Antimicrobial and Antifungal Activity of Newly Synthesized 4-Hydroxy Quinoline Derivatives

Mukesh Sharma[1]*, Rakesh Goyal[1], Dharmendra Ahuja[2], Ashok Sharma[3], Shankar Lal Soni[3],

Research Scholar, Department of Pharmaceutical Sciences, Jayoti vidyapeeth women's University, Mahla- Jobner Link Road, Jharna, Jaipur, Rajasthan 303122
Professor, Department of Pharmaceutical Sciences, Jayoti Vidyapeeth Women's University, Jaipur
Research Scholar, Department of Pharmaceutical Sciences, BN University, Udaipur, India

Address for correspondence
Mr. Mukesh Sharma
A Bhairav Nager, ESIC Hospital Road,
Sodala, Jaipur(Raj.)
Pin – 302006
Email Id – mukesharya9829@gmail.com

Abstract

The synthesis of 4- Hydroxy quinolin-2-one derivatives by three deferent synthetic pathways and the formyl substitution on the 3 rd position one heterocyclic quinoline ring. The Schiff base reaction reacts with 4-Hydroxy-3-formylquinolin-2-one and form twelve different derivatives by using four different hydrazine derivatives. These derivative show satisfactory antimicrobial and anti fungal activity. The newly synthesized compounds were screened for their antibacterial activity against B. subtilis, S. aureus, E.coli and K. pneumonia by cup plate method. A control was also prepared for the plates in the using solvent DMSO. Activity of each compound was compared with ciprofloxacin as standard. The newly synthesized compounds were also screened for their antibacterial activity against A. nige and C. albicans by cup plate method. A control was also prepared for the plates in the using solvent DMSO. Activity of each compound was compared with Griseofulvin as standard. The investigation of antibacterial and antifungal screening data revealed that all the tested compounds and showed moderate to good inhibition at 50-100 µg/ml in DMSO. The compound P1-a, P1-b, P2-a, P2-b, P3-a and P3-c showed comparatively very good activity against all the bacterial strains. The good activity is attributed to the presence of pharmacologically active phenyl hydrazones and semicarbazone on position 3 on quinoline ring. Presence of phenyl group on the position-1 also increases the antimicrobial activity. A new series of Substituted 4-Hydroxy quinoline-2-one derivatives have been synthesized. The research study reports the successful synthesis and antimicrobial activity of new 4-Hydroxy-3-substituted-1-H/Methyl/Phenylquinolin-2-one carrying biologically active groups. Their antimicrobial activity study revealed that all the compounds tested showed moderate to very good antibacterial and antifungal activities against pathogenic strains.

***Key Word**: 4-Hydroxy Quinoline, Hydrazones, Antimicrobial activity, Antibacterial*

INTRODUCTION

Quinoline is the bicyclical compound, which give a verity of pharmacological activity. The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties. Quinine was isolated as the active ingredient from the bark of Cinchona trees and successively replaced the crude bark for the malaria therapy. Despite its relatively low efficacy and

chemical tolerability, 4- hydroxyquinine still plays an important role in the treatment of multi resistant malaria.

The 4-Hydroxy-3-substitutedquinolin-2-ones and the derivatives show antihypertensive and anti-viral activity. 4- Hydroxy Quinoline compounds are also play an important part as intermediates in formation of many useful derivatives. in the present work 4- Hydroxy quinoline derivatives are prepared by three different pathway and then they react with hydrazones by the Schiff base reaction and form novel derivatives.

