Synthesis and Pharmacological Studies on Novel Heterocycles

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ABSTRACT: New 2-(2'-Chloro-benzo[h]quinolin-3-yl)-3-phenyl(4''-methoxy phenyl)-6-phenyl-5-carbethoxy-4,5-dihydrofuro[2,3-d]thiazolidine(2) and 2-(2'-Chloro-benzo[h]quinolin-3-yl)-3-(4''-methoxy phenyl)-7-phenyl-2,3-dihydrothiazololo[4,5-d] pyrimidin-5-ol quinolines(3) were synthesized from benzylidenederivatives of quinolinetiazolidinone(1). The benzylidene was reacted with ethoxy carbonyl methylene triphenylphosphorane in ethyl acetate (50mL) was refluxed for 24h. A solution of benzylidene intermediates(1) thus obtained was utilized for the synthesis of furoquinolines. The pharmacology of Furoquinolines is quite interesting and several compounds reported to possess vasodialating and other therapeutically potential properties. Recently thiazopyrimidines has received considerable attention to their pharmacological studies. Theophylline [6] present in tea leaves, it is used as diuretic and bronchilators. Caffeine[7] found in coffee and tea is mildly acting stimulant. The benzylidene compounds were as a good intermediate in the synthesis of various thiazolidinone fused heterocyclics such as thiazolopyrimidinopyrimidines,thiazolooxadiazolopyrimidines[8],diazepines[9],pyrimidines[10],and pyrimidinethiones[10], furo and pyrazolinothiazolidinone[7] Derivatives. With this pretext, we aimed to utilize the benzylidene compounds in the synthesis of Furo, Pyrimidothiazolidinones.

KEYWORDS: Furoquinoline, Pyrimidoquinoline

I. INTRODUCTION

Pyrimidineshave been studied extensively for their broad spectrum of pharmacological activities such as analeptics, sedatives, hypnotics [1, 2], anticonvulsant, anti-inflammatory [3], antimalarial [4], as central nervous stimulant, bronchilators and diuretics, antitumor [5] agents. The pharmacology of Furoquinolines is quite interesting and several Furoquinolines are reported to possess vasodialating and other therapeutically potential properties. Recently thiazopyrimidines has received considerable attention to their pharmacological studies. Theophylline [6] present in tea leaves, it is used as diuretic and bronchilators. Caffeine[7] found in coffee and tea is mildly acting stimulant. The benzylidene compounds were as a good intermediate in the synthesis of various thiazolidinone fused heterocyclics such as thiazolopyrimidinopyrimidines,thiazolooxadiazolopyrimidines[8],diazepines[9],pyrimidines[10],and pyrimidinethiones[10], furo and pyrazolinothiazolidinone[7] Derivatives. With this pretext, we aimed to utilize the benzylidene compounds in the synthesis of Furo, Pyrimidothiazolidinones.

II. RESULTS AND DISCUSSION

Synthesis of 2-(2'-Chloro-benzo[h]quinolin-3-yl)-3-phenyl(4''-methoxyphenyl)-6-phenyl-5-carbethoxy-4,5-dihydrofuro[2, 3-d] thiazolidine(2a-h):

First the benzylidene intermediate (1) thus obtained was utilized for the synthesis of furoquinolines. A solution of benzylidene compound 5-benzylidine-2[3'-(2'-chlorobenzo[h]quinolyl)]-3-(4''-methoxyphenyl)-4-thiazolidinone (1a) (0.0005mol, 0.245g) ethoxy carbonyl methylene triphenylphosphorane (0.0005mol, 0.4474g) in ethyl acetate (50mL) was refluxed for 24h. After evaporation of the solvent, the residue was subjected to column chromatography over silicagel eluted with PE: EA (85:15) gave a white coloured compound which was identified as triphenylphosphine. Further eluates of PE: EA (75:25) gave yellowish orange crystal with m.p 161°C. IR spectrum of the compound (2a) showed signals at 1718cm⁻¹(COO), 1672 cm⁻¹(C-O-C), 748 cm⁻¹(C-S-C).

