Antimicrobial Evaluation of Benzophenone-N-Ethyl Piperidine Ether Derivatives

Zabiulla[a], Mahima Jyothi[a], Yasser Hussein Issa Mohammed[a], Noor Fathima Khanum[b], Shaukath Ara Khanum[a*]

[a]*Department of Chemistry, Yuvaraja's College (Autonomous), University of Mysore, Karnataka, India.*

[b]*Department of Food Science and Nutrition, Maharani's Science College for Women ,Mysore, Karnataka, India*

Abstract - Microorganisms are closely associated with the health and welfare of human beings. Whereas some microorganisms are beneficial, others are detrimental. Bacterial infections often produce inflammation and pains and in some instances, infections result in high mortality. Any subtle change in the drug molecule, which may not be detected by chemical methods, can be revealed by a change in the antimicrobial activity and hence microbiological assays are very useful. A series of substituted Benzophenone-N-ethyl piperidine ether Derivatives were screened for their antibacterial and antifungal activities. The bioassays indicated that most of the synthesized compounds showed potential antibacterial and antifungal agents.

Key words: Benzophenone-N-ethyl piperidine ether, Antibacterial and Antifungal.

I. INTRODUCTION

Discovery of new drugs for systemic opportunistic microbial infections is a major challenge in infectious disease research. Microbial infections have increased in recent years, particularly those that are of nosocomial origin, leading to a broad use of agents with activity against pathogens [1]. Antimicrobial resistance of different pathogens also became widespread [2]. Benzophenone and its derivatives are an emerging class of molecules with multiple pharmacokinetic properties. New molecules with benzophenone moiety emerging day by day with potent biological activity in recent times [3-5]. Benzophenones, the precursor for the synthesis of the title compounds are essential due to their diverse biological and chemical properties. For instance, these analogues possess a high analgesic [6] efficacy and also endowed with anti-inflammatory [7] anticancer [8], antimicrobial property [9]. Synthesis of piperidine derivatives has attracted much interest because of their biological activities and the importance of piperidines in natural product synthesis [10–14]. Depending on the regio- and stereochemistry of substituents, different synthetic routes to control the regio- and stereoselectivity have been proposed [15–18]. Wide range of biological activities was also reported for the molecules containing piperidine ring [19-22]. With the motivation of obtaining more potent antioxidant, anti-Alzheimer and anticancer agents for lung cancer [23].

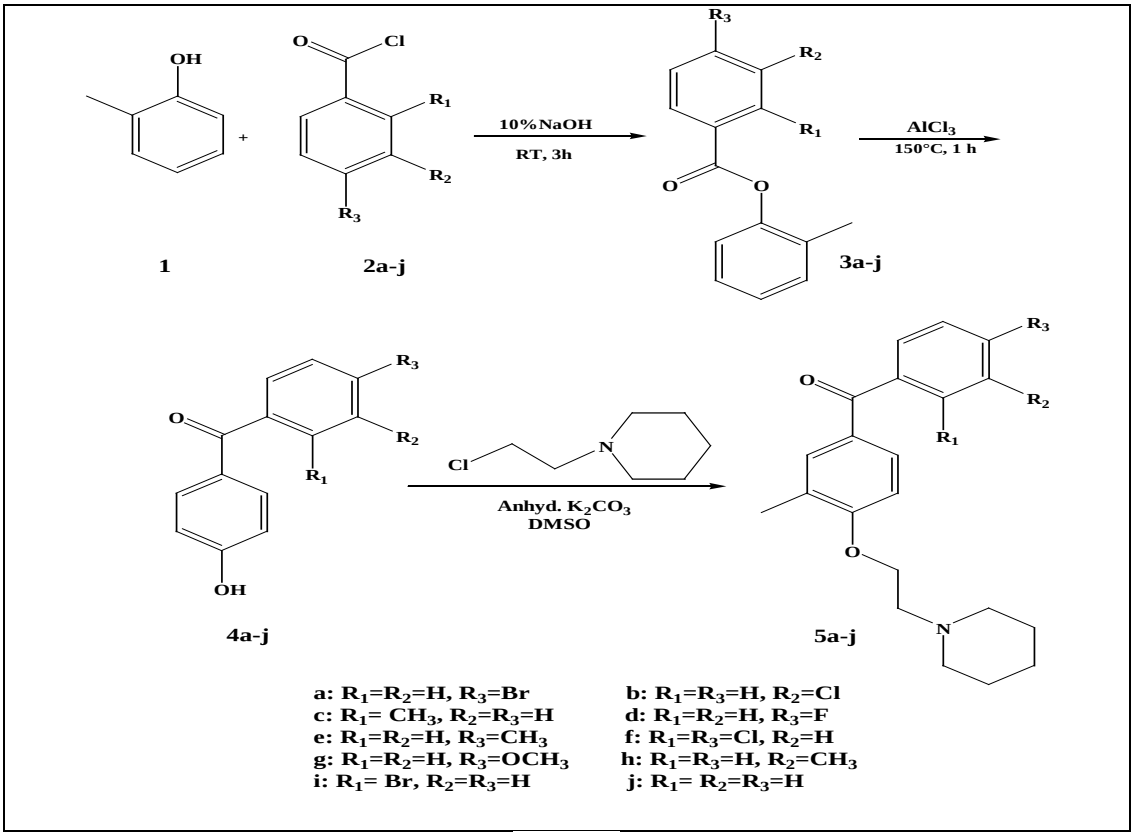
The literature investigation reveals that no endeavor was proposed toward the evolution of antimicrobial activity of benzophenone-N-ethyl piperidine ether analogues to verify the importance of title compounds on the pharmacological activity. Based on this information and in our search for new molecules with antimicrobial activity, it was considered valuable to synthesize benzophenone-N-ethyl piperidine ether analogues (5a–j) as antimicrobial agents as explained below, for a rational study of the structure–activity relationships.

