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Research Article

# SYNTHESIS AND ANTIFUNGAL ACTIVITY OF 1-ALKYL/*H*-2[4-(ALKYL/ ARYL-PIPERAZIN-1-YL)-METHYL]-BENZIMIDAZOLE DERIVATIVES

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**ABSTRACT**

Benzimidazole and Piperizine are the most important group of systemic fungicides currently in use for controlling the fungal diseases. The major types of fungicidal piperizine derivatives are Ketoconazole, Itraconazole. Although these are effective against many groups of fungi, there are some major groups of fungi ( e.g. Alternaria solani), which are quite insensitive to these compounds. In last decade many condensation products of benzimidazole and piperizines have been patented for variety of biological activities namely in the treatment of antibacterial, anti-inflammatory, antihypertensive, anthelmintic disorders. Therefore, we turned to synthesize various piperazinyl benzimidazole derivatives and decided to screen them for antifungal activity. Therefore in present work substituted benzimidazoles were condensed with various substituted piperazine to synthesize the library of benzimidazole derivatives. Substituted benzimidazoles were synthesized from corresponding o-phenylene diamines and then refluxed 8 hrs with monochloro acetic acid in concentrated hydrochloric acid. The substituted piperazines were condensed with substituted benzimidazole by refluxing in dioxane and Triethylamine as base. The antifungal activity of synthesized compounds was taken by using Disk diffusion method against Candida albicans using Ketoconazole as reference standard. The compound showed comparable antifungal activity to Ketoconazole.

**Keywords:** Benzimidazole, Piperazines, Antifungal activity

## INTRODUCTION

Benzimidazole is one of the commonly used nucleus due to its widespread pharmacological activities; it has earned an important place in the list of chemotherapeutic agents. The biological significance of benzimidazoles is due to its close relationship with structure of purines. The vital role of purines in the biological system was established and it was discovered that 5, 6- dimethyl-1-(α-D-ribofuranosyl) benzimidazole is an integral part of structure of Vit.B12[1]. A fungal selective 14α-demethylase inhibitor is expected to act as an antifungal agent. Considerable effort has been invested in the design of fungal – selective 14α-demethylase inhibitors and this has resulted in useful, orally active antifungal agent which are effective against both topical (and vaginal) and systemic fungal infections[2].

An imidazole and triazole heterocycles are common structural feature of these inhibitors, together with a lipophilic aromatic or aral/alkyl group. Beginning in late 1960's an extensive series of azoles compounds have been synthesized and tested for antifungal activity[3]. The azoles represent a class of versatile antifungal agents with an apparently unique mechanism of action. Early members of the class, such as clotrimazole and miconazole, were highly substituted imidazoles.These findings stimulated great interest in the chemistry of imidazoles and related compounds, and considerable success has accured from these studies.Piperazines and benzimidazoles play an important role in medicinal chemistry. During the past 5-10yrs, many condensation products of benzimidazole and piperazines have been patented for variety of biological activities.

Further exploitation of benzimidazole nucleus found its use in different therapeutic categories like; Domperidone as antiemetic, Albendazole as anthelmintic, Bendazol as coronary vasodilator, Omeprazole, Lansoprazole, pantoprazole (altana pharmaceuticals, 1994) as proton pump inhibitors, Pimobendan (Boehringer Ingelheim, 1994) as cardiotonic.

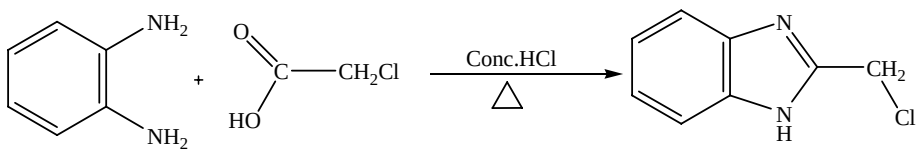
## CHEMISTRY

2-(chloromethyl)-1*H*-benzimidazole and 2-(chloromethyl)-methyl-benzimidazole, basic moieties, were synthesized by heating corresponding carboxylic acid with appropriate ortho-phenylenediamines (OPD) and N-methyl-2-phenylenediamines (N-methyl-OPD) respectively using dehydrating agent (Scheme 1). During the synthesis, concentrated Hydrochloric acid was used as the condensation reagent according to the well known Phillips method.

The derivatives of benzimidazole were synthesized by treatment of 2-(chloromethyl)-1*H*/methyl-benzimidazole with N-alkyl/aryl piperazines and/or substituted anilines in dioxane and triethylamine in order to obtain the target compounds (Scheme-2). The structures of all the synthesized compounds were supported by spectral data like FTIR, GC-MS, $^1$H NMR spectra.

