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Synthesis and antibacterial activity of 2-2-[(4-chlorophenyl) sulfanyl] ethoxy-3-methoxy-5-[5-(3,4,5-trimethoxyphenyl)-2-furyl]benzonitrile

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ABSTRACT

The present paper describes the synthesis and of (2-(4-chlorophenylthio)ethoxy)-3-methoxy-5-(5-(3,4,5-trimethoxyphenyl)furan-2-yl)benzonitrile from commercially available vanillin and 3,4,5-trimethoxy acetophenone as starting materials utilizing green reagents and solvents. The antibacterial test results indicated that the title compound displayed excellent activity against both Gram-positive bacteria (Staphylococcus aureus and Bacillus cereus) and Gram-negative bacteria: (Escherichia Coli and Pseudomonas aeruginosa).

Keywords: Antibacterial activity, Furan, 3,4,5-trimethoxy acetophenone, vanillin, synthesis

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INTRODUCTION

Furan derivatives are versatile synthetic intermediates for the preparation of a wide range of cyclic and acyclic organic compounds [1-3]. Derivatives of furan occur ubiquitously in nature [4, 5] appear in the structure of diverse therapeutic agents (e.g., Ranitidine or Zantac), and serve as useful intermediates in organic synthesis [6,7]. The furan derivatives are emerging as a useful pharmacophore in several therapeutic areas such as antitumor activity [8,9], adenosine A_{2A} receptor antagonist[10,11], antimicrobial activities [12,13], cytotoxicity [14], anti-cancer acitivity [15,16], anti-inflammatory activity [17], selectivity for the estrogen receptor [18], inhibitor of β-rafkinase [19]. The present paper describes the antibacterial activity and synthesis and of (2-(4-chlorophenylthio)ethoxy)-3-methoxy-5-(5-(3,4,5-trimethoxyphenyl)furan-2-yl)benzonitrile from commercially available vanillin and 3,4,5-trimethoxy acetophenone as starting materials utilizing green reagents and solvents. The title compound is a hybrid scaffold of the earlier reported work on 2, 5-diaryltetrahydrofuran [20-24].

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 400 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

3-(N,N-dimethylamino)-1-(3,4,5-trimethoxyphenyl)propan-1-one (2)

To a stirred mixture of 3,4,5-Timethoxyacetophenone (10 g, 47.62 mmol), 40% aq soln. dimethyl amine (8.58 g, 190.48 mmol) and paraformaldehyde (5.72 g, 190.48 mmol) in distill water (25 mL) was added methane sulphonic acid (15 mol%) solution and refluxed for 12 h. The completion of reaction was monitored by periodic TLC. The reaction mixture was evaporated under reduced pressure and the resulting residual viscous liquid was extracted with isopropyl acetate. The organic layer was washed with water, followed by brine solution, dried over Na_2SO_4, and concentrated to afford Mannich product **2** as a pale yellow viscous liquid (11.44 g, Yield: 90%) and was utilized as such in the next step.

1-(3,4,5-trimethoxyphenyl)-prop-2-en-1-one (4)

A solution of Mannich base **2** (11.44 g, 42.80 mmol) and methyl iodide (6.68 g, 47.08 mmol) in isopropyl acetate (110 mL) was stirred under nitrogen at room temperature for 2 h. The precipitated methiodide salt **3** was removed by filtration and dried in *vacuo* overnight at room temperature. The methiodide salt **3** was suspended in water (100 mL) and isopropyl acetate (100 mL) and heated under reflux with rapid stirring for 4 h. The mixture was cooled and the pale yellow organic layer was removed. Fresh isopropyl acetate (70 mL) was added, the mixture was once again heated under reflux for 1 h, and the process was repeated once again. The organic extracts were combined, washed with brine, dried over $MgSO_4$, and evaporated to afford **4**.Off-white solid; m.p. 46-47°C. Yield: 9.32 g, 98%; IR (neat): υ_{max} 3446, 2938, 1668, 1508, 1459, 1251, 1166, 1126, 954, 783 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 2 H, -Ar-H), 7.18 (dd, 1H, J = 9.0 & 16.0 Hz, -CH=CH2), 6.64 (dd, 1H, J = 1.5 & 16.0 Hz, -CH=CH2), 5.92 (dd, 1H, J = 1.5 & 9.0 Hz, -CH=CH2), 3.96 (s, 6H, 2 x OCH3), 3.94 (s, 3H, -OCH3); EI-MS: m/z (rel.abund.%) 222.1 (M^+, 100).

