SYNTHESIS OF SOME NOVEL PIPERIDONE LINKED BISQUINOLINES

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ABSTRACT

Some novel piperidone linked bisquinolines were synthesized efficiently in 2 steps. In step I, 6-substituted-2-chloro-3-formyl quinolines were prepared by Vilsmeier-Hearl reaction. The compounds so formed in step I were treated with ammonium acetate and different ketones in alcohol to yield required piperidone linked bisquinolines. The synthesized compounds were identified by FTIR, 1H and 13NMR spectroscopic techniques.

Key words: Piperidone linked bisquinolines, IR, NMR, Mass spectroscopy.

INTRODUCTION

Bisquinolines, as name suggests are compounds that contain 2 quinoline nuclei combined through an aliphatic or aromatic linker. Bisquinolines are known to be active against chloroquine resistant strains of malaria1-6 and acts as antimicrobial7, antymycobacterial8, antifilarial9, cytotoxic 10, antileishmanial 11, antiprion 12, haem detoxification13, antiprotocoal and retroviral14. Bisquinolines are prominent compounds against malaria parasites due to their accumulation in the food vacuole of both; chloroquine sensitive and chloroquine resistant parasites15. Similarly, piperidones were also reported to possess anticancer16, analgesic 17, antiinflammatory18, local anaesthetic 19 and antimicrobial20 activities.

In view of the above observations, an attempt was made towards the synthesis of piperidone linked bisquinolines to investigate the combination, which could influence the bacterial and fungal activity.
EXPERIMENTAL

All the melting points were determined in Vergo Vmp I melting point apparatus and are uncorrected. The purity of the compounds was determined by TLC on silica gel –G plate. IR spectra were recorded in Perkin-Elmer FTIR spectrophotometer. The $^1$H NMR spectra were recorded on Bruker spectroscope 200 MHz using DMSO as solvent and TMS as internal standard.

Synthesis of compounds$^{21-32}$

Step I: Synthesis of 2-choro-3-formyl quinolines

To a solution of acetonilide (5 mmoles) in dry DMF (15 mmoles) at 0-5°C temperature, phosphoryl chloride (60 mmoles) was added dropwise with stirring and mixture was then stirred at 85-90°C for time ranging between 4-16 hours. The mixture was poured onto crushed ice, stirred for 5 minutes and the resulting solid was filtered, washed well with water and dried. The compound was recrystallised from ethyl acetate.

\[ \text{Acetonilide} + \text{Dimethylformamide} + \text{Phosphoryl trichloride} \rightarrow \text{2-Chloro-3-formyl-quinoline} \]

Step II: Synthesis of 3-substituted-2,6-bisquinolinyl-piperidin-4-ones

A mixture of ketone (50 mmoles), ammonium acetate (50 mmoles) and substituted 2-chloro-3-formyl quinoline (100 mmoles) in ethanol was heated to simmering carefully. It was kept at room temperature for 24 hours. To a viscous liquid obtained, ether (25 mL) was
added, followed by concentrated hydrochloric acid (15 mL) and cooled in ice water. The precipitated hydrochloride was filtered and washed with ethanol-ether (1 : 5) mixture. The hydrochloride was suspended in acetone and made alkaline using ammonia solution. On dilution with excess of water, the base was precipitated, which was filtered, dried and recrystallised from absolute alcohol.

\[
\text{2-Chloro-3-formyl-quinoline} + \text{CH}_3\text{COCH}_2\text{R} + \text{NH}_4^+ \rightarrow \text{3-Substituted-2,6-bisquinolyl-piperidine-4-one}
\]

**Spectral analysis**

**Compound I**

2-Chloro-3-formyl quinoline

\[
\text{CHO} \quad \text{Cl} \\
\text{N} \\
\text{R} \\
\text{Cl}
\]

**IR Spectral data (cm}^{-1})**

3043.6 (C-H stretching aromatic), 2872.24 (C-H stretching aldehyde), 1688.65 (C=O stretching), 1613.94, 1578.4, 1489.93 (C=C & C=N stretching; aromatic), 1045.74 (C-Cl stretching; aromatic).
NMR Spectral data (δ)

10.57 (strong) Aldehydic proton, 8.77 Heteroaromatic proton, 7.26-8.1 (multiplet) Aromatic hydrogen.

**Compound (Ia)**

2,6-Bis(2-chloroquinolin-3-yl)-3-methylpiperidin-4-one

IR Spectral data (cm⁻¹)

3275.82 (N-H stretching), 2976.74 (C-H stretching; aromatic), 1702.09 (C = O stretching), 1498.34 (N-H bending), 1026.28 (C-Cl stretching; aromatic).

NMR Spectral data (δ)

7.248-8.25 (Aromatic proton; quinoline), 4.06 (Methyne proton; piperidone), 2.39 (Amine proton), 1.185 (Methyl proton).

**Compound (Ib)**

2,6-Bis(2-chloroquinolin-3-yl)-3-isopropylpiperidin-4-one

IR Spectral data (cm⁻¹)

3423.47 (N-H stretching), 1708.3 (C=O stretching), 1653.75 (N-H Overtone), 1404.08 (C-H bending), 1036.41 (C-Cl stretching; aromatic).
Compound (IIb)

2,6-Bis(2,6-dichloroquinolin-3-yl)-3-isopropylpiperidin-4-one

IR Spectral data (cm⁻¹)

3194.5 (N-H stretching), 1700.2 (C=O stretching), 1504.76 (N-H bending), 1093.67 (C-Cl stretching; aromatic).

