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*Research Article*

# SYNTHESIS, CHARACTERIZATION AND ANTIFUNGAL ACTIVITY OF BENZIMIDAZOLE CONTAINING CHALCONE DERIVATIVES

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**ABSTRACT**

Derivatives of 2-acetylated benzimidazole chalcone's posses pharmacological action. A series of 2-substituted benzimidazole Chalcone derivatives were synthesized and were characterized by IR and $^{1}$H NMR spectroscopy. All these synthesized compounds were tested for their Antifungal activity against C.albicans (MTCC 227) in polar solvent DMSO. Among the screened compounds, SP3 containing bromine group as substituent exhibited most potent antifungal activity.

**Keywords:** 2- substituted benzimidazoleChalcone, docking, antifungal.

## INTRODUCTION

Fungal diseases are a worldwide public health issue. The illnesses caused by fungi can range from superficial (athlete's foot), to life threatening infections.However, starting from the 1960s, opportunistic fungi started causing more number of infections, especially in the immunocompromised host. More recently, newer and less common fungal agents are being increasingly associated with infection in immunosuppressed hosts[1].

The clinical relevance of fungal diseases has increased enormously in the second half of the twentieth century, mainly because of an increasing population of immunocompromised hosts, including individuals infected with HIV, transplant recipients and patients with cancer. Therefore, the study of fungi is a research priority. Because fungal pathogens are eukaryotes, and therefore share many of their biological processes with humans, many antifungal drugs can cause toxicity when used therapeutically. No standardized vaccines exist for preventing any of the human infections caused by fungi — a situation that is attributable to both the complexity of the pathogens and their sophisticated strategies for surviving in the host and evading immune responses. Although not unique among infectious agents, fungi have complex and unusual relationships with the vertebrate immune system, partly due to some prominent features. Among these are their ability to exist in different forms and to reversibly switch from one to the other during infection[2].

Substituted benzimidazole derivatives have found diverse therapeutic applications such as in antiulcer, antihypertensive, antiviral, antifungal and antihistaminics[3].The literature survey reports have been revealed that the 2-substituted 1H-benzimidazole compounds has reported to possess antibacterial , antifungal. The benzimidazolyl chalcones also reported to have potent antimicrobial properties. So we planned to merge the Chalcone nucleus with benzimidazole at 2nd position to exhibit some better biological activity[4].

## EXPERIMENTAL SECTION

### Synthesis

### Synthesis of Benzimidazole amine

### Synthesis of 1-(1H-benzeimidazol-2yl)methanamine

A solution of (2.7 g, 0.025 mole) of o-phenylenediamine and (2.813 g, 0.0375mole) of Glycine in (25ml) of 5.5N hydrochloric acid was refluxed for 7 minutes at 8 watt in a microwave till the reaction completed. The completion of the reaction was monitored by TLC. The solution was allowed to stand in the cold overnight. The solid crystal obtained was filtered out. It was recrystallized from ethanol with the aid of

decolourizing carbon. Product obtained as violet crystals.

**Actylation of 2-Aminomethylbenzimidazole**

**Synthesis of N-((1H-benzo[d]imidazol-2-yl)methyl)acetamide:** 1-(1H-benzeimidazol-2yl) methanamine (0.3 g) was added to 5 ml of acetic anhydride and 3 ml of pyridine. The solution was then refluxed for 1hr at 6 watt in microwave till the reaction completed. The completion of the reaction was monitored by TLC. Pyridine was removed by vacuum distillation. The solid crystal obtain were purified by column chromatography.

**Procedure for synthesis of Chalcones of 2-Acetylated Benzimidazole**

A solution of (1g, 0.005 mole) of N-((1H-benzo[d]imidazol-2-yl)methyl)acetamide in 30 ml ethanol and ( 0.005 mole) of aldehyde in presence of 50% potassium hydroxide was refluxed for 15min. at 3 watt in microwave apparatus till the reaction completed. The completion of the reaction was monitored by TLC. The excess ethanol was distilled off and the solution was allowed to cool. The solution was then poured on crushed ice and solution was then neutralized by using hydrochloric acid. The solid obtained was purified by column chromatography.

