ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 10, Issue, 10, pp.74092-74095, October, 2018

DOI: https://doi.org/10.24941/ijcr.32660.10.2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

SYNTHESIS, ANTI MICROBIAL AND ANTI CANCER EVALUTION AND MOLECULAR DOCKING STUDIES OF SOME QUINOLINYL HETEROCYCLES

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ARTICLE INFO

Article History:
Received 20th July, 2018
Received in revised form
29th August, 2018
Accepted 24th September, 2018
Published online 30th October, 2018

Key Words:
Anti-microbial activity,
Calcium/cadmoduline dependent protein kinase1D inhibitor.

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 thiazolidinones were synthesized from 8-hydroxy quinoline through (quinolin-8yloxy) acetyl hydrazide intermediates. All the synthesized compounds were characterized by IR, H1NMR spectral data and molecular docking studies carried out against calcium/cadmoduline dependent protein kinase1D and evaluated for their anti-microbial activity.

Citation: ***Srinivas Sangu and Anil Kumar Middha,*** **2018.** "Synthesis, anti microbial & anti cancer evalution and molecular docking studies of some quinolinyl heterocycles", *International Journal of Current Research*, 10, (10), 74092-74095.

INTRODUCTION

Quinoline and its derivatives are found to posses anti microbial (John Thurmond, 2008), anti inflammatory (Lee Tai Liu, 2007), cytotoxicity activity. Azetidinones and thiazolidinones are found to possess significant anti-bacterial, antifungal and anti-inflammatory activities (John Thurmond, 2008; Lee Tai Liu, 2007 and Peter Ballard, 2007). The incorporation of 4(substituted aryl)- 2 azetidinone and 2(substituted aryl)-4 thiazolitinone 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 methyloxy) quinoline (schiff's bases) were synthesized by the condensation of 2-quinolin 8yloxy 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 molecular docking studies carried out against calcium/cadmoduline dependent protein kinase1D and evaluated for their anti-microbial activity.

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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.

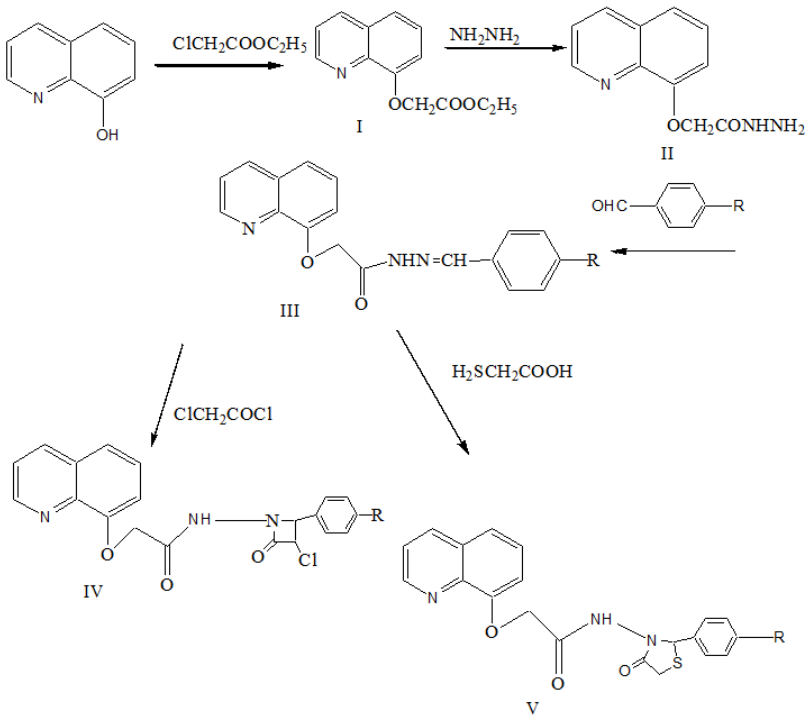
Chemistry

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).



III	IV	V
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

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 3 Chloro 8 quinolinyl oxy acetamidyl 4 (substituted aryl) 2 azetidinone 4a: To the solution of shiff'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 unreacted shiff'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 3[(2 (4substituted aryl) 8quinolinile) oxy acetamidyl]- 4thiazolidinone 5a: Shiff'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 unreacted 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).

Molecular Docking Studies: All the derivatives of Quinolinyl-azetidinones and Quinolinyl-thiazolidinones (Iva-e & Va-e) were selected for their molecular docking studies on selected X-ray crystal structure of human calcium/cadmoduline dependent protein kinase1D (pdb code; 2jc6) was retrieved from protein data bank using glid (Schrodinger, OPLS-2005 software), the ligands preparation was done in ligprep modules on glide program and selected protein was minimized and docked with prepared ligands was carried out by using extra precision(XP) modules on glide software, the Docking score (kcal/moles) given in Table 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

Table 1. Physical characterization of 8-substituted quinolines

Si.no.	R	Mol. formula	Mol. weight	%Yield	m.p.°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

Table 2. Showing the docking scores of Quinolinyl-azetidinones and Quinolinyl-thiazolidinones (Iva-e & Va-e)

