



## SYNTHESIS OF NOVEL BENZIMIDAZOLE DERIVATIVES AS POTENT ANTIMICROBIAL AGENT.

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### ABSTRACT

The reaction of o-phenylenediamine with p-amino benzoic acid yielded the 4-(1H-benzo[d]imidazol-2yl) benzenamide (1). 4-(1H-benzo[d]imidazol-2yl) benzenamide (1) was condensed with different aromatic aldehydes offered Schiff bases (2). The Schiff bases on cyclization with chloro acetyl chloride in presence of triethylamine as catalyst furnished 1-(4-(1H-benzo[d]imidazol-2-yl) phenyl)-3-chloro-4-phenyl azetidin-2-one (3a). The compounds were synthesized in good yield and the chemical structures of the compounds were elucidated by their TLC, IR, <sup>1</sup>HNMR, and elemental analysis. Their antimicrobial activity against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and Salmonella typhosa and antifungal activity against Aspergillus niger, Candida albicans were investigated. The results showed that all of the compounds have exhibited antimicrobial activity.

**Key Words:** - Azetidin-2-one, Benzimidazole, Antimicrobial, Antifungal.

### INTRODUCTION

The development of drug resistance to existing antimicrobial treatment has lent to research for novel more effective antimicrobial and antifungal agents. In view of these data, we aimed the synthesis of new benzimidazole and azetidin-2-one derivatives as novel antimicrobial agents. Literature survey shows that benzimidazole derivatives play a vital role in biological fields such as antidiabetic<sup>1</sup>, antimicrobial<sup>2</sup>, antiviral<sup>3</sup>, antispasmodic<sup>4</sup>, and anticancer<sup>5</sup> activities. Schiff base has good antimicrobial<sup>6</sup>, antifungal<sup>7</sup> activity and it can be prepared by the acid catalysed reaction of aldehyde or ketone and amines<sup>8</sup>. Further azetidin-2-one derivatives have been exhibited to possess biological properties like antimicrobial<sup>9</sup>, antifungal<sup>10</sup>, anti-inflammatory<sup>11</sup>, antibiotic<sup>12</sup> activities. The compound o-phenylenediamine was treated with p-amino benzoic acid to yield 4-(1H-benzo[d]imidazol-2yl) benzenamide (1) Reaction with different aromatic aldehydes to yield Schiff base 4-(1H-benzo [d] imidazol-2-yl)-N-benzylidenebenzenamine (2). The Schiff bases with chloroacetyl chloride in the presence of triethylamine using dry benzene as solvent yielded compounds (3a-3l). All the synthesized compounds were characterised by TLC, IR, <sup>1</sup>HNMR, elemental analysis and physical data.

### EXPERIMENTAL

The melting points were recorded on electrothermal apparatus and are uncorrected. IR spectra were recorded in KBr on a perkin-Elmer model-983. <sup>1</sup>HNMR spectrum recorded on Varian Mercury 300MHz

instrument using CDCl<sub>3</sub>, DMSO-d<sub>6</sub> as solvent (chemical shift in  $\delta$  ppm), using TMS as internal standard. Elemental analysis was performed on a Heracus CHN analyzer.

**Synthesis of 4-(1H-benzo[d]imidazol-2-yl) benzenamide (1)<sup>13</sup>:**

A mixture of o-phenylenediamine (0.1mol) and p-amino benzoic acid (0.1mol) was heated on a water bath for 2 hr. it was cooled and 10% sodium hydroxide solution was added slowly with constant stirring until just alkaline. The crude product was filtered, washed with ice-cold water, decolorized and washed repeatedly and dried. The product was then recrystallized from ethanol. Yield: 70%; m.p. 108°C; IR (KBr, cm<sup>-1</sup>): 3170(N-H str), 1685(C=N str), 1585(aromatic str); Anal. Calc. For C<sub>13</sub>H<sub>11</sub>N<sub>3</sub>: Calculated (Found): C 74.62 (74.90), H 5.30 (5.25), N 20.08 (20.00).

