Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2010, 2(5): 178-183
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X

Synthesis and Biological Evaluation of Potent Benzimidazolone Derivatives

Jabali J Vora*, Dinesh R Patel, Nilesh V Bhimani and Parag V Ajudia[#]

Department of Chemistry, Hemchandracharya North Gujarat University, Patan, Gujarat, India

---

ABSTRACT

Some benzimidazolone derivatives containing piperidine ring derivatives were synthesized and characterization was done by CHN analysis, IR, Mass and ^{1}H NMR spectral data. The benzimidazolone derivatives were evaluated for their antibacterial activity against both gram-positive and gram-negative bacteria. The bacterial strengths were E. coli, B. subtilis, B. megaterium, P. fluorescens and found good results.

Keywords: Antibacterial activity, benzimidazolone derivatives.

INTRODUCTION

Heterocycles are in the center of research due to their versatile application [1]. The benzimidazolone ring structure is of particular interest especially within the realm of medicinal chemistry because of their different biological activity and clinical applications[2-4]. They exhibit a wide variety of interesting biochemical and pharmacological Properties including antagonize neurotransmitters[5-7], inhibit aldose reductase[8], show antiulcer and antisecretory properties[9-10], enhance pulmonary surfactant secretion[11] and modulate ion channels[12-13]. Benzimidazolone as well as piperidine derivatives[14] are also medicinally important. Research in the field of pharmaceutical has its most important task in the development of new better drugs and their successful introduction into clinical practice due to bacterial resistance over old drugs and other effects. Owing such properties by benzimidazolone derivatives lead us to synthesised their new derivatives and evaluate their antibacterial properties.

MATERIALS AND METHODS

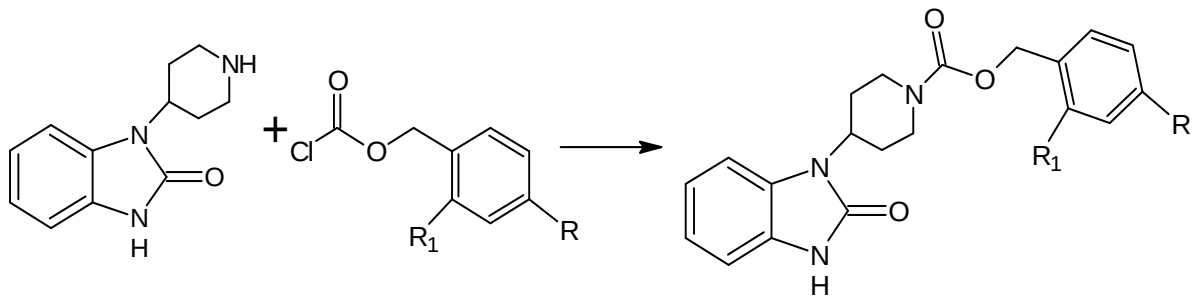
All melting points were recorded in open capillaries and on Veergo melting point apparatus. The ^{1}H NMR spectra were recorded on a Bruker 300 MHz spectrometer at 300 MHz using TMS as an internal standard. The IR spectra were recorded on a Perkin Elmer Spectrum 100 FTIR

spectrometer where as Mass spectra were recorded on a Waters Micromass Q-ft instrument. The chemicals were used are of LR grade and obtained from the local market.

Reaction scheme and general procedure for the synthesis of compound (2a-d)

To a solution of Compound-1(20.0gm) in dichloromethane, diisopropylethylamine (1.15M eq.) was added then resulting reaction mixture was cooled to 0 to 5^{o}C. The solution of benzylchloroformate compound (1.02M eq.) in dichloromethane was added slowly under agitation. Progress of the reaction mass was monitored by TLC then water was added and separated out organic layer. Washed the organic layer with water and solvent was evaporated under vacuum. Dichloromethane was added to the residue and filtered then washed with cold methanol. The resulting product dried and weighed.

