SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 3-PHENYL SUBSTITUTED QUINAZOLINONE DERIVATIVES VIA CHALCONES

G. Sudhakar Rao*, VK. Kalaichelvan1 and Ganguri Sudhakar Rao2
1Department of Pharmacy, Annamalai University, Chidambaram, Tamil Nadu, India.
2Department of Pharmacy, Vishwa Bharathi College of Pharmaceutical Sciences, Perecherla, Guntur, Andhra Pradesh, India.

ABSTRACT
Synthesis of a new series of pyrazoline derivatives (Q1.4,P1.4,Ph1.4& Py1.4) have been obtained from the starting materials anthranilic acid (A) and benzoyl chloride (B) to 2[phenyl]-benzo(1,3)oxazine-4-one (C) in pyridine further reaction with p-amino acetophenone gives 3-(4-acetyl phenyl)-2-(phenyl)-3H quinazoline-4-one (D) derivatives. Then on condensation with different substituted aromatic aldehydes afforded four Q1.4 compounds. Then further incorporated into pyrazoline, N-phenyl pyrazoline and N-acetyl pyrazoline ring systems at position 3 of the quinazoline ring. The newly synthesized compounds have been supported by spectral data IR, H1NMR and Mass spectra. The compounds Q1.4 and P1.4 were screened for antibacterial activity by using cup plate method.

INTRODUCTION
Quinazoline have been frequently used in medicine because of their wide range of biological activities. Different quinazoline derivatives have been reported for their antibacterial, antifungal, anti HIV, anthelimentics, CNS depressants and ant tubercular activities. Besides these the quinazolinones kelton is frequently encountered as building block or hundreds of naturally occurring alkaloids and hence the exploration of this skelton as privileged new chemical entities in drug discovery research is beyond doubt of paramount importance for the synthetic chemist.

Experimental section
Melting points of the synthesized compounds were determined in open capillary tubes and were uncorrected. IR spectra were recorded on BRUKER FT-IR spectrometer using ATR. H1NMR spectra of the compounds in deuteriated dimethyl sulfoxide (DMSO) and CDCl3 was recorded on BRUKER Av 400 spectrometer. Mass spectra were recorded on LCMS QP 5000 Shimadzu. Thin layer chromatography was performed using pre-coated aluminium plates, coated with silica gel GF254 [E.Merck]. Ethylacetate: Methanol in the ratio of 3 : 2 was used as the eluent. The spots were visualized in the UV/Iodine chamber.

METHOD OF SYNTHESIS
Synthesis of 3-(4-acetyl phenyl)-2-(phenyl)-3H quinazoline-4-one derivatives(D)
To 0.01 moles of Anthralinic acid is added to 0.02 moles of benzoyl chloride in pyridine (100ml). Kept for a reflux for 1hr 45 min. The mixture was shaken for 10 min and then set aside at room temp for further 1hr with occasional shaking. The reaction mixture was poured in to cold water with stirring then solid white color product was separated out, filtered and dried in a vacuum desiccator up to complete drying of compound. The compound was recrystallized from dioxane. Percentage yield 98%w/w was obtained and melting point was found to be 58-60°C. To a mixture of compound (C) (0.01 moles) and p-amino acetophenone was heated at 150°C on sand bath for 1hr. After cooling the crude mass was crystallised from ethanol twice to give reddish brown crystals.
Synthesis of 3(4(3(4-substituted phenyl) acryloyl)phenyl) 2-phenyl quinazoline (4H)-one (Q_{4,4})

Equimolar mixture of compound D (0.01mole) and the appropriate aromatic aldehydes (0.01mole) p-chlorobenzaldehyde, p-nitro benzaldehyde, p-methoxybenzaldehyde and p-methoxybenzaldehyde were dissolved in ethanol and cold solution of 40% NaOH (15mL) was added in portion keeping the temperature below 10°C with continuous stirring. The reaction mixture was kept overnight. Then it was acidified with dilute HCl and poured ice cold water with stirring. The product obtained was filtered, washed with cold water dried and recrystallized from ethanol.

