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A NOVEL SYNTHESIS AND BIOLOGICAL ACTIVITY OF ARYL (3-HYDROXY-2, 4-DIMETHOXYPHENYL) METHANONES LINKED 5-(CHLOROMETHYL)-2-PHENYLTHIAZOLE DERIVATIVES BY COUPLING METHOD.

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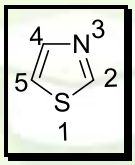
Abstract: In this study, a series of novel Synthesis of **(2,4-dimethoxy-3-((2-phenylthiazol-5-yl)methoxy)phenyl)(phenyl)methanones(8a-p),** were synthesized from condensation of an equimolar quantity of **aryl (3- hydroxy-2, 4-dimethoxyphenyl) methanones(4a-d)** and **5-(chloromethyl)-2-phenylthiazole(7a-d)** in DMF solvent by employing anhydrous potassium carbonate (K_2CO_3) as a base. The chemical structure of the synthesized novel compounds was characterized by analytical and spectral (FTIR, ^{1}HNMR, ^{13}CNMR and HRMS) techniques. The desired title compounds were screened for qualitative (zone of inhibition) analysis by agar well method, respectively. Among the synthesized compounds in the series, the compounds **8f and 8g** were found to show major antibacterial activity at a lower concentration, against Gram-positive bacteria such as Bacillus subtilis, Staphylococcus aureus and Gram-negative bacteria such as Salmonella typhimurium, Escherichia coli, Pseudomonas aeruginosa, and Klebsiella pneumoniae. The rest of the compounds exhibited ample antibacterial activity when compared to the standard positive controls, Chloramphenicol.

Index Terms - 2,6-dimethoxy phenol, aryl (3-hydroxy2, 4-dimethoxyphenyl) methanones, 5-(chloromethyl)-2-phenylthiazole, **(2,4-dimethoxy-3-((2-phenylthiazol-5-yl)methoxy)phenyl)(phenyl)methanones,**agar well method, antibacterial activity.

I. INTRODUCTION

Thiazole was first described by Hantzsch and Weber in 1887 which shows very characteristic properties [1-2]. In organic chemistry the heterocyclic compounds containing sulfur and nitrogen like thiazole and thiadiazole have maintained the interest of research through decades of historical development [3]. Thiazole has the molecular formula C_3H_3NS and it is a pale yellow liquid with pyridine like odor [4-5]. Thiazole rings are planar and aromatic which contains larger pi-electron delocalization when compared to corresponding oxazoles [4].

Heterocyclic ring containing nitrogen atom and one other heteroatom are known as 1,3-azoles. 1,3-azoles are isomeric with 1,2-azoles and are known as isothiazole [6]. The high pharmacological properties of thiazole have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents [7-10]. Nowadays, the substituted thiazoles have gained prominent interest in the area of drug research and development of the modifications in the substituted thiazole ring has showed high effectiveness to improve potency and lesser toxicity [11]. Some thiazoles derivatives resemble the thiophene, furan or glyoxaline derivatives by their properties and behavior[12]. Thiazoles are important classes of heterocyclic compounds, found in many potent biologically active molecules like the vitamin Thiamine[6] (B1). Thiazole shows a numbering system as depicted below



Benzophenones, like other ketone functionalities, consist of a carbonyl carbon that undergoes intersystem crossing in high yields, making it a robust triplet photosensitizer for use in organic and biological chemistry [13]. Its extensive chemical and physical properties have been studied; however, notable physical and chemical features relevant to this review are discussed here. They are also found in natural products that have broad-spectrum biological effects such as anticancer, antiviral, antimicrobial, and anti-inflammatory effects [14].

However, some research groups continue to explore benzophenone groups in their drug discovery efforts, and the interested reader may consult a recent review [15] for further insight into the medicinal properties of benzophenone-containing natural products. The benzophenone analogues have been synthesized by implementing A. Ghinet et al., procedure [16]. Methodologies for synthesizing the core heterocycle linked benzophenones mainly rely upon Friedel craft's acylation, the coupling of hydroxyl benzophenones [17] with 1,2- isoxazolines using potassium carbonate. This leads us to combine both the bioactive molecules in a single molecular frame to determine the chemical effect towards the antibacterial activity. In recent years, the production of heterocyclic compounds linking multi-structure in a molecule has received significant interest

in organic chemistry.

Recently, owing to their variable substituents and complex ring systems, many more new benzophenones, especially the polyprenylated benzophenones (PPBS), have been identified and reported from higher plants and certain fungi, and some of these reported new compounds have unusual rearranged skeletons with strong antibacterial or anticancer activity [18]. In addition, the strategy to synthesize benzophenones has attracted considerable attention. Heterocycle [19] are well known in all kinds of organic compounds and serves as a key template for various therapeutic agents' development. Researchers have shown much devotion to finding the optimal synthetic approaches for different heterocyclic compounds [20].

II. RESEARCH AND METHODOLOGY

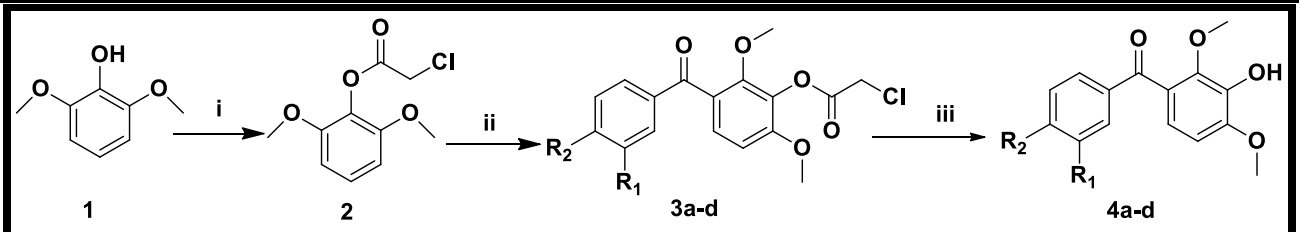
2.1 Materials and Chemistry

The solvents and reagents used were of Analytical Reagent grade and commercially accessible. All melting points were determined by subjecting a compound in melting point apparatus. The ^{1}HNMR spectra were recorded on Shimadzu AMX 400-Bruker, 400MHz spectrometer using $CDCl_3$ as a solvent and TMS as internal standard (chemical shift δ in ppm). The Elemental (C, H, N) analyses were achieved on Vario ELIII Elementar. Column chromatography was performed using Merck Silica gel (100-200 mesh) and Merck made TLC plates were used for reaction monitoring. Mass spectra were documented on LC-MS Agilent 1100 series with MSD (Ion trap) using 0.1% aqueous TFA in acetonitrile system on C18-BDS Column for 10 minute duration.

