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*RESEARCH ARTICLE*

# SYNTHESIS OF A FEW DERIVATIVES OF BAYLIS-HILLMAN ADDUCTS: BIO-EVALUATION AGAINST ASPERGILLUS NIGER AND CANDIDAALBICANS

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## *Abstract*

A report of the synthesis of a few adducts of Baylis-Hillman adducts (BHA) using green protocol is established. The bioactivities of the adducts were evaluated against *Aspergillus nigar* and *Candida albicans*, two fungal pathogens.A few synthesized compounds were tested and found to have moderate to good anti-fungal activities against these two pathogens.



## Introduction:-

In recent years, fungal diseases have increased, particularly in patients with impaired immunity.[1] The growing number of cases of fungi involved is particularly of the candida species, as the fourth most common isolate in nosocomial bloodstream infections in some developed countries.[2] On the other hand, invasive candidiasis is also a problem for ill patients, particularly for those in the intensive care unit.[3a] Due to the increase in clinically important fungal infections caused by non-dermatophyte agents and the availability of a small number of antifungal agents, searching for new, more effective, and less toxic drug molecules is necessary these days. There is considerable alarm amongst the medical profession regarding fungal disease. Dermatophyte infections such as tinea pedis and candidiasis, are widespread throughout the world. Few other fungal diseases are far darker in reputation and significance. Pathogens such as *Candida albicans*, *Cryptococcus neoformans*, *Pneumocystis carinii*and *Aspergillus fumigates*are the cause of considerable morbidity and mortality.[3b]Candida albicans, the most common human pathogenic fungus, causes a persistent lethal infection in the intestine of the microscopic nematode *Caenorhabditiselegans*.

The literature reviewed that some of Baylis-Hillman adducts and their derivatives have properties like anti-inflammatory, anti-malarial, hypolipidemic activity, antitumoral, anti-microbial, and antifungal activity, and have found widespread application in medicinal chemistry.[4-9] Many researchers working on biological studies of such compounds, where one report published by Bhat and his group of research workers focused on the antifungal activity of some Baylis-Hillman adducts.[10] In their study it was observed that the introduction of different groups on the linked aromatic ring led to variation in biological activity.

Baylis-Hillman chemistry has been given immense interest from the time of 70's after its discovery.[11,12] The Development of new methodologies as well as the transformation of Baylis-Hillman adduct to many more biologically potent molecules are now paid more interest. Studies revealed that BH moiety has potent antimicrobial activity, antimalarial activity, etc.[13,14,15] Report on antimalarial activity was found for BH adducts containing particularly BH adducts synthesized from aryl, heteroaryl aldehydes, and acrylonitrile compounds.[16] Therefore studies revealed that the presence of BH moiety plays a significant role in their bioactivity.

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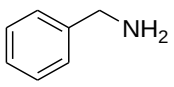
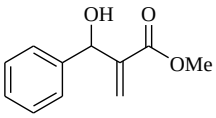
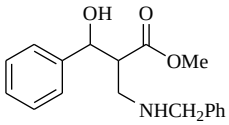
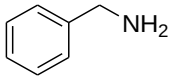
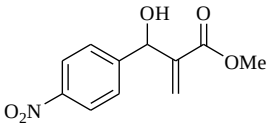
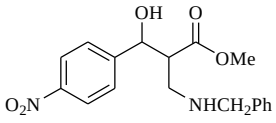
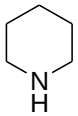
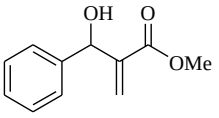
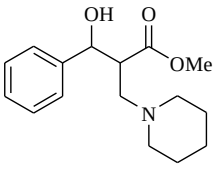
Inspired by the reports available in the literature, our objective of this study was to prepare some derivatives starting from the Baylis-Hillman adduct and to find out their activities against two fungal agents *Candida albicans* and *Aspergilliousnigar*. The details of the synthesis and bio-evaluation are discussed in this present study.

