Volume 3 (2), 2015, Page-573-577
CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

PHS Scientific House
PHARMAHEALTHSCIENCES

International Journal of Pharma Research and Health Sciences

Available online at www.pharmahealthsciences.net

Original Article

Synthesis, Characterization and Biological Evaluation of Some Nitro-Aniline Condensed Azetidinones

Sarada Prasad Sarangi[1,*], L.Abiram[1], N Dorababu [2], K.Pavan Kumar [3], S Venu [1]

[1] Dept.of Pharmaceutical Chemistry, Santhiram College of Pharmacy, Nandyal, A.P-518112, India.
[2] Dept.of Pharmacognosy, Santhiram College of Pharmacy, Nandyal, A.P-518112, India.
[3] Dept. of Pharmaceutics, Santhiram College of Pharmacy, Nandyal, A.P-518112, India

ARTICLE INFO

Received: 12 Mar 2015
Accepted: 11 Apr 2015

ABSTRACT

Para-nitro aniline on addition with different aromatic aldehyde gives Schiff's bases. The Schiff's base so formed on treatment with chloroacetyl chloride and triethylamine as a base catalyst in 1,4-dioxane gives various substituted azetidinones. The lead compounds were characterized by melting point, TLC, IR, and ^{1}H NMR studies. All the newly synthesized azetidinone derivatives were evaluated for their antimicrobial activity. Compounds were screened for antimicrobial activity against both strains of gram positive *Staphylococcus aureus, Bacillus cereus*), gram negative (*Pseudomonusaeruginosa, E.coli*). Ciprofloxacin was used as standard for the antibacterial activity. All compounds showed good antibacterial activity.

Kew words*:* aniline, azetidinones, chloroacetyl chloride, β-lactam, antibacterial.

1. INTRODUCTION

Azetidinones which are part of β-lactam antibiotics structure are known to exhibit interesting biological activities. Various antibiotics like penicillin, cephalosporin, carumonam, aztreonam, thienamycine, nocardicinssalbactums etc. possess this moiety, which is responsible for various broad spectrum activities. The β-lactam heterocyclics are still the most prescribed

Corresponding author *
Sarada Prasad Sarangi Dept.of Pharmaceutical Chemistry, Santhiram College of Pharmacy, Nandyal, A.P-518112, India
E mail – sharda.su@gmail.com

antibiotics used in medicine. They are considered as an important contribution of science to humanity[1-5].

Hence, with a view to further assess the pharmacological profile of this class of compounds, it was thought worthwhile to synthesize some new derivatives of β-lactam heterocyclics.

The present work deals with the synthesis of 3-chloro-1-(4-nitrophenyl)-4- phenylazetidin-2-one derivatives. The synthesized compounds were characterized by spectral data such as IR, NMR, and mass spectrum data. The synthesized compounds were screened for antimicrobial activity against strains of gram positive (*Staphylococcus aureus, Bacillus cereus*), gram negative (*Pseudomonusaeruginosa, E.coli*). All compounds showed good to moderate antibacterial activity.

2. MATERIAL AND METHODS

Melting points of the synthesized compounds were determined in open capillary tubes and were uncorrected. IR spectra were recorded on Shimazdu FTIR Spectrophotometer with KBr pellets. Mass Spectra were recorded on GCMS QD 5000 Shimadzu. H^1NMR Spectra was recorded on Bruker AV 400MHz. The test compounds were synthesized by the following procedure.

2.1 Synthesis of Schiff's bases (sa-sh)

A mixture of equimolar amount (0.01mmol) of 4-nitro aniline, and appropriate aromatic aldehyde in ethanol (20ml) and glacial acetic acid (2-3 drops) was refluxed for 3hrs on water bath.The reaction mixture was concentrated and cooled.The solid obtained was filtered and recrystallized from ethanol to give Schiff bases[1,5]. Yield of compounds obtained were between 50-80%. The I.R spectra of all the compounds did not show any absorption bands for NH_2 functional group which confirmed the formation of required compounds.

