Synthesis, characterization and antibacterial activity of benzimidazole derivatives carrying quinoline moiety

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A new series 2-(1H-benzimidazol-2-yl)-6-substitutedthieno[2,3-b]quinolines 4 have been synthesized by a one-step process in which 2-(chloromethyl)-1H-benzimidazole 2/2-(mercaptomethyl)-1H-benzimidazoles 6 undergo nucleophilic substitution and cyclisation with 2-mercaptoquinoline-3-carbaldehyde 1/2-chloroquinoline-3-carbaldehyde 5. The compounds have been synthesized by two methods to select a method of higher yield. The newly synthesized compounds have been characterized by IR, CHNS analysis, LC-MS and 1H NMR and also screened for antibacterial activity.

Keywords: Benzimidazoles, quinolines, 2-(1H-benzimidazol-2-yl)thieno[2,3-b]quinoline, antibacterial activity

Benzimidazole is a well-known heterocyclic nucleus which is present in many anti-ulcer drugs and H2-antihistaminic agents which inhibit gastric secretion by altering the activity of H+/K+ ATPase, which is final common step of acid secretion in parietal cells. Quinoline is another heterocyclic compound and it constitutes the basic structural unit of many antimalarial drugs. Recently a number of quinoline derivatives were reported for their antimicrobial activity and anti-inflammatory activity. Benzimidazole-substituted quinoline derivatives are useful as antihypertensive agents. These observations prompted the synthesis of a new series of 2-(1H-benzimidazol-2-yl)thieno[2,3-b]quinolines, which contain biologically active quinoline, thiophene and benzimidazole moieties.

Results and Discussion

The primary aim was to prepare a uncyclised compound of the type 3 by substitution reaction of 2-mercaptoquinoline-3-carbaldehyde 1 with 2-(chloromethyl)-1H-benzimidazole 2 and then to prepare the chalcones by treating with different acetophenones. In this case, the reaction did not proceed at room temperature, but at higher temperature the reaction ended with the cyclised product 4 (Route I). However, the yield obtained by this method was less than 50%. A successful attempt was made to improve the yield (>85%) (Route II) by condensing 2-chloroquinoline-3-carbaldehyde 5 with 2-(mercaptomethyl)-1H-benzimidazoles 6 in ethanol medium using pyridine as base (Scheme I). 2-Mercaptoquinoline-3-carbaldehyde 1, 2-(chloromethyl)-1H-benzimidazole 2, 2-chloroquinoline-3-carbaldehyde 5 and 2-(mercaptomethyl)-1H-benzimidazole 6 were prepared according to literature methods and characterized by their melting points. The structures of the newly synthesized compounds 4a-h were established on the basis of analytical and spectral data. The IR spectra of these compounds showed absorption bands in the region of 3375-3454 cm⁻¹ characteristic of the N-H group. The C=N absorption was observed around 1535-1600 cm⁻¹. In a typical example of the 1H NMR spectra of 2-(1H-benzimidazol-2-yl)thieno[2,3-b]quinoline 4a, the N-H proton of benzimidazole came into resonance at δ 13.41. The 3-H of thiophene ring and 4-H of quinoline appeared as singlets at δ 8.24 and 8.96 respectively. The other eight aromatic protons appeared as a multiplet in the region of δ 7.25-8.14. In the mass spectrum of this compound, the molecular ion peak was observed at m/z 302.8, (M+1) (Molecular formula C18H11N3S) which is also the base peak thereby indicating the stability of the molecule.

Similarly, the spectral details for a few other compounds are given below.
Experimental Section

Melting points of the newly synthesized compounds were determined in open capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer 577 spectrophotometer in KBr pellets. ¹H NMR spectra were recorded on a Bruker AMX 400 (400 MHz) spectrometer using DMSO-d₆ as solvent and TMS as an internal standard. All chemical shifts values are reported in δ scale downfield from TMS. Mass spectrum was recorded on a Jeol model JMS-D300 mass spectrometer operating at 70 eV. CHN analysis was carried out on a Vario-EL (Elementar-III) model. Homogeneity of the compounds was checked by TLC on silica gel plates.

General procedure for the synthesis of 2-(chloromethyl)-1H-benzimidazole 2/2-mercaptomethyl benzimidazole, 6

The mixture of o-phenylenediamine (0.09 mol) and chloroacetic acid/mercaptoacetic acid (0.1 mol) was dissolved in 4N HCl (10 mL) and refluxed at 100°C for 12 hr. The completion of reaction was checked by TLC. The reaction mixture was cooled to RT, poured into ice-cold water and neutralized with NaHCO₃ solution to get 2-(chloromethyl)-1H-benzimidazole 2/2-mercaptomethyl benzimidazole 6. Compounds prepared as per this procedure are:

2a: 2-(Chloromethyl)-1H-benzimidazole, m.p. 145°C, Yield 90%.
2b: 2-(Chloromethyl)-5-nitro-1H-benzimidazole, m.p. 159°C, Yield 85%.
6a: 2-(Mercaptomethyl)-1H-benzimidazole, m.p. 173°C, Yield 87%.