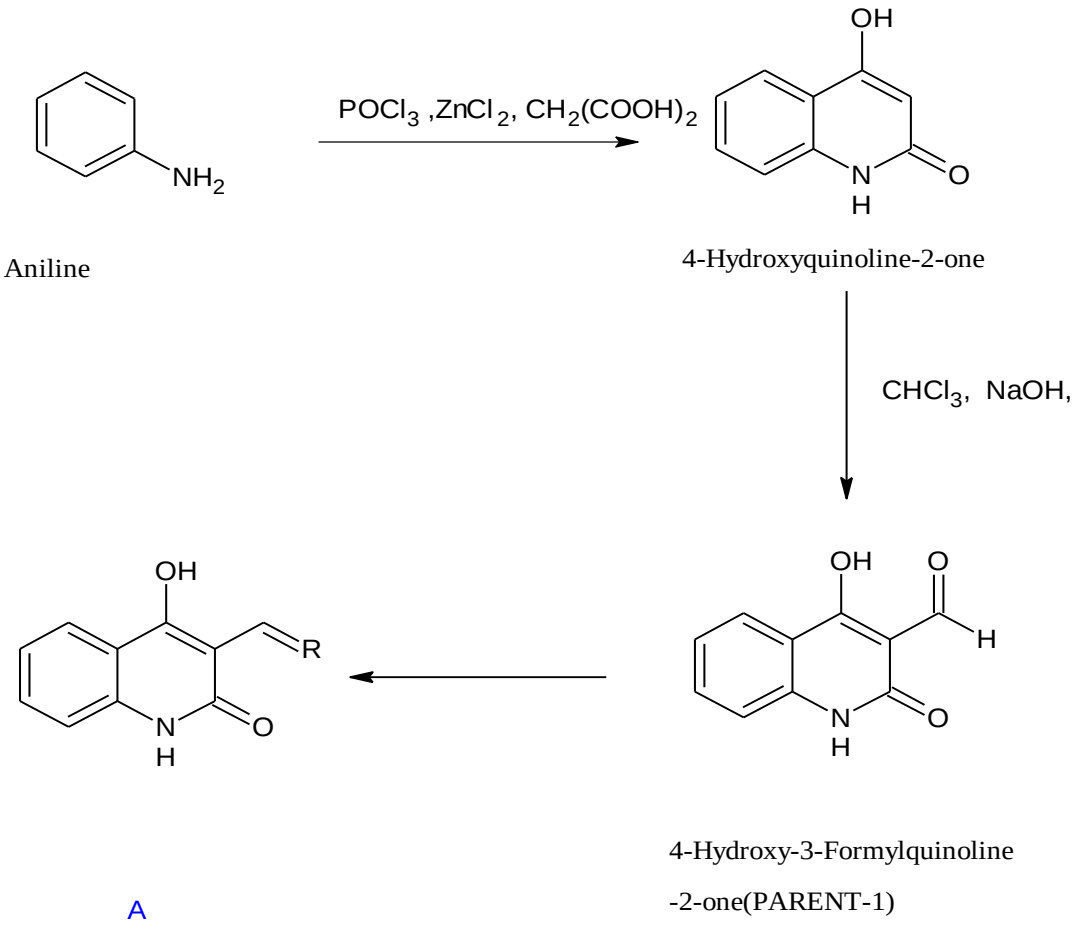
MATERIAL AND METHODS

Experimental methods

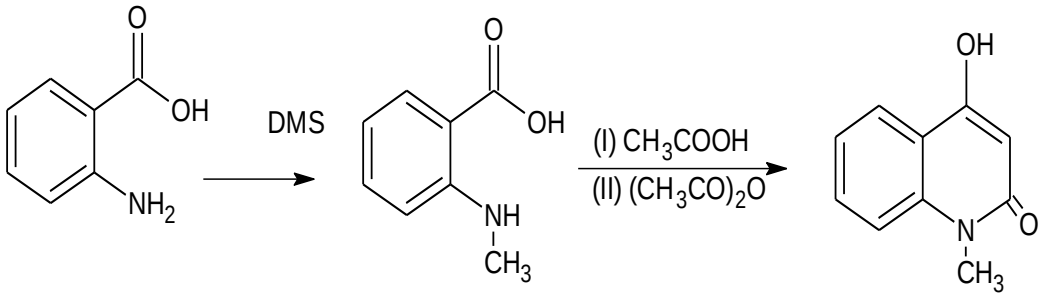
The all-raw chemicals were purchased from merck and loba chemicals. Electronic spectra specta were recorded on Shimadzu UV spectrophotometer. IR spectra were recorded in KBr pellets in the affinity Shimadzu spectrophotometer and ^1H NMR in $CDCl_3$ on Hitachi R-1500, 60 MHz spectrophotometer by using TMS as reference standard