³¹H-NMR spectrum of the compound signals at δ1.3 (t, 3H, CH₃), δ 4.2 (unresolved q, 2H, CH₂CH₃) δ3.7 (s, OCH₃) δ8.1 (s, 1H, C=4H) δ7.3-8 (m, 6H) δ7.3-7.6 (m, 12H). Mass spectrum of the compound peaks at m/z 594.5. Elemental analysis of the compound confirmed to be C₉₁H₈₀O₂₂SCl. The spectral and analytical data unambiguously attested the compound to be Synthesis of 2-(2' -Chloro-benzo[h] quinolin-3-yl)-3-phenyl (4''-methoxyphenyl)-6-phenyl-5-carbethoxy-4,5-dihydrofuro-[2, 3-d]-thiazolidine(2a).
The sequence of the reaction was extended to synthesis its derivatives 2(b-h).

Synthesis of 2-(2′-Chloro-benzo[h]quinolin-3′-yl)-3-(4″-methoxy-phenyl)-7-phenyl-2,3-dihydrothiazolo[4,5-d]pyrimidin-5-ol quinolines 3(a-h)

Next we focussed our interest towards the synthesis of pyrimidines and pyrimidine thiol. 3-benzylidene-2[3′-2-(2′-chlorobenzo[h]quinolyl)]-3-(4″-methoxyphenyl)-4-thiazolidinone (1a) (0.0005mol, 0.245g) and urea (0.0005mol, 0.040g) were dissolved in glacial acetic acid (15mL) and anhydrous CH3COONa (0.00163mol, 0.1375g) was added. The reaction mixture was heated to reflux for 12h. On cooling, bright yellow crystals appeared gradually. After complete crystallization, the reaction mixture was filtered and recrystallised from glacial acetic acid. m.p 126°C Yield 0.63g (75%).

IR spectrum of the compound 3a showed signals at 1033 cm⁻¹, 1596 cm⁻¹, 746 cm⁻¹ for C-Cl, C=N,(C=S-C) respectively. ¹H-NMR spectrum of the compound signals at δ4.3 (s, 3H, OCH₃), δ6.8-6.9 (m, 5H) δ7.2-8 (m, 12H). Mass spectrum showed m/z peak at 532.5. Elemental analysis of the compound confirmed to be C_{31}H_{21}ON_{4}ClS. The spectral and analytical data unambiguously attested the compound to be 2-(2′-Chloro-benzo[h]quinolin-3′-yl)-3-(4″-methoxy-phenyl)-7-phenyl-2,3-dihydrothiazolo[4,5-d]pyrimidin-5-ol quinolines (3a)
The sequence of the reaction was extended to synthesis its derivatives 3(b-h).

\[
\begin{align*}
\text{a)} & \quad R^1 = R^2 = R^4 = R^5 = H, \quad R^3 = \text{OMe} \\
\text{b)} & \quad R^1 = R^2 = R^3 = R^4 = R^5 = H \\
\text{c)} & \quad R^2 = R^3 = R^4 = R^5 = H, \quad R^1 = \text{CH}_3 \\
\text{d)} & \quad R^1 = R^2 = R^4 = R^5 = H, \quad R^2 = \text{CH}_3 \\
\text{e)} & \quad R^1 = R^2 = \text{CH}_3, \quad R^3 = R^4 = R^5 = H \\
\text{f)} & \quad R^1 = R^2 = R^3 = R^4 = R^5 = H, \quad R^2 = \text{OMe} \\
\text{g)} & \quad R^1 = R^3 = R^5 = H, \quad R^2 = \text{OMe} \\
\text{h)} & \quad R^1 = R^3 = \text{CH}_3, \quad R^2 = R^4 = R^5 = H
\end{align*}
\]

**PHARMACOLOGICAL RESULT**

The antibacterial antifungal and anti oxidant activity of the synthesized compounds were tested. Antibacterial activities of the compounds were against the bacteriaes Escherichia coli (E.c), Pseudomonas aeruginosa (P.a)Vibriocholerae(V.c)and fungalAspergillusniger(A.n)at various concentrations 100µg/L,50µg/L,25µg/L.

