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Antimicrobial and antimalarial evaluation of aminoalkyl substituted aryl benzyl ether derivative

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Abstract: A Some *N*-benzyl(or methyl)-*N*-methyl-3-*p*-substituted phenyl-3-((trifluoromethyl or nitro) substituted phenoxy)propan-1-amine derivatives have been synthesized by the reaction of (trifluoromethyl or nitro)substituted chlorobenzene with 3-*N*-benzyl(or methyl)-3-*N*-methyl-1-*p*-substituted phenyl propane-1-ol [obtained by the Mannich reaction of *para* substituted acetophenone with paraformaldehyde and *N,N*-dimethyl amine(or *N*-methyl-*N*-benzyl amine) in isopropanol followed by reduction with Sodium borohydride] in presence of potassium *tert*-butoxide and DMSO. All the synthesized compounds were characterized by elemental analysis, IR, ¹H NMR and MS. These were screened for in-vitro antimicrobial activity against two gram positive (*Streptococcus Pyogenes* and *Staphylococcus aureus*) and two gram negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*) as well as for antifungal and antimalarial activity against *plasmodium falciparum* strain.

Keywords: *p*-substituted acetophenone, paraformaldehyde, substituted chlorobenzene, Antimicrobial and antimalarial activity.

Introduction

Development of drug resistance in microorganisms is a tussle between science and nature. In recent decades, microbial diseases are more prevalent than they were during the first half of the last century and are still difficult to be diagnosed clinically. To combat them, various synthetic and semi-synthetic

antimicrobial drugs have been used in clinical practice [1,2]. In literature, a number of research paper are available describing the antimicrobial behaviour of aromatic and heterocyclic compound [3-5]. But, in the treatment of microbial infections only limited numbers of efficacious antimicrobial drugs are used even after availability of a number of antimicrobial agents. Many of the currently available drugs

are toxic, enable recurrence because they are bacteriostatic/fungistatic and not bactericidal/fungicidal or lead to the development of resistance due in part to the prolonged periods of administration. The impact is more acute in developing countries due to non-availability of desired medicines [6,7]. There is a real perceived need for the discovery of new compounds that are endowed with antibacterial and antifungal activities, possibly acting through mechanism of actions, which are distinct from those of well known classes of antimicrobial agents to which many clinically relevant pathogens are now resistant [8-10].

Aromatic ethers and their derivatives have been studied extensively over the past decade. Day by day aromatic ethers are frequently applied for the betterment of human welfare. The importance of aromatic ethers is due to its versatile nature. A large number of aryl ethers and their derivative find applicability in agriculture, engineering and biochemistry[11]. The linkage C-O-C in ether compounds has a significant role in the drug action[12]. For example diphenyl ethers and their halo derivatives have agrochemical uses such as herbicide and fungicides. Similarly, phenolic ethers find application in chemical engineering, as food colouring material, perfumes and additive of polymers[13].

Looking at the importance of these heterocyclic nuclei, it is thought of interest to devote some attention for the synthesis of aminoalkylsubstituted aryl benzyl ether derivatives and to evaluate these derivatives for antimicrobial and antimalarial activity against *plasmodium falciparum* strain.

2.1 Antimicrobial activity :

All the synthesized compounds were tested against two gram positive bacteria (*Staphylococcus aureus*, *Streptococcus Pyogenes*) and two gram negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*) using micro broth dilution method [14-17] for the determination of minimal inhibition

concentration. For the antifungal activity the common standard strains that were used, are *C.Albicans*, *A.Niger* and *A.Clavatus*. Muller Hinton broth (Microcare laboratory & Tuberculosis Research Centre, Surat-3, India) was used as nutrient medium to grow and dilute the drug suspension for the test bacteria. Inoculum Size for Test Strain was adjust to 10^8 Cfu [Colony Forming Unit] per milliliter by comparing the turbidity. DMSO was used as diluents / vehicle to get desired concentration of drugs to test upon Standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. In primary screening 1000 μ g/ml, 500 μ g/ml, and 250 μ g/ml concentrations of the synthesized compounds were taken. The active synthesized compounds found in this primary screening were further tested in a second set of dilution against all microorganisms. The highest dilution showing at least 99 % inhibition zone is taken as MIC. The test mixture should contain 10^8 organism/ml. Standard drugs Ampicillin and Chloramphenicol were used as antibacterial for comparison. Standard drugs Nystatin and Greseofulvin were used as antifungal for comparison.

2.2 Antimalarial activity :

The in vitro antimalarial assay was carried out in 96 well microtitre plates according to the microassay protocol reference. The cultures of *Plasmodium falciparum* strain were maintained in medium RPMI 1640 supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum. The asynchronous parasites of *Plasmodium falciparum* were synchronized after 5% D-sorbitol treatment to obtain only the ring stage parasitized cells. For carrying out the assay, an initial ring stage parasitaemia of 0.8 to 1.5% at 3% haematocrit in a total volume of 200 μ l of medium RPMI-1640 was determined by Jaswant Singh Bhattacharya (JSB) staining to assess the percentparasitaemia (rings) and uniformly maintained with 50% RBCs (O+). A stock solution of 5mg/ml of each of the test samples was prepared in DMSO and subsequent dilutions were prepared with

culture medium. The diluted samples in 20 μ l volume were added to the test wells so as to obtain final concentrations (at fivefold dilutions) ranging between 0.4 μ g/ml to 100 μ g/ml in duplicate well containing parasitized cell preparation. The culture plates were incubated at 37°C in a candle jar. After 36 to 40 h incubation, thin blood smears from each well were prepared and stained with JSB stain. The slides were microscopically observed to record maturation of ring stage parasites into trophozoites and schizonts in presence of different concentrations of the test agents. The test concentration which inhibited the complete maturation into schizonts was recorded as the minimum inhibitory concentrations (MIC). Quinine was taken as the reference drug.