Synthesis of pyrazolines (P_{4,4})/ N-acetylpyrazolines (P_{Y,4}) / N-phenylpyrazolines (Ph_{4,4})

Mixture of compound Q_{4,4} (0.01mole) and phenyl hydrazine/hydrazide hydrate dissolved in 20 ml of 1, 4 dioxide/gla.aceticacid/ethanol. To this reaction added 2-3 drops of sulphuric acid and the contents were refluxed for 4-5 hrs. After cooling the reaction mixture pour the contents in ice cold water. The obtained solid allow drying and recrystallized from ethanol (Scheme-I).

Q1: 3(4(3(4-chloro phenyl) acryloyl)phenyl) 2-phenyl quinazoline (4H)-onem. p. 140-142°C; yield (%): 63; R_{f}:0.43; IR (ATR,Cm\textsuperscript{-1}): 1644 (C=O of chalcone, str), 1701 (C=O of quinazoline, str), 1610 (C=N, str), 1567 (C=C, str), 2970 (C-H Ali, str), 3107 (C-H Aro, str), 819 (C-Cl, str); \textsuperscript{1}H NMR (6ppm; CDCl\textsubscript{3}/DMSO-d\textsubscript{6}) : 7.10-9.12 (17H,m,Ar-H), 6.75 (2H,s,chalcone); Mass: m/z 142.

Q2: 3(4(3(4-nitro phenyl) acryloyl)phenyl) 2-phenyl quinazoline (4H)-onem. p. 168-170°C; yield (%): 73; R_{f}:0.68; IR (ATR,Cm\textsuperscript{-1}): 1647 (C=O of chalcone, str), 1707 (C=O of quinazoline, str), 1608 (C=N, str), 1565 (C=C, str), 2979 (C-H Ali, str), 3117 (C-H Aro, str), 1463 (N=O, str); \textsuperscript{1}H NMR (6ppm; CDCl\textsubscript{3}/DMSO-d\textsubscript{6}) : 7.3-9.9 (17H,m,Ar-H), 6.79 (2H,s,chalcone); Mass: m/z 170.

Q3: 3(4(3(4-methyl phenyl) acryloyl)phenyl) 2-phenyl quinazoline (4H)-onem. p. 210-212°C; yield (%): 79; R_{f}:0.88; IR (ATR,Cm\textsuperscript{-1}): 1651 (C=O of chalcone, str), 1707 (C=O of quinazoline, str), 1596 (C=N, str), 1560 (C=C, str), 2935 (C-H Ali, str), 3113 (C-H Aro, str); \textsuperscript{1}H NMR (6ppm; CDCl\textsubscript{3}/DMSO-d\textsubscript{6}) : 7.10-9.12 (17H,m,Ar-H), 6.75 (2H,s,chalcone); Mass: m/z 212.

Q4: 3(4(3(4-methoxy phenyl) acryloyl)phenyl) 2-phenyl quinazoline (4H)-onem. p. 178-180°C; yield (%): 83; R_{f}:0.94; IR (ATR,Cm\textsuperscript{-1}): 1668 (C=O of chalcone, str), 1701 (C=O of quinazoline, str), 1608 (C=N, str), 1556 (C=C, str), 2955 (C-H Ali, str), 3104 (C-H Aro, str), 1117 (C-O-C, str); \textsuperscript{1}H NMR (6ppm; CDCl\textsubscript{3}/DMSO-d\textsubscript{6}) : 7.2-9.0 (17H,m,Ar-H), 6.45 (2H,s,chalcone); Mass: m/z 180.