**MATERIAL AND METHODS**

The melting point of all the synthesized compounds was determined by using thermometer. The characterization of all these compounds was done by IR and NMR. The IR spectra were recorded on Shimadzu IR Affinity-1. Nuclear Magnetic Resonance (NMR) spectroscopy was done by recording the spectra 1HNMR on FT/NMR 400MHz analyzer. . All reactions were carried out on Catalyst Microwave Synthesizer (CATAR).

**Docking**

All molecular modeling studies were performed using the Molecular Design Suite (VLife MDS software package , version 4.4; from VLife Sciences, Pune, India). Molecular Docking carried out using dell PC with a Platinum IV processor and Windows 7 operating system.[5]

The crystal structure of Flavin-Adenine dinucleotide with PDB code 4HB9 was used for the docking studies. The protein structure was corrected for atom and bond types, hydrogen's were added.

Best docking poses were selected and compared with reference to TERBINAFINE AND NAFTIFINE.

**Antifungal Activity**

Fungii used for Antifungal screening of synthesized compounds is C. albicans (MTCC 227).

Antifungal activity of all the synthesized Benzimidazole derivatives was screened against Candida albicans by tube dilution and cup plate method (agar cup diffusion method) at Microcare laboratory surat. Greseofulvin was used as standard drug.

**RESULTS AND DISCUSSION**

The compounds synthesized (SP1 to SP4) were analysized by their IR and NMR. The spectral data of all the compounds are given below:

**SP1: FTIR (KBr, cm-1)**

1249.93 (C-N stretch), 1494.90 (C=N stretch), 3026.44 and 2925.17 (N-H 1$^{o}$ amine), 970.24 (C-H alkene), 1600.02 (C=C aromatic), 749.38 (C-H bending), 1679.11 (C=O stretch).

**SP2: FTIR (KBr, cm-1)**

1259.57 (C-N stretch), 1568.19 (C=N stretch), 3069.84 and 2995.58 (N-H 1$^{o}$ amine), 941.30 (C-H alkene), 1684.89 (C=C aromatic), 749.38 (C-H bending), 1770.73 (C=O stretch), 550.70 (C-Br stretch).

**SP3: FTIR (KBr, cm-1)**

1244.14 (C-N stretch), 1587.48 (C=N stretch), 2923.25 and 2852.84 (N-H 1$^{o}$ amine), 849.68 (C-H alkene), 1679.11 (C=C aromatic), 757.09 (C-H bending), 1770.73 (C=O stretch), 546.84 (C-Br stretch).

**$^{1}$H NMR (DMSO δ ppm)**

7.87 (t,7H), 7.60 (m, 3H), 4.89 (d, 2H), 2.65 (s, 1H).

**SP4: FTIR (KBr, cm-1)**

1262.46 (C-N stretch), 1587.48 (C=N stretch), 3442.12 and 2980.15 (N-H 1$^{o}$ amine), 948.05 (C-H alkene), 1587.48 (C=C aromatic), 774.45 (C-H bending), 1680.07 (C=O stretch), 744.56 (C-Cl stretch), 1046.43 (C-F stretch).

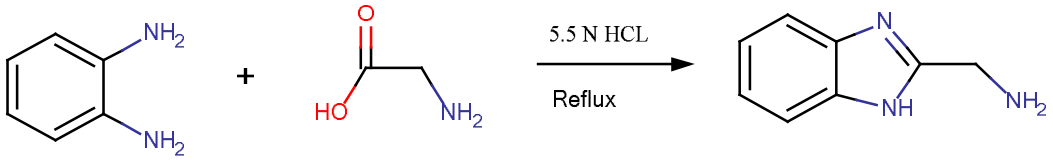
The antifungal activity was measured by the average diameter of the inhibition zones, expressed in mm. Table. 2, 3 and 4 shows docking and antifungal activity results of the synthesized 2-substitued benzimidazoleChalcone derivatives.

Docking results (fig. 6, 7) shows the binding affinity of the drug to the receptor. SP4 and SP3 have greatest affinity among all the synthesized products Table 2.

