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SYNTHESIS AND ANTIMICROBIAL STUDIES OF SOME NOVEL 2-AZETIDINONES

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ABSTRACT

*4-(4-ethylpiperazine-1yl)benzenamine **(1)** on condensation with substituted aromatic aldehydes in alcohol in presence of glacial acetic acid yielded the Schiff bases. These Schiff bases on cyclocondensation with chloroacetic acid in presence of triethyl amine gave the 2-azetidinones.The newly synthesized compounds were established on the basis of elemental and spectral studies and were screened for their in-vitro growth inhibitory activity against various microbes.*

Keywords: Schiff base, 2-azetidinones, antimicrobial activity

I. INTRODUCTION

2-Azetidinones, commonly known as β-lactums, are well known heterocyclic compounds among organic and medicinal chemists [1-5] since it forms a part of the antibiotic molecules. The most widely used antibiotics such as Penicillins, Nocardicins, Cephalosporins contains the β-lactum ring. Recently, some other types of biological activities besides the antibacterial activity have been reported in compounds containing 2-azetidinone ring [6, 7]. Such biological activities include anti-tubercular [8, 9], antifungal [10, 11], anticonvulsant [12], anti-inflammatory [13], analgesic [14], CNS depressant activity [15], antimicrobial [16, 17], and antiviral [18]. The β-lactums also serve as synthons for many biologically important class of organic compounds. Inspired by the wide range of biological properties shown by the Azetidinones, we planned to synthesize a new series of Azetidinone derivatives containing piperazine moiety and evaluated their antibacterial and antifungal properties.

In the present study, we have synthesized ten substituted 2-azetidinones by cyclocondensation of various Schiff base in chloro acetyl chloride in presence of triethyl amine (scheme-I). The structures of these compounds were assigned on the basis of elemental analysis, IR spectra and ^{1}H NMR and were screened for their antimicrobial activity.

II. RESULTS AND DISCUSSION

2.1 Chemistry

The synthetic route for the target analogs **3a-3j** is outlined in Scheme 1. The initial analog 4-(4-ethylpiperazin-1-yl)benzenamine (**1**) was synthesized by the condensation reaction of *N*-ethylpiperazine and 4-chloroaniline. Schiff base **2a-2j** derivatives were synthesized by reacting analog **1** with various aldehydes. The cyclization of **2a-2j** with chloro acetyl chloride yields final 2-azetidinone derivatives **3a-3j.** Characterization data of all the synthesized compounds are mentioned in Table 2 and 3.

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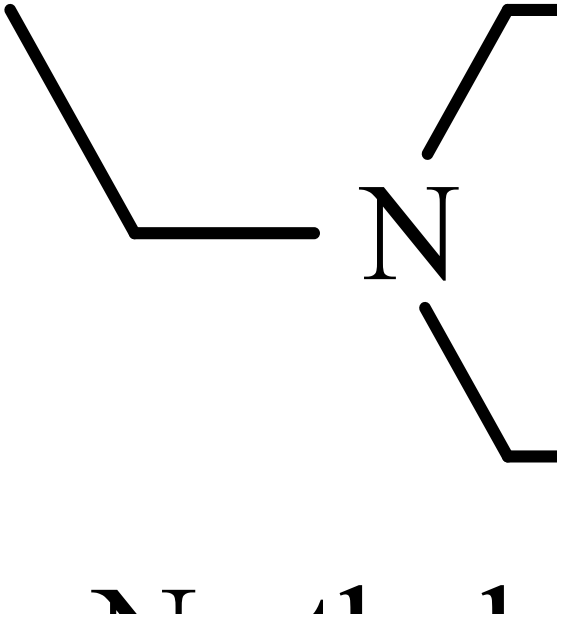

Scheme 1. Synthetic rout for 2-aztidinone derivatives 3a-3j

2.2 Pharmacology

2.2.1 Antibacterial Activity

The *in vitro* results of antimicrobial activity of the newly synthesized compounds **3a-3j** are presented in Table 1 as a minimal inhibitory concentration (MIC). Some of the compounds displayed moderate to good inhibition in the range of 32-128 µg/mL. Analog **3f** with the presence of electron donating hydroxyl group displayed highest inhibition at 32 µg/mL against *S. aureus* and 64 µg/mL against *S. pyogenus* when compared with Ciprofloxacin (50 µg/mL). Moreover, compounds **3b, 3c** and **3i** having 4-chloro, 4-methoxy and 3,4,5-trimethoxy substituents displayed good activity (MIC 128 µg/mL) against *S. aureus*.

