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Synthesis, characterization and biological evaluation of some novel N_1,N_3-substituted 1-piperidin-4-yl-1,3-dihydro-*2H*-benzimidazol-2-one derivatives

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ABSTRACT

Synthesis of some novel N_1,N_3-substituted *1-piperidin-4-yl-1,3-dihydro-2H-benzimidazol-2-one derivatives (**7-10**) were prepared from commercially available 1,2-phenylenediamine. Compounds (**7-10**) were tested for Gram positive: Streptococcus pyrogenes and Staphylococcus aureus. Gram negative: Escherichia coli, Pseudomonas arzenous, Proteus vulgaris, Salmonella typhi bacterial cultures. Compounds **7-10** were found to be highly active against Streptococcus pyogenes and Escherichia coli.*

Keywords: antibacterial activity, CDI and N_1,N_3-substituted dihydro-2H-benzimidazol-2-one.

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 [7-10] to check their medicinal properties. Several N_1,N_3-substituted 1-piperidin-4-yl-1,3-dihydro-2H-benzimidazol-2-ones 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 **1** represents the core skeleton of a large number of biologically active, structurally intriguing compounds found in a multitude of pharmaceutically important compounds [11]. Both mono- and disubstituted benzimidazol-2-one derivatives **1** have been identified as potent NK1 antagonists [12], CGRP receptor antagonists [13], farnesyl transfer inhibitors [14], p38 inhibitors [15], cathepsin S inhibitors [16], 5-HT4 agonists and antagonists [17], progesterone receptor antagonist [18], respiratory syncytial virus (RSU) inhibitors [19], vasopressin 1a receptor antagonists [20], aldose reductase inhibitors [21], and neurotransmitter antagonists [22]. The development of efficient and practical methods for construction of this important heterocycle remains as an active area of synthetic research **(Fig. 1).** Herein, we report on the synthesis and characterization of some novel N_1,N_3-substituted 1-piperidin-4-yl-1,3-dihydro-2H-benzimidazol-2-one derivatives.

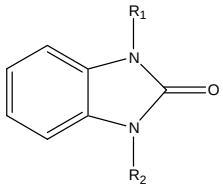
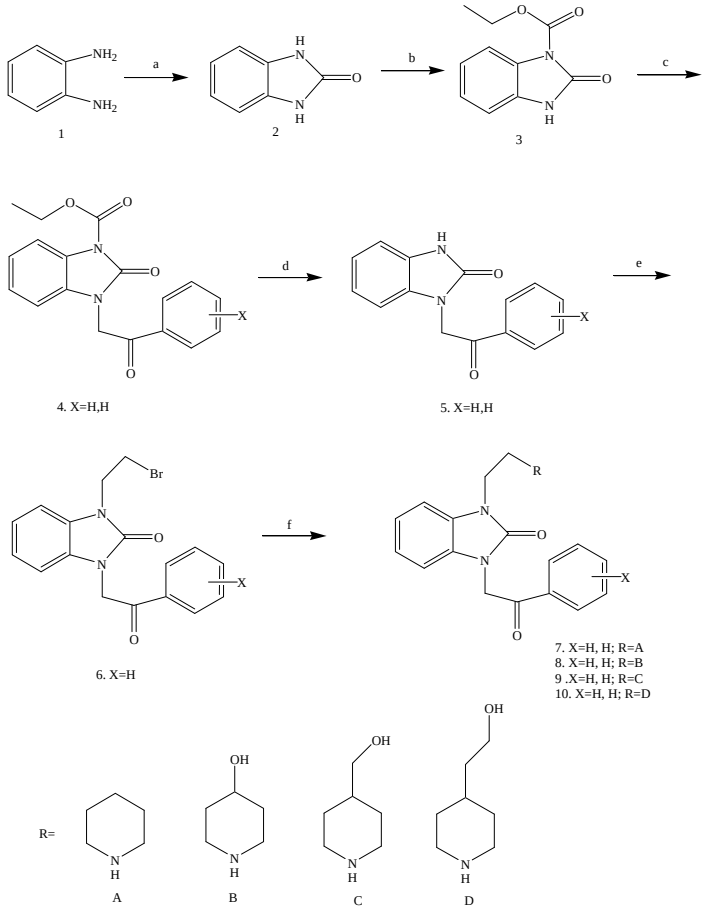


Fig.1

MATERIALS AND METHODS

Synthesis of some novel N_1,N_3-substituted 1-piperidin-4-yl-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. A compound 4 is prepared by alkylation of compound **3** with phenacyl bromide. Hydrolysis of compound **4** with 5N NaOH at room temperature afforded compound **5** in 90% yield. Reaction of compound **5** with 1,2-Dibromoethane in acetonitrile gave compound **6** in 50% yield. Reaction of Compound 6 with piperidines **(A- D)** with K_2CO_3 in acetonitrile afforded compounds **7 - 10**.