P_{1}: 3 (4-(5-(chlorophenyl) 4, 5 dihydro-1H- pyrazol-3-yl) phenyl quinazoline 4(3H) one m. p. 190-192°C; yield (%): 43; R_{f}:0.79; IR (ATR,Cm\textsuperscript{-1}): 1710 (C=O of quinazoline, str), 3610 (N-H, str), 1555 (C=C, str), 1598 (C=N, str), 2930 (C-H Ali, str), 3097 (C-H Ar, str), 788 (C-Cl, str); \textsuperscript{1}H NMR (6ppm; CDCl\textsubscript{3}/DMSO-d\textsubscript{6}) : 5. 60 (1H,s,N=Ar-H ) , 8.05 (1H,s,N=Ar-H ), 7.11-9.08 (17H,m,Ar-H ),3.20 (2H,dd,C\textsubscript{8}-pyrazole), 2.20 (1H,s,C\textsubscript{8}-H-pyrazole); Mass: m/z 192.

P_{2}: 3 (4-(5-(nitrophenyl) 4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline 4(3H) onem. p. 110-112°C; yield (%): 85; R_{f}:0.76; IR (ATR,Cm\textsuperscript{-1}):1708 (C=O of quinazoline, str), 3590 (N-H, str), 1562 (C=C, str), 1596 (C=N, str), 2976 (C-H Ali, str), 3111 (C-H Ar, str); \textsuperscript{1}H NMR (6ppm; CDCl\textsubscript{3}/DMSO-d\textsubscript{6}) : 5. 82 (1H,s,N=Ar-H ) , 7.21-8.98 (17H,m,Ar-H ).3.20 (2H,dd,C\textsubscript{8}-pyrazole), 2.20 (1H,s,C\textsubscript{8}-H-pyrazole); Mass: m/z 112.

P_{3}: 3 (4-(5-(methylphenyl) 4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline 4(3H) onem. p. 234-236°C; yield (%): 56; R_{f}:0.82; IR (ATR,Cm\textsuperscript{-1}):1699 (C=O of quinazoline, str), 3608 (N-H, str), 1560 (C=C, str), 1590 (C=N, str), 2970 (C-H Ali, str), 3127 (C-H Ar, str); \textsuperscript{1}H NMR (6ppm; CDCl\textsubscript{3}/DMSO-d\textsubscript{6}) : 5. 82 (1H,s,N=Ar-H ) , 7.32-9.01 (17H,m,Ar-H ),3.10 (2H,dd,C\textsubscript{8}-pyrazole), 2.36 (1H,s,C\textsubscript{8}-H-pyrazole), 1.56 (3H,s,Ar-methyl); Mass: m/z 236.

P_{4}: 3 (4-(5-(methoxyphenyl) 4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline 4(3H) one m. p. 161-163°C; yield (%): 78; R_{f}: 0.68; IR (ATR,Cm\textsuperscript{-1}):1699 (C=O of quinazoline, str), 3627 (N-H, str), 1550 (C=C, str), 1593 (C=N, str), 2989 (C-H Ali, str), 3115 (C-H Ar, str); \textsuperscript{1}H NMR (6ppm; CDCl\textsubscript{3}/DMSO-d\textsubscript{6}) : 5. 82 (1H,s,N=Ar-H ) , 7.32-9.01 (17H,m,Ar-H ),3.10 (2H,dd,C\textsubscript{8}-pyrazole), 2.36 (1H,s,C\textsubscript{8}-H-pyrazole), 2.06 (3H,s,Ar-methoxy); Mass: m/z 163.

P_{5}: 3 (4-(1-phenyl- 5-(chlorophenyl) 4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline-4(3H) one m. p. 176-178°C; yield (%): 59; R_{f}: 0.93; IR (ATR,Cm\textsuperscript{-1}): 1706 (C=O of quinazoline, str), 1556 (C=C, str), 1598 (C=N, str), 2908 (C-H Ali, str), 3110 (C-H Aro, str), 820 (C-Cl, str); \textsuperscript{1}H NMR (6ppm; CDCl\textsubscript{3}/DMSO-d\textsubscript{6}) : 7.32-9.01 (23H,m,Ar-H ),3.10 (2H, d,CH\textsubscript{2} of pyrazole ), 4.36 (1H,s,CH-pyrazole), 1.56 (3H,s,Ar-methyl); Mass: m/z 178.

