SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL PYRAZOLINE AND FLAVONE DERIVATIVES DERIVED FROM FURAN CHALCONES

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ABSTRACT

A new series of 1-(3-(2-hydroxyphenyl substituted )-5-(furan-2-yl 4,5dihydropyrazol-1-yl) ethanone(4a-g) and 2-(furan-2-yl)-4H-chromen-4 -one derivatives(5a-g) were synthesized by reacting 3-(Furan-2-yl)-1-(2- hydroxyl phenyl substituted ) prop-2-en-1-one (3a-g)with hydrazine hydrate in acetic acid and DMSO in catalytic quantity of iodine respectively. These compounds were characterized by means of their IR, ¹H NMR spectroscopic data. The synthesized products were evaluated for their antimicrobial activity .All the compounds exhibited significant antibacterial and antifungal activity.

KEYWORDS: Chalcons, pyrazolines, flavones, furan, antibacterial, antifungal activity.

INTRODUCTION

Heterocyclic compounds bearing nitrogen or oxygen as hetero atom in ring system like pyrazoline, flavones are gaining importance due to their wide range of pharmacological activites.

novel flavones derivatives remains a main focus of chemist, due to their established pharmacological effects such as anti-oxidant, \(^{[14-17]}\)  Anxiolytic, \(^{[18]}\) anticancer, \(^{[19]}\) analgesic, \(^{[20-21]}\) and antimicrobial, \(^{[22]}\) anti-inflammatory activity.\(^{[23-24]}\)

Taking in to consideration such broad spectrum of utilities of pyrazolines and flavones derivatives it was contemplated to synthesize a novel series of pyrazoline \(4a-g\) and flavone derivatives \(5a-g\) derived from \(3-(\text{furan}-2\text{-yl})-1-(2\text{-hydroxy phenyl substituted})\) prop-2en-1-one. These derivatives contain furan moiety, literature survey revealed that bioheterocycle derived from furan enhanced biological activity \(^{[25]}\) at the same time aryl furan derivatives are useful in the treatment of diseases, by raising the level of cyclic adenosine 3', 5'-monophosphate (cAMP) through the inhibition of phosphodiesterase IV (PDE IV). Some furan derivatives are useful as chemotherapeutic agents. The semicarbazone of 5-nitrofuran-2-carbaldehyde is a bactericide; Ranitidine is an important chemotherapeutic agent for peptic ulcer. Hence it was thought worthwhile to synthesize the title compound with the hope that furan substituent in these nucleus may enhance biological activity. The results of these studies are presented in paper.

MATERIAL AND METHODS

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded using Perkin –Elmer spectrometer. \(^{1}\)H NMR spectra were recorded on Brucker Advance II 400 spectrometer in DMSO by using TMS as internal standard. Thin layer chromatography was performed with E. Merk precoated TLC plates, silica gel 60F\(_{254}\) with thickness of 0.25mm and spots were visualised by irradiation with ultraviolet light (254 nm).

General procedure for the synthesis of \(3-(\text{Furan}-2\text{-yl})-1-(2\text{-hydroxyl phenyl substituted})\) prop-2-en-1-one \(3a-g\)

A mixture of substituted \(\alpha\)-hydroxy acetophenone (0.01mol) and 2-furaldehyde (0.01mol) was dissolved in ethanol (20 ml) and then a solution of potassium hydroxide 10ml (15%) was added to it. The mixture was stirred and kept overnight. It was then poured on ice cold water and acidified with HCl. The Chalcone derivatives precipitates as solid, filtered, washed with water and crystallised from ethanol.
General procedure for the synthesis of 1-(3-(2-hydroxyphenyl substituted)-5-(furan-2-y1 4, 5-dihydropyrazol-1-yl)ethanone 4a-g

A solution of Chalcone (0.01mol) and hydrazine hydrate (0.02mol) in 20 ml glacial acetic acid was refluxed for 8 hrs. The resulting solution was kept overnight, then poured on ice cold water, washed with water and crystallised from ethanol. Physical data of compounds are given in table 1.