1-(3,4,5-trimethoxyphenyl)prop-2-en-1-ol (6)

Vinyl bromide (1.63 g, 15.30 mmol) in 2-MeTHF (10 mL) was added to a stirred mixture of zinc (1.08 g, 15.30 mmol) in 2-MeTHF (10 mL) and after stirring for 1 h, 3,4,5-trimethoxy benzaldehyde (3 g, 15.30 mmol) in 2-MeTHF (15 mL) was added. The mixture was stirred at room temperature for 2 h, and then saturated aqueous NH_4Cl solution (25 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-Me THF; the combined organic extracts were dried over $MgSO_4$ and concentrated in *vacuo* to afford compound **6** as a yellow viscous liquid (2.73 g, Yield: 80%). The crude compound was taken to next step without further purification.

Conversion of compound 6 to compound 4 (oxidation procedure in air)

Under air, a reaction tube was charged with CsOH (330 mg, 20 mol %), compound **6** (2.5 g, 11.15 mmol) and 2-MeTHF (30 mL). The mixture was heated under air at reflux temperature for 18 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: 2.22 g, 90%.

3-Methoxy-4-hydroxy-5-iodo benzaldehyde (7)

A solution of vanillin (5 g, 32.86 mmol) in ethanol (200 mL) was cooled to 0 $^{\circ}$C and was added sodium iodide (5.91 g, 39.43 mmol) followed by drop wise addition of 5.25% w/w sodium hypochlorite (32.86 mmol, 55.0 mL) over a period of 1 h and stirred at room temperature for 30 min. After the completion of starting material checked by TLC, the reaction mixture was diluted with ~ 7 mL of sodium thiosulfate (10% w/w) and then acidified with 3.2 M HCl. Ethanol was evaporated to 1/4th volume and the reaction contents were cooled in ice bath and the precipated solids were filtered and dried under vacuum to afford 5-iodo-vanillin **7**. Yellow solid, m.p. 183-184 ^{o}C, Yield: 17.53 g, 96%; IR (KBr): υ_{max} 3186, 2847,1666, 1459, 1259, 854, 670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98 (s, 3 H), 7.34 (s, 1 H), 7.81 (s, 1 H), 9.73 (s, 1 H),10.04 (s,1 H); EI-MS: m/z (rel.abund.%) 278 (M+, 100).

3-Methoxy-4-(bromoethoxy)-5-iodo benzaldehyde (8)

To a stirred solution of K_2CO_3 (14.17 g, 102.0 mmol) in 2-MeTHF (125 mL) was added drop wise a solution of compound **7** (25 g, 85.0 mmol) in 2-MeTHF (50 mL) at room temperature. The reaction mixture was stirred for 30 min and then 1,2-dibromoethane (24.57 mL, 275.0 mmol) was added drop wise. After the addition, the reaction

mixture was stirred at 80 °C for 4 hours. The reaction was quenched with water and extracted with isopropyl acetate. The organic layer was washed with water (2 x 100 mL) followed by brine solution (2 x 50 mL), dried over $MgSO_4$, filtered and evaporated in *vacuo* to yield **8.** Yellow solid; m.p.73-75 °C, Yield: 25.40 g, 81%; IR (KBr): υ_{max} 3448, 2965, 1675, 1476, 1447, 1280,1160, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.70 (t, 2 H, *J* = 6.0 Hz), 3.90 (s, 3 H), 4.40 (t, 2 H, *J* = 6.0 Hz), 7.41 (s, 1H), 7.82 (s, 1H), 9.8 (s,1H); EI-MS: m/z (rel.abund.%) 384 (M+, 100).

3-Methoxy-4-(4-chlorophenyl thioethoxy)-5-iodo-benzaldehyde (9)
To a stirred mixture of compound **8** (3 g, 7.40 mmol), 4-chlorothiophenol (1.20 g, 8.2 mmol) in water (30 mL) was added K_2CO_3 (8.80 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°C to obtain crude compound **9.** The residue was purified by flash column chromatography (silica gel, 3:1 hexane/ethyl acetate) to afford compound **9.** Pale yellow crystalline solid; m.p. 65 °C, Yield: 15.0 g, 88%; IR (neat): υ_{max} 3447, 2831, 1695, 1451, 1382, 1266, 1136, 1038, 976,814, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.35 (t, 2 H, *J* = 6.2 Hz), 3.88 (s, 3 H), 4.22 (t, 2 H, *J* = 6.2 Hz), 7.31 (m, 4 H), 7.38 (s, 1H), 7.84 (s, 1H), 9.82 (s,1H); EI-MS: m/z (rel.abund.%) 447 (M+, 100).

