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RESEARCH ARTICLE

AN EFFICIENT SYNTHESIS OF NOVEL 2-AZETIDINONE DERIVATIVES VIA SCHIFF BASE CYCLIZATION AND THEIR BIOLOGICAL STUDIES

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ABSTRACT

The synthesis of novel 2-azetidinone (β-lactam) derivatives has attracted considerable attention owing to their diverse biological and pharmaceutical applications. In the present study, a series of substituted 2-azetidinone derivatives were synthesized through the cyclocondensation of Schiff bases with chloroacetyl chloride in the presence of an appropriate base catalyst. The Schiff bases were initially prepared by the condensation of substituted aromatic aldehydes with various aromatic amines and subsequently converted into the corresponding β-lactam derivatives via Staudinger cyclization. The synthesized compounds were purified and characterized using various spectroscopic techniques including FT-IR, 1H NMR, ^13C NMR, and mass spectral analysis, which confirmed the formation of the azetidinone ring system. The synthesized derivatives were evaluated for their biological potential, and preliminary studies revealed promising antimicrobial activity against selected bacterial strains. Structural modifications on the aromatic ring significantly influenced the biological activity of the compounds. The presence of electron-withdrawing substituents enhanced the antimicrobial efficacy, suggesting an important structure–activity relationship. The developed synthetic protocol provided good yields, shorter reaction times, and facile isolation of products.

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INTRODUCTION

2-Azetidinones, commonly known as β-lactams, constitute one of the most important classes of four-membered nitrogen-containing heterocyclic compounds in medicinal chemistry. The β-lactam ring system is a highly strained cyclic amide that exhibits unique chemical reactivity and remarkable biological activities. Since the discovery of penicillin, β-lactam-containing compounds have played a crucial role in the treatment of bacterial infections and have become one of the most successful classes of therapeutic agents. The simplest member of this family is 2-azetidinone, which serves as the core structural unit of numerous clinically important antibiotics such as penicillins, cephalosporins, carbapenems, and monobactams. The significant biological importance of 2-azetidinone derivatives has stimulated extensive research in synthetic and medicinal chemistry. Apart from their well-known antibacterial properties, substituted 2-azetidinones have been reported to exhibit a broad spectrum of pharmacological activities including antifungal, antitubercular, anti-inflammatory, analgesic, antitumor, antiviral, antidiabetic, anticonvulsant, and enzyme inhibitory activities. The versatility of the β-lactam scaffold has made it an attractive pharmacophore for the development of novel therapeutic agents.

The remarkable biological profile of β-lactams is attributed not only to their ability to inhibit bacterial cell wall synthesis but also to the inherent ring strain of the four-membered lactam system, which facilitates interactions with various biological targets. Consequently, the synthesis of structurally diverse 2-azetidinone derivatives has emerged as an important area of research aimed at discovering compounds with enhanced biological efficacy and reduced resistance problems.Among the various synthetic methodologies available for the preparation of 2-azetidinones, the Staudinger ketene–imine [2+2] cycloaddition remains the most widely employed and versatile approach. In this method, Schiff bases (imines) react with ketenes generated in situ from acid chlorides in the presence of a base to afford β-lactam rings. This strategy allows the introduction of diverse substituents at different positions of the azetidinone nucleus, thereby enabling the synthesis of a wide range of biologically active derivatives.In recent years, increasing attention has been directed toward the synthesis of novel substituted 2-azetidinones incorporating various aromatic, heterocyclic, and pharmacologically active moieties. Structural modifications of the β-lactam ring have been shown to significantly influence biological activity, making the design and synthesis of new derivatives an active field of investigation. Therefore, the present study focuses on the synthesis of novel 2-azetidinone derivatives and their

subsequent characterization and biological evaluation, with the objective of identifying new compounds possessing enhanced pharmacological potential.