2.2 Methodology

2.3 General procedure for the synthesis of (3-hydroxy-2,4-dimethoxyphenyl) (phenyl) methanones (4a-d) from 2,6-dimethoxy phenol (1) via 2,6-dimethoxyphenyl 2-chloroacetate (2)

To a solution of **2,6-dimethoxy phenol (1)** and chloroacetylchloride in tetrahydrofuran was added pyridine carefully with stirring. This crude product was recrystallized using methanol to obtain pure white crystalline solid **2,6-dimethoxyphenyl 2-chloroacetate (2)**. To a solution of 2,6-dimethoxyphenyl 2-chloroacetate **(2)** and aromatic benzoic acids in Eaton's reagent (($MeSO_3H$/ P_2O_5) was refluxed for 4 h and the completion of the reaction was monitored through thin layer chromatography. This crude product was purified by column chromatography on silica gel to afford **3-benzoyl-2,6-dimethoxyphenyl 2-chloroacetate(3a-d)**. To a solution of 3-benzoyl-2,6-dimethoxyphenyl 2-chloroacetate (3a-d) and sodium acetate in methanol was refluxed for 4h and the completion of the reaction was monitored through thin layer chromatography. This crude product was recrystallized using methanol to obtain pure white crystalline solid **(3-hydroxy-2,4-dimethoxyphenyl)(phenyl)methanones (4a-d) [Scheme-1]**.



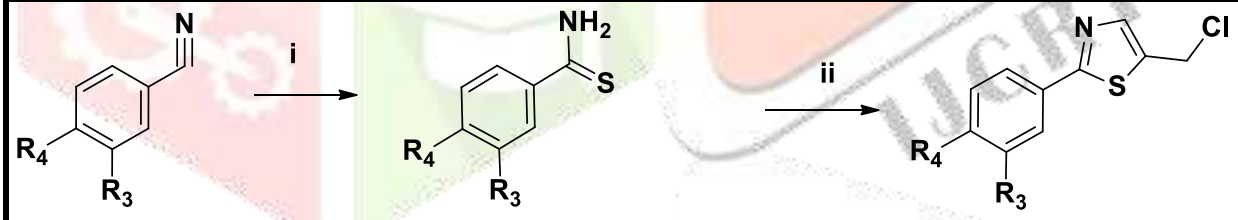
a: R_1=H,R_2=OMe
b: R_1=H,R_2=H
c: R_1=OMe,R_2=OMe
d: R_1=H,R_2=Cl

Reagents and conditions; (i) chloroacetyl chloride, pyridine, THF, 2h; (ii) Eaton's reagent Aromatic acids, 4h; (iii) Sodium acetate (4.5eq), methanol.

Scheme 1

2.4 General procedure for the synthesis of 5-(chloromethyl)-2-phenylthiazole (7a-d) from benzonitrile via Benzothioamides

To a stirred solution of **benzonitrile (5)** in toluene was added diphosphrous pentasulfide slowly at 10-20°C. The reaction mixture was heated to reflux temperature for 8 h. The crude product was filtered and recrystallized from anhydrous ethanol to yield **benzothioamide** (6) as white crystals. A mixture of **benzothioamide(5)** and 1,3-dichloroacetone was refluxed for 2 h to yield **5-(chloromethyl)-2-phenylthiazole (7a-d)** [Scheme-2] as a white solid: MP, 177-180°C.



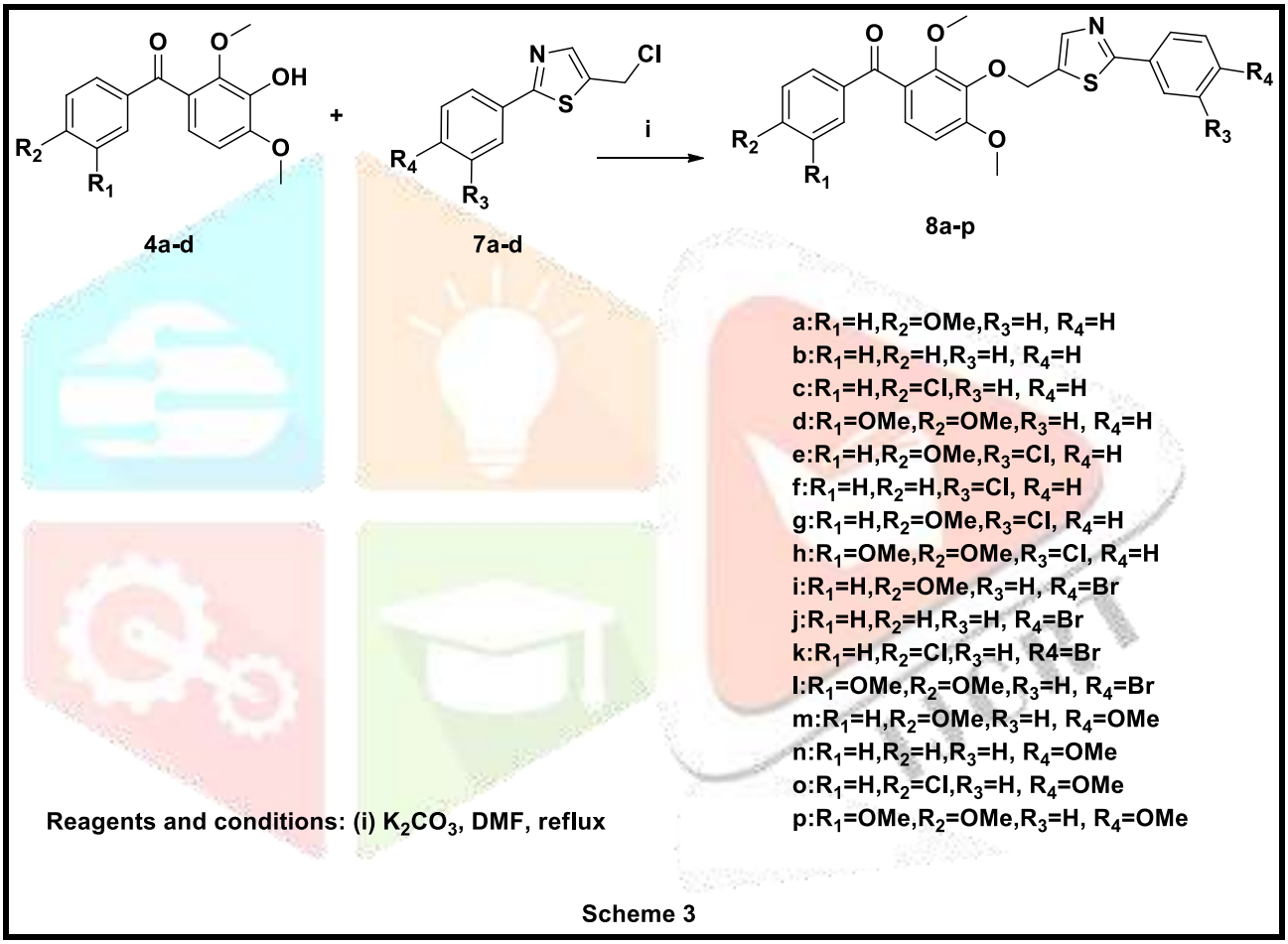
a:R_3=H, R_4=H
b:R_3=Cl R_4=H
c:R_3=H, R_4=Br
d:R_3=H, R_4=OMe

