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Research Article

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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-dibromphenyl)-1,3-dihydro-2H-benzimidazol-2-one derivatives (**6A-6D**) were prepared from commercially available 1,2-henylenediamine. Compounds (**6A-6D**) were tested for Gram positive: Streptococcus pyogenes and Staphylococcus aureus. Gram negative: Escherichia coli, Pseudomonas arzenous, Proteus vulgaris, Salmonella typhi 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

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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 antiulcer and 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.

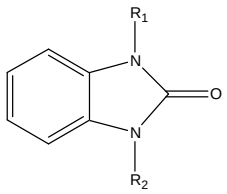


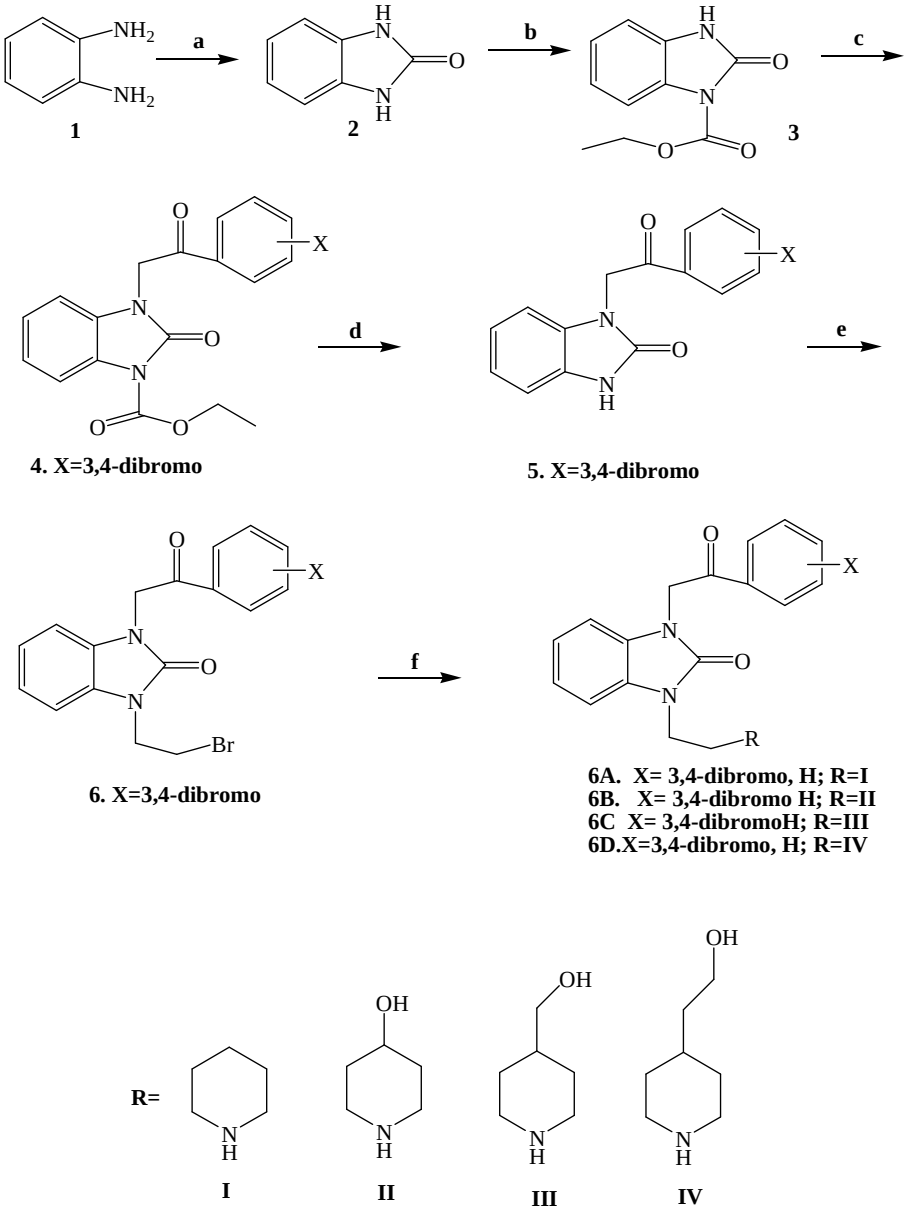
Figure 1

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 **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 **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-HT4 agonists and antagonists [18], progesterone receptor antagonist [19], respiratory syncytial virus (RSU) 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 K_2CO_3 in 2-methyl THF afforded compounds **6A-6D**



Scheme-1

Reagents and Conditions : *a) CDI, DMF, RT; b) ethylchloroformate, K_2CO_3,2-methyl THF, Δ; c) 3,4 -dibromo phenacyl bromide, K_2CO_3, 2-methyl THF, Δ; d) 5N NaOH, Ethanol, RT, 1,2-dibromoethane, K_2CO_3, 2-methyl THF Δ; f) RNH, K_2CO_3, 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^{o}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^{6} cell/mL. The plates were allowed to set at room temperature and later dried at 37^{o}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^{o}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 arzenous, 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 activityof compounds(6A-6D)

