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Research Article

SYNTHESIS OF 7- SUBSTITUTED-4-HYDROXYQUINOLIN-2(1H)-ONE FOR ANTI-BACTERIAL AND ANTI-FUNGAL ACTIVITY

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Abstract

The present work is carried out for the synthesis of 4-Hydroxy-1*H*-quinolin-2-ones derivatives with well established procedures. A new series of 4-Hydroxy-1*H*-quinolin-2-ones derivatives were synthesized and the structures of these compounds were confirmed by IR, HNMR and Mass Spectroscopy. The title compounds were screened for antibacterial activity and antifungal activity.

Keywords: 7- Substituted-4-hydroxyquinolin-2(1H)-one, IR, HNMR, Antibacterial and Antifungal activity.

Introduction

Many 4-hydroxy quinolone compounds are useful intermediates for biologically active substances [1-3] and many industrial products such dye stuffs [4, 5] and herbicides [6, 7]. Recent reports [8, 9] describe novel class of 4-hydroxy quinolone derivatives, i.e., 4-hydroxy-3-arylquinoline-2(1H)-one and 4-hydroxy-3-nitroquinoline-2(1H)-one as potent and selective N-methyl-D-aspartate (NMDA) receptor glycine site antagonist after oral administration. Many of these compounds have been derived from the 4-hydroxyquinoline-2(1H)-one nucleus. A variety of routes for the synthesis of 4-hydroxy quinolone compounds have been reported in the literature [10-15].

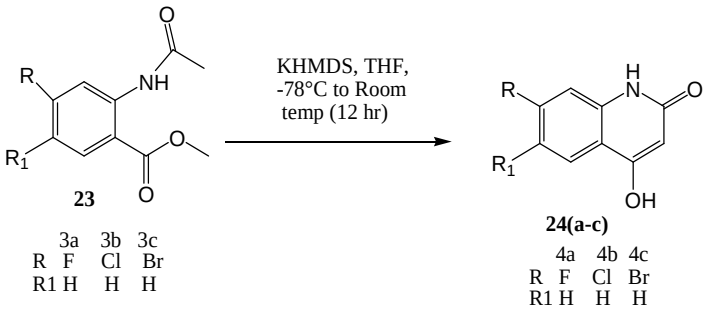
Materials and Methods

Synthesis of 7-fluoro-4-hydroxyquinolin-2(1H)-one:

To a solution of methyl 2-acetamido-4-fluorobenzoate (3.0 gm, 14.218 mmoles) in THF (40 mL) was added slowly Potassium bis (trimethylsilyl) amide (commonly abbreviated as KHMDS) (42.65 mL, 21.327 mmoles) (0.5 M solution in toluene) at -78°C. The reaction mixture was then allowed to room temperature and stirred at room temperature for 12 hours under nitrogen atmosphere. The reaction was monitored by TLC, after completion of reaction the reaction mixture was quenched with water (50 mL).The aqueous layer was washed with

Ethyl acetate (50 mL), separate the layers, taken aqueous layer and cooled to 10°C and slowly pH adjusted 2.5 -3.5 with 5N HCl, to give a white solid, which was collected by filtration and dried in vacuum to give 7-fluoro-4-hydroxyquinolin-2(1H)-one **as** a white solid (Figure-1).

Figure: 1 Synthesis of 7- Substituted-4-hydroxyquinolin-2(1H)-ones from Methyl 2-acetamido-4- substituted benzoates.



	3a	3b	3c
R	F	Cl	Br
R1	H	H	H

	4a	4b	4c
R	F	Cl	Br
R1	H	H	H

3a methyl 2-acetamido-4-fluorobenzoate, 3b methyl 2-acetamido-4-chlorobenzoate 3c methyl 2-acetamido-4-bromobenzoate, 4a 7-fluoro-4-hydroxyquinolin-2(1H)-one 4b 7-chloro-4-hydroxyquinolin-2(1H)-one, 4c 7-bromo-4-hydroxyquinolin-2(1H)-one

Synthesis of 7-chloro-4-hydroxyquinolin-2(1H)-one and Synthesis of 7-bromo-4-Hydroxyquinolin-2(1H)-one:

According to the same procedure (Synthesis of 7-fluoro-4-hydroxyquinolin 2(1H)-one) 7-chloro-4-hydroxyquinolin-2(1H)-one Compound was obtained from methyl 2-acetamido-4-chlorobenzoate 75% yield, White solid, 7-bromo-4-hydroxyquinolin-2(1H)-one Compound was obtained 76% yield from methyl 2-acetamido-4-bromobenzoate, White solid.

