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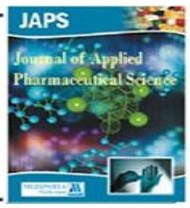

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Synthesis and antimicrobial activity of novel (3,5-dichloro-4-((5-aryl-1,3,4-thiadiazol-2-yl)methoxy) phenyl) aryl methanones

V. Srinivasa Murthy, B. K. Manuprasad and S. Shashikanth

ABSTRACT

A series of novel (3,5-dichloro-4-((5-aryl-1,3,4-thiadiazol-2-yl)methoxy)phenyl) aryl methanones (**10a-f**), were synthesized by condensing 2-chloromethyl-5-aryl-1,3,4-thiadiazole (**9a-c**) with aryl(3,5-dichloro-4-hydroxyphenyl) methanones (**4a-b**) using TBAB and K_2CO_3. The chemical structure of the newly synthesised compounds was characterized by analytical and spectral (IR, ^{1}H NMR, and LC-MS) methods. The title compounds were screened for qualitative (zone of inhibition) and quantitative antimicrobial activity (MIC) by agar well and microbroth dilution technique, respectively. Among the synthesized compounds in the series, the compound **10f** was found to exhibit significant antibacterial activity at lower concentration, against Gram positive bacteria such as *Bacillus subtilis, Staphylococcus aureus, Staphylococcus epidermidis*, and *Bacillus cereus* and Gram negative bacteria such as *E.coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, and *Klebsiella pneumoniae*. The rest of the analogues in the series displayed moderate antimicrobial activity when compared to the standard positive controls gentamicin and nystatin.

Keywords: 2,6-dichlorophenol, aryl (3,5-dichloro-4-hydroxyphenyl)methanone, (3,5-dichloro-4-((5-aryl-1,3,4-thiadiazol-2-yl)methoxy)phenyl) aryl methanones

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INTRODUCTION

The development of biologically active molecules based on molecular recognition is an attractive and challenging task for various research groups in medicinal chemistry. Increasingly, the treatment of microbial infections has become an important problem due to the emergence of multidrug resistance in pathogenic microorganisms. During recent years, intense investigations and tremendous efforts have been deployed to find a suitable candidate which will combat the resistance developed within the microorganisms. Heterocyclic compounds containing five-membered ring, in particular 1,3,4-thiadiazole gained importance because of their versatile biological properties such as antimicrobial, (Desai *et al.,* 1992; Gawande *et al.,* 1987; Mamolo *et al.,* 1996) antituberculosis, (Shucla *et al.,* 1984) anti-inflammatory, (Mullican *et al.,* 1993; Song *et al.,* 1999; Labanauskas *et al.,* 2001) anticonvulsant, (Chapleo *et al.,* 1988) antihypertensive, (Turner *et al.,* 1988) local anaesthetic, (Mazzone *et al.,* 1993) anticancer (Miyamoto *et al.,* 1985; Chou *et al.,* 2003) and hypoglycemic activities. (Hanna *et al.,* 1995) Benzophenone is a prototypical aromatic carbonyl compound that has been extensively studied. The structural features of benzophenones have been of tremendous interest in medicinal, chemical and industrial fields.

The greater importance of these substances is fundamentally due to the biological and chemical properties that they possess, which is explained by their polar feature of the carbonyl group. Functionalised phenols such as 2-hydroxy benzophenones represent important building blocks in organic and medicinal chemistry. Benzophenones are usually obtained from natural products or by synthetic methods. The literature on potential use of various benzophenone analogues is quite voluminous. Benzophenones have acquired much importance as they have been investigated for their CNS depressant, (Lindley *et al*., 1984) antimalarial, (Winter *et al.*, 1996) antimitotic, (Jing-Ping *et al*., 2002) antiprotozoal, (Ndjakou *et al.*, 2007) antiulcer, (Fumio *et al.*, 2000) antibacterial, (Sunil *et al.*, 2009) antioxidant, insecticidal, pesticidal, spermicidal, (Negi *et al.*, 1994) antifungal, antitumor and anti-inflammatory activities. Hydroxy benzophenones are also used as photoreceptors in electrophotography as it shows low residual potential and high photosensitivity in repeated use. The synthesis of heterocyclic compounds containing multi-structure in a molecule has received considerable interest in recent years. Encouraged by these observations and in continuation of our research work on synthesis of hydroxy benzophenones and isoxazole rings, it prompted us to incorporate both the bioactive molecules in a single molecular frame to examine the additive effect towards the antimicrobial activity.