2.2 Synthesis of azetidinones (8a-8h)

To the solution of substituted Schiff's bases of aniline (8a-8h) (0.01mol), in 1,4dioxane (25ml) andtriethylamine (0.01mol), chloroacetylchloride (0.01mol) was added drop wise with constant stirring at 0-20^{0}C. The reaction mixture was kept for 30 min and then refluxed for 6-7 hours. Excess of solvent was distilled off and the residue was poured into ice-cold water. The solid obtained was filtered and recrystallized from ethanol. The spectral analysis of the compounds was reported in analytical data[5,8].

Analytical data

3-chloro-1-(4-nitrophenyl)-4- phenyl azetidin-2-one (8a)

I.R(KBr.cm^{-1});3125cm^{-1}(ArC-H), 1723cm^{-1} (C=Oβ-lactam), 1549cm^{-1}(Ar C=C), 1348cm^{-1}(C-N) 774cm^{-1}(C-Cl). ^{1}HNMR(DMSO) δ; 7.8 (m,6H,phenyl),6.7(d-1H,3-CH of β-lactam),6.4(d,1H,4-CH of β-lactam), m/z:301.03

3-chloro-4-(4-chlorophenyl)-1-(4-nitrophenyl) azetidin-2-one (8b)

I.R (KBr.cm-1); 3123cm^{-1}(Ar C-H), 1720cm^{-1} (C=O β-lactam), 1546cm^{-1}(Ar C=C), 1347cm^{-1}(C-N) 772cm^{-1}(C-Cl). ^{1}H NMR (DMSO) δ; 8.2 (m,4H,chlorophenyl),6.9(d-1H,3-CH of β-lactam), 6.6(d,1H,4-CH of β-lactam), m/z:302.93

3-chloro-4-(4-methoxyphenyl)-1-(4 nitrophenyl)azetidin-2-one(8c)

I.R (KBr.cm-1); 3126cm^{-1}(Ar C-H), 1721cm^{-1} (C=O β-lactam), 1544cm^{-1}(Ar C=C), 1349cm^{-1}(C-N) 774cm^{-1}(C-O). ^{1}H NMR (DMSO) δ; 8.0 (m,4H,methoxyphenyl), 6.8 (d-1H,3-CH of β-lactam), 6.7(d,1H,4-CH of β-lactam)

1.4 (s,3H,CH_3), m/z: 331.16.

3-chloro-4-(4-hydroxyphenyl)-1-(4-nitrophenyl)azetidin-2-one(8d)

I.R (KBr.cm-1); 3200cm^{-1} (-OH), 3136cm^{-1}(Ar C-H), 1731cm^{-1} (C=O β-lactam), 1541cm^{-1}(Ar C=C), 1345cm^{-1}(C-N).^{1}H NMR (DMSO) δ; 8.0

(m,4H,hydroxyphenyl), 6.6 (d-1H,3-CH of β-lactam), 6.8(d,1H,4-CH of β-lactam)

3.4 (s,1H,ArOH), m/z: 317.84

3-chloro-4-(2-hydroxyphenyl)-1-(4-nitrophenyl)azetidin-2-one(8e)

I.R (KBr.cm-1); 3200cm-1 (-OH), 3136cm-1(Ar C-H), 1731cm-1 (C=O β-lactam), 1541cm-1(Ar C=C), 1345cm-1(C-N). 1H NMR (DMSO) δ; 8.0 (m, 4H, hydroxyl phenyl), 6.6 (d-1H, 3-CH of β-lactam), 6.8(d, 1H, 4-CH of β-lactam) 3.3 (s,1H,ArOH), m/z: 317.04

3-chloro-4-(3-nitrophenyl)-1-(4-nitrophenyl) azetidin-2-one(8f)

I.R (KBr.cm^{-1}); 3136cm^{-1}(Ar C-H), 1731cm^{-1} (C=O β-lactam), 1541cm^{-1}(Ar C=C), 1345cm^{-1}(C-N),1509.67 cm^{-1} (NO_2).^{1}H NMR (DMSO) δ; 8.0 (m,4H,nitrophenyl), 6.6 (d-1H,3-CH of β-lactam), 6.8(d,1H,4-CH of β-lactam),m/z: 346.01

3-chloro-4-(4-(dimethylamino)phenyl)-1-(4-nitrophenyl)azetidin-2-one (8g)