6b: 2-(Mercaptomethyl)-5-nitro-1H-benzimidazole, m.p. 195°C, Yield 75%.

General procedure for the synthesis of 6/8-substituted 2-chloroquinoline-3-carbaldehyde, 5

Dimethylformamide (9.13 g, 0.125 mol) was cooled to 0°C in a flask equipped with a drying tube and phosphorous oxychloride (53.7 g, 0.35 mol) was added drop-wise with stirring. Acetanilide (6.55 g, 0.05 mol) was then added to the solution and the solution was heated at 70-80°C for 16 hr. The reaction mixture was cooled to RT, poured into ice water and stirred for 30 min at 0-10°C to get 6/8-substituted 2-chloro-3-formyl quinoline 5 as a yellow solid. It was filtered, washed with water and purified by recrystallization from ethyl acetate.

The quinolines prepared are:

5a: 6-Methoxy-2-chloroquinoline-3-carbaldehyde, m.p. 144°C, Yield 58%.

5b: 6-Methyl-2-chloroquinoline-3-carbaldehyde, m.p. 123°C, Yield 64%.

5c: 2-Chloroquinoline-3-carbaldehyde, m.p. 148°C, Yield 68%.

5d: 8-Methyl-2-chloroquinoline-3-carbaldehyde, m.p. 137°C, Yield 67%.

General procedure for the preparation of 2-(1H-benzimidazol-2-yl)-6-substituted-thieno[2,3-b]quinolines, 4

A mixture of 2-chloroquinoline-3-carbaldehyde, 5 (2.82 mmol), 2-mercaptomethyl)-1H-benzimidazole, 6 (2.82 mmol) and pyridine (2.82 mmol) in ethanol were heated on a water bath for 5-6 hr. Completion of the reaction was checked by TLC. The reaction mixture was concentrated to dryness and stirred with water to get a solid product. The crude product was then purified by recrystallization from N,N-dimethylformamide. The yield, melting point and other characterization data of the compounds are given in Table I.

Spectral characterization of synthesized compounds

2-(1H-Benzimidazol-2-yl)-6-methylthieno[2,3-b]quinoline 4b. 1H NMR (DMSO-d6): δ 2.51 (s, 3H, Me), 7.26-7.29 (m, 2H, benzimidazole 4-H and 7-H), 7.64-7.67 (m, 3H, quinoline 7-H, benzimidazole 5-H and 6-H), 7.88 (s, 1H, quinoline 5-H), 8.21 (s, 1H, thiophene 3-H), 8.85 (s, 1H, quinoline 4-H), 13.44 (s, 1H, benzimidazole NH); LC-MS: m/z 316.2 (M+1), Mol. formula C19H13N3S.

2-(1H-Benzimidazol-2-yl)-6-methoxythieno[2,3-b]quinoline 4c. 1H NMR (DMSO-d6): δ 3.93 (s, 3H, Me),
Table II — Antibacterial activity data of 2-(1H-benzimidazol-2-yl)-6-substituted-thieno[2,3-b]quinolines, 4a-h

<table>
<thead>
<tr>
<th>Compd</th>
<th>(Minimum inhibitory concentration in μg/mL)</th>
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<tr>
<td></td>
<td>Escherichia coli</td>
</tr>
<tr>
<td>4a</td>
<td>R</td>
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<td>4b</td>
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<td>4h</td>
<td>12.5</td>
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<tr>
<td>Nitrofurazone</td>
<td>6.25</td>
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<tr>
<td>R = Resistant</td>
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OMe), 7.25-7.28 (m, 2H, benzimidazole 4-H and 7-H), 7.46-7.49 (m, 2H, benzimidazole 5-H and 6-H), 7.65-7.68 (m, 2H, quinoline 5-H and 7-H), 7.97-8.00 (d, 1H, quinoline 8-H), 8.20 (s, 1H, thiophene 3-H), 8.84 (s, 1H, quinoline 4-H), 13.42 (s, 1H, benzimidazole NH); LC-MS: m/z 331.8 (M^+1), Mol. formula C_{19}H_{13}N_{10}OS.

