Synthesis, Characterization and biological evaluation of some novel disubstituted heterocyclic derivatives

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ABSTRACT

Synthesis of some novel di-substituted 1-piperidin-4-yl(3,4-dibromophenyl)-1,3-dihydro-2H-benzimidazol-2-one derivatives (6A-6D) were prepared from commercially available 1,2-phenylenediamine. Compounds (6A-6D) were tested for Gram positive: Streptococcus pyogenes and Staphylococcus aureus. Gram negative: Escherichia coli, Pseudomonas aeruginosa, Proteus vulgaris, Salmonella typhimurium bacterial cultures. Compounds 6A-6D were found to be highly active against Streptococcus pyogenes and Escherichia coli.

Keywords: Antibacterial activity, CDI and novel disubstituted heterocyclic derivatives

INTRODUCTION

Benzimidazolones are a class of cyclic urea derivatives demonstrating a wide variety of biochemical and pharmacological properties. They antagonize neurotransmitters [1], inhibit aldose reductase [2], show antisecretory properties [3], enhance pulmonary surfactant secretion [4] and modulate ion channels [5]. Several of these compounds show activity against leukemia [6]. A number of such compounds with different substitution patterns have been synthesized [7-12] to check their medicinal properties. Several novel di-substituted 1-piperidin-4-yl(3,4-dibromophenyl)-1,3-dihydro-2H-benzimidazol-2-one were synthesized and evaluated as antibacterial activity.

In order to overcome these emerging resistance problems, there is an urgent need to discover novel antibacterial agents in structural classes distinct from existing antibiotics. In recent years, some of the 1,3-dihydro-2H-benzimidazole-2-one ring system \textbf{1} represents the core skeleton of a large number of biologically active, structurally intriguing compounds found in a multitude of pharmaceutically important compounds [13]. Both mono- and disubstituted benzimidazol-2-one derivatives \textbf{1} have been identified as potent NK1 antagonists [14], CGRP receptor antagonists [15], farnesyl transfer inhibitors [16], p38 inhibitors [17], cathepsin S inhibitors [18], 5-HT\textsubscript{4} agonists and antagonists [19], progesterone receptor antagonist [20], respiratory syncytial virus (RSV) inhibitors [20], vasopressin 1a receptor antagonists [21], aldose reductase inhibitors [22], and neurotransmitter antagonists [23]. The development of efficient and practical methods for construction of this important heterocycle remains as an active...
area of synthetic research (Figure 1). Herein, we report on the synthesis and characterization of novel disubstituted 1-piperidin-4-yl(3,4-dibromophenyl)-1,3-dihydro-2H-benzimidazol-2-one

EXPERIMENTAL SECTION

Synthesis of some novel di-substituted 1-piperidin-4-yl(3,4-dibromophenyl)-1,3-dihydro-2H-benzimidazol-2-one derivatives are outlined in (Scheme 1). Reaction of 1,2-phenylenediamine with CDI in DMF gave compound 2 in 98% yield. Compound 3 was prepared by alkylation of compound 2 with ethylchloroformate in 85% yield. Compounds 4 is prepared by alkylation of compound 3 with 3,4 dibromo phenacyl bromide. Hydrolysis of compound 4 with 5N NaOH at room temperature afforded compound 5 in 85% yield. Reaction of compound 5 with 1,2-Dibromoethane in 2-methyl THF gave compound 6 in 65% yield. Reaction of Compound 6 with piperidines (A-D) with K₂CO₃ in 2-methyl THF afforded compounds 6A-6D

Reagents and Conditions: a) CDI, DMF, RT; b) ethylchloroformate, K₂CO₃, 2-methyl THF, ∆; c) 3,4-dibromo phenacyl bromide, K₂CO₃, 2-methyl THF, ∆; d) 5N NaOH, Ethanol, RT, 1,2-dibromoethane, K₂CO₃, 2-methyl THF, ∆; f) RNH, K₂CO₃, 2-methyl THF.