II. RESULT AND DISCUSSION

Chemistry:

The synthesis of the title compounds 5a–j was accomplished by a synthetic procedure as shown in Scheme 1. All the synthesized compounds were established by IR, proton NMR and mass spectral data. First, the benzoylated products 3a–j were synthesized by the benzoylation of 2-methyl- phenol 1 with substituted benzoyl chlorides 2a-j under low temperature and the structures were confirmed by the appearance of the carbonyl stretching band for the ester group in the IR spectra and the disappearance of broad singlet of the OH proton of 2-methyl- phenol 1 in proton NMR spectra. Fries rearrangement of compounds 3a–j using anhydrous aluminium chloride as a catalyst under neat condition afforded hydroxy benzophenones 4a–j, and these compounds were established by the disappearance of the carbonyl stretching band of the ester group and appearance of the OH stretching band in IR spectra and also, the appearance of broad singlet for OH proton and decrease in one aromatic proton in proton NMR spectra. Finally, compounds 4a–j and 1-(2-chloroethyl) piperidine hydrochloride was refluxed in presence of anhydrous potassium carbonate and dimethyl sulfoxide as solvent afforded the expected title compounds 5a–j in a good yield (70–90%). This was supported by the disappearance of the OH stretching of compounds 4a–j in the IR absorption spectra. The proton NMR observations of these compounds revealed that, broad singlet for the OH proton of compounds 4a–j disappeared and also appearance

of ten CH_2 protons, which was clearly evident for the formation of products.



Scheme-1

Biology:

Antimicrobial activities of the compounds 5a-j were evaluated against various gram positive, gram negative bacteria and fungi, namely, *B. cereus, Staphylococcus aureus*(*MTCC 7443), Enterobacter aerogenes (MTCC 111), Staphylococcus aureus (MRSA) (MTCC 84), B. subtilis*, (gram positive bacteria) *Escherichia coli, Klebsiella pneumoniae(MTCC 109), Salmonella paratyphi-B(MTCC 733), Salmonella typhimurium(MTCC 2488), P. aeruginosa*, (gram negative bacteria) and fungi *Botyritis cinerea* (*MTCC 2880*), *Candida krusei* (*MTCC 231*), *F. solani, Candida albicans* (*MTCC 227*), *A.niger, A.flavus, C. gloeosporioides, Malassesia pachydermatis, C.parapsilosis, F. moniliforme* .The antimicrobial activities were evaluated by the agar disc diffusion method as per the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS). The screening results of the tested compounds 5a-j against microorganisms are summarized in Table 1-2.

