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# Synthesis & Pharmacological Studies on Novel Chalcones Derived from 1-acetyl-4-(4-hydroxy phenyl) piperazine

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**ABSTRACT**

Treatment of 1-acetyl-4-(4-hydroxy phenyl) piperazine with aromatic or substituted aromatic aldehydes in presence of methanol and potassium hydroxide, formed 3-substituted phenyl-1--(4-(4-hydroxyl phenyl)- piperzin-1-yl)-Prop-2-en-1-one derivatives (RC-1 to RC-10). These are assayed for their antibacterial activity against Bacillus pumilus, Bacillus subtilis, Escherichia coli, and Proteus vulgaris; for antifungal activity against Aspergillus niger, Candida albicans strains. Antibacterial assay revealed that Bacillus subtilis and Proteus vulgaris were the most sensitive bacterial strains to compounds RC-2, 3, 4, 7, 10 and in the antifungal assay, compounds RC-1, 3, and 10 were highly effective against Aspergillus niger when compared to other investigated strains.

**Key words:** 1-acetyl-4-(4-hydroxy phenyl) piperazine, aldehydes, potassium hydroxide, methanol, antibacterial activity, antifungal activity.

## INTRODUCTION

Chalcones[1] is a generic term given to compounds bearing the 1,3-diphenyl-2-propen-1-one frame work. Chalcones are bichromophoric molecules separated by a keto vinyl chain and belong to the flavanoid family. Chemically they consist open chain flavanoids in which the two aromatic rings

are joined by a three carbon α,β- unsaturated carbonyl system, which is responsible for the wide spectrum of biological activities.

There[2,3] are several modified preparative methods available for the preparation of simple chalcones and new methods are being constantly investigated due to incessant interest in the chemistry and wide range of pharmacological activity[4] that chalcones possess. In the present study, a novel synthetic method has been designed for the preparation of new series of chalcones from the reaction of 1-acetyl-4-(4-hydroxy phenyl) piperazine with various aromatic or substituted aromatic aldehydes. The synthesized compounds were purified and screened for the antimicrobial activity against various bacterial and fungal strains[5].

## MATERIALS AND METHODS

### Antimicrobial Activity

The synthesized compounds were screened for antimicrobial activity against gram-positive bacteria like Bacillus pumilus, Bacillus subtilis and gram negative bacteria like Escherichia coli and Proteus vulgaris. Similarly the compounds were screened for antifungal activity against fungi like Aspergillus niger and Candida albicans by using cup-borer method. Ciprofloxacin and Miconazole nitrate were used as standard drugs. DMSO was used as solvent.

## EXPERIMENTAL

Melting points of the synthesized compounds were determined by open capillary method and are uncorrected. Purity of the compounds was verified on TLC plates coated with silica gel. IR spectra were recorded on thermo Nicolet IR 200 spectrometer using KBr disc method. $H^1$NMR spectra were recorded on BRUKER amx-400 NMR spectrometer where $CDCl_3$ is used as internal standard. Results of Combustion analysis were found to be within the limits of permissible errors.

### Synthesis of Piperazine containing chalcone derivatives

1E.q of 1-acetyl-4-(4-hydroxy phenyl) piperazine was dissolved in 10ml methanol and 2 E.q of ortho or para substituted aromatic aldehyde or unsubstituted aromatic aldehyde was added to it. To this mixture 3 E.q of 40% KOH was added drop wise at room temperature. This mixture was

acidified with 1:1 hydrochloric acid and water with constant stirring. The obtained solid was purified and re crystallized by using a mixture of chloroform and n-hexane (6:4).

