed by triethylamine (0.14 mL, 1.03 mmol) at room temperature. The reaction mixture was heated to 50 ^oC for 2 h. Reaction contents was cooled to room temperature, added triethylamine (0.35 mL, 2.47 mmol) followed by *N*-methyl hydroxyl amine hydrochloride and stirred at room temperature for 16 h. The reaction mixture was diluted with 2-Me-THF and washed with water followed by brine solution and dried over $MgSO_4$, filtered and concentrated in *vacuo* to get crude compound **13** which and was purified by flash column chromatography eluting with hexanes-ethyl acetate (1:1) to afford the title compound **13** as white solid. Yield 74%; m.p. 69-70$^\circ C$; IR (KBr): 3429, 2928, 1721, 1646, 1592, 1531, 1462, 1419, 1328, 1233, 1127, 1062, 1008, 822, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz, δ ppm): 1.97 (m, 2 H), 2.44 (m, 2 H), 3.12 (s, 3 H), 3.27 (t, *J* = 7 Hz, 2 H), 3.82 (s, 3 H), 3.83 (s, 3 H),

3.87 (s, 6 H), 4.16 (t, *J* = 7 Hz, 2 H), 4.41 (d, *J* = 5.5 Hz, 2 H), 5.17 (m, 2 H), 6.02 (s, 1 H), 6.41 (m, 1H), 6.61 (s, 2 H), 6.91 (s, 2 H), 7.25 (br.s, 1 H), 7.31 (d, *J* = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 200 MHz, δ ppm): 33.7, 35.4, 35.5, 38.8, 39.6, 55.6, 56.1, 60.7, 70.7, 81.1, 81.3, 102.5, 109.0, 118.4, 128.9, 130.6, 132.2, 134.3, 139.0, 152.1, 153.2, 161.5; EI-MS (m/z, %): 632.8 (M+1); HRMS: $C_{31}H_{37}N_2O_8NaSCl$ Calculated m/z: 655.1856 (M+Na).