3. MATERIALS AND METHODS

3.1 General Procedures:

Reagent grade chemicals were used without further purification. All the melting points were taken in open capillaries and are uncorrected. The purity and mass of the synthesized compounds was checked by MS. ¹H NMR spectral was recorded in CDCl₃/DMSO with tetramethylsilane (TMS) as the internal standard at 400 MHz on a Bruker DRTX-400 spectrophotometer. The chemical shifts are reported as parts per million (ppm). Elemental analysis was performed using a (EURO EA 3000 instrument). Acme silica gel-G and Merck silica gel (100 to 200, 60 to 120 meshes) were used for analytical TLC and Column chromatography respectively.

3.2 Chemistry:

We have prepared the novel N-benzyl(or methyl)-N-methyl-3-(p-substituted phenyl)-3-((trifluoromethyl or nitro)substituted phenoxy)-propane-1-amine in three steps, using p-substituted acetophenone, paraformaldehyde, N,N-dimethyl amine(or N-methyl-N-benzyl amine) and trifluoromethyl(or nitro)substituted chlorobenzene as the starting materials. Para substituted acetophenone on Mannich reaction

with paraformaldehyde and N,N-dimethyl amine(or N-methyl-N-benzyl amine) in isopropanol with few drops of hydrochloric acid results 3-N-benzyl(or methyl)-3-N-methyl-1-p-substituted phenyl propane-1-one which on reduction, using NaBH₄ results 3-N-benzyl(or methyl)-3-N-methyl-1-p-substituted phenyl propane-1-ol and further by coupling reaction with (trifluoromethyl or nitro)substituted chlorobenzene in presence of potassium tert-butoxide and DMSO results N-benzyl(or methyl)-N-methyl-3-p-substituted phenyl-3-((trifluoromethyl or nitro)substituted phenoxy)propan-1-amine derivatives. The clear procedure for the preparation of desired aminoalkyl substituted aryl benzyl ether derivatives are given below.

4. Preparation of desired N-benzyl(or methyl)-N-methyl-3-p-substituted phenyl-3-((trifluoromethyl or nitro) substituted phenoxy)propan-1-amine derivatives :

4.1 General procedure for the synthesis of 3-N-benzyl(or methyl)-3-N-methyl-1-p-substituted phenyl propane-1-one derivatives (Intermediate-A) :

A mixture of p-substituted acetophenone (0.01 mole), benzyl methyl amine(or dimethyl amine) (0.012 mmol) was dissolved in isopropanol (20 ml). To it was added Paraformaldehyde (0.02 mole) in small portions (one-fifth of the required mole). pH of the reaction mixture was maintained acidic by adding HCl (0.4-0.5 ml). The suspension was stirred and refluxed at 110-115°C and other 4 portions of Para formaldehyde were added in small portions, within a period of 1 hour. Finally the reaction mixture was refluxed for 3 hours at 110-115°C. Reaction was then concentrated under reduced pressure in a rotavapor and cooled. The solid separated was washed with hexane (5-7 times), filtered and dried, which results to give intermediates-A, 1(a-e).

Spectral data of intermediates-A: 3-(benzyl(methyl)amino)-1-p-tolylpropan-1-

one1(a):

IR(cm^{-1}): 1676 (C=O stretch), 1601 (C=C aromatic), 1325 & 1229 (C-N stretching). $^1\text{H-NMR}$ (400MHz, CDCl_3): δ 7.83 (d, $J=8.0$ Hz, 2H), 7.28-7.22 (m, 7H), 3.55 (s, 2H), 3.21-3.12 (m, 2H), 2.86 (t, $J=7.0$ Hz, 2H), 2.40 (s, 3H), 2.25 (s, 3H). MS (ESI+) m/z : 268 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{NO}$: C- 80.86%; H- 7.92%, N- 5.24%, O-5.98%, Found :C- 80.83%; H- 7.90%, N- 5.21%, O-5.96%.

3-(benzyl(methyl)amino)-1-(4-methoxyphenyl)propan-1-one1(b):

IR(cm^{-1}): 1671 (C=O stretch), 1604 (C=C aromatic), 1321 & 1266 (C-N-stretching). $^1\text{H-NMR}$ (400MHz, CDCl_3): 7.91 (d, $J=2.0$ Hz, 2H), 7.29-7.26 (m, 5H), 6.92 (d, $J=2.0$ Hz, 2H), 3.86 (s, 3H), 3.55 (s, 2H), 3.14 (t, $J=7.0$ Hz, 2H), 2.86 (t, $J=7.0$ Hz, 2H), 2.25 (s, 3H). MS (ESI+) m/z : 284 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_2$: C- 76.29%; H- 7.47%, N- 4.94%, O-11.29%, Found :C- 76.24%; H- 7.43%, N- 4.93%, O-11.28%.