**SCHEME 1**

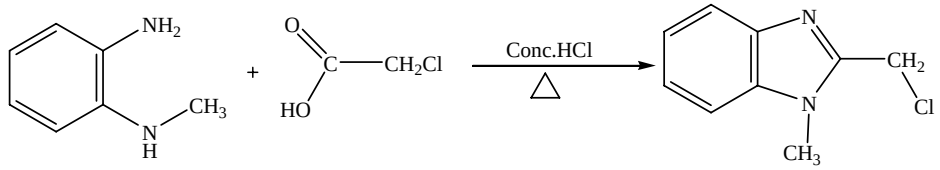
**A) Synthesis of 2-(chloromethyl)-1*H*-benzimidazole**




OPD Monochloroacetic acid 2(Chloromethyl)-1*H*-benzimidazole

(I)

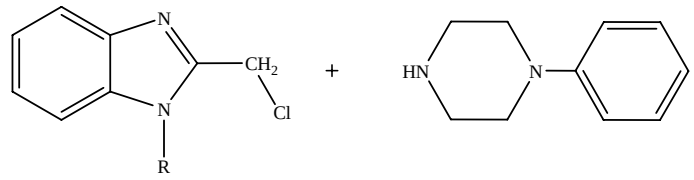
**B) Synthesis of 2(Chloromethyl)-1-methyl-benzimidazole**



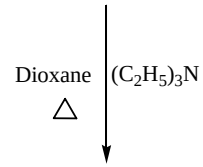

N-methyl-OPD Monochloroacetic acid 2(Chloromethyl)-1-methyl-benzimidazole

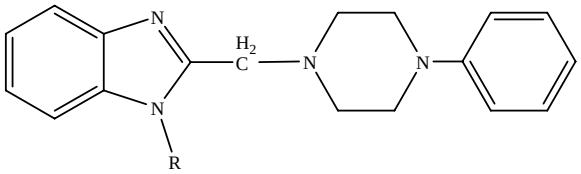
**SCHEME 2**

**Synthesis of 2-[(4-phenylpiperazin-1-yl) methyl]-N-substituted-benzimidazole**




2-(chloromethyl)-N-substituted-benzimidazole 1-phenylpiperazine



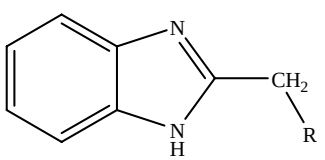

2-[(4-phenylpiperazin-1-yl)methyl]-N-substituted-benzimidazole

R= H, 2-[(4-phenylpiperazin-1-yl) methyl]-1H-benzimidazole, R=$CH_3$, 2-[(4-phenylpiperazin-1-yl) methyl]-N-methyl-benzimidazole

**EXPERIMENTAL**

All chemicals used were of Ranbaxy Laboratories Ltd. Delhi. Thin Layer Chromatography was performed using Silica Gel coated on glass plates and precoated Aluminum sheets no. 1.55503 (E-Merck) and the spots were visualized, by exposure to iodine vapors and in the CAMAG UV cabinet with dual wavelength UV lamp at 254nm & 366nm wavelength. FTIR spectra were recorded on FTIR-8400S SHIMADZU spectrometer. $^1$H-NMR spectra were recorded on NMR spectrometer, model: advance DPX 300, Bruker, Germanys with TMS as an internal standard. Chemical shifts (δ) were expressed in parts per million (δ ppm). GC-MS spectra & chromatogram were recorded on GCMS-QP 2010 SHIMADZU instrument. Melting points were determined on digital scientific melting point apparatus. Solvents were dried and distilled before use. Solvent extracts were dried on anhydrous sodium sulphate.

**General structure**



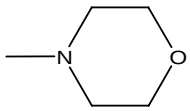
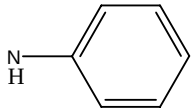
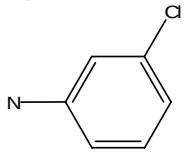
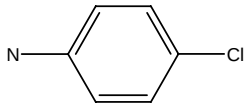
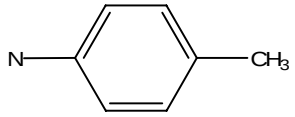
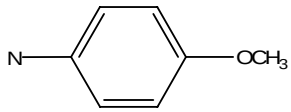

**SCHEME 1**

**A) 2-(chloromethyl)-1*H*-benzimidazole**

O-phenylenediamine (0.13mol), monochloroacetic acid (0.104 mol) and 25 ml of conc. hydrochloric acid were taken in an RBF and refluxed for 8hrs. The reaction was monitored by TLC. A test portion was dumped in water and basified with ammonia solution. The solid was extracted with ether and TLC of this ether extract was checked for the completion of reaction. After completion of the reaction, the reaction mixture was poured in ice-cold water. It was then basified with conc. ammonia solution. The solid precipitated was filtered immediately and dried.

MP 144-146$^0$C, Yield 87%; IR (Ar-CH Str) 3024.48, (C=C Str) 1491.02, (C=C bend) 887.28, (C-N Str ) 1203.62, (C-Cl Str) 736.83; Mass spectrum m/z 166 ($M^+$), 167 ($M^+$+1), 168 ($M^+$+2)

**Table 1: Substituted Benzimidazole derivatives**

| Sr. No. | R |
|---|---|
| a |  2-(morpholinomethyl)-1*H*-benzimidazole |
| b |  N-[(1*H*-benzimidazol-2yl)methyl]benzenamine |
| c |  N-[(1*H*-benzimidazol-2-yl)methyl]-3-chlorobenzenamine |
| d |  N-[(1*H*-benzimidazol-2-yl)methyl]-4-chlorobenzenamine |
| e |  N-[(1*H*-benzimidazol-2-yl)methyl]-4-methylbenzenamine |
| f |  N-[(1*H*-benzimidazol-2-yl)methyl]-4-methoxybenzenamine |

**a) 2-(morpholinomethyl)-1*H*-benzimidazole**

Procedure is same as scheme 1(A) using morpholine. mp 132-134 °C, Yield 75%; IR (Ar C-H Str) 3053.42, (C=C bend) 740.69, (C-N str) 1271.13, (N-H Str) 3419.90.