l-[3-Methoxy-4-(4-chlorophenylthioethoxy)-5-iodophenyl]-4-(3,4,5- trimethoxyphenyl)butane-l,4-dione (10)
To a stirred suspension of catalyst (0.76 g, 0.81 mmol) in [bmim] [PF_6] (1.5 mL) was added Et_3N (3.38 mmol), compound **4** (0.5 g, 2.25 mmol) and compound **9** (1.15 g, 2.58 mmol) at room temperature. The temperature was raised to 80 °C and stirred for 8 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%**.** Yellow solid, m.p.115-117 °C, Yield: 6.2 g, 89%; IR (KBr): υ_{max} 3470, 2931,1651, 1458, 1403, 1272, 1125, 1093, 858 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 3.33 (t, 2 H, *J* = 7.3 Hz), 3.41 (m, 4 H), 3.84 (s, 3 H), 3.92 (s, 9 H), 4.26 (t, 2 H, *J* = 7.3 Hz), 7.26 (m, 4 H), 7.34 (s, 2 H), 7.52 (s, 1 H), 8.02 (s, 1 H); EI-MS: m/z (rel.abund.%) 671 (M+, 100).

2-(4-2-[(4-chlorophenyl)sulfanyl]ethoxy-3-iodo-5-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)furan (11)
A mixture of compound **10** (0.50 g, 0.745 mmol), catalytic amount of methane sulphonic acid (10 mol %) in acetic acid was subjected to reflux for 1 h. After completion of the reaction, as indicated by TLC, work up with water afforded compound **11** as a yellow syrupy liquid which was utilized in the next step as such without further purification. Yield: 74%.

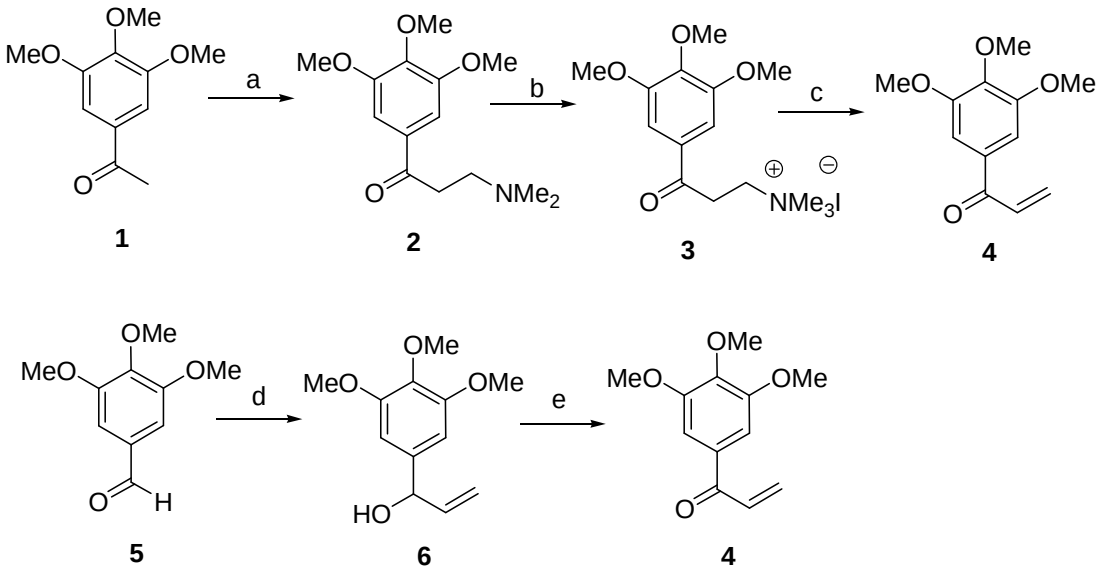
2-2-[(4-chlorophenyl)sulfanyl]ethoxy-3-methoxy-5-[5-(3,4,5-trimethoxyphenyl)-2-furyl]benzonitrile (12)
A mixture of CuCN (1.53 mmol), compound **11** (0.5 g, 0.765 mmol) in 2.5 mL of 1-*n*-butyl-3-methylimidazolium iodide (bmiI) in sealed tube was heated at 100°C with stirring for 10 h. A complete conversion of compound **11** was observed. Product was extracted using cyclopentyl methyl ether (CPME) as solvent, further purification afforded compound **12**. Yellow solid, m.p.95-97 °C, Yield: 75%; IR (KBr): υ_{max} 3432, 3076, 2995, 2960, 2224 (-CN strt), 1609, 1587, 1540, 1494, 1481, 1464, 1388, 1345, 1328, 1290, 1243, 1220, 1127, 1072, 860, 758, 858 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, 1 H, *J* = 6.2 Hz), 7.38- 7.32 (m, 3 H), 7.30 – 7.26 (m, 2 H), 6.92 (s, 2 H), 6.75 (d, J = 7.2 Hz, 1 H), 6.68 (d, J = 7.2 Hz, 1H), 4.32 (t, J = 8.2 Hz, 2 H), 3.96 (s, 6 H), 388 (s, 3 H), 3.86 (s, 3 H), 3.32 (t, J = 8.2 Hz, 2 H); ^{13}C NMR (400 MHz,$CDCl_3$): δ 33.42, 56.09 (2C), 60.95, 72.17, 101.48 (2C), 107.13, 108.05, 111.88, 116.03, 119.38, 125.83, 127.78, 129.11 (2C), 131.10 (2C), 132.51, 133.76, 138.35, 149.06, 150.70, 152.64, 153.63 (2C), 154.15; EI-MS: m/z (rel.abund.%) 552.51 (M+, 100).