The results of antibacterial and antifungal activity shown in (Table 1-2) indicated that Gram-negative bacteria were more susceptible towards the tested compounds than Gram-positive ones. It was observed that compounds 5a, 5b, 5d, 5f, 5i displayed higher activity than 5c, 5e, 5g, 5h, 5j compared with standard drug Streptomycin. This may be due to the presence of electron withdrawing group attached to aromatic ring. Compounds 5a, 5c, 5d, 5f and 5i showed good activity against *E. coli*, 5a, 5b, 5d and 5f against *S. aureus*, 5b, 5d and 5f against *S. aureus (MRSA)*, 5b, 5d and 5h against *P. aeruginosa*, 5d and 5i against *B. cereus*, 5b and 5f against *K. pneumonia*, 5a and 5b against *S.Paratyphi-B*, 5a and 5d against *S. typhimurium*, 5i against *B. subtilis*. Further synthesized compounds 5a-j showed significant antifungal activity against the standard drug Ketoconazole. Compounds 5b, 5c, 5f and 5j against *Candida krusei* (*MTCC 231*), 5a, 5b, 5d and 5f against *A.niger*, 5b, 5f, 5h and 5i against *Malassesia pachydermatis*, 5b, 5d *and* 5e *Candida albicans* (*MTCC 227*), 5b, 5c and 5d against *C. gloeosporioides*, 5a, 5d and 5j against *F. moniliforme*, 5a and 5d against *Botyritis cinerea* (*MTCC 2880*), 5a and 5i against *F. solani*, 5a and 5d against *C.parapsilosis*, and 5d against *A.flavus.*

When compared with all the synthesized compounds, compound 5d with flouro group at para position of aromatic ring showed excellent activity against both gram-positive, gram-negative bacteria and also exhibited a excellent antifungal activity. Compounds 5a with bromo and 5b with chloro group at para and meta position respectively, of aromatic ring showed good antibacterial and antifungal activity and 5f with two chloro group at ortho and meta position of aromatic ring exhibited moderate antimicrobial and antifungal activity. Compounds 5e with methyl, 5g with methoxy and 5h with

methyl group at para, para and meta position respectively, of aromatic ring exhibited lowest antibacterial activity and also compound 5g showed lowest antifungal activity.

III.EXPERIMENTAL SECTION

Materials and methods:

Chemicals were purchased from Aldrich Chemical Co. TLC was performed on aluminium-backed silica plated with visuali- zation by UV-light. Melting points were determined on a Tho- mas Hoover capillary melting point apparatus with a digital thermometer. IR spectra were recorded in Nujol on FT-IR Shima- dzu 8300 spectrometer and ^{1}H NMR spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$. Chemical shifts were recorded in parts per million downfield from tetramethylsilane. Mass spectra were obtained with a VG70-70H mass spectrometer and elemental analysis results are within 0.4% of the calculated value.

General procedure for the synthesis of phenyl benzoates 3a-j

To 2-methyl- phenol (1, 13.9 mmol), corresponding benzoyl chlorides (2a–j, 13.9 mmol) were added with constant stirring. The reaction mixture was cooled to 0 °C, made alkaline by adding 10% sodium hydroxide solution and stirring was continued for about 1 h. The separated oil was extracted with ether (3 × 20 ml), the organic layer was washed with 10% sodium hydroxid solution (3 × 15 ml) and with distilled water (3 × 30 ml). Finally, the organic layer was dried over anhydrous sodium sulfate and ether was removed to afford substituted 2-methylphenyl benzoates (3a–j).

3a: IR (Nujol): 1725 cm^{-1} (ester, C=O); 1H NMR ($CDCl_3$): d 2.0 (s, 3H, CH_3), 6.9–7.3 (m, 8H, Ar-H). Anal. Calcd for $C_{14}H_{11}BrO_2$ (291): C, 57.76; H, 3.81; Br, 27.45. Found: C, 57.61; H, 3.89; Br, 27.32.

General procedure for the synthesis of (4-hydroxy phenyl) phenyl methanones 4a-j

Substituted hydroxy benzophenones (4a–j) were synthesized by Fries rearrangement of 3a–j. A mixture of anhydrous aluminum chloride (6.1 mmol) and 3a–j (4.1 mmol) was heated over oil bath at 80–90 °C for 45 min. At the end of this period the solution was cooled and decomposed by ice-cold water. The residual solid was crushed into powder, dissolved in ether (40 ml) and extracted with 10% sodium hydroxide (3 × 30 ml). The basic aqueous solution was neutralized with 10% hydrochloric acid. The filtered solid was washed with distilled water (3 × 30 ml) and recrystallized from ethanol to afford 4a–j.

