Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2010, 2(6): 363-367
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X

Synthesis and Antibacterial Evaluation of Substituted 3-Benzylquinoxaline Derivatives

[a]V.P.Devmurari*, [b]M.b.Goyani, [b]N. P Jivani

[a] Jodhpur National University, Department of Pharmaceutical Science, Jhavar Road, Narnadi, Jodhpur
[b] Smt R.B.Patel Mahila Pharmacy College, ATKOT, Ta:Jasdan Dist:Rajkot, Gujarat, India

---

ABSTRACT

In the present study, seven substituted 3-benzylquinoxalines were synthesized from substituted phenyl pyruvic acid and o-phenylenediamine. All the synthesized compounds were structurally elucidated by IR, Mass, NMR spectroscopy. Antibacterial activity of the synthesized compound was analyzed against a set of three gram negative and three gram positive microorganism by agar well diffusion method. Compound 5 showed very good antibacterial activity among all the compounds.

Key words: 3-benzyl quinoxalines, Antibacterial activity, agar well diffusion method

---

INTRODUCTION

Discovery and development of effective as well as safe drugs to counterbalance bacterial infection had brought a revolution in the medical treatment of infectious disease since 19th century [1]. But unfortunately progressive era in human healthcare is accompanied by drug resistant bacterial strains. Nowadays increasing antibacterial resistance is becoming severe health problem globally [2, 3]. In addition to trying to control bacterial resistance there is a corner stone requirement for the development of new antibiotics to help redress balance of resistant microorganisms versus available antibiotics [4-8]. An exhaustive research of the literature has revealed that the quinoxalines are an important class of antibiotics that bind to DNA and thereby modify its biological activities. So, synthetic quinoxaline derivatives can be good lead for future antibacterial agent. In present study synthetic quinoxaline derivatives have been synthesized and evaluated for their antibacterial potential against selected bacterial strains [9-11].

MATERIAL AND METHOD

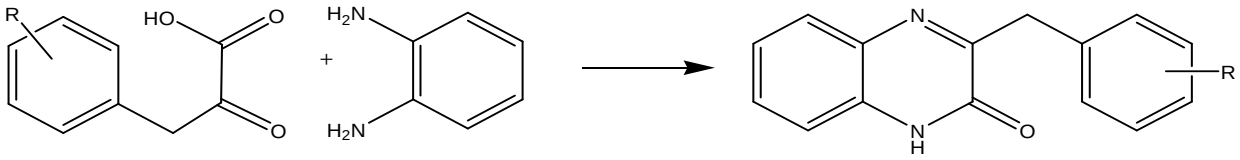
The melting points were taken in a remi M.P.apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 881 and FTIIR 8201 PC Shimadz spectrophotometer and values are

expressed in cm^{-1}. NMR spectra were recorded on Bruker WM-200 spectrometer. The chemical shifts are expressed in ppm using TMS as an internal standard. Mass spectra were recorded on JEOL JMS-D-3000 spectrometer with an ionization potential of 70 eV and are reported in the form of m/z and FAB on SX-102 instrument. All the reactions were monitored by thin layer chromatography over pre-coated silica gel plates, using UV lamp, iodine vapors or $KMnO_4$ spray as developing agents.

A series of 3-substituted benzylquinoxalines were synthesized by general procedure. Substituted phenylpyruvic acids were prepared from reported methods [12-15]. *o*-Phenylenediamine was purchased from Sd fine chemicals.

General procedure

Equimolar amount of substituted phenyl pyruvic acid and o-phenylenediamine were dissolved in ethanol and refluxed for 3 hour. Crude product was washed with ethanol and dried. Physical characterization of the synthesized compounds is given in Table 1.



3-Benzylquinoxalin-2-one

IR (KBr, cm^{-1}): 3322.75 (Secondary amide stretch.), 1499.6 (NH bend.), 1660.41 (C=O (I) stretch.), 1559.17 (C=O (II)), 664.358 (N-H wagging), 1296.89 (C-N stretch.), 2962.13 (C-H stretch.). ; Mass m/z: 237.2 (M^++1) ; ^{1}H NMR $CDCl_3$, δ = 7.167 – 7.329 (m , 5H , phenyl) , δ = 7.401 – 7.525 (m , 3H , $H_{5/6/7}$) , δ = 7.823 – 7.863 (d ,1H , J=8.04 Hz , H_8) δ = (s , 2H , benzyl – CH_2).

