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Synthesis, Antimicrobial and Antitubercular Activities of Some Novel Carboxamide Derivatives of 2-quinolones

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ABSTRACT

A series of novel substituted N-(3-acetyl-2-oxoquinolin-1(2*H*)-yl)benzamide (AJQC1-AJQC12) have been synthesized upon refluxing 3-acetyl-1-amino-quinolin-2-one and substituted benzoic acid in the presence of dry redistilled pyridine and silicon tetrachloride as coupling agent. 3-acetyl-1-amino-quinolin-2-one (AJQ1-AJQ12) were synthesized from substituted 3-acetyl coumarin upon refluxing with hydrazine hydrate and ethanol. The structures of the final carboxamide derivatives were confirmed by IR, ^{1}H NMR and mass spectra. The synthesized compounds were screened for their antimicrobial activity by tube dilution method and antitubercular activity by microplate Alamar blue assay. Most of the compounds have exhibited promising antibacterial, antifungal and antitubercular activities.

Key words: 2-Quinolones, carboxamide, antimicrobial activity, Minimum inhibitory concentration, antitubercular activity.

INTRODUCTION

2-Quinolones (carbostyrils or 1-aza coumarins) are isosteric with coumarins and isomeric to 4-quinolones could become the probable potential candidate for antibacterial activity[1]. 2-Quinolone derivatives were found to be associated with various biological activities such as antitumor[2], anti-inflammatory[3], antiplatelet, antitubercular[4], antioxidant[5] and antidepressant activity. Pyrazinamide is a nicotinamide analogue that has been used as a first-line drug to treat tuberculosis[6]. Various compounds possessing the –NHCO– group were found to inhibit photosynthetic electron transport[7]. Amides are usually stable, neutral and have both hydrogen-bond acceptor/donator properties which are very important for the synthesis of versatile heteroaromatic molecules. The amide functionality is the common backbone of numerous organic molecules and natural

products that bear diverse chemical and pharmacological features[8]. A series of quinoline carboxamide derivatives have also been evaluated for positive inotropic activity[9], as potential radio ligands in the neurodegeneration systems[10] and antiviral against acyclovir resistant herpes simplex virus[11]. By considering the above potent pharmacological properties of these quinoline ring containing compounds, it was contemplated to synthesize some novel 2-quinolone carboxamide derivatives. The final synthesized compounds were evaluated for their *in vitro* antimicrobial and antitubercular activities and compared with standard drugs.

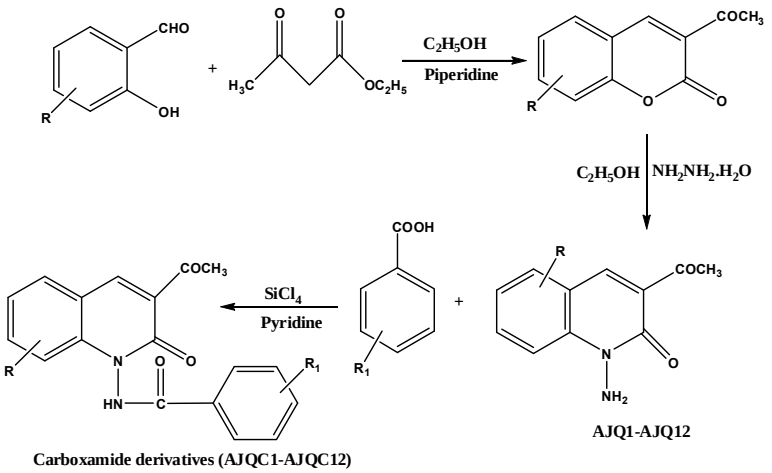
MATERIAL AND METHODS

All the chemicals were of analytical grade: substituted salicylaldehyde, ethylacetoacetate, absolute ethanol, piperidine, hydrazine hydrate, substituted benzoic acid, silicon tetrachloride and dry redistilled pyridine. Melting points were determined by open capillary method and are uncorrected. The purity of the compounds was monitored by thin layer chromatography (TLC) using silica gel G plates. The spots were visualized under UV light and by the exposure to iodine vapors. The homogeneity of the compounds were checked on silica gel-G coated plate by using Chloroform: Methanol (7:3) as solvent. All IR spectra were recorded in Alpha Bruker using ATR method. ^{1}H NMR spectra were recorded on Bruker spectrophotometer (400 MHz) in DMSO-d_6 solvent using tetra methyl silane (TMS) as an internal standard. Mass spectra was recorded by LCMS method.

General Procedure

Synthesis of substituted 3-acetyl-1-amino-quinolin-2-one (AJQ1-AJQ12) (12)

Substituted 3-acetyl coumarin (0.01 mol) with excess hydrazine hydrate 99% (0.1 mol) in 25 ml ethanol was refluxed for 12 hours. It was then cooled and poured into crushed ice with stirring. The solid product formed was filtered and recrystallised from ethanol.