**Fig.1. Scheme of piperazine containing chalcone derivatives**

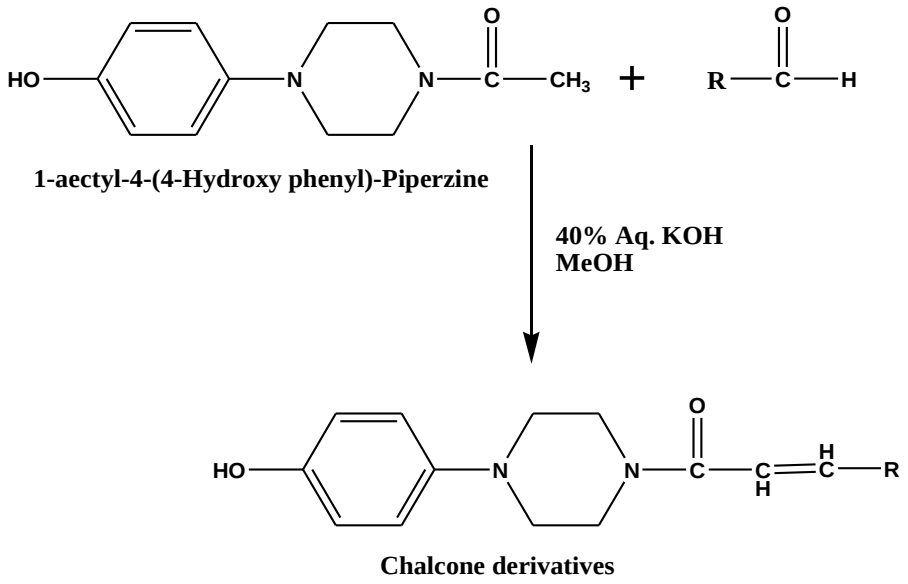
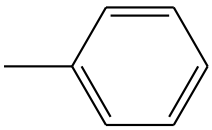
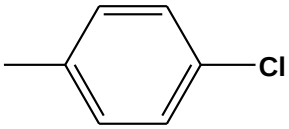



**Table.1. Compound code containing derivatives**

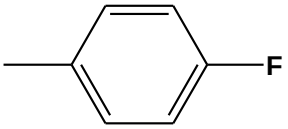
| Compound code | R |
|---|---|
| RC-1 | Phenyl |
| RC-2 | 4-cholro phenyl |
| RC-3 | 4- fluoro phenyl |
| RC-4 | 4- nitro phenyl |
| RC-5 | 4- methoxy phenyl |
| RC-6 | 2- ethoxy-4- hydroxy phenyl |
| RC-7 | 2,4- dimethoxy phenyl |
| RC-8 | N,N- dimethyl amino phenyl |
| RC-9 | Napthyl |
| RC-10 | 2,4-dichloro phenyl |



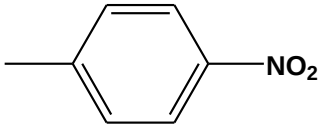
**RC 1**



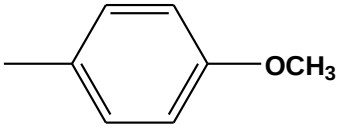

**RC 2**



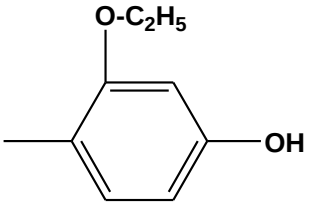

**RC 3**



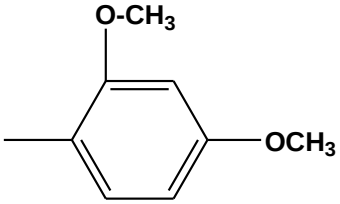

**RC 4**



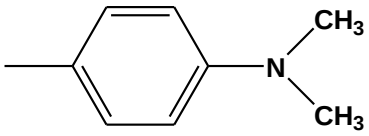

**RC 5**



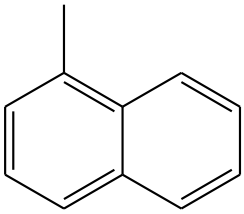

**RC 6**



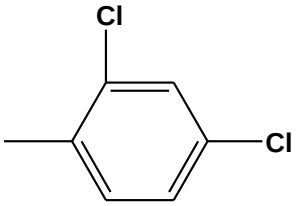

**RC 7**




**RC 8**



**RC 9**




**RC 10**

**Spectral details:**

**RC-1:** 1-(4-(4- hydroxyl phenyl)- piperzin-1-yl)-3-phenyl Prop-2-en-1-one; Yield 55.6%; mp 112 -114$^0$C; IR (KBr) νcm$^{-1}$ 3418.09 (-OH, str), 1613.83(-C=O, str), 1503.97(-C=C-, str); H$^1$ NMR □(ppm) 2.026 & 2.933 (8H, piperazinyl protons), 6.692(1H, d, C-2H), 6.772(1H, d, C-3H), 7.281- 7.905(9H, aromatic protons), 8.564(1H, s, phenolic –OH).