**b) N-[(1*H*-benzimidazol-2yl)methyl]benzenamine**

Procedure is same as scheme 1(A) using aniline. mp 84-88°C, Yield 72%; IR (C=C Str)1616.40, (C=C bend)860.28, (C=N Str)1645.33, (C-N str) 1246.06, (N-H Str) 3308.03 & 3365.90.

**c) N-[(1*H*-benzimidazol-2-yl)methyl]-3- chlorobenzenamine**

Procedure is same as scheme 1(A) using 3-chlorobenzeneamine. mp 74-78°C, Yield 67%; IR (C=C Str) 1614.47, (C=C bend)788.91, (C-N str) 1294.28, (C=N Str) 1635.69, (N-H Str) 3306.10 & 3327.32.

**d) N-[(1*H*-benzimidazol-2-yl)methyl]-4-chlorobenzenamine**

Procedure is same as scheme 1(A) using 4-chlorobenzenamine. mp 78-82°C, Yield 65%; IR (C=C Str) 1614.47, (C=C bend) 788.91, (C-N str) 1294.28, (C=N Str) 1635.69, (N-H Str) 3306.10 & 3327.32.

**e) N-[(1*H*-benzimidazol-2-yl)methyl]-4-methylbenzenamine**

Procedure is same as scheme 1(A) using 4-methylbenzenamine. mp 82-84°C, Yield 72%; IR (C=C bend) 786.98, (C-N str)1234.48, (C=N Str)1633.76, (N-H Str)3298.38 & 3398.69.

**f) N-[(1*H*-benzimidazol-2-yl)methyl]-4-methoxybenzenamine**

Procedure is same as scheme 1(A) using 4-methoxybenzenamine. mp 96-98°C, Yield 71%; IR (Ar C-H Str) 3051.49, (C=C Str) 1483.31, (C=C bend) 846.78, (C-N str) 1244.13, (N-H Str) 3333.10 & 3362.04,(Asymmetric C-O-C Str in ether) 1271.13.

**B) 2(Chloromethyl)-1-methyl-benzimidazole**

Reaction is carried out with N-methyl o-phenylenediamine and mono chloroacetic acid. Procedure is same as scheme 1 (A).

IR (Ar-CH Str) 3024.48, (C=C Str) 1616.4 & 1481.38, (C=C bend) 881.50, (C-N Str) 1290.42, (C-Cl Str) 742.62; Mass spectrum m/z 180($M^+$), 181($M^+$+1), 182($M^+$+2).

**SCHEME 2**

**2-[(4-phenylpiperazin-1-yl) methyl]-1*H*-benzimidazole**

2-chloromethyl-1*H*-benzimidazole (0.005mol), of 1-phenylpiperazine (0.005mol) were separately dissolved in dioxane and mixed in an RBF, triethylamine (0.005mol) was added and the reaction mixture was refluxed for 4hrs.The reaction was monitored by TLC. The reaction mixture was then dumped in ice cold water and the precipitate was collected by suction and dried. The solid was recrystallised from acetone.

mp 238-240$^0$C, Yield 78%; IR **(**Ar CH Str) 3024.48, (C=C Str) 1599.04 & 1492.95, (C=C bend) 748.41, (C-N Str) 1215.19.

**General Structure**

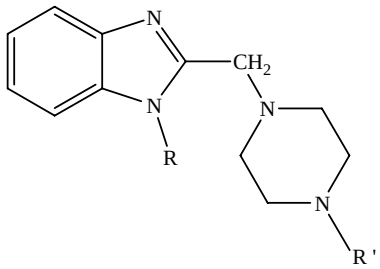
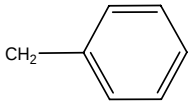
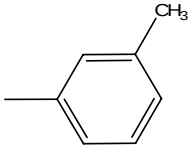
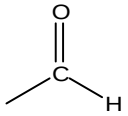
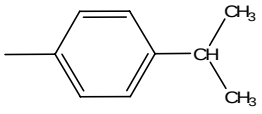
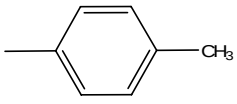
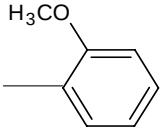
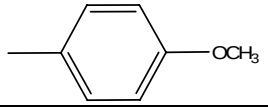
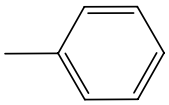
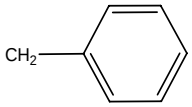
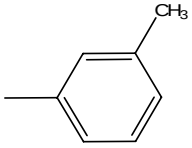
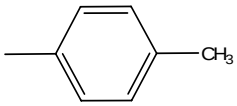
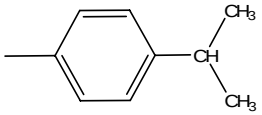
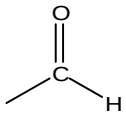