Experimental

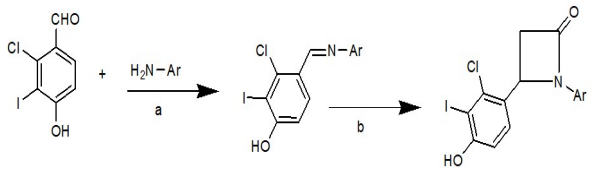
MATERIALS AND METHODS

The chemicals used in the present studies are of synthetic grade. The products were characterized by IR, and ^{1}HNMR. The melting points were determined by open capillary method and are uncorrected. The IR spectra were recorded on FTIR Spectrophotometer Model RZX (Perkin-Elmer) in the form of KBr pallet. ^{1}HNMR spectra were recorded in DMSO on a FTNMR Cryomagnet Spectrometer 400 MHz (Bruker) using TMS as an internal standard. The purity of compounds was checked by TLC. The crude products were recrystallized from 80% ethanol.

Present Work: In the present work, first the Schiff base were prepared from aromatic halo substituted aldehyde and heterocyclic aromatic amine, which on further react with ketene obtain from acetyl chloride using base triethyl amine then the final product i.e. azitidinone was obtain

Step I: General Procedure for Synthesis of Azitidinone: A mixture of alcohol (25 ml) and aromatic aldehyde (0.02 mol) was taken into a 100 mlround bottom flask. The mixture was stirred until a homogeneous solution was obtained,aromatic amine (0.02 mol) was added with stirring. (As the reaction is exothermic it should becarried out by placing flask in a freezing mixture). Reaction mass is stirred for another 45 min.the Schiff base was precipitated out. The reaction mixture was cool with stirring. The isolatedcrude product is purified by the washing in acetone.

The solution of Triethyl amine and acetyl chloride (0.01mole) was taken in roundbottom flask to this a mixture of schiff base in alcohol was added drop wise at 0 to 5^{o}C. The reaction mixture wasstir for 2-4 hours. The solid cake formed was filtered and the concentration of the filtrate wascarried out to obtain solid residue which was purified by crystallization from ethyl alcohol.Similar technique is used for obtaining remaining compounds. TLC technique is used to confirmthe purity; mobile phase used was n-hexane and alcohol.



Scheme I. Reaction Condition a: Acetic Acid reflux at rt, b: acetyl chloride & triethyl amine rt

D_1:IR (KBr):IR (KBr)cm^{-1} : 3163.75 O-H Stretching (Phenolic), 2922.79 Aromatic C-H stretching, 2870.43 Aliphatic C-H,1775.53 C=O Stretching, 1565.67 C=C Aromatic Stretching,749.42 C-Cl Stretching, 719.81 C-I Stretching.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.77 (s, 1 H), 5.6 (d, 2H), 5.70 (s1H), 7.26 (d, 1H), 7.4 (d, 2H), 7.5 (m, 1H) 7.7 (d, 1H),7.9 (s, dH).

^{13}C NMR (75 MHz, $CDCl_3$):171 s for carbonyl Lactam Ring (C=O), 151s for Aromatic C, 139 d for Ar CH,134 d for Aromatic CH, 133d for Aromatic CH, 131d for Aromatic CH, 130 s for Ar-C, 129 d for Aromatic CH, 126 d for Aromatic CH, 125s for Aromatic C, 125 s for Ar-C, 123s for Ar-C, 76.68 AliphaticLactam Ring CH,40.52 Aliphatic CH

D_2: IR (KBr):2922.60 O-H Stretching (Phenolic), 2851.89 Ar C-H stretching, 2851.89 Aliphatic C-H, 1713.00 Carbonyl Stretching, 1491 C=C Aromatic Stretching, 724.26 C-Cl Stretching, 649.48 C-I Stretching.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46(d, 2H), 4.48 (t, 1H), 6.17 – 6.46 (m, Ar-H), 7.11-7.36 (d, Ar-H), 7.96- 8.03 (m, Ar 4H) 9.12 (s, 1H).