3-(benzyl(methyl)amino)-1-(4-bromophenyl)propan-1-one 1(c):

IR(cm^{-1}): 1679 (C=O stretch), 1586 (C=C aromatic), 1323 (C-N-stretching), 1071 (C-Br stretching). $^1\text{H-NMR}$ (400MHz, CDCl_3): 7.77 (d, $J=8.0$ Hz, 2H), 7.58 (d, $J=5.0$ Hz, 2H), 7.30-7.26 (m, 5H), 3.54 (s, 2H), 3.13 (t, $J=7.6$ Hz, 2H), 2.85 (t, $J=7.6$ Hz, 2H), 2.25 (s, 3H). MS (ESI+) m/z : 332.2 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{BrNO}$: C- 61.46%; H- 5.46%, Br-24.05%, N- 4.92%, O-4.82%, Found :C- 61.43%; H- 5.42%, Br- 24.01%, N- 4.90%, O-4.79%.

3-(benzyl(methyl)amino)-1-(4-chlorophenyl)propan-1-one 1(d):

IR(cm^{-1}): 1680 (C=O stretch), 1590 (C=C aromatic), 1325 (C-N-stretching), 1095 (C-Cl stretching). $^1\text{H-NMR}$ (400MHz, CDCl_3): 7.85 (d, $J=2.0$ Hz, 2H), 7.41 (d, $J=1.7$ Hz, 2H), 7.30-7.22 (m, 5H), 3.54 (s, 2H), 3.13 (t, $J=7.6$ Hz, 2H), 2.85 (t, $J=7.6$ Hz, 2H), 2.25 (s, 3H). MS (ESI+) m/z : 288 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{ClNO}$: C- 70.95%; H- 6.30%, Cl-12.32%, N- 4.87%, O-5.56%, Found :C- 70.93%; H- 6.28%, Cl- 12.29%, N- 4.85%, O-5.52%.

1-(4-bromophenyl)-3-(dimethylamino)propan-1-one 1(e):

IR(cm^{-1}): 1683 (C=O stretch), 1587 (C=C aromatic), 1334 (C-N-stretching), 1083 (C-Br stretching). $^1\text{H-NMR}$ (400MHz, CDCl_3): 7.79 (d, $J=8.0$ Hz, 2H), 7.58 (d, $J=6.8$ Hz, 2H), 3.13 (t, $J=7.6$ Hz, 2H), 2.85 (t, $J=7.6$ Hz, 2H), 2.28 (s, 6H). MS (ESI+) m/z : 256.1 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{BrNO}$: C- 51.58%; H- 5.51%, Br-31.20%, N- 5.47%, O-6.25%, Found :C- 51.56%; H- 5.49%, Br-31.17%, N- 5.43%, O-6.23%.

4.2 General procedure for the synthesis of 3-N-benzyl(or methyl)-3-N-methyl-1-p-substituted phenyl propane-1-ol (Intermediate-B) :

To a solution of compound (Intermediate-A) (0.01 mole)) in methanol (50 ml), sodium borohydride (0.015 mole) was added in small portions at 0 $^{\circ}\text{C}$ within a period of 1hr. The reaction mixture was stirred at low temperature for 1hr. and at room temp for 4hr. Reaction mixture was then quenched with sat.soln. of NH_4Cl and extracted with Ethyl acetate. The organic layer was washed with water and dried over Na_2SO_4 . The organic layer was evaporated and purified by column chromatography by using 100-200 silica gelat 2% methanol in chloroform which results to give intermediate-B, 2(a-e).

Spectral data of intermediate-B:**3-(benzyl(methyl)amino)-1-p-tolylpropan-1-ol 2(a):**

IR(cm^{-1}): 3397 (O-H stretch), 1597 (C=C aromatic), 1354 (C-N-stretching), 1039 (C-O stretching). $^1\text{H-NMR}$ (400MHz, CDCl_3): 7.31-7.07(m, 9H), 4.85 (t, $J=7.2$ Hz, 1H), 3.67-3.42 (m, 2H), 2.80-2.53 (m, 2H), 2.33 (s, 3H), 2.25 (s, 3H), 1.85-1.83 (m, 2H). MS (ESI+) m/z : 270 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}$: C- 80.26%; H- 8.61%, N- 5.20%, O-5.94%, Found :C- 80.23%; H- 8.59%, N- 5.18%, O-5.92%.

3-(benzyl(methyl)amino)-1-(4-methoxyphenyl)propan-1-ol 2(b):

IR(cm^{-1}): 3467 (O-H stretch), 1614 (C=C aromatic), 1246 & 1175 (C-N-stretching), 1035

(C-O stretching). $^1\text{H-NMR}$ (400MHz, CDCl_3): 7.32-7.20 (m, 7H), 6.80 (d, $J=2.0$ Hz, 2H), 4.83-4.77 (m, 1H), 3.77 (s, 3H), 3.66-3.40 (m, 2H), 2.58 (m, 2H), 2.25 (s, 3H), 1.87-1.84(m, 2H). MS (ESI+)m/z: 286 (M^++1). Anal.Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_2$: C- 75.76%; H- 8.12%, N- 4.91%, O-11.21%, Found :C- 75.74%; H- 8.11%, N- 4.89%, O-11.19%.

