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Synthesis and antibacterial activity of novel (3,5-dimethoxy-4-((3-aryl-1,2,4-oxadiazol-5-yl)methoxy)phenyl)aryl methanones

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ABSTRACT

In the present study, a series of novel (3,5-dimethoxy-4-((3-aryl-1,2,4-oxadiazol-5-yl)methoxy)phenyl)aryl methanones(8a-l), were synthesizedby condensing5-(chloromethyl)-3-aryl-1,2,4-oxadiazole7(a-f) with aryl (3-hydroxy-2, 4-dimethoxyphenyl) methanones (4a-b)using K_2CO_3. The chemical structure of the newly synthesized compounds was characterized by analytical and spectral (^{1}HNMR, ^{13}CNMR and HRMS) techniques. The title compounds were screened for qualitative (zone of inhibition) by agar welltechnique, respectively. Among the synthesized compounds in the series, the compounds 8b, 8c, 8f and 8l were found to exhibit significant antibacterial activity at 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*Klebsiellapneumoniae*. The rest of the compounds showed moderate antibacterial activity when compared to the standard positive controls Chloramphenicol.

Keywords: 2,6-dimethoxy phenol, aryl (3-hydroxy-2, 4-dimethoxyphenyl) methanones, (3,5-dimethoxy-4-((3-aryl-1,2,4-oxadiazol-5-yl)methoxy)phenyl)aryl methanones, antibacterial activitv.

1. INTRODUCTION

Heterocycles are well represented in both natural products and pharmaceuticals, where nitrogen heterocycles are very important. In the field of medicinal chemistry, the research work has been done on biologically active molecules based on molecular recognition, which has allowed us to review thoroughly the material included in the earlier stage to make amendments in the light of new knowledge and to include in the recent work.Heterocyclic compounds containing five-membered ring, in particular 1,2,4-oxadiazole possess versatile biological properties such as antibacterial [1], anticonvulsant, anti-inflammatory [2], antiallergic [3], anticancer [4], antifungal [5], antihistamic [6], activities.

The benzophenone analogues have been synthesized by adopting A. Ghinet et al [7-10] procedure. The structural features of benzophenones form the prominent position in organic chemistry and of at most practical and theoretical importance.Functionalized phenols such as 3-hydroxy benzophenones represent important building blocks in medicinal and organic chemistry due to their contribution. The polar nature of the carbonyl group possesses biological and chemical properties which are extensively studied. As a result, great deals of research activities are carried out in several laboratories. Benzophenone analogues have displayed versatile biological activities such as anti-microbial, anit-cancer, anti-convulsant, anti-pyretic, anti-hypertensive, anti-diabetic, anti-inflammatory and analgesic by their polar feature of carbonyl group.Benzophenone is used as anultraviolet (UV)-curing agent in sunglasses, andto prevent UV light from damaging scents and colors in products such as perfumes and soaps.Besides, benzophenones occur naturally in food such as Muscat grape and mango.

Methodolgies for synthesizing the core heterocycle linked benzophenones mainly rely upon, Friedel craft's acylation, coupling of hydroxyl benzophenones with 1,2,4-oxadiazoles using K_2CO_3. This leads us to incorporate both the bioactive molecules in a single molecular frame to determine the additive effect towards the

antibacterial activity. In recent years, the synthesis of heterocyclic compounds linking multi-structure in a molecule has received considerable interest in organic chemistry.

2. MATERIALS AND METHODS

2.1. Chemistry

All the solvents and reagents used were of AR grade and commercially available; used as such without further purification. All melting points were taken in open capillary tube and are uncorrected. The ^{1}H NMR spectra were recorded on Shimadzu AMX 400-Bruker, 400 MHz spectrometer using $CDCl_3$ as a solvent and TMS as internal standard (chemical shift δ in ppm). The Elemental (C, H, N) analyses were obtained on Vario EL III Elementar. Slica gel column chromatography was performed using Merck Silica gel (100-200 mesh) and Merck made TLC plates were used for reaction monitoring. Mass spectra were recorded on LCMS Agilent 1100 series with MSD (ion trap) using 0.1% aqueous TFA in acetonitrile system on C18-BDS Column for 10 min duration.

