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SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL EVALUATION OF AZETIDINONES BY MODIFYING THE PHARMACOPHORIC SITES USING BETTI'S PROTOCOL OF 8-HYDROXYQUINOLINE PRECURSOR

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ABSTRACT

An efficient synthesis of series of different novel *β*-lactams via cycloaddition reaction (Staudinger reaction) of Schiff base has been reported in the present communication. A series of newly substituted 8-hydroxyquinoline Schiff base derivatives have been synthesized efficiently following Betti's condensation protocol with 8-hydroxyquinoline and different aldehydes under ambient reaction conditions. The structures of the newly synthesized Schiff base derivatives and *β*-lactams were confirmed by IR, ^{1}H NMR, elemental analysis and mass spectroscopic data. In-vitro anti-bacterial evaluations of β-lactams were done against gram-positive and gram-negative bacterial strains using the well diffusion method. It has been observed that some of these derivatives posses potent anti-bacterial characteristics against these bacteria.

KEYWORDS: **Azetidinone, 8-hydroxyquinoline, betti's condensation, staudinger reaction, schiff's base, anti-bacterial activity.**

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INTRODUCTION

The chemistry of quinoline has gained increasing attention due to its versatile pharmacological activities. Quinoline ring fused with five- or six-membered ring in linear fashion is found in natural products as well as synthetic compounds of biological interest [1]. Quinolones are extensively investigated as broad spectrum anti-bacterial, anti-diabetic, anti-cancer, anti-convulsant, anti-inflamatory, anti-viral and anti-HIV agents. Quinoline family compounds are widely used as a parent compound to make drugs (especially anti-malarial medicines), fungicides, biocidal. Of all the hydroxyquinoline derivatives, 8-hydroxyquinoline is the most interesting one to be explored, owing to its multifunctional properties, such as diverse bioactivities and therapeutic potentials. 8-Hydroxyquinoline is the only one, among seven isomeric monohydroxyquinolines, capable of forming complexes with divalent metal ions through chelation. Most bioactivities of 8-hydroxyquinoline and its derivatives originate from their chelating ability [2]. In the present scenario, developments of newer quinolines have immense possibilities and scope for drug development scientist. Study of chemistry of the Betti's bases started at the beginning of the 20th century, when Betti, a pioneer of asymmetric synthesis, reported that condensation of 2-naphthol, benzaldehyde and ammonia gave a product with the ratio of 1:2:1 respectively [3]. Preparation of the substituted Betti's base derivatives via the modified Mannich reaction had subsequently become an important area in synthetic chemistry because of C–C bond formation under mild experimental conditions. In later years, attention has been paid to the Betti's reaction, and a similar reaction can be performed by either using other naphthols or quinolinols or by replacing ammonia with alkyl amines [4-8].

The *β*-lactam skeleton is the key structural element of the most widely used family of antimicrobial agents to date, the *β*-lactam antibiotics, which includes as representative structural classes the Penams, Cephems, Penems, Monobactams, Carbapenems, and Trinems, among others [9]. *β*-Lactam antibiotics are the most commonly used antibiotics. The 2-carbonyl derivative of azetidine (four-membered heterocyclic ring with nitrogen as the heteroatom) is designated as 2-azetidinone or, more commonly, *β*-lactam [10]. Azetidin-2-one, a four-membered cyclic lactam (*β*-lactam) skeleton has been recognized a useful building block for the synthesis of a large number of organic molecules by exploiting the strain energy associated with it. Efforts have been made in exploring such new aspects of *β*-lactam chemistry versatile intermediates for their synthesis of aromatic *β*-amino acid and their derivatives, peptides, polyamines, polyamino alcohols, amino sugars and polyamino ethers [11]. The cyclic 2-azetidinone skeleton has been extensively used as a template to build the heterocyclic structure fused to the four membered rings. The *β*-lactam heterocycles are still the most prescribed antibiotics used in medicine. They are considered as an important contribution of science to humanity [12]. The most widely used antibiotics such as the penicillins, cephalosporins, carumonam, thienamycine, aztreonam and the norcardicins all contain *β*-lactum rings [13]. The long-term use of *β*-lactam antibiotics exerts selective pressure on bacteria and permits the proliferation of resistant organisms. Azetidinones are of great biological interest, especially as anti-bacterial [14, 15], anti-fungal [16], anti-inflammatory, anti-convulsant activity [17], and anti-tubercular [18] agent, and others [19]. As part of interest in heterocycles that have been explored for developing pharmaceutically important molecule, it was thought worthwhile to synthesize some new 2-azetidinones derivatives possessing 8-hydroxyquinoline moiety in the same molecule. Earlier, our research group has reported synthesis of different biological active azetidinone derivatives [20-23]. All newly synthesized compounds were characterized using spectral and elemental analysis data. Series of azetidinone derivatives were tested against