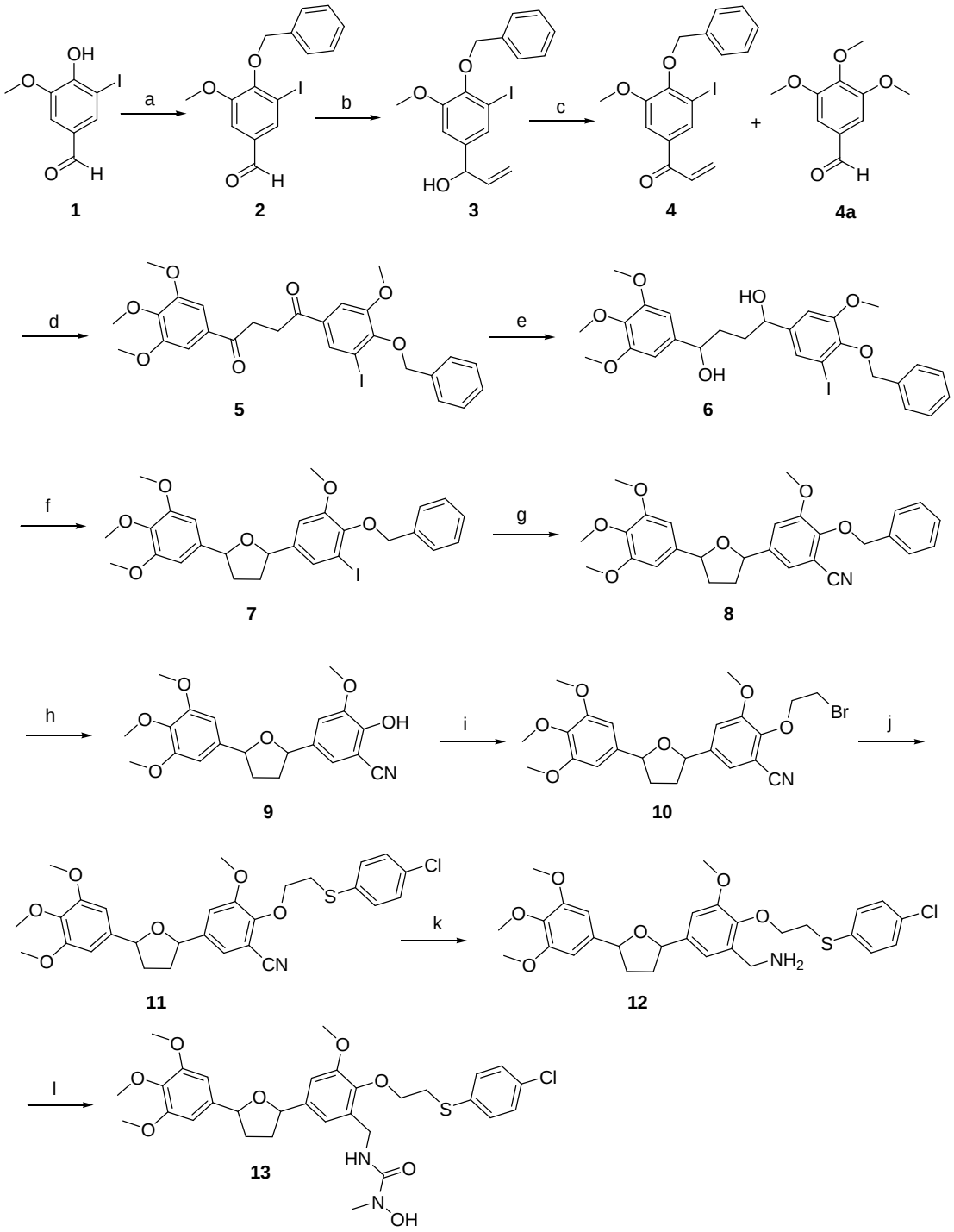
RESULTS AND DISCUSSION

Some of the trans-2,5-diaryltetrahydrofurans synthesized so far are CMI-392 [21], CMI-206 [22], MK-287 [23-24], L-659,989 [25], L-652,731 [26]. We have earlier reported the synthesis of the title compound using vanillin, vanillin acetate and acetovanillone as starting materials under non-green reaction conditions [27-31]. In this paper, we wish to report the synthesis of title compound applying green methodologies, from commercially available 5-iodovanillin and 3,4,5-trimethoxy benzaldehyde as starting materials (**Scheme 1**). Benzylation of 5-iodovanillin was carried out in [bmim][PF_6] as RTILs (room temperature ionic liquid) in presence of NaOH and water, the presence of room temperature ionic liquid and water makes the reaction system a greener method [32]. Conversion of aldehyde **2** to 1,4-di-ketone **5** (**Scheme 1**) was accomplished in three steps from 5-iodovanillin utilizing the green conditions reported by us recently [33]. Conversion of aldehyde **2** to carbinol **3** was achieved using Barbier reaction conditions over the Grignard reaction. Aldehyde **2** was treated with vinyl bromide in presence of zinc metal in 2-Methytetrahydrofuran at r.t. for 5 hours. The reaction is similar to the Grignard reaction but the crucial difference is that the Barbier reaction is a one-pot synthesis whereas a Grignard reagent is prepared separately before addition of the carbonyl compound. Barbier reactions are nucleophilic addition reactions that usually take place with relatively inexpensive and water insensitive metals or metal compounds in contrast to Grignard reagents or organolithium reagents thus making the procedure part of green chemistry. Oxidation of carbinol **3** was done using CsOH in presence of air [34] in toluene at 110 ^oC for 10 hours resulted in the formation of vinyl ketone **4.** Conversion of vinyl ketone **4** to 1,4-diketone **5** was carried out by Stetter reaction using thiazolium catalyst [27 - 31] in presence of triethyl amine in [bmim] [PF_6] as ionic liquid. The Stetter reaction can be performed in imidazolium type RTILs (room temperature ionic liquids) as solvents [35], with thiazolium salts and triethyl amine as catalysts. In these conditions the 1,4-diketones were isolated in good yields, usually higher than those obtained in classical organic solvents. Reduction of 1,4-diketone **5** was carried out in presence of $NaBH_4$ in [bmim]PF_6 as ionic liquid [36] at room temperature for 1 hour to afford 1,4-diol **6** in 92 % yield. Cyclisation of 1,4-diol **6** was accomplished using 10 % of methane sulphonic acid in acetic acid at reflux for 1 hour, to give an equilibrium mixture of *cis* and *trans* isomers of 2,5-diaryl tetrahydrofuran **7**. The geometrical isomers **7** were separated by column chromatography by eluting ethyl acetate/hexanes (15:85) to get the desired *trans* isomer **7**. Methane sulphonic acid is an efficient organocatalyst, is considered to be natural product and is part of the natural sulfur cycle [37]. Rosenmund–Von Braun reaction of compound **7** to compound **8** was carried out using CuCN (2 eq) in presence of 1-*n*-butyl-3-methylimidazolium iodide (bmiI) in sealed tube at 100°C for 19 h. Product isolation was achieved by simple extraction using organic solvents. The copper catalyst immobilized in ionic liquid media can be reused continuously. De-benzylation of benzyl ether **8** was carried out using conc; HBr (47%) in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate at 115 °C for 5 h, resulted in compound **9** [38] **.** The advantage of this protocol for benzyl ether cleavage and its effectiveness using only a moderate excess of hydrobromic acid in presence of ionic liquid makes it attractive as a green chemical method. Alkylation of compound **9** with 1,2-dibromo ethane in presence of K_2CO_3 in 2-MeTHF at 80 ^oC for 6 h resulted in compound **10**. Further alkylation of compound **10** to compound **11** was carried out using p-chloro thiophenol in presence of K_2CO_3 in water at room temperature for 12 h. Reduction of compound **11** was achieved using $LiAlH_4$ in presence of $AlCl_3$ in 2-MeTHF at room temperature for 4 h to obtain amine **12** in 55% yield. Compound **12** was treated with triphosgene followed by *N*-methyl hydroxyl amine hydrochloride in presence of Et_3N in 2-MeTHF at 50 ^oC afforded the title compound in 74 % yield.