3-(benzyl(methyl)amino)-1-(4-bromophenyl)propan-1-ol 2(c):

IR(cm^{-1}): 3410 (O-H stretch), 1593 (C=C aromatic), 1217 & 1130 (C-N-stretching), 1074 (C-O stretching). $^1\text{H-NMR}$ (400MHz, CDCl_3): 7.44 (d, $J=7.25$ Hz, 2H), 7.42-7.28 (m, 5H), 7.22 (d, $J=7.2$ Hz, 2H), 4.85 (t, $J=7.2$ Hz, 1H), 3.67-3.47 (m, 2H), 2.86-2.77 (m, 1H), 2.63-2.56 (m, 1H), 2.30 (s, 3H), 1.87-1.82(m, 2H). MS (ESI+) m/z: 334.2 (M^++1). Anal.Calcd for $\text{C}_{17}\text{H}_{20}\text{BrNO}$: C- 61.09%; H- 6.03%, Br-23.91%, N- 4.19%, O-4.79%, Found :C- 61.07%; H- 6.01%, Br- 23.89%, N- 4.16%, O-4.76%.

3-(benzyl(methyl)amino)-1-(4-chlorophenyl)propan-1-ol 2(d):

IR(cm^{-1}): 3370 (O-H stretch), 1596 (C=C aromatic), 1197 & 1130 (C-N-stretching), 1083 (C-O stretching). $^1\text{H-NMR}$ (400MHz, CDCl_3): 7.33-7.25 (m, 9H), 4.87 (t, $J=7.2$ Hz, 1H), 3.67-3.43(m, 2H), 2.81-2.74 (m, 1H), 2.62-2.54 (m, 1H), 2.26 (s, 3H), 1.85-1.81 (m, 2H). MS (ESI+) m/z: 290 (M^++1). Anal.Calcd for $\text{C}_{17}\text{H}_{20}\text{ClNO}$: C- 70.46%; H- 6.96%, Br-12.23%, N- 4.83%, O-5.52%, Found :C- 70.44%; H- 6.94%, Br- 12.21%, N- 4.82%, O-5.50%.

1-(4-bromophenyl)-3-(dimethylamino)propan-1-ol 2(e):

IR(cm^{-1}): 3460 (O-H stretch), 1589 (C=C aromatic), 1241 & 1173 (C-N-stretching), 1071 (C-O stretching). $^1\text{H-NMR}$ (400MHz, CDCl_3): 7.35 (d, $J=7.25$ Hz, 2H), 4.89 (t, $J=7.2$ Hz, 1H), 3.85-3.57(m, 2H), 2.26 (s, 3H), 2.20 (s, 3H), 1.87-1.82(m, 2H). MS (ESI+) m/z: 258.1 (M^++1). Anal.Calcd for $\text{C}_{11}\text{H}_{16}\text{BrNO}$: C- 51.18%; H- 6.25%, Br-30.95%, N- 5.43%, O-6.20%, Found :C- 51.16%; H- 6.23%, Br- 30.91%, N- 5.41%, O-6.19%.

4.3 General procedure for the synthesis of desired N-benzyl(or methyl)-N-methyl-3-p-substituted phenyl-3-((trifluoromethyl or nitro) substituted phenoxy)propan-1-amine derivatives:

To a solution of compound (intermediate-B) (0.01 mole) in DMSO (10 mL) was added potassium tert-butoxide(0.03 mole) followed by trifluoromethyl (or nitro) substitutedchlorobenzene and the reaction mixture was heated at 90-95 $^{\circ}\text{C}$ for 3hrs. After completion, the reaction mixture was quenched with water. The compound was extracted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 , evaporated and purified by column chromatography by using 100-200 silica gelat 40% ethyl acetate in hexane which results to give desired compound 3(a-l) Scheme-1.

Spectral data of desired aminoalkyl substituted aryl benzyl ether derivatives:

N-benzyl-N-methyl-3-p-tolyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine (3a) :

IR(cm^{-1}): 1610 (C=C aromatic), 1387 (C-N-stretching), 1350 & 1253 (CF_3 stretching), 1116 (C-O stretching); $^1\text{H-NMR}$ (400MHz, CDCl_3): 7.41 (d, $J=8.0$ Hz, 2H), 7.35-7.09 (m, 9H), 6.83 (d, $J=8.0$ Hz, 2H), 5.27 (t, $J=7.2$ Hz, 1H), 3.56-3.40 (m, 2H), 2.61-2.44 (m, 2H), 2.31 (s, 3H), 2.21 (s, 3H), 2.17-2.14 (m, 1H), 2.02-1.93 (m, 1H), MS (ESI+)m/z: 414 (M^++1). Anal.Calcd for $\text{C}_{25}\text{H}_{26}\text{F}_3\text{NO}$: C- 72.62%; H- 6.34%, F- 13.78%, N-3.39%, O-3.87%, Found :C- 72.60%; H- 6.31%, F- 13.75%, N-3.37%, O-3.86%.