R: H, 6-NO_2, 6-Cl

R_1: H, 2-Cl, 4-Cl, 2-OH, 4-$N(CH_3)_2$, 2 NH_2

Fig. 1: General Scheme of Synthesis

Synthesis of Substituted N-(3-acetyl-2-oxoquinolin-1(2*H*)-yl)benzamide (AJQC1-AJQC12) (13)

A mixture of substituted 3-acetyl-1-amino-quinolin-2-one (0.01 mol) and substituted benzoic acid (0.01 mol) was refluxed for 24 hours with stirring in 10 ml of dry redistilled pyridine and silicon tetrachloride as coupling reagent. After the completion of the reaction, the reaction mixture was poured into crushed ice. The precipitated solid was filtered, washed with cold water and recrystallised from ethanol.

Spectral data

3-acetyl-1-aminoquinolin-2(1*H*)-one (AJQ1)

IR (cm^{-1})

1506(Ar C=C str), 829 (Ar C-H bend), 2950(C-H aliphatic str), 1701 (C=O str), 3362, 3398 (N-H str).

^{1}H NMR

(400 MHz, DMSO-d_6): δ 7.25-8.27 (m, 5H, Ar-H), 3.73(s, 2H, NH_2), 2.59 (s, 3H, $COCH_3$).

Mass (m/z): 202 (M^+).

N-(3-acetyl-2-oxoquinolin-1(2*H*)-yl)benzamide (AJQC1)

IR (cm^{-1})

1511(Ar C=C str), 832 (Ar C-H bending), 3030 (Ar C-H str), 1696 (C=O str), 3160 (NH str 2°C amide).

^{1}H NMR

(400 MHz, DMSO-d_6) **:** δ 7.21-7.92 (m, 10H, Ar-H), 10.13 (s, 1H, -NHCO-), 2.59 (s, 3H, $COCH_3$).

Mass (m/z): 306 (M^+).

N-(3-acetyl-6-nitro-2-oxoquinolin-1(2*H*)-yl)-2-chlorobenzamide (AJQC7)

IR (cm^{-1})

1508(Ar C=C str), 836 (Ar C-H bending), 3028 (Ar C-H str), 1692 (C=O str), 3158 (NH str 2°C amide), 1356 (Ar-NO_2), 730 (C-Cl).

^{1}H NMR (400 MHz, DMSO-d_6) **:** ´7.12-7.87 (m, 8H, Ar-H), 10.24 (s, 1H, -NHCO-), 2.54 (s, 3H, $COCH_3$).

Mass (m/z): 386 (M+1).

N-(3-acetyl-6-chloro-2-oxoquinolin-1(2*H*)-yl)-2-aminobenzamide (AJQC12)

IR (cm^{-1})

1502(Ar C=C str), 830 (Ar C-H bending), 3032 (Ar C-H str), 1690 (C=O str), 3152 (NH str 2°C amide), 3360 (N-H str), 732 (C-Cl).

^{1}H NMR

(400 MHz, DMSO-d_6) **:** δ7.12-7.85 (m, 8H, Ar-H), 10.19 (s, 1H, -NHCO-), 3.72(s, 2H, NH_2), 2.52 (s, 3H, $COCH_3$).

Mass (m/z): 356 (M+1).

Antimicrobial Activity

All the synthesized compounds were evaluated for their minimum inhibitory concentration by tube dilution method (14). The synthesized test compounds were tested at different concentrations and ciprofloxacin and fluconazole was used as standard. Serial dilutions of the test compound was made in a liquid medium which was inoculated with a standardized number of organisms and incubated for 24 hrs. The lowest concentration of test compound preventing appearance of turbidity is considered to be the minimal inhibitory concentration (MIC). After preparation of different concentrations of the antimicrobial agent in brain heart infusion broth (by using the broth dilution method), we inoculate them with the tested organism. Then after incubation we can determine the MIC by choosing the lowest concentration in which no growth occurs.

Antitubercular activity

The antitubercular activity of test compounds were assessed against Mycobacterium tuberculosis using microplate Alamar blue assay[15]. This methodology is non toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method. 200 µl of sterile deionized water was added to all outer perimeter wells of sterile 96 well plate to minimised evaporation of medium in the test wells during incubation. The 96 well plate received 100 µl of the Middlebrook 7H9 broth and serial dilution of compounds were made directly on plate. The final drug concentrations of the tested compounds were 0.01 to 20.0 µl/ml. The plates were covered and sealed with parafilm and incubated at 37¿C for 5 days. After this, 25 µl of freshly prepared 1:1 mixture of Alamar blue reagent and 10% tween 80 was added to the plate and incubated for 24 hours. A blue color in the well was interpreted as no bacterial growth and pink color was interpreted as growth. The minimum inhibitory concentration was defined as lowest drug concentration which prevented the color change from blue to pink.