**RC-2:** 3-(4- chloro phenyl)-1-(4-(4- hydroxyl phenyl)- piperzin-1-yl)-Prop-2-en-1-one; Yield 59.4%; mp 118 -120$^0$C; IR (KBr) νcm$^{-1}$ 3421.54 (-OH, str), 1618.30(-C=O, str), 1506.44(-C=C-, str); H$^1$ NMR □(ppm) 2.030 & 2.948(8H, piperazinyl protons), 6.670(1H, d, C-2H), 6.789(1H, d, C-3H), 7.268-7.849(9H, aromatic protons), 9.364(1H, s, phenolic –OH).

**RC-3:** 3-(4- fluro phenyl)-1-(4-(4- hydroxyl phenyl)- piperzin-1-yl)-Prop-2-en-1-one;Yield 68.1%; mp 122 -124$^0$C; IR (KBr) νcm$^{-1}$ 3161.36(-OH, str), 1619.09(-C=O, str), 1508.68(-C=C-, str) ; H$^1$ NMR □(ppm) 2.30 & 2.885(8H, piperazinyl protons), 6.666(1H, d, C-2H), 6.795(1H, d, C-3H), 9.041(1H, s, phenolic –OH).

**RC-4:** 1-(4-(4- hydroxyl phenyl)- piperzin-1-yl)-3-(4- nitro phenyl)-Prop-2-en-1-one; Yield 68.7%; mp 128 -130$^0$C; IR (KBr) νcm$^{-1}$ 3407.93(-OH, str), 1695.08(-C=O, str), 1604.17(-C=C-, str) ; H$^1$ NMR □(ppm) 1.983 & 2.990(8H, piperazinyl protons), 8.116(1H, d, C-2H), 8.316(1H, d, C-3H), 6.672-8.433(9H, aromatic protons), 8.693(1H, s, phenolic –OH).

**RC-5:** 1-(4-(4- hydroxyl phenyl)- piperzin-1-yl)-3-(4- methoxy phenyl)- Prop-2-en-1-one; Yield 64.2%; mp 131 -133$^0$C; IR (KBr) νcm$^{-1}$ 3431.74(-OH, str), 1621.74(-C=O, str), 1505.83(-C=C-, str) ; H$^1$ NMR □(ppm) 2.035 & 2.987(8H, piperazinyl protons), 6.676(1H, d, C-2H), 6.784(1H, d, C-3H), 6.840-7.915(9H, aromatic protons), 8.921(1H, s, phenolic –OH).

**RC-6:** 3-(3-ethoxy-4- hydroxy phenyl)-1-(4-(4- hydroxyl phenyl)- piperzin-1-yl)-3-phenyl Prop-2-en-1-one; Yield 71.3%; mp 127 -129$^0$C; IR (KBr) νcm$^{-1}$ 3423.59(-OH, str), 1599.32(-C=O, str), 1511.66(-C=C-, str) ; H$^1$ NMR □(ppm) 1.335 & 2.943(8H, piperazinyl protons), 6.667(1H, d, C-2H), 6.782(1H, d, C-3H), 7.148-7.238(9H, aromatic protons), 9.501(1H, s, phenolic –OH).

**RC-7:** 3-(3,4-dimethoxy phenyl)-1-(4-(4- hydroxyl phenyl)- piperzin-1-yl)-3-phenyl Prop-2-en-1-one; Yield 56%; mp 128 -130$^0$C; IR (KBr) νcm$^{-1}$ 3432.57(-OH, str), 1616.30(-C=O, str), 1503.72(-C=C-, str) ; H$^1$ NMR □(ppm) 2.091 & 2.949(8H, piperazinyl protons), 6.658(1H, d, C-2H), 6.794(1H, d, C-3H), 7.171-7.578(9H, aromatic protons), 9.853(1H, s, phenolic –OH).

**RC-8:** 3-(4- dimethyl amino phenyl)1-(4-(4- hydroxyl phenyl)- piperzin-1-yl)-3-phenyl Prop-2-en-1-one; Yield 57.2%; mp 132 -134$^0$C; IR (KBr) νcm$^{-1}$ 3293.86(-OH, str), 1649.84(-C=O, str), 1506.47(-C=C-, str) ; H$^1$ NMR □(ppm) 2.016 & 2.874(8H, piperazinyl protons), 6.684(1H, d, C-2H), 6.743(1H, d, C-3H), 8.765(1H, s, phenolic –OH).