**Table 2: Synthesis of 1Alkyl/H-2-[4-(alkyl/aryl-piperazin-1-yl)-methyl]-Benzimidazole derivatives**

| Sr. No. | Compound | R | R' |
|---|---|---|---|
| a | 2-[(4-methylpiperazin-1-yl) methyl]-1*H*-benzimidazole | H | $CH_3$ |
| b | 2-[(4-ethylpiperazin-1-yl) methyl]-1*H*-benzimidazole | H | $C_2H_5$ |
| c | 2-[(4-benzylpiperazin-1-yl) methyl]-1*H*-benzimidazole | H |  |
| d | 2-[(4-m-tolylpiperazin-1-yl) methyl]-1*H*-benzimidazole | H |  |
| e | 4-[(1*H*-benzimidazol-2-yl) methyl] piperazine-1-carbaldehyde | H |  |
| f | 2-[(4-isopropylpiperazin-1-yl) methyl]-1*H*-benzimidazole | H |  |
| g | 2-[(4-p-tolylpiperazin-1-yl) methyl]-1*H*-benzimidazole | H |  |
| h | 2-[{4-(2-methoxyphenyl) piperazin-1-yl} methyl]-1*H*-benzimidazole | H |  |
| i | 2-[{4-(4-methoxyphenyl) piperazin-1-yl}methyl]-1*H*-benzimidazole | H |  |

| | | | |
|---|---|---|---|
| j | 1-methyl-2-[(4-methylpiperazin-1-yl)methyl]-benzimidazole | $CH_3$ | $CH_3$ |
| k | 2-[(4-ethylpiperazin-1-yl) methyl]-1-methyl-benzimidazole | $CH_3$ | $C_2H_5$ |
| l | 1-methyl-2-[(4-phenylpiperazin-1-yl)methyl]-benzimidazole | $CH_3$ |  |
| m | 2-[(4-benzylpiperazin-1-yl) methyl]-1-methyl-benzimidazole | $CH_3$ |  |
| n | 1-methyl-2-[(4-m-tolylpiperazin-1-yl)methyl]-benzimidazole | $CH_3$ |  |
| o | 1-methyl-2-[(4-p-tolylpiperazin-1-yl)methyl]-benzimidazole | $CH_3$ |  |
| p | 2-[(4-(4-isopropylphenyl) piperazin-1-yl)methyl]-1-methyl-benzimidazole | $CH_3$ |  |
| q | 4-[(1-methyl-1H-benzimidazol-2-yl)methyl]piperazine-1carbaldehyde | $CH_3$ |  |

**a) 2-[(4-methylpiperazin-1-yl) methyl]-1*H*-benzimidazole**

Procedure is same as scheme 2 using methyl piperizine instead of phenyl piperazine. mp 70-72°C, Yield 71%; IR (Ar CH Str) 3036.06, (C=C Str)1597.11 & 1491.02, (C=C bend ) 900.79, (C=N Str) 1683.91,(C-N str) 1224.84,(N-H Str) 3360.90.

**b) 2-[(4-ethylpiperazin-1-yl) methyl]-1*H*-benzimidazole**

Procedure is same as scheme 2 using ethyl piperazine instead of phenyl piperazine. mp 87-89°C, Yield 65%; IR (Ar CH Str)3030.27, (C=C Str)1600.97 & 1489.10, (C=C bend) 927.72, (C=N Str) 1670.41, (C-N Str) 1249.91, (N-H Str) 3296.46.

**c) 2-[(4-benzylpiperazin-1-yl) methyl]-1*H*-benzimidazole**

Procedure is same as scheme 2 using benzyl piperazine instead of phenyl piperazine. mp 92-94°C, Yield 74%; (Ar CH Str) 3026.41, (C=C Str)1622.19 & 1456.30, (C=C bend)742.62 , (C=N Str) 1683.91, (C-N str) 1273.06.

**d) 2-[(4-m-tolylpiperazin-1-yl) methyl]-1*H*-benzimidazole**

Procedure is same as scheme 2 using m-tolylpiperazine instead of phenyl piperazine. mp 158-160°C, Yield 75%; IR (Ar CH Str)3051.49, (C=C Str)1599.04 & 1456.30, (C=C bend) 746.48, (C-N str) 1296.21.

**e) 4-[(1*H*-benzimidazol-2-yl) methyl] piperazine-1-carbaldehyde**

Procedure is same as scheme 2 using carbaldehyde piperazine instead of phenyl piperazine. mp 116-118°C, Yield 72%; IR (Ar CH Str) 3026.41, (C=C Str)1595.18 & 1489.1, (C=C bend) 798.56, (C-N str) 1224.84, (Aldehydic C-H Str) 2775.66 & 2831.60.

