SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL 1-[(QUINOLIN-8YLOXY)-METHYL UREA

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ABSTRACT:

An efficient method for preparing 1-[(quinolin-8yloxy)-methyl urea, commencing from hydrazides and substituted aromatic amines, has been developed. The reaction of hydrazides with aceticacid and sodiumnitrite in the presence of dioxane to yield (Quinolin-8yloxy)-acetylazide and further treating with amines to produce the title compounds 1-[(quinolin-8yloxy)-methyl urea (4a-j). The compounds thus obtained were identified by spectral data and have been screened for their antimicrobial activity.

KEYWORDS: *Quinoline, Acetylazide, carbamide, Antimicrobial activity*

INTRODUCTION

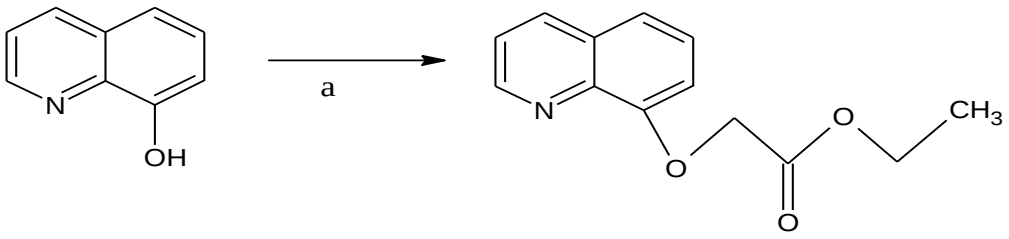
Carbamide is an organic compound commonly known as urea, the primary by-product of nitrogen metabolism in mammals and amphibians. It is characterized as a water-soluble, colorless, and odorless granular substance in its pure state. However, in the presence of moisture, carbamide gives slight ammonia smell.

A number of derivatives of carbmides and carbamates have been reported to possess significant antimicrobial[1], cytotoxicity[2], anti-inflammatory [3] activities. The Curtius rearrangement of appropriate carbonylazides under different reaction conditions constitutes a useful synthetic route for such compounds.

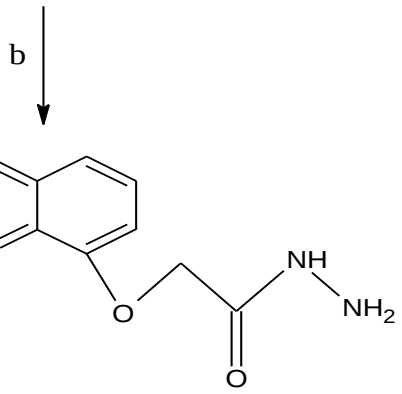
A comprehensive review on carbamides stimulated the synthesis of compounds containing both quinoline and carbamide in the same matrix to serve as a new scaffold for the synthesis of antimicrobial agents.1-[(quinolin-8yloxy)-methyl urea. An attempt is now made to synthesis of 2-(quinolin-8-yloxy) acetohydrazide (2) then reaction with the sodiumnitrite in presense of aceticacid to yield (Quinolin-8yloxy)-acetylazide) (3) with different aromatic amines to give 1-[(quinolin-8yloxy)-methyl urea derivatives. Finally, the structures of all the various synthesized compounds were assigned on the basis of IR and ^{1}H NMR spectral data and these compounds were screened for their antimicrobial activity.

MATERIALS AND METHODS

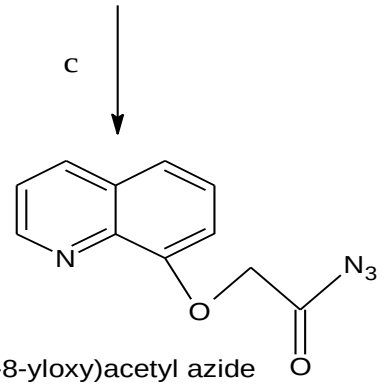
Melting points were determined with open capillary and are uncorrected. I.R spectra were recorded on a Shimadza FTIR model 8010 spectrophotometer, ^{1}H NMR spectra were recorded in CDCl3 on a Bruker supercon FT-NMR instrument using TMS as internal standard.



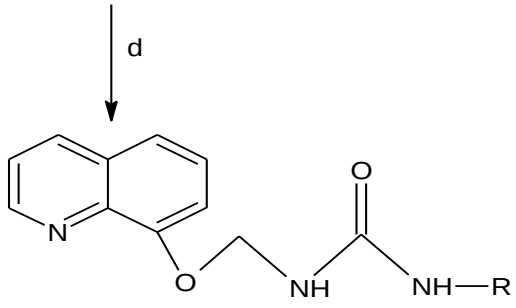
quinolin-8-ol ethyl (quinolin-8-yloxy)acetate



2-(quinolin-8-yloxy)acetohydrazide



(quinolin-8-yloxy)acetyl azide



1-[(quinolin-8-yloxy)methyl]urea

Where R: H, 4-OH, 4-Cl, 4-OCH_3, 2-Br, 2-Cl-4-NO_2, 2,4-$(Cl)_2$, 3,5-$(NO_2)_2$, 3,5-$(OCH_3)2$, 2,4-$(OH)_2$

Reagents and conditions:

a. dry acetone, K_2CO_3 reflux 24 h; **b.** NH_2NH_2, abs. EtOH, reflux 15 h;

c. dioxane, acetic acid, sodium nitrite, **d.** R-NH_2, toluene, reflex at 120^0 C for 4 hrs.