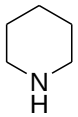
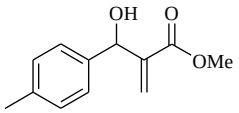
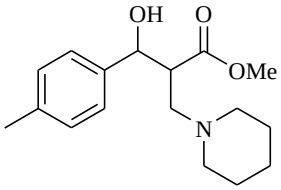
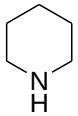
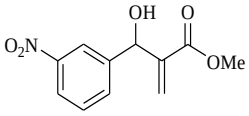
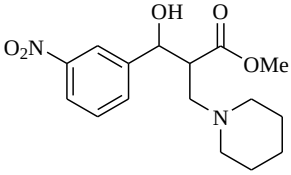
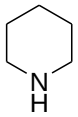
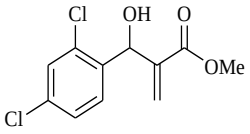
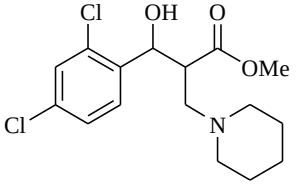
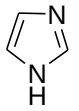
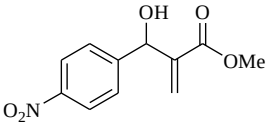
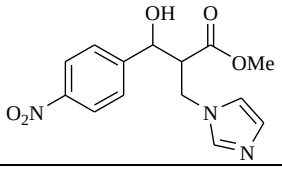
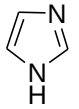
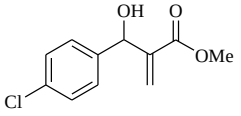
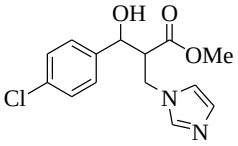
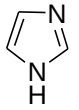
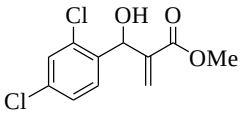
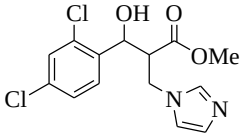
## Results and Discussion:-

S. V. Bhat and co-workers reported antifungal activity of a few Baylis-Hillman adducts that compounds containing nitro and halogen substituents on the aromatic ring were more active compounds than other unsubstituted Baylis-Hillman adducts.[10] Therefore we decided to synthesize a few Baylis-Hillman adducts (BHA) and their derivatives, of which some adducts contained nitro and halogen groups connected to the aromatic ring. Also, literature explored that aromatic Baylis-Hillman adducts are more reactive to their aliphatic counterpart.[17] Therefore we limited our study to only those compounds which are aromatic. The fungal zones of inhibition values (mm) are summarized in Table 2. S. V. Bhat and co-workers already established that Baylis-Hillman adducts which contain nitro- and halogen groups as substituents connected to the aromatic ring are much more active than the others towards *Aspergillus niger* and *Candida albicans*. In Table 2 the activity screened for nine numbers of Baylis-Hillman adducts were listed. Further, it was observed that the incorporation of Cl-, $NO_2$-, and $CH_3$- in the aromatic nucleus of BHA enhanced the activity (entries 2, 4, 5, 6, 7, 8, 9). Compounds containing heterocycles like piperidine, imidazole, and $PhNH_2$- group displayed comparable antifungal activity against *A. nigar* and *C. albicans* (entries 3, 4, 5, 6, 7, 8, 9). It was also observed that with increasing concentration, the zone of inhibition increased slightly.

Owing to the solubility of the amine in water, all the reactions were carried out in water extract of the ash of the banana catalyst, and a small amount of methanol was added to dissolve undissolved substrates left if any, one of our earlier established work.[18]All reactions performed, were clean with up to 95% yield in very short duration. Reactions were performed in a 1:1 molar ratio of the substrates in 5:2 (mL) ratio of WEABP and MeOH. In the previous report, we observed that neat WEABP is more effective and the rate enhancement using WEABP is probably due to water forming hydrogen bonds with the oxygen atom of the carbonyl group of *α,β*-unsaturated carbonyl compound thereby increasing the electrophilicity of *β*-carbon, where the nucleophilic amine attacks. On the other hand, water enhances the nucleophilicity of the N-atom of amine with its oxygen atom. Thus, water activates both the conjugated alkene as well as the amine and thereby greatly facilitates the addition. Besides that, the main basic component $CO_3^{2-}$ present in the water extract also helps in accelerating the reaction more.[18]

**Table I:-** Aza-Michael derivatives of Baylis-Hillman adducts.

| Entry | Amines (A) | *α,β*-unsaturated compounds (B) | Product [a] | Time (min) | Yield[b,c] (%) | Ref. |
|---|---|---|---|---|---|---|
| 1 |  |  |  | 15 | 90 | 18 |
| 2 |  |  |  | 10 | 92 | 18 |
| 3 |  |  |  | 15 | 87 | 18 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 4 |  |  |  | 12 | 90 | 18 |
| 5 |  |  |  | 15 | 89 | 18 |
| 6 |  |  |  | 14 | 90 | 18 |
| 7 |  |  |  | 25 | 89 | 18 |
| 8 |  |  |  | 35 | 88 | 18 |
| 9 |  |  |  | 45 | 89 | 18 |

[a] Amixture of benzyl amine (0.107 g, 1.0 mmol) and Baylis-Hillman adduct (BH1) (0.299 g, 1 mmol) was added in 5 mL 20 weight% of WEABP and 2 mL methanol at room temperature and stirred. The progress of the reaction was monitored by using TLC, after completion of the reaction, the solid crude product was isolated from water by filtration. All the products were characterized by NMR, IR, mass spectrometry, and CHN analysis.
[b] Isolated yields.

Spectral data of all the products are given below.

**(Benzylaminomethyl)-3-hydroxy-3-phenylpropanoic acid methyl ester (entry 1):**
Prepared according to the general procedure. The product was obtained in 90% yield. White solid, melting point 45°C. $^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.33-7.27 (m, 10H), 5.11 (d, J=6.3 Hz, 1H), 3.8-3.7 (m, 1H), 3.75 (d, J=3.9 Hz, 1H), 3.62 (s, 3H), 3.06-3.00 (m, 1H), 2.9 (s, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 173.61, 141.75, 139.39, 128.54, 128.32, 124.24, 128.03, 127.63, 127.25, 74.98, 53.82, 51.76, 48.34; IR (Thin film on KBr plate) 3425, 3313, 3066, 2912, 1728, 1597, 1446, 1269,1026 cm-1; MS (ESI) m/z 299 (M+); Elemental analysis: C, 72.22; H, 7.07; N, 4.68; found:72.10, H, 7.50; N, 4.62.

**(Benzylaminomethyl)-3-hydroxy-3-(p-nitrophenyl)propanoic acid methyl ester (entry 2):**
Prepared according to the general procedure. The product was obtained in 92% yield. Gummy semi-solid. $^1$H NMR (300 MHz, $CDCl_3$): δ 8.19-8.06 (m, 4H), 7.57-7.25 (m, 5H), 5.68 ( br s, 1H), 5.31 (d, J= 4.2 Hz, 1H), 3.8-3.4 (complex m, 8H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 171.97, 147.38, 138.65, 128.92, 128.79, 128.54, 128.49, 127.75, 73.05, 53.02, 52.40, 51.79; IR (Thin film on KBr plate) 3387, 3143, 3109, 1670, 1411,1226, 1080, 1033, 833 $cm^{-1}$; MS (ESI) m/z 345 ($M^+$+1), Elemental analysis: C, 62.78; H, 5.85; N, 8.13; found C, 62.80; H, 5.61; N, 8.05.

**Hydroxy-3-phenyl-2(piperidin-1-ylmethyl)propanoic acid methyl ester (entry 3):**
Prepared according to general procedure. The product was obtained with 87% yield. Gummy semi-solid. $^1$H NMR (300 MHz, $CDCl_3$) δ: 7.33-7.18 (m, 5H), 4.95 (d, J= 9.3 Hz, 1H), 3.67-3.64 (m,1H), 3.35 (s, 3H), 3.08-2.95 (m, 2H), 2.7-2.5 (m, 4H), 1.7-1.4 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 172.00, 128.16, 127.79, 127.71, 127.48, 72.85, 54.87, 49.86, 25.94, 25.85, 24.05; IR (Thin film on KBr plate) 3396, 2930, 2851, 1736, 1436, 1302, 1195, 1040, 819 $cm^{-1}$; MS (ESI) m/z 277(M+), 4. Elemental analysis: C, 69.29; H, 8.36; N, 5.05; found: C, 69.25; H, 8.30; N, 5.20.

**Hydroxy-2-(piperidin-1-ylmethyl)-3-p-tolylpropanoic acid methyl ester (entry 4):**
Prepared according to general procedure. The product was obtained in 90% yield. Yellowish solid, and melting point 70 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.26-7.10 (m, 4H), 4.92 (d, J=6 Hz, 1H), 4.3 (m, 1H), 3.4 (s, 3H), 3.2-2.4 (complex m, 13H), 2.0 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 172.71, 137.39, 133.07, 129.64, 124.19, 69.14, 68.24, 58.10, 57.96, 55.10, 54.40, 50.38, 25.93, 25.13, 24.19; IR (Thin film on KBr plate) 3439, 3112, 2946, 1743, 1636, 1443, 1229, 1240, 1033, 822, 809 $cm^{-1}$; MS (ESI) m/z 292 ($M^+$+1); Elemental analysis: C, 70.07; H, 8.65, N, 4.81; found: C, 70.01; 8.64; 4.78.

**Hydroxy-3-(m-nitrophenyl)-2-(piperidin-1-ylmethyl)propanoic acid methyl ester (entry 5):**
Prepared according to general procedure. The product was obtained in 89% yield. Gummy semi solid. $^1$H NMR (300 MHz, $CDCl_3$): δ 8.28 (s, 1H), 8.17 ( d, J=8.7 Hz, 1H), 7.71 ( d, J=6.9 Hz,1H), 7.53 (m, 1H), 5.04 ( d, J=7.8 Hz, 1H), 4.61 ( m, 1H), 4.35 (m, 2H), 3.51(s, 3H), 3.5-3.0 (m, 8H), 3.04 (m, 4H), 0.88-0.82 (m, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) 172.71, 148.74, 137.39, 133.07, 129.64, 190.00, 124.19, 69.14, 51.78, 51.26, 25.93, 24.19; IR (Thin film on KBr plate) 3444, 2937, 2854, 1732, 1634,1528, 1439, 1353, 1246, 1194, 756 $cm^{-1}$; MS (ESI) m/z 223 ($M^+$+1); 6. Elemental analysis: C, 59.61; H, 6.88; N, 8.69; found: C, 59.25; H, 6.85; N, 8.65.

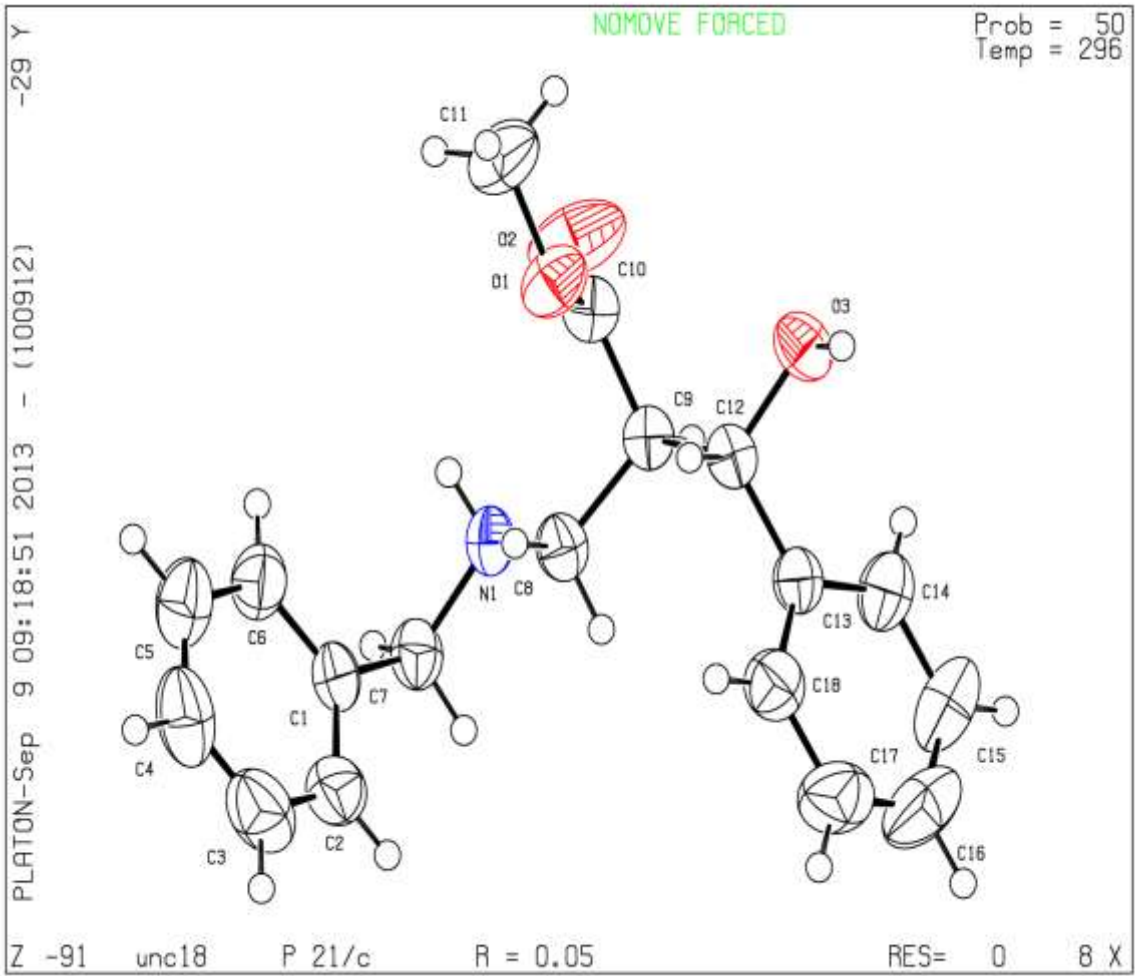
**(2,4-Dichlorophenyl)-3-hydroxy-2-(piperidin-1-ylmethyl)propanoic acid methyl ester (entry 6):**
Prepared according to general procedure. The product was obtained in 90% yield. White solid, and melting point 110 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.52-7.25 (m, 3H), 5.44 ( d, J=7.5 Hz, 1H), 3.53 (s, 3H ), 3.38 (m, 1H), 3.2-2.4 (m, 7H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 172.71, 148.74, 137.39, 133.07, 129.64, 129.00, 124.19, 58.10, 51.78, 51.26, 50.38, 40.77, 25.93, 24.19; IR (Thin film on KBr plate) 3444, 2937, 2854, 1745, 1634, 1439, 1353, 1246, 1194, 882, 756 $cm^{-1}$; MS (ESI) m/z 332 ($M^+$+1); Elemental analysis: C, 55.50; H, 6.11; N, 4.05; found: C, 55.45; H, 6.07; N, 4.10.

**Hydroxy-2-(imidazol-1-ylmethyl)-3-(4-nitrophenyl)propanoic acid methyl ester (entry 7):**
Prepared according to general procedure. The product was obtained in 89% yield. White solid, and melting point 168 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, J = 3.6 Hz, 2H), 8.09 ( m, 3H), 6.87 (m, 2H ), 6.75 (s, 1H) 4.89 (d, J=7.2 Hz, 1H), 4.44-4.12 (m, 3H), 4.20 (d, J=3.3 Hz, 2H), 3.11 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 175.76, 152.79, 132.04, 131.77, 128.24, 123.96, 59.54, 56.70, 44.99, 44.16; IR (Thin film on KBr plate) 3426, 3112, 2959, 2851, 1737, 1634, 1514, 1446, 1353, 1244, 1223, 1080, 856, 757 $cm^{-1}$; MS (ESI) m/z 305.99 ($M^+$+1); Elemental analysis: C, 55.08; H, 4.95; N, 13.76; found: C, 55.02; H, 4.87; N, 13.70.

**(p-Chlorophenyl)-3-hydroxy-2-(imidazol-1-ylmethyl)propanoic acid methyl ester (entry 8):**
Prepared according to general procedure. The product was obtained in 88% yield. White solid, and melting point 136 °C. $^1$H NMR (300 MHz, $CDCl_3$) δ: 7.4-7.3(m, 5H), 6.97-6.78 (m, 2H ), 4.99 (d, J=6.72 Hz, 1H), 4.81 (d, J=6 Hz, 2H), 4.27 (m, 1H), 3.59 (s, 3H), 2.0 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) 175.76, 152.79, 132.04, 131.77, 128.24, 123.96, 59.54, 45.27, 44.99, 44.16; IR (Thin film on KBr plate) 3391, 3119, 2952, 2849, 1732, 1509, 1490, 1437, 1334, 1209, 1089, 826, 771 $cm^{-1}$; MS (ESI) m/z 295 ($M^+$+1); Elemental analysis: C, 57.05; H, 5.13; N, 9.50; found: C, 57.01; H, 5.10; N, 9.45

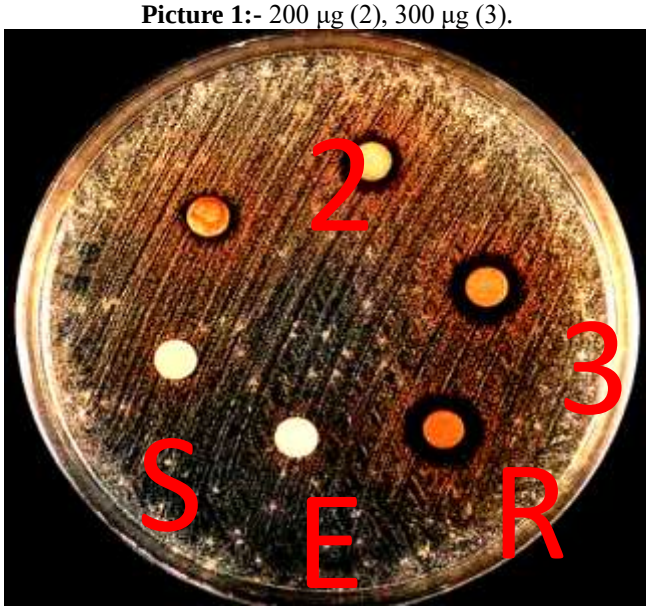
**(2,4-Dichlorophenyl)-3-hydroxy-2-(imidazol-1ylmethyl)propanoic acid methyl ester (entry 9):**
Prepared according to general procedure. The product was obtained with 89% yield. White solid, and melting point 123 °C. $^{1}$H NMR (300 MHz, $CDCl_3$) δ: 7.92-6.88 (m, 6H), 5.44 (d, J=4.8 Hz, 1H) 5.14 (d, J=4.7 Hz, 2H), 4.52-4.44 ( m, 1H), 4.33-2.69 (m, 1H), 3.60 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 171.35, 140.32, 137.93, 137.77, 137.09, 134.09, 133.45, 131.78, 129.22, 127.32, 68.86, 52.51, 52.07, 45.53; IR (Thin film on KBr plate) 3391, 3119, 2952, 2849, 1732, 1509, 1490, 1437, 1334, 1209, 1089, 826, 771 $cm^{-1}$; MS (ESI) m/z 328.9 ($M^{+}$+1); Elemental analysis: C, 51.08; H, 4.29; N, 8.51; found: C, 51.05; H, 4.25; N, 8.60.

**Figure 1:-** Single crystal data of 2-(Benzylaminomethyl)-3-hydroxy-3-phenylpropanoic acid methyl ester (entry 1).




The standard drug used in all the cases was Amphotercin-B and DMSO was loaded as the solvent. In each case, one empty hole was kept as a reference. The anti-fungal activity against the animal pathogen *Candida albicans* shown by the Baylis-Hillman adduct benzyl derivative (**entry 2**) is shown in Picture-1. In 60 µg concentration, it showed the least zone of inhibition range between 10 mm, and in 100 µg, 200 µg, and 300 µg concentrations it showed a moderate range of 14 mm, 16 mm, and 17 mm respectively. The antifungal activity of the same compound against the plant pathogen *Aspergillus niger* is shown in Picture-2. In holes 5 and 2 the concentrations were 40 µg and 60 µg respectively. The compound has shown a minimum range of zone of inhibition (ZOI) of 13 mm and 16 mm respectively. Likewise, the other molecules were also shown a different range of activity in different concentrations with different zones of inhibition (ZOI). We observed that the compounds from 1 to 9 required less amount to inhibit the growth of *Aspergillus niger* compared to *Candida albicans* which requires more amount of dose.
**R=** Reference**,** **E=**Empty**,** **S=**Solvent