2.2. General Procedure for the Synthesis of (3,5-dimethoxy-4-((3-aryl-1,2,4-oxadiazol-5-yl) methoxy)phenyl)(4-methoxyaryl) methanones (8a-l)

To a solution of 5-(chloromethyl)-3-aryl-1,2,4-oxadiazole **(7a-f)**and (3-hydroxy-2,4-dimethoxyphenyl)aryl methanone**(4a-d)**in DMFwas added K_2CO_3. The reaction mixture was refluxed for 4 h and the completion of the reaction was monitored through thin layer chromatography. The reaction mixture was cooled and carefully poured into crushed ice and allowed for stirring. The aqueous solution was extracted with diethyl ether; the organic layer was washed with brine solution, dried over sodium sulfate and concentrated under reduced pressure to get 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-((3-phenyl-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(4-methoxyaryl)methanones(8a-l).

2.3. Typical Procedure for the Synthesis of 3,5-dimethoxy-4-((3-aryl-1,2,4-oxadiazol-5-yl) methoxy)phenyl)(4-methoxyaryl)methanones 8c

To a solution of 5-(chloromethyl)-3-aryl-1,2,4-oxadiazole **7a**(0.25g, 0.8mmol) and (3-hydroxy-2,4-dimethoxyphenyl)aryl methanone**4a** (1.05g, 0.8mmol) in 5ml of DMF was added K_2CO_3 (0.34g, 2.46mmol). The reaction mixture was then refluxed for 4h and concentrated to get crude product. The reaction mixture was cooled and carefully poured into crushed ice and allowed for stirring.The aqueous solution was extracted with diethyl ether, the organic layer was washed with brine solution, dried over sodium sulfate and concentrated under reduced pressure to get the crude product. This crude product was purified by column chromatography on silica gel 60:120 and petroleum ether: ethyl acetate as an eluent to afford 0.6g (80%) (2,4-dimethoxy-3-((3-phenyl-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(4-methoxyaryl)methanone **8c** as a white solid.

^{1}HNMR ($CDCl_3$) δppm: 3.74 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 5.32 (s, 2H, methylene -H), 6.65 (d, 1H), 6.89 (d, 3H), 7.25 (m, 3H), 7.97 (d, 2H), 8.21 (d, 2H), MS: m/z= 447.2 (M+1). Anal. Calcd for $C_{25}H_{22}N_2O_6$: C, 67.26; H, 4.97; N, 6.27; O, 21.50; Found: C, 67.40; H, 4.71; N, 6.28; O, 21.61.

2.3.1. 3-((3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)methoxy)-2,4-dimethoxyphenyl)(4-methoxyaryl) methanone (8a)

^{1}HNMR ($CDCl_3$) δppm: 3.76 (s, 3H), 3.84 (s, 3H), 3.89 (s, 3H), 5.33 (s, 2H, methylene -H), 6.75 (d, 1H), 6.87 (d, 2H), 7.17 (m, 3H), 7.77 (d, 2H), 8.10 (d, 2H), MS: m/z= 465.0 (M+1). Anal. Calcd for $C_{25}H_{21}FN_2O_6$: C, 64.65; H, 4.56; F, 4.09; N, 6.03; O, 20.67; Found: C, 64.70; H, 4.51; F, 4.04; N, 6.08; O, 20.67.

2.3.2. 2,4-dimethoxy-3-((3-(4-(trifluoromethyl) phenyl)-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(4-methoxyaryl) methanone (8b)

^{1}HNMR ($CDCl_3$) δppm: 3.78 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 5.36 (s, 2H, methylene -H), 6.75 (d, 1H), 6.87 (d, 2H), 7.17 (m, 3H), 7.77 (d, 2H), 8.10 (d, 2H), MS: m/z= 515.1 (M+1). Anal. Calcd for $C_{26}H_{21}F_3N_2O_6$: C, 60.70; H, 4.11; F, 11.08; N, 5.45; O, 18.66; Found: C, 60.65; H, 4.15; F, 11.04; N, 5.58; O, 18.67.