METHOD

I. SCHEME (PARENT -1)



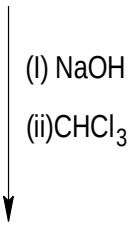
II. SCHEME – (PARENT-2)

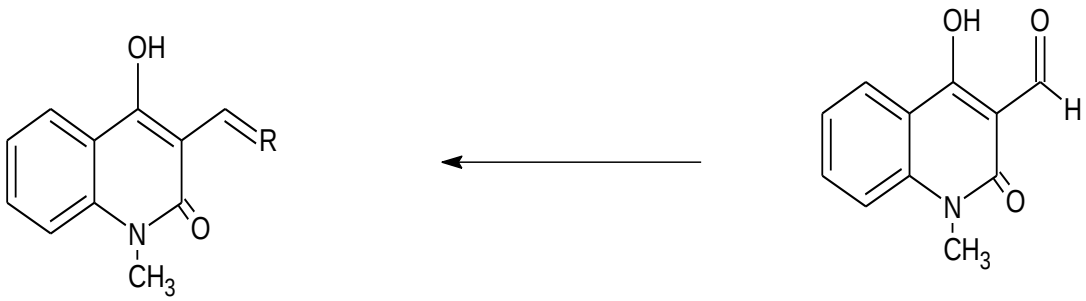


Anthranilic acid

N-Methylanthranilic acid

4-Hydroxy-1-Methylquinoline -2-one

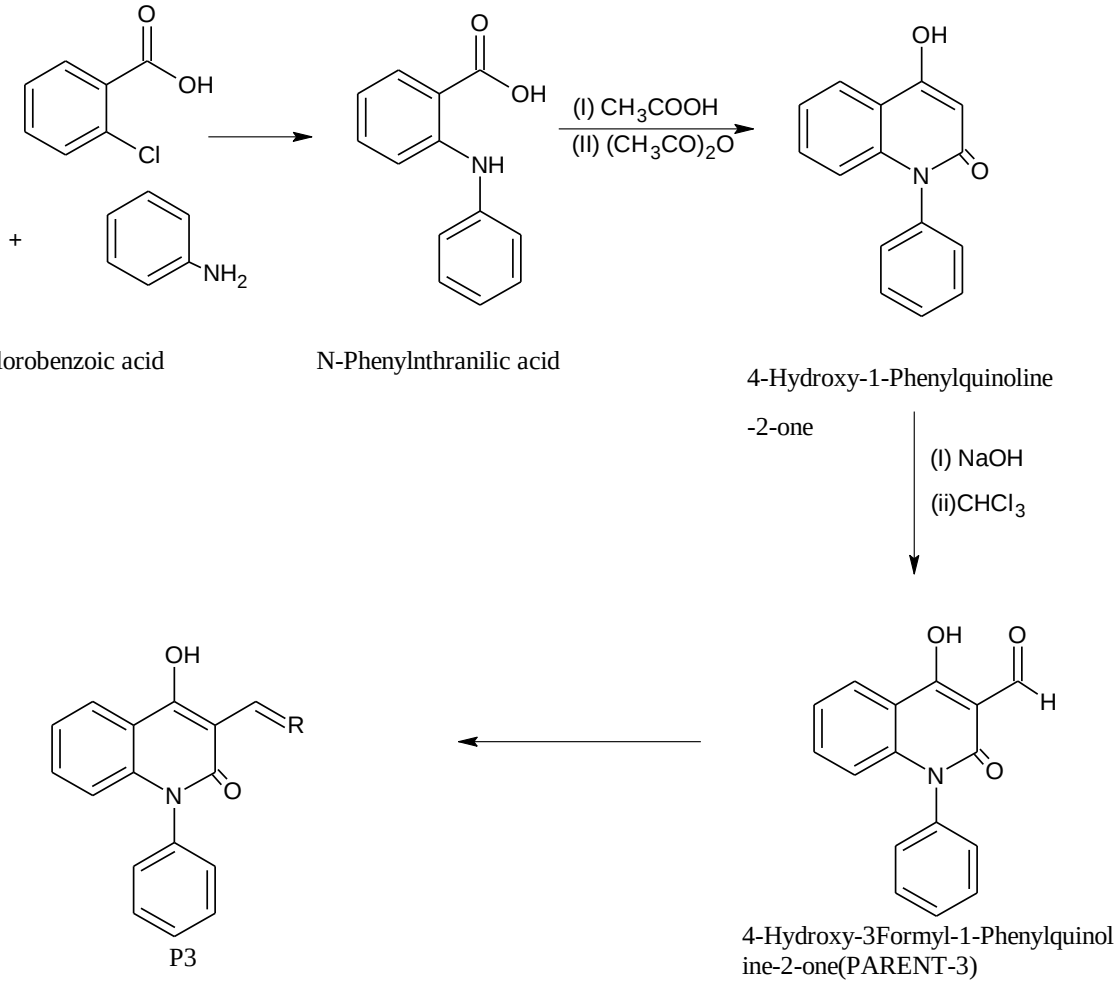




P2

4-Hydroxy-3Formyl-1-Methylquino line-2-one(PARENT-2)

III. SCHEME -3 (PARENT-3)



O-Chlorobenzoic acid

N-Phenylnthranilic acid

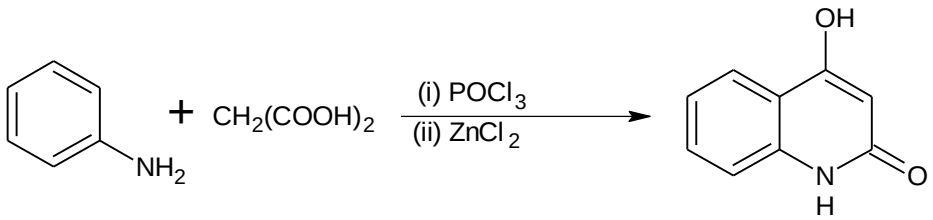
4-Hydroxy-1-Phenylquinoline -2-one

4-Hydroxy-3Formyl-1-Phenylquinol ine-2-one(PARENT-3)

P3

A. TO SYNTHESIZE 4-HYDROXY-3-FORMYLQUINOLIN-2-ONE (PARENT-1).

SYNTHESIS OF-4-HYDROXY QUINOLOIN-2-ONE



aniline

4- Hydroxyquinoline-2-one

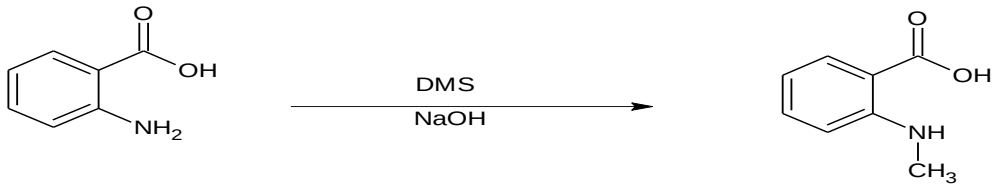
Procedure: -

A mixture of aniline 18.6g (0.2 Mole) and malonic acid 20.8g (0.2 Mole) acid was heated at 100˚c for 1hr. with phosphoryl chloride 92g (0.6 Mole) and anhydrous zinc chloride 54.6g (0.4Mole) .The reaction product was decomposed with ice and water, the resulting solid was filtered and washed with water. The solid was treated with 10% sodium hydroxide solution. Filtered and the filtrate on acidification with hydrochloric acid gave 4-hydroxy quinoline-2-one. Crystallization from methanol containing a small amount of hydrochloric acid.

Yeild 82%, m.p. >300, H^1NMR (DMSO-d_6): δ 5.77 (s, 1H, =CH-),7.00-7.64 (m, 3H, Ar- H), 7.75 (d, 1H, Ar-H, *J* = 7.81 Hz), 10.37 (s 1H, -NH), 10.59 (br s, 1H, -OH); IR(KBr): 3410 (O-H), 2914 (C-H), 1670 (C=O), 1620 cm^{-1}(C=C), R*f* 0.75

