International Journal for Pharmaceutical Research Scholars (IJPRS)

V-3, I-1, 2014 ISSN No: 2277 - 7873

RESEARCH ARTICLE

Synthesis and Biological Evaluation of Novel 4-[4-(1*H*-Benzimidazol-2ylmethoxy) phenyl]-6-(Substituted Phenyl) Pyrimidin-2-Amine as a Potent Antimicrobial Agents

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Manuscript No: IJPRS/V3/I1/00078, Received On: 13/02/2014, Accepted On: 21/02/2014

ABSTRACT

A series of potential bioactive compounds, 4-[4-(1*H*-benzimidazol-2ylmethoxy) phenyl]-6-(substituted phenyl) pyrimidin-2-amine has been synthesized and screened for antibacterial and antifungal activity. Among the series, compound G4g, G4k, G4n, G4d, G4h, G4f, G4l, G4m and G4e, G4g, G4k, G4l were found significant active against *E.coli* and *K.pneumoniae* while compounds G4d, G4o, G4e, G4l and G4i, G4j were found significant active against *A.niger* and *S.cerevisiae* as compared to standard. The new compounds were characterized by their IR, ^{1}HNMR, and GC mass spectroscopy.

KEYWORDS

Pyrimidine; MIC; Antibacterial; Antifungal

INTRODUCTION

The rise in antibiotic resistant microorganisms in recent years has led to an increasing search for new antibiotics[20]. Microorganisms resistant to multiple anti-infective agents have increased worldwide[21]. Therefore, there is a prime need to discover new antimicrobial agents to avert the emergence of resistance and ideally shorten the duration of therapy. As pathogenic microbes continuously evolve resistance to currently used antimicrobial agents, so the discovery of novel and potent antimicrobial agents is the best way to overcome microbial resistance and develop effective therapeutics. Azoles Fig.1 known structurally similar antimicrobial agents are currently in use as a therapeutic agents.

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Benzimidazole derivatives reported with diverse structural features and versatile biological properties such as antimicrobial[7], antifungal[7], anti-viral[9], anthelmintic[19], antiprotozoal[6] and antipsychotic activity[19]. The literature survey revealed that compounds with thiazolidinone ring have been reported to demonstrate a wide range of pharmacological activities like anti tubercular[3,7], antidiabetic[19], anticonvulsant[18], inhibitors of lymphocyte specific kinase[11], fungicidal, insecticidal[19], analgesic[16], antibacterial[2], diuretic[17], antihypertensive[5], anticancer[8].

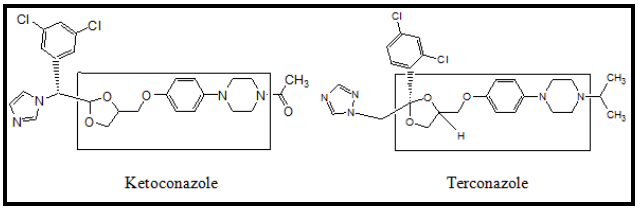


Figure 1: Structure of Ketaconazole and Terconazole

There are also some known drugs containing benzimidazole moiety, e.g. Pentaprozole, Rabeprazole, Lansoprazole, Omeprazole, Pimozide, Benperidol, Thiebendazole, Mebendazole, Albendazole, Metronidazole, Miconazole and Ketokonazole. Which are extensively used for various disease and disorders? In the present investigation we reported 4-[4-(1*H*-benzimidazol-2ylmethoxy) phenyl]-6-(substituted phenyl) pyrimidin-2-amine derivatives **(G4a-G4o)** and screened them for antibacterial and antifungal activity.

METHOD

Experimental

All reagents and solvents used in the present study are of analytical grade and procured from Loba chemie. The progress of the reactions is monitored by TLC using Merck silica gel precoated plate, with appropriate mobile phase, visualization by iodine vapour and UV chamber and product are purified by recrystallization technique. All the melting points were recorded on a Veego apparatus and were uncorrected.

All the synthesized compounds were characterized by their IR, ^{1}H-NMR, GC Mass spectroscopy. Infra-red (IR) spectra were recorded in KBr on BRUKER FT-IR instrument,^{1}H-NMR spectra were recorded on BRUKER AVANCE ^{1}H-NMR Spectrometer at 400 MHz in DMSO-d6, by using Varian instrument using TMS as internal standard and chemical shift values are given in ppm downfield to TMS (tetramethylsilane) and GC Mass were recorded on GCMS-QP-5050 schimadzu.

Synthesis of 2-(4-acetylphenoxy) Acetic Acid (Comp-1)

To a mixture of 4-hydroxy acetophenone (5.44 g,0.04 mol), mono chloro acetic acid (0.04 mol, 20% excess) and 30 ml of water contained in a 250 ml round bottomed flask, slowly added a solution of sodium hydroxide (0.08 mol) in 87.5 ml of water. The reaction mixture was refluxed for 4 h on oil bath at 120^{o}C. The reaction mixture was then cooled and acidified with conc. HCl. The solid crystals were filtered off, washed with water, dried and recrystalized from water and ethyl acetate (1:1) to yield title comp-1.

Scheme of synthesis of 2-(4-acetylphenoxy) acetic acid (Comp-1) is described in Fig.2. Melting Point-168-172^{0}C, % yield-73%, TLC mobile phase- Benzene: Methanol (4.5:0.5)[1].