Procedure for antimicrobial activity

The novel disubstituted 1-piperidin-4-yl(3,4-dibromophenyl)1,3-dihydro-2H-benzimidazol-2-one derivatives 6A-6D were dissolved in dimethyl sulphoxide at 200 µg/mL concentration. The composition of nutrient agar medium
was 10g Bactotryptone, 5g yeast extract, 10g NaCl, and final pH 7.4. After 18 h the exponentially growing cultures of the six bacteria in nutrient broth at 37°C were diluted in further sterile broth. From each of these diluted cultures, 1 mL was added to 100 mL sterilized and cooled nutrient agar media to give a final bacterial count of 1 x 10^5 cell/mL. The plates were allowed to set at room temperature and later dried at 37°C for 2h. Paper discs (6mm, punched from whatmann no. 41 paper) were ultraviolet sterilized and were used for the assays. Discs were soaked in different concentration of the test solution and placed on the inoculated agar media at regular intervals of 6-7cm, care was taken to ensure that excess solution was not on the discs. All the samples were taken in triplicates. The plates were incubated at 37°C in an inverted fashion.

Antibacterial activity of novel disubstituted 1-piperidin-4-yl(3,4-dibromo phenyl)-1,3-dihydro-2H-benzimidazol-2-one analogs (6A-6D): The following bacterial cultures were tested for their susceptibility to novel disubstituted 1-piperidin-4-yl(3,4-dibromophenyl)-1,3-dihydro-2H-benzimidazol-2-one derivatives (6A-6D) by the disc diffusion method in nutrient agar media (Table 1). Gram positive: Streptococcus pyogenes and Staphylococcus aureus. Gram negative: Escherichia coli, Pseudomonas arzenosa, Proteus vulgaris, Salmonella typhi. The results obtained are shown in Compound 6A and 6B are active against Proteus vulgaris and Salmonella typhi. Compound 6C is moderately active against bacterial cultures and inactive against proteus cultures. Compound 6D is moderately active against all the bacterial cultures.

Table 1 Antimicrobial activity of compounds (6A-6D)

<table>
<thead>
<tr>
<th>Compd (200 µg/mL in DMSO)</th>
<th>Streptococcus pyogenes</th>
<th>Staphylococcus aureus</th>
<th>Escherichia coli</th>
<th>Pseudomonas arzenosa</th>
<th>Proteus vulgaris</th>
<th>Salmonella typhi</th>
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<tbody>
<tr>
<td>6A</td>
<td>-</td>
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<tr>
<td>6B</td>
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<tr>
<td>6C</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>6D</td>
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Melting points were determined in open glass capillaries on a Mel-temp apparatus and are uncorrected. The homogeneity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate/hexane, 1:3). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave number s were given in cm⁻¹. The ¹H NMR spectra were recorded in CDCl₃/DMSO-d₆ on a Varian EM-360 spectrometer (300MHz). The ¹³C NMR spectra recorded in CDCl₃/DMSO-d₆ on a Varian VXR spectrometer operating at 125 MHz. All chemical shifts were reported in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on Jeol JMSID 300 and Finnigan Mat b at 70 eV with an emission current of 100µA.

RESULTS AND DISCUSSION

1H-benzo[α]imidazol-2(3H)-2-one (2):
1,2-phenylenediamine (10g, 0.092 mole) was dissolved in DMF (150 ml) and treated with 1,1’-carbonyldiimidazolo (14.99g, 0.092 mole). The resulting solution was stirred at rt for 22 h. The solvent was concentrated under reduced pressure, filtered, and recrystallized from Dichloromethane to afford a compound 2 (12.1g, 98%), mp. 100-102°C; ¹H NMR (300MHz, CDCl₃) : δ 6.92 (m, 4H), 10.6 (s, 2H); ¹³C NMR (125MHz, CDCl₃) : δ 121 (2C), 124.6 (2C), 129.9 (2C), 155.2; FT-IR(KBr) : υmax 3199, 2807, 1739, 1627, 1481 cm⁻¹; FAB MS: m/z 135 (M+H)⁺.