**CONCLUSION**

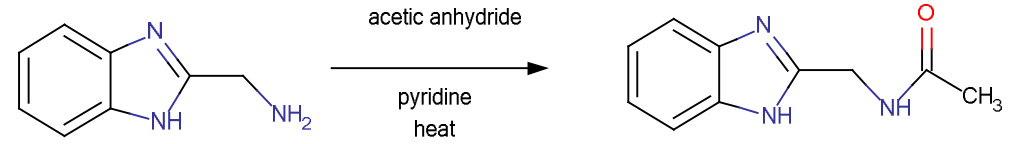
The docking and antifungal screening showed that compound **SP3** exhibited best receptor binding (as indicated by best docking score) as well as comparable antifungal activity.

**AKNOWLEDGEMENT**
I would like to thank my parents B.D. Rajput and M.B.Rajput for their support and well wishes, I would also like to thank my guide Mrs.Shraddha for her help, my all friends and Dr.L.H.Hiranandanicollege for providing facility.



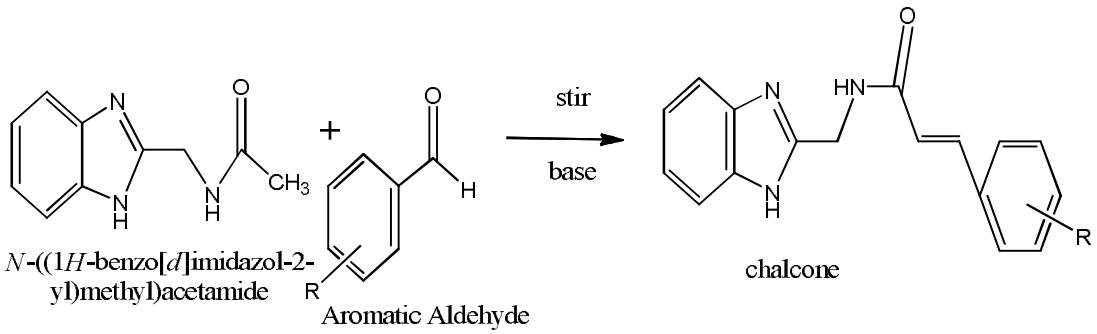

benzene-1,2-diamine Glycine 1-(1H-benzeimidazol-2yl)methanamine

**Step 1: Synthesis of 2-benzimidazole[6]**




1-(1H-benzeimidazol-2yl)methanamine N-((1H-benzo[d]imidazol-2-yl)methyl)acetamide