General procedure for the synthesis of 2-(furan-2-y1)-4H-chromen-4–one derivatives 5a-g

A solution of Chalcone (0.01mol) was dissolved in 20 ml DMSO, to this catalytic quantity of iodine was added. Contents were refluxed for 1 hr. and then the reaction mixture was left overnight. It was then poured on ice cold water the separated solid was filtered washed with cold water followed by dilute sodium thiosulphate solution. The product was also washed with 1% NaOH. The product was crystallised from ethanol. Their characterization data are given in table 1.

Scheme 1

Table1-Physical constants and yields of 4a-g, 5a-g

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>M.P °C</th>
<th>Yield %</th>
</tr>
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<tbody>
<tr>
<td>4a</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>186</td>
<td>90</td>
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<tr>
<td>4b</td>
<td>H</td>
<td>H</td>
<td>Br</td>
<td>196</td>
<td>80</td>
</tr>
<tr>
<td>4c</td>
<td>H</td>
<td>H</td>
<td>F</td>
<td>136</td>
<td>85</td>
</tr>
<tr>
<td>4d</td>
<td>Cl</td>
<td>H</td>
<td>Cl</td>
<td>202</td>
<td>92</td>
</tr>
</tbody>
</table>
RESULT AND DISCUSSION

The synthetic route to the title compounds is outlined in scheme 1. The intermediate, chalcones 3a-g were prepared as starting compound, by the action of substituted o-hydroxyl acetophenone 1a-g with 2-furaldehyde 2 in the presence of ethanol with 15\% aqueous potassium hydroxide by Claisen-Schmidt condensation. The synthesized chalcones further refluxed with hydrazine hydrate in glacial acetic acid to give pyrazoline derivatives 4a-g by Fischer and knovengeal method. Similarly these chalcones 3a-g were oxidatively cyclised in the presence of dimethyl sulphoxide & iodine to furnish the flavone derivatives 5a-g in good yields. All the compounds were characterized by using IR, and ¹H NMR data. The purity of these compounds was ascertained by TLC and spectral analysis.

The structure of synthesized compounds 4a-g was confirmed on the basis of spectral data. The IR spectrum of 4a-g exhibited a band at 1620-1617 cm⁻¹ due to C=N stretching of Pyrazoline ring and a band at 1665-1650 cm⁻¹ due to carbonyl group of -NCO-CH₃, -OH stretching is observed in the range 3150-3140 cm⁻¹. Further in their ¹H NMR (DMSO) spectrum the CH₂ protons of the Pyrazoline ring resonate as a pair of doublet of doublet near 3.51 ppm (H_A) and at 3.70 ppm (H_B). The CH (H_X) protons appeared as a doublet of doublet near 5.65 ppm due to vicinal coupling with the two magnetically non equivalent protons of methylene at position 4 of Pyrazoline ring. The methyl protons of –NCO-CH₃ appears at 3.35 δ as singlet. The protons belonging from aromatic ring and furan ring appears in 6 to 8δ with the expected chemical shift and integral value.

Similarly the structures of compounds 5a-g were confirmed on the basis of IR and ¹H NMR. The IR absorption at 1595 cm⁻¹ showed the presence of >C=O(pyrone ring) and the absence of OH group confirmed the oxidation of Chalcone in to flavones. Further in their ¹H NMR spectrum the appearance of signal at 6.69-6.67 δ(s, 1H, pyrone ring), Supported the flavones derivatives showed in spectral data section.
Spectral data of compounds

1-(3-(5-chloro-2-hydroxyphenyl)-5-(furan-2-yl)-4,5-dihydropyrazol-1-yl)ethanone (4a)
Elemental analysis Calcd for C_{15}H_{13}ClN_{2}O_3: C, 59.12; H, 4.30; Cl, 11.63; N, 9.19; Found: C, 59.09; H, 4.28; Cl, 11.60; N, 9.15 %; IR (KBr pellets cm^{-1}) 3150(OH), 3110(N-Str), 1660(C=O), 1620(C=N) 1H NMR (DMSO, 400MHz) δ 3.30(s, 3H, CH_3), 3.55-3.56 (dd, 1H, CH_A), 3.72-3.79(dd, 1H, CH_B), 5.62-5.66(dd, 1H, CH_X), 6.35-6.39(dd, 2H, furanring), 6.95-6.97(d, 1H, Ar-H) 7.40-7.43(m, 2H, Ar-H), 10.22 (s, 1H, OH).