Scheme-1

Reagents and Conditions : *a) CDI, DMF, RT; b) ethylchloroformate, K_2CO_3, Acetonitrile, Δ; c) 2-bromo-acetophenone, K_2CO_3, Acetonitrile, Δ; d) 5N NaOH, Ethanol, RT, e) 1,2-dibromoethane, K_2CO_3, Acetonitrile, Δ; f) RNH, K_2CO_3, Acetonitrile.*

Procedure for antimicrobial activity

The novel N_1,N_3-substituted-1-piperidin-4-yl-1,3-dihydro-2H-benzimidazol-2-one derivatives **7-10** were dissolved in dimethyl sulphoxide (DMSO) 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 hr 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, 1mL 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 2hrs. Paper discs (6mm, punched from whatman filter paper no. 41) 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 6-7 cm, 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 N_1,N_3-substituted 1-piperidin-4-yl-1,3-dihydro-2h-benzimidazol-2-one analogs (7-10):

The following bacterial cultures were tested for their susceptibility to N_1,N_3-substituted 1-piperidin-4-yl-1,3-dihydro-2H-benzimidazol-2-one derivatives (**7-10**) 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 **7** is highly active against all the bacterial cultures and inactive against Proteus vulgaris and Salmonella typhi. Compound **8** is highly active against Streptococcus Pyogenes, Escherichia coli and Salmonella typhi and inactive against the other bacterial cultures. Compound **9** is highly active against Streptococcus Pyogenes, Escherichia coli and moderately active against Proteus vulgaris. Compound **10** is highly against all the bacterial cultures and moderately active against Proteus vulgaris and Salmonella typhi.

Table 1 Antimicrobial activityof compounds (7-10)

Compd (200 µg/mL in DMSO)	*Streptococcus pyrogenes*	*Staphylococcus aureus*	*Escherechia coli*	*Pseudomonas arzenosa*	*Proteus vulgaris*	*Salmonella typhi*
7	++	++	++	+++	-	-
8	+++	-	++	-	-	++
9	++	-	++	-	+	-
10	++	++	++	++	+	+
Zone of inhibition (DMSO as solvent); +++ = 15-20 mm; ++ = 8-14 mm; + = 5-7mm; - = No inhibition						

GENERAL METHODS

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 hr. The solvent was concentrated under reduced pressure, filtered, and recrystallized from Dichloromethane to afford a compound **2** (12.1g, 98%), m.p. 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 dropwise over 30min. 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 hr. 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 .m.p.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-H 7.2 (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$(M+H)^+$.

2-Oxo-3-(2-oxo-2-phenyl-ethyl)-2,3-dihydro-benzoimidazole-1-carboxylic acid ethyl ester (4)

A mixture of compound **3** (10g, 0.0308 mole), 2-bromoacetophenone (6.09g, 0.0308 mole), K_2CO_3 (13.385g, 0.0969 mole) in acetonitrile (100mL) was refluxed at 90^{o}C for 4.5 hr. After that the solvent was removed, diluted with water and extracted with ethyl acetate, organic layer dried over $MgSO_4$, filtered and evaporated in *vacuo* to give **4** as crude solid (12g, 76.33%) m.p.124-127°C which was carried to next step without further purification, m.p.114^{o}C; ^{1}H NMR (300MHz**,** $CDCl_3$): δ 1.48 (t, 3H), 4.53 (q, 2H), 7.05 to 7.20 (m, 3H), 7.77 (d, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ 13.8, 58.3, 121.8, 124.6, 127.3, 129.9, 150.2, 151.4; FT-IR (KBr): υ_{max} 3414, 2806, 1711, 1695, 1602, 1417, 1265 cm^{-1}; FAB MS: *m/z* 325.0 $(M+H)^+$.