**Synthesis of 4-(1H-benzo[d]imidazol-2-yl)-N-benzylidenebenzenamine (2):**

To the 4-(1H-benzo[d]imidazol-2-yl) benzenamide (0.01mol) in 30ml of ethanol containing few drops of glacial acetic acid, benzaldehyde (0.01mol) was added in a round bottom flask and the mixture was refluxed for 3hr. It was then cooled at room temperature, poured into crushed ice, filtered, washed, dried and recrystallized from ethanol to yield 4-(1H-benzo[d]imidazol-2-yl)-N-benzylidenebenzenamine (2a). Other Schiff bases were obtained in similar manner. Yield: 68%; m.p. 140-142 °C.

**Synthesis of 1-(4-(1H-benzo[d]imidazol-2-yl) phenyl)-3-chloro-4-phenylazetididin-2-one (3a):**

To a stirred solution of 4-(1H-benzo[d]imidazol-2-yl)-N-benzylidene benzene amine (0.01mole) in 25 ml 1,4 dioxane; triethylamine (0.01 mole, 1 ml) and chloro- acetyl chloride (0.01 mole, 2 ml) were added slowly drop wise with stirring at 0-20 °C. The reaction mixture was kept at room temperature for 30 minutes. Then reflux for 5 hrs. The excess of solvent distilled off and the residue was poured into ice-cold water. The solid separated was filtered and recrystallised with DMSO. Other azetididin-2-ones were obtained in similar manner. Yield: 70%; m.p: 164-166°C ; IR (KBr, cm<sup>-1</sup>): 3170(N-H str), 1685(C=N str), 1674 (C=O str  $\beta$ -lactum), 738 (C-Cl bending); <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>,  $\delta$  ppm): 7.21-7.53 (m, 4H, benzimidazole); 7.02-7.20 (m, 5H, aromatic); 5.21 (d, 1H, C-C<sub>6</sub>H<sub>5</sub> of azetididin-2-one); 5.51 (d, 1H, C-Cl of azetididin-2-one); 12.5 (s, 1H, N-H of benzimidazole); Anal. Calc. For C<sub>22</sub>H<sub>16</sub>ClN<sub>3</sub>O: Calculated (Found): C, 70.68 (70.72); H, 4.31 (4.28); N, 11.24 (11.19).

**Characterization data of compounds:**

1-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-3-chloro-4-(4-hydroxyphenyl)azetididin-2-one (3b):- Yield: 65%; m.p: 176-178°C ; IR (KBr, cm<sup>-1</sup>): 3184(N-H str), 1685(C=N str), 1674 (C=O str  $\beta$ -lactum), 738 (C-Cl bending), 2995 (O-H str); <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>,  $\delta$  ppm): 7.22-7.60 (m, 4H, benzimidazole); 7.01-7.12 (m, 4H, aromatic); 5.16 (d, 1H, C-C<sub>6</sub>H<sub>5</sub> of azetididin-2-one); 5.44 (d, 1H, C-Cl of azetididin-2-one); 5.0 (s, 1H, OH of aromatic); 12.15 (s, 1H, N-H of benzimidazole); Anal. Calc. For C<sub>22</sub>H<sub>16</sub>ClN<sub>3</sub>O<sub>2</sub>: Calculated (Found): C, 67.78 (67.80); H, 4.14 (4.10); N, 10.78 (10.80).

1-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-3-chloro-4-(3-nitrophenyl)azetididin-2-one (3d): Yield:60%; m.p: 164-166°C ; IR (KBr, cm<sup>-1</sup>): 3107(N-H str), 1690(C=N str), 1673 (C=O str  $\beta$ -lactum), 787 (C-Cl bending), 1578 (N=O str); <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>,  $\delta$  ppm): 7.26-7.70 (m, 4H, benzimidazole); 7.47-8.05 (m, 4H, aromatic); 5.20 (d, 1H, C-C<sub>6</sub>H<sub>5</sub> of azetididin-2-one); 5.40 (d, 1H, C-Cl of azetididin-2-one); 12.15 (s, 1H, N-H of benzimidazole); Anal. Calc. For C<sub>22</sub>H<sub>15</sub>ClN<sub>4</sub>O<sub>3</sub>: Calculated (Found): C, 63.09 (63.13); H, 3.61 (3.55); N, 13.38 (13.31).