Scheme 1



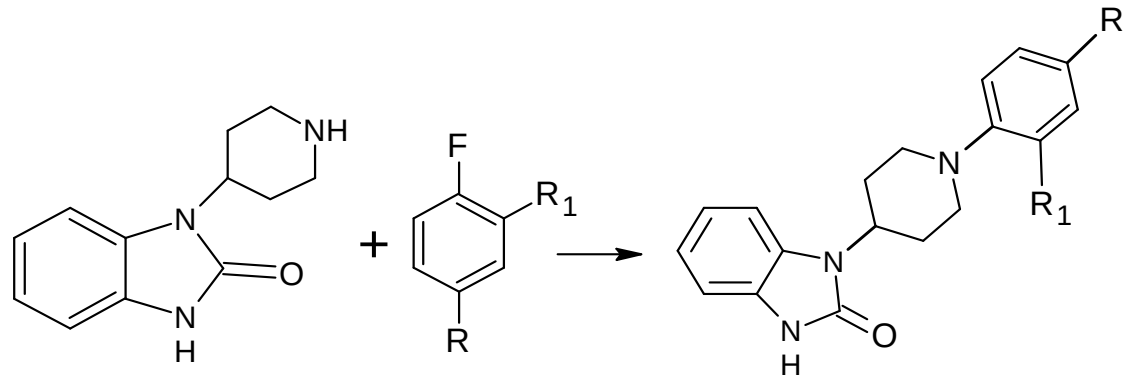
compound -1 benzylchloroformate compound compound -2

Where compound 2a: R=H, R1=H, compound 2b: R=NO_2, R1=H, compound 2c: R=H, R1=Cl, compound 2d: R=H, R1=Br

Reaction scheme and general procedure for the synthesis of compound (3a-f)

To a solution of Compound-1(20.0gm) in ethylacetate, fluoro compound (1.06M eq.) was added at room temperature. Diisopropylethylamine (1.1M eq.) was added slowly under agitation. Progress of the reaction mass was monitored by TLC. Filtered the product then washed with methanol. The resulting material dried and weighed.

Scheme 2



compound -1 fluoro compound compound -3

Where compound 3a: R=NO2, R1=F, compound 3b: R=NO2, R1=H, compound 3c: R=CH3, R1=H, compound 3d: R=Cl, R1= Cl, compound 3e: R=OCH3, R1=H, compound 3f : R=Cl, R1=H

Table 1 Characteristics and Yield of Synthesised compounds

Compound code	Molecular formula	Molecular weight (g mol^{-1})	M.P. (^oC)	Yield (%)	R_f[a] value
Compound 2a	$C_{20}H_{21}N_3O_3$	351	155	62.10	0.45
Compound 2b	$C_{20}H_{20}N_4O_5$	396	176	59.27	0.52
Compound 2c	$C_{20}H_{20}N_3O_3Cl$	386	201	56.36	0.46
Compound 2d	$C_{20}H_{20}N_3O_3Br$	430	165	45.90	0.49
Compound 3a	$C_{18}H_{17}N_4O_3F$	356	254	72.18	0.48
Compound 3b	$C_{18}H_{18}N_4O_3$	338	125	64.00	0.45
Compound 3c	$C_{19}H_{21}N_3O$	307	171	67.00	0.50
Compound 3d	$C_{18}H_{17}N_3OCl_2$	362	119	49.25	0.47
Compound 3e	$C_{19}H_{21}N_3O_2$	323	132	54.72	0.51
Compound 3f	$C_{18}H_{18}N_3OCl$	328	178	59.50	0.48

[a]*Solvent Systems: Ethylacetate: Hexane: Methanol (4.5:4.5:1)*

Preparation of Plates and Microbiological Assays

The in *vitro* antibacterial activity of the synthesised compounds was tested against some clinically important bacteria by the well diffusion method using Mueller-Hinton agar No.2 as the nutrient medium. Solutions of the synthesized compounds were prepared (10 mg ml^{-1}) in dimethylformamide. The bacterial strains were activated by inoculating a loop full of the test strain in to 25 ml of nutrient broth and incubated for 24 hrs in an incubator at 37 ^oC. The activated strain (0.2 ml) was inoculated in Mueller Hinton agar at 45 ^oC. It was then poured into Petri dishes and allowed to solidify then 0.85 cm ditch was made in the plates using a sterile cork borer and these were completely filled with the compound solution. The dishes were incubated for 24 hrs at 37 ^oC. The experiment was repeated three times simultaneously under the same condition for each compound and the mean value obtained for three wells was used to calculate the inhibition zone growth. The controls were maintained for each bacterial strain with the solvent, where pure solvent was inoculated into the well. The inhibition zone, formed by the compounds against the particular bacterial strain was subtracted from the control, thereby determining the antibacterial activities of the benzimidazolone derivatives.