1-(3-(5-bromo-2-hydroxyphenyl)-5-(furan-2-yl)-4,5-dihydropyrazol-1-yl) ethanone (4b)
Elemental analysis Calcd for C_{15}H_{13}BrN_{2}O_3: C, 51.60; H, 3.75; Br, 22.88; N, 8.02; Found: C, 51.55; H, 3.70; Br, 22.78; N, 7.98 %; IR (KBr pellets cm^{-1}) 3139 (OH), 3116(N-Str), 1658(C=O), 1617(C=N), 1225(C-O-N) 1H NMR(DMSO, 400MHz) δ 3.35(s, 3H, CH_3), 3.51-3.52(dd, 1H, CH_A), 3.75-3.82(dd, 1H, CH_B), 5.60-5.64(dd, 1H, CH_X), 6.30-6.35(dd, 2H, furanring), 6.90-6.92(d, 1H, Ar-H) 7.37-7.40(m, 2H, Ar-H), 10.18(s, 1H, OH).

1-(3-(5-fluoro-2-hydroxyphenyl)-5-(furan-2-yl)-4,5-dihydropyrazol-1-yl)ethanone (4c)
Elemental analysis Calcd for C_{15}H_{13}FN_{2}O_3: C, 62.50; H, 4.55; F, 6.59; N, 9.72; Found: C, 62.49; H, 4.51; F, 6.55; N, 9.70 %; IR (KBr pellets cm^{-1}) 3160(OH), 3105(N-Str), 1665(C=O), 1625 (C=O), 1230(C-O-N) 1H NMR(DMSO, 400MHz) δ 3.35(s, 3H, CH_3), 3.51-3.54(dd, 1H, CH_A), 3.70-3.75 (dd, 1H, CH_B), 5.65-5.69 (dd, 1H, CH_X), 6.37-6.42 (dd, 2H, furanring), 6.95 6.97(d, 1H, Ar-H), 7.40 -7.43 (m, 2H, Ar-H), 10.25(s, 1H, OH).

1-(3-(5-chloro-6-methyl-2-hydroxyphenyl)-5-(furan-2-yl)-4,5-dihydropyrazol-1-yl)ethanone (4e)
Elemental analysis Calcd for C_{16}H_{15}ClN_{2}O_3: C, 60.29; H, 4.74; Cl, 11.12; N, 8.79; Found: C, 60.26; H, 4.70; Cl, 11.09; N, 8.75 %; IR (KBr pellets cm^{-1}) 3160(OH), 3106(N-Str), 1650(C=O), 1620(C=O), 1220(C-O-N) 1H NMR (DMSO, 400MHz) δ 3.05 (s, 3H, CH_3), 3.35(s, 3H, CH_3), 3.51-3.52(dd, 1H, CH_A), 3.70-3.77(dd, 1H, CH_B), 5.65-5.69(dd, 1H, CH_X), 6.30-6.35(dd, 2H, furanring), 6.90-6.92(d, 1H, Ar-H), 7.37-7.40(S, 1 H, Ar-H), 10.30 (s, 1H, OH).