Synthesis of 1-[4-(1H-Benzimidazole-2yl methoxy) phenyl] acetyl) ethanone (Comp-2)

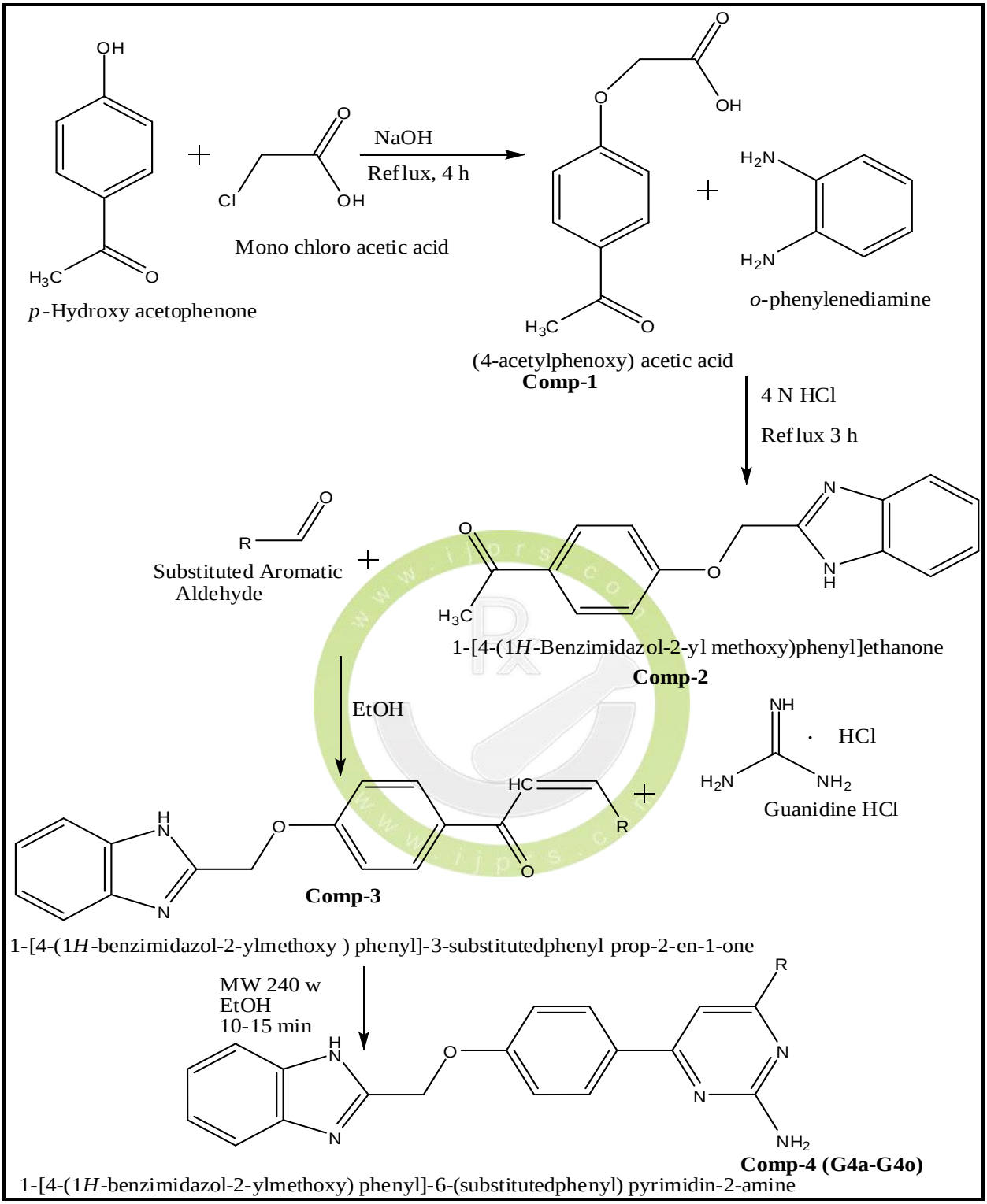
The comp-1 (0.1 mol) and *o*-phenylene diamine (0.1 mol) were refluxed in 10 ml of 4 N HCl in round bottom flask 100 ml equipped with reflux condenser for 3-4 h on oil bath. The solution on cooling gave a precipitate which was filtered, washed with water, dried and recrystalized from aqueous ethanol (1:1) to yield title comp-2. Scheme of synthesis of 1-[4-(1*H*-Benzimidazole-2ylmethoxy) phenyl] acetyl) ethanone (Comp-2) is described in Fig.2. Melting Point- 230-233 ^{0}C, % yield-67%, TLC mobile phase- Cyclohexane: Toluene: Ethyl Acetate (4:1:1)[13].

General Procedure for Synthesis of 1-[4-(1H-benzimidazol-2-ylmethoxy) phenyl]-3-substitutedphenyl prop-2-en-1-one (Comp-3(G3a-G3o))

Equimolar quantity of appropriately substituted aromatic aldehydes (0.02 mol) and 1-[4-(1*H*-Benzimidazole-2yl methoxy) phenyl] acetyl) ethanone comp-2 (0.02 mol) were dissolved in approximately 20 ml of ethanol.