**f) 2-[(4-isopropylpiperazin-1-yl) methyl]-1*H*-benzimidazole**

Procedure is same as scheme 2 using isopropyl piperazine instead of phenyl piperazine. mp 134-136°C, Yield 76%; IR (Ar CH Str)3024.48, (C=C Str)1600.97 & 1456.30, (C=C bend) 840.99, (C-N str) 1224.84.

**g) 2-[(4-p-tolylpiperazin-1-yl) methyl]-1*H*-benzimidazole**

Procedure is same as scheme 2 using p-tolylpiperazine instead of phenyl piperazine. mp 178-182°C, Yield 78%; IR (Ar CH Str) 3026.41, (C=C Str)1491.01, (C=C bend) 896.93, (C-N str) 1224.84.

**h) 2-[{4-(2-methoxyphenyl) piperazin-1-yl} methyl]-1*H*-benzimidazole**

Procedure is same as scheme 2 using 2-methoxy phenyl piperazine instead of phenyl piperazine. mp 162-164°C, Yield 80%; IR (Ar CH Str) 3055.35, (C=C Str) 1500.67, (C=C bend) 740.69 , (C-N str) 1226.77, (Asymmetric C-O-C Stretch in ether) 1271.13, (Symmetric C-O-C Stretch in ether)1028.09.

**i) 2-[{4-(4-methoxyphenyl) piperazin-1-yl} methyl]-1*H*-benzimidazole**

Procedure is same as scheme 2 using 4-methoxy phenyl piperazine instead of phenyl piperazine. mp 84-86°C, Yield 77%; IR (C=C Str)1498.74, (C=C bend)742.65, (C-N str) 1240.27, (Asymmetric C-O-C Stretch in ether) 1271.13.

**j) 1-methyl-2-[(4-methylpiperazin-1-yl) methyl]-benzimidazole**

Carry out the same procedure as in scheme 1(B) using N-methyl-o-phenylenediamine and scheme 2 using methyl piperizine. mp 66-68°C, Yield 65%; IR (Ar C-H Str) 3022.55, (C=C Str) 1616.40 & 1473.66, (C=C bend ) 875.71, (C-N str) 1263.42.

**k) 2-[(4-ethylpiperazin-1-yl) methyl]-1-methyl-benzimidazole**

Carry out the same procedure as in scheme 1(B) using N-methyl-o-phenylenediamine and scheme 2 using ethyl piperizine. mp 64-66°C, Yield 71%; IR (Ar CH Str) 3037.99, (C=C Str) 1475.59, (C=C bend) 763.84, (C-N str) 1263.42.

**l) 1-methyl-2-[(4-phenylpiperazin-1-yl) methyl]-benzimidazole**

Carry out the same procedure as in scheme 1(B) using N-methyl-o-phenylenediamine and scheme 2 using phenyl piperizine. mp 168-170°C, Yield 78%; IR (Ar C-H Str)3003.27, (C=C Str)1467.88, (C=C bend) 785.05, (C-N str)1251.84, (C=N Str) 1633.76.

$^1$H NMR δ 3.882 (s, 3H, -N-$CH_3$ ), δ 3.894 (s, 2H, -C-$CH_2$-N- ), δ 2.688-2.720 (t, 4H, -N-$CH_2$-$CH_2$), δ 3.165-3.195 (t, 4H, -$CH_2$-$CH_2$ –N-), δ 6.835-7.777 (m, 9H, Ar-H ).

**m) 2-[(4-benzylpiperazin-1-yl) methyl]-1-methyl-benzimidazole**

Carry out the same procedure as in scheme 1(B) using N-methyl-o-phenylenediamine and scheme 2 using benzyl piperizine. mp 90-92°C, Yield 72%; IR (C=C Str)1479.45, (C=C bend) 831.33, (C-N str) 1288.49.

**n) 1-methyl-2-[(4-m-tolylpiperazin-1-yl) methyl]-benzimidazole**

Carry out the same procedure as in scheme 1(B) using N-methyl-o-phenylenediamine and scheme 2 using m-tolyl piperizine. mp 108-110°C, Yield 78%; IR (Ar CH Str) 3086.21, (C=C Str) 1604.83 & 1473.66, (C=C bend) 796.63, (C-N str) 1195.91, (C=N Str) 1635.69.

**o) 1-methyl-2-[(4-p-tolylpiperazin-1-yl) methyl]-benzimidazole**

Carry out the same procedure as in scheme 1(B) using N-methyl-o-phenylenediamine and scheme 2 using p-tolyl piperizine. mp 176-180°C, Yield 73%; IR (Ar CH Str) 3022.55, (C=C Str) 1475.59, (C=C bend)873.78, (C-N str) 1271.13.

**p) 2-[(4-(4-isopropylphenyl) piperazin-1-yl) methyl]-1-methyl-benzimidazole**

Carry out the same procedure as in scheme 1(B) using N-methyl-o-phenylenediamine and scheme 2 using isopropyl phenyl piperizine. mp 112-114°C, Yield 72%; IR (Ar CH Str) 3032.20, (C=C Str) 1614.47 & 1473.66, (C=C bend ) 819.77, (C-N str) 1273.06, (C=N Str) 1668.48.