RESULTS AND DISCUSSION

Antimicrobial Activity

The final synthesized compounds (AJQC1-AJQC12) were screened for their minimum inhibitory concentration by tube dilution method. Compounds AJQC2, AJQC6, AJQC7 and AJQC12 showed significant antibacterial activity against gram +ve bacteria and compounds AJQC3, AJQC5 and AJQC11 showed significant antibacterial activity against gram -ve bacteria. Compounds AJQC1, AJQC4, AJQC6, AJQC9, AJQC10 and AJQC12 showed significant antifungal activity against *C.albicans* and compounds AJQC4, AJQC5, AJQC8, AJQC9, AJQC10 and AJQC12 showed significant antifungal activity against *A.niger*. The results of the minimum inhibitory concentration are summarized in Table 2.

Antitubercular Activity

The test compounds (AJQC1- AJQC12) were evaluated for their antitubercular activity against *M.tuberculosis* using Microplate Alamar Blue assay. A blue colour in the well was interpreted

Table 1: Physicochemical data of the compounds AJQC1-AJQC12

Comp.code	R	R_1	Mol.formula	Mol. wt	M.P °C	R_f Value	% Yield
AJQC1	H	H	$C_{18}H_{14}N_2O_3$	306	172-174	0.58	78
AJQC2	H	2-Cl	$C_{18}H_{13}ClN_2O_3$	340	180-182	0.70	72
AJQC3	H	4-Cl	$C_{18}H_{13}ClN_2O_3$	340	188-190	0.62	75
AJQC4	H	2-OH	$C_{18}H_{14}N_2O_4$	322	196-198	0.56	70
AJQC5	H	4-$N(CH_3)_2$	$C_{20}H_{19}N_3O_3$	349	184-186	0.68	73
AJQC6	H	2-NH_2	$C_{18}H_{15}N_3O_3$	321	206-208	0.60	76
AJQC7	6-NO_2	2-Cl	$C_{18}H_{12}ClN_3O_5$	385	190-192	0.74	62
AJQC8	6-NO_2	2-NH_2	$C_{18}H_{14}N_4O_5$	366	212-214	0.64	58
AJQC9	6-Cl	4-Cl	$C_{18}H_{12}Cl_2N_2O_3$	374	202-204	0.76	65
AJQC10	6-Cl	2-OH	$C_{18}H_{13}ClN_2O_4$	356	220-222	0.70	68
AJQC11	6-Cl	4-$N(CH_3)_2$	$C_{20}H_{18}ClN_3O_3$	383	208-210	0.68	60
AJQC12	6-Cl	2-NH_2	$C_{18}H_{14}ClN_3O_3$	355	226-228	0.72	66

Table 2: Minimum inhibitory concentration of the compounds (AJQC1-AJQC12) by tube dilution method

Comp Code	Minimum inhibitory concentration (µg)					
	B. subtilis	***S. aureus***	***E.coli***	***P. aeruginosa***	***C.albicans***	***A.niger***
AJQC1	3.2	12.5	1.6	25	12.5	100
AJQC2	1.6	1.6	R	R	25	R
AJQC3	100	R	1.6	1.6	R	R
AJQC4	50	50	25	50	12.5	3.2
AJQC5	25	R	6.25	0.8	50	6.25
AJQC6	3.2	1.6	6.25	50	1.6	100
AJQC7	3.2	6.25	25	12.5	R	100
AJQC8	3.2	50	12.5	0.8	50	3.2
AJQC9	100	50	50	100	3.2	6.25
AJQC10	12.5	1.6	100	100	6.25	6.25
AJQC11	25	50	6.25	1.6	100	100
AJQC12	3.2	1.6	25	12.5	6.25	3.2
Ciprofloxacin	1	2	2	1		
Fluconazole					16.6	8.3

as no bacterial growth and pink colour was scored as growth. Most of the test compounds AJQC4, AJQC5, AJQC6, AJQC8, AJQC10, AJQC11 and AJPY12 showed promising antitubercular activity compared to the standard drug streptomycin and isoniazid. The presence of 2-quinolone moiety with electron donating groups like methyl, hydroxy, amino and dimethylamino has accounted for their antitubercular activity. The results of the antitubercular activity are summarized in Table 2.

Table 3: Antitubercular activity of compounds (AJQC1-AJQC12) by Microplate Alamar blue assay

Comp.Code	R	R_1	MICin µg
AJQC1	H	H	50
AJQC2	H	2-Cl	25
AJQC3	H	4-Cl	25
AJQC4	H	2-OH	6.25
AJQC5	H	4-$N(CH_3)_2$	3.125
AJQC6	H	2-NH_2	6.25
AJQC7	6-NO_2	2-Cl	50
AJQC8	6-NO_2	2-NH_2	6.25
AJQC9	6-Cl	4-Cl	25
AJQC10	6-Cl	2-OH	3.125
AJQC11	6-Cl	4-$N(CH_3)_2$	12.5
AJQC12	6-Cl	2-NH_2	6.25
Standard	INH		0.2
	Streptomycin		6.25

CONCLUSION

This study reports the successful synthesis of carboxamide derivatives of 2-Quinolone moiety with moderate yields and most of the synthesized compounds showed potent antimicrobial and antitubercular activity.

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