Reagents and conditions: i) P_4S_{10}, toluene, reflux ii) 1,3-dichloroacetone, acetone, reflux

Scheme 2

2.5 General procedure for the synthesis of (2, 4-dimethoxy-3-((2-phenylthiazol-5-yl)methoxy)phenyl)(phenyl)methanones (8a-p)

Individually, the **(3-hydroxy-2,4-dimethoxyphenyl)arylmethanone(4a-d)** molecules and **5-(chloromethyl)-2-phenylthiazole (7a-d)** molecules were taken in round bottomed flask and dissolved in DMF solvent and added a base potassium carbonate. The reaction mixture was refluxed for 4 hours and the completion of the reaction was examined through thin layer chromatography. The reaction mixture was cooled and guardedly poured into crushed ice and allowed for stirring. The aqueous solution was extracted with diethyl ether; the organic layer was washed with water, followed by brine solution, dried over sodium sulfate and concentrated under reduced pressure to acquire the crude product. The crude product was purified by column chromatography using petroleum ether: ethyl acetate as an eluent to afford **(2,4-dimethoxy-3-((2-phenylthiazol-5-yl)methoxy)phenyl)(phenyl)methanones(8a-p) [Scheme-3]**.



Scheme 3

2.6 A typical procedure is described for the synthesis of (2,4-dimethoxy-3-((2-phenylthiazol-5-yl)methoxy)phenyl)(phenyl)methanone (8b) - Scheme 3

To a solution of **(3-hydroxy-2, 4-dimethoxyphenyl) (phenyl) methanone (4a)** (0.2 g, 0. 0007 mol) and **5-(chloromethyl)-2-phenylthiazole (7a)** (0.14 g, 0. 0007 mol) in 10ml of DMF were added K_2CO_3 (0.19 g, 0. 0014 mol) as a base. The reaction mixture was then stirred for 3 h, the reaction progress was monitored through TLC and after the completion of the reaction; the reaction mixture was added to 10 ml ice cold water. The reaction mixture was extracted with 15 mL of diethyl ether, washed with 15 ml of brine solution, dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product. The crude product was purified by column chromatography using silica gel 60:120 and petroleum ether: ethyl

acetate as an eluent to afford **(2,4-dimethoxy-3-((2-phenylthiazol-5-yl)methoxy)phenyl)(phenyl)methanone(8b)**, as a white solid (0.29 g, 86%).

2.6.1 (2,4-dimethoxy-3-((2-phenylthiazol-5-yl)methoxy)phenyl)(phenyl)methanone (8b)

^{1}H NMR (400MHz, $CDCl_3$): δ 3.76(s,3H, OCH_3), 3.93(s,3H, OCH_3), 5.29(s,2H,CH_2), 6.76(d, *J*=8.02Hz, 1H, Ar-H), 7.16(m,3H), 7.25(s,1H, Ar-H),7.46(t,*J*=7.00Hz, 2H, Ar-H), 7.72(t,*J*=6.80Hz, 2H, Ar-H), 7.80(d,*J*=7.20Hz, 2H, Ar-H), 8.02(d,*J*=7.20Hz, 2H, Ar-H);**^{13}C NMR (400MHz,$CDCl_3$)**: δ 56.21, 62.15, 77.00, 106.75, 116.86, 123.19, 124.78, 126.29, 127.40, 129.55, 132.39, 132.71, 132.72, 138.60, 141.44, 152.69, 154.40, 156.36, 167.50, 195.45; **LCMS**:*m/z*= 432.02 (M+1);Anal. Calcd for $C_{25}H_{21}NO_4S$ C, 69.59; H, 4.91; N, 3.25; O, 14.83; S, 7.43; Found: C, 68.59; H, 4.71; N, 3.35; O, 15.83; S, 7.53

2.6.2 (2,4-dimethoxy-3-((2-phenylthiazol-5-yl)methoxy)phenyl)(4-methoxyphenyl)methanone (8a)

^{1}H NMR (400MHz,$CDCl_3$): δ 3.75(s,6H, OCH_3), 3.93(s,3H, OCH_3), 5.28(s,2H,CH_2), 6.75(d, *J*=7.20Hz, 1H, Ar-H), 7.07(d,*J*=6.42Hz, 2H), 7.26(s,1H, Ar-H), 7.45(t,*J*=6.20Hz, 2H, Ar-H), 7.71(d,*J*=6.42Hz, 2H, Ar-H), 7.81(d,*J*=7.72Hz, 2H, Ar-H), 8.01 (d,*J*=7.72Hz, 2H, Ar-H); **^{13}C NMR (400MHz,$CDCl_3$):** δ 56.12, 62.04, 77.00, 106.87, 116.76, 124.26, 125.48, 126.50, 127.16, 129.75, 132.09, 132.51, 132.72, 138.35, 140.54, 152.89, 154.36, 156.26, 166.84, 195.50; **LCMS:***m/z*= 462.00 $(M+1)^+$; Anal. Calcd for $C_{26}H_{23}NO_5S$ C, 67.66; H, 5.02; N, 3.03; O, 17.33; S, 6.95; Found: C, 65.36; H, 5.12; N, 4.13; O, 17.43; S, 7.95