2.3.3. (3-((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methoxy)-2,4-dimethoxyphenyl)(4-methoxyaryl) methanone(8d)

^{1}HNMR ($CDCl_3$) δppm: 3.75 (s, 3H), 3.84 (s, 3H), 3.89 (s, 3H), 5.33 (s, 2H, methylene -H), 6.75 (d, 1H), 6.87 (d, 2H), 7.17 (d, 1H), 7.46 (d, 2H), 7.77 (d, 2H), 8.04 (d, 2H), MS: m/z= 481.1,(M+1): 483.1 (M+3). Anal. Calcd for $C_{25}H_{21}ClN_2O_6$: C, 62.44; H, 4.40; Cl, 7.37; N, 5.83; O, 19.85; Found: C, 62.40; H, 4.54; Cl, 7.34; N, 5.89; O, 19.94.

2.3.4. 2,4-dimethoxy-3-((3-phenyl-1,2,4-oxadiazol-5-yl) methoxy) phenyl) (aryl) methanone (8e)

^{1}HNMR ($CDCl_3$) δppm: 3.84 (s, 3H), 3.89 (s, 3H), 5.35 (s, 2H, methylene -H), 6.73 (d, 2H), 6.87 (d, 1H), 7.36 (m, 5H), 7.77 (d, 2H), 8.04 (d,

2H), MS: m/z= 417.1(M+1). Anal. Calcd for $C_{24}H_{20}N_2O_5$: C, 69.22; H, 4.84; N, 6.73; O, 19.21; Found: C, 69.20; H, 4.74; N, 6.83; O, 19.24.

2.3.5. 3-((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methoxy)-2,4-dimethoxyphenyl) (phenyl) methanone (8f)

^{1}HNMR ($CDCl_3$) δppm: 3.84 (s, 3H), 3.89 (s, 3H), 5.35 (s, 2H, methylene -H), 6.73 (d, 1H), 6.87 (d, 1H), 7.36 (m, 5H), 7.77 (d, 2H), 8.04 (d, 2H), MS: m/z= 451.1 (M+1). Anal. Calcd for $C_{24}H_{19}ClN_2O_5$: C, 63.93; H, 4.25; Cl, 7.86; N, 6.21; O, 17.74; Found: C, 63.90; H, 4.27; Cl, 7.80; N, 6.23; O, 17.24.

2.3.6. 2,4-dimethoxy-3-((3-(p-tolyl)-1,2,4-oxadiazol-5-yl) methoxy) phenyl) (aryl) methanone (8g)

^{1}HNMR ($CDCl_3$) δppm: 2.23 (s, 3H), 3.84 (s, 3H), 3.89 (s, 3H), 5.33 (s, 2H, methylene -H), 6.75 (d, 1H), 6.86 (d, 1H), 7.16 (m, 2H), 7.46 (d, 2H), .77 (d, 1H), 8.04 (d, 2H), 8.64 (d, 2H), MS: m/z= 431.2 (M+1). Anal. Calcd for $C_{25}H_{22}N_2O_5$: C, 69.76; H, 5.15; N, 6.51; O, 18.58; Found: C, 69.70; H, 5.27; N, 6.40; O, 18.44.

2.3.7. 3-((3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)methoxy)-2,4-dimethoxyphenyl) (aryl) methanone (8h)

^{1}HNMR ($CDCl_3$) δppm: 3.75 (s,3H), 3.84 (s, 6H), 3.89 (s, 3H), 5.33 (s, 2H, methylene -H), 6.75 (d, 1H), 6.86 (d, 2H), 7.26 (d, 1H), 7.46 (d, 3H), 7.77 (d, 1H), 8.04 (d, 2H)MS: m/z= 477.2 (M+1). Anal. Calcd for $C_{26}H_{24}N_2O_7$: C, 65.54; H, 5.08; N, 5.88; O, 23.50; Found: C, 65.90; H, 5.27; N, 5.23; O, 23.24.

2.3.8. 2,4-dimethoxy-3-((3-(p-tolyl)-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(4-fluoroaryl) methanone (8i)

^{1}HNMR ($CDCl_3$) δppm: 2.23 (s, 3H), 3.84 (s, 3H), 3.89 (s, 3H), 5.34 (s, 2H, methylene -H), 6.75 (d, 1H), 6.86 (d, 1H), 7.56 (d, 2H), 7.87 (d, 2H), 8.14 (d, 2H), 8.74 (d, 2H), MS: m/z= 449.1 (M+1). Anal. Calcd for $C_{25}H_{21}F\ N_2O_5$: C, 66.96; H, 4.72; F, 4.24; N, 6.25; O, 17.84; Found: C, 66.90; H, 4.57; F, 4.30; N, 6.23; O, 17.74.

2.3.9. 3-((3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)methoxy)-2,4-dimethoxyphenyl)(4-fluoroaryl) methanone (8j)

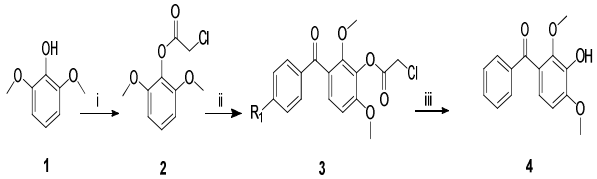
^{1}HNMR ($CDCl_3$) δppm: 3.75 (s, 3H), 3.84 (s, 3H), 3.89 (s, 3H), 5.33 (s, 2H, methylene -H), 6.75 (d, 1H), 6.86 (d, 2H), 7.26 (d, 1H), 7.46 (d, 2H), 7.77 (d, 1H), 8.04 (d, 2H), MS: m/z= 495.1 (M+1). Anal. Calcd for $C_{26}H_{23}FN_2O_7$: C, 63.15; H, 4.69; F, 3.84; N, 5.67; O, 22.65; Found: C, 63.10; H, 4.77; F, 3.80; N, 5.53; O, 22.64.

2.3.10. 2,4-dimethoxy-3-((3-phenyl-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(4-nitroaryl) methanone (8k)

^{1}HNMR ($CDCl_3$) δppm: 3.84 (s, 3H), 3.89 (s, 3H), 5.35 (s, 2H, methylene -H), 6.76 (d, 1H), 6.87 (d, 1H), 7.36 (m, 5H), 7.77 (d, 2H), 8.30 (d, 2H), MS: m/z= 462.1 (M+1). Anal. Calcd for $C_{24}H_{19}N_3O_7$: C, 62.47; H, 4.15; N, 9.11; O, 24.27; Found: C, 62.50; H, 4.17; N, 9.23; O, 24.24.

2.3.11. 3-((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methoxy)-2,4-dimethoxyphenyl)(4-nitrophenyl) methanone (8l)

^{1}HNMR ($CDCl_3$) δppm: 3.84 (s, 3H), 3.89 (s, 3H), 5.35 (s, 2H, methylene -H), 6.76 (d, 1H), 6.87 (d, 1H), 7.37 (m, 4H), 7.77 (d, 2H), 8.30 (d, 2H), MS: m/z= 496.1 (M+1): 498.1 (M+3). Anal. Calcd for $C_{24}H_{18}Cl\ N_3O_7$: C, 58.13; H, 3.66; Cl, 7.15; N, 8.47; O, 22.59; Found: C, 58.10; H, 3.57; Cl, 7.10; N, 8.43; O, 22.54.



a: R_1=H
b: R_1=OMe
c: R_1=F
d: R_1=NO_2

Scheme 1 : Reagents and conditions; (i) chloroacetyl chloride, pyridine, THF, 2h; (ii) Eaton's reagent, aromatic acids, 4h; (iii) Sodium acetate(4.5eq), methanol.

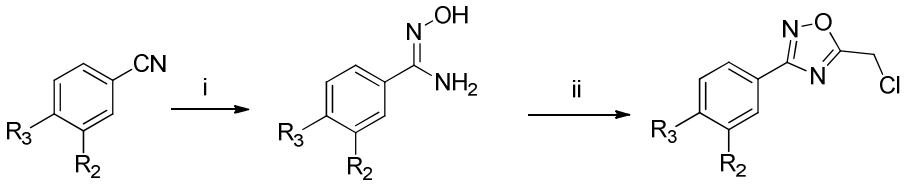
Table - 1: Antibacterial activity data of (3,5-dimethoxy-4-((3-aryl-1,2,4-oxadiazol-5-yl)methoxy) phenyl) aryl methanones(8a-l) Zone of Inhibition in mm