1-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-3-chloro-4-(2-chlorophenyl) azetididin-2-one (3f):Yield: 65%; m.p: 160-162°C ; IR (KBr, cm<sup>-1</sup>): 3107(N-H str), 1690(C=N str), 1673 (C=O str  $\beta$ -lactum), 735 (C-Cl bending); <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>,  $\delta$  ppm): 7.20-7.50 (m, 4H, benzimidazole); 7.06-7.22 (m, 4H, aromatic); 5.18 (d, 1H, C-C<sub>6</sub>H<sub>5</sub> of azetididin-2-one); 5.45 (d, 1H, C-Cl of azetididin-2-one); 12.05 (s, 1H, N-H of benzimidazole); Anal. Calc. For C<sub>22</sub>H<sub>15</sub>Cl<sub>2</sub>N<sub>3</sub>O: Calculated (Found): C, 64.72 (64.75); H, 3.70 (3.68); N, 10.29 (10.25).

1-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-3-chloro-4-(3-methoxyphenyl)azetididin-2-one (3g): Yield: 60%; m.p: 168-170°C ; IR (KBr, cm<sup>-1</sup>): 3107(N-H str), 1690(C=N str), 1673 (C=O str  $\beta$ -lactum), 785 (C-Cl

bending), 1241 (Ph-O-C str); <sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ ppm): 7.28-7.70 (m, 4H, benzimidazole); 7.01-7.10 (m, 4H, aromatic); 5.20 (d, 1H, C-C<sub>6</sub>H<sub>5</sub> of azetidin-2-one); 5.44 (d, 1H, C-Cl of azetidin-2-one); 3.75 (s, 1H, OCH<sub>3</sub> of aromatic); 12.10 (s, 1H, N-H of benzimidazole); Anal. Calc. For C<sub>23</sub>H<sub>18</sub>ClN<sub>3</sub>O<sub>2</sub>: Calculated (Found): C, 68.40 (68.48); H, 4.49 (4.51); N, 10.40 (10.35).

**1-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-3-chloro-4-(3,4,5-trimethoxyphenyl):**

azetidin-2-one (3h):- Yield: 60%; m.p: 170-172<sup>o</sup>C ; IR (KBr, cm<sup>-1</sup>): 3107(N-H str), 1690(C=N str), 1673 (C=O str β-lactum), 735 (C-Cl bending), 1235 (Ph-O-C str); <sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ ppm): 7.30-7.70 (m, 4H, benzimidazole); 7.01-7.10 (m, 4H, aromatic); 5.22 (d, 1H, C-C<sub>6</sub>H<sub>5</sub> of azetidin-2-one); 5.44 (d, 1H, C-Cl of azetidin-2-one); 3.75 (s, 1H, OCH<sub>3</sub> of aromatic); 12.10 (s, 1H, N-H of benzimidazole); Anal. Calc. For C<sub>25</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>4</sub>: Calculated (Found): C, 64.72 (64.78); H, 4.78 (4.74); N, 9.06 (9.10).

**1-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-3-chloro-4-(4-(dimethylamino)phenyl) azetidin-2-one (3i):**  
Yield 65%; m.p: 158-162<sup>o</sup>C ; IR (KBr, cm<sup>-1</sup>): 3184(N-H str), 1684(C=N str), 1672 (C=O str β-lactum), 745 (C-Cl bending), 1365 (C-N str); <sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ ppm): 7.26-7.70 (m, 4H, benzimidazole); 6.94-7.55 (m, 4H, aromatic); 5.20 (d, 1H, C-C<sub>6</sub>H<sub>5</sub> of azetidin-2-one); 5.40 (d, 1H, C-Cl of azetidin-2-one); 12.90 (s, 1H, N-H of benzimidazole); 2.85 (s, 3H, CH<sub>3</sub>); Anal. Calc. For C<sub>24</sub>H<sub>21</sub>ClN<sub>4</sub>O: Calculated (Found): C, 69.14 (69.18); H, 5.08 (5.04); N, 13.44 (13.40).