<table>
<thead>
<tr>
<th>compound</th>
<th>INHIBITION ZONE in mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vibrio cholerae</td>
</tr>
<tr>
<td></td>
<td>100  50  25</td>
</tr>
<tr>
<td>2a</td>
<td>7    6    7</td>
</tr>
<tr>
<td>2c</td>
<td>8    7    7</td>
</tr>
<tr>
<td>3a</td>
<td>8    6    6</td>
</tr>
<tr>
<td>3c</td>
<td>8    7    8</td>
</tr>
</tbody>
</table>
The table shows the antibacterial activities and antifungal activities of the compounds 2(a),2(c) and 3(a),3(c) It was found that the compounds were active against Vibrio cholerae, Pseudomonas aeruginosa, Escherichia coli (E.c), and is almost equal to the standard Gentamicin. The compounds 2a and 3c were inactive towards the fungal Aspergillus niger and 2c,3a were active against the fungal.

ANTIOXIDANT ACTIVITY

DPPH ASSAY

Samples- sample extracts at concentrations (62.5-1000μg) in methanol

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>CONCN(µg)</th>
<th>Compound 2a</th>
<th>Compound 3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>62.5</td>
<td>21.03 ± 0.0208</td>
<td>21.03 ± 0.0408</td>
</tr>
<tr>
<td>2.</td>
<td>125</td>
<td>26.36 ± 0.01155</td>
<td>31.58 ± 0.01115</td>
</tr>
<tr>
<td>3.</td>
<td>250</td>
<td>31.58 ± 0.0115</td>
<td>47.37 ± 0.0451</td>
</tr>
<tr>
<td>4.</td>
<td>500</td>
<td>47.37 ± 0.0058</td>
<td>56.14 ± 0.02646</td>
</tr>
<tr>
<td>5.</td>
<td>1000</td>
<td>56.14 ± 0.02646</td>
<td>64.91 ± 0.0462</td>
</tr>
</tbody>
</table>

Table shows the antioxidant activity of compounds 2(a) and 3(a). Both the samples show good antioxidant activity. It was found from the table that as the concentration increases the antioxidant activity also increases.

III. EXPERIMENTAL RESULTS

Preparation of 5-benzylidene-2-(2’-Chloro-benzo[h] quinolin-3’-yl)-6-phenyl thiazolidine 2(a-h)

A solution of benzylidene compound and ethoxy carbonyl methylene triphenylphosphorane (in ethyl acetate (50mL) was refluxed for 24h. After evaporation of the solvent, the residue was subjected to column chromatography over silicagel eluted with PE: EA (85:15) gave a white coloured compound which was identified as triphenylphosphine. Further eluates of PE: EA (75:25) gave yellowish orange crystals.

Preparation of 5-benzylidene-2-(2′-Chloro-benzo[h]quinolin-3′-yl)-3-(4-methoxyphenyl) thiazolidine 4-one 2(a)

A solution of benzylidene compound 5-benzylidene-2[3′-(2′-chlorobenzo[h]quinolyl)]-3-(4′-methoxyphenyl)-4-thiazolidinone (1a) (0.0005mol, 0.245g) ethoxy carbonyl methylene triphenylphosphorane (0.0005mol, 0.4474g) in ethyl acetate (50mL) was refluxed for 24h. After evaporation of the solvent, the residue was subjected to column chromatography over silicagel eluted with PE: EA (85:15) gave a white coloured compound which was identified as triphenylphosphine. Further eluates of PE: EA (75:25) gave yellowish orange crystals.

2-(2’-Chloro-benzo[h] quinolin-3′-yl)-3, 6-diphenyl-5-carbethoxy-4, 5-dihydrofuro [2, 3-d] thiazolidine 2b

3-benzylidene-2[3-(2-chlorobenzo[h]quinolyl)]-3-(phenyl)-4-thiazolidinone:0.4474g (0.00055mol)(1b). Ethyl acetate-50mL, Reflux time:24h, mp:260°C, Yield:1.467g(45%), IR (KBr) v_max: 1718cm⁻¹(COO), 1672 cm⁻¹(C=O-C), 748 cm⁻¹ (C-S-C). Anal.Calcd. (%) for C₃₃H₂₂O₅N₅SCl (565.04): C, 68.85; H, 4.24; N, 4.72; S, 5.40; found: C, 68.62; H, 4.02; N, 4.61, S, 5.10.
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2-(2'-Chloro-benzof[h]quinolin-3'-yl)-3-(2'-methoxyphenyl)-6-phenyl-5-carboxethoxy-4,5-dihydrofuro[2, 3-d] thiazolidine 2c
5-benzylidene-2-[3-(2-chlorobenzof[h]quinolyl)-3-(2'-methoxyphenyl)-4-thiazolidinone:0.250g (0.0005070mol)(1e), Ethyloxycarbonylmethylene (triphenylphosphorane): 0.1695g, (0.0005070mol), Ethyl acetate-20mL, Reflux time:21h, Temperature: 85°C, mp:136°C, Yield:0.1539g(50%), IR (KBr) ν_max: 1718cm⁻¹(COO), 1672 cm⁻¹(C-O-C), 748 cm⁻¹(C-S-C). Anal.Calcd. (%) for C₃₄H₂₂O₃N₂SCI (595.06): C, 70.52; H, 4.69; N, 4.83; S, 5.53; found: C, 70.25; H, 4.56; N, 4.76, S, 5.36.

2-(2'-Chloro-benzof[h]quinolin-3'-yl)-3-(3'-methylphenyl)-6-phenyl-5-carboxethoxy-4,5-dihydrofuro[2, 3-d] thiazolidine 2d
5-benzylidene-2-[3-(2-chlorobenzof[h]quinolyl)-3-(3'-methylphenyl)-4-thiazolidinone:0.250g (0.0005070mol)(1d), Ethyloxycarbonylmethylene (triphenylphosphorane): 0.1695g, (0.0005070mol), Ethyl acetate-20mL, Reflux time:22h, Temperature: 85°C, mp:142°C, Yield:0.1598g(49%), IR (KBr) ν_max: 1718cm⁻¹(COO), 1672 cm⁻¹(C-O-C), 748 cm⁻¹(C-S-C). Anal.Calcd. (%) for C₃₄H₂₂O₃N₂SCI (597.07): C, 70.52; H, 4.69; N, 4.83; S, 5.53; found: C, 70.25; H, 4.52; N, 4.62, S, 5.26.

2-(2'-Chloro-benzof[h]quinolin-3'-yl)-3-(3'-methylphenyl)-6-phenyl-5-carboxethoxy-4,5-dihydrofuro[2, 3-d] thiazolidine 2e
5-benzylidene-2-[3-(2-chlorobenzof[h]quinolyl]-3-(3'4'-methylphenyl)-4-thiazolidinone:0.220g (0.0004462mol)(1e), Ethyloxycarbonylmethylene (triphenylphosphorane): 0.1491g, (0.0004462mol), Ethyl acetate-25mL, Reflux time:24h, Temperature: 85°C, mp:146°C, Yield:0.1408g(52%), IR (KBr) ν_max: 1718cm⁻¹(COO), 1672 cm⁻¹(C-O-C), 748 cm⁻¹(C-S-C). Anal.Calcd. (%) for C₃₄H₂₂O₃N₂SCI (597.07): C, 69.24; H, 4.48; N, 4.61; S, 5.28; found: C, 69.14; H, 4.42; N, 4.32, S, 5.02.

2-(2'-Chloro-benzof[h]quinolin-3'-yl)-3-(2'-methoxyphenyl)-6-phenyl-5-carboxethoxy-4,5-dihydrofuro[2, 3-d] thiazolidine 2f
5-benzylidene-2-[3-(2-chlorobenzof[h]quinolyl]-3-(2'-methoxyphenyl)-4-thiazolidinone:0.200g (0.000392mol)(1f), Ethyloxycarbonylmethylene (triphenylphosphorane): 0.1313g, (0.000392mol), Ethyl acetate-25mL, Reflux time:22h, Temperature: 85°C, mp:144°C, Yield:0.1196g(49%), IR (KBr) ν_max: 1728cm⁻¹(COO), 1656 cm⁻¹(C-O-C), 752 cm⁻¹(C-S-C). Anal.Calcd. (%) for C₃₄H₂₂O₃N₂SCI (595.06): C, 68.62; H, 4.57; N, 4.70; S, 5.38; found: C, 68.53; H, 4.36; N, 4.65, S, 5.22.

2-(2'-Chloro-benzof[h]quinolin-3'-yl)-3-(3'-methylphenyl)-6-phenyl-5-carboxethoxy-4,5-dihydrofuro[2, 3-d] thiazolidine 2g
5-benzylidene-2-[3-(2-chlorobenzof[h]quinolyl]-3-(3'-methylphenyl)-4-thiazolidinone:0.200g (0.000392mol)(1g), Ethyloxycarbonylmethylene (triphenylphosphorane): 0.1313g, (0.000392mol), Ethyl acetate-25mL, Reflux time:22h, Temperature: 85°C, mp:148°C, Yield:0.1221g(49%), IR (KBr) ν_max: 1728cm⁻¹(COO), 1656 cm⁻¹(C-O-C), 752 cm⁻¹(C-S-C). Anal.Calcd. (%) for C₃₄H₂₂O₃N₂SCI (595.06): C, 68.62; H, 4.57; N, 4.70; S, 5.38; found: C, 68.53; H, 4.26; N, 4.52, S, 5.16.

2-(2'-Chloro-benzof[h]quinolin-3'-yl)-3-(3'-methylphenyl)-6-phenyl-5-carboxethoxy-4,5-dihydrofuro[2, 3-d] thiazolidine 2h
5-benzylidene-2-[3-(2-chlorobenzof[h]quinolyl]-3-(3'-methylphenyl)-4-thiazolidinone:0.180g (0.0003549mol)(1h), Ethyloxycarbonylmethylene (triphenylphosphorane): 0.1187g, (0.0003549mol), Ethyl acetate-25mL, Reflux time:22h, Temperature: 85°C, mp:148°C, Yield:0.1124g(49%), IR (KBr) ν_max: 1728cm⁻¹(COO), 1650 cm⁻¹(C-O-C), 752 cm⁻¹(C-S-C). Anal.Calcd. (%) for C₃₄H₂₂O₃N₂SCI (595.06): C, 67.46; H, 4.36; N, 4.49; S, 5.14; found: C, 67.14; H, 4.02; N, 4.24, S, 5.02.

Synthesis of 2-(2-Chloro-benzof[h]quinolin-3'-yl)-7-phenyl-2,3-dihydrothiazolo[4,5-d] pyrimidin-5-ol 3(a-g)
A solution of benzidine compound and urea were dissolved in glacial acetic acid (15mL) and anhydrous CH₃COONa was added. The reaction mixture was heated to reflux for 12h. On cooling, crystals started to form gradually. After complete crystallization, the reaction mixture was filtered and recrystallised from glacial acetic acid.

2-(2-Chloro-benzof[h]quinolin-3'-yl)-3-(4-methoxyphenyl)-7-phenyl-2,3-dihydrothiazolo[4,5-d] pyrimidin-5-ol 3a
5-benzylidene-2-[3'-(2-chlorobenzof[h]quinolyl]-3-(4'4'-methoxyphenyl)-4-thiazolidinone: 0.202g (0.0004mol), urea: 0.024g (0.0004mol), Glacial acetic acid: 15mL, CH₃COONa:0.137g, IR (KBr) ν_max:1033(C-Cl), 1596(C=N), 746 cm⁻¹ (C-S-C).
IV. CONCLUSION

The utility of 5-benzylidene-3(2'-chlorobenzo[h]quinolyl)-4-thiazolidinones (1) in the synthesis of various novel heterocycles viz., 2-(2'-Chloro-benzo[h]quinolin-3-yl)-3(4'-methoxyphenyl)-6-phenyl-5-carbethoxy-4,5-dihydrofururo[2,3-d]thiazolidine (2) and 2-(2'-Chloro-benzo[h]quinolin-3-yl)-3(4'-methoxy-phenyl)-7-phenyl-2,3-dihydrothiazolo[4,5-d] pyrimidin-5-ol (3) by reacting with ethoxy carbonyl diethylene triplyl phosphorane and urea respectively. It was characterized by IR, NMR, and Mass spectral analysis. The antibacterial antifungal and antioxidant activity of the synthesised compounds were found to be active.

REFERENCES

[10] Bhawani Singh, Deepika Mehta, Lalit K. Baregama and G.L. Taleswara Synthesis And Biological evaluation Of 7-N-(N-Alkoxyphalimidio)-2-