MATERIALS AND METHODS

Chemistry

All the solvents and reagents used were of AR grade and used as such without further purification. The ^{1}H NMR spectra were recorded on Shimadzu AMX 400-Bruker, 400 MHz spectrometer using DMSO-d_6 as a solvent and TMS as internal standard (chemical shift δ in ppm). The IR spectra (γ_{max}) were recorded on Perkin Elmer FT-IR spectrophotometer using KBr method. Elemental (C, H, N) analyses were obtained on Vario EL III Elementar. Silica 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 LC-MS Agilent 1100 series with MSD (ion trap) using 0.1% aqueous TFA in acetonitrile system on C18-BDS column for 10 min duration.

General procedure for the synthesis of (3,5-dichloro-4-((5-aryl-1,3,4-thiadiazol-2-yl)methoxy)phenyl) aryl methanones (10a-f)

To a solution of 2-chloromethyl-5-aryl-1,3,4-thiadiazole (**9a-c**) and (3,5-dichloro-4-hydroxyphenyl) aryl methanone (**4a-b**) in acetone were added K_2CO_3 and a catalytic amount of TBAB. The reaction mixture was refluxed for 3 h and the completion of the reaction mixture was monitored through thin layer chromatography. The reaction mixture was concentrated and extracted with diethyl ether, the organic layer then washed with brine, dried over Na_2SO_4 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 pure product (3,5-dichloro-4-((5-aryl-1,3,4-thiadiazol-2-yl)methoxy)phenyl) aryl methanones **(10a-f)**.

Typical procedure for the synthesis of (3,5-dichloro-4-((5-(p-tolyl)-1,3,4-thiadiazol-2-yl)methoxy)phenyl)(p-tolyl)methanone (10f)

To a solution of **9c** 2-chloromethyl-5-(*p*-tolyl)-1,3,4-thiadiazole (0.25g, 0.82mmol) and **4b** (3,5-dichloro-4-hydroxyphenyl)(*p*-tolyl)methanone (0.24g, 0.82 mmol) in 10 mL of acetone were added K_2CO_3 (0.34g, 2.46mmol) and a pinch of TBAB. The reaction mixture was then refluxed for 3 h and concentrated to get the crude product. To the reaction mixture 10 mL of water was added and extracted with 15 mL of diethyl ether. The combined organic layer was washed with 15 mL of brine, 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 0.7g (84%) of (3,5-dichloro-4-((5-(*p*-tolyl)-1,3,4-thiadiazol-2-yl)methoxy)phenyl)(*p*-tolyl)methanone, **10f** as a white solid.

IR (cm^{-1}): 673, 1232, 1640; ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 6H), 5.20 (s, 2H), 7.2 (s, 2H), 7.45 (d, 2H), 7.58 (d, 2H), 7.63 (d, 2H), 7.68 (d, 2H); MS: *m/z* = 468 (M^+), 470 (M+2). Anal. Calcd for $C_{24}H_{18}Cl_2N_2O_2S$: C, 61.41; H, 3.87; N, 5.97; Found: C, 61.28; H, 3.98; N, 6.01

(3,5-dichloro-4-((5-phenyl-1,3,4-thiadiazol-2-yl)methoxy)phenyl) (phenyl)methanone (10a).

IR (cm^{-1}): 678, 1239, 1632; ^{1}H NMR ($CDCl_3$): δ 5.12 (s, 2H), 7.43-7.45 (m, 3H), 7.46-7.48 (m, 5H), 7.50-7.54 (m, 4H); MS: *m/z* = 440 (M^+), 442 (M+2). Anal. Calcd for $C_{22}H_{14}Cl_2N_2O_2S$: C, 59.87; H, 3.20; N, 6.35; Found: C, 59.99; H, 3.28; N, 6.01.