RESULTS AND DISCUSSION

Table 1 shows the molecular formula, molecular weight, melting point, percentage yield and R_f value of all synthesised compounds. The IR, NMR and Mass spectral data are given below.

Characterization of Compound 2a-2d

Compound 2a: found (calcd): C, 68.52 (68.36); H, 5.98 (6.04); N, 11.86 (11.96); IR (KBr, cm^{-1}): 3300 (-NH str.), 1720 (O-C=O str.), 1690 (N-C=O str.), 1602 (-C=C str.), 1528 (-NH ben.), 1436 (-C-N str.), 1136 (-C-O-C str.). MS: 351[M.]; ^{1}H NMR (ppm)($CDCl_3$): 9.32 (1H, singlet, =NH), 6.97-7.33 (9H, multiplet, Ar-H), 5.11 (2H, singlet, -OCH_2), 4.35-4.48 (3H, multiplet, piperidine), 2.89-2.97 (2H, triplet, piperidine), 2.26-2.30 (2H, doublet, piperidine), 1.77-1.81 (2H, doublet, piperidine).

Compound 2b: found (calcd): C, 60.30 (60.60); H, 5.15 (5.09); N, 14.25 (14.13); IR (KBr, cm^{-1}): 3290 (-NH str.), 1721 (O-C=O str.), 1688 (N-C=O str.), 1598 (-C=C str.), 1525 (-NH ben.), 1430 (-C-N str.), 1332 ($-NO_2$ str.), 1125 (-C-O-C str.). MS: 396[M.]; ^{1}H NMR (ppm)($CDCl_3$): 9.49 (1H, singlet, =NH), 6.97-8.15 (8H, multiplet, Ar-H), 5.08 (2H, singlet, $-OCH_2$), 4.31-4.44 (3H, multiplet, piperidine), 2.84-2.93 (2H, triplet, piperidine), 2.25-2.29 (2H, doublet, piperidine), 1.80-1.84 (2H, doublet, piperidine).

Compound 2c: found (calcd): C, 62.01 (62.26); H, 5.14 (5.22); N, 10.80 (10.89); IR (KBr, cm^{-1}): 3292 (-NH str.), 1717 (O-C=O str.), 1685 (N-C=O str.), 1600 (-C=C str.), 1527 (-NH ben.), 1432 (-C-N str.), 1128 (-C-O-C str.), 1092 (-Cl aro.). MS: 387[M+1.]; ^{1}H NMR (ppm)($CDCl_3$): 9.32 (1H, singlet, =NH), 6.94-7.64 (8H, multiplet, Ar-H), 5.10 (2H, singlet, $-OCH_2$), 4.30-4.44 (3H, multiplet, H-piperidine), 2.85-2.93 (2H, triplet, piperidine), 2.23-2.27 (2H, doublet, piperidine), 1.79-1.83 (2H, doublet, piperidine).

Compound 2d: found (calcd): C, 56.01 (55.83); H, 4.52 (4.68); N, 9.97 (9.77); IR (KBr, cm^{-1}): 3296 (-NH str.), 1718 (O-C=O str.), 1684 (N-C=O str.), 1594 (-C=C str.), 1532 (-NH ben.), 1428 (-C-N str.), 1130 (-C-O-C str.). MS: 431[M+1]; ^{1}H NMR (ppm)($CDCl_3$): 9.41 (1H, singlet, =NH), 6.98-7.59 (8H, multiplet, Ar-H), 5.18 (2H, singlet, $-OCH_2$), 4.34-4.47 (3H, multiplet, piperidine), 2.88-2.96 (2H, triplet, piperidine), 2.27-2.31 (2H, doublet, piperidine), 1.79-1.83 (2H, doublet, piperidine).

Characterization of Compound 3a-3f

Compound 3a: found (calcd): C, 60.87 (60.67); H, 4.64 (4.81); N, 15.84 (15.72); IR (KBr, cm^{-1}): 3296 (-NH str.), 1688 (N-C=O str.), 1605 (-C=C str.), 1535 (-NH ben.), 1433 (-C-N str.). MS: 356[M.]; ^{1}H NMR (ppm)(DMSO-D_6): 10.88 (1H, singlet, -NH), 8.11-8.15 (2H, doublet, Ar-H), 6.98-7.28 (5H, multiplet, Ar-H), 4.41-4.49 (1H, multiplet, piperidine), 3.84-3.88 (2H, doublet, piperidine), 3.10-3.18 (2H, triplet, piperidine), 1.79-1.83 (2H, doublet, piperidine).

