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Research Article

SYNTHESIS AND ANTI MICROBIAL EVALUATION OF SOME NOVEL QUINOLINE INCORPORATED AZETIDINONES, THIAZOLIDINONES

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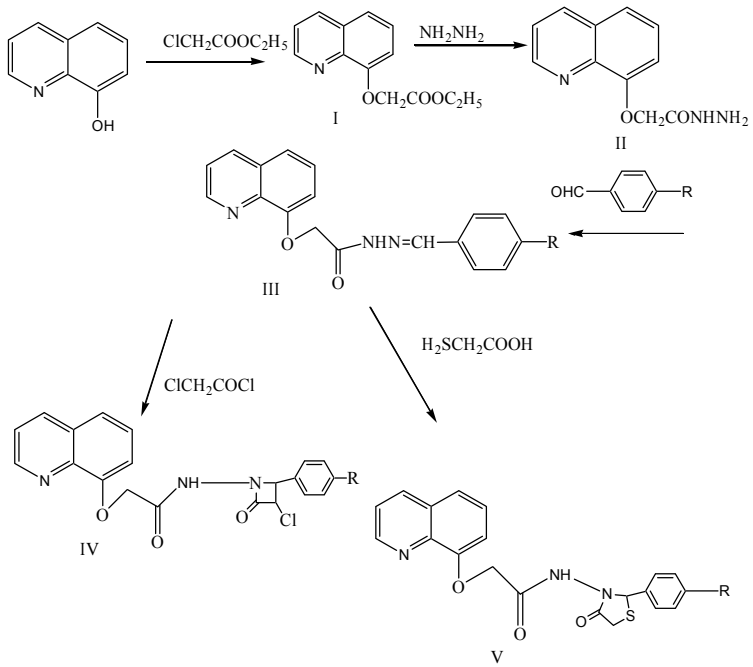
ABSTRACT:-
Quinoline derivatives are reported to have anti microbial, anti inflammatory, analgesic and anti cancer activities. The incorporated oxymethyl carbamide at 8th position of the quinoline ring was found to influence the biological activities of the molecules with this some of new quinolinyl oxymethyl azetidinones and quinolinyl oxymethyl azetidinones and thiazolidinones were synthesized from 8-hydroxy quinoline through (quinolin-8-yl-oxy) acetyl hydrazide intermediates. All the synthesized compounds were characterized by IR, H^1NMR spectral data and evaluated for their anti microbial activity.
Keywords: anti microbial activity, 8-substituted quinolines.

INTRODUCTION:

Quinoline and its derivatives are found to posses anti microbial[1], anti inflammatory[2], cytotoxicity[2] activity. Azetidinones and thiazolidinones are found to posses significant anti bacterial, antifungal and anti inflammatory activities[1-3].The incorporation of 4(substituted aryl)-2 azetidinone and 2(substituted aryl)-4 thiazolidinone moieties to quinoline via (OCH_2CONH-) linkage was through to enhance the biological activities. Hence in the present study the 8th position of quinoline was used as target for chemical modification by incorporation azetidinones & thiazolidinones. 4(substituted benzylidine hydrazido methyl oxy) quinoline (Schiff's bases) were synthesized by the condensation of 2-quinolin 8-yl oxy acetyl hydrazide with different substituted benzaldehydes, reaction of these Schiff's bases with chloroacetyl chloride and mercapto acetic acid yielded 3-chloro-(8quinolinyl-oxy acetamidyl)-4(substituted aryl) azetidinones and 4-(substituted aryl) 3-[(8quinolinyl)-oxy acetamidyl]. These synthesized compounds characterized by IR, H^1NMR spectral data and evaluated for their antimicrobial activity.

MATERIAL AND METHOD:

Melting points were determined with open capillary and are uncorrected. IR spectra were recorded on a PerkinElmer FTIR240 spectrophotometer using KBr optics. H^1-NMR spectra were recorded on 300MHz, bruker spectrometer in DMSO or $CDCl_3$ using TMS as an internal standard. All reactions were monitored by TLC on precoated silica gel $60F_{254}$ (mesh), spots were visualized with UV light.