Compd (200 µg/mL in DMSO)	*Streptococcus pyrogenes*	*Staphylococcus aureus*	*Escherichia Coli*	*Pseudomonas arzenosa*	*Proteus vulgaris*	*Salmonella typhi*
6A	-	-	+	-	-	-
6B	-	-	+	-	-	-
6C	+	+	+	+	-	+
6D	+	+	+	+	+	+
Zone of inhibition (DMSO as solvent); +++ = 16-21mm; ++ = 6-12 mm; + = 4-8mm; - = No inhibition						

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 numbers were given in cm^{-1}. The ^{1}H NMR spectra were recorded in $CDCl_3$/DMSO-*d* on a Varian EM-360 spectrometer (300MHz).The ^{13}C NMR spectra recorded in $CDCl_3$/DMSO-*d* 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 JMS\D 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'-carbonyldiimidazole (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^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) : δ 6.92 (m, 4H), 10.6 (s, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 121 (2C), 124.6 (2C), 129.9 (2C), 155.2; FT-IR(KBr) : υ_{max} 3199, 2807, 1739, 1627, 1481 cm^{-1}; FAB MS: *m/z* 135 $(M+H)^{+}$.

Ethyl -2,3-dihydro-2-oxobenzo[α]imidazole-1-carboxylate (3):
Ethylchloroformate (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 K_2CO_3 (18.53g, 0.134 mole) in Acetonitrile (240 ml). The reaction mixture was stirred at 90^{o}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^{o}C. ^{1}H NMR (300MHz, $CDCl_3$): δ CH_3 1.48 (t,3H), CH_2 4.53 (q,2H), NH 11.2 (s,1H), Ar-H7.2 (m,3H), 7.7 (d,1H), ^{13}C NMR (125MHz, $CDCl_3$): δ 13.8, 58.3, 121.8 (2C), 124.6 (2C) , 127.3, 129.9, 150.2, 151.4; FT-IR (KBr): υ_{max} 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-benzoimidazole-1-carboxylic acid ethyl ester (4): A mixture of compound **3**(10g, 0.0308 mole), 3,4-dibromophenacyl bromide (11.0g, 0.0308 mole), K_2CO_3 (13.39g, 0.0969 mole) in 2-methyl THF (100 ml) was refluxed at 80^{o}C for 6 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate, organic layer dried over $MgSO_4$, filtered and evaporated in *vacuum* to give **4** as crude solid. m.p: 129-131°C. (18g, 76.33%) and was taken to next step without further purification. ^{1}H NMR (300MHz**,** $CDCl_3$): δ $CH_3$1.48 (t,3H), CH_2 4.54 (q,2H), N-CH_2 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). ^{13}C NMR (125MHz, $CDCl_3$): δ 13.8, 49.7, 121.8, 124.6,

128.3, 130.2, 133.3, 136.3, 137.8, 151.2, 152.6, 195.4. FT-IR (KBr): υ_{max} 3410, 2927, 1711, 1695, 1417, 1198, 620-680 cm^{-1}; FAB MS: *m/z* 483.93 $(M+H)^+$.

1[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 Na_2SO_4 filtered and evaporated to afford compound **5** (8.6g, 85%); mp.165-167°C. ^{1}H NMR (300MHz**,** $CDCl_3$): δ**:** N-CH_2 5.2 (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).; ^{13}CNMR (125MHz, $CDCl_3$): 49.7, 121.8, 124.6, 128.3, 130.2, 130.3, 133.3, 136.3, 154.6, 195.4.; FT-IR (KBr): υ_{max} 3179, 3022, 1700, 1488, 620-670 cm^{-11}; FAB MS: *m/z* 411.91

1-(2-Bromo-ethyl)-3-[2-(3,4-dibromo-phenyl)-2-oxo-ethyl]-1,3-dihydrobenzoimidazol-2-one (6): To a stirred mixture of compound **5** (8.5 g, 0.0260 mole) and K_2CO_3 (9.3g, 0.0674 mole) in 2-methyl THF (42.5ml) was added drop wise 1,2-Dibromoethane (14.4g, 0.0767 mole) over 30 min. The reaction mixture was refluxed at 80^{o}C for 8 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and saturated NaCl, dried over Na_2SO_4, filtered and evaporated in *vacuum.* The product 6 were purified by flash column chromatography using silicagel with hexane-ethyl acetate as eluant to afford compounds **6** (7.5 g, 75%); mp.136-138°C. ^{1}H NMR (300MHz,$CDCl_3$): 3.68 (t, 2H), 4.318 (t, 2H), 5.21 (s, 2H), Ar-H 7.05-7.21 (m, 3H), 7.77 (d, 1H), 6.8 (t, 1H), 8.1 (s, 1H), 7.92 (t, 1H).; ^{13}C NMR (125MHz, $CDCl_3$): : 27.9, 49.7, 55.8, 121.8, 124.6, 121.8, 124.6, 128.3, 130.2, 130.3,133.3, 136.3, 154.6, 195.4 FT- IR(KBr): υ_{max} 3401, 2920, 1716, 1695 ,1496,1213,532 cm^{-1}; FAB MS: *m/z* 518 $(M+H)^+$.