(3,5-dichloro-4- (5- (4-chlorophenyl) -1,3,4-thiadiazol-2-yl) methoxy)phenyl)(phenyl) methanone (10b).

IR (cm^{-1}): 672, 1229, 1650; ^{1}H NMR ($CDCl_3$): δ 5.16 (s, 2H), 7.23-7.25 (m, 3H), 7.35 (s, 2H), 7.42-7.45 (m, 4H), 7.54 (d, 2H); MS: *m/z* = 474 (M^+), 476 (M+2). Anal. Calcd for $C_{22}H_{13}Cl_3N_2O_2S$: C, 55.54; H, 2.75; N, 5.89; Found: C, 55.78; H, 2.87; N, 6.01.

(3,5-dichloro-4-((5-(p-tolyl)-1,3,4-thiadiazol-2-yl)methoxy)phenyl) (phenyl)methanone (10c).

IR (cm^{-1}): 676, 1249, 1645; ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H), 5.26 (s, 2H), 7.26 (s, 2H), 7.35-7.38 (m, 2H), 7.39-7.42 (m, 5H), 7.52 (d, 2H); MS: *m/z* = 454 (M^+), 456 (M+2). Anal. Calcd for $C_{23}H_{16}Cl_2N_2O_2S$: C, 60.67; H, 3.54; N, 6.15; Found: C, 60.99; H, 3.28; N, 6.01.

(3,5-dichloro-4-((5-phenyl-1,3,4-thiadiazol-2-yl) methoxy)phenyl) (p-tolyl)methanone (10d).

IR (cm^{-1}): 680, 1259, 1675; ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H), 5.46 (s, 2H), 7.20 (s, 2H), 7.45-7.48 (m, 3H), 7.50-7.52 (m, 4H), 7.53 (d, 2H); MS: *m/z* = 454 (M^+), 456 (M+2). Anal. Calcd

for $C_{23}H_{16}Cl_2N_2O_2S$: C, 60.67; H, 3.54; N, 6.15; Found: C, 60.59; H, 3.68; N, 6.31.

(3,5-dichloro-4 - ((5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl) methoxy)phenyl)(p-tolyl) methanone (10e)

IR (cm^{-1}): 667, 1267, 1657; ^{1}H NMR ($CDCl_3$): δ 5.46 (s, 2H), 7.20 (s, 2H), 7.42 (d, 2H), 7.45 (d, 2H), 7.54 (d, 2H), 7.56 (d, 2H); MS: *m/z* = 488 (M^+), 490 (M+2). Anal. Calcd for $C_{23}H_{15}Cl_3N_2O_2S$: C, 56.40; H, 3.09; N, 5.72; Found: C, 56.59; H, 3.48; N, 5.33.

Biology

Antimicrobial activity by well diffusion method

The antimicrobial activity of the newly synthesized compounds **9a-f** was evaluated by agar well diffusion method. All the microbial cultures were adjusted to 0.5 McFarland standards, i.e., microbial suspension of approximately 1.5 ×10^8 cfu/ml. 20 ml of Mueller Hinton (for bacteria) and Sabouraud's agar (for fungi) media was poured into each Petri plate and plates were swabbed with 100 µl inocula of the test microorganisms (Singh *et al.*, 2009). Using sterile cork borer of 8 mm diameter, wells were bored into the seeded agar plates and these were loaded with a 50µl volume with concentration of 1.0 mg/ml of each compound reconstituted in the dimethylformamide (DMF). All the plates were incubated at 37°C for 24 h. Antimicrobial activity of all the synthesized compounds **10a-f** was evaluated by measuring the zone of inhibition against the test microorganisms. The medium with dimethylformamide (DMF) as solvent was used as a negative control whereas gentamicin (standard antibacterial drug) and nystatin (standard antifungal drug) were used as positive control at concentration of 10 µg/well from 1mg/ml of stock solution. The experiments were performed in triplicates.