4a: mp 166–168 °C; IR (Nujol): 1640 (C=O), 3515–3630 cm^{-1} (OH);1H NMR ($CDCl_3$): d 2.1 (s, 3H, CH_3), 6.9–7.4 (m, 7H, Ar-H), 9.0 (br s, 1H, OH); EI-MS: m/z 290 (M+, 84), 292 (M+, 81), 289 (100), 291 (94), 135 (56), 107 (51). Anal. Calcd for $C_{14}H_{11}BrO_2$ (291): C, 57.73; H, 3.78; Br, 27.49. Found: C, 57.67; H, 3.88; Br, 27.39.

General procedure for the synthesis of [3-Methyl-4-(2-piperidin-1-yl-ethoxy)-phenyl]-phenyl-methanones 5a-j

A mixture of 4a–j (2.06 mmol) and 1-(2-chloroethyl) piperidine hydrochloride (2.06 mmol) in presence of anhydrous potassium carbonate (5.15 mmol) and dimethyl sulfoxide (10 ml) was re- fluxed for 9 h then cooled. The residual mass was triturated with ice water to remove potassium carbonate and dimethyl sulfoxide and extracted with ethyl acetate (3 × 20 ml). The ethyl acetate layer was washed with saturated sodium chloride solution (3 × 20 ml), 10% sodium hydroxide solution (3 × 20 ml) followed by distilled water (3 × 30 ml) and then dried over anhydrous so- dium sulfate. Finally the ether layer was evaporated to dryness to get crude product, which on recrystallization with ethanol gave pasty mass of the title compounds 5a–j. The compounds 5a–j were characterized by IR, 1H NMR, and mass spectrophotometer.

5a: IR (Nujol): 1650 cm^{-1} (C=O); 1H NMR ($CDCl_3$): d 1.2–1.5 (m, 6H, ring-3CH_2), 2.0 (s, 3H, CH_3), 2.35 (t, 4H, ring-2NCH_2), 2.78 (t, 2H, NCH_2), 4.1 (t, 2H, OCH_2), 6.8–7.4 (m, 7H, Ar-H); EI-MS: m/z 403 (M+, 65) and 401 (M+, 62). Anal. Calcd for $C_{21}H_{24}BrNO_2$ (402): C, 62.69; H, 6.01; Br, 19.86; N, 3.48. Found: C, 62.54; H, 6.21; Br, 19.69; N, 3.32.

5b: IR (Nujol): 1655 cm^{-1} (C=O); 1H NMR ($CDCl_3$): d 1.25–1.52 (m, 6H, ring-3CH_2), 2.2 (s, 3H, CH_3), 2.4 (t, 4H, ring-2NCH_2), 2.8 (t, 2H, NCH_2), 4.15 (t, 2H, OCH_2), 6.8–7.55 (m, 7H, Ar-H); EI-MS: m/z 357.5 (M+, 63). Anal. Calcd for $C_{21}H_{24}ClNO_2$ (357.5): C, 70.48; H, 6.76; Cl, 9.91; N, 3.91. Found: C, 70.37; H, 6.65; Cl, 9.82; N, 3.81.

5c: IR (Nujol): 1605 cm^{-1} (C=O); 1H NMR ($CDCl_3$): d 1.22–1.51 (m, 6H, ring-3CH_2), 2.3 (s, 6H, 2CH_3), 2.55 (t, 4H, ring-2NCH_2), 2.81 (t, 2H, NCH_2), 4.15 (t, 2H, OCH_2), 6.8–7.65 (m, 7H, Ar-H); EI-MS: m/z 337 (M+, 60). Anal. Calcd for $C_{22}H_{27}NO_2$ (337): C, 78.30; H, 8.06; N, 4.15. Found: C, 78.39; H, 8.16; N, 4.25.