**q) 4-[(1-methyl-1H-benzimidazol-2-yl) methyl] piperazine-1carbaldehyde**

Carry out the same procedure as in scheme 1(B) using N-methyl-o-phenylenediamine and scheme 2 using carbaldehyde piperizine. mp 138-140°C, Yield 75%; IR (C=C Str) 1614.47 & 1473.66, (C=C bend) 860.28, (C-N str) 1273.06, (Aldehyde C-H Str ) 2763.06 & 2820.02.

$^1$H NMR δ 3.880 (s, 3H, -N-$CH_3$ ), δ 3.895 (s, 2H, -C-$CH_2$-N- ), δ 2.685-2.716 (t, 4H, -N-$CH_2$-$CH_2$), δ 3.11-3.143 (t, 4H, -$CH_2$-$CH_2$ –N-), δ 6.819-7.37 (m, 4H, Ar-H ), δ 7.771 (s, 1H, -CHO(-N-C- )

**ANTIFUNGAL ACTIVITY**

**Evaluation of antifungal activity [4,- 10]**

The evaluation of antifungal activity was done by the Bauer-Kirby method of disk diffusion.

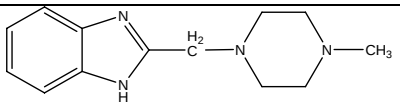
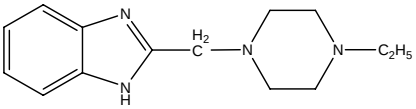
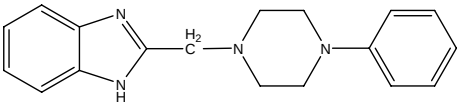
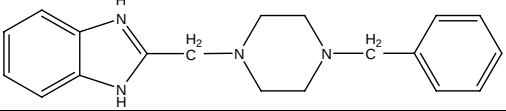
**Medium:** Mueller-Hinton agar is the recommended medium because it produces rapid growth of most of pathogen, contains no inhibitors, and can be used with sulpha compound and gives sharp end point.

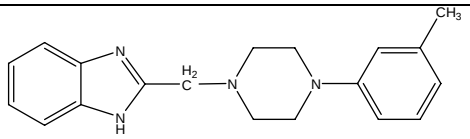
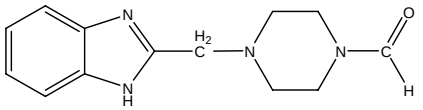
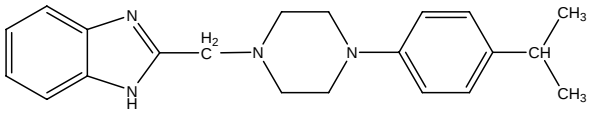
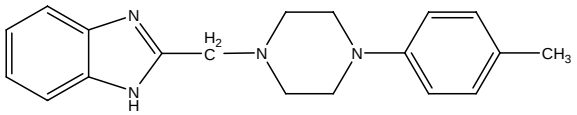
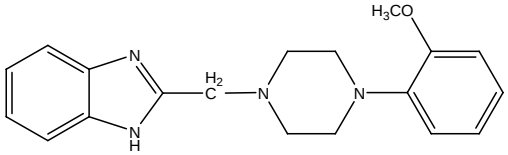
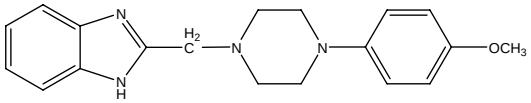
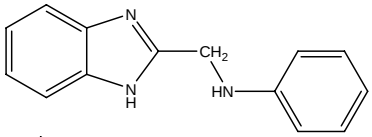
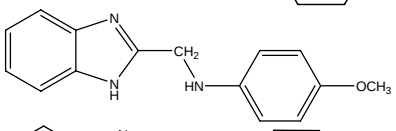
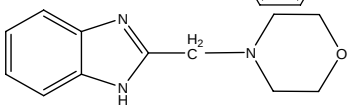
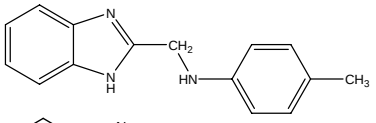
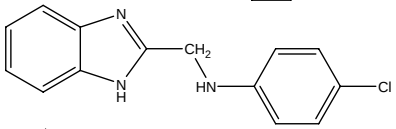
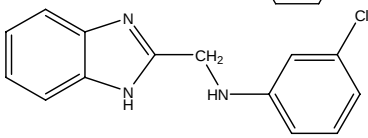
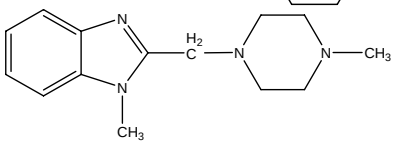
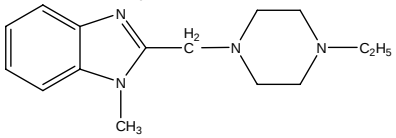
**Fungal strains used:** *Candida albicans* ATCC