A. TO SYNTHESIZE 4-HYDROXY-3-FORMYL-1-METHYLQUINOLIN-2-ONE (PARENT-2).

(a)*N*-METHYL ANTHRANILIC ACID



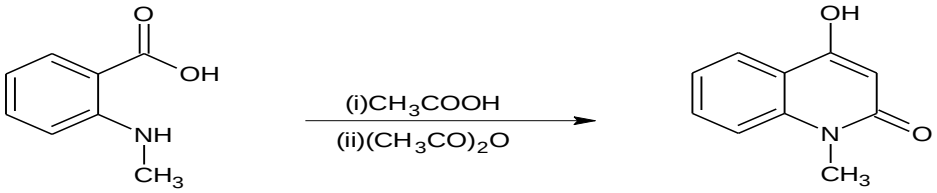
Anthranilic acid N-Methyl Anthranilic acid

Procedure: -

Dissolve 45g .of anthranilic acid in 117ml.of 5% aqueous sodium hydroxide, in conical flask. Add 14.4ml of dimethyl sulphate, and shake the securely stoppered flask vigorously. The N-methylanthranilic acid rapidly separates. Cool the mixture in ice-water, filter off thr acid at the pump, and wash thoroughly with water and drain. The crude acid now and dried weight yield- 31.5g.

Yield 63.52 , m.p. 186-89, H^1NMR ($CDCl_3$): δ 3.65 (s, 3H, -NH-CH_3) 6 .83 (d, 2H, Ar- H, *J* =7.5), 7.62 (t, 1H, Ar-H, J=7.81 Hz),-8.10 (d, 1H, Ar-H, *J* = 7.3 Hz), 9.10 (br s 2H, COOH and NH- CH_3); IR (KBr): 3381 (N-H), 2970 (Ar-H), 1673 (C=O), 1581 cm^{-1}(C=C), R*f* 0.64

b. SYNTHESIS OF-4-HYDROXY-1-METHYL QUINOLOIN-2-ONE



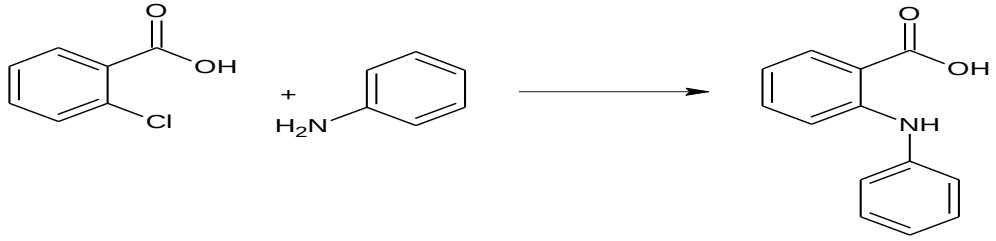
N-Methylanthranilic acid N-Methyl-4-Hydroxyquinoline -2-one(p-2)

Procedure:-*N*-Methyl anthranilic acid 20.5 g (0.15 mole) was dissolved in of 75 ml acetic acid and of 75 ml acetic anhydride was added. This was heated at 120˚c for 6 hr and poured into ice. After basification with sodium hydroxide, the residue was filtered and the filtrate was taken and acidified with hydrochloric acid and cooled. The solid precipitate was filtered and washed with benzene. The compound showed a single spot in TLC, no column chromatography employed for purification.

Yield, m.p. >300, H^1NMR (DMSO-d_6): δ 5.77 (s, 1H, =CH-),7.00-7.64 (m, 3H, Ar- H), 7.75 (d, 1H, Ar-H, *J* = 7.81 Hz), 10.37 (s 1H, -NH), 10.59 (br s, 1H, -OH); IR(KBr): 3410 (O-H), 2914 (C-H), 1670 (C=O), 1620 cm^{-1}(C=C)

A.TO SYNTHESIZE 4-HYDROXY-3-FORMYL-1-PHYNYLQUINOLIN-2-ONE (PARENT-3).