III R	IV R	V R
a- H	a-H	a- H
b- Cl	b-Cl	b-Cl
c- OH	c-OH	c- OH
d- CH_3	d- CH_3	d- CH_3
e- OCH_3	e- OCH_3	e- OCH_3

CHEMISTRY:

Method of synthesis of ethyl (Quinoline 8-yl oxy) acetate (1)

An equimolar mixture of 8 hydroxy quinoline, ethyl chloro acetate and anhydrous potassium carbonate in dry acetone was refluxed on water both for 24hrs. The solid was filtered and the excess solvent was removed on a rotavapour.

Synthesis of 2 (Quinoline 8-yl oxy) acetohydrozide (2)

A mixture of compound 1 in absolute ethanol, hydrozenehydrate was added and the reaction mixture was refluxed for 15 hrs. The solution was concentrated and the solid that separate out on cooling was filtered at pump and re crystallized from absolute alcohol.

IR (KBr, cm^{-1}): 1762(C=O), 1616(CONH-), 3216(-NH-), 3056-2916(C-H); ^{1}H-NMR ($CDCl_3$, ppm)δ: 7.3-7.9,(m, 4H, AR-H), 8.84(s, 1H, AR-H), 4.83(s,2H,OCH_2), 8.0(s,1H, CONH),2.0(s,2H,-NH_2).

General procedure for the synthesis of 4-(substituted benzilidine-hydrazido methyl oxy)-8 quinoline (3a-e)

An equimolar mixture of hydrazide and benzaldihyde was refluxed in alcohol per period of 6-8 hrs. The reaction mixture was cooled and poured into a beaker containing ice cold water with stirring and neutralized with sodium bi sulphate solution. The product was filtered and re crystallized from ethanol. Similarly compounds (3b-e) were prepared from 2 by reacting with 4 substituted benzaldihyde and physical data are given in table **1.**

General procedure for the synthesis of N-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-(quinolin-8-yl oxy) acetamide 4a.

To the solution of schiff's base 3 in dry benzene, tri ethyl amine was added. To this chloro acetyl chloride was added drop wise with stirring. The mixture was then refluxed for 5 hrs. Tri ethyl amine hydrochloride formed was filtered and washed several times with dry benzene. The filtrate, washings were mixed and concentrated under reducing pressure. The residue obtained was washed with pet ether to remove the un reacted schiff's bases. The solid was then re crystallized from ethanol. The compound 4 b-e were prepared in the same manner from 3a-e, their physical data are given in table **1**.

IR (KBr,cm^{-1}): 3445.2(-NH-),1762(C=O,cyclic), 1682 (C=O,CONH), 1624(C=N),801(C-Cl). ^{1}H-NMR ($CDCl_3$, ppm)δ: 7.08-7.12,(m, 5H, AR-H), 7.3-7.9,(m, 4H, AR-H), 8.84(s, 1H,AR-H),5.05.4(s,1H,lactam)4.6-4.83(s,2H,OCH_2),8.0(s,1H,CONH),2.0(s,2H,NH_2).

General procedure for synthesis of *N*-(4-oxo-2-phenyl-1, 3-thiazolidin-3-yl)-2-(quinolin-8-yloxy) acetamide 5a.

Schiff's bases 3 were dissolved in dry benzene and to this thioglycolic acid was added. A pinch of fused zinc chloride was added to the reaction mixture and refluxed for 20hrs. The excessive of benzene was removed by distillation. The above mixture was then cooled to room temperature and pored into a beaker containing ice cold water. The reaction mixture neutralized with sodium bicarbonate to remove the un reacted thioglycolic acid. The solid obtain was re crystallized from absolute alcohol to yield 5a. The compound 5b-e was prepared in the same manner from 3b-e and their physical data are given **table 1**. IR (KBr,cm^{-1}): 3448(-NH-),1668(C=O, cyclic), 1632 (C=O,CONH), 603(C-S). ^{1}H-NMR ($CDCl_3$, ppm)δ: 7.6-7.14,(m, 5H, AR-H), 7.3-7.9,(m, 4H, AR-H), 4.6-4.83(s,2H,OCH_2),8.0(s,1H,CONH),3.3(s,2H,-CH_2).