General procedure for the Synthesis of

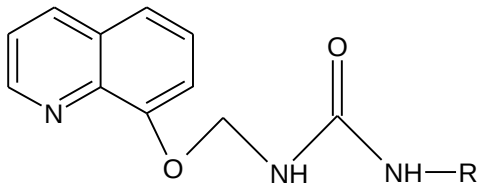
Ethyl (quinolin-8-yloxy) acetate: (1)[4]

An equimolar mixture of 8- hydroxy quinoline ethyl chloroacetate and anhydrous potassium carbonate (0.02 mol) in dry acetone (60 ml) was refluxed on a water bath for 24 hr. The inorganic solid was filtered and the excess solvent was removed on a rota vapour. **IR (KBR) γ max:** 3553, 3048, 1747, 1578, 1507, 1472, 1372, 1285, 1165, 1093, 973, 817, 741 cm^{-1}.**H^1 NMR ($CDCl_3$, 400 MH_z): δ** 8.94-7.18 (m, 6H, Phenyl), 4.95 (s, 2H, -OCH_2), 4.21 (m, 2H, CH_2 of ethyl), 1.20 (m, 3H, CH_3 of ethyl).

2-(quinolin 8yloxy) acetohydrazide (2)[4]

To a suspension of **(1)** (0.01 mol) in absolute ethanol (200 ml), hydrazine hydrate (99%, 0.015 mol) was added and the reaction mixture was refluxed for 15hr. The solution was concentrated and allowed to cool overnight. The resulting solid obtained was filtered, washed with cold ethanol, dried and recrystalized from ethanol. The compound was separated as brown crystals.**IR (KBR) γ max:** 3326, 3257, 1662, 1610, 1504, 1474, 1382, 1257, 1118, 1079, 819, 751 cm^{-1}**H^1 NMR ($CDCl_3$, 400 MH_z): δ** 8.96 (s, 1H, NH), 8. 80-7. 12 (m, 6H, Ar), 4.90 (s, 2H, -OCH_2), 3.10 (br, s, 2H, NH_2).

Table 1: Physicochemical Characterization Of 5-(8-Hydroxylquinolinoxymethyl) 1, 3, 4-Oxadiazole 4a-j



Sl No	*R*	Physical state	Mol. formula	% Yield	m.p.˚C
4a	H	brown crystals	$C_{18}H_{13}N_3O_2$	63	160-62
4b	4-Cl	yellow crystals	$C_{18}H_{12}N_3O_2Cl$	87	175-77
4c	4-Br	brown crystals	$C_{18}H_{12}N_3O_2Br$	72	152-54
4d	4-NO_2	cream crystals	$C_{18}H_{12}N_4O_4$	66	75-77
4e	4-OH	pale yellow crystals	$C_{18}H_{13}N_3O_3$	74	142-45
4f	4-Me	colorless crystals	$C_{19}H_{15}N_3O_2$	70	179-82
4g	4-OMe	cream crystals	$C_{19}H_{15}N_3O_2$	65	110-13
4h	4-$N(CH_3)_2$	yellow crystals	$C_{20}H_{18}N_4O_2$	74	114-16
4i	3-OH, 4-OMe	colorless crystals	$C_{19}H_{15}N_3O_4$	76	108-10
4j	3,4-$(OMe)_2$	white crystals	$C_{20}H_{17}N_3O_4$	68	205-07

(Quinolin-8yloxy)-acetylazide (3)[5]

2-(quinolin 8yloxy) acetohydrazide (0.5 mol) (2) was suspended in a mixture of dioxan (60ml) and acetic acid (60 ml) and cooled to 0°C in freezing mixture. An ice cold solution of sodium nitrite (5.25g) in water (20ml) was introduced into it in small portions with vigorous stirring. The temp of the reaction mixture was maintaining below 2°. After the complete addition the reaction mixture was allowed to stay at room temperature for 30min and the pale yellow solid that separated was collected, washed with cold water. The product was dried over phosphorous pentoxide in vacuum.

IR (KBR) γ max: 3432, 3040, 1694, 1630, 1572, 1463, 1323, 1238, 1118, 1106, 868, 736cm^{-1}.