2-Oxo-3-(2-oxo-2-phenyl-ethyl)-1,3-dihydro-benzoimidazol-2 -one (5)

Compound **4** (12g, 0.037 mole) dissolved in EtOH (28mL) and aqueous NaOH (5N, 100 mL) was added. The reaction mixture was stirred for 2 hr at rt. Ethanol was evaporated under reduced pressure and extracted with ethyl acetate. The extract was washed with water and saturated NaCl solution, dried with Na_2SO_4 filtered and evaporated to afford compound **5** (8.5g, 91%) m.p. 198-200^{o}C; ^{1}H NMR (300MHz**,** $CDCl_3$): δ 5.2 (s, 2H), 7.05 to 7.20 (m, 3H), 7.77 (d, 1H), 7.2 to 7.35 (m, 5H); ^{13}CNMR (125MHz, $CDCl_3$): δ 49.7, 121.8 (2C), 129.9, 128.7 (2C), 128.8 (2C), 133.2 , 136.8, 151.7, 195.1; FT-IR (KBr): υ_{max} 3414, 2690, 1700, 1488,1695, 1613 cm^{-1}; FAB MS: *m/z* 253 $(M+H)^+$.

1-(2-Bromo-ethyl)-3-(2-oxo-2-phenyl-ethyl)-1,3-dihydro-benzoimidazol-2-one (6)

To a stirred suspension of K_2CO_3 (9.3g, 0.0674 mole) in ACN (42.5 mL) was added dropwise a solution of compound **5** (8.5g, 0.0337 mole) in ACN (25 mL) at rt. The reaction mixture was stirred for 30 min. and then 1,2-Dibromoethane (18.92g, 0.101 mole) was added dropwise. After the addition, the reaction mixture was refluxed at 90^{o}C for 6 hr. The mixture was quenched in 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 *vacuo*. The product **4, 5** were purified by flash column chromatography using silicagel with hexane-ethyl acetate as eluant to afford compounds **4, 5** (6g , 49.71%); m.p.184-185°C; ^{1}H NMR (300MHz, $CDCl_3$): δ 2.79 (t, 2H), 3.8 (t, 2H), 5.2 (s, 2H), 7.05 to 7.20 (m, 3H), 7.77 (d, 1H), 7.2 to 7.35 (m, 5H); ^{13}C NMR (125MHz, $CDCl_3$): δ 27.9, 55.8, 124.6 (2C), 121.8 (2C), 128.7 (2C), 128.8 (2C), 133.3 (2C), 136.8, 154.6, 195.4; FT- IR(KBr): υ_{max} 3414, 2690, 1700, 1488, 1213 cm^{-1}; FAB MS: *m/z* 360.1 $(M+H)^+$.

1-(2-oxo-2-phenyl-ethyl)-3-(2-piperidin-1-yl-ethyl)-1,3-dihydro-benzoimidazol-2-one (7)

A mixture of compound **6** (0.15g, 0.00041 mole), piperidine (0.052g, 0.000615 mole), K_2CO_3 (0.113g, 0.00082 mole) in ACN (1.5 mL) was refluxed for 8 hr. 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 eluant to furnish compound **7 (**0.070g, 87.5 %). m.p. 136-138°C; ^{1}H NMR (300MHz, $CDCl_3$): δ 1.78 (m, 4H), 1.92 (d, 1H), 2.28 (m, 4H), N-CH_2 3.68 (t, 2H), N-CH_2 4.31 (t, 2H), N-CH_2 5.2 (s, 2H), Ar-H 7.2 (m, 3H), 7.7 (d, 1H), 7.31 (m, 5H); ^{13}C NMR (125MHz, $CDCl_3$): δ 25.9 (3C), 49, 50.0, 50.2, 54.3 (2C), 121.8 (2C), 124.6 (2C), 128.8 (2C), 128.7 (2C), 133.2, 133.3 (2C), 136.8, 154.6, 195.4; FT-IR (KBr): υ_{max} 3414, 2992, 2690, 1700, 1695, 1488 cm^{-1}; FAB: MS: *m/z* 379 ($M+H)^+$.