P_{6}: 3 (4-(1-phenyl- 5-(nitrophenyl) 4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline-4(3H) one m. p. 267-269°C; yield (%): 81;
Antibacterial activity

The synthesised compounds (Q₄₋₄ & P₁₋₄) were screened for their in vitro antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* by measuring the zone of inhibition in mm². The antibacterial activity was performed by filter paper disc plate method at concentration 100 µg/mL and reported in Table-1. Muller Hinton agar & Sabouroud Dextrose agar were employed as culture medium and DMSO was used as solvent control for antibacterial activity. Ciprofloxacin was used as standard for antibacterial activity respectively.

RESULTS AND DISCUSSION

Synthesis of 16 novel compounds involves in three steps. The key intermediate compound D was prepared from Anthraquinone and benzoyl chloride in presence of pyridine to give 2-phenylbenzo(1,3) oxazoline-4-one and further treated with p-aminacetophenone to give 3-(4-acetylphenyl)-2-phenyl-3H quinazoline-4-one derivatives. The later refluxed with different substituted aromatic aldehydes in ethanol and cold solution of 40% alkali yielded the chalcone compounds Q₁₋₄ and further treated with hydrazine hydrate and acetic acid yielded the desired compound P₁₋₄, Ph₁₋₄ & P₃₋₄ in good yield. For P₄₋₄ the IR spectra showed intense peaks at 1698 cm⁻¹ for (C=O of chalcone, str), 1725 cm⁻¹ for (C=O of quinazoline, str), 1550-1585 cm⁻¹ for (C=C, str) and 1590-1620 cm⁻¹ for (C=N, str). The H NMR showed singlet at 6.50-6.65 (2H, s, CH=CH) indicating the presence of chalcone group. The targeted compounds P₁₋₄, Ph₁₋₄ & P₃₋₄ obtained from P₁₋₄ in presence of hydrazine hydrate and acetic acid in good yield. The IR showed intense peak at 3650-3590 cm⁻¹ for (NH of pyrazoline, str) presence at P₁₋₄, absence in Ph₁₋₄ and P₃₋₄. The H NMR showed singlet at 5.6-6.4 (1H, s, NH for pyrazoline). The mass spectra of the all 16 compounds showed molecular ion peaks at corresponding to their molecular formula. The newly synthesized compounds were screened for antibacterial activity and it was found that the compounds Q₁₋₄ showed no significant activity and the compounds P₁₋₄ showed moderate activity when compared to standard.
ACKNOWLEDGMENT

The authors are thankful to management Vishwabharathi College of Pharmacy, Perecherla Guntur for providing laboratory facilities. The authors are also thankful to sophisticated instrumentation facility Lailaimpex, Vijayawada for providing spectral studies.

Scheme-I

\[
\text{A} + \text{B} \xrightarrow{\text{Pyridine}} \text{C} \xrightarrow{\text{COCH}_3} \text{D} \xrightarrow{\text{CHO}} \text{Q1-4}
\]
Table 1: Antibacterial activity of synthesized compounds (Q₁₋₄ & P₁₋₄)

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Compound</th>
<th>Zone of inhibition (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>E.Coli (443)</td>
</tr>
<tr>
<td>1</td>
<td>Q1</td>
<td>09</td>
</tr>
<tr>
<td>2</td>
<td>Q2</td>
<td>08</td>
</tr>
<tr>
<td>3</td>
<td>Q3</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>Q4</td>
<td>09</td>
</tr>
<tr>
<td>5</td>
<td>P1</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>P2</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>P3</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>P4</td>
<td>28</td>
</tr>
<tr>
<td>9</td>
<td>std</td>
<td>31</td>
</tr>
</tbody>
</table>

REFERENCES