5d: IR (Nujol): 1655 cm^{-1} (C=O); 1H NMR ($CDCl_3$): d 1.2–1.5 (m, 6H, ring- 3CH_2), 2.0–2.3 (d, 6H, 2CH_3), 2.56 (t, 4H, ring-2NCH_2), 2.85 (t, 2H, NCH_2), 4.2 (t, 2H, OCH_2), 6.9–7.7 (m, 7H, Ar-H); EI-MS: m/z 230 (M+, 61). Anal. Calcd for $C_{21}H_{24}FNO_2$ (341): C, 73.88; H, 7.09; F,

5.56; N, 4.10. Found: C, 73.77; H, 7.18; F, 5.42; N, 4.22.

5e: IR (Nujol): 1615 cm^{-1} (C=O); 1H NMR ($CDCl_3$): d 1.23–1.53 (m, 6H, ring-3CH_2), 2.0–2.2 (d, 6H, 2CH_3), 2.5 (t, 4H, ring-2NCH_2), 2.8 (t, 2H, NCH_2), 4.1 (t, 2H, OCH_2), 6.9–7.6 (m, 7H, Ar-H); EI-MS: m/z 337 (M+, 61). Anal. Calcd for $C_{22}H_{27}NO_2$ (337): C, 78.30; H, 8.06; N, 4.15. Found: C, 78.38; H, 8.18; N, 4.26.

5f: IR (Nujol): 1675 cm^{-1} (C=O); 1H NMR ($CDCl_3$): d 1.24–1.53 (m, 6H, ring-3CH_2), 2.1 (s, 3H, CH_3), 2.42 (t, 4H, ring-2NCH_2), 2.85 (t, 2H, NCH_2), 4.2 (t, 2H, OCH_2), 6.9–7.8 (m, 6H, Ar-H); EI-MS: m/z 392 (M+, 63). Anal. Calcd for $C_{21}H_{23}Cl_2NO_2$ (392): C, 64.29; H, 5.91; Cl, 18.07; N, 3.57. Found: C, 64.15; H, 5.62; Cl, 18.16; N, 3.44.

5g: IR (Nujol): 1605 cm^{-1} (C=O); 1H NMR ($CDCl_3$): d 1.21–1.52 (m, 6H, ring-3CH_2), 2.1 (d, 6H, 2CH_3), 2.45 (t, 4H, ring-2NCH_2), 2.75 (t, 2H, NCH_2), 3.8 (s, 3H, OCH3), 4.2 (t, 2H, OCH_2), 6.95–7.75 (m, 7H, Ar-H); EI-MS: m/z 353 (M+, 59). Anal. Calcd for $C_{22}H_{27}NO_3$ (353): C, 74.76; H, 7.70; N, 3.96. Found: C, 74.82; H, 7.61; N, 3.83.

5h: IR (Nujol): 1610 cm^{-1} (C=O); 1H NMR ($CDCl_3$): d 1.24–1.54 (m, 6H, ring- 3CH_2), 2.1–2.25 (d, 6H, 2CH_3), 2.6 (t, 4H, ring-2NCH_2), 2.85 (t, 2H, NCH_2), 4.2 (t, 2H, OCH_2), 6.9–7.65 (m, 7H, Ar-H); EI-MS: m/z 337 (M+, 60). Anal. Calcd for $C_{22}H_{27}NO_2$ (337): C, 78.30; H, 8.06; N, 4.15. Found: C, 78.35; H, 8.11; N, 4.21.

5i: IR (Nujol): 1620 cm^{-1} (C=O); 1H NMR ($CDCl_3$) δ (ppm): 1.25–1.55 (m, 6H, ring-3CH_2), 2.1 (s, 3H, CH_3), 2.36 (t, 4H, ring-2NCH_2), 2.8 (t, 2H, NCH_2), 4.2 (t, 2H, OCH_2), 6.9–7.3 (m, 7H, Ar-H); EI-MS: m/z 403 (M+, 64) and 401 (M+, 60). Anal. Calcd for $C_{21}H_{24}BrNO_2$ (402): C, 62.69; H, 6.01; Br, 19.86; N, 3.48. Found: C, 62.76; H, 6.15; Br, 19.63; N, 3.58.

5j: IR (Nujol): 1620 cm^{-1} (C=O); 1H NMR ($CDCl_3$): d 1.21–1.5 (m, 6H, ring-3CH2), 2.1 (s, 3H, CH_3), 2.55 (t, 4H, ring-2NCH_2), 2.8 (t, 2H, NCH_2), 4.2 (t, 2H, OCH_2), 6.9–7.7(m, 8H, Ar-H); EI-MS: m/z 337 (M+, 60). Anal. Calcd for $C_{21}H_{25}NO_2$ (323): C, 77.98; H, 7.79; N, 4.33. Found: C, 77.82; H, 7.64; N, 4.26.

Biological assays

Cells:

Bacterial strains *B. cereus, Staphylococcus aureus*(*MTCC 7443), Enterobacter aerogenes (MTCC 111), Staphylococcus aureus (MRSA) (MTCC 84), B. subtilis*, gram negative bacteria *Escherichia coli, Klebsiella pneumoniae(MTCC 109), Salmonella paratyphi-B(MTCC 733), Salmonella typhimurium(MTCC 2488), P. aeruginosa* and fungi *Botyritis cinerea* (*MTCC 2880*), *Candida krusei* (*MTCC 231*), *F. solani, Candida albicans* (*MTCC 227*), *A.niger, A.flavus, C. gloeosporioides, Malassesia pachydermatis, C.parapsilosis, F. moniliforme* obtained from Department of Microbiology, University of Mysore, Mysuru, Karnataka, India.

Antimicrobial activity:

The in vitro antimicrobial study was carried out by agar well diffusion method against test organisms [24, 25]. Nutrient broth (NB) plates were swabbed with 24 h old broth culture (100 ml) of test bacteria. Using the sterile cork borer, wells (6 mm) were made into each petriplate. The compounds were dissolved in DMSO of 5 mg/ml and from this 2.5, 5, 10 and 20 ml (12.5, 25, 50, 100 mg/well) were added into the wells by using sterile pipettes. Simultaneously the standard antibiotics, Streptomycin for antibacterial activity and Ketoconazole for antifungal activity (as positive control) were tested against the pathogens. The samples were dissolved in DMSO which showed no zone of inhibition acts as negative control. The plates were incubated at 37 ^{0}C for 24 h for bacteria and at 28 ^{0}C for 48 h for fungi. After appropriate incubation the diameter of zone of inhibition of each well was measured. Duplicates were maintained and the average values were calculated for eventual antimicrobial activity.

Broth dilution test was used to determine minimum inhibitory concentration (MIC) of the above mentioned samples [26, 27]. Freshly prepared nutrient broth was used as diluents. The 24 h old culture of the test bacteria *B. cereus, Staphylococcus aureus*(*MTCC 7443), Enterobacter aerogenes (MTCC 111), Staphylococcus aureus (MRSA) (MTCC 84), B. subtilis*, gram negative bacteria *Escherichia coli, Klebsiella pneumoniae(MTCC 109), Salmonella paratyphi-B(MTCC 733), Salmonella typhimurium(MTCC 2488), P. aeruginosa* and the test fungi fungi *Botyritis cinerea* (*MTCC 2880*), *Candida krusei* (*MTCC 231*), *F. solani, Candida albicans* (*MTCC 227*), *A.niger, A.flavus, C. gloeosporioides, Malassesia pachydermatis, C.parapsilosis, F. moniliforme* were diluted 100 folds in nutrient broth (100 ml bacterial cultures in 10 ml NB). The stock solution of the synthesized compounds was prepared in dimethyl sulfoxide (DMSO) by dissolving 5 mg of the compound in 1 ml of DMSO. Increasing concentrations of the test samples (1.25, 2.5, 5, 10, 20, 40 ml of stock solution contains 6.25, 12.5, 25, 50, 100, 200 mg of the compounds) were added to the test tubes containing the bacterial and fungal cultures. All the tubes were incubated at 37 ^{0}C for 24 h for bacteria and at 28 ^{0}C for 48 h for fungi. The tubes were examined for visible turbidity and using NB as control. Control without test samples and with solvent was assayed simultaneously.

The lowest concentration that inhibited visible growth of the tested organisms was recorded as MIC.

To determine the minimum bactericidal concentration (MBC) [28] and minimum fungicidal concentration (MFC) [29] for each set of test tubes in the MIC determination a loopful of broth was collected from those tubes which did not show any growth and inoculated on sterile nutrient broth (for bacteria) and PDA (for fungi) by streaking. Plates inoculated with bacteria and fungi were incubated at 37 ^{0}C for 24 h and at 28 ^{0}C for 48 h respectively. After incubation the lowest concentration was noted as MBC (for bacteria) or MFC (for fungi) at which no visible growth was observed.