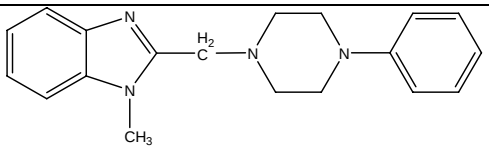
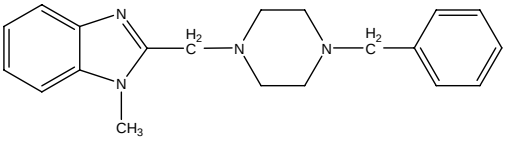
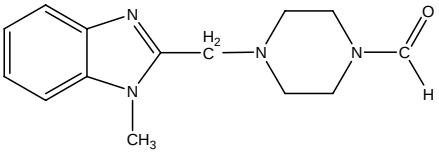
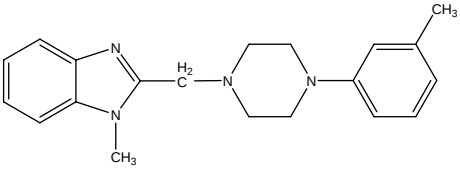
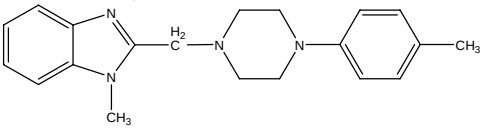
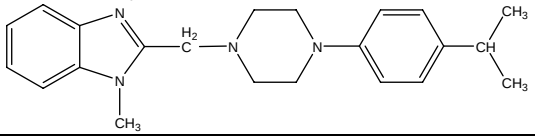
**Procedure**

Pick up 3-5 isolated colonies and suspend in 5ml of any suitable broth (tryptone soya broth). Incubate isolated broth for 3-5 hrs to get just visible turbidity. It should be comparable to opacity of 0.5 McFarland Nephelometeric standards. If less turbid, incubate further, if more turbid, dilute with sterile normal saline. Dip a sterile cotton swab in the broth; remove extra broth by rotating the swab against the wall of the tube. Swab Mueller-Hinton agar plate thoroughly by turning the plate. Leave the swab plate at room temperature for 3-5 minutes to dry the inoculum. Pick up individual disc or polydisc ring with flamed forceps and put on the swabbed medium with gentle press. Discs should be at least 18-24 mm apart from each other. Polydisc should be put at the center of the plate. Incubate the plates at $37^0$ C for minimum of 18 hrs. Measure the zone of inhibition and interpret the result

**Table 3: Antifungal activity of synthesized compounds against *Candida albican***

| Code | Compound | Compound | Structure | *Candida albicans* |
|---|---|---|---|---|
| $D_1$ | 2-[(4-methylpiperazin-1-yl) methyl]-1*H*-benzimidazole | Benz-4MeP |  | - |
| $D_2$ | 2-[(4-ethylpiperazin-1-yl) methyl]-1*H*-benzimidazole | Benz-4EtP |  | - |
| $D_3$ | 2-[(4-phenylpiperazin-1-yl)methyl]-1*H*-benzimidazole | Benz-4PhP |  | - |
| $D_4$ | 2-[(4-benzylpiperazin-1-yl) methyl]-1*H*-benzimidazole | Benz-4BenzP |  | - |

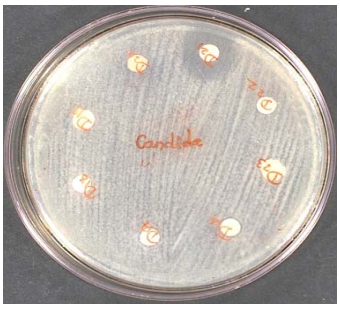
| | | | | |
|---|---|---|---|---|
| $D_5$ | 2-[(4-m-tolylpiperazin-1-yl) methyl]-1*H*-benzimidazole | Benz-4PhP$_1$ |  | - |
| $D_6$ | 4-[(1*H*-benzimidazol-2-yl) methyl] piperazine-1-carbaldehyde | Benz-4FrmP |  | - |
| $D_7$ | 2-[(4-isopropylpiperazin-1-yl) methyl]-1*H*-benzimidazole | Benz-4PhP$_2$ |  | - |
| $D_8$ | 2-[(4-p-tolylpiperazin-1-yl) methyl]-1*H*-benzimidazole | Benz-4PhP$_3$ |  | - |
| $D_9$ | 2-[{4-(2-methoxyphenyl) piperazin-1-yl} methyl]-1*H*-benzimidazole | Benz-4PhP$_4$ |  | - |
| $D_{10}$ | 2-[{4-(4-methoxyphenyl) piperazin-1-yl}methyl]-1*H*-benzimidazole | Benz-4PhP$_5$ |  | - |
| $D_{11}$ | N-[(1*H*-benzimidazol-2yl)methyl]benzenamine | Benz-2Anlne |  | - |
| $D_{12}$ | N-[(1*H*-benzimidazol-2-yl)methyl]-4-methoxybenzenamine | Benz-2Anlne$_1$ |  | - |
| $D_{13}$ | 2-(morpholinomethyl)-1*H*-benzimidazole | Benz-2Morp |  | - |
| $D_{14}$ | N-[(1*H*-benzimidazol-2-yl)methyl]-4-methylbenzenamine | Benz-2Anlne$_2$ |  | - |
| $D_{15}$ | N-[(1*H*-benzimidazol-2-yl)methyl]-4-chlorobenzenamine | Benz-2Anlne$_3$ |  | - |
| $D_{16}$ | N-[(1*H*-benzimidazol-2-yl)methyl]-3-chlorobenzenamine | Benz-2Anlne$_4$ |  | - |
| $D_{17}$ | 1-methyl-2-[(4-methylpiperazin-1-yl)methyl]-benzimidazole | BenzMe-4MeP |  | - |
| $D_{18}$ | 2-[(4-ethylpiperazin-1-yl) methyl]-1-methyl-benzimidazole | BenzMe-4EtP |  | - |