The mixture was allowed to stir for 15-20 minutes. A 10 ml aliquot of a 40% aqueous sodium hydroxide solution was then slowly added drop wise to the reaction mixture and allowed to stand overnight at room temperature. On acidification by conc. HCl, a precipitate formed was collected by filtration, washed with water, dried and recrystalized from aqueous ethanol (1:1) to yield title comp-3(G3a-G3o).

Scheme of synthesis of 1-[4-(1*H*-benzimidazol-2-ylmethoxy) phenyl]-3-substitutedphenyl prop-2-en-1-one (Comp-3(G3a-G3o)) is described in Fig.2. TLC mobile phase- Petroleum Ether: Toluene: Ethyl Acetate (2:2:2)[15].



Where R = *o*-OH Ph, *m*- OH Ph, *p*-OH Ph, *o*-Cl Ph, *p*-Cl Ph, *o*-NO_2 Ph, *m*-NO_2 Ph, *p*-CH_3 Ph, *p*-OCH_3 Ph, *p*-F Ph, *p*-Br Ph, *p*-aminodimethyl Ph, *p*-OH & *m*-OCH_3 Ph, *p*-OH & *m*-OCH_3, Br Ph, Furan

Figure 2: Synthesis of comp-4(G4a-G4o)

General Procedure for Synthesis of 1-[4-(1H-benzimidazol-2-ylmethoxy) phenyl]-6-(substituted phenyl) pyrimidin-2-amine (Comp-4(G4a-G4o))

The mixture of 1-[4-(1*H*-benzimidazol-2-ylmethoxy) phenyl]-3-substitutedphenyl prop-2-en-1-one (Comp-3(G3a-G3o) 0.001 mol) with guanidine hydrochloride (0.001 mol) in alkaline medium potassium hydroxide (0.003 mol) in the presence of ethanol (10 ml). The above mixtures were subjected to microwave irradiation with magnetic stirring for 10–18 min and with a maximum power of 280 W. Reaction progress was monitored by TLC and the reaction mixture was poured in ice cold water. The precipitate formed was filtered off, washed with water, dried and recrystallized from ethanol to yield title comp-4(G4a-G4o). Scheme of synthesis of 1-[4-(1H-benzimidazol-2-ylmethoxy) phenyl]-6-(substituted phenyl) pyrimidin-2-amine, (Comp-4(G4a-G3o)) is described in Fig.2. TLC mobile phase- Toluene: Methanol (7:3)[10].

Spectral Characterizations of Synthesized 1-[4-(1H-benzimidazol-2-ylmethoxy) phenyl]-6-(substituted phenyl) pyrimidin-2-amine comp-4(G4a-G4o) are given below.

(G4a): 2-[2-amino-6[4(1H-benzimidazol-2-ylmethoxy) phenyl] pyrimidin-4-yl] phenol

Melting Point- 122-125^{0}C. R_f-value-0.57, Yield-53.15 % (Ethanol), Chemical formula:

$C_{24}H_{19}N_5O_2$. I R ν $_{max}$ (KBr, cm^{-1}): 3263.83(N-H, Amine), 3144.91(C-H, Methylene), 2917.29 (C=N, Aromatic), 1534.76 (C-C, Aromatic), 1170.53(C-C, Aromatic),1006.42(C-O-C, Ether).^{1}H-NMR (400 MHz, δH, DMSO-d6) in ppm: 5.39 (s,2H,CH_2, Methylene), 6.65 (s,2H, NH_2, Aromatic, *J*=1.040 Mz),7.09-8.198(m,8H,Phenyl), 7.194 (s,1H, Phenyl, *J*=7.28, 2.1Mz), 7.52(s,1H,OH) 7.84(s,1H,Pyrimidine). MS: $[M]^+$ at m/z 410.

(G4b):3-[2-amino-6-[4-(1H-benzimidazol-2-ylmethoxy) phenyl] pyrimidin-4-yl] phenol

Melting Point- 150-152^{0}C. R_f-value-0.62, Yield-47.13 % (Ethanol), Chemical formula:

$C_{24}H_{19}N_5O_2$. I R ν $_{max}$ (KBr, cm^{-1}): 3263.83(N-H, Amine), 1534.76 (C=N, Aromatic), 1408.83 (C-N, Aromatic), 1251.25(C-O-C, Ether), 1170.53(C-C, Aromatic). ^{1}H-NMR (400 MHz, δH, DMSO-d6) in ppm: 5.38 (s,2H, Methylene),6.54 (s,2H, NH_2, Aromatic, *J*=1.80 Mz),7.08-7.54 (m,8H, Phenyl), 7.84 (s,1H,Pyrimidine), 7.59 (s,2H,Benzimidazole,*J*=7.5,3.5Mz), 7.61 (s,2H,Benzimidazole, *J*=1.040 Mz), 8.46(s,1H,OH), 12.69 (s,1H,NH, Benzimidazole). MS:$[M]^+$ at m/z 410.