(a)*N*-PHENYL ANTHRANILC ACID



o-Chlorobenzoic acid Aniline N-Phenylanthranilic acid

Procedure:-

15.6 g(0.1 mole) of *ortho* chlorobenzoic acid 9.3 g (0.1 mole) of aniline , 13.8 g (0.1 mole) of potassium carbonate and 0.5 g (0.006) of cupric oxide were dissolved in 100ml of *N*,*N*-dimethyl formamide. The reaction-mixture was heated at 80˚C on water bath for 6 hr. After completion of the reaction, thr contents were poured into ice-cold water and the unreacted aniline was removed under steam distillation and the residual solution contained potassium *N*-phenyl anthranilic acid. Residual solution was extracted with ether and the aqueous layer was acidified with dilute hydrochloric acid. On cooling the solution precipitate of *N*-phenyl anthranilic acid was obtained. It was filtered, washed with water, dried and recrystallized from ethanol.

Yield16.8g (78%) , m.p. 182-85, H^1NMR ($CDCl_3$): δ 4.78(br s, 1 H, NH)6 .73 (dd, 1 H, Ar- H, J_1 =7.2 Hz and J_2 =7.7 Hz), 7.22-7.55(m, 7H, Ar-H), 7.93 (d, 1 H, Ar-H, *J* = 8.3 Hz), 9.21(br s 1H, COOH); Ir (KBr): 3379 (N-H), 3005 (Ar-H), 1669 (C=O), 1593 cm^{-1}(C=C)

(b) SYNTHESIS OF 4-HYDROXY-3-FORMYL-1H/METHYL/PHENYL QUINOLOIN-2-ONE

Procedure: Sodium hydroxide (80 ml of 15%) was charged with 0.0124 mole of 4-hydroxyquinoline-2-one and was cooled to 4˚c and stirred. Subsequently the temperature inside the flask was maintained at 80˚c on a water-bath. At 80˚c, 40 ml (0.5 mole) of chloroform was introduced in three portions at intervals of fifteen minutes down the condenser on hot water-bath. Stirring was continued for 12 hr, and the reaction-mixture was cooled to RT. The orange coloured liquid was acidified with dilute sulphuric acid. It was extracted with ethyl acetate and dried with anhydrous sodium sulphate. Ethyl acetate was removed under vacuum and the solid obtained was purified by column chromatography in hexane, ethyl acetate (7:3) mixture. Yield 39%, m.p. 178-180.

TO SYNTHESIZE 3-SUBSTITUTED DERIVATIVES OF PARENT 1, 2 & 3

Dissolve 0.5g of colorless phenyl hydrazine hydrochloride/ semicarbazide hydrochloride/ hydroxylamine hydrochloride/ hydrazine sulphate and 0.8g of sodium acetate in 5ml of water , add a solution of 0.2-0.4g of P1/P2/P3 in the in a little ethanol. Shake the mixture until a clear solution is obtained and add a little more ethanol, if necessary warm on a water bath for 10-15 minutes and cool. Filter off the crystalline derivatives, and recrystallise them from dilute ethanol or water.

(P1-a) 4-hydroxy-3-[(*E*)-(2-phenylhydrazinylidene)methyl]quinolin-2(1*H*)-one.

Yield 74.46 %, H^1 NMR ($CDCl_3$): δ 6.71 (s, 1H, -NH-), 7.20-7.62 Ar-H 8.20 (s, 1H, -OH) 9.00, IR (KBr): 3462(O-H),1701(C=O),1566(C=N), 1558(C=C) UV($CHCl_3$) λ max 374, R*f* 0.73

(P1-b) (2*E*)-2-[(4-hydroxy-2-oxo-1,2-dihydroquinolin-3- yl) methylidene] hydrazinecarboxamide.

Yield 69.23%, H^1 NMR ($CDCl_3$): δ 6.21 (s, 1H, -NH-), 6.8 Ar-H 7.20 (s, 1H, -OH) 9.10 , IR (KBr): 3446(O-H),1649(C=O),1601(C=N), 1580(C=C) UV($CHCl_3$) λ max 380, R*f* 0.64

(P1-c)4-hydroxy-3-[(*E*)-(hydroxyimino)methyl]quinolin-2(1*H*)-one.

Yeild 67%, H^1 NMR ($CDCl_3$): δ 6.71 (s, 1H, -NH-), 7.20-7.62 Ar-H 8.20 (s, 1H, -OH) 9.00, IR (KBr): 3462(O-H),1701(C=O),1566(C=N), 1558(C=C) UV($CHCl_3$) λ max 374, R*f* 0.55

(P1-d)3-[(*E*)-hydrazinylidenemethyl]-4-hydroxyquinolin-2(1*H*)-one.