^{13}C NMR (400 MHz, $CDCl_3$):190.85 for Lactam ring Carbonyl C=O, 172 Aromatic CH, 164 Aromatic CH, 162 Aromatic CH, 153 Aromatic CH, 152 Aromatic CH, 139 Aromatic CH, 134 Aromatic CH, 69 for lactam ring CH, 39for lactam ring CH_2.

D_3 : IR (KBr) cm^{-1} :3314.32 O-H Strthing (Ar-OH), 2954.00 Aromatic C-H stretching, 2852.43 Aliphatic C-H,1670.16 C=O Stretching, 1549.47 C=C Aromatic Stretching, 724.69 C-Cl Stretching, 703.82 C-I Stretching.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51 (d, 2H), 3.82 (t, 1H), 6.26 (s, for Ar 1H), 7.52-7.56 (d, 1H), 7.79-8.03 (d, 3H), 8.39 (m, 2H) 9.22 (m, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): 190 s, for lactam ring Carbonyl C=O, 161 d for Aromatic CH, 158 d for Aromatic two CH, 156 d for Aromatic two CH, 145 s, for Aromatic C, 138 s for Aromatic C, 137 s, for Aromatic C, 137 s for Aromatic C, 134 d for aromatic CH, 130 d for Aromatic CH, 57 t for Aliphatic CH_2, 37d for Aliphatic CH.

D_4: IR (KBr)cm^{-1} :3064.09 O-H Stretching, 2954.00 Aromatic C-H stretching, 2925.04 Aliphatic C-H, 1626.62 Carbonyl Stretching,1489.63 C=C Aromatic Stretching, 878.01 C-Cl Stretching, 755.39 C-I Stretching.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51(s, 2H), 3.82 (s, 1H), 6.25 (s1H), 7.11-7.16 (d, for Ar 2H), 7.31-7.36 (d, 2H), 8.00- 8.03 (m, Ar 2H) 9.12 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 191s, for lactam ring Carbonyl (C=O) carbon,157 s, for aromaticAr-C,155 d for two aromaticAr-CH,148 d for Aormatic CH,148 s forAromatic-C,135.69 s for Aromatic-C ,131 s forAromatic-C,128.89 s forAromatic-C,122 d for Aromatic CH,121 d for Aromatic -CH,55 t forlactam ring Aliphatic CH_2, 29 d for lactam ring Aliphatic CH.

Antibacterial Evaluation: A total Eight derivatives have been synthesized recrystallized at three different concentrations of each compound were prepared and further used individually to analyze its antibacterial activity against three human pathogens viz. Escherichia coli, Salmonella typhi and Pseudomonas aeruginosa. The data on antimicrobial activity of metal complexes against four human pathogens are presented in table-(II), (III) and table (IV). From the results it was observed that the compound has showed giant antibacterial potential against all the three pathogens.

RESULTS AND DISCUSSION

The present synthetic strategy provides an efficient and straightforward approach for preparing novel 2-azetidinone derivatives in excellent yields under mild reaction conditions. Spectroscopic characterization unequivocally confirmed the formation of the β-lactam framework.

Biological evaluation demonstrated that halogen-substituted derivatives possess enhanced antimicrobial activity, indicating that electronic effects play an important role in determining biological efficacy. The observed structure–activity relationship suggests that further structural modification of the β-lactam scaffold may lead to more potent antimicrobial agents with improved pharmacological properties.All the eight derivatives of 2-azitidinone derivatives D_1 to D_8 containing