During the course of the synthesis of title compound we have utilized 2-MeTHF as the choice of the solvent instead of tetrahydrofuran, 2-Methyl tetrahydrofuran is evolving as a green alternative solvent, which is derived from renewable resources such as corncobs and bagasse, 2-MeTHF offers both economical and environmentally friendly advantages over tetrahydrofuran. Furthermore, we have utilized isopropyl acetate as the choice of solvents which was preferred over ethyl acetate as an extraction solvent since the relatively high solubility of EtOAc in water (and water in EtOAc) due to which the aqueous waste is contaminated with more organic material, thus making it difficult to dispose off and also the product could be lost in the aqueous layer. Synthesis of compound **5**, **6**, **8** and **9** was carried out using room temperature ionic liquids (RTILs), these ionic liquid can be recycled, eliminating classical organic solvents entirely, thus making the reaction medium a greener protocol. A detailed experimental procedure for the synthesis of the title compound including green and non-green methods is given under experimental methods section.

Scheme 1: *Experimental Conditions:* **greener conditions**: a) NaOH, H_2O, benzyl bromide, [bmim][PF_6], r.t., 10 hours; b) vinyl bromide, Zn, 2-MeTHF, r.t., 5 hours; c) air, CsOH, toluene, 110 ^oC, 10 hours; d) **4a**, 3-benzyl-5 (2-

hydroxy ethyl)-4-methyl-thiazolium chloride, [bmim][PF_6], Et_3N, 80 ^oC, 6 hours; e) [bmim][PF_6], $NaBH_4$, r.t., 1 hour; f) 10% methane sulphonic acid, Acetic acid, reflux, 1hour; g) CuCN, bmiI, 100 ^oC, 19 hours; h) conc; HBr, 1-n-butyl-3-methylimidazolium tetrafluoroborate, 115 ^oC, 5 hours or H_2, 10% Pd/C, MeOH, r.t., 6 hours; i) 1,2-dibromoethane, K_2CO_3, 2-MeTHF, 80 ^oC, 6 hours; j) p-chloro-thiophenol, K_2CO_3, H_2O, r.t., 12 hours; k) $AlCl_3$, $LiAlH_4$, 2-MeTHF, r.t., 4 hours; l) triphosgene, 2-MeTHF, Et_3N, N-methyl hydroxyl amine hydrochloride, 50 ^oC, 2 hours. **non-green conditions**: a) benzyl bromide, K_2CO_3, DMF, r.t, 90 min; b) vinyl magnesium bromide (1M in THF), CH_2Cl_2, r.t., 1 hour; c) MnO_2, CH_2Cl_2, r.t., overnight; d) **4a**, 3-benzyl-5 (2-hydroxy ethyl)-4-methyl-thiazolium chloride, DMF, Et_3N, 70 ^oC, 3 hours; e) $NaBH_4$, MeOH, r.t., 30 min; f) o-H_3PO_4, toluene, 80 – 85 ^oC, 6 hour; g) CuCN, DMF, 130-135^oC, 3 hours; h) H_2, 10% Pd/C, MeOH, r.t., 6 hours (also categorized as green condition) ; i) 1,2-dibromoethane, K_2CO_3, DMF, 70 -75 ^oC, 2 hours; j) p-chloro-thiophenol, NaOMe, DMF, r.t., 1 hour; k) $AlCl_3$, $LiAlH_4$, THF, r.t., 4 hours; l) triphosgene, THF, Et_3N, 50 ^oC, 2 hours ; N-methyl hydroxyl amine hydrochloride, Et_3N, r.t.,16 h.