**Step 2: Acetylation of 2-aminomethylbenzimidazole[7]**




*N*-((1*H*-benzo[*d*]imidazol-2-yl)methyl)acetamide Aromatic Aldehyde chalcone

**Step 3: Synthesis of chalcones[8]**

**Fig. 1: Synthesis scheme of 2-acetylated benzimidazolechalcone's derivatives**

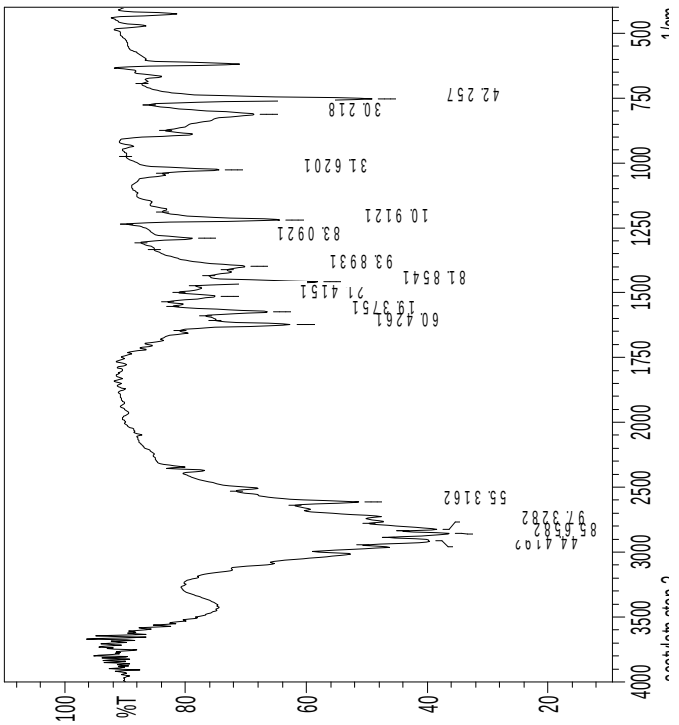



**Fig. 2: IR Spectra of N-((1H-benzo[d]imidazol-2-yl) methyl)acetamide**

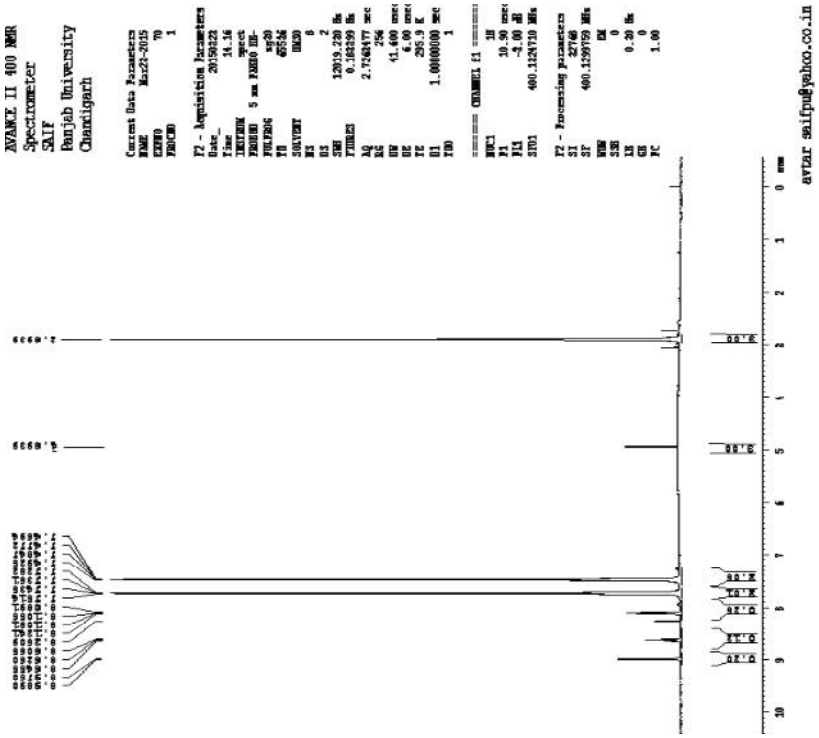



**Fig. 3: $^{1}$H NMR Spectra of N-((1H-benzo[d]imidazol-2-yl)methyl)acetamide**

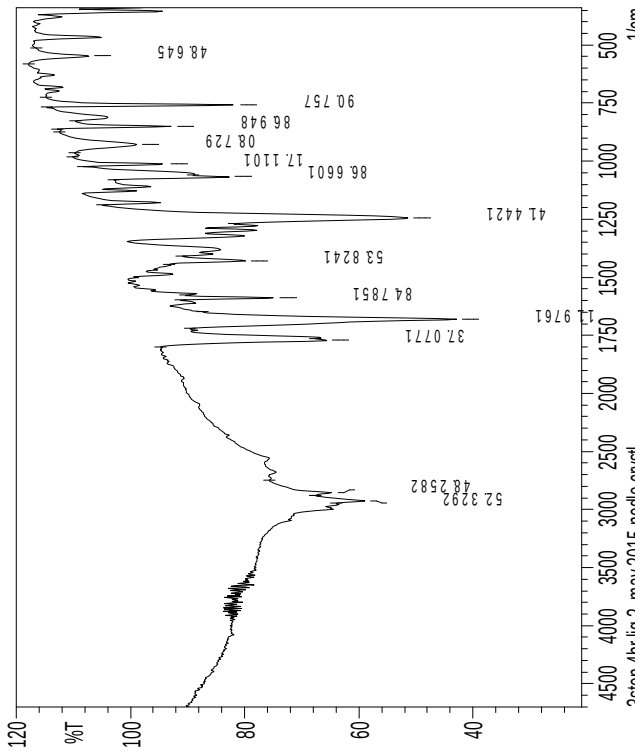



**Fig. 4: IR Spectra of SP3**

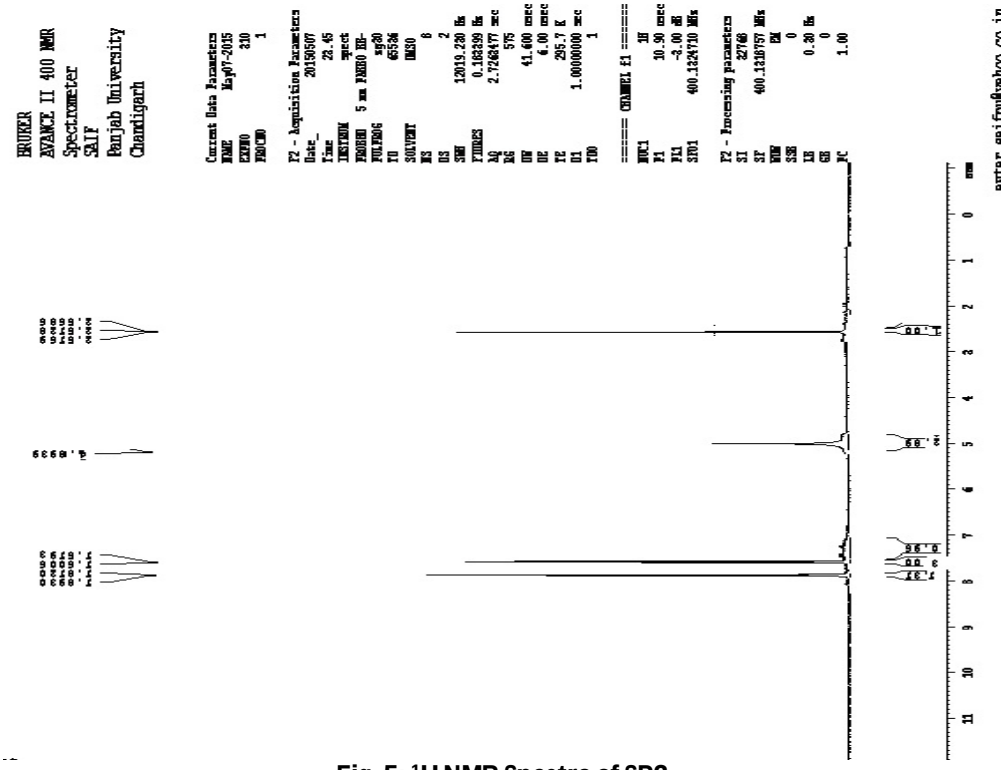



**Fig. 5: $^1$H NMR Spectra of SP3**

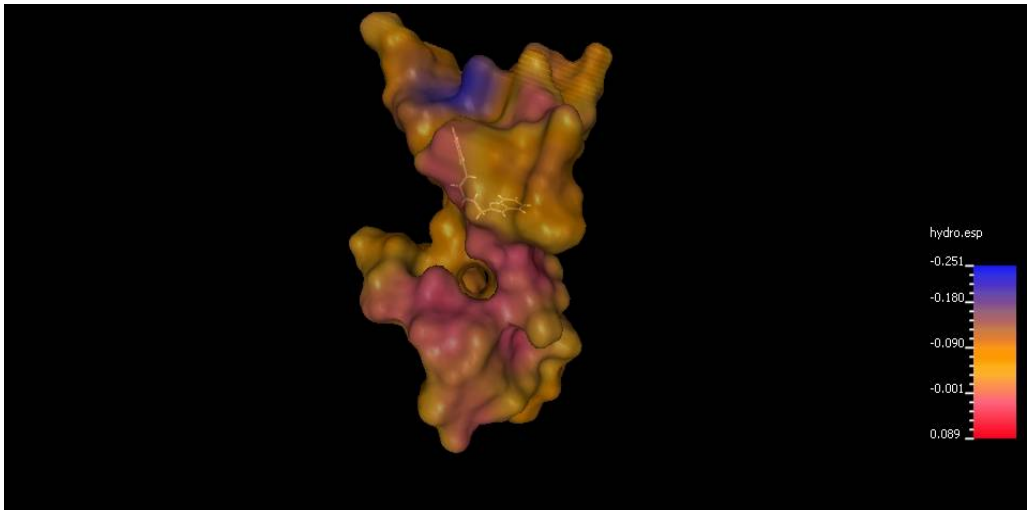