different gram-positive and gram-negative bacterial stains.

MATERIALS AND METHODS

(i) General

All the chemicals and solvents were obtained from E-Merck, India (AR grade) and were used without further purification. Melting points were taken in an open capillary tube. IR spectra were recorded on a Shimadzu Dr-8031 instrument. Elemental analyses were carried out using a Perkin-Elmer, CHN elemental analyzer model 2400. ^{1}H-NMR spectra of the synthesized compounds were recorded at 400 MHz on a Bruker-Avance spectrophotometer using $CDCl_3$ solvent and TMS as an internal standard. EI-MS spectra were determined on a LCQ ion trap mass spectrometer (Thermo Fisher, San Jose, CA, USA), equipped with an EI source.

(ii) Synthesis of 7-((arylbenzylideneamino)(aryl)methyl)-quinolin-8-ol (1a-1e)

In the present work, 7-((arylbenzylideneamino)(arylphenyl)methyl)-quinolin-8-ol was obtained by the reaction of 8-hydroxyquinoline , aldehydes and ammonia via Betti's condensation reaction. The compound was synthesized by the reaction of 8-hydroxyquinoline in ethanol (0.01 mol) and aldehydes (0.02 mol). This mixture was slightly warmed and the solution of ammonia in ethanol was added in slightly excess amount. This reaction mixture was kept for two hours in the stopper conical flask at room temperature. Compounds (1a-1e) were obtained after 15 hours standing of the reaction mixtures. These compounds (1a-1e) were recrystallized in absolute alcohol. 7-((arylbenzylideneamino)(arylphenyl)methyl)quinolin-8-ol was used as the key intermediate for further synthesis.

(iii) Synthesis of 3-chloro-1-((8-hydroxyquinolin-7-yl)(aryl)methyl)-4-(aryl)azetidin-2-one (2a-2e)

Compound (1a-1e) (0.01 mol) and chloroacetic acid (0.01 mol) was dissolved in dichloromethane (10 ml) in stoppered conical flask, cooled and stirred. In cold condition of the reaction mixture, triethylamine [TEA, (0.01 mol)] was added in it, followed by dropwise addition of $POCl_3$ (0.01 mol) in dichloromethane with vigorous stirring. The reaction mixture was then stirred for additional 16 hr. The completion of the reaction was monitored by TLC. Thus, the titled compounds (2a-2e) were obtained (Scheme 1). The reaction mixture was washed with water and dried over sodium sulphate. The products that were obtained after removing the solvent were purified from chloroform.

(iv) Antibacterial Activity

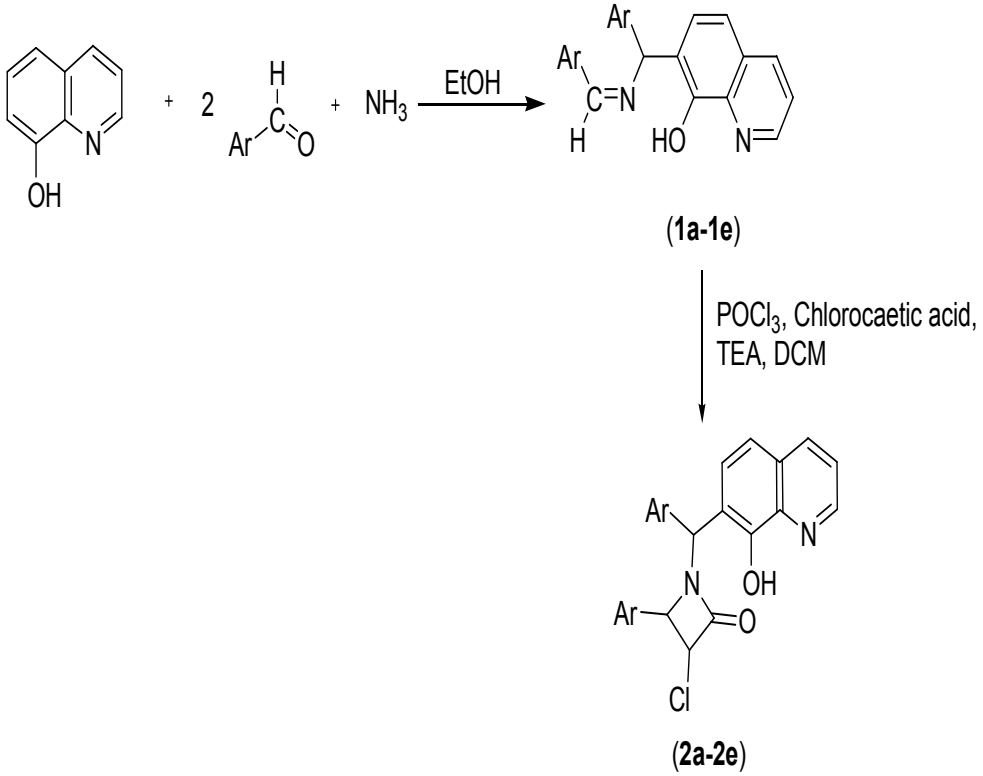
The newly synthesized compounds were examined for anti-bacterial and anti-fungal activity using the well diffusion method against the panel of different gram positive and gram negative bacterial stains and fungi stains. Different bacterial stains used for the screening were *S. aureus* (Gram Positive), *B. subtilis* (Gram Positive), *Pseudomonas sp.* (Gram Negative) and *E. coli* (Gram Negative). The stock solutions of newly synthesized compounds or standard drug in dimethyl sulfoxide (100 µg/mL) were prepared for the study. The sterilized petri dishes and agar medium were used in the present work. The antibacterial activities of compounds were evaluated by measuring the zone of inhibition on nutrient agar plate. Muller Hinton agar was used in the anti-bacterial study. The composition of nutrient agar medium to culture the bacterial strains used in the present study was: Peptone (10 gm), Agar powder (20 gm), Sodium chloride powder (10 gm), Beaf extract (5 gm) and distilled water (1000 ml). The pH of the nutrient agar medium was adjusted to 7.2. The nutrient agar medium was mixed well and was autoclaved at 15 lbs pressure at 120^0 C for at least 15 minutes. In the sterilized agar medium, 10 ml of one day old bacterial cultures were added. Bacterial culture were inoculated into nutrient broth and incubated at $(37 \pm 2)^0$ C on rotary shaker at 100 rpm. After 36 hr incubation, bacterial suspensions were used for further tests. This media were poured in petri dishes and allowed to set. Two well were created using a 5 mm cork borer. In this well 0.1

ml of test sample/standards were filled. All the nutrient agar plates were incubated at 37^0 C for 24 hrs in anti-bacterial study. The plates were observed in the clear zone of inhibition. Then diameters of the zone of inhibition for these compounds were measured. The biological activities were tested for at least three times for all the compounds against all microorganisms and average value has been reported here. The results of antimicrobial activity of the newly synthesized 3-chloro-1-((8-hydroxyquinolin-7-yl)(aryl)methyl)-4-(aryl)azetidin-2-one (2a-2e) have been collected in Table 1.

RESULTS AND DISCUSSION

(i) General chemistry

Synthesis of 3-chloro-1-((8-hydroxyquinolin-7-yl)(aryl)methyl)-4-(aryl)azetidin-2-one (2a-2e) has been obtained by condensation reaction of 7-((arylbenzylideneamino) (aryl) methyl)quinolin-8-ol (1a-1e) with $POCl_3$ and TEA. The compound 1 has been synthesized by one pot condensation of 8-hydroxyquinoline, aromatic aldehydes and ammonia in ethanol. In Table 1 are depicted the physical data of compounds 1a-1e and 2a-2e.



Scheme 1

Synthesis of 3-chloro-1-((8-hydroxyquinolin-7-yl)(aryl)methyl)-4-(aryl)azetidin-2-one (2a-2e)

Table 1
Yield and physical data of newly synthesized compounds.

Compound	Substituent (R)	m. p. (^{0}C)	Yield (%)
1a	-C_6H_5	90	84
1b	2-OH-C_6H_4	102	80
1c	4-OH-C_6H_4	105	75
1d	2-NO_2-C_6H_4	110	76
1e	4-NO_2-C_6H_4	115	70
2a	-C_6H_5	96	80
2b	2-OH-C_6H_4	110	72
2c	4-OH-C_6H_4	116	69
2d	2-NO_2-C_6H_4	114	62
2e	4-NO_2-C_6H_4	120	63

(ii) Spectral analysis of newly synthesized compounds

Characterization data of 7-(benzylideneamino)(phenyl)methyl)quinolin-8-ol (1a):

IR (KBr): 1630 (N=C); 3210 (Ar-OH); ^{1}H NMR: 5.10 (s, 1H, Ar-OH); 5.70 (s, 1H, Ar-CH); 7.10-7.30 (m, 13H, Ar-CH); 7.70 (d, 2H, Ar-CH); 8.20 (s, 1H, N=CH); Elemental Analysis For $C_{23}H_{18}N_2O$, Calcd. : C, 81.63; H, 5.36; N, 8.28; Found: C, 81.60; H, 5.30; N, 8.20 ; Mass spectra, m/z = 338.10 (100%).

Characterization data of 7-(2-hydroxybenzylideneamino)(2-hydroxyphenyl)methyl)quinolin-8-ol (1b):

IR (KBr): 1650 (N=C); 3240 (Ar-OH); ^{1}H NMR: 5.20 (s, 3H, (Ar-OH)$_3$); 5.80 (s, 1H, Ar-CH); 6.80-7.10 (m, 13H, Ar-CH); 8.30 (s, 1H, N=CH); Elemental Analysis For $C_{23}H_{18}N_2O_3$, Calcd. : C, 74.58; H, 4.90; N, 7.56; Found: C, 74.50; H, 4.80; N, 7.50 ; Mass spectra, m/z = 370.10 (100%).

Characterization data of Synthesis of 7-(4-hydroxybenzylideneamino)(4-hydroxyphenyl)methyl)qui nolin-8-ol (1c):

IR (KBr): 1640 (N=C); 3270 (Ar-OH); ^{1}H NMR: 5.40 (s, 3H, (Ar-OH)$_3$); 5.70 (s, 1H, Ar-CH); 6.90-7.20 (m, 13H, Ar-CH); 8.60 (s, 1H, N=CH); Elemental Analysis For $C_{23}H_{18}N_2O_3$, Calcd. : C, (s, 1H, Ar-CH); 6.80-7.10 (m, 15H, Ar-CH); Elemental Analysis 74.58; H, 4.90; N, 7.56; Found: C, 74.40; H, 4.70; N, 7.50 ; Mass spectra, m/z = 370.00 (100%).

Characterization data of Synthesis of 7-(2-nitrobenzylideneamino)(2-nitrophenyl)methyl)quinolin-8-ol (1d):

IR (KBr): 1680 (N=C); 3290 (Ar-OH); ^{1}H NMR: 5.50 (s, 1H, (Ar-OH); 5.90 (s, 1H, Ar-CH); 7.20-7.40 (m, 13H, Ar-CH); 8.80 (s, 1H, N=CH); Elemental Analysis . For $C_{23}H_{16}N_4O_5$, Calcd. : C, 64.48; H, 3.76; N, 13.08; Found: C, 64.40; H, 3.70; N, 13.00 ; Mass spectra, m/z = 428.10 (100%).

Characterization data of Synthesis of 7-(4-nitrobenzylideneamino)(4-nitrophenyl)methyl)quinolin-8-ol (1e):

IR (KBr): 1650 (N=C); 3260 (Ar-OH); ^{1}H NMR: 5.30 (s, 1H, (Ar-OH); 5.80 (s, 1H, Ar-CH); 7.10-7.50 (m, 13H, Ar-CH); 8.60 (s, 1H, N=CH); Elemental Analysis For $C_{23}H_{16}N_4O_5$, Calcd. : C, 64.48; H, 3.76; N, 13.08; Found: C, 64.30; H, 3.60; N, 13.10 ; Mass spectra, m/z = 428.00 (100%).

Characterization data of 3-chloro-1-((8-hydroxyquinolin-7-yl)(phenyl)methyl)-4-phenylazetidin-2-one (2a):

IR (KBr): 1350 (N-C); 1760 (C=O, *β*-lactam); 3240 (Ar-OH); ^{1}H NMR: 4.60 (s, 1H, Ar-CH); 5.20 (s, 1H, (Ar-OH); 5.40 (s, 1H, Ar-CH); 6.10

For $C_{25}H_{19}ClN_2O_2$, Calcd. : C, 72.37; H, 4.62; N, 6.75; Found: C, 72.30; H, 4.60; N, 6.70 ; Mass spectra, m/z = 414.10 (100%).

Characterization data of 3-chloro-4-(2-hydroxyphenyl)-1-((2-hydroxyphenyl)(8-hydroxyquinolin-7-yl)methyl)-azetidin-2-one (2b):

IR (KBr): 1370 (N-C); 1790 (C=O, *β*-lactam); 3250 (Ar-OH); ^{1}H NMR: 4.80 (s, 1H, Ar-CH); 5.40 (s, 3H, $(Ar\text{-}OH)_3$); 5.70 (s, 1H, Ar-CH); 6.30 (s, 1H, Ar-CH); 6.80-7.10 (m, 13H, Ar-CH); Elemental Analysis For $C_{25}H_{19}ClN_2O_4$, Calcd. : C, 67.19; H, 4.29; N, 6.27; Found: C, 67.10; H, 4.20; N, 6.20 ; Mass spectra, m/z = 446.10 (100%).

Characterization data of 3-chloro-4-(4-hydroxyphenyl)-1-((4-hydroxyphenyl)(8-hydroxyquinolin-7-yl)methyl)-azetidin-2-one (2c):

IR (KBr): 1350 (N-C); 1740 (C=O, *β*-lactam); 3190 (Ar-OH); ^{1}H NMR: 4.40 (s, 1H, Ar-CH); 5.20 (s, 3H, $(Ar\text{-}OH)_3$); 5.80 (s, 1H, Ar-CH); 6.50 (s, 1H, Ar-CH); 6.90-7.30 (m, 13H, Ar-CH); Elemental Analysis For $C_{25}H_{19}ClN_2O_4$, Calcd. : C, 67.19; H, 4.29; N, 6.27; Found: C, 67.20; H, 4.20; N, 6.10 ; Mass spectra, m/z = 446.00 (100%).

Characterization data of 3-chloro-1-((8-hydroxyquinolin-7-yl)(2-nitrophenyl)methyl)-4-(2-nitrophenyl)azetidin-2-one (2d):

IR (KBr): 1340 (N-C); 1760 (C=O, *β*-lactam); 3280 (Ar-OH); ^{1}H NMR: 4.60 (s, 1H, Ar-CH); 5.20 (s, 1H, Ar-OH); 5.60 (s, 1H, Ar-OH); 6.40 (s, 1H, Ar-CH); 7.20-7.50 (m, 13H, Ar-CH); Elemental Analysis For $C_{25}H_{17}ClN_4O_6$, Calcd. : C, 59.47; H, 3.39; N, 11.10; Found: C, 59.40; H, 3.30; N, 11.00 ; Mass spectra, m/z = 504.00 (100%).

Characterization data of 3-chloro-1-((8-hydroxyquinolin-7-yl)(2-nitrophenyl)methyl)-4-(2-nitrophenyl) azetidin-2-one (2e):

IR (KBr): 1380 (N-C); 1770 (C=O, *β*-lactam); 3250 (Ar-OH); ^{1}H NMR: 4.40 (s, 1H, Ar-CH); 5.50 (s, 1H, Ar-OH); 5.90 (s, 1H, Ar-OH); 6.50 (s, 1H, Ar-CH); 7.50-7.90 (m, 13H, Ar-CH); Elemental Analysis For $C_{25}H_{17}ClN_4O_6$, Calcd. : C, 59.47; H, 3.39; N, 11.10; Found: C, 59.45; H, 3.30; N, 11.00 ; Mass spectra, m/z = 504.10 (100%).

(iii)Biological activity of newly synthesized compounds

The antimicrobial activity of the newly synthesized 3-chloro-1-((8-hydroxyquinolin-7-yl)(aryl)methyl)-4-(aryl)azetidin-2-one (2a-2e) were evaluated using well diffusion method by measuring the zone of inhibition on agar plates against the panel of different gram positive and gram negative bacterial strains. Different bacterial strains used for the screening were *Staphylococcus aureus* (Gram Positive), *Bacillus subtilis* (Gram Positive), *Pseudomonas* sp. (Gram Negative) and *Escherichia coli* (Gram Negative).

Table 2

Biological activities of 3-chloro-1-((8-hydroxyquinolin-7-yl)(aryl)methyl)-4-(aryl) azetidin-2-one

Bacterial strain	Zone of inhibition in mm along without well diameter (5mm)					
	Chemical compounds					
	2a	2b	2c	2d	2e	Standard Amphicilin
S. aureus	-	-	-	5.6	4.6	9
B. subtilis	-	-	-	6.2	5.4	6
Pseudomonas sp.	10.2	9.3	6.0	10.6	11.8	12
E. coil	13.5	14.6	10.9	14.3	13.5	17

"-" represent "not active"

From the above Table 2, it can be seen that some of the newly synthesized compounds have shown promising activity against some gram-negative and gram-positive bacteria. Whereas, others compounds found to be inactive or moderately active against these bacterial stains.

CONCLUSION

The efficient synthesis of 3-chloro-1-((8-hydroxyquinolin-7-yl)(aryl)methyl)-4-(aryl)azetidin-2-one (2a-2e) has been presented by condensation reaction of 7-((arylbenzylideneamino) (aryl) methyl)quinolin-8-ol (1a-1e) with $POCl_3$ and TEA. Betti's condensation reaction which involves one pot condensation of 8-hydroxyquinoline, aromatic aldehydes and ammonia in ethanol was successfully used for synthesis of Schiff's base analogues (1a-1e) of 8-hydroquinoline moiety. These newly synthesized compounds were evaluated for their anti-bacterial study and from the results it was found that some of these compounds posses promising activity against some gram-negative and gram-positive bacteria and thus can be useful for the drug development.

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