RESULTS AND DISCUSSION

The present paper describes the synthesis of title compound **12**, which is a hybrid scaffold of the earlier reported work on 2,5-diaryltetrahydrofuran [20-24], utilizing green methodologies and using inexpensive commercially available vanillin and 3,4,5-trimethoxy acetophenone as starting materials. Vinyl ketone **4 (Scheme 1)** was obtained in three steps from 3,4,5-trimethoxy acetophenone by modifications of the previously described procedures [20,25]. Mannich reaction of 3,4,5-trimethoxy acetophenone was carried out using aqueous; 40% dimethyl amine solution in presence of water as solvent and methane sulphonic acid as an efficient organo catalyst. The presence of water and methane sulphonic acid makes the reaction medium as an entirely green and highly efficient one-pot Mannich reaction [26,27]. Conversion of aldehyde **5** to carbinol **6** was achieved using Barbier reaction conditions over the Grignard reaction. Aldehyde **5** was treated with vinyl bromide in presence of zinc metal in 2-methytetrahydrofuran

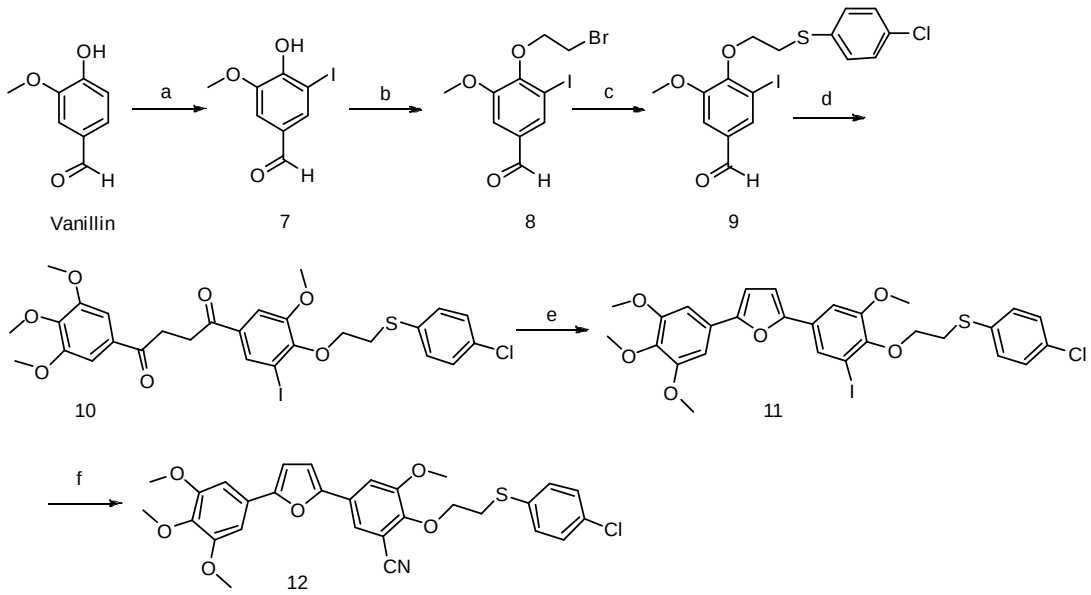
at r.t. for 3 hours. The reaction is similar to the Grignard reaction but the crucial difference is that the Barbier reaction is a one-pot synthesis whereas a Grignard reagent is prepared separately before addition of the carbonyl compound. Barbier reactions are nucleophilic addition reactions that usually 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 **6** using CsOH in presence of air [28] in toluene at 90 ^{o}C for 16 hours resulted in the formation of vinyl ketone **4.**