(G4c):4-[2-amino-6-[4-(1H-benzimidazol-2-ylmethoxy) phenyl] pyrimidin-4-yl] phenol

Melting Point- 206-210 ^{0}C. R_f-value-0.54, Yield-55.67 % (Ethanol), Chemical formula:

$C_{24}H_{19}N_5O_2$. I R ν $_{max}$ (KBr, cm^{-1}): 3221.15 (N-H, Amine), 1570.71 (C=N, Aromatic), 1423.93 (C-N,Aromatic),1169.69 (C-C,Aromatic),1118.19 (C-O-C,Ether). ^{1}H-NMR (400 MHz, δH, DMSO-d6) in ppm: 5.33 (s,2H, Methylene), 6.61 (s,2H, NH_2, Aromatic, *J*=1.88 Mz), 6.94-7.56 (m,8H, CH, Phenyl), 7.60 (s,2H, Benzimidazole, *J*=1.040 Mz) , 7.85(s,1H,CH, 2-Pyrimidine), 7.21(s,2H, Benzimidazole, *J*=7.3,3.1 Mz), 12.30 (s,1H, NH, Benzimidazole). MS: $[M]^+$ at m/z 410.

(G4d):4-[4-(1H-benzimidazol-2-ylmethoxy) phenyl]-6-(2-chlorophenyl) pyrimidin-2-amine

Melting Point- 138-140^{0}C. R_f-value-0.67, Yield-89.81 % (Ethanol), Chemical formula:

$C_{24}H_{18}ClN_5O$. I R ν $_{max}$ (KBr, cm^{-1}): 3369.65 (N-H, Amine), 2917.54 (C-H, Methylene), 1513.35 (C=N, Aromatic), 1345.37 (C-N, Aromatic), 1145.30 (C-O-C, Ether), 731.45 (C-Cl, Aromatic). ^{1}H-NMR (400 MHz, δH, DMSO-d6) in ppm: 5.33 (s,2H, Methylene),6.61 (s,2H, NH_2, Aromatic , *J*=1.78 Mz),7.05-7.56 (m,8H, Phenyl), 7.23 (s,2H , Benzimidazole, *J*=7.18,3.2 Mz), 7.59(s,2H , Benzimidazole, *J*=7.4,3.12 Mz),7.86 (s,1H,Pyrimidine),12.51 (s,1H, NH, Benzimidazole). MS: $[M]^+$ at m/z 429.

(G4e):4-[4-(1H-benzimidazol-2-ylmethoxy) phenyl]-6-(4-chlorophenyl) pyrimidin-2-amine

Melting Point- 146-150^{0}C. R_f-value-0.55, Yield-91.53 % (Ethanol), Chemical formula:

$C_{24}H_{18}ClN_5O$. I R ν_{max} (KBr, cm^{-1}): 3243.33 (N-H, Amine), 3062.13 (C-H, Aromatic), 2915.49 (C-H, Methylene), 1575.32(C=N, Aromatic), 1391.89 (C-N, Aromatic), 1172.43 (C-O-C, Ether), 1050.54 (C-C, Aromatic), 710.26 (C-Cl, Aromatic). ^{1}H-NMR (400 MHz, δH, DMSO-d6) in ppm: 5.33 (s,2H, Methylene), 6.59 (s,2H, NH_2, Aromatic, *J*=1.83 Mz),7.05-7.94 (m,8H, Phenyl), 7.21 (s,2H , Benzimidazole, *J*=7.1,3.4 Mz), 7.84 (s,1H, Pyrimidine), 7.60 (s,2H , Benzimidazole, *J*=7.31,3.17 Mz), 12.69 (s,1H, NH, Benzimidazole). MS: $[M]^+$ at m/z 429.

(G4f):4-[4-(1H-benzimidazol-2-ylmethoxy) phenyl]-6-(2-nitrophenyl) pyrimidin-2-amine

Melting Point- 225-227^{0}C. R_f-value-0.61, Yield-41.25 % (Ethanol), Chemical formula:

$C_{24}H_{18}N_6O_3$. I R ν_{max} (KBr, cm^{-1}): 3291.97 (N-H,Amine), 2917.52 (C-H, Aromatic), 1530.51 (C=N, Aromatic), 1438.68(N=O,C-NO_2), 1245.97(C-O-C, Ether), 1175.5 (C-C, Aromatic). ^{1}H-NMR (400 MHz, δH, DMSO-d6) in ppm: 5.40 (s,2H, Methylene), 6.52 (s,2H, NH_2,Aromatic, *J*=1.72 Mz),7.19-8.05 (m,8H, Phenyl), 7.65 (s,1H, Pyrimidine),7.21 (s,2H , Benzimidazole, *J*=7.34,3.08 Mz) , 7.57(s,2H , Benzimidazole, *J*=7.44,3.18 Mz), 12.60 (s,1H,NH, Benzimidazole). MS:$[M]^+$ at m/z 439.