| | | | | |
|---|---|---|---|---|
| $D_{19}$ | 1-methyl-2-[(4-phenylpiperazin-1-yl)methyl]-benzimidazole | BenzMe-4PhP |  | - |
| $D_{20}$ | 2-[(4-benzylpiperazin-1-yl) methyl]-1-methyl-benzimidazole | BenzMe-4BenzP |  | - |
| $D_{21}$ | 4-[(1-methyl-1H-benzimidazol-2-yl)methyl]piperazine-1carbaldehyde | BenzMe-4FrmP |  | ++ |
| $D_{22}$ | 1-methyl-2-[(4-m-tolylpiperazin-1-yl)methyl]-benzimidazole | BenzMe-4PhP$_1$ |  | - |
| $D_{23}$ | 1-methyl-2-[(4-p-tolylpiperazin-1-yl)methyl]-benzimidazole | BenzMe-4PhP$_2$ |  | - |
| $D_{24}$ | 2-[(4-(4-isopropylphenyl) piperazin-1-yl)methyl]-1-methyl-benzimidazole | BenzMe-4PhP$_3$ |  | - |

++++ indicates highly active, +++ indicates moderately active, ++ indicates less active, - indicates inactive

**RESULT AND DISCUSSION**

The Benzimidazole derivative was obtained in pure form. The identity of the product was confirmed by M.P. and IR. The antifungal activity of synthesized compounds was taken by using Disk diffusion method against Candida albicans using Ketoconazole as reference standard. The compound D21 showed comparable antifungal activity to Ketoconazole.



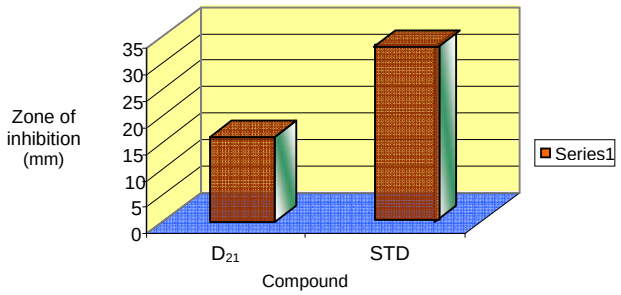



**Fig 1: Antifungal activity of synthesized D21 against Candida albicans**

**D21:** 4-[(1-methyl-1H-benzimidazol-2-yl) methyl] piperazine-1carbaldehyde. **STD:** Standard Ketoconazole

From experimental data it is concluded that alkyl group at 1-position may require for antifungal activity. The compound having aldehyde group on piperizine nitrogen (N4) has shown significant activity.

**ACKNOWLEDGEMENTS**

I take this privilege and pleasure to acknowledge the contributions of many individuals who have been inspirational and supportive throughout my work and endowed me with the most precious knowledge to see success in my endeavor.

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**REFERENCES**


1. The Merck Index, An Encyclopedia of chemicals, drugs and Biologicals, 13th edition, Merck Research Lab., 2001.
2. Harsch C, Sammes PG, Taylor JB, Ramsden CA. Comprehensive Medicinal Chemistry 1st edition, Oxford: Pergamon Press, 1990, 4:528.
3. Delgado JN, Remers WA. Introduction to Wilson and Giswold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, 10th edition, Philadelphia: Lippincott Williams and Wilkins, 1998.
4. Romeo G, Materia L, Manetti F, Cagnotto A, Mennini T, Nicoletti F, Botta M, Russo F, Minneman PK. J.Med.Chem. 2003; 46:2877-94.
5. Smith JL, Dell BJ. Capability of selective media to detect heat – injured Shigella flexneri, J. Food Protect. 1990;53:141.
6. Garison RG. Studies of the respiratory activity of Histoplasma Capsulatum, J. of infect.Dis. 1961; 108: 120-4.
7. Mc Culloug NB. Laboratory tests in the diagnosis of brucellosis, Amer. J. of puplic health. 1949; 39:866-9.
8. Jean F, Mac Faddin, Media for Isolation-Cultivation-Identification-Maintenance of Medicalacteria, Vol. 1; Baltimore, MD.: Williams &Wilkins, 1985.
9. Bauer et al. Am. J. CIin. Path., 1966; 45:493.
10. Ericsson and Sherris. Acta. Pathol. Microbiol, Scand. Sec. B. Suppl., 1971; 217.
11. Heeres J, Blackx LJJ, Mastman J, Van Custem J. J. Med. Chem. 1979; 22(8):1003.