2.6.3 (2,4-dimethoxy-3-((3-phenyl-4,5-dihydroisoxazol-5-yl)methoxy)phenyl)(4-methoxyphenyl)methanone (8b)

^{1}H NMR (400MHz, $CDCl_3$): δ 3.32 (dd, 1H, J=6.4, 16.6Hz), 3.36 (dd, 1H, J=8.6, 10.4Hz), 3.46 (dd, 1H, J=10.6, 17.2Hz), 3.87 (s, 9H, OCH3), 4.12 (dd, 1H, J=6.2, 10.6Hz), 4.99 (m,1H), 6.64 (d, 1H, J=8.62Hz, Ar-H), 7.06 (d, 3H, J=7.23Hz, Ar-H), 7.54 (d,3H, J=7.90, Ar-H); **LCMS:** m/z= 448.12 (M+1)+; Anal. Calcd for $C_{26}H_{25}NO_6$C, 69.79; H, 5.63; N, 3.31; O, 21.45; Found: C, 68.59; H, 5.53; N, 4.41; O, 21.65.

2.6.4 (4-chlorophenyl)(2,4-dimethoxy-3-((2-phenylthiazol-5-yl)methoxy)phenyl)methanone (8c)

^{1}H NMR (400MHz,$CDCl_3$): δ 3.74(s,3H, OCH_3), 3.90(s,3H, OCH_3), 5.29(s,2H,CH_2), 6.78(d,*J*=8.02Hz, 1H, Ar-H), 7.15(d,*J*=8.02Hz, 1H), 7.26(s,1H), 7.42(m,3H, Ar-H), 7.72(d,*J*=7.02Hz, 2H, Ar-H), 7.86 (d,*J*=7.70Hz, 2H, Ar-H) 8.04(d,*J*=7.70Hz, 2H, Ar-H); **^{13}C NMR (400MHz, $CDCl_3$):**δ 56.30, 62.10, 77.00, 106.67, 116.76, 123.30, 124.59, 126.20, 127.45, 129.70, 132.41, 132.60, 132.80, 138.66, 140.60, 151.75, 153.20, 156.20, 166.50, 195.30; **LCMS:***m/z*= 466.02 $(M+1)^+$, 468.03 $(M+3)^+$; Anal. Calcd for $C_{25}H_{20}ClNO_4S$; C, 64.44; H, 4.33; Cl, 7.61; N, 3.01; O, 13.73, S, 6.88; Found: C. C, 62.64; H, 5.23; Cl, 7.51; N, 4.21; O, 13.53, S, 6.88

2.6.5 (2,4-dimethoxy-3-((2-phenylthiazol-5-yl)methoxy)phenyl)(3,4-dimethoxyphenyl)methanone (8d)

^{1}H NMR (400MHz, $CDCl_3$): δ 3.84(s,6H, OCH_3), 3.86(s,6H, OCH_3), 5.31(s,2H,CH_2), 6.76(d, *J*=8.08Hz, 1H, Ar-H), 7.15(d,*J*=8.08Hz, 1H,Ar-H), 7.25(s,1H), 7.32(s, 1H, Ar-H), 7.44 (m,3H, Ar-H), 7.71 (d,*J*=6.98Hz, 2H, Ar-H), 7.90 (d, *J*=7.20Hz, 1H, Ar-H), 8.04(d,*J*=7.20Hz, 1H, Ar-H); **^{13}C NMR (400MHz, $CDCl_3$):**δ 56.40, 62.40, 77.00, 106.45, 115.56, 123.50, 124.20, 126.58, 127.30, 129.20, 131.23, 132.30, 132.50, 138.40, 139.50, 151.50, 153.50, 156.10, 166.60, 195.50; **LCMS:**m/z= 492.18 $(M+1)^+$; Anal. Calculated for $C_{27}H_{25}NO_6S$; C, 65.97; H, 5.13; N, 2.85; O, 19.53, S, 6.52; Found: C, 63.57; H, 5.23; N, 3.95; O, 20.63, S, 6.62

2.6.6 (3-((2-(3-chlorophenyl)thiazol-5-yl)methoxy)-2,4-dimethoxyphenyl)(4-methoxyphenyl)methanone (8e)

^{1}H NMR (400MHz, $CDCl_3$): δ 3.82(s,6H, OCH_3), 3.84(s,3H, OCH_3), 5.33(s,2H,CH_2), 6.68(d,*J*=8.00Hz, 1H, Ar-H), 7.14(d,*J*=7.50Hz, 2H,Ar-H), 7.16(d,*J*=8.00Hz, 1H, Ar-H), 7.28(s,1H), 7.45(d,*J*=7.50Hz, 2H, Ar-H), 7.72(m,2H, Ar-H), 7.85 (d, *J*=7.00Hz, 1H, Ar-H) 8.05(s,1H, Ar-H); **^{13}C NMR (400MHz, $CDCl_3$):**δ 56.89, 62.78, 77.00, 106.93, 114.56, 123.20, 124.70, 126.58, 127.10, 129.50, 130.23, 132.10, 132.50, 138.57, 139.10, 151.67, 153.12, 156.45, 166.30, 196.80; **LCMS:***m/z***=** 496.02 $(M+1)^+$, 498.09 $(M+3)^+$; Anal. Calcd for $C_{26}H_{22}ClNO_5S$; C, 62.96; H, 4.47; Cl, 7.15; N, 2.82; O, 16.13; S, 6.47; Found: C, 61.56; H, 5.67; Cl, 7.25; N, 2.92; O, 16.23; S, 6.37.