(G4g):4-[4-(1H-benzimidazol-2-ylmethoxy) phenyl]-6-(3-nitrophenyl) pyrimidin-2-amine

Melting Point- 209-212^{0}C. R_f-value-0.65, Yield-37.60% (Ethanol), Chemical formula:

$C_{24}H_{18}N_6O_3$. I R ν_{max} (KBr, cm^{-1}): 3314.51 (N-H, Amine), 2870.04 (C-H, Methylene), 1556.42 (C=N, Aromatic), 1458.50 (N=O,C-NO_2),1310.15 (C-O-C, Ether),1016.06 (C-C, Aromatic). ^{1}H-NMR (400 MHz, δH, DMSO-d6) in ppm: 5.40 (s,2H, Methylene), 6.50 (s,2H, NH_2, Aromatic, *J*=1.81 Mz),7.19-8.20 (m,8H, Phenyl), 7.21(s,2H, Benzimidazole, *J*=7.1,3.00 Mz) ,7.60(s,2H , Benzimidazole, *J*=7.5,3.2 Mz), 7.80 (s,1H, Pyrimidine),12.69 (s,1H,NH, Benzimidazole). MS:$[M]^+$ at m/z 439.

(G4h):4-[4-(1H-benzimidazol-2-ylmethoxy) phenyl]-6-(4-methoxyphenyl) pyrimidin-2-amine

Melting Point- 120-123^{0}C. R_f-value-0.56, Yield-83.27 % (Ethanol), Chemical formula:

$C_{25}H_{21}N_5O_2$. I R ν_{max} (KBr, cm^{-1}): 1506.30 (C=N, Aromatic), 1421.88 (C-N, Aromatic), 1215.55 (C-C, Aromatic), 1155.05 (C-O-C, Ether). ^{1}H-NMR (400 MHz, δH, DMSO-d6) in ppm: 3.39 (s,3H, Methyl),5.42 (s,2H, Methylene),7.16-7.55 (m,8H, Phenyl), 7.55-7.91(s,1H, CH, Pyrimidine),7.20(s,2H, Benzimidazole, *J*=7.22,3.08 Mz),7.50(s,2H , Benzimidazole, *J*=7.41,3.22 Mz),12.50(s,1H, NH, Benzimidazole).MS:$[M]^+$at m/z 424.

(G4i):4-[4-(1H-benzimidazol-2-ylmethoxy) phenyl]-6-(4-methylphenyl) pyrimidin-2-amine

Melting Point- 161-164^{0}C. R_f-value-0.53, Yield-69.18 % (Ethanol), Chemical formula:

$C_{25}H_{21}N_5O$. I R ν_{max} (KBr, cm^{-1}): 2917.01 (C-H, Methylene), 1507.53 (C=N, Aromatic), 1433.46 (C-H, Methyl), 1336.50 (C-N, Aromatic), 1169.10 (C-C, Aromatic), 1114.66 (C-O-C, Ether). ^{1}H-NMR (400 MHz, δH, DMSO-d6) in ppm: 3.50 (s,3H,Methyl),5.38 (s,2H, Methylene),7.03 (s,2H, NH_2, Aromatic, *J*=2.1 Mz),7.05-7.55 (m,8H, Phenyl), 7.19(s,2H , Benzimidazole, *J*=7.04,3.2 Mz),7.59(s,2H , Benzimidazole, *J*=7.48,3.1 Mz) 7.84 (s,1H , Pyrimidine).MS:$[M]^+$ at m/z 408.

(G4j):4-[4-(1H-benzimidazol-2-ylmethoxy) phenyl]-6-(4-fluorophenyl) pyrimidin-2-amine

Melting Point- 132-135^{0}C. R_f-value-0.50, Yield-59.40 % (Ethanol), Chemical formula:

$C_{24}H_{18}FN_5O$. I R ν_{max} (KBr, cm^{-1}): 3293.37 (N-H, Amine), 3170.55 (C-H, Aromatic), 3012.25 (C-H, Methylene), 1547.89 (C=N, Aromatic), 1406.21 (C-N, Aromatic), 1264.59 (C-F, Aromatic), 1200.59 (C-O-C, Ether). ^{1}H-NMR (400 MHz, δH, DMSO-d6) in ppm: 5.31 (s,2H, Methylene),6.54 (s,2H, NH_2, Aromatic, *J*=1.9 Mz),7.04-8.14 (m,8H, CH, Phenyl), 7.19 (s,2H , Benzimidazole, *J*=7.1,3.06 Mz) , 7.44 (

s,2H , Benzimidazole, *J*=7.3,2.96 Mz),7.84 (s,1H, Pyrimidine). MS:$[M]^+$ at m/z 412.

(G4k):4-[4-(1H-benzimidazol-2-ylmethoxy) phenyl]-6-(4-bromophenyl) pyrimidin-2-amine

Melting Point- 142-144^{0}C. R_f-value-0.69, Yield-49.32 % (Ethanol), Chemical formula:

$C_{24}H_{18}BrN_5O$. I R ν $_{max}$ (KBr, cm^{-1}): 3548.57 (N-H, Amine), 1512.90 (C=N, Aromatic), 1362.68 (C-N, Aromatic), 1155.57 (C-O-C, Ether), 1067.39 (C-C, Aromatic), 820.79 (C-Br, Aromatic). ^{1}H-NMR (400 MHz, δH, DMSO-d6) in ppm: 5.41(s,2H, Methylene),6.50 (2H, NH_2, Aromatic, *J*=2.2 Mz),7.15-7.65 (m,8H, Phenyl), 7.20 (s,2H, Benzimidazole, *J*=7.18, 3.16 Mz), 7.62 (s,2H, Benzimidazole, *J*=7.40,3.2 Mz), 7.67 (s,1H, Pyrimidine). MS:$[M]^+$ at m/z 472.