Scheme1: Synthesis and Antibacterial Activity of (±)-trans-2-[-methoxy-4-(4-chlorophenylthioethoxy)-5-(*N*-methyl-*N*-hydroxyureidyl) methylphenyl]-5-(3,4,5-trimethoxyphenyl) tetrahydrofuran.

Antibacterial Bioassay

The title compound and its intermediates have been screened against five bacterial strains such as three Gram positive, *Staphylococcus aureus*, *Bacillus sphaericus*, *Bacillus megaterium* and two Gram negative, *Pseudomonas putida*, *Enterobacter aerogenes*, *Pseudomonas Putida* for the bioassay. The organisms were maintained on agar slopes at 4°C and sub cultured for 24 hours before use. The agar plate well diffusion method was used as described by Desta [39]. A standardized inoculum 1-2 10^7 cfu/mL 0.5 MC Farland standards was introduced onto the surface of sterile agar plate and evenly distributed the inoculum by using a sterile glass spreader. Simultaneously 8 mm wells were cut from the plate using a sterile cork borer 100 µl of extract at a concentration of 100 mg/mL was introduced into each well. The agar plates were incubated aerobically at 37°C. After 24 hours the inhibition zones were measured with a ruler and compared with the control well containing only solvent and 10 mg/ml of streptomycin served as control. All the tests were conducted in triplicates. The data of all the parameters were statistically analyzed and expressed as mean ± S.D. The results of the preliminary antimicrobial activities are shown in **Table 1**.

The result revealed that compounds showed varying degrees of inhibition against the tested microorganisms. In general, the best antibacterial activity was displayed by compounds **4**, **12** and **13**. Compound **13** i.e., the title compound displayed excellent activity against *Gram-positive bacteria: Staphylococcus aureus*, *Bacillus sphaericus*, *Bacillus megaterium and Gram-negative bacteria: Enterobacter aerogenes*, while compounds **4, 5, 9, 10** and **12** showed good activity against *Gram positive bacteria: Staphylococcus aureus* and *Bacillus sphaericus* and compounds **10** and **13** showed good activity against *Gram negative: Enterobacter aerogenes*. Also, compounds **4**, **5** and **12** displayed slight active against *Gram negative: Pseudomonas putida*, and all other compounds either showed less active or inactive with both the *Gram positive* and *Gram negative bacteria*.

Table 1: Antibacterial activity of all the synthesized compounds (2-13) (Inhibition zone in mm)

Compound No.	*Gram positive bacteria*			*Gram negative bacteria*	
	Staphylococcus aureus	*Bacillus sphaericus*	*Bacillus megaterium*	*Enterobacter aerogenes*	*Pseudomonas Putida*
	Zone of inhibitions in mm				
2	-	5	-	5	5
3	8	8	5	5	5
4	11	9	10	13	12
5	11	10	-	8	10
6	-	-	-	3	1
7	-	8	3	9	8
8	8	8	-	-	-
9	12	11	9	10	9
10	10	12	9	12	9
11	11	12	8	11	8
12	13	11	12	11	11
13	15	13	15	13	10

Note: *Excellent activity = (inhibition zone > 12 mm); Good activity = (inhibition zone 10 - 12 mm); Slightly active = (inhibition zone 8 - 10 mm); Inactive = (inhibition zone < 6 mm)*

CONCLUSION

In conclusion, the present paper describes facile route to the synthesis of the title compound in a few high yielding steps utilizing green methodologies from commercially available 5-iodovanillin and 3,4,5-trimethoxy benzaldehyde as starting materials. Compound **13** displayed excellent against *Gram-positive bacteria: Staphylococcus aureus*, *Bacillus sphaericus*, *Bacillus megaterium and Gram-negative bacteria: Enterobacter aerogenes*, while compounds **4, 5, 9, 10** and **12** showed good activity against *Gram positive bacteria: Staphylococcus aureus* and *Bacillus sphaericus.*

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