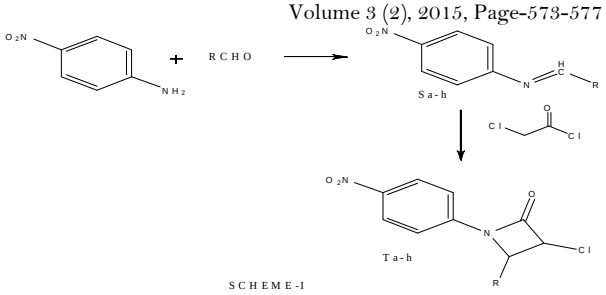
IR (KBr) cm-1: 3124.28cm-1 (Ar C-H), 1716.12cm-1(C=O β-lactam), 1531.60 cm-1 (Ar C=C), 1347.46cm-1 (C-N), 776.52cm-1 (C-Cl),

NMR(DMSO) δ; 8.5 (m,4H, dimethylamino phenyl), 7.6-8 (m,4H, phenyl), 6.4(d,1H,3-CH of β-lactam), 6.5(d,1H,4-CH of β-lactam),1.25(s,6H,CH_3),

m/z: 344.19

3-chloro-4-(4-nitrophenyl)-1-(4-nitrophenyl)azetidin-2-one(8h)

I.R (KBr.cm^{-1}); 3135cm^{-1}(Ar C-H), 1731cm^{-1} (C=O β-lactam), 1541cm^{-1}(Ar C=C), 1345cm^{-1}(C-N), 1507.67 cm^{-1} (NO_2). ^{1}H NMR (DMSO) δ; 8.0 (m, 4H, nitrophenyl), 6.6 (d, 1H,3-CH of β-lactam), 6.8(d,1H,4-CH of β-lactam), m/z: 345.43



SCHEME-I

Table 1: Physical constants of different azetidinone derivatives (8a-8h)

Compound	R	Mol.formula	Melting point (°C)	Rf Value	% Yield
8a	C_6H_5	$C_{15}H_{11}ClN_2O_3$	217-219	0.64	41
8b	4-Cl-C_6H_5	$C_{15}H_{10}C_{l2}N_2O_3$	89-92	0.49	64
8c	4-OCH_3-C_6H_5	$C_{16}H_{13}ClN_2O_4$	131-133	0.72	55
8d	4-OH-C_6H_5	$C_{15}H_{11}ClN_2O_4$	198-199	0.6	67
8e	2-OH-C_6H_5	$C_{15}H_{11}ClN_2O_4$	113-115	0.38	45
8f	3-NO_2-C_6H_5	$C_{15}H_{10}ClN_3O_5$	154-156	0.7	67
8g	4-N-$(CH_3)_2C_6H_5$	$C_{17}H_{16}ClN_3O_3$	187-189	0.57	53
8h	4-NO_2-C_6H_5	$C_{15}H_{10}ClN_3O_5$	112-114	0.9	64

Antimicrobial Activity

The synthesized compounds were exposed to antimicrobial activity. Antimicrobial activities were observed for all compounds using strains of gram positive such as (*Staphylococcus aureus*, *Bacillus cereus*), gram negative (*Pseudomonusaeruginosa*, *E.coli*). The antimicrobial activities of the synthesized compounds were studied by disc diffusion method. Bacterial inoculums were spread on nutrient agar. After the inoculums dried, 6 mm diameter wells were made in the agar plate with a sterile cork borer. The synthesized compounds were dissolved in DMF at concentrations of 10µg, 20µg, per ml. Ciprofloxacin 50µg/ml was used as standard for the antibacterial activity. The Petri plates were incubated at 37°C for 24 hours. The Zone of inhibition was measured in mm to estimate the potency of the test compounds[4, 6, 9]. Results are shown in **Table-2**.