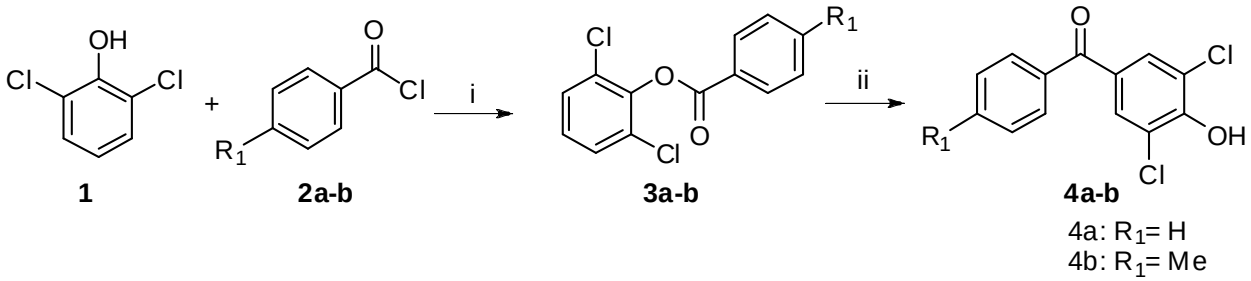
Determination of minimum inhibitory concentration

The minimum inhibitory concentrations (**MIC**) were evaluated by the microbroth dilution technique (Dragana *et al*.,2009) in 96-well microtitre plates using standard inocula consisted of 2×10^6 CFU/ml for bacteria and 2×10^5 CFU/ml fungi respectively. Two- fold serial dilutions of the test compounds, dissolved in dimethylformamide (DMF) were prepared in the concentrations range from 200-0.18 µg/ml in 100µl Mueller-Hinton Broth and Sabourauds dextrose broth for bacteria and fungi respectively. To each well 10µl of microbial inocula were added. 20µl triphenyltetrazolium chloride (TTC) for bacteria and MTT (Methyl thioazyltetrazolium bromide) for fungi (Aldrich Chemical Company Inc., USA) at concentration of (0.05% w/v) was added to the culture medium as a microbial growth indicator. The microbial growth was determined by the absorbance at 600 nm using a universal microplate reader (Merck) after incubation at 37°C for 24 h for the bacteria, and at 26°C for 48 h for the fungi. The MIC is defined as the lowest concentration of the compound at which the microorganism does not demonstrate visible growth.