IV. CONCLUSION

In conclusion, the present observations confirm the presence of antimicrobial activity in all examined compounds. Among the series of biologically active benzophenone-*N*-ethyl piperidine ether analogues 5a-j were screened for antibacterial and antifungal activities. Compounds 5d with flouro group at para position of aromatic ring have shown excellent antibacterial and antifugal activity as compared to the other compounds in the series with MIC value 9.37 □g/ml. Further investigation may help to develop novel antimicrobial drugs for future chemotherapy.

V. ACKNOWLEDGEMENTS

Zabiulla gratefully acknowledges the financial support provided by the Department of Science and Technology, New Delhi, Under INSPIRE-Fellowship scheme [IF140407]. Shaukath Ara Khanum thankfully acknowledges the financial support provided by VGST, Bangalore, under CISEE Programme [Project sanction order: No. VGST/ CISEE /282].

REFERENCES

[1] D.M. Livermore, M. Warner, S. Mushtaq, M. Doumith, J. Zhang, N. Woodford, Int. J. Antimicrob. Agents 37, 2011, 415–419.

[2] L.L. Silver, Clin. Microbiol. Rev. 24, 2011, 71–109.

[3] L. de Almeida, K.F. Alves, C.M. Maciel-Rezende, O. Jesus Lde, F.R. Pires, C.V. Junior, M. A. Izidoro, W.A. Júdice, M.H. Dos Santos, M.J. Marques, Biomed Pharmocother, 75, 2015, 93-9.

[4] J. Heo, H. Shin, J. Lee, T. Kim K.S. Inn, N.J.Kim, Bioorg. Med. Chem. Lett. 25(17), 2015, 3694-8.

[5] Tzvetomira Tzanova Mariana Gerova, Ognyan Petrov, Margarita Karaivanova, Denyse Bagrel, Eur. J. Med. Chem. 44, 2009, 2724-2730.

[6] J. Jiri, P. Miroslav, P Josef, W. Stanislav, Csech CS, 271, 1991, 185. Through Chem. Abstr. 117, 1992, 170994d.

[7] A. Palomer, J. J. Perez, S. Navea, O. Llorens, J. Pascual, M. L. Garcia, D. M. Mauleon, J. Med. Chem. 2000, 43, 2280.

[8] Zabiulla , H.G. Shamanth Neralagundi , A. Bushra Begum , B.T. Prabhakar , S. A. Khanum, Eur. J. Med. Chem., 115, 2016, 342-351

[9] S.A. Khanum, S. Shashikanth, S. Umesha, R. Kavitha, Eur. J. Med. Chem. 40, 2005, 1156-1162.

[10] A. Elbein, R. Molyneux, Chemical and Biological Perspectives; Pelletier, S. W., Ed., John Wiley & Son: New York, 1987.

[11] A. R. Pinder, Nat. Prod. Rep. 3, 1986, 171.

[12] A. R. Pinder, Nat. Prod. Rep. 9, 1992, 491.

[13] A. O. Plunkett, Nat. Prod. Rep. 11, 1994, 581.

[14] D. O'Hagan, Nat. Prod. Rep. 17, 2000, 435.

[15] A. J. Nadin, Chem. Soc., Perkin Trans. 1, 1998, 3493.

[16] P. M. Weintraub, J. S. Sabol, J. M. Kane, D. R. Borcherding, Tetrahedron 59, 2003, 2953.

[17] M. G. P. Buffat, Tetrahedron 60, 2004,1701.

[18] P. D. Bailey, P. A. Millwood, P. D. Smith, Chem. Commun. 1998, 633.

[19] X. Tiana, F. m. Zhang, W. g. Li, Life Sci. 70, 2002, 2433-2443

[20] G. Roman, Eur. J. Med. Chem. 89, 2015, 743-816.

[21] J. Jayabharathi, A. Thangamani, M. Padmavathy, B. Krishnakumar, Med. Chem. Res. 15, 2007, 431-442.