1-[2-(3,4-Dibromophenyl)-2-oxo-ethyl]-3-(2-piperidin-1-yl)-ethyl)-1,3-dihydro-benzoimidazol-2-one (6A): A mixture of compound **6**(1.5g, 0.0029 mole), piperidine (0.37g, 0.0369 mole), K_2CO_3 (1.13g, 0.0082 mole) in 2-methyl THF (25ml) was refluxed for 10 h. The mixture was concentrated in *vacuum* and the residue diluted with H_2O 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 **7** (0.5g, 50 %); mp. 124-126°C. ^{1}H NMR(300MHz, $CDCl_3$) : 1.72 (m, 6H), 2.28 (m, 4H), 3.68 (t, 2H), 4.31 (t, 2H), 5.21 (s, 2H), 6.83 (d 1H), 7.05-7.2 (m, 3H), 7.72 d,1H),7.9(d,1H,), 8.2 (s, 1H; ^{13}C NMR (125MHz, $CDCl_3$): δ25.9, 33.8, 48.1, 49.0, 54.3, 67.8, 50.2, 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): υ_{max} 2992, 2690, 1716, 1695, 1496 cm^{-1}; 610-680 cm^{-1};FAB: MS: *m/z* 522.24 ($M+H)^+$.

1-[2-(3,4-Dibromoophenyl)-2-oxo-ethyl]-3-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-1,3-dihydro-benzoi- midazol-2-one (6B): A mixture of compound **6** (1.5g, 0.0029 mole), piperdine1-ol (0.53g, 0.00525 mole), K_2CO_3 (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 H_2O 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; ^{1}H NMR (300MHz, $CDCl_3$): δ1.78 (m, 4H), 2.28 (m, 4H), 3.38 (m, 1H), 2.79 (t, 2H), 3.8 (t, 2H), 5.2 (s, 2H), 7.05 to7.20 (m, 3H), 7.77 (d, 1H), 7.2 to 7.35 (m, 5H); ^{13}C NMR (125MHz, $CDCl_3$) : δ 33.8, 48.1, 49.1, 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): υ_{max} 3401, 2920, 1716, 1694,1496, 1227, 1137$cm^{-1,}$ 610-670 cm^{-1}; FAB: MS: *m/z* 538.24($M+H)^+$.

1-[2-(3,4-Dibromophenyl)-2-oxo-ethyl]-3-[2-(4-hydroxymethyl-piperidin-1-yl)-ethyl]-1,3-dihydro -benzoimidazol-2-one(6C): A mixture of compound **6** (1.5g, 0.0029 mole), 4-piperdinemethanol (0.60g, 0.00522 mole), K_2CO_3 (1.14g, 0.0082 mole) in 2-methyl THF (25ml) was refluxed for 12 h. The mixture was concentrated in *vacuum* and the residue diluted with H_2O 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; ^{1}H NMR(300MHz, $CDCl_3$): δ1.69 (m,4H) ,1.98m,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);

^{13}C NMR(125 MHz, $CDCl_3$): δ26.3, 34.3, 49.0, 50.0, 50.2, 50.2, 67.6, 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): υ_{max} 3401, 2920, 1716, 1695,1496, 1227,1137 ,610-670 cm^{-1},cm^{-1}; FAB: MS: *m/z* 552.27 ($M+H)^+$.

1-[2-(3,4-Dibromophenyl)-2-oxo-ethyl]-3-{2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-ethyl}-1,3-dihy-drobenzoimidazol-2-one (6D): A mixture of compound **6**(1.5g, 0.0029 mole), 4-hydroxy ethyl piperidine (0. 68g, 0.0053 mole), K_2CO_3 (1.13g, 0.0082 mole) in 2-methyl THF (15ml) was refluxed for 8 h. The mixture was concentrated in *vacuum* and the residue diluted with H_2O 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; ^{1}H NMR(300MHz, $CDCl_3$): δ1.69 (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), 8.2 (s, 1H); ^{13}C NMR(125 MHz, $CDCl_3$): δ33.8, 48.1, 49.1, 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): υ_{max} 3412, 2920, 1716,1695, 1496, 1227 ,1137, 610-670 cm^{-1}; FAB: MS: *m/z* 566.3 ($M+H)^+$.

CONCLUSION

As a part of our ongoing studies in developing new derivatives of Novel N_1,N_3-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 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 pyrogenes and Escherichia coli.

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