3-(4-Chlorobenzyl) quinoxalin-2-one

IR (KBr, cm^{-1}): 3316 (Secondary amide stretch.), 1483.96 (NH bend.), 1661.37 (C=O (I) stretch.), 1556.27 (C=O (II)), 660.5(N-H wagging), 1294 (C-N stretch.), 2970.8(C-H stretch.).
Mass (*m/z* [M+1]): 271.08; ^{1}H NMR (DMSO-d_6, δ, ppm): 12.43 (s, 1*H*, -NH), 7.26 -7.72 (m, 8*H*, Aromatic protons), 4.12 (s, 2*H*, Methylene proton)

3-(4-Methoxybenzyl) quinoxalin-2-one

IR (KBr, cm^{-1}): 3311.18 (Secondary amide stretch.), 1509 (NH bend.), 1660.41 (C=O (I) stretch.), 1605.45 (C=O (II)), 684.60 (N-H wagging), 1246.75 (C-N stretch.), 2959.23 (C-H stretch.)

3-(2-Nitrobenzyl) quinoxalin-2-one

IR (KBr, cm^{-1}): 3314.07 (Secondary amide stretch.), 1557.2 (NH bend.), 1668.12 (C=O (I) stretch.), 1519.63 (C=O (II)), 659.53 (N-H wagging), 1294 (C-N stretch.), 2938.98 (C-H stretch.).

3-(4-Nitrobenzyl) quinoxalin-2-one

IR (KBr, cm^{-1}): 3426.89 (Secondary amide stretch.), 1347.3 (NH bend.), 1596.77 (C=O (I) stretch.), 1516.74 (C=O (II)), 652.78 (N-H wagging), 1187.94 (C-N stretch.), 2932.23 (C-H stretch.).

3-(4-Methylbenzyl) quinoxalin-2-one
IR (KBr, cm^{-1}): 3311.18 (Secondary amide stretch.), 1509 (NH bend.), 1660.41 (C=O (I) stretch.), 1605.45 (C=O (II)), 684.60 (N-H wagging), 1246.75 (C-N stretch.), 2959.23 (C-H stretch.)

3-(2-Chlorobenzyl) quinoxalin-2-one
IR (KBr, cm^{-1}): 3302.5 (Secondary amide stretch.), 1428.03 (NH bend.), 1661.37 (C=O (I) stretch.), 1609.31 (C=O (II)), 659.53 (N-H wagging), 1201.43 (C-N stretch.).

Table 1: physical data of the synthesized compounds

Sr. No.	Sr. No.	Molecular formula	Mol. Weight	R_f	M.P.(°C)
1	3-Benzylquinoxalin-2-one	$C_{15}H_{12}N_2O$	236.26	0.70	154-156
2	3-(4-Chlorobenzyl) quinoxalin-2-one	$C_{15}H_{11}ClN_2O$	270.06	0.75	192-194
3	3-(4-Methoxybenzyl) quinoxalin-2-one	$C_{16}H_{14}N_2O_2$	266.29	0.77	138-140
4	3-(2-Nitrobenzyl) quinoxalin-2-one	$C_{15}H_{11}N_3O_3$	281.26	0.72	142-144
5	3-(4-Methylbenzyl) quinoxalin-2-one	$C_{16}H_{14}N_2O$	250.30	0.61	156-158
6	3-(4-Nitrobenzyl) quinoxalin-2-one	$C_{15}H_{11}N_3O_3$	281.26	0.74	166-168
7	3-(2-Chlorobenzyl) quinoxalin-2-one	$C_{15}H_{11}ClN_2O$	270.06	0.83	175-177

Antibacterial Evaluation
In the present research work, the activity spectrum of all the synthesized compounds was analyzed by agar well diffusion method in triplicate. [16-20] Digital colony counter (Toshiba, EIE-1901) was used for inoculum preparation. Antibiotic zone reader (EIE Instruments) was used to measure diameters of inhibition zones. For the antibacterial assay, 3 strain of Gram positive bacteria *S. aureus* (MTCC 737)**,** *M.lueus (*ATCC 9341), *B. pumillus* (ATCC 14884) and 3 strain of gram negative bacteria S.abony *(*NTCC 6017)**,** *P.aeruginosa* (MTCC 25619)**,** *E. coli* (ATCC 9002) strains were used. Inoculum size was adjusted to 1 to 2 × 10^7 CFU (Colony Forming Units)/ml by serial dilution with sterilized nutrient broth media. Stock solution of 10000µg/ml was prepared in 20 % v/v water in DMSO. Using the stock solution, 6000µg/ml, 4000µg/ml, 2000µg/ml and 1500µg/ml solutions were prepared from which 100 µl solution was taken for assay. Ciprofloxacin was used as a standard and solution manufactured by Cipla. All the dilution was done by Water for Injection (WFI) manufactured by *nirlife* health care. 20 % v/v WFI in DMSO was used as a control. 20 % WFI in DMSO was used as a control. The results of the study were interpreted by mean diameter of inhibition zone in mm and given in table 2 & 3.