	Bacterial Strains	8a	8b	8c	8d	8e	8f	8g	8h	8i	8j	8k	8l	+ve control Chloroamphenicol
Gram +ve	*Bacillus subtilis*	_	7	8	–	7	6	–	–	5	–	–	18	22
	Staphylococcus aureus	6	7	12	–	12	6	6	–	–	10	–	16	30
	Escherichia coli	–	8	6	–	–	8	8	7	8	–	8	16	16
Gram -ve	*Klebsiella pneumoniae*	8	8	–	6	–	–	8	–	–	6	–	14	15
	Pseudomonas aeruginosa	–	–	8	–	–	12	–	–	_	–	–	–	22
	Salmonella typhimurium	_	–	_	–	–	_	–	–	_	–	–	_	28

Values are zones of inhibition in mm. "-" Not sensitive

2.4. Antibacterial Activity by Well Diffusion Method

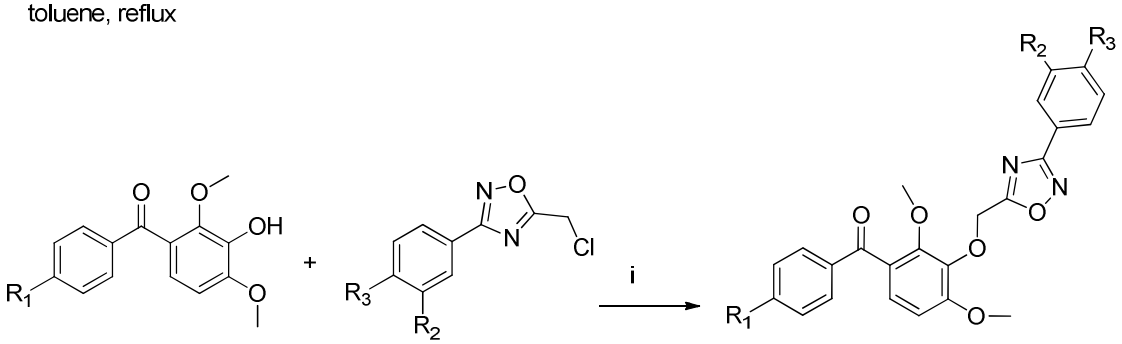
The antibacterial activity of the synthesized novel (3,5-dimethoxy-4-((3-aryl-1,2,4-oxadiazol-5-yl)methoxy)phenyl)aryl methanones(8a-l) was investigated by following the well diffusion method of Odeyemi and Fagbohun, 2005. Sterile solidified nutrient agar plates were prepared and inoculated with different test bacterial strain by spread plate method. 6mm wells were made in the nutrient agar plates and were filled with the predetermined concentration of different test samples (10 µg). The loaded plates were then kept for incubation at 37^0C for 24 hrs. Antibacterial activity of all the synthesized novel compounds 8a-l were evaluated by measuring the zone of inhibition against the test microorganisms.DMF (Dimethyl formamide) was used as negative control and 10 µg chloramphenicol was used as a positive control. After incubation, the inhibition zone formed around the wells was measured in millimeter. The study was performed in triplicate.



5 6 7

a: R_2=H, R_3=F
b: R_2=H, R_3=CF_3
c: R_2=H, R_3=H
d: R_2=H, R_3=Cl
e: R_2=H, R_3=Me
f: R_2=OMe, R_3=OMe

Scheme.2: Reagents and conditions: (i) hydroxylamine hydrochloride, K_2CO_3, EtOH; (ii) chloroacetyl chloride, toluene, reflux



4 7 8

a: R_1=OMe
b: R_1=H
c: R_1=F
d: R_1=NO_2

a: R_2=H, R_3=F
b: R_2=H, R_3=CF_3
c: R_2=H, R_3=H
d: R_2=H, R_3=Cl
e: R_2=H, R_3=Me
f: R_2=OMe, R_3=OMe

a: R_1=OMe,R_2=H,R_3=F
b: R_1=OMe,R_2=H,R_3=CF3
c: R_1=OMe,R_2=H, R_3=H
d: R_1=OMe,R_2=H, R_3=Cl
e: R_1=H,R_2=H, R_3=H
f: R_1=H,R_2=H, R_3=Cl
g: R_1=H,R_2=H, R_3=Me
h: R_1=H,R_2=OMe, R_3=OMe
i: R_1=F,R_2=H, R_3=Me
j: R_1=F,R_2=OMe, R_3=OMe
k: R_1=NO2,R_2=H R_3=H
l: R_1=NO2,R_2=H, R_3=Cl

