Synthesis of Functionalized Dihydropyrimidothiazinoquinoline Derivatives via Reaction of 3-(Chloromethyl)-2-chloroquinolines and 2-Thioxo-2,3-dihydropyrimidin-4(1H)-one

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An efficient method for the synthesis of novel dihydropyrimidothiazinoquinoline derivatives through the reaction of 2-chloro-3-(chloromethyl)quinolines and 2-thioxo-2,3-dihydropyrimidin-4(1H)-one in the presence of K₂CO₃ is demonstrated.

Keywords: Quinoline, Cyclization, 3-(Chloromethyl)-2-chloroquinolines, Cascade reaction

INTRODUCTION

Quinoline is one of the most widespread N-heteroaromatic cores incorporated into the structures of various pharmaceuticals. Quinolines signify an important group of heterocyclic compounds, as they are critical moieties of various biologically potent naturally occurring compounds as well as diverse pharmacologically fascinating compounds [1-3]. The quinoline ring has also gained a remarkable interest because of its significant applications in many areas, for instance, they can be used as corrosion inhibitors [4], precursors of oil-soluble food colorants, and as chemo sensors in luminescence chemistry [5].

Moreover, quinolines contain various pharmacological and biological properties including antifungal [6], antileishmanial [7], antitumor [8], antibacterial [9], and antiamebic [10] and also chloroquinolines are extensively applied for the treatment of malaria [11].

Because of the importance and various usages of quinolines, different classical methods, such as the Skraup [12], Doebner [13], Doebner-von Miller [14], Pfitzinger [15], Combes [16] and Friedländer protocols [17] were reported to from the quinoline unit.

2-Chloroquinoline-3-carbaldehydes [18] as significant synths were used for the formation of a number of heterocyclic compounds such as pyrazolo[3,4-b]quinolines [19], pyrano-[4,3-b]quinolines [20], quinolino[3,2-f][1,2,4] triazolo[4,3-b]-1,2,4 triazepines [21], isoxazolo[5,4-b] quinolines [22], and benzo[g]naphtho[6][1,8]naphthyridines [23]. Nawaz Khan et al. in (2010) reported the synthesis of 3-[(2-chloroquinolin-3-yl)methyl]pyrimidin-4-(3H)-ones using potassium hydroxide and Fe nano particles [24]. Various quinoline based 1,3,4-oxadiazoles were synthesized via a chloro-amine coupling reaction in the presence of iodobenzenediaacetate. These compounds were examined for their antifungal, antibacterial, anti-malarial, and antituberculosis properties. Some of them demonstrated good antituberculosis property [25].

In continuation of our interest on quinolines chemistry [26-35], herein, we report the synthesis of novel dihydropyrimido-thiazinoquinolinone derivatives using substituted 2-chloro-3-chloromethyl quinoline as a starting material.

EXPERIMENTAL

Chemicals and Apparatus

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. Melting points are uncorrected. The FT-IR spectra were recorded on a FT-IR
Tensor 27 Spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 and 500 MHz Spectrometer in DMSO-d$_6$ as the solvent. All products were characterized using IR, $^1$H NMR and $^{13}$C NMR spectroscopies.

**General procedure for the synthesis of dihydro pyrimido[2',1':2,3][1,3]thiazino[4,5-b]quinolin-1(6H)-one (5a-g).** 3-(Chloromethyl)-2-chloroquinolines 3a-g (0.5 mmol) and 2-dioxo-2,3-dihydropyrimidin-4(1H)-one 4 (0.5 mmol) in DMF in the presence of K$_2$CO$_3$ (1 mmol) was heated under reflux conditions for 4-9 h. The progress of the reaction was monitored by TLC (ethyl acetate: petroleum ether (9:1)). After completion, the reaction was quenched with ice-water. The mixture was filtered and the precipitate washed with MeOH to afford the product. The crude solid was purified with 95:5 ethyl acetate: n-hexane using column chromatography to obtain the pure white product.

**Spectra Data**

**11-Methyl-4,4a-dihydropyrimido[2',1':2,3][1,3]thiazino[4,5-b]quinolin-1(6H)-one:** (C$_{14}$H$_{12}$N$_4$O$_3$) (5a). White powder (81%), m.p.: 289-291 °C; FT-IR (KBr): $\nu_{\max}$ = 1480, 1500, 1748 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ = 2.74 (3H, s, CH$_3$), 4.56 (2H, s, CH$_2$), 6.32 (1H, d, $^3$J$_{HH}$ = 8.0 Hz, CH-16), 7.59 (1H, t, $^4$J$_{HH}$ = 7.6 Hz, CH-1), 7.72 (1H, d, $^3$J$_{HH}$ = 7.2 Hz, CH-6), 7.91 (1H, d, $^3$J$_{HH}$ = 7.6 Hz, CH-2), 8.50 (1H, s, CH-10), 8.97 (1H, d, $^3$J$_{HH}$ = 8.0 Hz, CH-17) ppm; $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ = 18.0, 27.4, 111.9, 120.1, 127.3, 127.7, 131.3, 136.4, 137.2, 139.8, 144.4, 146.3, 161.6, 167.0 ppm.

**9-Chloro-4,4a-dihydropyrimido[2',1':2,3][1,3]thiazino[4,5-b]quinolin-1(6H)-one:** (C$_{14}$H$_{11}$ClN$_4$O$_3$) (5d). White powder (77%), m.p.: 283-285 °C; FT-IR (KBr): $\nu_{\max}$ = 1474, 1646 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ = 4.57 (2H, s, CH$_2$), 6.30 (1H, d, $^3$J$_{HH}$ = 8.0 Hz, CH-16), 7.87, 7.89 (1H, d, $^3$J$_{HH}$ = 2.4 Hz, CH-6), 8.06 (1H, d, $^3$J$_{HH}$ = 1474 Hz, CH-2), 8.25 (1H, d, $^3$J$_{HH}$ = 2.0 Hz, CH-3), 8.51 (1H, s, CH), 8.85 (1H, d, $^3$J$_{HH}$ = 8.0 Hz, CH-17) ppm; $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ = 27.4, 111.8, 121.6, 127.0, 128.0, 130.6, 132.0, 132.2, 136.2, 139.7, 134.9, 147.7, 147.8, 161.5, 166.9 ppm.

**9-Bromopyrimido[2',1':2,3][1,3]thiazino[4,5-b]quinolin-1(6H)-one:** (C$_{14}$H$_{10}$BrN$_4$O$_3$) (5e). White powder (80%), m.p.: 279-281 °C; FT-IR (KBr): $\nu_{\max}$ = 1650, 1795, 2922 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ = 4.57 (2H, s, CH$_2$), 6.3 (1H, d, $^3$J$_{HH}$ = 8.0 Hz, CH-16), 7.98 (2H, d, $^3$J$_{HH}$ = 1.6 Hz, CH-2,6), 8.4 (1H, s, CH-3), 8.5 (1H, s, CH-10), 8.85 (1H, d, $^3$J$_{HH}$ = 8.0 Hz, CH-17) ppm; $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ = 27.4, 111.8, 120.8, 121.6, 128.5, 130.3, 130.7, 134.5, 136.0, 139.7, 144.1, 147.8, 161.5, 166.9 ppm.

**9-Methoxypyrimido[2',1':2,3][1,3]thiazino[4,5-b]quinolin-1(6H)-one:** (C$_{14}$H$_{11}$O$_2$N$_4$S) (5f). White powder (89%), m.p.: 244-246 °C; FT-IR (KBr): $\nu_{\max}$ = 1415, 1597, 2850, 2919 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ = 4.07 (3H, s, CH$_3$), 4.63 (2H, s, CH$_2$), 6.3 (1H, d, $^3$J$_{HH}$ = 8.0 Hz, CH-16), 7.90 (1H, d, $^3$J$_{HH}$ = 4.8 Hz, CH-2), 8.07 (1H, d, $^3$J$_{HH}$ = 9.2 Hz, CH-3), 8.6 (1H, s, CH-6), 8.83 (1H, d, $^3$J$_{HH}$ = 8.0 Hz, CH-17) ppm; $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ = 27.5, 57.5, 111.8, 114.6, 119.0, 122.1, 126.0, 129.0, 132.2, 139.7, 140.8, 146.1, 153.7, 161.4, 166.9 ppm.

**Benzo[hp]pyrimido[2',1':2,3][1,3]thiazino[4,5-b]quinolin-1(6H)-one:** (C$_{14}$H$_{11}$N$_4$OS) (5g). White powder.
RESULTS AND DISCUSSION

2-Chloroquinoline-3-carbaldehydes 1 was reduced to the corresponding alcohols 2 using NaBH₄ (Scheme 1). Then, alcohols 2 converted to the corresponding 2-chloro-3-(chloromethyl)quinolines 3 with SOCl₂ [36].

Next, 2-chloro-3-(chloromethyl)-8-methylquinoline 3a reacted with 2-thioxo-2,3-dihydropyrimidin-4(1H)-one 4 in the presence of K₂CO₃ under reflux in DMF for 5 hours. Surprisingly, fused polycyclic 11-methylpyrimido[2',1':2,3] [1,3]thiazino[4,5-b]quinolin-1(6H)-one 5a was obtained as the only product (Scheme 2).

To find the optimal reaction conditions, the effects of solvent, promoter and temperature were examined in a model reaction involving 2-chloro-3-(chloromethyl)-8-methylquinoline 3a and 2-thioxo-2,3-dihydropyrimdin-4(1H)-one 4. The results are shown in Table 1. The best result was obtained when the reaction was performed in the presence of K₂CO₃ in DMF under the reflux condition, that product 5a was synthesized in 81% yield in 5 h (Table 1, entry 1). Other solvents such as EtOH, MeOH, H₂O, DMSO, CH₃CN, toluene and dioxane provided the desired products 5a in 35-75% yields (Table 1).

The ¹H NMR spectrum of 5a exhibited the singlet picks at δ = 2.74 for CH₃ and at δ = 4.56 for CH₂. Two peaks as a doublet in 6.32 and 8.97, respectively, are related to hydrogens of alpha and beta positions of carbonyl. The aromatic protons of quinoline ring appeared at 7.59 to 7.91 ppm; ¹³C NMR spectrum of 5a showed absorption bands at δ = 160.9, 174.0 and 167.0 ppm, respectively, and all data verified the molecular structure of 5a.

Relied on the optimal reaction conditions, the scope of
Table 1. Examination of Various Conditions in the Reaction of 2-Chloro-3-(chloromethyl)-8-methylquinoline 3a and 2-Thioxo-2,3-dihydropyrimidin-4(1H)-one 4a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Isolated yield (%)</th>
</tr>
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<tr>
<td>1</td>
<td>K$_2$CO$_3$</td>
<td>DMF</td>
<td>Reflux</td>
<td>5</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>K$_2$CO$_3$</td>
<td>MeOH</td>
<td>Reflux</td>
<td>10</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>K$_2$CO$_3$</td>
<td>H$_2$O</td>
<td>Reflux</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>K$_2$CO$_3$</td>
<td>EtOH</td>
<td>Reflux</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>K$_2$CO$_3$</td>
<td>DMSO</td>
<td>135</td>
<td>5</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>K$_2$CO$_3$</td>
<td>CH$_3$CN</td>
<td>Reflux</td>
<td>7</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>K$_2$CO$_3$</td>
<td>toluene</td>
<td>Reflux</td>
<td>6</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>K$_2$CO$_3$</td>
<td>Dioxane</td>
<td>Reflux</td>
<td>7</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>Cs$_2$CO$_3$</td>
<td>DMF</td>
<td>Reflux</td>
<td>6</td>
<td>61</td>
</tr>
<tr>
<td>10</td>
<td>L-proline</td>
<td>DMF</td>
<td>Reflux</td>
<td>12</td>
<td>35</td>
</tr>
<tr>
<td>11</td>
<td>None</td>
<td>DMF</td>
<td>Reflux</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>K$_2$CO$_3$</td>
<td>DMF</td>
<td>r.t.</td>
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<td>0</td>
</tr>
</tbody>
</table>

Table 2. Diversity in the Synthesis of Dihydropyrimidothiazinoquinolinones 5a-g

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>m. p. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>H</td>
<td>5a</td>
<td>5</td>
<td>81</td>
<td>289-291</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Me</td>
<td>5b</td>
<td>6</td>
<td>85</td>
<td>317-319</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>H</td>
<td>5c</td>
<td>4</td>
<td>87</td>
<td>295-297</td>
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<tr>
<td>4</td>
<td>H</td>
<td>Cl</td>
<td>5d</td>
<td>8</td>
<td>77</td>
<td>283-285</td>
</tr>
<tr>
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<td>Br</td>
<td>5e</td>
<td>9</td>
<td>80</td>
<td>279-281</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>OMe</td>
<td>5f</td>
<td>8</td>
<td>89</td>
<td>244-246</td>
</tr>
<tr>
<td>7</td>
<td>-CH=CH-</td>
<td>H</td>
<td>5g</td>
<td>7</td>
<td>85</td>
<td>292-294</td>
</tr>
</tbody>
</table>
this reaction was examined using various 6-(un)substituted-2-chloro-3-(chloromethyl)quinolines 3a-d. As shown in Scheme 1, 3a-d containing electron-donating and halogen substituents and 2-thioxo-2,3-dihydropyrimidin-4(1H)-one 4 were applied and afforded the new dihydropyrimidothiazinoquinolinone derivatives 5a-g. The results are summarized in Table 2. Electron-donating and electron-withdrawing groups such as halogen on the aryl substituents worked well under aforementioned conditions. To the best of our knowledge, no analogous products have been reported in the literature so far.

A plausible mechanism for the synthesis of 5a is shown in Scheme 3. Reaction is initiated with hydrogen abstraction of N-H of 2-thioxo-2,3-dihydro-1H-pyrimidin-4-one with base, as shown in Scheme 3. After removal of hydrogen and then tautomerization with C=S, sulfur atom attacks to CH₂Cl of 2-chloro-3-chloromethyl-8-methyl-quinoline (3a) to generate intermediate I. Second hydrogen abstraction of N-H of I and then tautomerization prepared N as a nucleophile to intramolecular cyclization to form the desired product 5a (Scheme 3).

**CONCLUSIONS**

In summary, we have developed an efficient method for the synthesis of substituted, functionalized dihydropyrimidothiazinoquinolinone derivatives by the reaction of 3-(chloromethyl)-2-chloroquinolines and 2-thioxo-2,3-dihydropyrimidin-4(1H)-one in the presence of K₂CO₃ in DMF under the reflux condition. Some advantages of this method are good yields, mild reaction conditions, short reaction times and high selectivity. This method affords a simple and an effective route for the synthesis of novel dihydropyrimidothiazinoquinolines.

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**REFERENCES**