RESULT AND DISCUSSION

Structural elucidation of the synthesized compound was done by IB, Mass & NMR Spectroscopy. Result of microbial assay showed that compound 2, 4, 5 possess good activity against gram positive microorganism. While compound 1,4,5 exhibited good activity against all gram negative organism. Compound 5 consists of very good antibacterial activity against all test organisms. The entire series of compounds have good activity against gram positive organism than gram negative organism.

Table 2: Zone of inhibition of synthesized compounds against gram positive micro organism

	Zone of Inhibition (mm)											
	S. aureus				***M.lueus***				***B. pumillus***			
	150 µg/well	200 µg/ well	400 µg/ well	600 µg/ well	150 µg/well	200 µg/ well	400 µg/ well	600 µg/ well	150 µg/well	200 µg/ well	400 µg/ well	600 µg/ well
STD	23.20 ± 0.72	31.03 ± 0.84	35.33 ± 0.70	39.10 ± 0.95	33.10 ± 1.05	36.67 ± 0.61	43.00 ± 0.92	54.87 ± 0.76	16.40 ± 0.40	18.53 ± 0.50	24.73 ± 0.70	30.67± 0.61
1	5.67 ± 1.50	8.17 ±1.17	9.27 ± 0.70	11.10 ± 0.95	6.40 ± 0.34	8.33 ± 0.42	8.40 ± 0.40	10.67 ± 0.61	1.93 ± 0.31	4.60 ± 0.20	8.20 ± 0.20	10.40 ± 0.35
2	9.87 ± 1.21	11.70 ± 0.75	12.87 ± 0.70	13.70 ± 0.95	8.20 ± 0.20	12.53 ± 0.61	13.07 ± 0.31	16.13 ± 0.42	8.40 ± 0.40	10.67± 0.61	11.73 ± 0.61	12.67 ± 0.23
3	4.10 ± 0.98	4.90 ± 1.08	5.33 ± 0.70	5.83 ± 0.95	4.40 ± 0.40	5.80 ± 0.20	6.33 ± 0.31	10.73 ± 0.81	2.40 ± 0.20	3.40 ± 0.20	6.20 ± 0.20	8.47 ± 0.42
4	6.93 ± 1.03	7.37 ± 0.78	11.47 ± 0.72	15.30 ± 0.95	4.33 ± 0.30	7.40 ± 0.20	8.33 ± 0.31	12.33 ± 0.31	2.33 ± 0.31	6.20 ± 0.20	8.33 ± 0.42	10.47± 0.42
5	15.40± 0.72	25.30 ± 0.75	15.53 ± 0.72	29.23 ± 0.95	5.00 ± 0.20	7.13 ± 0.31	8.67 ± 0.42	10.33 ± 0.31	10.33 ± 0.31	12.33 ± 0.31	12.93 ± 0.23	14.60 ± 0.60
6	7.37 ± 0.71	9.10 ± 1.35	9.27 ± 0.72	9.23 ± 0.95	4.46 ± 0.41	6.33 ± 0.31	7.67 ± 0.42	8.53 ± 0.42	2.27 ± 0.23	2.60 ± 0.35	4.20 ± 0.20	7.47 ± 0.31
7	0	0	0	3.23± 0.95	7.00 ± 0.20	8.20 ± 0.20	9.00 ± 0.20	10.67 ± 0.61	8.33 ± 0.31	8.83 ± 0.38	11.07 ± 0.61	12.40 ± 0.35

Table 3: zone of inhibition of synthesized compounds against gram positive micro organism