H^1 NMR (CDCl$_3$, 400 MH$_z$): δ 8. 80- 7. 12 (m, 6H, Ar), 4.90 (s, 2H, -OCH$_2$).

1-[(quinolin-8yloxy)-methyl urea (4)[5]

A mixture of (quinolin-8yloxy)-acetylazide (0.217g, 0.001mol) and appropriate aromatic amine (0.01mol) in anhyd.toluene (15ml) was heated under gentle reflux (120°) in an oil bath for 4hrs. the crystalline product that separated out from the reaction mixture was collected and washed with toluene and pet.ether.

IR (KBR) γ max: 3780, 3695, 3628, 3051, 2917, 1664, 1597, 1377, 1274, 1166, 890, 788, 702cm^{-1}.

H^1 NMR (CDCl$_3$, 400 MH$_z$): δ 8.96 (s, 1H, NH), 8. 80-7. 12 (m, 6H, Ar), 4.90 (s, 2H, -OCH$_2$), 3.10 (br, s, 2H, NH$_2$).

***In Vitro* Evaluation of Antimicrobial Activity of Compounds**

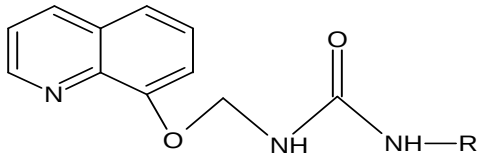
The antibacterial and antifungal activity of title compounds was determined by *invitro* by using cup-plate method (21). The agarmedia for each microorganism were prepared as per by institute of microbial technology, Chandigarh, India. The zone of inhibition (ZI) in mm was measured. The compounds were screened against two Gram +ve (*S. aureus, B.Subtilis)* and Gram –ve (*E. Coli and S.typhi)* bacteria respectively by broth dilution method. The concentrations (5-100 µg/ml) of the test compounds were prepared by dissolving the compounds in dimethyl sulphoxide (DMSO). Under identical conditions, ampicillin and clotrimazole were tested as standard drug (25µg/ml) for bacteria and fungi respectively. Antibacterial and antifungal activity shown by active compounds towards various bacteria is recorded in Tables-2.

RESULTS AND DISCUSSION:

The results of antibacterial and antifungal effect of the newly synthesized compounds are reported as MIC against *Staphylococcus aureus, Bacillus subtilis,(*gram positive) and *Escherichia coli, Salmonella typhi (*gram negative) and two fungi *Candida albicans and Aspergillus niger.*

Compounds like **4d** showed potent activity and **4b & 4c** showed moderate activity against *Staphylococcus aureus*. **4b & 4c** showed significant activity and **4d & 4i** exhibt similar activity compared to standard drug against *Bacillus subtilis*. Compounds like **4e,4g & 4i** showed good activity and compounds like **4e, 4g & 4j** showed similar activity compared to standard drug against *Escherichia coli*. Compounds **4i & 4f** exhibit significant activity against *Salmonella typhi*. Compounds like **4e & 4j** exhibit potent activity against *Candida albicans*. Compounds like **4b& 4d** exhibit good activity against. However, the activities of tested compounds are much significant than those of standard antibacterial and antifungal agents used.

Table 2: In vitro Anti-bacterial and Anti-fungal activity data of N'-arylidene-2-(quinolin-8-yloxy) aceto hydrazides 4a-j



MINIMUM INHIBITORY CONCENTRATIONS (MICs) µg/ml							
Sl. No.	R	*S. aureus*	*B.Subtilis*	*E. Coli*	*S.typhi*	*C.Albicans*	*A.niger*
4a	H	50.0	50.0	25.0	50.0	75.0	50.0
4b	4-Cl	12.5	10.0	25.0	20.0	15.0	15.0
4c	4-Br	25.0	10.0	15.0	25.0	25.0	20.0
4d	4-NO_2	10.0	12.5	50.0	25.0	30.0	5.0
4e	4-OH	25.0	15.0	10.0	12.5	10.0	25.0
4f	4-Me	50.0	30.0	70.5	10.0	15.0	10.5
4g	4-OMe	12.5	50.0	10.5	12.5	30.0	50.0
4h	4-$N(CH_3)_2$	15.0	50.0	25.0	75.0	20.0	15.0
4i	3-OH, 4-OMe	25.0	12.5	10.0	5.0	15.0	12.5
4j	3,4-$(OMe)_2$	20.0	25.0	50.0	12.5	10.0	30.0
	Ampicillin	>12.5	>12.5	>12.5	>12.5	-----	-----
	Clotrimazole	----	----	----	-----	>25	>25

Acknowledgment:

The author are thankful to HOD, Department of Pharmaceutical chemistry, NGSM Institute of Pharmaceutical sciences, Mangalore for providing laboratory facilities, authors are also thankful to the head RSIC, SAIF, Chandighar for spectral data.

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