Yield 75%, H^1 NMR ($CDCl_3$): δ 6.71 (s, 1H, -NH-), 7.20-7.62 Ar-H 8.20 (s, 1H, -OH) 9.00 , IR (KBr): 3462(O-H),1701(C=O),1566(C=N), 1558(C=C) UV($CHCl_3$) λ max 374, R*f* 0.57

(P2-a) 4-hydroxy-1-methyl-3-[(*E*)-(2-phenylhydrazinylidene)methyl]quinolin-2(1*H*)-one.

Yield 83%, H^1 NMR ($CDCl_3$): δ 6.71 (s, 1H, -NH-), 7.20-7.62 Ar-H 8.20 (s, 1H, -OH) 9.00 , IR (KBr): 3410(O-H),1668(C=O),1634(C=N), 1602(C=C), 2906(C-H), UV($CHCl_3$) λ max 374, R*f* 0.62

(P2-b) (2*E*)-2-[(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3- yl) methylidene] hydrazinecarboxamide.

Yield 84%, H^1 NMR ($CDCl_3$): δ 6.71 (s, 1H, -NH-), 7.20-7.62 Ar-H 8.20 (s, 1H, -OH) 9.00 , IR (KBr): 3458(O-H),1627(C=O),1603(C=N), 1597(C=C), 2922(C-H), UV($CHCl_3$) λ max 374, R*f* 0.54

(P2-c) 4-hydroxy-3-[(*E*)-(hydroxyimino) methyl]-1-methylquinolin-2(1*H*)-one.

Yield 76 %, H^1 NMR ($CDCl_3$): δ 6.71 (s, 1H, -NH-), 7.20-7.62 Ar-H 8.20 (s, 1H, -OH) 9.00 , IR (KBr): 3442(O-H),1647(C=O),1635(C=N), 1595(C=C), 2922(C-H), UV($CHCl_3$) λ max 374, R*f* 0.73

(P2-d) 3-[(*E*)-hydrazinylidenemethyl]-4-hydroxy-1-methylquinolin-2(1*H*)-one.

Yield 78%, H^1 NMR ($CDCl_3$): δ 6.71 (s, 1H, -NH-), 7.20-7.62 Ar-H 8.20 (s, 1H, -OH) 9.00 , IR (KBr): 3442 (O-H),1639(C=O),1597(C=N), 1558(C=C) UV($CHCl_3$) λ max 374, R*f* 0.66

(P3-a)4-hydroxy-1-phenyl-3-[(*E*)-(2-phenylhydrazinylidene)methyl]quinolin-2(1*H*)-one.

Yield 85%, H^1 NMR ($CDCl_3$): δ 6.71 (s, 1H, -NH-), 7.20-7.62 Ar-H 8.20 (s, 1H, -OH) 9.00 , IR (KBr): 3437(O-H),1668(C=O),1535(C=N), 1604(C=C), 2924(C-H), UV($CHCl_3$) λ max 374, R*f* 0.63

(P3-b) (2*E*)-2-[(4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)methylidene] hydrazinecarboxamide

Yield 80 %, H^1 NMR ($CDCl_3$): δ 6.71 (s, 1H, -NH-), 7.20-7.62 Ar-H 8.20 (s, 1H, -OH) 9.00 , IR (KBr): 3410(O-H),1648(C=O),1620(C=N), 1598(C=C), 2926(C-H), UV($CHCl_3$) λ max 374, R*f* 0.64

(P3-c) 4-hydroxy-3-[(*E*)-(hydroxyimino)methyl]-1-phenylquinolin-2(1*H*)-one

Yield 83%, H^1 NMR ($CDCl_3$): δ 6.71 (s, 1H, -NH-), 7.20-7.62 Ar-H 8.20 (s, 1H, -OH) 9.00 , IR (KBr): 3430(O-H),1658(C=O),1610(C=N), 1598(C=C), 2930(C-H) UV($CHCl_3$) λ max 374, R*f* 0.74

(P3-d) 3-[(*E*)-hydrazinylidenemethyl]-4-hydroxy-1-phenylquinolin-2(1*H*)-one

Yield 80%, H^1 NMR ($CDCl_3$): δ 6.71 (s, 1H, -NH-), 7.20-7.62 Ar-H 8.20 (s, 1H, -OH) 9.00 , IR (KBr): 3420(O-H),1648(C=O),1590(C=N), 1560(C=C), 2945(C-H), UV ($CHCl_3$) λ max 374, R*f* 0.62

PHARMACOLOGICAL SCREENING

1. Antibacterial activity

Method: Cup-plate agar well diffusion method using Mueller-Hinton Agar.