Scheme. 3: Reagents and conditions: (i) K_2CO_3, DMF, reflux

3. RESULTS AND DISCUSSION

3.1. Chemistry

The desired compounds **8a-l**were synthesized as outlined in the scheme-3. Compounds 8a-lwere synthesized by condensing**4a-d** with **7a-f** in presence of potassium carbonate as a base and DMF as solvent. The synthetic route for designed intermediates **4a-d** and **7a-f**were depicted in the scheme 1 and scheme 2 respectively. The desired 3-hydroxy-2, 4-dimethoxybenzophenones **4a-d** were synthesized from 2,6-dimethoxyphenyl 2-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 afford 3-benzoyl-2,6-dimethoxyphenyl 2-chloroacetate3a-d.To a solution of **3a-d** and sodium acetate in methanol was refluxed for 4h, then the reaction mixture was concentrated and 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 using methanol to obtain pure white crystalline solid (3-hydroxy-2,4-dimethoxyphenyl) (phenyl)methanones **4a-d** in excellent yield.

The compounds **7a-f** were synthesized as shown in the scheme 2. Aryl nitriles **5a-f** were converted into respective aryl amidoximes **6a-f** by treating them with hydroxylamine hydrochloride followed by heating. The aryl amidoximes 6a-f were reacted with chloroacetyl chloride in dry toluene to obtain 5-(Chloromethyl)-3-aryl-1,2,4-oxadiazoles from cyclodehydration of *O*-acylamidoxime. In scheme 1, the formation of 4a-d was confirmed by ^1H NMR, ^{13}C NMR, Mass spectroscopyand elemental analysis. In ^1H NMR, the *para* proton of 2,6-dimethoxy phenoxy group appeared as a triplet at δ7.20 -7.35, whereas the *meta* proton as a doublet at δ 6.65-7.00. 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 **7a-f** was confirmed by ^1H NMR. The methylene proton and aromatic proton were appeared in the range δ 5.45-5.62 and 7.0-7.75 respectively. The formation of title compounds **8a-l** was confirmed by ^1H NMR and Mass spectroscopy. The methylene proton appeared in the range δ 5.30 -5.40.

3.2. Biology

In vitro antibacterial activity data of compounds **8a-l** against tested organisms displayed the varying antibacterial activity against used test cultures. The test sample of 8a-l series was active against *Bacillus subtilis*except 8a, 8d, 8g, 8h, 8j, 8k. 8l was stronger when compared to the other sample of the series. Sample 8a, 8b, 8c,8e, 8f, 8g, 8j – showed the bacteriostatic activity, whereas8l showed the strong bacterialcidal activity against *Staphylococcus aureus*. In case of *Escherichia coli,* 8b, 8c, 8f, 8g, 8h, 8i, 8kwas active and 8lwas stronger as the positive control used. Sample 8a, 8b, 8d, 8g, 8j, 8l showed bacteriostatic activity against *Klebsiella pneumoniae.*Whereas, *Pseudomonas aeruginosa* and*Salmonella typhimurium*showed the resistance against used test sample of 8a-lseries. Overall among the 8a-lseries sample tested for their antibacterial activity against different bacterial strains, 8l was potent and followed by 8f, 8c and 8b. And the present work concludes that sample 8l can be used potent as positive control against respective test cultures.

4. CONCLUSIONS

In conclusion, we have reported a facile route for the rapid synthesis of novel(3,5-dimethoxy-4-((3-aryl-1,2,4-oxadiazol-5-yl)methoxy)phenyl)aryl methanones**(8a-l)**from 5-(chloromethyl)-3-aryl-1,2,4-oxadiazole**(7a-f)** with aryl (3-hydroxy-2, 4-dimethoxyphenyl) methanones **(4a-b)** using K_2CO_3. The new molecular frame work has shown broad spectrum antibacterial activity which is substantiated by the presence of hydroxyl, carbonyl group and electronegative atoms, among the synthesized compounds **(8a-l)**, compound8l bearing electronegative atoms respectively in the molecular frame work have exhibited potent antibacterial activity, when compared to the standard positive controls.

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