1-[2-(4-Hydroxy-piperdin-1-yl)-ethyl]-3-(2-oxo-2-phenyl-ethyl)-1,3-dihydro-benzoimidazol-2-one (8).

A mixture of compound **6** (1.5g, 0.0041 mole), 4-hydroxy piperidine (0.62g, 0.0062 mole), K_2CO_3 (1.15g, 0.0083 mole) in ACN (15 mL) was refluxed for 8 hr. 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** (0.85gm, 50%). m.p.179-181°C; ^{1}H NMR (300MHz, $CDCl_3$): δ 1.78 (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 26.3, 34.3, 52.1, 67.8, 50.2, 50.0, 49.0, 121.8, 124.6, 128.7, 133.2, 136.8, 154.6, 195.4; FT-IR(KBr): υ_{max} 3416, 2690, 1700, 1488, 1213 cm^{-1}; FAB: MS: *m/z* 394.48($M+H)^+$.

1-[2-(4-Hydroxymethyl-piperdin-1-yl)-ethyl]-3-(2-oxo-2-phenyl-ethyl)-1,3-dihydro-imidazol-2-one (9).

A mixture of compound **6** (1.5g, 0.0041 mole), 4-hydroxy methylpiperidine (0.62g, 0.0062 mole), K_2CO_3 (1.15g, 0.0083 mole) in ACN (15mL) was refluxed for 8 hr. 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 **9** (0.85g, 50%); m.p.202-205°C; ^{1}H NMR(300MHz, $CDCl_3$): δ 1.59 (q, 4H), 1.98 (t, 1H), 2.29 (t, 4H), 1.58 (m, 1H), 3.49 (d, 2H), 2.79 (t, 2H), 3.8 (t, 2H), 5.2 (s, 2H), 7.05-7.20 (m, 3H), 7.77 (d, 1H), 7.2-7.35 (m, 5H); ^{13}C NMR(125MHz, $CDCl_3$): δ 26.3 (2C), 34.3, 52.1 (2C), 67.8, 50.2, 50.0, 49.0, 121.8 (2C), 124.6 (2C), 128.7 (2C), 133.2 (2C), 136.8, 154.6, 195.4; FT-IR (KBr): υ_{max} 3416, 2690, 1700, 1488, 1213 cm^{-1}; FAB: MS: *m/z* 394.48 (M+H)$^+$.

1-{2-[4-(2-Hydroxy-ethyl)-piperdin-1-yl)-ethyl]-ethyl}-3-(2-oxo-2-phenyl-ethyl)-1,3-dihydro-benzoimidazol -2-one (10). A mixture of compound **6** (1.5g, 0.0041 mole), 4-hydroxy piperidine ethanol (0.73g, 0.0061 mole), K_2CO_3 (1.15g, 0.0083 mole) in ACN (15 mL) was refluxed for 8 hr. 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 **10** (0.82g, 50%); m.p.242-245°C. ^{1}H NMR(300MHz, $CDCl_3$): δ 1.59 (m, 7H), 1.98 (t, 4H), 1.98 (m, 1H), 3.49 (d, 2H), 3.59 (t, 2H), 3.68 (t, 2H), 4.39 (t, 2H) , 5.2 (s, 2H), 7.05-7.20 (m, 3H), 7.77 (d, 1H), 7.2-7.35 (m, 5H); ^{13}C NMR(125MHz, $CDCl_3$): δ 15.8, 30.3 (2C), 37.1, 49.0, 50.0, 50.2, 52.1 (2C), 34.3, 52.1 (2C), 121.8 (2C), 124.6 (2C), 128.7 (2C), 133.2 (2C), 136.8, 154.6, 195.4; FT- IR (KBr): υ_{max} 3414, 2690, 1700, 1488, 1213 cm^{-1}; FAB: MS: *m/z* 408.51(M+H)$^+$.

CONCLUSION

Novel N_1,N_3-substituted 1-piperidin-4-yl-1,3-dihydro-2H-benzimidazol-2-one derivatives (**7-10**) were prepared from commercially available 1,2-phenylenediamine and tested for Gram positive and Gram Negative bacterial cultures. Among the N_1,N_3-substituted 1-piperidin-4-yl-1,3-dihydro-2H-benzimidazol-2-one analogs (**7-10**), compounds **7-10** were found to be highly active against Streptococcus pyogenes and Escherichia coli.

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