NMR Spectral data (δ)

1.2 (Methyl proton), 4.675-4.777 (Methylene proton), 1.76 (Amino proton), 7.26-8.13 (Heteroaromatic hydrogen).

Compound (IIIa)

2,6-Bis(6-bromo-2-chloroquinolin-3-yl)-3- methylpiperidin-4-one

IR Spectral data (cm⁻¹)

3414.8 (N-H stretching), 2919.68 (C-H stretching), 1722.67 (C=O stretching), 1392.92 (C-H bending), 1070.82 (C-Br stretching; aromatic).

Compound (IIIc)

Ethyl 2,6-bis(6-bromo-2-chloroquinolin-3-yl)-4- oxopiperidine-3-carboxylate
IR Spectral data (cm\(^{-1}\))

3435.98 (N-H stretching), 2921.89 (C-H stretching), 1770.07 (C=O stretching), 1615.09 (N-H Overtone), 1071.58 (C-Br stretching; aromatic).

NMR Spectral data (δ)

2.93-2.96 (Methyl proton), 3.94-3.99 (Methylene proton; quartet), 2.404 (Amino proton), 6.914-7.525 (Heteroaromatic hydrogen).

**Compound (IVa)**

2,6-Bis(6-amino-2-chloroquinolin-3-yl)-3-methylpiperidin-4-one

IR Spectral data (cm\(^{-1}\))

3414.36 (N-H stretching), 2921.53 (C-H stretching), 1695.53 (C=O stretching), 1615.1 (N-H bending), 1393.03 (C-N stretching; aromatic).

**Compound (IVb)**

2,6-bis(6-amino-2-chloroquinolin-3-yl)-3-isopropylpiperidin-4-one
IR Spectral data (cm$^{-1}$)

3421.02 (N-H stretching), 2920.02 (C-H stretching), 1706.07 (C=O stretching), 1614.94 (N-H bending), 1392 (C-N stretching; aromatic).

**Compound (IVc)**

**Ethyl 2,6-bis(6-amino-2-chloroquinolin-3-yl)-4-oxopiperidine-3-carboxylate**

IR Spectral data (cm$^{-1}$)

3422.96 (N-H stretching), 2921.88 (C-H stretching), 1706.1 (C=O stretching), 1615.82 (N-H bending), 1392.36 (C-N stretching; aromatic).

**Table 1: Physical data of compounds**

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<tr>
<th>Compound</th>
<th>Molecular formula</th>
<th>Molecular weight</th>
<th>Melting point (°C)</th>
<th>Yield (%)</th>
<th>R$_f$ value</th>
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<td>I</td>
<td>C$_{10}$H$_6$NOCl</td>
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<td>C$_{10}$H$_7$N$_2$ClO</td>
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<td>Ia</td>
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<tr>
<td>Ib</td>
<td>C$<em>{26}$H$</em>{23}$N$_3$Cl$_2$O</td>
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Cont…
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<tr>
<th>Compound</th>
<th>Molecular formula</th>
<th>Molecular weight</th>
<th>Melting point (°C)</th>
<th>Yield (%)</th>
<th>Rf value</th>
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<td>0.68</td>
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<td>523.12</td>
<td>245</td>
<td>65</td>
<td>0.62</td>
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</tbody>
</table>

Synthesis of piperidone linked bisquinolines

Step I: Synthesis of 2-chloro-3-formyl quinolines

\[ X \text{ CHO} \]

<table>
<thead>
<tr>
<th>S. No.</th>
<th>X</th>
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<tbody>
<tr>
<td>I</td>
<td>H</td>
</tr>
<tr>
<td>II</td>
<td>Cl</td>
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<tr>
<td>III</td>
<td>Br</td>
</tr>
<tr>
<td>IV</td>
<td>NH_{2}</td>
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Step II: Synthesis of 3-substituted-2,6-bisquinolinyl-piperidin-4-ones

3-Substituted-2,6-bisquinolyl-piperidine-4-one
RESULTS AND DISCUSSION

Twelve novel piperidone linked bisquinolines were synthesized from the substituted 2-chloro-3-formyl quinoline. The 2-chloro-3-formyl quinolines were synthesized by refluxing acetanilides with Vilsmeir-Haack reagent. The obtained aldehydic quinoline was mixed with ammonium acetate and ketone in ethanol and kept for 24 hours. To this viscous solution, ether and conc. HCl were added and cooled in ice water to get precipitates. Ammonia solution was added to these precipitates. On excess dilution with water, base was liberated, as the desired piperidone linked bisquinoline. The purity of the compounds was checked by TLC using silica gel G as an adsorbent, ethyl acetate and chloroform (9.8 : 0.2) were used as mobile phase. The spot was visualized by iodine vapor or dinitrophenyl hydrazine solution. The structure of the synthesized compounds was characterized by its IR and $^1$H NMR spectral analysis, which coincides with the expected values.

REFERENCES


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