(G4l):4-(4-((1H-benzo[d]imidazol-2-yl) methoxy) phenyl)-6-(4-(dimethylamino) phenyl) pyrimidin-2-amine

Melting Point- 106-108^{0}C. R_f-value-0.60, Yield-94.75 % (Ethanol), Chemical formula:

$C_{26}H_{24}N_6O$. I R ν $_{max}$ (KBr, cm^{-1}): 3339.92 (N-H, Amine), 1565.62 (C=N, Aromatic), 1495.64 (C-N, Aromatic), 1426.38 (C-H, Methyl), 1234.51 (C-O-C, Ether). ^{1}H-NMR (400 MHz, δH, DMSO-d6) in ppm: 3.03 (s,3H, Dimethyl), 5.40 (s,2H, Methylene),6.70 (s,2H, NH_2, Aromatic, *J*=2.3 Mz), 6.72-7.54 (m,8H, Phenyl), 7.21 (s,2H , Benzimidazole, *J*=7.18,3.16 Mz) , 7.57(s,2H , Benzimidazole, *J*=7.42,3.28 Mz), 7.67 (s,1H , Pyrimidine) , 12.69 (s,1H,NH, Benzimidazole),MS:$[M]^+$ at m/z 437.

(G4m):4-(6-(4-((1H-benzo[d]imidazol-2-yl) methoxy)phenyl)-2-aminopyrimidin-4-yl)-2-methoxyphenol

Melting Point- 170-173^{0}C. R_f-value-0.54, Yield-73.51 % (Ethanol), Chemical formula:

$C_{25}H_{21}N_5O_3$. IR ν $_{max}$ (KBr, cm^{-1}): 3339.92 (N-H, Amine), 1565.62 (C=N, Aromatic), 1495.64 (C-N, Aromatic), 1426.38 (C-H, Methyl),1234.51(C-O-C, Ether).^{1}H-NMR (400 MHz, δH, DMSO-d6) in ppm: 3.03 (s,3H, Dimethyl), 5.40 (s,2H, Methylene),6.70 (s,2H, NH_2, Aromatic, *J*=2.24 Mz), 6.72-7.54 (m,8H, Phenyl), 7.21 (s,2H, Benzimidazole, *J*=7.13,3.04 Mz) , 7.57 (s,2H ,Benzimidazole, *J*=7.41, 2.94 Mz), 7.67 (s,1H, Pyrimidine), 12.69 (s,1H, NH, Benzimidazole).MS:$[M]^+$ at m/z 440.

(G4n):4-(6-(4-((1H-benzo[d]imidazol-2-yl) methoxy) phenyl)-2-aminopyrimidin-4-yl)-2-bromo-6-methoxyphenol

Melting Point- 134-136^{0}C. R_f-value-0.59, Yield-41.51 % (Ethanol), Chemical formula: $C_{25}H_{20}BrN_5O_3$. I R ν $_{max}$ (KBr, cm^{-1}): 3369.65 OH, 3302.45 (N-H, Amine), 1678.42 (C=N, Aromatic), 1433.22 (C-H, Methoxy),1345.37 (C-O-C,Ether), 731.45 (C-Br, Aromatic).^{1}H-NMR (400 MHz, δH, DMSO-d6) in ppm: 3.39 (s,3H, Dimethyl), 5.41 (s,2H, Methylene),7.15-7.56 (m,8H, Phenyl), 7.81 (s,1H, Pyrimidine), 7.19 (s,2H , Benzimidazole, *J*=7.16,3.11 Mz) , 7.55(s,2H , Benzimidazole, *J*=7.50,3.17 Mz) , 9.81 (s,1H, OH), 12.70 (s,1H, NH, Benzimidazole). MS:$[M]^+$ at m/z 518.

(G4o):4-[4-(1H-benzimidazol-2-ylmethoxy) phenyl]-6-(furan-2-yl) pyrimidin-2-amine

Melting Point- 176-180^{0}C. R_f-value-0.52, Yield-68.02 % (Ethanol), Chemical formula:

$C_{22}H_{17}N_5O_2$.I R ν $_{max}$ (KBr, cm^{-1}): 3336.68 (N-H, Amine), 2915.34 (C-H, Aromatic), 1502.09 (C=N, Aromatic), 1326.18 (C-N, Aromatic), 1170.73 (C-O-C, Ether).^{1}H-NMR (400 MHz, δH, DMSO-d6) in ppm: 5.32 (s,2H, Methylene), 6.45 (s,2H, NH_2, Aromatic, *J*=2.24 Mz), 7.05-7.56 (m,8H , Phenyl), 6.95 (s,1H, Furan, *J*=7.4,1.6 Mz), 6.90 (s,1H, Furan, *J*=7.6,1.6 Mz), 7.21 (s,2H, Benzimidazole, *J*=7.12,3.04 Mz), 7.59(s,1H,Furan, *J*=7.5,1.4 Mz),7.69(s,2H, Benzimidazole, *J*=7.4,2.96 Mz),12.64 (s,1H, NH, Benzimidazole). MS: $[M]^+$ at m/z 484.