6-chloro-2-(furan-2-yl)-4H-chromen-4-one (5a)
Elemental analysis Calcd for C_{13}H_{7}ClO_3: C, 63.30; H, 2.86; Cl, 14.37; Found: C, 63.28; H, 2.80; Cl, 14.35 %; IR (KBr pellets cm^{-1}) 3110(Ar-H asym), 3065(Ar-H), 1658(C=C), 1595(C=O), 1230(C-O-C) 1H NMR (DMSO, 400MHz) δ 6.60 (s, 1H, pyrone ring), 6.70-
6.72(d, 1H, furan ring) 7.30-7.32(d, 1H, J=8H, Ar-H), 7.62-7.64(d, 1H, J=8H, Ar-H), 7.90 -
7.92(dd, 1H, furan ring), 8.14-8.15(d, 1H, furan ring), 8.25 (s, 1H, Ar-H).

6-bromo -2-(furan-2-yl)-4H-chromen-4 –one (5b)
Elemental analysis Calcd for C_{13}H_{7}BrO_3: C, 53.64; H, 2.42; Br, 27.45; Found: C, 53.60; H,
2.38; Br, 27.41 %; IR (KBr pellets cm^{-1}) 3110(Ar-H asym), 3065(Ar-H), 1658(C=C),
1595.(C=O), 1230(C-O-C); ^1H NMR(DMSO, 400MHz)δ 6.70(s, 1H, pyrone ring), 6.77-
6.79(d, 1H, furan ring), 7.35-7.36 (d, 1H, J=8H, Ar-H), 7.64-7.66(d, 1H, J=8H,)
7.92-7.94(dd, 1H, furan ring), 8.18-8.19 (d, 1H, furan ring), 8.25(s, 1H, Ar-H).

6-fluro-2-(furan-2-yl)-4H-chromen-4 -one (5c)
Elemental analysis Calcd for C_{13}H_{7}FO_3: C, 67.83; H, 3.07; F, 8.25; Found: C, 67.80; H, 3.00;
F, 8.21 %; IR (KBr pellets cm^{-1}) 3110(Ar-H asym), 3065(Ar-H), 1658(C=C), 1595(C=O),
1230 (C-O-C); ^1H NMR(DMSO, 400MHz)δ 6.67(s, 1H, pyrone ring), 6.70-6.72(d, 1H,
furan ring) 7.30-7.32 (d, 1H, J=8H, Ar-H), 7.62-7.64(d, 1H, J=8H), 7.90-7.93(dd, 1H,
furan ring), 8.10-8.12 (d, 1H, furan ring), 8.24 (s, 1H, Ar-H)

6, 8- dichloro-2-(furan-2-yl)-4H-chromen-4 -one (5d)
Elemental analysis Calcd for C_{13}H_{6}Cl_{2}O_3: C, 55.55; H, 2.15; Cl, 25.23; Found: C, 55.51; H,
2.10; Cl, 25.20 %; IR (KBr pellets cm^{-1}) 3110(Ar-H asym), 3065(Ar-H), 1658(C=C),
1595(C=O), 1230 (C-O-C) ^1H NMR(DMSO, 400MHz)δ 6.67(s, 1H, pyrone ring), 6.75-
6.77(d, 1H, furan ring), 7.62-7.64(d, 1H, Ar-H), 7.89-7.92(dd, 1H, furanring), 8.12-8.13(d,
1H, furan ring),8.18(s, 1H, Ar-H)

Table 2-Antibacterial screening results of the compounds 4a-g, 5a-g

<table>
<thead>
<tr>
<th>Compd.</th>
<th>E.coli</th>
<th>Salmonella typhi</th>
<th>Staphylococcus aureus</th>
<th>Bacillus subtilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>12</td>
<td>10</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>4b</td>
<td>14</td>
<td>15</td>
<td>15</td>
<td>17</td>
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<tr>
<td>4c</td>
<td>13</td>
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<td>17</td>
<td>14</td>
</tr>
<tr>
<td>4d</td>
<td>12</td>
<td>13</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>4e</td>
<td>11</td>
<td>17</td>
<td>14</td>
<td>18</td>
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<td>4f</td>
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<td>5a</td>
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<td>5b</td>
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<td>14</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>5c</td>
<td>10</td>
<td>12</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>5d</td>
<td>09</td>
<td>11</td>
<td>21</td>
<td>13</td>
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<td>Penicillium</td>
<td>18</td>
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<tr>
<td>DMSO</td>
<td>-ve</td>
<td>-ve</td>
<td>-ve</td>
<td>-ve</td>
</tr>
</tbody>
</table>