S.NO	Docking score (kcal/moles)	XP G Score (kcal/moles)	Glide energy (kcal/moles)	XP H Bond (Å)
IVa	-6.783	-6.783	-29.711	0
IVb	-6.975	-6.975	-34.87	0
IVc	-7.38	-7.38	-42.042	0
IVd	-6.904	-6.904	-33.812	-1.065
IVe	-7.789	-7.789	-38.14	0
Va	-7.265	-7.265	-37.553	-0.7
Vb	-5.787	-5.787	-41.701	-0.35
Vc	-7.627	-7.627	-38.548	-1.362
Vd	-7.786	-7.786	-37.388	-0.898
Ve	-7.529	-7.529	-38.327	0

Table 3. In vitro Anti-microbial activity of 8-substituted quinolines (IVa-e & Va-e)

	Zone of inhibition (in mm) for the Quantity in 100 µg					
	E. coli*	*S. a**	*B. s**	*K .p**	*C. a**	*A .f**
IVa	18	15	20	15	-	-
IVb	20	22	26	17	17	18
IVc	18	14	21	15	15	18
IVd	10	14	18	12	-	-
IVe	15	15	18	14	12	14
Va	20	22	24	18	-	-
Vb	21	21	25	20	18	20
Vc	16	18	22	15	-	18
Vd	12	15	15	12	15	18
Ve	17	16	18	15	10	14
Std1	25	28	24	25	-	-
Std2	-	-	-	-	24	23

E.coli- Escherichia coli**, ***S.a- Staphylococcus aureus, B.s- Bacillus subtilis, K.p- Klebsiella pneumonia, C.a- Candida albicans, A.f- Aspargillus flavum* Std1: Gatifloxocin, std2: Fluconazole

Table 4. Anti cancer activity of of Quinolinyl azetidinones and Quinolinyl thiazolidinones derivatives (IVa-e & Va-e)

Compound	Percent inhibition(µg/mL)	
	IC 50 (MCF- 7)	IC 50 (Hep G2)
IVa	65.12	78.3
IVb	62.51	74.65
IVc	165.2	146.02
IVd	125.6	135.24
IVe	121	117.65
Va	74.24	85.64
Vb	72.15	79.85
Vc	185.15	152.22
Vd	130.75	142.12
Ve	138.15	125.55
Cisplatin	13.4	6.8

antifungal activity, whole keeping DMSO as control the MIC value of all tests and standard compound are given in Table 3.

RESULT AND DISCUSSION

Molecular docking: The molecular docking simulations for these compounds to human calcium/calmoduline dependent protein kinase1D (pdb code; 2jc6) was performed using the glid (Schrodinger, OPLS-2005 software), based on the x-ray crystal structure of calcium/calmoduline dependent protein kinase1D was retrieved from protein data bank (pdb code; 2jc6). The docking and subsequent scoring were performed using the default parameters of the glid program demonstrated that all the molecules under study have a nice interaction with amino acids of calcium/calmoduline dependent protein kinase1D and the docking scores were given in Table 2.

Anti-Microbiological Activity: The entire test compounds (quinoline derivatives i.e., Iva-e & Va-e, table. No:3) showed a varied degree of antibacterial activity against the test organisms employed. However, among this series of compounds IVb and Vb shows similar and high activity against *E.coli, B. subtilis* and *Staphylococcus aureus.* The compounds IVa and IVc have shown to exhibit equipotence against all bacterial test organisms used in this study. Whereas compounds Va and Ve showed relatively moderate activity against all bacterial test organism used in this study. The antifungal activity of test compounds shows that the newly synthesized Quinolinyl azetidinones and Quinolinyl-thiazolidinones derivatives (Iva-e & Va-e) IVd and Va shown to exhibit more anti fungal activity against *Candida albicans* and *Aspargillus flavum.* whereas the test compounds i.e., IVb, IVe, Vd and Ve moderate more activity against *Candida albicans*, while IVe and Ve exhibited mild to moderate activity against *Aspargillus flavum*.

Anti cancer activity: The percent inhibition and IC_{50} values for the tested compounds Quinolinyl azetidinones and Quinolinyl-thiazolidinones derivatives (IVa-e & Va-e, scheme-II) were calculated, and the results are given in the Table. No 3. The compound IVb showed highest activity against adino carcinoma of breast (MCF-7) and Hepatocellular carcinoma (HepG2) cell lines with IC_{50} values at 62.51and 74.65 µg/ml respectively which may be due to the presence of p-chloro phenyl substituent at 4^{th} position of Quinolinyl azetidinones pharmacophore and the compound Vb showed highest activity against adino carcinoma of breast (MCF-7) and Hepatocellular carcinoma (HepG2) cell lines with IC_{50} values at 72.15and 79.85 µg/ml respectively which may be due to the presence of p-chloro phenyl substituent at 4^{th} position of Quinolinyl-thiazolidinones pharmacophore and the compound Vb While the compounds IVa and Va were shows moderate activity and other compounds did not show cytotoxic activity against MCF-7 and HepG2 cell lines. Base on the results demonstrated that the quinazoline and quinoline nucleus posses the cytotoxic activity and can be used as anticancer agents.

Conclusion

In the present investigation we have synthesized some Quinolinyl-azetidinones (IVa-e) and Quinolinyl-thiazolidinones (Va-e) and evaluated for their anti microbial and anticancer activities helpful in further details study on these derivatives to develop the high therapeutically potential.

Acknowledgment

The authors are thankful to the chairman, Sura labs, Hyderabad for providing the facilities.

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