2.6.7 (3-((2-(3-chlorophenyl)thiazol-5-yl)methoxy)-2,4-dimethoxyphenyl)(phenyl)methanone (8f)

^{1}H NMR (400MHz, $CDCl_3$): δ 2.84(s,3H, OCH_3), 2.95(s,3H, OCH_3), 5.28(s,2H,CH_2), 6.65(d, *J*=7.96Hz, 1H, Ar-H), 7.16(d,*J*=7.96Hz, 1H, Ar-H), 7.26(s,1H), 7.42(d,*J*=6.76Hz, 2H, Ar-H), 7.72(m, 3H, Ar-H), 7.76(s,1H, Ar-H), 7.79 (m, 2H,Ar-H) 8.05(d,*J*=7.00Hz, 1H, Ar-H); **^{13}C NMR (400MHz, $CDCl_3$)**: δ 56.79, 62.50, 77.00, 106.65, 115.79, 123.38, 124.20, 126.48, 127.80, 129.35, 130.40, 132.30, 132.60, 138.57, 139.10, 151.67, 153.12, 156.45, 166.30, 196.80; **LCMS:***m/z***=** 466.00 $(M+1)^+$, 468.08 $(M+3)^+$; Anal. Calcd for $C_{25}H_{20}ClNO_4S$ C, 64.44; H, 4.33; Cl, 7.61; N, 3.01; O, 13.73; S, 6.88; Found: F C, 62.44; H, 5.23; Cl, 7.51; N, 4.11; O, 13.78; S, 6.93

2.6.8 (4-chlorophenyl)(3-((2-(3-chlorophenyl)thiazol-5-yl)methoxy)-2,4-dimethoxyphenyl)methanone (8g)

^{1}H NMR (400MHz, $CDCl_3$): δ 3.75(s,3H, OCH_3), 3.92(s,3H, OCH_3), 5.28(s,2H,CH_2), 6.75(d,*J*=7.88Hz, 1H, Ar-H), 7.12(d,*J*=7.88Hz,1H, Ar-H), 7.25(s,1H), 7.46(d,*J*=6.80Hz, 1H, Ar-H), 7.72(d,*J*=8.50Hz, 2H, Ar-H), 7.85(m,2H, Ar-H), 7.95 (d,*J*=8.50Hz, 2H, Ar-H) 8.02(s,1H, Ar-H); **^{13}C NMR (400MHz, $CDCl_3$):**δ 36.94, 56.12, 62.10, 77.00, 79.60, 106.72, 125.42, 126.3, 127.86, 128.30, 129.62, 132.71, 135.76, 140.68, 155.63, 161.42, 170.27, 195.35;**LCMS:***m/z***=** 500.00 $(M+1)^+$, 502.01 $(M+3)^+$, 504.04 $(M+5)^+$; Anal. Calcd

for $C_{25}H_{19}Cl_2NO_4S$; C, 60.01; H, 3.83; Cl, 14.17; N, 2.80; O, 12.79; S 6.41; Found: C, 59.01; H, 3.63; Cl, 14.27; N, 2.80; O, 12.69; S 7.61.

2.6.9 (3-((2-(3-chlorophenyl)thiazol-5-yl)methoxy)-2,4-dimethoxyphenyl)(3,4-dimethoxyphenyl)methanone (8h)

^{1}H NMR (400MHz, $CDCl_3$): δ 3.74(s,6H, OCH_3), 3.93(s,6H, OCH_3), 5.29(s,2H,CH_2), 6.75(d, *J*=8.02Hz, 1H, Ar-H), 7.12(d,*J*=8.02Hz, 1H,Ar-H), 7.14(d,*J*=6.16Hz,1H,Ar-H), 7.25(s,1H, Ar-H), 7.34(m,2H, Ar-H), 7.46(m,2H), 7.95 (d,*J*=6.96Hz,1H) 8.04(s,1H, Ar-H); **^{13}C NMR (400MHz, $CDCl_3$):** δ 56.57, 62.50, 77.00, 106.56, 114.78, 123.37, 124.46, 126.29, 127.80, 129.80, 130.53, 132.25, 132.50, 138.60, 139.50, 151.35, 153.78, 156.35, 166.68, 195.80;**LCMS:***m/z***=** 526.00 $(M+1)^+$, 528.02 $(M+3)^+$; Anal. Calcd for $C_{27}H_{24}ClNO_6S$; C, 61.65; H, 4.60; Cl, 6.74; N, 2.66; O, 18.25; S, 6.10; Found: C, 61.45; H, 4.50; Cl, 6.84; N, 2.88; O, 18.30; S, 6.20

2.6.10 (3-((2-(4-bromophenyl)thiazol-5-yl)methoxy)-2,4-dimethoxyphenyl)(4-methoxyphenyl)methanone (8i)

^{1}H NMR (400MHz, $CDCl_3$): δ 3.75(s,6H, OCH_3), 3.90(s,3H, OCH_3), 5.27(s,2H,CH_2), 7.17(d,*J*=8.6Hz,1H,Ar-H), 7.26-7.43(m,3H, Ar-H), 7.53-7.58 (m,3H, Ar-H), 7.80 (m, 4H, Ar-H); **^{13}C NMR (400MHz, $CDCl_3$):** δ 56.35, 62.20, 77.00, 106.60, 114.45, 123.45, 124.27, 126.79, 127.45, 129.76, 131.67, 132.90, 132.95, 138.90, 139.50, 151.49, 153.35, 156.78, 166.12, 195.59; **LCMS**:*m/z*= 540.10 $(M+1)^+$, 542.02 $(M+3)^+$; Anal. Calcd for $C_{26}H_{22}BrNO_5S$; C, 58.83; H, 3.95; Br, 15.66; N, 2.74; O, 12.54; S, 6.28; Found: C, 56.63; H, 4.75; Br, 15.56; N, 2.84; O, 12.64; S, 6.48.

2.6.11 (3-((2-(4-bromophenyl)thiazol-5-yl)methoxy)-2,4 dimethoxyphenyl)(phenyl)methanone (8j)

^{1}H NMR (400MHz, $CDCl_3$): δ 3.75(s,6H, OCH_3), 3.90(s,3H, OCH_3), 5.27(s,2H,CH_2), 6.74(d, *J*=8.0Hz, 1H, Ar-H), 7.16(d,*J*=8.0Hz,1H,Ar-H), 7.26(s,1H, Ar-H), 7.45(m,3H, Ar-H), 7.71(d,*J*=7.02Hz, 2H, Ar-H), 7.79 (d, *J*= 7.50Hz, 2H, Ar-H) 7.82(d,*J*=7.50Hz, 2H, Ar-H); **^{13}C NMR (400MHz, $CDCl_3$):**δ 56.89, 62.59, 77.00, 106.30, 114.67, 123.28, 124.46, 126.68, 127.34, 129.30, 131.47, 132.49, 132.38, 138.30, 139.20, 151.89, 153.45, 156.59, 166.20, 195.89**; LCMS:***m/z***=** 510.00 $(M+1)^+$, 512.10 $(M+3)^+$; Anal. Calcd for $C_{25}H_{20}BrNO_4S$; C, 58.83; H, 3.95; Br, 15.66; N, 2.74; O, 12.54; S, 6.28; Found: C, 56.63; H, 4.75; Br, 15.56; N, 2.84; O, 12.64; S, 6.48.

2.6.12 (3-((2-(4-bromophenyl)thiazol-5-yl)methoxy)-2,4-dimethoxyphenyl)(4-chlorophenyl)methanone (8k)

^{1}H NMR (400MHz, $CDCl_3$): δ 3.75(s,6H, OCH_3), 3.90(s,3H, OCH_3), 5.27(s,2H,CH_2), 6.75(d,*J*=8.64Hz, 1H, Ar-H), 7.17(d,*J*=8.48Hz, 1H,Ar-H), 7.25-7.42(m,3H, Ar-H), 7.56(d,*J*=8.28Hz, 2H, Ar-H), 7.71(d,*J*=2.36Hz, 2H, Ar-H), 7.81 (d,*J*=8.16Hz, 2H, Ar-H) ; **^{13}C NMR (400MHz, $CDCl_3$)**:δ 56.50, 62.10, 77.00, 106.15, 114.58, 123.20, 124.50, 126.30, 127.20, 129.80, 131.27, 132.78, 132.20, 138.40, 139.47, 151.30, 153.50, 155.30, 166.37, 195.20;**LCMS:***m/z***=** 544.00 $(M+1)^+$, 546.02 $(M+3)^+$, 548.04 $(M+5)^+$; Anal. Calcd for $C_{25}H_{19}BrClNO_4S$; C, 55.11; H, 3.51; Br, 14.67; Cl, 6.51; N, 2.57; O, 11.75; S, 5.88; Found: C, 52.01; H, 4.31; Br, 15.77; Cl, 7.41; N, 2.67; O, 11.65; S, 5.98

2.6.13 (3-((2-(4-bromophenyl)thiazol-5-yl)methoxy)-2,4-dimethoxyphenyl)(3,4-dimethoxyphenyl)methanone (8l)

^{1}H NMR (400MHz, $CDCl_3$): δ 3.84(s,6H, OCH_3), 3.86(s,6H, OCH_3), 5.31(s,2H,CH_2), 6.76(d,*J*=7.94Hz, 1H, Ar-H), 7.15(d,*J*=7.94Hz, 1H,Ar-H), 7.25(s,1H), 7.27(d,*J*=7.4, 1H, Ar-H), 7.44(d,*J*=7.4Hz, 1H, Ar-H), 7.52(s,1H, Ar-H), 7.71(t,*J*=6.98Hz, 2H, Ar-H), 8.04(d,*J*=6.98Hz, 2H, Ar-H);**^{13}C NMR (400MHz, $CDCl_3$):**δ 56.35, 62.48, 77.00, 106.20, 114.20, 123.59, 124.27, 126.70, 127.45, 129.50, 131.89, 132.29, 132.50, 138.90, 139.42, 151.67, 153.30, 155.90, 166.10, 195.45**; LCMS:***m/z*=569.01 $(M+1)^+$, 572.06 $(M+3)^+$; Anal. Calcd for $C_{27}H_{24}BrNO_6S$ C, 56.85; H, 4.24; Br, 14.01; N, 2.46; O, 16.83; S, 5.62; Found: C, 55.65; H, 4.34; Br, 13.11; N, 3.56; O, 16.63; S, 6.72

2.6.14 (2,4-dimethoxy-3-((2-(4-methoxyphenyl)thiazol-5-yl)methoxy)phenyl)(4-methoxyphenyl)methanone (8m)

^{1}H NMR (400MHz, $CDCl_3$): δ 3.80(s,6H,OCH_3), 3.83(s,6H,OCH_3), 5.23(s,2H,CH_2), 6.75(d,*J*=7.96Hz, 1H, Ar-H), 7.16(d,*J*=7.96Hz, 1H,Ar-H), 7.18(d,*J*=7.20Hz, 2H,Ar-H), 7.20(s,1H, Ar-H), 7.26(d,*J*=7.46Hz,2H, Ar-H), 7.71(d,*J*=7.20Hz, 2H,Ar-H), 7.82(d, *J*=7.40Hz, 2H, Ar-H); **^{13}C NMR (400MHz, $CDCl_3$):**δ 56.40, 62.15, 77.00, 106.29, 114.49, 123.29, 124.39, 126.29, ; 127.10, 129.25, 131.83, 132.20, 132.39, 138.56, 139.29, 151.45, 153.20, 155.55, 166.20, 195.55;**LCMS:***m/z***=** 492.10 $(M+1)^+$; Anal. Calcd for $C_{27}H_{25}NO_6S$; C, 65.97; H, 5.13; N, 2.85; O, 19.53; S, 6.52; Found: C, 64.77; H, 5.23; N, 3.85; O, 19.33; S, 6.82.

2.6.15 (2,4-dimethoxy-3-((2-(4-methoxyphenyl)thiazol-5 yl)methoxy)phenyl)(phenyl)methanone (8n)

^{1}H NMR (400MHz, $CDCl_3$): δ 3.83(s,6H,OCH_3), 3.86(s,3H,OCH_3), 5.26(s,2H,CH_2), 6.78(d, *J*=8.02Hz, 1H, Ar-H), 7.16(d,*J*=8.02Hz, 1H,Ar-H), 7.20(s,1H,Ar-H), 7.26(m,3H, Ar-H), 7.71(t, *J*=7.20Hz, 2H,Ar-H), 7.91 (t,*J*=7.20Hz, 1H,Ar-H), 8.01(d,*J*=7.64Hz, 2H,Ar-H); **^{13}C NMR (400MHz, $CDCl_3$):** δ 56.50, 62.10, 77.00, 106.15, 114.58, 123.20, 124.50, 126.30, 127.20, 129.80, 131.27, 132.78, 132.20, 138.40, 139.47, 151.30, 153.50, 155.30, 166.37, 195.20;**LCMS:***m/z***=** 462.06 $(M+1)^+$; Anal. Calcd for $C_{26}H_{23}NO_5S$; C, 67.66; H, 5.02; N, 3.03; O, 17.33; S, 6.95; Found: C, 65.56; H, 5.12; N, 4.23; O, 17.53; S, 7.55

2.6.16 (4-chlorophenyl)(2,4-dimethoxy-3-((2-(4-methoxyphenyl)thiazol-5-yl)methoxy)phenyl)methanone (8o)