Table 2: Zone of Inhibition by Disc Diffusion method in mm

Sl.no	Compounds	Concentration (µgm/ml)	Zone of Inhibition (mm)			
			S.aureus	*B.cereus*	*E.coli*	*P.aeruginosa*
1	8a	10	16	11	23	17
		20	21	18	31	24
2	8b	10	16	14	30	20
		20	30	29	38	36
3	8c	10	14	19	24	26
		20	25	26	33	33
4	8d	10	15	14	18	15
		20	17	18	30	17
5	8e	10	15	13	21	24
		20	21	19	29	27
6	8f	10	18	16	25	26
		20	23	20	31	29
7	8g	10	16	14	28	13
		20	26	29	34	17
8	8h	10	16	23	30	23
		20	32	33	40	39
9	Std.	50	38	37	43	41

3. RESULT AND DISCUSSION

All the synthesized compounds were characterized by spectral data such as IR, NMR, and mass spectrum data. They showed expected characteristic absorption bands for various groups like C=O, C-N, C-Cl, C-CH_3 etc. The synthesized compounds were screened for antimicrobial activity against strains of gram positive and gram negative. All compounds showed good to moderate antibacterial activity.

4. CONCLUSION

A set of eight compounds were synthesized, characterized and subjected to antimicrobial activities against Ciprofloxacin. Concentration at 20µg/ml showed better activities against gram positive and gram negative bacterial strains. Among all the compounds compound **8h** and **8b** showed better activities, this may be because of presence of electron withdrawing functional groups like Nitro (NO_2) and Chloro(Cl) at 4^{th} (Para) positions. All the synthesized compounds can be compared with that of the standard.

5. REFERENCES

1. Ahmed M. Jasim. Preparation and Characterization of novel 3-(4-chloro phenyl)-1- nitrophenyl-5-(substituted phenyl)-formazans, Journal of Basrah Researches (Sciences) 2011; 37, Num.5.A,.
2. Pratap Y pawar, Swati U. Kalure, et.al, Synthesis and pharmacological screening of some new azetidinonederivatives, International Journal of Pharmacy and Pharmaceutical Sciences, 2012; (4), Suppl. 5,.
3. Rajiv Dua and S.K.Srivastav, Synthesis,Characterization andantimicrobial activity of 2-[2'-{4-substituted-aryl-3-chloro-2-oxaazetidine}-acetyl-amino-mercapto]-5-methyl-1,3,4-thiadiazoles,International Journal of Pharma and Bio-science 2010; 1 (2), 1-7,.
4. Sujit Kumar Mohanty, AnuradhaKhuntia et al. Synthesis, Characterization and Antimicrobial Activity ofSome Oxazole and Thiazole Derivatives,International Journal of Pharmacy and Pharmaceutical Research, 2015; (2) 3: 60-66.
5. Karthikeyan E. et.al, Design Synthesis and Biological evaluation of some novel isoniazid cyclocondensed azetidinones, Drug Invention Today, 2013; 1-5.
6. Ameya A. Chavan and Nandini R. Synthesis and Biological Activity ofN-Substituted-3-chloro-2-azetidinones, Molecules, 2007; 12, 2467-2477.
7. Ilango K. and Arunkumar S., Synthesis and antitubercularactivities of Some Novel TrihydroxyBenzamido Azetidin-2-oneDerivatives, Tropical Journal of Pharmaceutical Research, 2011; 10(2), 219-229.
8. S.ramprasad et.al: Synthesis, characterization and antimicrobial activity of some hetero benzocaine derivatives, International Journal of Pharmacy and Pharmaceutical Sciences, 2012; (4), 5.
9. Ashok K, Pratibha S, Ravi S, Pankaj M . Synthesis andanti-microbial screening of N-substituted-3-

chloro-4-dithiocarbamate azetidin-2-ones. Indian J. Chem. 2003; 42: 416-420.

10. Shobhana and Gangwar K.R., Synthesis of 3-chloro-1-[5-(2- hydroxyl phenyl)-1, 3, 4-thiadiazoll-2-yl]-4-substituted azetidin-2-ones derivatives, Indian drug 2010; 47(5): 65-68.
11. Rajesh K Goel et al, Evaluation of anti-hyperglycemic activity of some novel monocyclic beta lactams, Journal PharmPharmaceutical Science 2004; 7(1): 80-83.
12. Patel, HS, Patel VK. Synthesis and anti-microbial activity ofsome new N (4,4'- disubstituted amino sulphonyl phenyl)-3-chloro-4-phenyl azetidine-2-ones, Oriental J. Chem. 2004; 17: 425-28.