Table-1: *In-vitro* antibacterial and antifungal activity of compounds 3a-3j

Entry	R	Minimum Inhibitory Concentrations (µg/mL)						
		Gram-positive bacteria		Gram-negative bacteria		Fungus		
		S. aureus	*S. pyogenus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*	*A. clavatus*
3a	H	512	512	512	512	512	512	256
3b	4-Cl	128	128	128	128	128	128	128
3c	4-OCH_3	128	512	512	128	256	512	128
3d	3-NO_2	512	256	128	128	256	128	256
3e	3-OCH_3	256	128	256	256	256	512	256
3f	4-OH	32	64	64	128	128	256	512

3g	2-Cl	256	512	512	512	512	512	512
3h	2-OH	256	512	128	128	128	256	256
3i	3,4,5-OCH_3	128	256	512	256	256	256	256
3j	3,4-OCH_3	512	512	512	256	512	512	512
Ampicilin	-	250	100	100	100	-	-	-
Chloramphenicol	-	50	50	50	50	-	-	-
Ciprofloxacin	-	50	50	25	25	-	-	-
Nystatin	-	-	-	-	-	100	100	100
Griesofulvin	-	-	-	-	-	500	100	100

2.2.2 Antifungal

Compounds **3b, 3f** and **3h** having 4-chloro, 4-hydroxy and 2-hydroxy substituents showed better activity (MIC 128 μg/mL) against *C. albicans* when compared with Griseofulvin and moderate against Nystatin. Compounds **3a, 3g** and **3j** having H, 2-chloro and 3,4-dimethoxy displayed poor activity (MIC 512 μg/mL) against *C. albicans* when compared with Griseofulvin. Compounds **3c, 3d, 3e** and **3i** displayed very good activity (MIC 253 μg/mL) against *C. albicans* when compared with Griseofulvin.

III. EXPERIMENTAL

3.1 General

All chemicals were purchased from Sigma Aldrich, Merck and Fluka. Solvents used were of analytical grade. All reactions were routinely checked by TLC. TLC was performed on aluminum-backed silica gel plates (silica gel 60 F254 grade, Merck DC) with spots visualized by UV light. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on a Shimadzu 8400S FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Hitachi 300 MHz using TMS as an internal standard and elemental analysis had been carried out on Perkin-Elmer CHNS-2400.

3.2 4-(4-ethylpiperazin-1-yl) benzenamine (1)

A mixture of *N*-ethylpiperazine (0.1 mmol) and *p*-chloroaniline (0.1 mmol) and anhydrous K_2CO_3 in absolute alcohol (20 mL) was refluxed for 4 h. The resultant mixture was cooled to room temperature and poured into ice-cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol[18].

3.3 General synthetic procedure for Schiff bases (2a-2j)

A mixture of 4-(4-ethylpiperazin-1-yl)benzenamine (0.1 mmol) and benzaldehyde (0.1 mmol) in absolute alcohol (20 mL) was refluxed for 2 h. After the completion of reaction it was poured into ice-cold water with stirring. The solid product obtained was filtered, washed with water and recrystallized from ethanol. Similarly, the remaining Schiff bases as shown in the scheme were prepared (**2a-2j**)[19].

3.4 General synthetic procedure for Azetidinones (3a-3j)

To a stirred solution of substituted Schiff bases **2a-2j** (0.01 mmol), triethylamine (0.02 mmol) in dry dioxane (50ml), monochloroacetylchloride (0.02 mmol) was added drop wise at room temperature. The reaction mixture was stirred for 30 min. and then refluxed for 12 h. After completion of reaction, it was poured into water. The separated solid was filtered, washed with water and recrystallized from ethanol[19].