Compound 3b: found (calcd): C, 64.00 (63.89); H, 5.28 (5.36); N, 16.40 (16.56); IR (KBr, cm^{-1}): 3288 (-NH str.), 1684 (N-C=O str.), 1601 (-C=C str.), 1519 (-NH ben.), 1438 (-C-N str.). MS: 338[M.]; ^{1}H NMR (ppm)(DMSO-D_6): 10.65 (1H, singlet, -NH), 8.12-8.16 (2H, doublet, Ar-H), 6.97-7.27 (6H, multiplet, Ar-H), 4.40-4.48 (1H, multiplet, piperidine), 3.82-3.86 (2H, doublet, piperidine), 3.09-3.17 (2H, triplet, piperidine), 1.80-1.84 (2H, doublet, piperidine).

Compound 3c: found (calcd): C, 74.07 (74.24); H, 6.93 (6.89); N, 13.54 (13.67); IR (KBr, cm^{-1}): 3290 (-NH str.), 1686 (N-C=O str.), 1598 (-C=C str.), 1525 (-NH ben.), 1431 (-C-N str.). MS: 307[M.]; ^{1}H NMR (ppm)(DMSO-D_6): 10.20 (1H, singlet, -NH), 6.99-7.38 (8H, multiplet, Ar-H), 4.37-4.45 (1H, multiplet, piperidine), 3.80-3.84 (2H, doublet, piperidine), 3.02-3.10 (2H, triplet, piperidine), 1.74-1.78 (2H, doublet, piperidine), 2.21 (3H, singlet, -CH3).

Compound 3d: found (calcd): C, 59.75 (59.68); H, 4.67 (4.73); N, 11.71 (11.60); IR (KBr, cm^{-1}): 3298 (-NH str.), 1687 (N-C=O str.), 1590 (-C=C str.), 1540 (-NH ben.), 1433 (-C-N str.). MS: 363[M+1]; ^{1}H NMR (ppm) (DMSO-D_6): 10.50 (1H, singlet, -NH), 6.98-7.76 (7H, multiplet, Ar-H), 4.41-4.49 (1H, multiplet, piperidine), 3.83-3.87 (2H, doublet, piperidine), 3.10-3.18 (2H, triplet, piperidine), 1.81-1.85 (2H, doublet, piperidine).

Compound 3e: found (calcd): C, 70.76 (70.57); H, 6.44 (6.55); N, 13.05 (12.99); IR (KBr, cm^{-1}): 3291 (-NH str.), 1687 (N-C=O str.), 1599 (-C=C str.), 1529 (-NH ben.), 1441 (-C-N str.). MS: 323[M.]; ^{1}H NMR (ppm)(DMSO-D_6): 10.62 (1H, singlet, -NH), 6.98-7.42 (8H, multiplet, Ar-H), 4.38-4.46 (1H, multiplet, piperidine), 3.84-3.88 (2H, doublet, piperidine), 3.08-3.16 (2H, triplet, piperidine), 1.79-1.83 (2H, doublet, piperidine).

Compound 3f: found (calcd): C, 65.78 (65.95); H, 5.61 (5.53); N, 12.68 (12.82); IR (KBr, cm^{-1}): 3294 (-NH str.), 1689 (N-C=O str.), 1600 (-C=C str.), 1543 (-NH ben.), 1436 (-C-N str.). MS: 329[M+1]; ^{1}H NMR (ppm) (DMSO-D_6): 10.80 (1H, singlet, -NH), 6.98-7.38 (8H, multiplet, Ar-H), 4.36-4.44 (1H, multiplet, piperidine), 3.86-3.90 (2H, doublet, piperidine), 3.10-3.18 (2H, triplet, piperidine), 1.75-1.79 (2H, doublet, piperidine).