Anti bacterial activity:

The antibacterial activity of synthesized compounds was studied by the disc diffusion method against the following pathogenic organisms. The gram-positive bacterial screened were Bacillus subtilis ATCC 6633 and gram negative bacterial screened were Escherichia coli ATCC. The synthesized compounds were used at the concentration of 50µg, 100µg and 150µg using DMSO as a solvent. The Streptomycin sulphates were used as a standard. (Raghavendra Institute of pharmaceutical Education and Research (RIPER) Anantapur, Andhra pradesh).

Anti fungal activity:

The antifungal activities of synthesized compounds were studied by disc diffusion method against the organisms of Aspergillus Niger MTCC F2723. Compounds were treated at the concentrations of 50 µg/ml, 100

μg/ml and 150 μg/ml using DMSO as a solvent. The standard used was Amphotericin 50 μg/ml against both the organisms.

Results and Discussion

Characterization of 7-fluoro-4-hydroxyquinolin-2(1H)-one:

From the above scheme, synthesis of 7-fluoro-4-hydroxyquinolin-2(1H)-one **was** characterized by 1H NMR and Mass. Yield = 2.0 gm, (78.53 %), melting Point = 290-291.5°C and HPLC purity = 98.80 %. Thus, its IR (in KBr) showed a strong peak at 3604 cm^{-1} due to -OH grouping, 1686 cm^{-1} due to –NH-C=O grouping and 1630 cm^{-1} due to –C=O grouping. Its ^{1}H NMR (DMSO-d6/TMS): δ 5.70-5.80 (s, 1H), 7.20-7.25 (d, 1H), 7.40-7.50 (s, 1H), 7.70-7.80 (d, 1H), 11.10-11.20 (s, 1H), 11.40-11.45 (s, 1H) and its ESI mass spectrum showed molecular ion peak at 180.22 (M^{+}+1) corresponding to the molecular mass of179.34 (M^{+}).

Characterization of 7-chloro-4-hydroxyquinolin-2(1H)-one:

Synthesis of 7-chloro-4-hydroxyquinolin-2(1H)-one was characterized by 1H NMR and Mass. Melting Point = 300-301°C and HPLC purity = 98.10 %. Thus, its IR (in KBr) showed a strong peak at 3604 cm^{-1} due to -OH grouping, 1686 cm^{-1} due to –NH-C=O grouping and 1630 cm^{-1} due to –C=O grouping. Its ^{1}H NMR (DMSO-d6/TMS): δ 5.72-5.82 (s, 1H), 7.25-7.35 (d, 1H), 7.45-7.55 (s, 1H), 7.75-7.85 (d, 1H), 11.0-11.10 (s, 1H), 11.20-11.30 (s, 1H) and its ESI mass spectrum showed molecular ion peak at 196.12 (M^{+}+1) corresponding to the molecular mass of 195.14 (M^{+}).

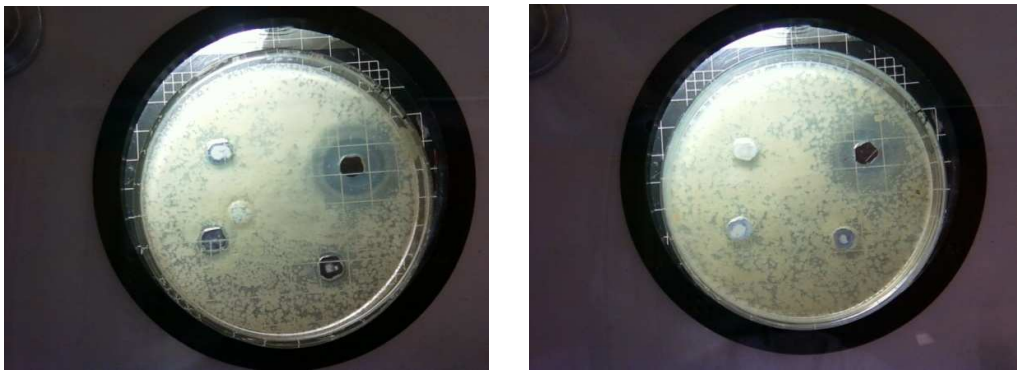
Characterization of 7-bromo-4-hydroxyquinolin-2(1H)-one:

Synthesis of 7-bromo-4-hydroxyquinolin-2(1H)-one was characterized by 1H NMR and Mass. Melting Point = 320-321°C and HPLC purity = 98.10 %. Thus, its IR (in KBr) showed a strong peak at 3604 cm^{-1} due to -OH grouping, 1686 cm^{-1} due to –NH-C=O grouping and 1630 cm^{-1} due to –C=O grouping. Its ^{1}H NMR (DMSO-d6/TMS): δ 5.75-5.82 (s, 1H), 7.35-7.37 (d, 1H), 7.46-7.57 (s, 1H), 7.78-7.90 (d, 1H), 11.1-11.20 (s, 1H), 11.25-11.35 (s, 1H) and its ESI mass spectrum showed molecular ion peak at 239.9 (M^{+}+1) corresponding to the molecular mass of 239.0 (M^{+}).

Anti bacterial and Anti fungal activity:

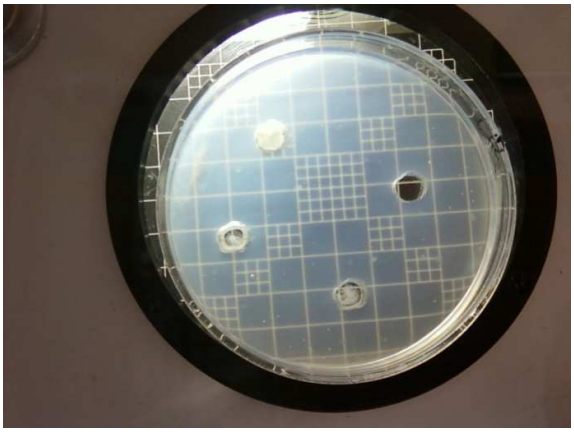
All the synthesized compounds were screened of antimicrobial studies against antibacterial and antifungal activity by disc diffusion method and MIC by serial dilution method. All the synthesized compounds were subjected to preliminary antibacterial screening by disc diffusion method against Bacillus subtilis ATCC 6633 (gram positive) and Escherichia coli ATCC 11229 (gram negative). In this, Substituted-4-hydroxyquinolin-2(1H)-one **4a-c** series did not showed antibacterial activity against all tested organism Escherichia coli ATCC 11229 (gram negative) at the concentration of 50 µg/ml, 100 µg/ml and 150 µg/ml solutions (Table 1) (Figure. 2). In this Substituted-4-hydroxyquinolin-2(1H)-one **4a-c** series did not showed antifungal activity against all tested organism Aspergillus Niger MTCC F2723 at the concentration of 50 µg/ml, 100 µg/ml and 150 µg/ml solutions. (Table-2)(Figure-3).

Figure 2: Antibacterial activity by disc diffusion method.



4a, 4b and 4c Bacillus **4a, 4b and 4c Escherichia**

Figure 3: Antifungal activity by disc diffusion method.



4a, 4b and 4c Aspergillus

Table-1: Antibacterial activity by disc diffusion method for 7- Substituted-4-hydroxyquinolin-2(1H)-one 4a-c:

S.No	Comp	R	R1	Zone of inhibition (mm)					
				1.Bacillus subtilis			2. Escherichia coli		
				50µg	100µg	150µg	50µg	100µg	150µg
1	4a	F	H	3mm	5mm	6mm	NS	NS	NS
2	4b	Cl	H	3mm	4mm	5mm	NS	NS	NS
3	4c	Br	H	3mm	5mm	6mm	NS	NS	NS

Zone of inhibition for standard samples: Bacillus subtilis (11mm) and Escherichia coli (10mm).

Abbreviation: NS= Not significant.

Table-2: Antifungal activity by disc diffusion method for 7- Substituted-4-hydroxyquinolin-2(1H)-one 4a-c:

S.No	Compd	R	R1	Zone of inhibition (mm)		
				Aspergillus Niger		
				50µg	100µg	150µg
1	4a	F	H	NS	NS	NS
2	4b	Cl	H	NS	NS	NS
3	4c	Br	H	NS	NS	NS

Zone of inhibition for standard samples: Aspergillus Niger (08mm).

Abbreviation: NS= Not significant

Conclusion:

We have synthesized some novel 4-Hydroxy-1*H*-quinolin-2-ones derivatives. The newly synthesized 4-Hydroxy-1*H*-quinolin-2-ones derivatives are characterized by spectral data and further evaluated for antimicrobial activity. All compounds show moderate to good activity.

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