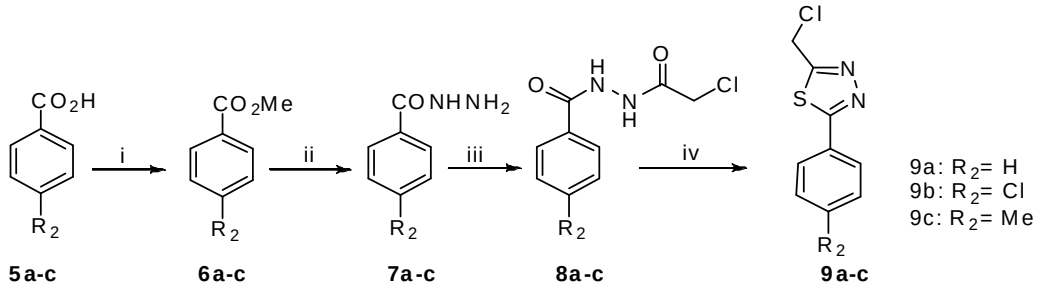
RESULTS AND DISCUSSION

Chemistry

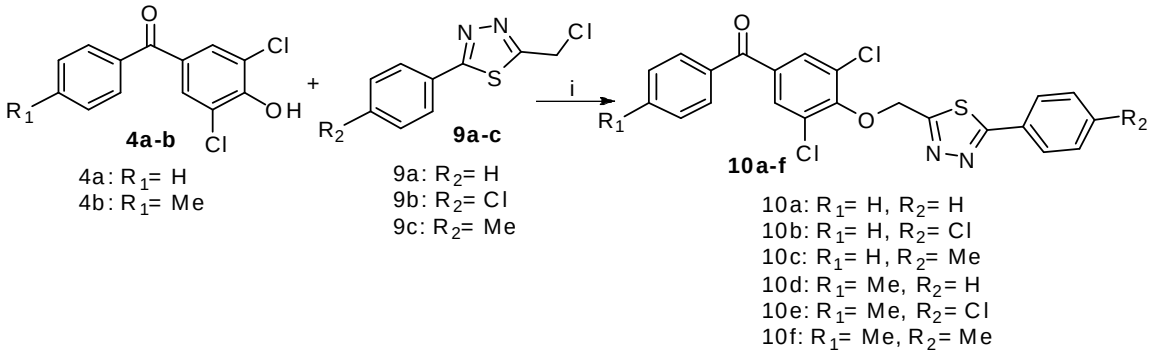
The desired compounds **10a-f** were synthesized as outlined in the scheme 3. Compounds **10a-f** were synthesized by condensing **4a-b** with **9a-c** in presence of potassium carbonate as a base and acetone as solvent. The synthetic route for designed intermediates **4a-b** & **9a-c** were depicted in the scheme 1 & scheme 2 respectively. The desired 4-hydroxy-3,5-dichlorobenzophenones **4a-b** were synthesized from its corresponding 2,6-dichlorophenylbenzoates (**3a-b**) on heating with anhydrous Aluminium Chloride at 140°C. After the completion of the reaction, the reaction mixture was treated with cold Conc.HCl and heated to 60°C with stirring for overnight. The reaction mixture was filtered and dissolved in diethylether, washed with 10% NaOH solution. The sodium hydroxide layer was neutralized with cold Conc.HCl to obtain brown precipitate. The precipitate was filtered, dried well and then purified by column chromatography to furnish white solid **4a-b** in moderate yield. The compounds **3a-b** were obtained by stirring 2,6-dichlorophenol **1**, with substituted benzoyl chloride in presence of 10% sodium hydroxide solution at rt for 24h. The crude solid **3a-b** obtained was filtered from the reaction mixture, washed with cold water, dried well and recrystallized from ethanol to get pure white crystals **3a-b** in excellent yield.



Scheme. 1: Reagents and condition: (i) 10% NaOH solution H_2O, rt, 24h; (ii) anhydrous $AlCl_3$, 140 ^oC.



Scheme. 2: reagents and conditions: (i) thionyl chloride, methanol, reflux; (ii) hydrazine hydrate, methanol, refux; (iii) chloroacetyl chloride, dry triethyl amine, dry THF, reflux; (iv) lawesson's reagent, p-xylene, reflux.



Scheme. 3: Reagents and conditions: (i) K_2CO_3, Ca. tetra-n-butylammonium bromide (TBAB), Acetone 60 °C.

Table. 1: Antimicrobial activity data of (3,5-dichloro-4-((5-aryl-1,3,4-thiadiazol-2-yl)methoxy)phenyl) aryl methanones **(10a-f)** Zone of inhibition in mm (MIC in µg/ml)

Compd no	Test Bacteria								Test Fungi	
	Gram+ bacteria					Gram-bacteria			Filamentous	yeast
	Bacillus subtilis	*Staphylococcus aureus*	*Staphylococcus epidermidis*	*Bacillus cereus*	*E-coli*	*Pseudomonas aeruginosa*	*Salmonella typhi*	*Klebsiella pneumoniae*	*Aspergillus niger*	*Candida albicans*
10a	18(12.5)	23(20.0)	17(20.0)	18(24.5)	-	-	12(50.52)	12(48.0)	12(25.0)	10(25.4)
10b	18(15.0)	12(25.0)	12(25.0)	16(25.0)	-	-	-	-	-	-
10c	25(1.35)	32(1.35)	27(4.0)	25(1.56)	20(12.2)	20(24.0)	25(10.33)	17(23.52)	17(7.22)	20(10.53)
10d	28(2.35)	27(2.85)	26(6.25)	25(4.53)	24(7.35)	19(28.3)	20(15.53)	15(25.0)	18(6.00)	17(8.48)
10e	20(15.0)	15(23.29)	14(20.0)	16(21.2)	14(25.0)	-	-	14(25.0)	10(25.20)	12(25.0)
10f	32(0.20)	30(2.22)	26(2.5)	30(0.25)	28(3.52)	22(6.0)	29(1.25)	20(6.0)	25(4.0)	20(5.0)
Gentamicin	30(0.39)	28(1.56)	25(3.12)	28(0.39)	25(3.125)	18(12.5)	30(0.39)	15(25.0)	NT	NT
Nystatin	NT	NT	NT	NT	NT	NT	NT	NT	15(12.5)	15(25.0)