^{1}H NMR (400MHz, $CDCl_3$): δ 3.75(s,6H,OCH_3), 3.92(s,3H,OCH_3), 5.28(s,2H,CH_2), 6.75(d, *J*=8.00Hz, 1H, Ar-H), 7.16(d,*J*=8.00Hz, 1H,Ar-H), 7.18(d,*J*=7.72Hz, 2H,Ar-H), 7.26(s,1H), 7.71(d, *J*=6.80Hz, 2H,Ar-H), 7.81(d,*J*=7.72Hz, 2H,Ar-H), 8.01(d,*J*=6.80Hz,2H, Ar-H); **^{13}C NMR (400MHz, $CDCl_3$):**δ 56.10, 62.90, 77.00, 106.10, 114.88, 123.20, 124.60, 126.26, 127.53, 129.35, 131.44, 132.27, 132.59,

138.44, 139.88, 151.28, 153.33, 155.37, 166.41, 195.99;**LCMS:***m/z*= 496.00 $(M+1)^+$, 498.01 $(M+3)^+$; Anal. Calcd for $C_{26}H_{22}NO_5S$; C, 62.96; H, 4.47; Cl, 7.15; N, 2.82; O, 16.13; S, 6.47; Found: C, 62.56; H, 5.57; Cl, 6.25; N, 3.62; O, 16.33; S, 6.67

2.6.17 (2,4-dimethoxy-3-((2-(4-methoxyphenyl)thiazol-5-yl)methoxy)phenyl)(3,4-dimethoxyphenyl)methanone (8p)

^{1}H NMR (400MHz, $CDCl_3$): δ 3.75(s,6H,OCH_3), 3.83(s,6H,OCH_3), 3.92(s,3H,OCH_3), 5.25(s, 2H, CH_2), 6.75(d, *J*=8.12Hz, 1H, Ar-H) 7.16(d,*J*=8.12Hz, 1H,Ar-H), 7.18(d,*J*=7.52Hz, 2H,Ar-H), 7.20(s,1H), 7.39(d, *J*=6.98Hz, 1H, Ar-H), 7.58(d, *J*=6.98Hz, 1H, Ar-H), 7.71(d, *J*=7.52Hz, 2H, Ar-H) 7.82(s,1H);**^{13}C NMR (400MHz, $CDCl_3$):** δ 56.39, 62.15, 77.00, 106.85, 114.38, 123.29, 124.54, 126.37, 127.22, 129.89, 131.57, 132.88, 132.30, 138.40, 139.47, 151.30, 153.50, 155.30, 166.37, 195.20;**LCMS:***m/z*= 522.10 $(M+1)^+$; Anal. Calcd for $C_{28}H_{27}NO_7S$ C, 64.48; H, 5.22; N, 2.69; O, 21.47; S, 6.15; Found: C, 62.28; H, 5.12; N, 3.89; O, 21.47S, 9.25.

2.7 Antibacterial Activity by Well Diffusion Technique *(*determination of zone of inhibition)

The antibacterial activity of the synthesized novel **(2,4-dimethoxy-3-((3-phenyl-4,5-dihydroisoxazol-5-yl)methoxy)phenyl)(phenyl)methanone (8a-p)** series were examined by following the well diffusion technique of Odeyemi and Fagbohun, 2005 [21-24]. Sterile solidified nutrient agar plates were prepared and immunized with different test bacterial strain by spread plate method. 6mm wells were made in the nutrient agar plates and were filled with the preset concentration of different test samples (10µg). The loaded plates were then kept for incubation at 37^{O}C for 24 hrs. Antibacterial activities of all the synthesized novel compounds (8a-p) were estimated by measuring the zone of inhibition against the test microorganisms. DMF (Dimethyl formamide) was used as negative control and 10µg chloramphenicol was used as a positive control. After incubation, the inhibition zone formed around the wells was measured in millimeter. The study was achieved in triplicate.

III. RESULTS AND DISCUSSION

3.1 Chemistry

In-vitro antibacterial activity of synthesized compounds **(8a-p)** were performed against a panel of Gram positive and Gram negative human phytopathogenic baceteria by agar well diffusion method using chloroamphenicol along with 20% dimethylformamide (DMF) as positive and negative controls respectively.

The final coupled compounds **(8a-p)** were synthesized as outlined in the **scheme-3.** Compounds **(8a-p)** were obtained by condensing **(4a-d)** with **(7a-d)** in presence of potassium carbonate as a base and DMF as solvent. The intermediates **(4a-d)** and **(7a-d)** were obtained by synthetic route which is represented in the **scheme 2** and **scheme 3** respectively. The desired 3-hydroxy-2,4-dimethoxybenzophenones **(4a-d)** were synthesized from 2,6-dimethoxyphenyl2-chloroacetate **(2)** and

aromatic benzoic acids in Eaton's reagent (($MeSO_3H/P_2O_5$) at 80^oC. After the completion of the reaction, the reaction mixture was cooled and diluted with dichloromethane and carefully poured into a beaker containing 10%$NaHCO_3$, allowed for stirring, the aqueous solution was extracted with CH_2Cl_2 and the combined organic layers were washed with water, brine solution, dried over sodium sulfate and concentrated under reduced pressure to produce a brownish oil as crude product. This crude product was purified by column chromatography on silica gel to give 3-benzoyl-2,6-dimethoxyphenyl2-chloroacetate **(3a-d)**. The **(3a-d)** compounds and sodium acetate were taken in round bottomed flask, followed by dissolving in methanol and refluxed for 4h, then the reaction mixture was extracted with ethyl acetate, the organic layer then washed with water, brine solution, dried over sodium sulfate and concentrated with reduced pressure to get crude product. This crude product was recrystallized taking methanol to obtain pure white crystalline solid (3-hydroxy-2,4-dimethoxyphenyl)(phenyl)methanones **(4a-d)** in excellent yield.

The compounds **(7a-d)** were synthesized as shown in the **scheme2**. Substituted aromatic nitriles **(5a-d)** were converted into **thioamide** (**6a-d)** by refluxing the mwith diphosphrous pentasulfide in toluene. The **thioamide** (**6a-d)** were treated with 1,3-dichloroacetone in acetone, followed by reflux to obtain **5-(chloromethyl)-2-phenylthiazole (7a-d).** In scheme1, the formation of **4a-d** was confirmed by ^{1}HNMR, ^{13}CNMR, Mass spectroscopy and elemental analysis. In ^{1}HNMR, the para proton of 2,6-dimethoxy phenoxy group appeared as a triplet at δ7.20 -7.35, whereas the meta proton as adoublet at δ6.65-7.00. After friedel craft's acylation, para and meta protons appeared as doublet at δ 7.28 and 6.70 respectively corresponding to hydroxy proton in (4a-d). The formation of the compounds 7a-d was confirmed by ^{1}HNMR. The thiazole protons and aromatic proton were appeared in the range δ 5.20-5.29 and 7.21-8.30 respectively.