Ethyl-2,3-dihydro-2-oxobenzo[a]imidazole-1-carboxylate (3):
Ethylchlororormate (12g ,0.111 mole) was added drop wise over 30 min to a stirred suspension of 1H-benzo[α]imidazol-2(3H)-2-one (2) (15g, 0.111 mole) and K₂CO₃ (18.53g, 0.134 mole) in Acetonitrile (240 ml). The reaction mixture was stirred at 90°C for 10 h. The mixture was concentrated in vacuo and the residue diluted with water. The solid filtered, washed with water, dried in air to afford a compound 3. Crude solid recrystallized from a mixture Dichloromethane and Hexane. mp.149-150°C. ¹H NMR (300MHz, CDCl₃) : δ CH₃ 1.48 (t,3H), CH₂ 4.53 (q,2H), NH 11.2 (s,1H), Ar-H 7.7 (d,1H); ¹³C NMR (125MHz, CDCl₃) : δ 13.8, 58.3, 121.8 (2C), 124.6 (2C), 127.3, 129.9, 150.2, 151.4; FT-IR (KBr) : υmax 3270, 1780 , 2812, 1627, 1261, 1480 cm⁻¹; FAB MS: m/z 207(M+H)⁺.

3-[2-(3,4-Dibromo-phenyl)-2-oxo-ethyl]-2-oxo,2,3-dihydro-benzimidazole-1-carboxylic acid ethyl ester (4): A mixture of compound 3(10g, 0.0308 mole), 3,4-dibromobenzylic bromide (11.0g, 0.0308 mole), K₂CO₃ (13.39g, 0.0969 mole) in 2-methyl THF (100 ml) was refluxed at 80°C for 6 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate, organic layer dried over MgSO₄, filtered and evaporated in vacuo to give 4 as crude solid. m.p: 129-131°C. (18g, 76.33%) and was taken to next step without further purification. ¹H NMR (300MHz, CDCl₃) : δ CH₃ 1.48 (t,3H), CH₂ 4.54 (q,2H), N-CH₂ 5.2(s,2H), Ar-H 7.2 (m,3H), 7.7 (d,1H), 6.8 (t,1H), 8.2 (s,1H), 7.92 (t, 2H). ¹³C NMR (125MHz, CDCl₃) : δ 13.8, 49.7, 121.8, 124.6,
I[2-(3,4-Dibromo-phenyl)-2-oxo-ethyl]-4-ethylideneimidazolidin-2-one (5): To a stirred solution of Compound 4 (12 g, 0.0248 mole) in EtOH (28ml) was added NaOH (5N, 100 ml). The reaction mixture was stirred for 2 h at rt. The reaction mixture was concentrated under reduced pressure and extracted with ethyl acetate. The organic layer was washed with water and saturated NaCl solution, dried over Na₂SO₄ filtered and evaporated to afford compound 5 (8.6g, 85%); mp.165-167°C. ¹H NMR (300MHz, CDCl₃): δ: N-CH₂,2.2 (s, 2H), Ar-H 7.2(m,3H), 7.7 (d, 1H), 6.8 (t, 1H), 8.1 (s, 1H), 7.92 (t, 1H), 8.91(s,1H); ¹³C NMR (125MHz, CDCl₃): 49.7, 121.8, 124.6, 128.3, 130.2, 130.3, 133.3, 136.3, 154.6, 195.4. FT-IR (KBr): 518 (M+H).

1-(Bromo-ethyl)-3-[2-(3,4-Dibromo-phenyl)-2-oxo-ethyl]-1,3-dihydrobenzoimidazol-2-one (6A): A mixture of compound 6 (1.5g, 0.0029 mole), piperidine (0.37g, 0.00369 mole), K₂CO₃ (1.13g, 0.0082 mole) in 2-methyl THF (25ml) was refluxed for 10 h. The mixture was concentrated in vacuo and the residue diluted with H₂O and extracted with EtOAc. The residue was chromatographed on a column of silicagel using a mixture of Methanol and Dichloromethane (3-4%) as eluent to furnish compound 6A: δ: 1.69 (m,4H),1.98(m, 1H),2.28(m, 4H), 3.49 (d, 2H), 3.59 (t, 2H), 3.68 (t, 2H), 4.31 (t, 2H), 5.21 (s, 2H), 7.05-7.21 (m, 3H), 7.2(m,3H), 7.7(d,1H), 6.8 (t, 1H), 8.1 (s, 1H), 7.92 (t, 1H), 8.91(s,1H); FAB MS: m/z 522.24 (M+H)+.