RESULTS AND DISCUSSION

Chemistry

Cyclization of 1-[4-(1H-benzimidazol-2-ylmethoxy) phenyl]-3-substitutedphenyl prop-2-en-1-one (3a–3o) with guanidine HCl by using the microwave irradiation method to give various 4-[4-(1*H*-benzimidazol-2ylmethoxy) phenyl]-6-(substituted phenyl) pyrimidin-2-

amine is described in Fig. 2. From the IR spectra, it was observed that functional groups present in the molecule appeared at their characteristic frequency C–Cl str. At 710cm^{-1},C-Br str. bteween 731-820 cm^{-1},C-F at 1264, N–H str. between 3221 and 3548 cm^{-1}, C-O-C str. between 1114-1345 cm^{-1}, etc. The chemical shift (d) for methylene hydrogen was observed in the range of 5.31–5.41 ppm, d value for aromatic hydrogen was observed in the range of 7.08-7.54 ppm, d value for pyrimidine hydrogen was observed in the range of 7.65-7.84 ppm ,d value for benzimidazole NH hydrogen was observed in the range of 12.30 -12.69ppm.The m/e value was observed, e.g., in case of G4a-G4o at 410-518(M)$^{+}$.So, from the physical and spectral data, we can conclude that the desired compounds synthesized successfully.

Antibacterial and Antifungal Activity

All the synthesized compounds were screened for both antimicrobial and antifungal activity. Compounds were screened for in vitro against two Gram positive strains *Staphylococcus aureus* (*S.aureus*, NCIM 2079), *Bacillus subtilis* (*B.subtilis*, NCIM 2711) and two Gram negative *Escherichia coli* (*E.coli*, NCIM 2685), *Klebsiella pneumonia* (*K.pneumoniae*, NCIM 295*)* bacteria for antibacterial and two fungal species *Aspergillus nigar* (*A.nigar*, NCIM 596) and *Sacharomyces cerevisiae* (*S.cerevisiae*, NCIM 3102) for antifungal activity, respectively using the broth micro dilution method[22]. Minimum inhibitory concentration (MIC) was determined and compared with standard drugs Ampicillin for antibacterial activity (Table1) and Ketoconazole for antifungal activity (Table 2).

From in vitro anti-bacterial activity, all the tested derivatives showed least activity against *S.aureus and B.subtillis* with MIC in the range of 100–260 µg/ml. In case of *E. coli* and *K. pneumonia*, derivative G4g, G4k, G4n, G4d, G4h, G4f, G4l, G4m (*m*-NO_2, *p*-Br, *p*-OH & *m*-OCH_3,BrPh,*o*-Cl, *p*-OCH_3, *o*-NO_2, *p*-dimethyl, *p*-OH & *m*-OCH_3) were found to have significant activity which is 1-2 folds less than the standard drug Ampicillin, while compound G4e, G4i, G4j, G4o (*p*-Cl, *p*-CH_3, *p*-F, furan) showed moderate activity against *E. coli*. All other compounds G4a, G4b, G4c showed least activity against *E.coli* ,while compound G4e, G4g, G4k, G4l (*p*-Cl, *m*-NO_2, *p*-Br, *p*-dimethyl amino) were found to have significant activity which is 1-2 folds less than the standard drug Ampicillin, while compound G4f, G4j, G4m, G4n (*o*-NO_2, *p*-F, *p*-OH & *m*-OCH_3 *p*-OH & *m*-OCH_3,Br Ph) showed moderate activity against *K. pneumonia*. All other compounds G4a, G4b, G4c, G4h, G4i and G4o showed least activity against *K. pneumonia* (Fig. 3). Thus from the obtained antibacterial activity data we can conclude that the electron-withdrawing groups substituted at specific position on phenyl ring i.e., (*m*-NO_2, *p*-Br, *p*-OH & *m*-OCH_3,Br Ph,*o*-Cl, *p*-OCH_3, *o*-NO_2, *p*-dimethyl amino, *p*-OH & *m*-OCH_3, *p*-Cl, *p*-CH_3, *p*-F, furan) is contributing positively for antibacterial activity against *E.coli* and *K. pneumonia*.

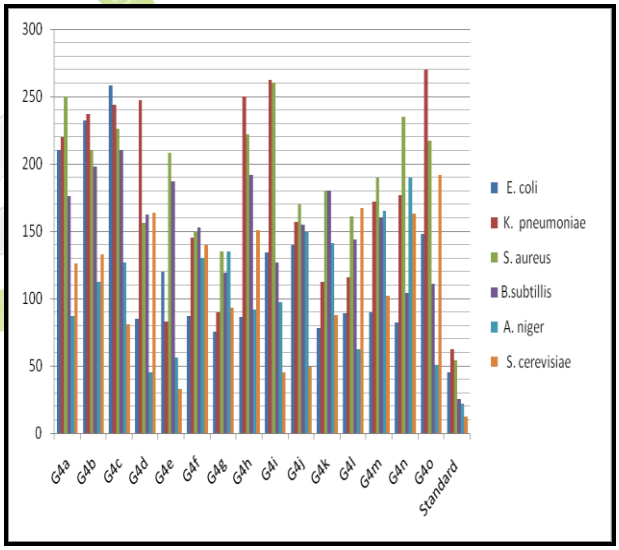


Figure 3: MIC of synthesized Comp-4(G4a-G4o) in comparison with standard against different microbial strains

In case of antifungal results, compound G4d, G4o, G4e, G4l (*o*-Cl, furan, *p*-Cl, *p*-dimethylamino) were found to have significant activity as compared to reference standard Ketoconazole against *A.niger*, while derivative G4a, G4h, G4i (*o*-OH, *p*-OCH_3, *p*-CH_3) having moderate activity as that of standard against *A. niger*.