**1-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-3-chloro-4-(4-bromophenyl)azetidin-2-one:**

(3k):- Yield: 55%; m.p: 166-168<sup>o</sup>C ; IR (KBr, cm<sup>-1</sup>): 3198(N-H str), 1689(C=N str), 1672(C=O str β-lactum), 739(C-Cl bending), 554(C-Br bending); <sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ ppm): 7.26-7.70 (m, 4H, benzimidazole); 7.01-7.38 (m, 4H, aromatic); 5.16 (d, 1H, C-C<sub>6</sub>H<sub>5</sub> of azetidin-2-one); 5.44 (d, 1H, C-Cl of azetidin-2-one); 12.5 (s, 1H, N-H of benzimidazole); Anal. Calc. For C<sub>22</sub>H<sub>15</sub>ClBrN<sub>3</sub>O: Calculated (Found): C, 58.36 (58.40); H, 3.34 (3.30); N, 9.28 (9.24).

**1-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-3-chloro-4-(4-fluorophenyl)azetidin-2-one:**

(3l):- Yield: 58%; m.p: 152-154<sup>o</sup>C ; IR (KBr, cm<sup>-1</sup>): 3102(N-H str), 1684(C=N str), 1673 (C=O str β-lactum), 736 (C-Cl bending), 1095 (C-F str); <sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ ppm): 7.26-7.70 (m, 4H, benzimidazole); 7.10-7.53 (m, 4H, aromatic); 5.18 (d, 1H, C-C<sub>6</sub>H<sub>5</sub> of azetidin-2-one); 5.44 (d, 1H, C-Cl of azetidin-2-one); 12.15 (s, 1H, N-H of benzimidazole); Anal. Calc. For C<sub>22</sub>H<sub>15</sub>ClFN<sub>3</sub>O: Calculated (Found): C, 67.44 (67.50); H, 3.86 (3.84); N, 10.72 (10.68).

**Antimicrobial Activity:**

The synthesised compounds (3a-3l) were screened for their in vitro antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhosa* and antifungal activity against *Aspergillus niger*, *Candida albicans* by measuring the zone of inhibition in mm. The antimicrobial activity was performed by cup plate method<sup>14-15</sup> at concentration 50 μg/mL and reported in Table-1 for antimicrobial and antifungal activities. Nutrient agar was employed as culture medium and DMSO was used as solvent control for antimicrobial activity. Penicillin and griseofulvin were used as standard for antibacterial and antifungal activities respectively.