ANTIMICROBIAL ACTIVITY:

All the compounds were screened for their in vitro anti bacterial activity against two gram positive strains i.e, bacillus subtilis (NCIM 2921) and Staphylococcus aureus (NCIM 2079) and two gram negative strains Escherichia coli (NCIM 2068) and Klebsialla Pneumonia (NCIM 2957) and their anti fungal activity against two fungal strains Candida albican (NCIM 3471) and aspergillus flavus (NCIM 555). The specified strain of organisms was procured from The National Chemical Laboratory, Pune, India, and was used for the evolution of the test compounds by broth dilution method. Culture of test organisms were inoculated on nutrient agar slants and were sub cultured in nutrient broth prior to testing the media used was nutrient agar for bacterial strain and Sabourand dextrose agar media for candida albicans and czapexs dox agar media for aspegillus flavus procured from Hymenia Laboratory media, India. All the test compounds were dissolved in DMSO to give a concentration of 1mg/ml. the test compound were prepared in different concentrations from 5mg/ml to 500mg/ml in DMSO. Ciprofloxacin was used as standard for antibacterial activity and Amphotericin-B for antifungal activity, whole keeping DMSO as control the MIC value of all tests and standard compound are given in **table 2.**

RESULT AND DISCUSSION:

All the synthesized compounds are screened for their anti bacterial and anti fungal activities, and reported MIC values against two gram positive strains i.e, bacillus subtilis and Staphylococcus aureus and two gram negative strains Escherichia coli and Klebsialla Pneumonia and their anti fungal activity against two fungal strains Candida albican and Aspergillus flavus. Compounds like IVb, IVc shows good activities against test organisms IVe, IVd shows moderate activities against bacterial test organisms. IVa shows significant activity. IVa, Va dose not shows activity against fungal test organism. IVb, Vb shows good activities against test organisms, IVe, Ve shows less activity. The activities of tested compounds are much significant than those of standard anti bacterial & anti fungal agents used.

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Table1: **physical characterization of 8-substituted quinolines**

Si.no.	R	Mol. formula	Mol. weight	%Yield	m.p.^{o}c
Iva	H	$C_{20}H_{16}ClN_3O_3$	381	70	190-192
IVb	Cl	$C_{20}H_{15}Cl_2N_3O_3$	416	74	216-218
IVc	OH	$C_{20}H_{16}ClN_3O_4$	397	68	194-196
IVd	CH_3	$C_{21}H_{18}ClN_3O_3$	395	70	204-206
IVe	OCH_3	$C_{21}H_{18}ClN_3O_4$	411	75	180-182
Va	H	$C_{20}H_{17}N_3O_3S$	379	65	148-150
Vb	Cl	$C_{20}H_{16}ClN_3O_3S$	413	66	120-122
Vc	OH	$C_{20}H_{17}N_3O_4S$	395	70	120-122
Vd	CH_3	$C_{201}H_{19}N_3O_3S$	393	60	130-132
Ve	OCH_3	$C_{21}H_{19}N_3O_4S$	409	65	140-142

Table2: **In vitro Anti microbial activity of 8-substituted quinolines**

Antimicrobial activity MIC (µg/mL)						
Test compound	**E.coli**	**K.pneumonia**	**S.aureua**	**B.substilis**	**C.albicans**	**A.flavus**
Iva	18	15	15	20	-	-
IVb	20	17	22	26	17	18
IVc	18	15	14	21	15	18
IVd	10	12	14	18	-	-
IVe	15	14	15	18	12	14
Va	20	18	22	24	-	-
Vb	21	20	21	25	18	20
Vc	16	15	18	22	-	18
Vd	12	12	15	15	15	18
Ve	17	15	16	18	10	14
Ciprofloxacin	25	20	25	30	-	-
Aamphoterecin-B	-	-	-	-	22	24

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