Synthesis, Characterization and Wound Healing Activity of 1-(8-Methyl-Furo [2, 3-b] Quinolin-2yl) Ethanone Derivatives

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ABSTRACT

In the present work, eight novel 1-(8-methyl-furo[2,3-b]quinolin-2yl)ethanone derivatives [IVa-h] were synthesized by claisen schmidt condensation, it is condensation between 1-(8-methyl-furo[2,3-b]quinolin-2yl)ethanone (ketone) and substituted aryl aldehyde to yield 1-(8-methyl-furo[2,3-b]quinolin-2yl)ethanone derivatives [IVa-h] (chalcones). The structures of the synthesized compounds were characterized on the basis of IR, 1HNMR and Mass spectral data. Among all synthesized compounds only few selected compounds are screened for their wound healing activity by wound excision model, povidine iodine is employed as a reference standard. From the results it is concluded that, compound exhibited potent activity, some are the compounds exhibited mild to moderate activity.

Keywords: Chalcones, 2-Chloro-3-formyl-quinoline, claisen Schmidt condensation Furoquinoline derivatives, Wound healing activity.

1. INTRODUCTION

The chemistry of quinoline derivatives has been of increasing interest since many of these compounds have been found useful as chemotherapeutic agents against malaria[1] parasite and microbes[2]. It also reported that nitrogen and oxygen containing heterocycles are one of the most extensively synthesized and screened compounds as they show diverse pharmacological activities.

Chalcones constitute an important class of natural products belonging to the flavonoid family[3], which have been reported to possess a wide spectrum of biological activities, including anti-bacterial[4], anti-fungal[5], anti-inflammatory[6], anti tumor[7], and anti-mutagenic[8]. Additionally, some of chalcone derivatives have been found to inhibit several important enzymes in cellular systems, such as xanthine oxidase[9], protein tyrosine kinase[10]. Chalcones are also key precursors in the synthesis of many biologically important heterocycles such as benzothiazepin[11], pyrazolines[12], 1,4-diketones[13] and flavones[14]. Hence, the synthesis of chalcones has generated vast interest among organic as well as medicinal chemists.

But no reports or literature found for furoquinoline derivatives (chalcones) on wound healing activity. Hence this inspired us to synthesize 1-(8-methyl-furo[2,3-b]quinolin-2yl)ethanone derivatives and screen for their wound healing activity.

2. MATERIALS AND METHODS

All chemicals used were of analytical grade from, SD Fine. Melting points of all the synthesized compounds were determined by open capillary tube method. These are uncorrected. The purity of all compounds was checked by TLC was run on Silica Gel G plates using Chloroform and Methanol (9:1). Spots were visualized using iodine vapour chamber. IR spectra were recorded on Shimadzu IR spectrophotometer by using KBr pellets technique. 1H-NMR was recorded on Bruker AMX 60 MHz spectrophotometer by using DMSO as solvent.

2.1. Synthesis of 2-Chloro-8-methyl quinoline-3-carbaldehyde (I)
Dimethyl formamide (0.125 mol, 9.13 gm, 9.65 ml) was cooled to 0 °C (using freezing moisture) in a flask equipped with a drying tube and phosphorus oxychloride (0.35 mol, 53.55 gm, 32.2 ml) was added drop wise with stirring. To this solution 2-Methyl acetaldehyde (0.05 mol, 7.45 gm) was added and the contents of the flask were stirred for 15 minutes and the resulting solution was refluxed for 16 hours at 85-90 °C. The reaction mixture was poured into crushed ice, stirred for 5 minutes and the resulting solid was filtered, washed well with water and dried. Thus compound obtained was purified by recrystallisation from ethyl acetate to yield yellow shiny needle shaped crystals of 2-Chloro-8-methyl quinoline-3-carbaldehyde. Yield 77 %, m.p. 137 °C [15-16].

2.2. Synthesis of 2-Hydroxy-8-methylquinoline-3-carbaldehyde (II)

In to a clean round bottomed flask containing a mixture of 2-chloro-8-methylquinoline-3-carbaldehyde (0.01 mol, 1.9 gm) and aqueous hydrochloric acid (35 ml, 4 mol) was heated under reflux for 2 hrs and then allowed to cool to room temperature. The reaction mixture was poured on to crushed ice, when 2-Hydroxy-8-methyl quinoline separated as a yellow solid. It was filtered washed with water and dried. It was recrystallised from aqueous acetic acid into yellow silky needles.

2.3. Synthesis of 1-(8-methylfuro[2,3-b]quinolin-2yl)ethanone (III)

In to a clean dried round bottomed flask, a mixture of 2-hydroxy-8-methylquinoline-3-carbaldehyde (0.1 mol, 18.7 gm), chloroacetone (0.1 mol, 7.97 ml) in dimethyl formamide (80-90 ml) and anhydrous potassium carbonate (0.1 mol, 1.38 gm) was added and the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was kept for reflux on water bath for 36 hours at 80-90 °C, allowed to cool at room temperature and then filtered. The resulting filtrate was poured into ice cold water, precipitate thus separated out was filtered, dried and recrystallized from aqueous dimethyl formamide as brown solid powder. Yield 60 %, m.p. 110 °C.

2.4. Synthesis of 1-(8-methylfuro[2,3-b]quinolin-2yl)ethanone derivatives 17 (Chalcones) [IVa-h]

General procedure:

In a clean round bottomed flask, equimolar mixture of 1-(8-methylfuro[2,3-b] quinolin-2yl)ethanone (0.01 mol) and different aryl aldehydes (0.01 mol) in ethanol medium (40 ml) in presence aqueous solution of potassium hydroxide (40 %, 15 ml) is stirred continuously for 12-16 hours at room temperature. The reaction mixture was kept overnight at room temperature and then it was poured into 300 ml ice cold water, acidified with dilute HCl. The solid thus separated was filtered, air dried and recrystallized from aqueous ethanol. Physical data of synthesized compounds is given in Table-1

Table-1

<table>
<thead>
<tr>
<th>Compounds</th>
<th>R</th>
<th>R</th>
<th>R</th>
<th>R</th>
<th>R</th>
<th>R</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV (a-h)</td>
<td>H</td>
<td>4-</td>
<td>3-</td>
<td>4-</td>
<td>2-</td>
<td>4-</td>
<td>4-</td>
</tr>
<tr>
<td>Cl</td>
<td>Cl</td>
<td>CH3</td>
<td>OH</td>
<td>F</td>
<td>N(CH3)2</td>
<td>OCH3</td>
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</table>

2.4. BIOLOGICAL ACTIVITY

2.4.1. WOUND HEALING ACTIVITY

Wound healing activity of some selected new compounds was assessed using excision wound model18,19. The albino rats of either sex (150-200 gm) were divided in to six groups of five animals each. Test compounds (IV-a,c,e,f) were formulated as 2% w/w ointment for local application, using simple ointment as vehicle.

The various groups were treated as follows:

Group-I: Control (0.5 gm of simple ointment (vehicle) applied locally)
Group-II: Standard (5 % w/w povidine iodine ointment applied locally)
Group-III: Compound IV-a
Group-IV: Compound IV-c (0.5 gm of 2% w/w ointment of test compound
Group-V: Compound IV-e applied locally once a day till complete epithelization)
Group-VI: Compound IV-f
Animals were under light ether anesthesia throughout the surgical procedures. An impression of 2.5 cm diameter (500 sq. mm) was made after leaving at least 5 mm space from the ears. The skin of the impressed area was excised carefully to the complete thickness and a wound of 500 sq. mm was formed. Homeostasis was achieved by application of normal saline solution. The animals were kept individually in separate cages. The physical attributes of wound healing viz wound closure (contraction) and epithelization period were recorded. The wound contraction was studied by tracing the raw wound area on a transparent paper on 4th, 8th, 12th and 16th day. The criterion for complete epithelization was fixed as formation of the scar with absence of raw wound area. The wound area was measured planimetrically by the help of sq. mm scale graph paper. The percentage wound closure was calculated using the following formula:

\[
\text{Percentage wound closure} = 1 - \left(\frac{\text{Ad}}{\text{Ao}}\right) \times 100
\]

Where,

\[
\text{Ao} = \text{Wound area on day zero (500 sq. mm)}
\]

\[
\text{Ad} = \text{Wound area on corresponding days}
\]

The results are tabulated in Table-2. The results obtained were subjected to statistical analysis using ANOVA followed by Turkey-Kramer Multiple Comparison Test.

3. RESULTS AND DISCUSSION

3.1. Physical constant

Table 1. Characterization data of synthesized compounds IV[a-h]

<table>
<thead>
<tr>
<th>SL No</th>
<th>Comp. Code</th>
<th>Melting point °C</th>
<th>% Yield</th>
<th>MOL. FORM</th>
<th>M. Wt</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>IVa</td>
<td>268-270</td>
<td>64</td>
<td>C₁₀H₁₀N₂</td>
<td>313</td>
</tr>
<tr>
<td>2</td>
<td>IVb</td>
<td>160-162</td>
<td>72</td>
<td>C₁₀H₆ClNO₂</td>
<td>347</td>
</tr>
<tr>
<td>3</td>
<td>IVc</td>
<td>120-122</td>
<td>68</td>
<td>C₁₀H₆ClNO₂</td>
<td>347</td>
</tr>
<tr>
<td>4</td>
<td>IVd</td>
<td>168-170</td>
<td>67</td>
<td>C₁₀H₆ClNO₂</td>
<td>347</td>
</tr>
<tr>
<td>5</td>
<td>IVe</td>
<td>228-240</td>
<td>69</td>
<td>C₁₀H₆NO₂</td>
<td>329</td>
</tr>
<tr>
<td>6</td>
<td>IVf</td>
<td>200-202</td>
<td>60</td>
<td>C₁₀H₆F₃NO₂</td>
<td>331</td>
</tr>
<tr>
<td>7</td>
<td>IVg</td>
<td>232-234</td>
<td>55</td>
<td>C₁₀H₆N₂O₂</td>
<td>356</td>
</tr>
<tr>
<td>8</td>
<td>IVh</td>
<td>204-206</td>
<td>61</td>
<td>C₁₀H₆N₂O₂</td>
<td>343</td>
</tr>
</tbody>
</table>

3.2. Spectral Studies

a) IR spectrum of compound IV-c

Spectral data

IVc: IR (KBr) cm⁻¹: 1681 (C=O), 2947 (-CH), 1650 (C=N), 1583 (C=C), 1128 (-C-O-C), 3150 (Ar-CH).

\( ^1H \text{NMR (DMSO)} \delta \text{ ppm: } 1.3 \text{ (s, 3H, CH₃)}, 7.7-7.5 \text{ (m, 5H, Ar-H)}, 7.69-7.71 \text{ (2d, 4H, Ar-H)}, 7.89 \text{ (s, 2H, -CH=CH)}. \)

ESIMS (m/z): 347 (M⁺).

IVd: IR (KBr) cm⁻¹: 1689 (C=O), 2928 (-CH), 1651 (C=N), 1575 (C=C), 1022 (-C-O-C), 3186 (Ar-CH).

\( ^1H \text{NMR (DMSO)} \delta \text{ ppm: } 1.45 \text{ (s, 3H, CH₃)}, 2.37 \text{ (s, 3H, CH₃)}, 7.7-7.6 \text{ (m, 9H, Ar-H)}, 7.84 \text{ (s, 2H, -CH=CH)}. \)

ESIMS (m/z): 327 (M⁺).

IVe: IR (KBr) cm⁻¹: 1658 (C=O), 3036 (-CH), 1649 (C=N), 1572 (C=C), 1026 (-C-O-C), 3186 (Ar-CH).