1-(Bromo-ethyl)-3-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-1,3-dihydrobenzoimidazol-2-one (6B): A mixture of compound 6 (1.5g, 0.0029 mole), piperidinemethanol (0.60g, 0.00522 mole), K₂CO₃ (1.14g, 0.0082 mole) in 2-methyl THF (25ml) was refluxed for 12 h. The mixture was concentrated in vacuo and the residue diluted with H₂O and extracted with EtOAc. The residue was chromatographed on a column of silicagel using a mixture of Methanol and Dichloromethane (3-4%) as eluent to furnish compound 8 (0.90g, 60 %); mp.147-149°C; ¹H NMR (300MHz, CDCl₃): 0.78 (m, 6H), 2.28 (m, 4H), 3.38 (m, 1H), 2.79 (t, 2H), 3.8 (t, 2H), 5.2 (s, 2H), 7.05-7.20 (m, 3H), 7.77 (d, 1H), 7.2 to 7.35 (m, 5H); ¹³C NMR (125MHz, CDCl₃): δ:26.3, 34.3, 48.1, 49.0, 54.3, 67.8, 70.2, 121.8, 124.6, 128.3, 130.2, 130.3, 133.2, 133.2, 136.3, 137.8, 154.6, 195.4; FT-IR(KBr): mₜₜ 2992, 2690, 1716, 1695, 1496 cm⁻¹; 610-680 cm⁻¹; FAB: MS: m/z 522.24 (M+H)+.

1-(Bromo-ethyl)-3-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-1,3-dihydrobenzoimidazol-2-one (6C): A mixture of compound 6 (1.5g, 0.0029 mole), 4-hydroxy ethyl piperidine (0.68g, 0.00552 mole), K₂CO₃ (1.14g, 0.0082 mole) in 2-methyl THF (25ml) was refluxed for 12 h. The mixture was concentrated in vacuo and the residue diluted with H₂O and extracted with EtOAc. The residue was chromatographed on a column of silicagel using a mixture of Methanol and Dichloromethane (3-4%) as eluent to furnish compound 9 (1.2g, 60%); mp .157-159°C; ¹H NMR (300MHz, CDCl₃): δ:1.69 (m,4H),1.98(m, 1H),2.28(m, 4H) 3.49 (d, 2H), 3.59 (t, 2H), 3.68 (t, 2H), 4.39 (t,2H) , 5.21 (s, 2H), 6.83 (d, 1H), 7.05-7.20 (m, 3H), 7.72 (d, 1H), 7.9 (d, 1H), 8.13 (s, 1H); ¹³C NMR (125MHz, CDCl₃): δ:26.3, 34.3, 49.0, 50.0, 50.2, 67.8, 121.8, 124.6, 128.3, 130.2, 130.3, 133.2, 133.2, 136.3, 137.8, 154.6, 195.4; FT-IR(KBr): mₜₜ 3401, 2920, 1716, 1694,1496, 1227, 1137cm⁻¹; 610-670 cm⁻¹; FAB: MS: m/z 538.24 (M+H)+.

1-(Bromo-ethyl)-3-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-1,3-dihydrobenzoimidazol-2-one (6D): A mixture of compound 6 (1.5g, 0.0029 mole), 4-hydroxy ethyl piperidine (0.68g, 0.00552 mole), K₂CO₃ (1.14g, 0.0082 mole) in 2-methyl THF (15ml) was refluxed for 8 h. The mixture was concentrated in vacuo and the residue diluted with H₂O and extracted with EtOAc. The residue was chromatographed on a column of silicagel using a mixture of Methanol and Dichloromethane (3-4%) as eluent to furnish compound 10 0.70g, 87.5%; mp. 209-211°C; ¹H NMR (300MHz, CDCl₃): δ:1.69 (m,4H),1.98(m, 1H),2.28(m,
CONCLUSION

As a part of our ongoing studies in developing new derivatives of Novel N,N,N-substituted 1-piperidin-4-yl-(3,4-dibromomphenyl)1,3-dihydro-2H-benzimidazol-2-one derivatives (6A-6D) were prepared from commercially available 1,2-phenylenediamine and tested for Gram positive and Gram Negative bacterial cultures. Among the di-substituted 1-piperidin-4-yl-1,3-dihydro-2H-benzimidazol-2-one analogs (6A-6D), compounds 6A-6D were found to be highly active against Streptococcus pyogenes and Escherichia coli.

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