Table-2: Characterization data of the synthesized compounds (3a-3j)

Entry	R	Molecular Formula	M.P. °C	Yield %	Elemental analysis (%)					
					C		H		N	
					Calcd	*Found*	*Calcd*	*Found*	*Calcd*	*Found*
3a	H	$C_{21}H_{24}ClN_3O$	215-220	58.64	68.19	68.21	6.54	6.55	11.36	11.37
3b	4-Cl	$C_{21}H_{23}Cl_2N_3O$	160-165	50.89	62.38	62.40	5.73	5.75	10.39	10.38
3c	4-OCH_3	$C_{22}H_{26}ClN_3O_2$	70	50.24	66.07	66.08	6.55	6.56	10.51	10.53
3d	3-NO_2	$C_{21}H_{23}ClN_4O_3$	220-225	59.46	60.79	60.80	5.59	5.60	13.50	13.52
3e	3-OCH_3	$C_{22}H_{26}ClN_3O_2$	60-65	52.87	66.07	66.09	6.55	6.56	10.51	10.54
3f	4-OH	$C_{21}H_{24}ClN_3O_2$	150-160	55.68	65.36	65.37	6.27	6.29	10.89	10.88
3g	2-Cl	$C_{21}H_{23}Cl_2N_3O$	275-285	54.12	62.38	62.39	5.73	5.75	10.39	10.38
3h	2-OH	$C_{21}H_{24}ClN_3O_2$	195-200	60.45	65.36	65.37	6.27	6.29	10.89	10.90
3i	3,4,5-OCH_3	$C_{24}H_{30}ClN_3O_4$	170	70.35	62.67	62.69	6.57	6.59	9.14	9.16
3j	3,4-OCH_3	$C_{23}H_{28}ClN_3O_3$	55	61.00	64.25	64.27	6.56	6.58	9.77	9.79

Table-3: Spectral data of compounds 3a-3j

Entry	IR (KBr, cm^{-1})
3a	3447 (NH), 1647 (CONH), 1774 (C=O, β-lactum ring)
3b	3465 (NH), 1665 (CONH), 1772 (C=O, β-lactum ring)
3c	3470 (NH), 1669 (CONH), 1780 (C=O, β-lactum ring)
3d	3459 (NH), 1666 (CONH), 1760 (C=O, β-lactum ring)
3e	3463 (NH), 1667 (CONH), 1762 (C=O, β-lactum ring)
3f	3469 (NH), 1680 (CONH), 1775 (C=O, β-lactum ring)
3g	3464 (NH), 1667 (CONH), 1778 (C=O, β-lactum ring)
3h	3455 (NH), 1687 (CONH), 1767 (C=O, β-lactum ring)
3i	3465 (NH), 1664 (CONH), 1769 (C=O, β-lactum ring)
3j	3460 (NH), 1666 (CONH), 1770 (C=O, β-lactum ring)

3.5 Microbiology

The antimicrobial activity of synthesized analogs has been carried out against two Gram-positive bacteria (*S. Aureus* ATCC 6538P and *S. Pyrogenus* ATCC 8668), two Gram-negative bacteria (*E. Coli.* ATCC 8739 and *P.Aeruginosa* ATCC 9027) and against three fungal species (*C. Albicans* ATCC 10231, *A. Niger* ATCC16404

and *A. Clavatus* ATCC 9600). Here, ampicilline, chloramphenicol, ciprofloxacin (100 µg/disk) were used as control drugs for antibacterial activity while nystatin and griesofulvin for antifungal activity[20, 21].

IV. CONCLUSION

Here, we report an efficient synthesis of piperazine fused 2-azetidinone derivatives. It was observed that substitution of electron donating functional group on phenyl ring increase the antibacterial activity against Gram-positive bacteria. The hydroxyl group substituted 2-azetidinone derivative has displayed highest inhibition against *S. aureus* at 32 µg/mL as compared to the ciprofloxacin (50 µg/mL). Moreover, some of the other derivatives displayed moderately active in the range of 64-128 µg/mL MIC.

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REFERENCES

[1]. G.S. Singh, Recent progress in the synthesis and chemistry of azetidinones. Tetrahedron, 59(39), 2003, 7631-7649.

[2]. M.J. Brown, Literature Review of the Ester Enolate Imine Condensation. Heterocycles, 29(11), 1989, 2225-2244.

[3]. A.B. Patel, K.H. Chikhalia and P. Kumari, Facile synthesis of benzonitrile/nicotinonitrile based s-triazines as new potential antimycobacterial agents, European journal of medicinal chemistry 79, 2014, 57-65.

[4]. M.D. Mihovilovic, M. Spina, and P. Stanetty P. Synthesis and yeast - mediated bioreduction of α-keto-β-lactams bearing a functionalized and rigid side chain. Arkivoc, 5, 2005, 33-44.