N-benzyl-N-methyl-3-p-tolyl-3-(3-(trifluoromethyl)phenoxy)propan-1-amine(3b) :

IR(cm^{-1}): 1613 (C=C aromatic), 1379 (C-N-stretching), 1355 & 1256 (CF_3 stretching), 1119 (C-O stretching); $^1\text{H-NMR}$ (400MHz, CDCl_3): δ 7.40 (s, 1H), 7.39 (d, $J=8.0$ Hz, 2H), 7.36-7.08 (m, 8H), 6.87(d, $J=8.0$ Hz, 2H), 5.26 (t, $J=7.2$ Hz, 1H), 3.58-3.41 (m, 2H), 2.63-2.42 (m, 2H), 2.32 (s, 3H), 2.22 (s, 3H), 2.17-2.15 (m, 1H), 2.00-1.92 (m, 1H); MS (ESI+)m/z: 414 (M^++1).

Anal.Calcd for $C_{25}H_{26}F_3NO$: C- 72.62%; H- 6.34%, F- 13.78%, N-3.39%, O-3.87%, Found :C- 72.61%; H- 6.32%, F- 13.76%, N-3.35%, O-3.85%.

N-benzyl-3-(4-methoxyphenyl)-N-methyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine (3c):

IR(cm^{-1}):1643 (C=C aromatic), 1327 & 1250 (CF₃ stretching),1223 &1140 (C-N-stretching), 1115 (C-O stretching); ¹H-NMR (400MHz, CDCl₃): 7.43 (d, J=6.0 Hz, 2H), 7.31-7.11 (m, 7H), 6.93-6.81 (m, 4H), 5.32-5.28 (m, 1H), 3.82 (s, 3H), 3.56-3.44 (m, 2H), 2.65-2.57 (m, 1H), 2.46-2.38 (m, 1H), 2.25 (s, 3H), 2.21-2.14 (m, 1H), 2.02-1.91 (m, 1H);MS (ESI+) m/z: 429 (M⁺+1). Anal.Calcd for $C_{25}H_{26}F_3NO_2$: C-69.92%, H- 6.10%, F-13.27%, N-3.26%, O-7.45%, Found :C- 69.90%, H- 6.08%, F-13.26%, N-3.25%, O-7.43%.

N-benzyl-3- (4-methoxyphenyl)-N-methyl-3-(4-nitrophenoxy) propane-1-amine(3d) :

IR(cm^{-1}):1668 (C=C aromatic), 1512 (NO₂ asymmetric stretch), 1340 (NO₂ symmetric stretch), 1240 (C-N-stretching), 1111 (C-O stretching); ¹H-NMR (400MHz, CDCl₃): 8.06 (d, J=6.0 Hz, 2H), 7.24-7.13 (m, 7H), 6.83-6.77 (m, 4H), 5.32-5.30 (m, 1H), 3.76 (s, 3H), 3.48-3.40 (m, 2H), 2.54 (m, 1H), 2.39 (m, 1H), 2.22 (s, 3H), 2.19-2.17 (m, 1H), 2.00-1.91 (m, 1H);MS (ESI+)m/z: 407 (M⁺+1). Anal.Calcd for $C_{24}H_{26}N_2O_4$: C-70.92%, H-6.45%, N- 6.89%, O-15.74%, Found C- 70.89%, H-6.43%, N- 6.87%, O-15.73%.

N-benzyl-3- (4-methoxyphenyl)-N-methyl-3-(3-trifluoro methyl) phenoxy) propane-1-amine(3e) :

IR(cm^{-1}):1666 (C=C aromatic), 1329 & 1253 (CF₃ stretching),1249 &1185 (C-N-stretching), 1113 (C-O stretching) ;¹H-NMR (400MHz, CDCl₃): 7.48 (s, 1H) 7.46 (d, J=6.0 Hz, 2H), 7.32-7.12 (m, 6H), 6.92-6.80 (m, 4H), 5.34-5.30 (m, 1H), 3.80 (s, 3H), 3.56-3.45 (m, 2H), 2.66-2.56 (m, 1H), 2.44-2.36 (m, 1H), 2.24 (s, 3H), 2.22-2.16 (m, 1H), 2.04-1.92 (m, 1H);MS (ESI+)m/z: 429.9 (M⁺+1). Anal.Calcd for $C_{25}H_{26}F_3NO_2$: C- 69.92%, H- 6.10%,F-

13.27%, N-3.26%,O-7.45%, Found : C- 69.90%, H- 6.08%,F- 13.24%, N-3.25%,O-7.43%.

N-benzyl-3-(4-methoxyphenyl)-N-methyl-3-(2-(trifluoromethyl)phenoxy)propan-1-amine(3f) :

IR(cm^{-1}):1698 (C=C aromatic), 1328 & 1251 (CF₃ stretching),1245 &1180 (C-N-stretching), 1114 (C-O stretching);¹H-NMR (400MHz, CDCl₃): 7.44 (d, J=8.0 Hz, 2H), 7.42 (d, J = 6.0 Hz, 2H), 7.31-7.11 (m, 5H), 6.93-6.81 (m, 4H), 5.32-5.28 (m, 1H), 3.82 (s, 3H), 3.56-3.44 (m, 2H), 2.65-2.57 (m, 1H), 2.48-2.36(m, 1H), 2.25 (s, 3H), 2.21-2.14 (m, 1H), 2.02-1.91 (m, 1H);MS (ESI+)m/z: 429.8 (M⁺+1). Anal.Calcd for $C_{25}H_{26}F_3NO_2$:C- 69.92%, H- 6.10%,F- 13.27%, N-3.26%,O-7.45%, Found : C- 69.89%, H- 6.07%,F- 13.25%, N-3.24%,O-7.44%.

N-benzyl-3-(4-bromophenyl)-N-methyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine(3g) :

IR(cm^{-1}):1610 (C=C aromatic), 1327 & 1253 (CF₃ stretch), 1224&1140 (C-N-stretching), 1117 (C-O stretching), 1069 (C-Br stretching) ;¹H-NMR (400MHz, CDCl₃): 7.43-7.38 (m, 4H), 7.26-7.10 (m, 5H), 6.79 (m, 4H), 5.31-5.24 (m, 1H), 3.45-3.42 (m, 2H), 2.59-2.52 (m, 1H), 2.38-2.32 (m, 1H), 2.22 (s, 3H), 2.18-2.08 (m, 1H), 1.95-1.88 (m, 1H), MS (ESI+)m/z: 478 (M⁺+1). Anal.Calcd for $C_{24}H_{23}BrF_3NO$: C- 60.26%, H- 4.85%, Br-16.7, F- 11.92%, N-2.93, O-3.34%, Found : C- 60.23%, H- 4.83%, Br- 16.5, F- 11.90%, N-2.91, O-3.32%.

N-benzyl-3- (4-bromophenyl)-N-methyl-3-(3-trifluoromethyl) phenoxy) propane-1-amine (3h) :

IR(cm^{-1}):1615 (C=C aromatic), 1326 & 1251 (CF₃ stretch), 1235&1168 (C-N-stretching), 1115 (C-O stretching), 1067 (C-Br stretching);¹H-NMR (400MHz, CDCl₃): 7.49 (s, 1H), 7.42-7.37 (m, 4H), 7.28-7.12 (m, 4H), 6.77 (m, 4H), 5.30-5.22 (m, 1H), 3.45-3.42 (m, 2H), 2.58-2.50 (m, 1H), 2.39-2.33 (m, 1H), 2.23 (s, 3H), 2.20-2.10 (m, 1H), 1.93-1.87 (m, 1H);MS (ESI+)m/z: 478 (M⁺+1). Anal.Calcd for $C_{24}H_{23}BrF_3NO$: C- 60.26%, H- 4.85%, Br- 16.7, F- 11.92%, N-2.93, O-3.34%, Found : C-

60.24%, H- 4.84%, Br-16.4, F- 11.91%, N-2.89, O-3.31%.

N-benzyl-3- (4-chlorophenyl)-N-methyl-3-(4-trifluoromethyl) phenoxy) propane-1-amine(3i) :

IR(cm^{-1}):1624 (C=C aromatic), 1251 (CF_3 stretch), 1201&1144 (C-N-stretching), 1117 (C-O stretching), 1018 (C-Clstretch); $^1\text{H-NMR}$ (400MHz, CDCl_3): 7.24-7.22 (m, 9H), 6.85 (d, $J=6.0$ Hz, 2H), 6.32-5.31 (m, 2H), 5.35-5.31 (m, 1H), 3.55-3.44 (m, 2H), 2.60-2.43 (m, 2H), 2.24 (s, 3H), 2.01-1.99(m, 2H),MS (ESI+) m/z:434 (M^++1). Anal.Calcd for $\text{C}_{24}\text{H}_{23}\text{ClF}_3\text{NO}$: C- 66.43%, H- 5.34%, Cl-8.17, F- 13.14%, N-3.23%, O-3.69, Found : C- 66.41%, H- 5.32%, Cl-8.15, F- 13.12%, N-3.22%, O-3.65.

N-benzyl-3- (4-chlorophenyl)-N-methyl-3-(4-nitrophenoxy) propane-1 amine (3j) :

IR(cm^{-1}):1635 (C=C aromatic), 1510 (NO_2 asymmetric stretch), 1345 (NO_2 symmetric stretch), 1196 &1128 (C-N-stretching), 1110 (C-O stretching); $^1\text{H-NMR}$ (400MHz, CDCl_3): 8.30 (d, $J=7.2$ Hz, 2H), 8.10 (d, $J=7.2$ Hz, 2H), 7.31-7.14 (m, 5H), 6.83 (d, $J=7.0$ Hz, 2H), 6.83(d, $J=7.0$ Hz, 2H), 5.39-5.33 (m, 1H), 3.50-3.48 (m, 2H), 2.57-2.39(m, 2H), 2.25 (s, 3H), 2.01-1.98 (m, 2H),MS (ESI+)m/z: 411 (M^++1). Anal.Calcd for $\text{C}_{24}\text{H}_{23}\text{ClN}_2\text{O}_3$:C- 67.23%, H- 5.64%, Cl-8.63, N-6.82%, O-11.68%, Found : C- 67.23%, H- 5.64%, Cl-8.63, N-6.82%, O-11.68%.

3-(4-bromophenyl)-N, N-dimethyl-3-(4-(trifluoromethyl) phenoxy) propan-1-amine 3(k):

IR(cm^{-1}): 1604 (C=C aromatic), 1327 & 1253 (CF_3 stretching), 1246 &1199 (C-N-stretching), 1117 (C-O stretching), 1069 (C-Br stretching). $^1\text{H-NMR}$ (400MHz, CDCl_3): δ 8.30 (d, $J=7.4$ Hz, 2H), 8.10 (d, $J=7.4$ Hz, 2H), 7.31-7.14 (m, 2H), 6.83 (d, $J=7.2$ Hz, 2H), 5.39-5.33 (m, 1H), 3.50-3.48 (m, 2H), 2.25 (s, 6H), 2.15-1.99 (m, 2H).MS (ESI+)m/z: 402.5 (M^++1). Anal.Calcd for $\text{C}_{18}\text{H}_{19}\text{BrF}_3\text{NO}$: C- 53.75%; H- 4.76%, Br-19.86%, F-14.17, N- 3.48%, O-3.98%, Found :C- 53.74%; H- 4.74%, Br-19.84%, F-14.15%, N- 3.46%, O-3.97%.

3-(4-bromophenyl)-N, N-dimethyl-3-(3-(trifluoromethyl) phenoxy) propan-1-amine 3(l):

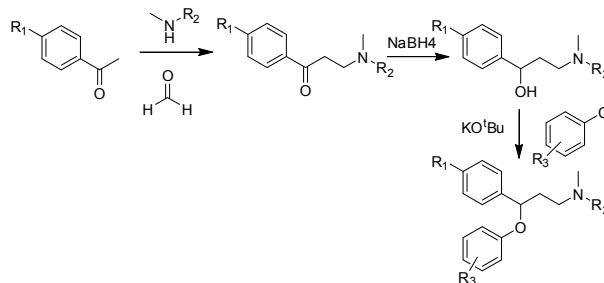
IR(cm^{-1}): 1615 (C=C aromatic), 1329 & 1255 (CF_3 stretching), 1251 &1187 (C-N-stretching), 1119 (C-O stretching), 1071 (C-Br stretching). $^1\text{H-NMR}$ (400MHz, CDCl_3): δ 8.31 (s, 1H), 8.09 (d, $J=7.0$ Hz, 2H), 7.31-7.15 (m, 3H), 6.87(d, $J=7.2$ Hz, 2H), 5.35-5.30 (m, 1H), 3.30-3.25 (m, 2H), 2.27 (s, 6H), 2.14-1.98 (m, 2H).MS (ESI+)m/z:402.3 (M^++1). Anal.Calcd for $\text{C}_{18}\text{H}_{19}\text{BrF}_3\text{NO}$: C- 53.75%; H- 4.76%, Br-19.86%, F-14.17, N- 3.48%, O-3.98%, Found :C- 53.72%; H- 4.75%, Br-19.83%, F-14.14%, N- 3.45%, O-3.96%.

5. Result and discussion

5.1.Chemistry

Para substituted acetophenone on Mannich reaction with paraformaldehyde and N,N-dimethyl amine(or N-methyl-N-benzyl amine) in isopropanol with few drops of hydrochloric acid results 3-N-benzyl(or methyl)-3-N-methyl-1-p-substituted phenyl propane-1-one which onreduction, using NaBH_4 results 3-N-benzyl(or methyl)-3-N-methyl-1-p-substituted phenyl propane-1-oland further by coupling reaction with (trifluoromethyl or nitro)substituted chlorobenzenein presence of potassium tert-butoxide and DMSO results N-benzyl(or methyl)-N-methyl-3-p-substituted phenyl-3-((trifluoromethyl or nitro)substituted phenoxy)propan-1-amine derivatives.. The lists of synthesized compounds are represented by Table-1.

Scheme-



List of synthesized compound Table-1

Compound	R1	R2	R3	M.P(°C)	Yield(%)
3a	4-CH ₃	Benzyl	4-CF ₃	170-172	67
3b	4-CH ₃	Benzyl	3-CF ₃	178-180	87
3c	4-OCH ₃	Benzyl	4-CF ₃	167-169	74
3d	4-OCH ₃	Benzyl	4-NO ₂	198-200	86
3e	4-OCH ₃	Benzyl	3-CF ₃	165-167	56
3f	4-OCH ₃	Benzyl	2-CF ₃	159-161	73
3g	4-Br	Benzyl	4-CF ₃	172-174	84
3h	4-Br	Benzyl	3-CF ₃	187-189	55
3i	4-Cl	Benzyl	4-CF ₃	162-164	69
3j	4-Cl	Benzyl	4-NO ₂	203-205	49
3k	4-Br	Methyl	4-CF ₃	148-150	58
3l	4-Br	Methyl	3-CF ₃	156-158	63

5.2 Antibacterial activity:

The antibacterial activity of all the synthesized compounds were tested in-vitro against pathogenic *E. coli*, *P.aeruginosa*, *S. aureus* and *S.pyogenus* and the results were compared with standard drugs (Ampicillin and Chloramphenicol). In case of *S.aureus* compounds 3b, 3d, 3g, 3h and 3i exhibit higher activity while compound 3a, 3e and 3f show good activity and rest of the compounds possess less activity. In case of *S.pyogenus* compounds 3a, 3b and 3e exhibit good activity while rest of the compound possess less activity. In case of *E. coli* Compounds 3d and 3g exhibit good activity while rest of the compounds possess less activity. In case of *P.aeruginosa* compound 3d and 3g exhibit higher activity and compound 3f show good activity while rest of the compounds possess less activity. The results are given in Table-2.

5.3 Antifungal activity:

The antifungal activity of all the synthesized compounds were tested in-vitro against fungi *C.Albicans*, *A.Niger* and *A.Clavatus* and the results were compared with standard drugs

(Nystatin and Greseofulvin). In case of *C.Albicans* compound 3d and 3j exhibit higher activity while 3g, 3h, 3k and 3l show good activity and rest of the compounds possess less activity. In case of *A.Niger* and *A.Clavatus* all the compounds possess less activity. The results are given in Table-3.

Table-2: Antibacterial activity (Minimum inhibitory concentration in µg/ml)

Compound	E.COLI	P.AERUG-INOSA	S. AUREUS	S. PYOGENUS
3(a)	250	500	250	100
3(b)	200	250	100	100
3(c)	125	200	125	125
3(d)	100	62.5	100	200
3(e)	250	250	250	100
3(f)	250	100	250	250
3(g)	100	62.5	100	250
3(h)	500	250	200	200
3(i)	500	200	200	250
3(j)	250	200	500	250
3(k)	200	125	500	125
3(l)	250	125	500	250
Ampicillin	100	100	250	100
Chloramphenicol	50	50	50	50

Table-3: Antifungal Activity(In MIC)

Compound	C.Albicans	A.Niger	A.Clavatus
3(a)	1000	500	1000
3(b)	>1000	>1000	>1000
3(c)	>1000	>1000	>1000
3(d)	250	>1000	>1000
3(e)	>1000	>1000	>1000
3(f)	>1000	500	500
3(g)	500	>1000	>1000
3(h)	500	>1000	>1000
3(i)	1000	500	500
3(j)	250	>1000	>1000
3(k)	500	500	1000
3(l)	500	500	500
Nystatin	100	100	100
Greseofulvin	500	100	100

Table-4: Antimalarial Activity

Compound	Mean IC ₅₀ (µg/ml)
3(a)	0.96
3(b)	0.85
3(c)	1.43
3(d)	0.68
3(e)	1.07
3(f)	1.38
3(g)	0.53
3(h)	2.22
3(i)	1.09
3(j)	1.43
3(k)	1.24
3(l)	1.10
Quinine	0.268

5.4 Antimalarial activity:

For antimalarial activity, Compounds 3d and 3g exhibit good activity closer to reference compound Quinine against plasmodium falciparum strain while rest of the compounds possess less activity. The results are given in Table-4.

6. Conclusion :

All the newly synthesized compounds were screened for antibacterial, antifungal and antimalarial activity. The data in the Table-2 indicate that among the synthesized compounds, compounds 3d and 3g exhibit excellent and compounds 3a, 3b, 3e and 3f possess good antibacterial activity. However, the activities of the tested compounds are much less than those of standard agents used. Compounds 3d and 3g also show potent antimalarial activity. From the results of various biological activities it is clear that these compounds would be of better use in drug development to combat bacterial infections and as antimalarial agents in the future.

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References :

- Ozgun Cuvas Apan, Teoman Zafer Apan, Alparslan Apan, Journal of Clinical Anesthesia, **2016**, 34, 407-411.
- Nicola D. Thompson, Lisa LaPlace, Lauren Epstein, Deborah Thompson et al., Journal of the American Medical Directors Association, **2016**, 17(12), 1151-1153.
- Ashish Bhatt, Rajesh Kumar Singh, Ravi Kant, Chem. Biol. Lett., **2016**, 3(2), 38-43.
- Bhatt A, Kant R, Singh RK, Med chem (Los Angeles), **2016**, 6, 257-263.
- Ashish Bhatt, Rajesh Kumar Singh, Ravi Kant, Pramod Kumar Chauhan, Chemistry & Biology Interface, **2016**, 6(5), 357-365.
- Tomar V., Bhattacharjee G., Kamaluddin, Kumar A. Bioorg. Med. Chem. Lett. **2007**, 17, 5321-5324.
- Sharma D., Narasimhan B., Kumar P., Judge V., Narang R., De Clercq E., Balzani J. Eur. J. Med. Chem. **2009**, 44 (6), 2347-2353.
- Sharma D., Narasimhan B., Kumar P., Jalbout A. Eur. J. Med. Chem. **2009**, 44, 1119-1127.
- Tuncbilek M., Kiper T., Altanlar N. Eur. J. Med. Chem. **2009**, 44, 1024-1033.
- Sharma S., Gangal S., Rauf A. Eur. J. Med. Chem. **2009**; 44: 1751-1757.
- Haser, A., Stumer, C., Organic synthesis based on Named Reactions and Unnamed reactions. Pergamon: Kidlington, **1994**, 419.
- Alvarez-Builla, J., Vaquer, J.J., Garcia-Navio, J.L., Cabello et al. Tetrahedron, **1990**, 46, 967.
- Fendler, J.H., Fendler, J.H., Catalysts in micellar and macromolecular system (Academic press, New York), **1975**, 538.
- Clinical microbiology procedure handbook, vol II, chapter 5 page no. 5.0.1 Henry d. Isenberg, 2nd edition.
- N.C Desai, P.N. Shihora, D.L. Moradia, Indian J. Chem., **2007**, 46B, 550-553.
- S. Shadomy. In Manual of Clinical Microbiology; Albert, B., Ed.; ASM Press: Washington, DC, **1991**; p 1173.
- A. Rattan. Antimicrobials in Laboratory Medicine; B. Churchill Livingstone: India, **2000**; p 85.