2-(1H-Benzimidazol-2-yl)-8-methylthieno[2,3-b]-quinoline, 4d. ^1^H NMR (DMSO-d_6): δ 2.80 (s, 3H, Me), 7.25-7.33 (m, 2H, benzimidazole 4-H and 7-H), 7.49-7.62 (m, 3H, quinoline 6-H, benzimidazole 5-H and 6-H), 7.69-7.71 (d, 1H, quinoline 7-H), 7.99-8.01 (d, 1H, quinoline 5-H), 8.25 (s, 1H, thiophene 3-H), 8.98 (s, 1H, quinoline 4-H), 13.44 (s, 1H, benzimidazole NH); LC-MS: m/z 316.2 (M^+1), Mol. formula C_{19}H_{13}N_{10}S.

2-(5-Nitro-1H-benzimidazol-2-yl)thieno[2,3-b]-quinoline, 4e. ^1^H NMR (DMSO-d_6): δ 7.59-7.64 (m, 2H, quinoline 6-H and 7-H), 7.78-7.81 (d, 1H, quinoline 5-H), 8.05-8.08 (d, 1H, quinoline 8-H), 7.98-8.00 (s, 1H, benzimidazole 7-H), 8.12-8.14 (d, 1H, benzimidazole 6-H), 8.35 (s, 1H, benzimidazole 4-H), 8.51 (s, 1H, thiophene 3-H), 8.80 (s, 1H, quinoline 4-H), 14.01 (s, 1H, benzimidazole NH); LC-MS: m/z 347.2 (M^+1), Mol. formula C_{19}H_{10}N_{10}O_{2}S.

6-Methoxy-2-(5-nitro-1H-benzimidazol-2-yl)thieno[2,3-b]quinoline, 4f. ^1^H NMR (DMSO-d_6): δ 2.76 (s, 3H, Me), 7.52-7.55 (s, 1H, quinoline 5-H), 7.69-7.71 (d, 1H, quinoline 7-H), 7.80-7.82 (d, 1H, benzimidazole 8-H), 7.98-8.00 (d, 1H, benzimidazole 7-H), 8.10-8.12 (d, 1H, benzimidazole 6-H), 8.35 (s, 1H, benzimidazole 4-H), 8.58 (s, 1H, thiophene 3-H), 8.98 (s, 1H, quinoline 4-H), 14.06 (s, 1H, benzimidazole NH); LC-MS: m/z 360.8 (M^+1), Mol. formula C_{19}H_{12}N_{10}O_{2}S.

6-Methoxy-2-(5-nitro-1H-benzimidazol-2-yl)thieno[2,3-b]quinoline, 4g. ^1^H NMR (DMSO-d_6): δ 3.92 (s, 3H, OMe), 7.23-7.48 (m, 2H, quinoline 7-H and 8-H ), 7.77-7.80 (d, 1H, benzimidazole 7-H), 7.98-8.00 (s, 1H, quinoline 5-H), 8.14-8.16 (d, 1H, benzimidazole 6-H), 8.30 (s, 1H, benzimidazole 4-H), 8.58 (s, 1H, thiophene 3-H), 8.88 (s, 1H, quinoline 4-H), 14.05 (s, 1H, benzimidazole NH); LC-MS: m/z 377 (M^+1), Mol. formula C_{19}H_{12}N_{10}O_{2}S.

8-Methyl-2-(5-nitro-1H-benzimidazol-2-yl)thieno[2,3-b]quinoline, 4h. ^1^H NMR (DMSO-d_6): δ 2.79 (s, 3H, Me), 7.52-7.55 (t, 1H, quinoline 6-H), 7.69-7.71 (d, 1H, quinoline 7-H), 7.80-7.82 (d, 1H, benzimidazole 7-H), 7.98-8.00 (d, 1H, quinoline 5-H), 8.13-8.16 (d, 1H, benzimidazole 6-H), 8.35 (s, 1H, benzimidazole 4-H), 8.61 (s, 1H, thiophene 3-H), 9.02 (s, 1H, quinoline 4-H), 14.09 (s, 1H, benzimidazole NH); LC-MS: m/z 360.8 (M^+1), Mol. formula C_{19}H_{12}N_{10}O_{2}S.

Antibacterial Activity

The newly synthesized compounds were screened for their antibacterial activity in vitro against Gram-positive bacteria namely Escherichia coli, Staphylococcus aureus and Gram-negative bacteria namely Pseudomonas aeruginosa and Klebsiella pneumoniae. The anti-bacterial activity of the newly synthesized compounds in the present investigation was assessed by Minimum Inhibitory Concentration (MIC) by serial dilution method. The test compounds were dissolved in N,N-dimethylformamide to obtain solutions of different concentrations. The concentration at which there was no turbidity was taken as Minimum Inhibitory Concentration (MIC). The results are shown in Table II. Compounds carrying nitro group at the 5-position of the benzimidazoles were more active.
midazole moiety namely, 4e, 4f, 4g and 4h showed a MIC of 12.5 µg/mL and others did not show any significant activity.

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References