**Fig. 6: Compound SP4 Drug-cavity image**

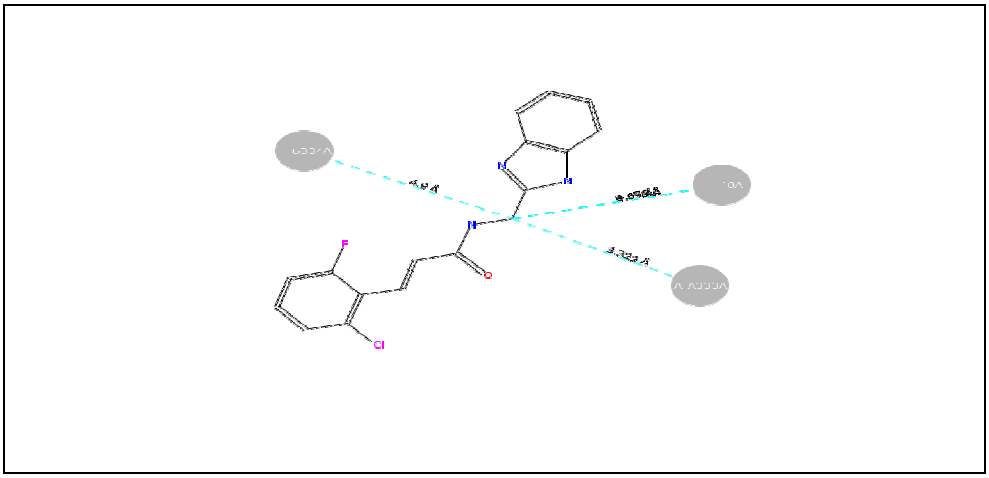



**Fig. 7: Compound SP4 Molecular interaction**

**Table 1: Characterization of products obtain from step 3**

| sr. No. | Compound Code | R | Time Required | % yield | M.P. | Rf |
|---|---|---|---|---|---|---|
| 1 | SP1 | H | 15 min | 16 | $90^0$ -$120^0$ | 0.33 |
| 2 | SP2 | 3-Br | 40 min | 18 | $140^0$-$142^0$ | 0.38 |
| 3 | SP3 | 4-Br | 30 min | 13 | $133^0$-$139^0$ | 0.44 |
| 4 | SP4 | 2-Cl-6- F | 45 min | 17 | $125^0$-$130^0$ | 0.56 |

**Table 2: Docking Score**

| Sr. No. | Compounds | Docking Score |
|---|---|---|
| 1 | Naftifine | 130.37 |
| 2 | Terbinafine | 137.14 |
| 3 | SP1 | 133.44 |
| 4 | SP2 | 97.60 |
| 5 | SP3 | 145.05 |
| 6 | SP4 | 147.14 |

**Table 3: MIC for Antifungal Activity**

| Sr. No. | Compound Code | Minimal Fungicidal Con. (microgram/ml) C.albicans (MTCC 227) |
|---|---|---|
| 1 | SP1 | 250 |
| 2 | SP2 | 125 |
| 3 | SP3 | 100 |
| 4 | SP4 | 500 |
| 5 | Griseofulvin | 500 |

**Table 4: Antifungal Activity of compounds**

| Antifungal Activity [Zone of Inhibition] | | | | | | |
|---|---|---|---|---|---|---|
| Sr. No. | Compound Code | C.ALBICANS MTCC 227 | | | | |
| | | 5µg/ml | 25µg/ml | 50µg/ml | 100µg/ml | 250µg/ml |
| 1 | SP1 | - | 14 | 16 | 19 | 22 |
| 2 | SP2 | - | 15 | 17 | 18 | 20 |
| 3 | SP3 | - | 15 | 18 | 19 | 21 |
| 4 | SP4 | - | 14 | 16 | 18 | 22 |
| 5 | Griseofulvin | 19 | 23 | 25 | 25 | 28 |

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