Scheme 1



Scheme 1: *Experimental conditions: a) paraformaldehyde (HCHO), aqueous 40%; dimethyl amine, water, methane sulphonic acid (15 mol%), reflux, 7 hours; b) MeI, Isopropyl acetate, r.t., 2 hours; c) H_2O, Isopropyl acetate, reflux, 3 hours; d) Vinyl bromide, Zn, aq; NH_4Cl, 2-MeTHF, r.t., 2 hours; e) CsOH, air, 2-MeTHF, reflux, 18 hours.*

Scheme 2



Scheme 2: *a) NaI, 5.25% w/w NaOCl, Ethanol, 0 ^{o}C -rt,30 min; b) 1,2-dibromoethane, K_2CO_3, 2-MeTHF, 80 ^{o}C, 2 hours; c) p-chloro-thiophenol, K_2CO_3, H_2O, r.t., 12 hours; d)* ***4****, 3-benzyl-5 (2-hydroxy ethyl)-4-methyl-thiazolium chloride, [bmim][PF_6], Et_3N, 80 ^{o}C, 8 hours; e) methane sulphonic acid (20 mol%), 2-Me-THF, reflux, 12 hours; (f) CuCN, bmiI, 100 ^{o}C, 10 hours*

The Synthesis of title compound is depicted in **Scheme 2**. Iodination of vanillin was carried out using NaI in presence of bleach (5% aq;NaOCl) in ethanol at 0^oC for 1 h, the method offers more environmentally benign reaction conditions [29]. Alkylation of compound **7** with 1, 2-dibromo ethane in presence of K_2CO_3 in 2-MeTHF at 80 ^oC for 6 h resulted in compound **8**. 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. Condensation of aldehyde **9** with vinyl ketone **4** to produce 1,4-diketone **10** was achieved by Stetter reaction using thiazolium catalyst [20-24] 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 [30], 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. Cyclisation of 1,4-diketone **10** was accomplished using 20 mol % of methane sulphonic acid in 2-MeTHF at reflux for 12 hour resulted in furan intermediate **11**. Rosenmund–Von Braun reaction of compound **11** to title compound **12** 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 [31]. Product isolation was achieved by simple extraction using organic solvents.

During the course of the synthesis of title compound, 2-MeTHF was used as the choice of the solvent instead of tetrahydrofuran. 2-MeTHF is obtained from furfural through hydrogenation which is in turn obtained from renewable sources such as corn cobs and sugar cane, through the intramolecular cyclisation of the naturally occurring pentoses. In contrast, THF is obtained from 1, 4-butanediol, an oil derived substance. 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 ethylacetate 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. The synthesis of 1,4-diketone **10** and the title compound **12** 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.

Anti- Bacterial Activity

The anti-bacterial activity of the title compound was determined by the disc diffusion method with Amoxicillin (100 µG / mL) and Cefaclor (100 µg/ mL) as the reference antibiotics [32]. The newly synthesized compounds were examined, against *Staphylococcus aureus*, *Bacillus Cereus*, *Escherichia Coli* and *Pseudomonas aeruginosa* bacteria. The test results indicated that the title compound (100 µg / mL) displayed excellent activity against both *Gram-positive bacteria (Staphylococcus aureus and Bacillus cereus) and Gram-negative bacteria: (Enterobacter aerogenes).*

Table 1: Antibacterial Activity of the title compound (Concentration Used 100 µg / mL)

Compound No	Gram negative bacteria		Gram positive bacteria	
	Escherichia Coli	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Bacillus Cereus*
	Zone of inhibition in mm			
Title compound	26	25	25	27
Amoxycillin	24	22	21	27
Cefaclor	19	20	19	22

Excellent activity = inhibition zone > 24 mm;

CONCLUSION

In conclusion, the title compound **12**, was synthesized efficiently utilizing green strategies using inexpensive commercially available vanillin and 3,4,5-trimethoxy acetophenone as starting materials.

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