Table 1: MIC values (µg/ml) against *E.coli*, *K.pneumoniae*, *S.aureus* and *B.subtillis*

Comp. Code	**R**	**MIC (µg/ml)**			***B.subtillis***
		E. coli	***K. pneumoniae***	***S. aureus***	
G4a	*o*-OH Ph	210	220	250	176
G4b	*m*-OH Ph	232	237	210	198
G4c	*p*-OH Ph	258	244	226	210
G4d	*o*-Cl Ph	85	247	156	162
G4e	*p*-Cl Ph	120	83	208	187
G4f	*o*-NO_2 Ph	87	145	149	153
G4g	*m*-NO_2 Ph	75	90	135	119
G4h	*p*-OCH_3 Ph	86	250	222	192
G4i	*p*-CH_3 Ph	134	262	260	127
G4j	*p*-F Ph	140	157	170	155
G4k	*p*-Br Ph	78	112	180	180
G4l	*p*-aminodimethyl Ph	89	116	161	144
G4m	*p*-OH &*m*-OCH_3 Ph	90	172	190	160
G4n	*p*-OH & *m*-OCH_3 ,Br Ph	82	177	235	104
G4o	Furan	148	270	217	111
Ampiciline	------	45	62	54	25
G4a	*o*-OH Ph	210	220	250	176

Table 2: MIC values (µg/ml) against *A.niger and S.cerevisiae*

Comp. Code	MIC (µg/ml)		Comp. Code	MIC (µg/ml)	
G4a	87	126	G4h	92	151
G4b	112	133	G4i	97	45
G4c	127	81	G4j	149	49
G4d	45	164	G4k	141	88
G4e	56	33	G4l	62	167
G4f	130	140	G4m	165	102
G4g	135	93	G4n	190	163
Ketoconazole	22	12	G4o	51	192

The compounds G4b, G4c, G4f, G4g, G4j, G4k, G4m, G4n showed least activity against *A.niger*. The compounds G4c, G4g, G4k, G4m (*p*-OH, *m*-NO_2, *p*-Br , *p*-OH & *m*-OCH_3 Ph) were found to have significant activity as compared to reference standard Ketoconazole against *S.cerevisiae*, while derivative G4e, G4i, G4j (*p*-Cl, *p*-CH_3 , *p*-F) having moderate activity as that of standard against *S.cerevisiae*. The compounds G4a, G4b, G4d, G4f, G4h, G4l, G4n and G4o showed least activity against *S.cerevisiae* (Fig. 3).

So, from this study it can be concluded that the electron-withdrawing groups substituted at specific position on phenyl ring i.e., (*o*-Cl, furan, *p*-Cl, *p*-dimethylamino, *p*-Cl, *p*-CH_3, *p*-F, *p*-OCH_3, *p*-Br, *p*-NO_2, *o*-OH, *p*-OH) is contributing positively for the antifungal activity against *A.niger* and *S.cerevisiae*. As far as benzimidazol nucleus with substitution at 6 position on pyrimidin-2-amine is considered for all the synthesized compounds, a key factor for both antibacterial as well as antifungal activities.

CONCLUSION

A series of 4-[4-(1*H*-benzimidazol-2ylmethoxy) phenyl]-6-(substituted phenyl) pyrimidin-2-amine have been synthesized and evaluated for antibacterial and antifungal activity. The compound G4d, G4o, G4e, G4l (*o*-Cl, furan, *p*-Cl, *p*-dimethylamino) was found to be having significant activity against *A. niger* and whereas compounds G4e, G4i, G4j (*p*-Cl, *p*-CH_3, *p*-F) were found active against *S. cerevisiae*. As far as antibacterial activity is concerned compound G4g, G4k, G4n, G4d, G4h, G4f, G4l, G4m (*m*-NO_2, *p*-Br, *p*-OH & *m*-OCH_3, Br Ph, *o*-Cl, *p*-OCH_3, *o*-NO_2, *p*-dimethyl, *p*-OH & *m*-OCH_3Ph) showed good activity against *E. coli* and whereas compound G4e, G4g, G4k, G4l (*p*-Cl, *m*-NO_2, *p*-Br, *p*-dimethyl amino) has promising activity only against *K. pneumoniae*. All the synthesized compounds showed very poor activity against *S. aureus and B.subtillis*. So, the results obtained from antibacterial and antifungal activities are more promising as the compounds showed significant activity as compared to standard or marketed drugs,

Ampicillin and Ketoconazole. These results can be used further to design and develop novel antimicrobial agents

ACKNOWLEDGEMENT

The authors thank MES`s College of Pharmacy, Sonai for providing all laboratory facilities, UDCT Dr. BAMU, Aurangabad for recording IR Spectra, ^{1}H NMR spectra at SAIF Punjab University, Chandigarh, GCMS spectra at University of Pune, Pune for recording spectra and Microbiology Dept., Pravara Medical Trust, Loni for Providing microbial cultures.

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