[22] D.G. Brown, P.R. Bernstein, Y. Wu, R.A. Urbanek, C.W. Becker, S.R. Throner, B.T. Dembofsky, G.B. Steelman, L.A. Lazor, C.W. Scott, M.W. Wood, S.S. Wesolowski, D.A. Nugiel, S. Koch, J. Yu, D.E. Pivonka, S. Li, C. Thompson, A. Zacco, C.S. Elmore, P. Schroeder, J. Liu, C.A. Hurley, S. Ward, H.J. Hunt, K. Williams, J. McLaughlin, V. Hoesch, S. Sydserff, D. Maier, D. Aharony, ACS Med. Chem. Lett. 4, 2013, 46-51.

[23] N. Karaman, E.E. Oruç-Emre, Y. Sicak, B. Çatikkas¸ , A. Karaküçük-_ Iyidogan, M. Oztürk, Med. Chem. Res. 25, 2016, 1590-1607.

[24] K.T. Chung, W.R. Thomasson, C.D. Wu-Yuan, J. Appl. Bacteriol. 69, 1990, 498-503.

[25] C. Azoro, World J. Biotechnol. 3, 2002, 347-357.

[26] D. Janovska, K. Kubikova, L. Kokoska, J. Food Sci. 21, 2003, 107-110.

[27] J. Bishnu, L. Sunil, S. Anuja, J. Sci. Eng. Technol. 5, 2009, 143-150.

[28] National Committee for Clinical Laboratory Standards Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, third ed., Approved

Standard, NCCLS Publication M7-A3, Villanova, PA, 1993.

[29] National Committee for Clinical Laboratory Standards, Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts, Proposed Standard, NCCLS Document M27-P, Villanova, PA, 1992.

TABLES

Table 1: Antibacterial activity of the compounds: 5a-j MIC in □g /mL

Compounds	Name of the microorganism MIC in □g /mL									
	Gram positive bacteria					Gram negative bacteria				
	B. cereus	S. aureus	E. aerogens	S. aureus (MRSA)	B. subtilis	E. coli	K. pneumonia	S. Paratyphi-B	S. typhimurium	P. aeruginosa
5a	18.75	9.73	18.75	18.75	18.75	9.73	18.75	9.73	9.73	150
5b	18.75	9.37	150	9.37	150	18.75	9.37	9.37	150	9.37
5c	150	18.75	9.37	300	18.75	9.37	300	18.75	150	300
5d	9.73	9.73	18.75	9.37	18.75	9.73	18.75	18.75	9.37	9.37
5e	150	300	18.75	300	150	300	150	18.75	150	300
5f	18.75	9.37	150	9.37	18.75	9.37	9.37	18.75	18.75	150
5g	300	18.75	300	150	150	18.75	300	18.75	300	300
5h	150	300	18.75	18.75	300	18.75	150	300	150	300
5i	9.37	18.75	150	18.75	9.37	18.75	18.75	150	18.75	9.37
5j	18.75	150	9.37	18.75	300	9.37	300	150	18.75	150
Streptomycin	1.16	2.33	4.67	2.33	2.33	2.33	4.67	4.67	4.67	2.32

Table 2: Antifungal activity of the compounds: 5a-j MIC in □g /mL

Compounds	Name of the microorganism MIC in □g /mL									
	Fungus									
	B. cinerea	C. Krusei	F. solani	C. albicans	A. niger	A. flavus	C. gloeosporioides	M. pachydermatis	C. parapsilosis	F. moniliforme
5a	9.37	18.75	9.37	150	9.37	18.75	18.75	18.75	9. 37	9.37
5b	18.75	9.37	150	9.37	9.37	18.75	9.37	9.37	18.75	150
5c	300	9. 37	150	18.75	150	18.75	9. 37	18.75	300	18.75
5d	9.37	18.75	18.75	9.37	9.37	9.37	9.37	18.75	9.37	9.37
5e	18.75	150	300	9. 37	18.75	18.75	18.75	18.75	300	18.75
5f	150	9. 37	18.75	18.75	9. 37	18.75	150	9. 37	18.75	18.75
5g	300	300	150	150	150	150	300	300	300	300
5h	18.75	18.75	18.75	300	150	150	18.75	9.73	300	18.75
5i	18.75	150	9. 37	150	300	150	150	9. 37	150	18.75
5j	18.75	9. 37	150	18.75	300	18.75	18.75	150	18.75	9. 37
Ketoconazole	4.67	2.33	2.33	4.67	2.33	1.16	2.33	4.67	4.67	2.33