-ve no antibacterial activity
Table 3 Antifungal screening results of the compounds 4a-g, 5a-g

<table>
<thead>
<tr>
<th>Compd</th>
<th>Aspergillus niger</th>
<th>Aspergillus flavus</th>
<th>Penicillium chrysogenum</th>
<th>Fusarium moniliforme</th>
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</thead>
<tbody>
<tr>
<td>4a</td>
<td>-ve</td>
<td>-ve</td>
<td>-ve</td>
<td>+ve</td>
</tr>
<tr>
<td>4b</td>
<td>-ve</td>
<td>-ve</td>
<td>-ve</td>
<td>RG</td>
</tr>
<tr>
<td>4c</td>
<td>-ve</td>
<td>-ve</td>
<td>-ve</td>
<td>+ve</td>
</tr>
<tr>
<td>4d</td>
<td>-ve</td>
<td>-ve</td>
<td>-ve</td>
<td>RG</td>
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<tr>
<td>4e</td>
<td>-ve</td>
<td>-ve</td>
<td>-ve</td>
<td>+ve</td>
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<tr>
<td>4f</td>
<td>RG</td>
<td>-ve</td>
<td>-ve</td>
<td>-ve</td>
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<tr>
<td>4g</td>
<td>-ve</td>
<td>-ve</td>
<td>+ve</td>
<td>-ve</td>
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<tr>
<td>5a</td>
<td>-ve</td>
<td>+ve</td>
<td>-ve</td>
<td>-ve</td>
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<tr>
<td>5b</td>
<td>-ve</td>
<td>-ve</td>
<td>+ve</td>
<td>-ve</td>
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<td>+ve</td>
<td>+ve</td>
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<td>5d</td>
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<td>-ve</td>
<td>RG</td>
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<tr>
<td>Griseofulvin</td>
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<td>-ve</td>
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<tr>
<td>DMSO</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
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</tbody>
</table>

-ve       No growth Antifungal activity present
+ve       Growth Antifungal activity absent
RG       Reduced growth

Antimicrobial activity

The compounds 4a-g and 5a-g were screened for their antibacterial activity against *E. coli*, *Salmonella typhi*, *Staphylococcus aureus* and *Bacillus subtilis* by agar cup method (26) using penicillin as standard and antifungal activity against *Aspergillus niger*, *Aspergillus flavus* *Penicillium chrysogenum*, *Fusarium moniliforme*, by poison plate method (26) using Griseofulvin as reference standard and DMSO as control solvent. The investigation of antibacterial screening results indicate that compound 4a-g showed promising activity against *E. coli*, *Salmonella typhi*, *Staphylococcus aureus* and *Bacillus subtilis*, whereas 5a-d showed moderate activity compared with standard drug Penicillum.

The investigation of antifungal activity data revealed that compounds 4a-e and 5d have promising activity against *Aspergillus niger*, *Aspergillus flavus* *Penicillium chrysogenum*, 4g showed activity against *Aspergillus niger*, *Aspergillus flavus*, *Fusarium moniliforme*...
compounds 5b and 5c showed activity against Aspergillus niger, Aspergillus flavus and Fusarium moniliforme and no activity for penicillium chrysogenum. Compounds 4a, 4c, 4e, 5c showed no antifungal activity against Fusarium moniliforme.

CONCLUSION

In this study we synthesised some novel 1-(3-(2-hydroxyphenyl substituted)-5-(furan-2-yl-4, 5-dihydropyrazol-1-yl)ethanone and of 2-(furan-2-yl)-4H-chromen-4-one derivatives and characterized by spectral analysis. All the compounds were screened for antibacterial and antifungal activity, and found to have promising antibacterial and antifungal activity.

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REFERENCES