[5]. N.M. Shirode, K.C. Kulkarni, V.K. Gumatse and A.R. Deshmukh, Microwave assisted rapid synthesis of 4-amino-3, 4-dihydroquinolin-2-ones from azetidin-2-ones. Arkivoc, 1, 2005, 53-64.

[6]. G.S. Singh, Beta-lactams in the new millennium. Part-I: monobactams and carbapenems. Mini-Reviews in Medicinal Chemistry, 4(1), 2004, 69-92.

[7]. G.S. Singh, Beta-lactams in the new millennium. Part-II: cephems, oxacephems, penams and sulbactam. Mini-Reviews in Medicinal Chemistry, 4(1), 2004, 93-109.

[8]. R.B. Patel, P.S. Desai, K.R. Desai and K.H. Chikhalia, Synthesis of pyrimidine based thiazolidinones and azetidinones: Antimicrobial and antitubercular agents. Indian Journal of Chemistry -Section B, 45-B(03), 2006, 773-778.

[9]. P.B. Trivedi, N.K. Undavia and N.C. Desai, Synthesis and Antimicrobial Activity of 4-oxothiazolidines, 4-oxoazetidines, malonanilic acid hydrazines and pyrazoline of phenothiazines, Indian Journal of Chemistry -Section B, 32-B(07), 1993, 760-765.

[10]. P.D. Mehta, N.P.S. Sengar and A.K. Pathak, 2-Azetidinone–A new profile of various pharmacological activities, European journal of medicinal chemistry 45(12), 2010, 5541-5560.

[11]. R.S. Keri, K.M. Hosamani, R.V. Shingalapur and H.R.S. Reddy, 2-Azetidinone derivatives: Design, synthesis, in vitro anti-microbial, cytotoxic activities and DNA cleavage study, European journal of medicinal chemistry 44(12), 2009, 5123-5130.

[12]. S.K. Srivastava, R. Yadav and S.D. Srivastava, Synthesis of new 1, 2, 4-triazolo-thiadiazoles and its 2-oxoazetidines as antimicrobial, anticonvulsant and antiinflammatory agents, Indian Journal of Chemistry - Section B, 41-B(07), 2002, 2357-2363.

[13]. K.I. Bhat, M. Mubeen and B. Kalluraya, Synthesis and Pharmacological Studies of Some Azetidinones bearing Ibuprofen Moiety, Indian Journal of Heterocyclic Chemistry, 13, 2003, 183-184.

[14]. S.K. Srivastava, R. Yadav and S.D. Srivastava, Synthesis of some new 2-mercaptobenzothiazolyl-2-oxoazetidines as antimicrobial and anthelmintic agents, Journal of the Indian Chemical Society 81(4), 2004, 342-343

[15]. S.R. Desai, U.V. Laddi, R.S. Bennur and S.C. Bennur, Synthesis and antimicrobial activities of some new azetidin-2-ones and thiazolidin-4-ones, Indian journal of pharmaceutical sciences 73(4), 2011, 478-482.

[16]. B. Naik and K.R. Desai, Novel approach for the rapid and efficient synthesis of heterocyclic Schiff bases and azetidinones under microwave irradiation, Indian Journal of Chemistry -Section B, 45 (1), 2006, 267-271.

[17]. S. Jubie, B. Gowramma, N.K. Muthal, R. Kalirajan, S. Gomathi and K. Elango, Synthesis and Antimicrobial Evaluation of some 2-Azetidinone derivatives, International Journal of ChemTech Research, 1, 2009, 153-157.

[18]. A.B. Patel, K.H. Chikhalia and P. Kumari, Access to antimycobacterial and anticancer potential of some fused quinazolines Research on Chemical Intermediates, 41(7), 2015, 4439-4455.

[19]. A.B. Patel, K.H. Chikhalia and P. Kumari, An efficient synthesis of new thiazolidin-4-one fused s-triazines as potential antimicrobial and anticancer agents, Journal of Saudi Chemical Society, 18, 2015, 646-456.

[20]. A.B. Patel, K.H. Chikhalia and P. Kumari, Synthesis and biological evaluation of novel quinazoline derivatives obtained by Suzuki C–C coupling, Medicinal Chemistry Research, 23(5), 2014, 2338-2346.

[21]. European Committee for Antimicrobial Susceptibility Testing (EUCAST) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID).