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Synthesis and Antimicorbial Studies of Some Azetidinone Derivatives from 8-Hydroxy Quinoline

K. ISHWAR BHAT*, SUPRIYA MAITY and E.V.S. SUBRAHMANYAM
Department of Pharmaceutical Chemistry, N.G.S.M Institute of Pharmaceutical Sciences, Mangalore-575 005, India
E-mail: bhatishwar@yahoo.co.in

A new series of azetidinone derivatives have been synthesized. Structures of these azetidinone derivatives have been confirmed by analytical and spectral data. The compounds have also been screened for antibacterial and antifungal activity.

Key Words: Synthesis, Biological activity, Substituted azetidinone derivatives.

INTRODUCTION

2-Carbonyl derivative of azetidine (4-membered heterocyclic ring with nitrogen as the hetero atom) is designated as 2-azetidinone or most commonly known as β-lactam. A large number of 3-chloromonocyclic β-lactams possess powerful antibacterial[1,2], antiinflammatory[3], antifungal[2,4,5], antimicrobial[6-8], sedative[7], anticonvulsant[9], antitubercular[2,10], analgesic[11] and herbicidal[12] properties. The quinoline derivatives are also known for their antimalarial activity.

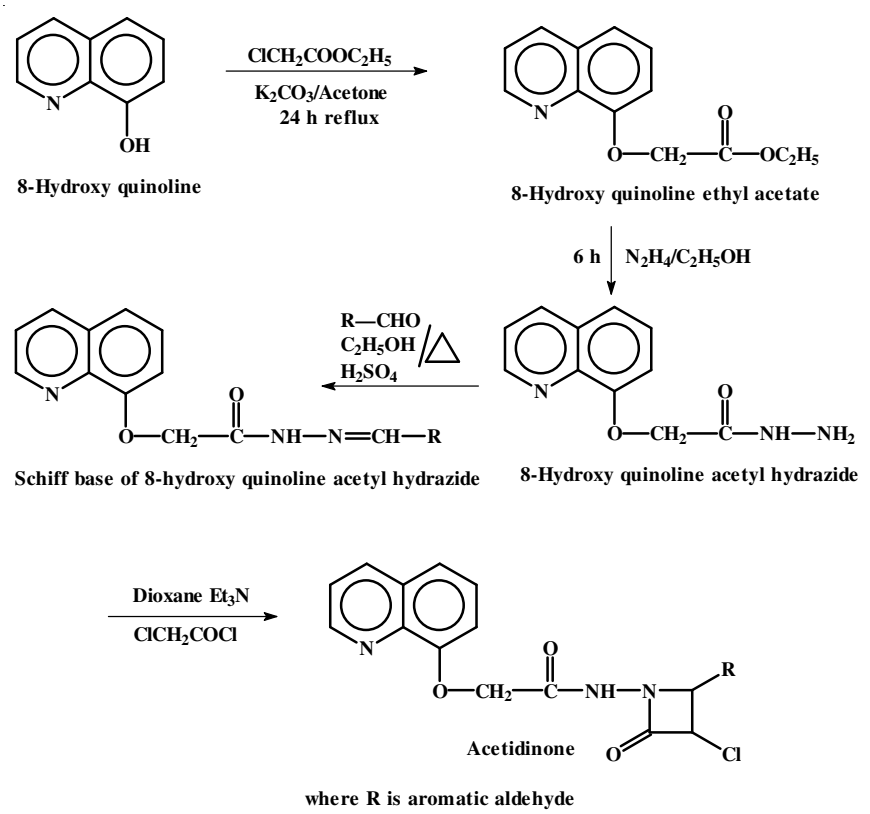
By considering the above factors, it was thought to synthesize some azetidinone derivatives from 8-hydroxy quinoline moiety and screened them for their antimicrobial and antifungal studies.

EXPERIMENTAL

Melting points of the newly synthesized compounds was determined by open capillary method and are uncorrected. Purity of the compounds was checked by TLC on silica gel G. ^{1}H NMR spectrum was recorded on Bruker DRX 300 using deuteriated methanol as solvent. The IR spectrum was recorded on Shimadzu 8201 PC. The FAB mass spectrum was recorded on Jeol SX 102/DA-6000 mass spectrometer using Ar/Xe as FAB gas.

General preparation: 8-Hydroxy quinoline was treated with ethyl chloro acetate to give 8-hydroxy quinoline ethyl acetate, which on hydrazonolysis gave 8-hydroxy quinoline acetyl hydrazide. This compound was converted to corresponding schiff's bases of 8-hydroxy quinoline acetyl

hydrazide by the reaction with different aromatic or heterocyclic aldehydes. Finally, the cyclization of Schiff's bases with chloroacetyl chloride in the presence of triethylamine and dioxane resulted in the formation of corresponding azetidinone derivatives (**Scheme-I**). The different aromatic or heterocyclic aldehydes used for the preparation of Schiff's bases is given in Table-1.



Scheme-I

TABLE-1
LIST OF ALDEHYDES USED

Compd.	Aldehydes used (-R)	Compd.	Aldehydes used (-R)
S_1	2,4-Dihydro benzaldehyde	S_6	Benzaldehyde
S_2	2-Nitro benzaldehyde	S_7	Salicylaldehyde
S_3	4-Chloro benzaldehyde	S_8	Anisaldehyde
S_4	Vanillin	S_9	Dimethyl amino benzaldehyde
S_5	*p*-Hydroxy benzaldehyde	S_{10}	Furfuraldehyde

8-Hydroxy quinoline ethylacetate: A mixture of 8-hydroxy quinoline (0.1 mol), ethylchloroacetate (0.1 mol) and anhydrous potassium carbonate (19.5 g, 0.15 mol) in dry acetone were refluxed on a water bath for 24 h at 70°C. The resultant reaction mixture was cooled and filtered. From the filtrate excess of acetone was removed by distillation. This reaction mixture of filtrate was then poured on to the ice cold water and stirred well. The organic layer was extracted with ether and further the ether layer was washed with 5 % HCl and dried over anhydrous sodium sulphate. Ether layer was evaporated by drying on water bath. The resultant collected liquid was purified under reduced pressure to yield pure 8-hydroxy quinoline ethyl acetate.

8-Hydroxy quinoline acetyl hydrazide: A mixture of 8-hydroxy quinoline ethylacetate (0.05 mol), hydrazine hydrate (99 % 0.07 mol) in ethanol (100 mL) was refluxed for 6 h. From the resultant mixture excess of ethanol was removed by distillation. On cooling, from the resultant mixture, white needle like crystals of 8-hydroxy quinoline acetyl hydrazide began to separate. It was collected and then recrystallized from ethanol.

Schiff's bases of 8-hydroxy quinoline acetyl hydrazide: Mixture of 8-hydroxy quinoline acetyl hydrazide (0.01 mol) (dissolved in minimum quantity of ethanol) and different aromatic or heterocyclic aldehydes (0.01 mol, dissolved in minimum quantity of ethanol) was refluxed together by employing sulphuric acid about 0.01 mol as catalyst in a round bottom flask on a water bath for 6 h. The precipitate was filtered, washed with ice cold water and recrystallized from ethanol

Azetidinone analogs: Chloroacetyl chloride was added dropwise to Schiff's base (0.01 mol) and triethylamine (0.02 mL) in dioxane (25 mL) at 5-10°C. The mixture was stirred for 20 h and left at room temperature for 3 d. The contents were filtered, dried and recrystallized from ethanol (Table-2).

IR (cm^{-1}): 3443 ν(N-H), 2973 ν(C-H), 1637 ν(C=O) of -CONH, 1727 ν(C=O) of azetidinone ring, 3259 ν(-OH). m/z: 413, 289, 154, 136, 102. ^{1}H NMR: δ 7.4-7.8 (m, 9H, Ar-H), 7.2 (s, 1H, NH), 4.2 (s, 2H, OCH_2),8.6 (s,1H, p-OH), 8.2 (s, 1H, o-OH), 3.1 (d, 1H, C_3-H azetidinone protons), 3.0 (d, 1H, C_4-H azetidinone protons).

IR (cm^{-1}): 3435 ν(N-H), 2969 ν(C-H), 1636 ν(C=O) of -CONH, 1733 ν(C=O) of azetidinone ring, 1347 ν(NO_2 symmetric stretching), 1525 ν(NO_2 asymmetric stretching). m/z: 426, 277, 154, 136, 102. ^{1}H NMR: δ 7.4-7.8 (m, 10H, Ar-H), 7.1 (s, 1H, NH), 4.1 (s, 2H, OCH_2) 3.1 (d, 1H, C_3-H azetidinone protons) 3.0 (d, H, C_4-H azetidinone protons).

IR (cm^{-1}): 3437 ν(N-H), 2984 ν(C-H), 1647 ν(C=O) of -CONH, 1728 ν(C=O) of azetidinone ring. m/z: 416, 232, 154, 136, 102. ^{1}H NMR: δ 7.3-7.8 (m, 10H, Ar-H), 7.1 (s, 1H, NH), 4.1 (s, 2H, OCH_2) 3.1 (d, 1H, C_3-H azetidinone protons) 3.0 (d, 1H, C_4-H azetidinone protons).

TABLE-2
PHYSICAL DATA OF AZETIDINONE DERIVATIVES

Compd.	m.f. / (m.w.)	Physical state	m.p. (ºC)	Yield (%)
SM_1	$C_{20}H_{16}N_3O_5Cl$ (413.5)	Brown crystals	250-252	60.3
SM_2	$C_{20}H_{15}N_{40}O_5Cl$ (426.5)	Yellow brown crystals	208-210	56.6
SM_3	$C_{20}H_{15}N_3O_3Cl_2$ (416)	Brown crystals	260-262	65.0
SM_4	$C_{21}H_{17}N_3O_4Cl_2$ (446)	Yellow crystals	208-210	59.3
SM_5	$C_{20}H_{16}N_3O_4Cl$ (397.5)	Dark red crystals	218-220	60.2
SM_6	$C_{20}H_{16}N_3O_3Cl$ (381.5)	Pale yellow crystals	215-217	62.0
SM_7	$C_{20}H_{16}N_3O_4Cl$ (397.5)	Brown crystals	238-240	54.2
SM_8	$C_{21}H_{18}N_3O_4Cl$ (411.5)	Orange crystals	216-218	58.4
SM_9	$C_{22}H_{21}N_4O_3Cl$ (424.5)	Brown crystals	244-246	51.2
SM_{10}	$C_{18}H_{14}N_3O_4Cl$ (371.5)	Dark brown crystals	258-260	58.5

Antibacterial and antifungal activity: Antibacterial activities of the synthesized compounds were screened against *S. aureus, B. subtilis, E. coli, P. aeuroginosea* using modified Kirby-Bauer method. The compounds were tested at 50 µg level. The result was compared with amoxicillin (10 µg/disk). All compounds showed moderate to good antibacterial activity (Table-3).

Antifungal activities of synthesized compounds were evaluated at 50 µg level for their activity against *Candida albicans* using modified Kirby-Bauer method compared with griseofulvin all compounds showed moderate to good activity.

RESULTS AND DISCUSSION

Various azetidinone derivatives derived from 8-hydroxy quinoline moiety at position 1, different aryl substituents at position 4 and chloride at position 3 were synthesized with a view of enhancing the biological activity. The synthesis of azetidinones by the described method resulted in products with good yield. The structures of newly synthesized compounds were confirmed by IR, ^{1}H NMR and mass spectral analysis.

TABLE-3
DATA OF ANTIMICROBIAL AND ANTIFUNGAL ACTIVITY OF AZETIDINONE DERIVATIVES

Compd.	Diameter of zone inhibition (mm)				
	B. subtitis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*
SM_1	13	19	13	15	12
SM_2	16	20	–	–	–
SM_3	13	14	14	14	10
SM_4	11	12	10	12	-
SM_5	12	15	15	-	13
SM_6	12	14	11	16	–
SM_7	10	11	16	13	–
SM_8	10	14	16	12	–
SM_9	13	14	12	15	10
Ampicillin	15	21	18	17	–
Griseofulvin	–	–	–	–	13

The compounds SM_1, SM_2, SM_5 have shown significant antibacterial activity and compounds SM_3, SM_4, SM_6, SM_8 have shown moderate activity compare with that of the standard drug ampicillin. The compounds SM_1, SM_3, SM_5 have shown significant antifungal activity when compared with that of the standard drug griseofulvin.

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