\( ^1H \text{NMR (DMSO)} \delta \text{ ppm: } 1.2 \text{ (s, 3H, CH₃)}, 5.06 \text{ (s, 1H, Ar-OH)}, 7.0-7.95 \text{ (m, 8H, Ar-H)}, 8.08 \text{ (s, 2H, -CH=CH)}. \)

ESIMS (m/z): 329 (M⁺).

IVf: IR (KBr) cm⁻¹: 1668 (C=O), 2970 (-CH), 1650 (C=N), 1575 (C=C), 1166 (-C-O-C), 3100 (Ar-CH).

\( ^1H \text{NMR (DMSO)} \delta \text{ ppm: } 1.6 \text{ (s, 3H, CH₃)}, 7.7-7.8 \text{ (m, 5H, Ar-H)}, 7.89 \text{ (s, 2H, -CH=CH)}. \)

ESIMS (m/z): 329 (M⁺).
9H, Ar-H), 7.92 (s, 2H, -CH=CH). ESIMS (m/z): 331(M+).

IVg: IR (KBr) cm⁻¹: 1662 (C=O), 2929 (-CH), 1612 (C=N), 1568 (C=C), 1118 (-C-O-C), 3115 (Ar-CH)

¹HNMR (DMSO) δ ppm: 2.1 (s, 3H, CH₃), 3.6(s, 6H, N-(CH₃)2) 7.2-7.9 (m, 9H, Ar-H), 8.1 (s, 2H, -CH=CH). ESIMS (m/z): 356 (M+).

3.3. In vivo Studies

3.3.1. Photographs showing the wound closer at different days

Table 2. Effect of topical application of 2% ointment of synthesized compounds on excision (open) wound parameters

<table>
<thead>
<tr>
<th>Group</th>
<th>% Contraction of wound on different days (sq.mm)</th>
<th>Epithelization time in days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4th day</td>
<td>8th day</td>
</tr>
<tr>
<td>Control</td>
<td>18.92 ± 2.12</td>
<td>29.84 ± 2.41</td>
</tr>
<tr>
<td>Povidine iodine</td>
<td>35.46 ± 2.82***</td>
<td>58.76 ± 3.98***</td>
</tr>
<tr>
<td>IV-a</td>
<td>26.72 ± 2.16*</td>
<td>41.58 ± 3.90*</td>
</tr>
<tr>
<td>IV-c</td>
<td>34.56 ± 2.01***</td>
<td>48.00 ± 2.32***</td>
</tr>
<tr>
<td>IV-e</td>
<td>32.36 ± 2.86***</td>
<td>56.44 ± 3.90***</td>
</tr>
<tr>
<td>IV-f</td>
<td>29.84 ± 2.22**</td>
<td>42.28 ± 2.76**</td>
</tr>
</tbody>
</table>
Values are Mean ± S.E.M, n=5. Where *P<0.05, **P<0.01 and ***P<0.001 vs Control.

The results of the present investigation indicate that all the four compounds on topical application in the form of ointment significantly promoted wound healing activity. This enhanced wound healing property was evident by significant increase in rate of wound contraction and significant reduction in epithelization period.

Among the screened compounds for the wound healing study, The wound healing activity of the compound IV-e was found closer (wound contraction 96.24% on day 16th and epithelization time in days is 18.3) to that of standard drug povidone iodine (97.27% wound contraction on 16th day and epithelization period on day 18.1). The Compound IV-c also promoted significant wound healing property (93.07 % and 18.8). The order of the wound healing efficacy of the test compound when compared to the control was found as IV-e > IV-c > IV-f > IV-a.

4. CONCLUSION

Few new selected compounds IV-a, c, e and f is screened for their wound healing activity. From the results obtained it is concluded that compound IV-c, IV-e shown potent and compound IV-a, IV-f shown mild to moderate wound healing activity when compared to control. Compound IV-e containing substituted benzaldehyde with electron releasing group like –OH which may favor significant wound healing activity. If work is further continued with different substituted benzaldehyde you may get potent pharmacophore which may promote significant wound healing activity.

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5. REFERENCES

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