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

The compounds **9a-c** were synthesized as shown in the scheme 2. Substituted benzoic acids **5a-c** were converted into respective esters **6a-c** by treating them with thionyl chloride and methanol, followed by reflux for 12 h. The esters **6a-c** were reacted with hydrazine hydrate in methanol by refluxing at 60°C to afford its respective hydrazide **7a-c**. Compounds **7a-c** were dissolved in dry tetrahydrofuran and treated with chloroacetyl chloride and triethyl amine, followed by reflux to furnish their respective *N*-chloroacetyl-*N'*-aroyl hydrazine **8a-c**. The compounds **8a-c** were transformed to **9a-c**, by treating them with Lawesson's reagent in *p*-xylene at 140°C. In scheme 1, the formation of **3a-b** was confirmed by ^{1}H NMR and Mass spectroscopy. In ^{1}H NMR, the *para* proton of 2,6-dichlorophenoxy group appeared as a triplet at δ 7.23-7.45, whereas the *meta* proton as a doublet at δ 6.67-7.00. After the Fries rearrangement, both the *para* pattern and *meta* pattern of 2,6-dichlorophenoxy disappeared to result in a single peak centered at δ 7.45-7.75 corresponding to the proton, which is *meta* to hydroxy and *ortho* to carbonyl group in **4a-b**. The formation of **9a-c** was confirmed by ^{1}H 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 the title compounds **10a-c** were confirmed by ^{1}H NMR and Mass spectroscopy. The methylene proton appeared in the range δ 5.0-5.5.

Biology

The antimicrobial activity of compounds **10a-f** was evaluated in vitro against some human pathogenic Gram positive bacteria such as *Bacillus subtilis* (MTCC 121), *Staphylococcus aureus* (MTCC 7443), *Staphylococcus epidermidis* (MTCC 435) *and Bacillus cereus* (MTCC 1272) and Gram negative bacteria *E.coli* (MTCC 7410), *Pseudomonas aeruginosa* (MTCC 7903), *Salmonella typhi* (MTCC 733) and *Klebsiella pneumoniae* (MTCC 7407). The compounds **10a-f** were evaluated against filamentous fungi such as *Aspergillus niger* (MTCC 1378), and yeast *Candida albicans* (MTCC 183). The corresponding zone of inhibition and minimum inhibitory concentrations were summarized in **Table 1**. Results indicate that the compound **10f** have exhibited broad spectrum antimicrobial activity against both bacteria and fungi,

whereas the rest of the compounds in the series have exhibited moderate antimicrobial activity when compared to positive controls. Antimicrobial spectrum indicates that Gram positive bacteria and fungi were more susceptible to the synthesized compounds than Gram negative bacteria. The thorough investigation of our synthesized compounds **10a-f**, pertaining to quantitative structure activity relationship highlighted that presence of more electron donating groups at para position in phenyl ring bearing thiadiazole has influenced the antimicrobial activity, while its counterpart electron withdrawing groups has shown its opposite effect. The compounds **10c** and **10d** have shown moderate activity when compared to positive controls. The unsubstituted title compound **10a** has shown better activity when compared to **10h** and **10e** which has chlorine group as substituent.

CONCLUSION

In conclusion, we have reported a facile route for the rapid synthesis of novel (3,5-dichloro-4-((5-aryl thiadiazol-2-yl)methoxy)phenyl) aryl methanones (**10a-f**), from 2-chloromethyl-5-aryl-1,3,4-thiadiazole (**9a-c**) and (3,5-dichloro-4-hydroxyphenyl) aryl methanones (**4a-b**) using TBAB and K_2CO_3. The new molecular framework has shown broad spectrum antimicrobial activity which is substantiated by the presence of carbonyl group and more electron donating groups. Among the synthesized compounds (**10a-f**), compound **10f** has exhibited potent antimicrobial activity, whereas the rest of the analogues have shown moderate activity when compared to the standard positive controls.

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