**RESULT AND DISCUSSION**

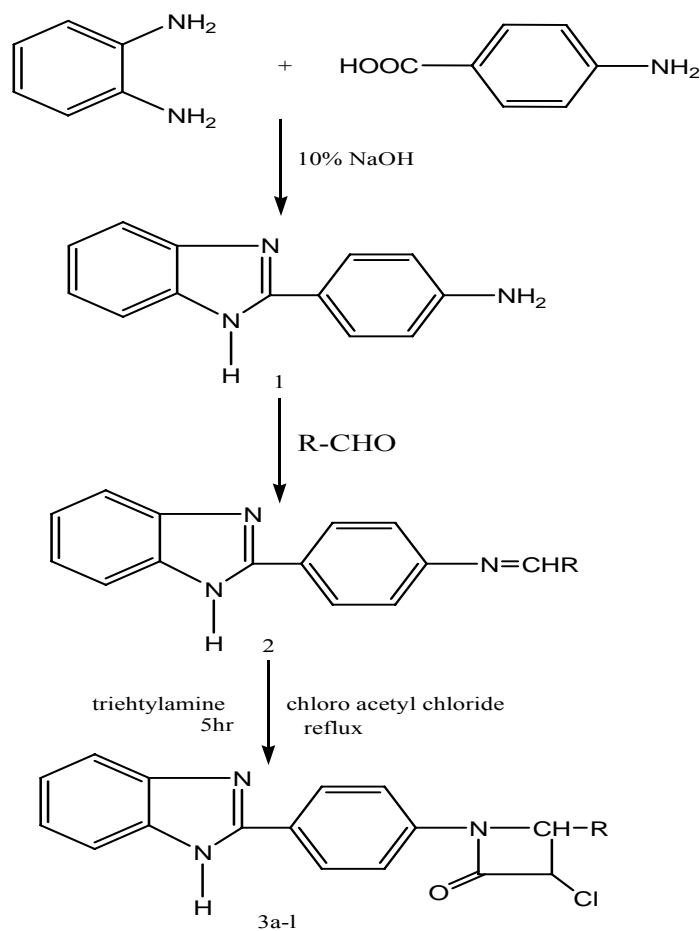
From the antimicrobial screening it was observed that all the compounds exhibited activity against all the organisms employed. Looking at the structure activity relation ship, marked inhibition in bacteria was observed in the compounds bearing R = C<sub>6</sub>H<sub>5</sub>, 4-OH C<sub>6</sub>H<sub>4</sub>, 2-OH C<sub>6</sub>H<sub>4</sub>, 4-OCH<sub>3</sub> C<sub>6</sub>H<sub>4</sub>, 3,4,5-(OCH<sub>3</sub>)<sub>3</sub> C<sub>6</sub>H<sub>2</sub>. (3a,3b,3c,3g,3h) substituents where as compound (3f,3j,3k,3l) showed moderate to good activity and compound (3d,3e,3i) showed least activity.

Fungicidal screening data also revealed that compounds bearing R =4-OH C<sub>6</sub>H<sub>4</sub>, 2-OH C<sub>6</sub>H<sub>4</sub>, 4-(CH<sub>3</sub>)<sub>2</sub>N C<sub>6</sub>H<sub>4</sub>, 4-Br C<sub>6</sub>H<sub>4</sub>. (3b,3c,3i,3k) imparted maximum activity to the compounds, where as compounds (3d,3f,3l) showed moderate to good activity and compounds (3a,3e,3g,3h,3j) showed least activity.

As we consider all results obtained from antibacterial and antifungal tests together we can say that entire compounds tested are active towards bacteria and fungi.

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Scheme-1

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**Table-1:** Antimicrobial and Antifungal Data.

Comps.	R	Antibacterial <sup>a</sup>				Antifungal <sup>a</sup>	
		S.a.	P.a.	E.c.	S.t.	A.n.	C.a.
3a	C <sub>6</sub> H <sub>5</sub> -	13	14	12	10	06	06
3b	4-OH C <sub>6</sub> H <sub>4</sub> -	12	11	10	09	14	10
3c	2-OH C <sub>6</sub> H <sub>4</sub> -	13	12	14	10	18	11
3d	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -	07	08	09	07	10	12
3e	2- NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -	09	07	10	09	09	07
3f	4-Cl C <sub>6</sub> H <sub>4</sub> -	08	11	09	11	11	09
3g	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> -	14	14	10	13	08	06
3h	3,4,5-(OCH <sub>3</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> -	10	12	12	14	07	05
3i	4-(CH <sub>3</sub> ) <sub>2</sub> N C <sub>6</sub> H <sub>4</sub> -	11	09	08	07	14	11
3j	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> -	12	10	14	11	06	09
3k	4-Br C <sub>6</sub> H <sub>4</sub> -	12	09	07	08	15	12
3l	4-F C <sub>6</sub> H <sub>4</sub> -	10	07	08	09	12	08
Penicillin		16	18	16	19	--	--
Griesofulvin		--	--	--	--	20	15

<sup>a</sup> zone of inhibition is measured in mm.

*Staphylococcus aureus* (S.a), *Escherichia coli* (E.c), *Pseudomonas aeruginosa* (P.a), *Salmonella typhosa* (S.t), *Aspergillus niger* (A.n), *Candida albicans* (C.a).

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