Table 1 : Physical Constant and Yield synthesized compounds

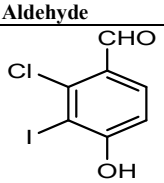
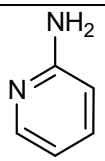
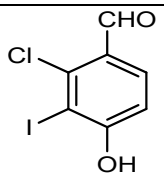
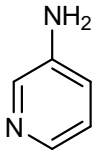
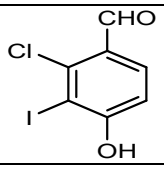
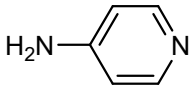
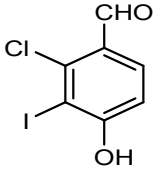
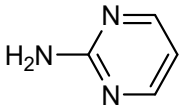
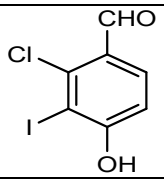
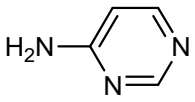
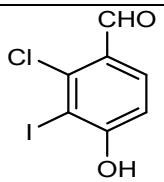
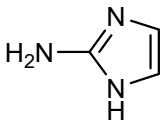
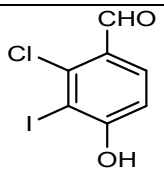
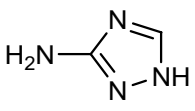
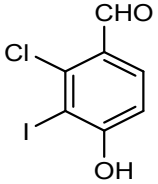
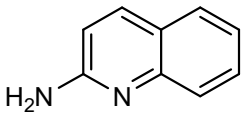
Entry	Aldehyde	Amine	Melting Point	Yield (%)
D_1			222	81
D_2			247	87
D_3			244	75
D_4			180	88
D_5			198	87
D_6			208	69
D_7			260	78
D_8			246	74

Table (II):- Effect of metal complexes of Ni for D_1-D_8 on the growth response of Escherichia coli

Conc. ,mg/mL	Zone of inhibition of sample in mm							
	D_1	D_2	D_3	D_4	D_5	D_6	D_7	D_8
1.0	I(12)	I(15)	NI	I(13)	I(15)	I(16)	I(20)	I(17)
2.0	I(10)	I(18)	I(14)	I(14)	I(12)	I(15)	I(21)	I(19)
3.0	I(15)	I(20)	I(19)	I(24)	I(12)	I(17)	I(18)	I(21)

I = Inhibition, values of inhibition are given in parenthesis, NI = Not inhibition

Table III. Effect of metal complexes of Ni for D_1-D_8 on the growth response of Staphylococcus aureus

Conc. ,mg/mL	Zone of inhibition of sample in mm							
	D_1	D_2	D_3	D_4	D_5	D_6	D_7	D_8
1.0	I(11)	I(14)	I(15)	I(16)	I(12)	NI	I(12)	I(17)
2.0	I(15)	I(15)	I(15)	I(12)	I(14)	NI	I(14)	I(19)
3.0	I(17)	I(18)	I(19)	I(16)	I(16)	I(12)	I(16)	I(20)

I = Inhibition, values of inhibition are given in parenthesis, NI = Not inhibition

Table IV.- Effect of metal complexes of Ni for D_1-D_8 on the growth response of Pseudomonas aeruginosa

Conc. ,mg/mL	Zone of inhibition of sample in mm							
	D_1	D_2	D_3	D_4	D_5	D_6	D_7	D_8
1.0	I(10)	I(12)	NI	I(18)	I(12)	NI	I(15)	NI
2.0	I(12)	I(16)	I(10)	I(14)	I(13)	I(10)	I(16)	NI
3.0	I(16)	I(12)	I(12)	I(10)	I(19)	I(12)	I(18)	NI

I = Inhibition, values of inhibition are given in parenthesis, NI = Not inhibition

nitrogen containing heterocyclic moiety were successfully synthesized in excellent yield and their structures are elucidated using elemental analysis, FTIR, ^{1}HNMR &^{13}C NMR spectroscopy. The results on antimicrobial activity reveals that all the eight newly synthesized compounds viz D_1 to D_8 found to have outstanding antibacterial effect against E.Coli, and Salmonella typhi nearly at all the concentrations analyzed. The results revealed, the broad spectrum potential of all thecompounds in inhibiting the growth of human pathogens, and this finding instruct the possible help to medicinal.

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