**RC-9:** 3-(1-napthyl)1-(4-(4- hydroxyl phenyl)- piperzin-1-yl)-3-phenyl Prop-2-en-1-one; Yield 59%; mp 326 -328$^0$C; IR (KBr) νcm$^{-1}$ 3423.86(-OH, str), 1618.63(-C=O, str), 1506.89(-C=C-, str) ; H$^1$ NMR □(ppm) 2.031 & 2.886(8H, piperazinyl protons), 6.663(1H, d, C-2H), 6.793(1H, d, C-3H), 7.543-8.311(9H, aromatic protons), 10.426(1H, s, phenolic –OH).

**RC-10:** 3-(2,4-dichloro phenyl)1-(4-(4- hydroxyl phenyl)- piperzin-1-yl)-3-phenyl Prop-2-en-1-one; Yield 80%; mp 121 -123$^0$C; IR (KBr) νcm$^{-1}$ 3384.74(-OH, str), 1665.82(-C=O, str), 1515.03(-C=C-, str) ; H$^1$ NMR □(ppm) 2.028 & 2.892(8H, piperazinyl protons), 6.658(1H, d, C-2H), 6.786(1H, d, C-3H), 7.615 – 7.886(9H, aromatic protons), 10.282(1H, s, phenolic –OH).

## RESULTS & DISCUSSION

In the present experiment the antimicrobial activity was tested by bore method. The antimicrobial activity of chalcones was tested and compared with the standard Sparfloxacin solution at two different concentrations i.e. 50 µg and 100 µg. DMSO was used as a control.

**Test organisms:**

Gram positive bacteria: *Bacillus subtilis*

Gram negative bacteria: *Escherichia coli*

**Table.2. Anti bacterial activity by cup-borer method**

| Compound code | Anti bacterial activity (Zone of inhibition mm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | B.subtilis | | B.pumilis | | E.coli | | P.Vulgaris | |
| | 0.5 mg/mL) | 1 (mg/mL) | 0.5 (mg/mL) | 1 (mg/mL) | 0.5 (mg/mL) | 1 (mg/mL) | 0.5 (mg/mL) | 1 (mg/mL) |
| RC-1 | - | 10 | - | - | - | 10 | - | 12 |
| RC-2 | 12 | 17 | 13 | 16 | 10 | 14 | 16 | 19 |
| RC-3 | 13 | 21 | 12 | 19 | 13 | 18 | 18 | 21 |
| RC-4 | 10 | 14 | 12 | 16 | 8 | 13 | 11 | 14 |
| RC-5 | 11 | 14 | - | 10 | - | 12 | - | 11 |
| RC-6 | 10 | 13 | - | 11 | - | 10 | - | 10 |
| RC-7 | 12 | 15 | 8 | 10 | - | 10 | 8 | 13 |
| RC-8 | 8 | 11 | - | 10 | - | 8 | - | 10 |
| RC-9 | - | 8 | - | - | - | - | - | - |
| RC-10 | 17 | 23 | 13 | 18 | 16 | 20 | 19 | 25 |
| Ciprofloxacin | 28 | | 32 | | 24 | | 30 | |
| Control(DMSO) | - | | - | | - | | - | |

**Table.3. Anti fungal activity by cup-borer method**

| Compound code | Zone of inhibition (mm) | |
|---|---|---|
| | 1(mg/mL) | |
| | A. niger | C. albicans |
| RC-1 | 11 | 8 |
| RC-2 | 10 | 10 |
| RC-3 | 15 | 13 |
| RC-4 | 8 | 10 |
| RC-5 | - | - |
| RC-6 | - | - |
| RC-7 | - | - |
| RC-8 | 10 | 8 |
| RC-9 | - | - |
| RC-10 | 14 | 16 |
| Miconazole nitrate | 30 | 27 |
| Control(DMSO) | - | - |

(-) no zone of inhibition

From the above results it is evident that synthesized chalcone compounds RC-1 to RC-10 showed significant gram positive antibacterial activity at both 0.5% (500µg/ml) and 1%(1000µg/ml) concentration levels and poor gram negative effect when compared with standard drug Sparfloxacin. In particular compounds RC-2, 3, 10 showed maximum activity and this may be due to presence of halogen atom as a substituent on the aromatic rings.

## CONCULSION

At the end of the study it is learnt that the prepared chalcone derivatives possessed significant anti bacterial activity and anti fungal activity, although not as intense as the tested standards.

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