Antibacterial Activity

The zones of inhibition of compounds are shown in Table 2. Overall all compounds are moderately active against tested bacterial strains. For bacterial strain *E. coli*, compound 3a, compound 2b and compound 3b showed maximum zone of inhibition respectively, as well as for bacterial strain *B. subtilis*, compound 3c followed by compound 2c and compound 3f showed maximum zone of inhibition. Compound 2b, compound 3a and compound 2d active against bacterial strain *B. megaterium*, however, Compound 5e, compound 3a and compound 2b active against bacterial strain *P. fluorescens*. Compound 2a and compound 3c showed lower activity against all tested bacterial strains, while compound 2d is moderate active against *B. megaterium* as well as compound 3d moderately active against *P. fluorescens*.

.

Table 2 Antibacterial Activity of synthesised compounds.

Compound code	Antibacterial activity Zone of inhibition (mm)			
	E. coli	*B. subtilis*	*B. megaterium*	*P. fluorescens*
compound 2a	11	14	15	12
compound 2b	17	16	22	18
compound 2c	13	17	15	14
compound 2d	12	13	18	12
compound 3a	20	15	21	19
compound 3b	16	16	15	12
compound 3c	11	15	13	13
compound 3d	15	14	13	16
compound 3e	12	15	17	21
compound 3f	14	18	16	11
DMF	10	11	12	10

CONCLUSION

It can be determined from the data that compound 2b and compound 3a is active against almost bacterial strains. Benzimidazolone attached with benzylchloroformates active against *B. megaterium*, while when it attached with fluoro compound active against *E. coli*. It can be

concluded that compounds substituted with electronegative groups increases antibacterial activity. Furthermore, compound substituted with fluoro or nitro group found to be more potent against tested bacterial strains.

Acknowledgement
Authors are thankful to head department of chemistry and biochemistry for providing necessary facilities.

REFRENCES

[1] J. J. Vora , S. B. Vasava, A. D. Patel, K. C. Parmar, S. K. Chauhan and S. S. Sharma, *E-J. Chem.*, **2009**, 6(1), 201.
[2] N. Eric, G. Joel, B. Thierry, J. Marie, C. Francois, V. Angela, D. Chantal, Alex, *J. Med. Chem.*,**1993**, 36(9), 1175.
[3] A.M. Monforte, P. Logoteta, S. Ferro, L. D. Luca, N. Iraci, G. Maga, E. D. Clercq, C.Pannecouque, Chimirri, *Bioorg. Med. Chem*., **2009**, 17(16), 5962.
[4] J. Ries, M. Gerhard, N. Berthold, H. Kai, W. Helmut, E. Michael,V.M. Jacobus, W. Wolfgang; H. Nobert, *J. Med. Chem*., **1993**, 36(25), 4040.
[5] F. D. Lee, M. A. Edward, (G. D. Searle & Co), WO 9400449(A1), **1994**
[6] K. Herbert, M. Anton, R. E. Otto, S. Kurt, Hoefke, Wolfgang, Muacevic, Gojko, (Boehringer Sohn Ingelheim), CA 1, 125, 751(A2), 1982
[7] R. Henning, R. Lattrell, H.J. Gerhards, M. Leven, *J. Med. Chem.*, **1987**, 30(5), 814.
[8] H. R. Howard, R. Sarges, T. W. Siegel, T. A. Beyer, *Eur J. Med. Chem.*, **1992**, 27, 779.
[9] B. Mario, B. Alina, R. Silvano, B. Fernando, M. Viviana, *Eur.J.Med.Chem.-Chim.Ther.*, **1981,** 16, 231.
[10] B. Mario, B. Alina, R. Silvano, B. Fernando, M.Viviana, *Eur.J.Med.Chem.-Chim.Ther.*, **1983**, 18(6), 495.
[11] H. Hiromu, M. Tatsuya, S. Munetoshi, T. Makoto, M. Toshiyasu,(Yamanouchi Pharma Co LTD) EP 454, 330(A1), 1991.
[12] M. M. Craig, D. Steven, M. Nicholas, O. Soeren, R. Peter H, L Irwin B, A John,P, G Valentin, *Neurophysiol*. **1994**, 71(5), 1873.
[13] V K Gribkoff, G Champigny, P Barbry, S I Dworetzky, N A Meanwell, M Lazdunski, *J. Biol. Chem.* **1994,** 269, 10983.
[14] F. Berardi, C. Abate, S. Ferorelli, N. A. Colabufo, R. Perrone, *Cent. Nerv. Syst. Agents.Med. Chem.*,**2009**, 9(3), 205.