**Picture 1:-** 200 µg (2), 300 µg (3).




**Picture 2:-**40 µg (5), 60 µg (2).

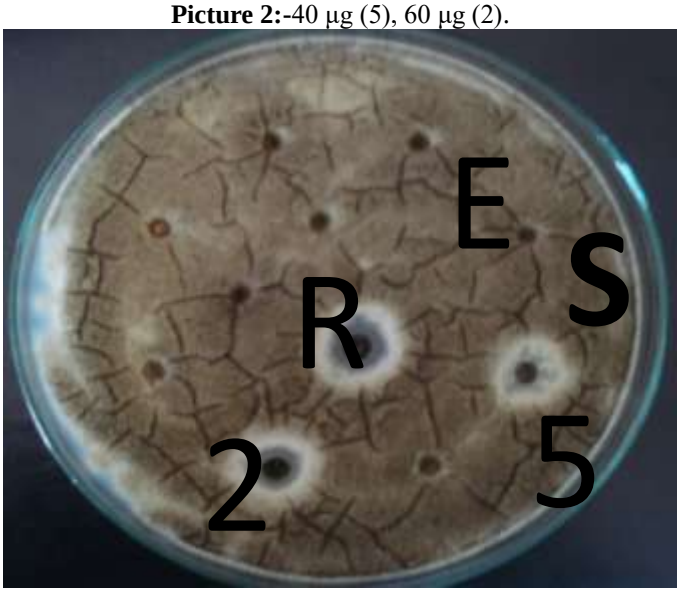
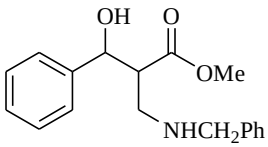
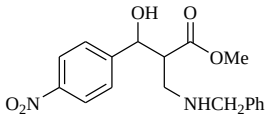
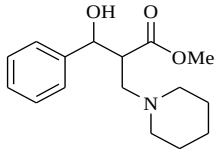
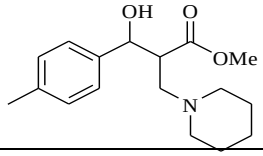
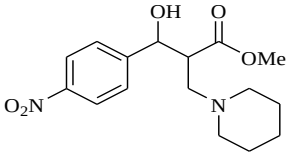
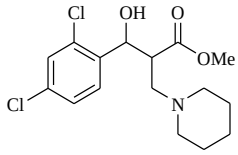
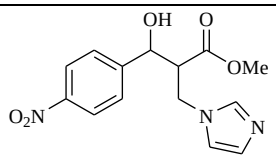
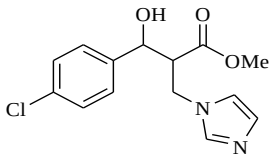
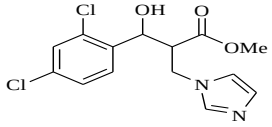



**Table 2:-** Bio-evaluation of aza-Baylis-Hillman adducts.

| Entry | BH Adducts | *Aspergillus niger* | | *Candida albicans* | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 40 (µg) | 60 (µg) | 40 (µg) | 60 (µg) | 100 (µg) | 200 (µg) | 300 (µg) |
| 1 |  | 12 mm | 14 mm | --- | ---- | 10 mm | 14 mm | 16 mm |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 2 |  | 13 mm | 16 mm | --- | 10 mm | 14 mm | 16 mm | 17 mm |
| 3 |  | 12 mm | 14 mm | --- | ---- | 15 mm | 16 mm | 16 mm |
| 4 |  | 12 mm | 14 mm | ---- | ---- | 15 mm | 16 mm | 16 mm |
| 5 |  | 13 mm | 15 mm | ---- | 10 mm | 16 mm | 16 mm | 17 mm |
| 6 |  | 13 mm | 15 mm | ---- | ---- | 15 mm | 16 mm | 16 mm |
| 7 |  | 14 mm | 16 mm | ----- | 10 mm | 16 mm | 17 mm | 17 mm |
| 8 |  | 13 mm | 15 mm | ---- | ---- | 14 mm | 16 mm | 17 mm |
| 9 |  | 13 mm | 15 mm | ---- | ---- | 14 mm | 16 mm | 16 mm |

## Conclusions:-

Here we have reported 9 new derivatives of Baylis-Hillman adduct and tested for their antifungal activity. The incorporation of $–NO_2$ and –Cl in the aromatic moiety of BHA enhances the activity against both the pathogens Aspergillus nigar and Candida albicans and other compounds showed moderate activity. Similarly, incorporation of N-heterocycles also moderately affects activity. The presence of Cl-, $NO_2$- and N-heterocycles enhances activity;

values observed for compounds listed in Table 2, established the increasing trend in reactivity of the derivatives. Hence, the BH moiety becomes more effective upon the incorporation of groups like $–NO_2$ and –Cl;where the heterocycles display an important role in biological activity.

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**Conflict of Interest:**
There is no conflict of interest regarding this article.

**Supplementary Information:**
All the spectroscopic data are enlisted in the supplementary section.

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