The formation of title compounds **(8a-p)** was confirmed by ^{1}HNMR and Mass spectroscopy. The methylene proton and methoxy protons appeared in the range δ 5.28 and 3.75- 3.92 respectively.

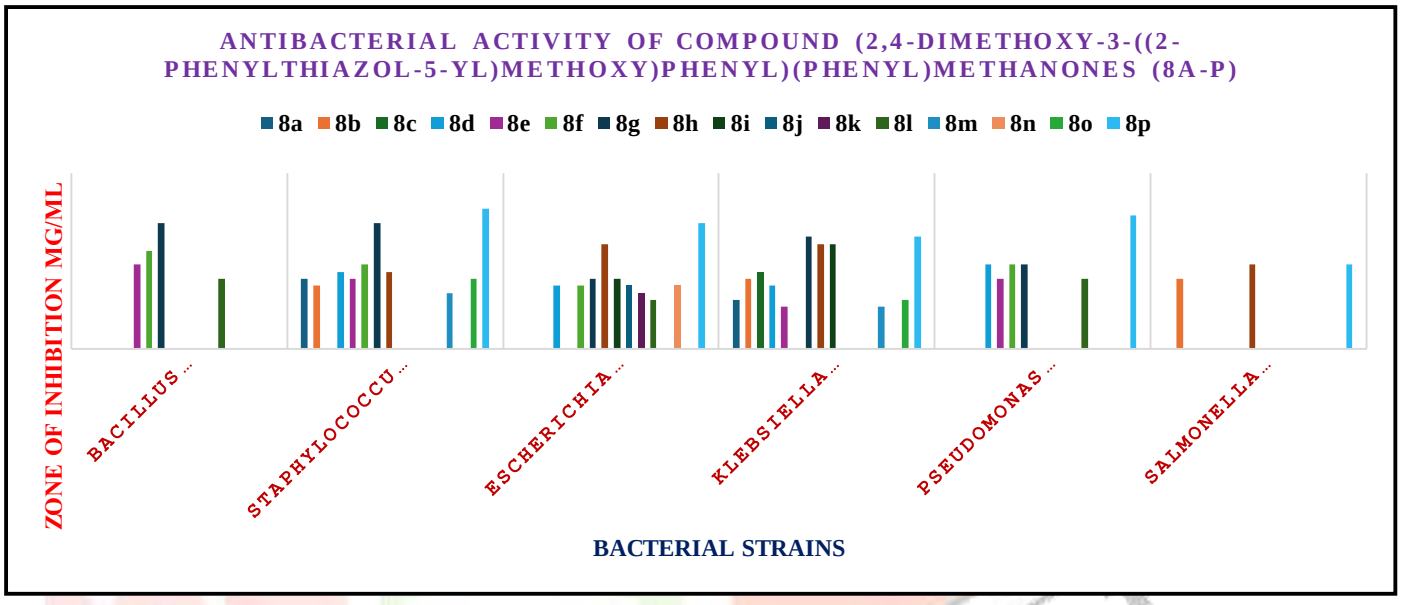
3.2 Biology

Invitro antibacterial activity data of compounds **(8a-p)** against tested organisms exhibited the varying antibacterial activity against used test cultures. Sample **8c**, **8g**, **8h**, **8i**, **8p** –displayed the bacteriostaticactivity, whereas **8f** and **8g** displayed the strong bacterialcidal activity against *Klebsiellapneumonae,* **8g** was more potent than positive control used. In case of *Bacillus subtilis,* only **8e** and **8l** were active and **8g** was stronger than the positive control used. Whereas, *Salmonella typhimurium* displayed the resistance against used test sample **(2,4-dimethoxy-3-((3-phenyl-4,5-dihydroisoxazol-5-yl)methoxy)phenyl)(phenyl)methanone (8a-p) series.** Overall among the **8a-p** series sample tested for the antibacterial activity against different bacterial strains, 8g was potent and followed by **8e**, **8f** and **8h**. And the present work concludes that sample **8g** and **8f** can be used to replace the positive control against respective test cultures.

Table 1: Antibacterial activity data of (2,4-dimethoxy-3-((2-phenylthiazol-5-yl)methoxy)phenyl)(phenyl)methanones (8a-p)Zone of Inhibition in mm

	Bacterial Strains	8a	8b	8c	8d	8e	8f	8g	8h	8i	8j	8k	8l	8m	8n	8o	8p	+ve control Chloroam phenicol
Gram +ve	*Bacillus subtilis*	–	–	–	–	12	14	18	–	–	–	–	10	–	–	–	–	20
	Staphylococcus aureus	10	9	–	11	10	12	18	11	–	–	–	–	8	–	10	20	19
Gram -ve	*Escherichia coli*	–	–	–	9	–	9	10	15	10	9	8	7	–	9	–	18	15
	Klebsiella pneumoniae	7	10	11	9	6	–	16	15	15	–	–	–	6	–	7	16	20
	Pseudomonas aeruginosa	–	–	8	12	10	12	12	–	–	–	–	10	–	–	–	19	18
	Salmonella typhimurium	–	10	–	–	–	–	–	12	–	–	–	–	–	–	–	12	26

Values are zones of inhibition in mm, "-" – Not sensitive



CONCLUSIONS

In conclusion, we have reported a facile route for the rapid synthesis of novel **(2,4-dimethoxy-3-((2-phenylthiazol-5-yl)methoxy)phenyl)(phenyl)methanones (8a-p),** from **5-(chloromethyl)-2-phenylthiazole (7a-d)** with **aryl(3-hydroxy-2,4-dimethoxyphenylmethanones (4a-d)** using DMF and K_2CO_3. The new molecular framework has displayed broad spectrum antibacterial activity which is validated by the presence of hydroxyl, carbonyl group and electronegative atoms, among the synthesized compounds **(8a-p)**, molecules **8f and 8g** bearing electronegative atoms respectively in the molecular framework have exhibited potent antibacterial activity, when compared to the standard positive controls.

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