E. coli					*Ps. aeruginosa*				S.abony			
	150 µg/well	200 µg/ well	400 µg/ well	600 µg/ well	150 µg/well	200 µg/ well	400 µg/ well	600 µg/ well	150 µg/well	200 µg/ well	400 µg/ well	600 µg/ well
STD	29.67 ± 1.53	35.60 ± 0.53	43.67 ± 1.53	52.33 ± 1.53	41.07± 1.01	42.00 ± 0.20	48.47± 0.64	54.67 ± 0.61	30.87 ± 0.76	36.53 ± 0.61	41.20 ± 1.11	42.07 ± 0.31
1	1.87 ± 0.42	3.20 ± 0.20	4.03 ± 0.25	4.67 ± 0.12	0	0	0	2.67 ± 0.31	4.20 ± 0.20	6.30 ± 0.30	9.33 ± 1.30	8.27 ± 0.31
2	0	3.23 ± 0.25	5.27 ± 0.31	6.40 ± 0.40	0	0	0	4.20 ± 0.20	6.07 ± 0.31	8.00 ± 0.20	10.20 ± 0.53	10.53 ± 0.61
3	0	0	0	2.47 ± 0.06	0	0	0	2.20 ± 0.20	2.30 ± 0.30	2.47 ± 0.31	4.33 ± 0.31	6.33 ± 0.31
4	1.60 ± 0.35	0	0	0	0	0	0	0	2.17 ± 0.21	3.53 ± 0.31	4.33 ± 0.31	5.53 ± 0.31
5	2.10 ± 0.56	2.90 ± 0.10	3.37 ± 0.32	3.23 ± 0.21	0	0	0	2.00 ± 0.20	6.07 ± 0.31	10.53 ± 0.46	12.40 ± 0.20	13.27 ± 0.23
6	2.97 ± 0.15	3.10 ± 0.26	3.20 ± 0.20	3.37 ± 0.32	0	0	0	0	2.00 ± 0.20	2.47 ± 0.12	4.33 ± 0.31	5.13 ± 0.31
7	0	1.17 ± 0.15	1.43 ± 0.21	2.20 ± 0.20	0	0	0	1.40 ± 0.20	0	0	1.27 ± 0.23	2.27 ± 0.31

REFERENCES

[1] R..Bax, N.Mullan, J. Verhoef,*International Journal of Antimicrobial Agents,* **2000**,16, (1), 51-59.
[2] G.Strobel, B.Daisy, *Microbiology and Molecular Biology Reviews*, **2003**, 21,491–502.
[3] M.Daneshtalab, *Heterocycl Chem*, **2006**, 11,153–206.
[4] D.M. Devitt, M.Rosenberg**,** *Trends in Microbiology***, 2001**, 9(12) 611-617.
[5] J.Trias, E.M Gordon**,** *Current Opinion in Biotechnology*, **1997**,8(6) 757-762.
[6] S.N. Maiti, R. P. Kamalesh Babu, R. Shan, *Heterocycl Chem*, **2006**,45, 207–246.
[7] K.W Bayles, *Trends Microbiol*, **2000,** *8*, 81274-81278.
[8] J.D. Baumgartner M.P. Glauser, *Arch. Intern. Med*, **1983,** 143, 1868-1873.
[9] G.Ughetto, A.H.J.Wang, G.J.Quigley,*Nucleic Acids Research*, **1985**, 13,104
[10] E.Marco, A. Negri, F. J.Luque, *Nucleic Acids Research*, **2005**, 33, 6214–6224.
[11] Y.T Pratt, The Quinoxalines – in The Chemistry of Heterocyclic Compounds, R. C. Elderfield Ed. John Wiley and sons INC. New York, **1957**, Vol. 6, 455-495.
[12] H.O. Liebigs, *Ann. Chem*, **1887**, 237, 1228.
[13] H.O. Liebigs, *Ann. Chem*, **1887**, 237, 351.
[14] H.O. Liebigs, *Ann. Chem*,**1896**,292, 245.
[15] A. Carta, S.Piras, *Mini Reviews in Medicinal Chemistry*, **2006**, 6, 1179-1200.
[16] D.G. White, J. Acar, F. Anthony, *Rev. Sci. Tech. Off. Int. Epiz*, **2001**, 20 (3), 849-858.
[17] H. J. Jorgensen, J.F. Mary, *Clinical Infectious Diseases,* University of Chicago, **1998,** *26*, 973–80.
[18] J.Kramer, A. Kirshbaum, *Appl Microbiol*, **1961**, *9*, 334-336.
[19] M.K. Lalitha, D.J. Manayani , *Indian J. Med Res.* **1997**, 106, 500-503.
[20] D.C. Morley, *J. Pathol Bacteriol*, **1945**, 57, 379-382.