One day prior to these testings, inoculation of the above bacterial cultures were made in the nutrient agar and incubated at 37^0C for 18-24 hr.

The agar was dissolved into distilled water and the pH was adjusted to 7.4±0.2. It was sterilized by autoclaving at 15 p.s.i. for 20 min.

Each test compound (5mg) was dissolved in dimethylformamide 95ml to give stock solution of concentration 1000 μg/ml. Then 0.10 ml and 0.15 ml of this solution was used for testing.

Standard drug Ciprofloxacin was used at two concentrations i.e. 5 mcg.

Method of testing:

Mueller-Hinton Agar plates were prepared by pouring 10-15 ml of the medium into each sterilized Petri dish and were allowed to set at room temperature. The cell suspension was standardized to the density of 530 nm using spectrophotometer and was inoculated over the surface of agar medium using sterile cotton swab. The three cups were scooped in each plate using a sterile cork borer of 8 mm diameter.

Then the solution of test compounds (0.10 ml/0.15ml) were added in cups by using micropipettes and these plates were incubated at 37^0C for 48 hr. The zone of inhibition was measured in mm for each organism.

Procedure for antibacterial assay:

Laminar airflow bench was swapped with 70% alcohol and UV was switched on. After 30 min the UV was switched off. All the reagents, media, inoculum, stock solutions and glass

wares were transferred to laminar airflow bench taking all aseptic conditions. The stock solution of ethanolic extract and standard drug were further diluted with distilled water to obtain the drug dilution. The sterilized nutrient agar medium was poured directly into the Petri dish. The Petri dishes were suitably marked for name of organism, name of plate and drug concentration. When the nutrient agar of each Petri dish was solidified, 0.1ml of inoculum was added on the surface of the agar media using sterile pipette. The inoculums was spread on the surface of the agar media using sterile "L" shaped glass rod. After this, four wells were prepared on the surface of the agar media using cork borer. Two wells were filled by same concentration of drug and after the diffusion of drug the plates were incubated at 37ºC for 24 hrs. Simultaneously negative control (medium without drug and without inoculums) and positive control (medium without drug but with inoculum) were prepared and kept in incubator at 37ºC for 24 hrs.

2. Antifungal activity

Antifungal screening method

All the Petri dishes were sterilized in oven at 160°C for I hour. Agar media, Filter paper discs and test solutions were sterilized in autoclave at 121°C 16l bs/square inches .Pouring the molten sterile agar in sterile Petri dishes asceptically. Allow to cool the agar at RT and pouring the bacterial suspension on the petri dishes asceptically.

RESULTS AND DISCUSSION

CHEMISTRY

A series of 4-Hydroxy-3-subsituted-1H/methyl/Phenylquinolin-2-one derivatives were prepared by using Quinoline as basic moiety. The Identify of compounds was confirmed on the basis of their chemical tests and spectral data.

In all the cases the TLC of the product showed the single spot confirming the chromatogram for only one product.

BIOLOGICAL ACTIVITIES

Antimicrobial Activity

The newly synthesized compounds were screened for their antibacterial activity against *B. subtilis, S. aureus, E.coli and K. pneumonia* by cup plate method. A control was also prepared for the plates in the using solvent DMSO. Activity of each compound was compared with ciprofloxacin as standard. Zone of inhibition was determined for all compound and the results are summarized in Table

COMPOUND	CONCENTRATION	ZONE OF INHIBITION(mm)			
	µg/ml.	***B. subtilis***	***S. aureus***	***E.coli***	***K. pneumonia***
P1-a	50	10	8	10.5	9
	100	12	10	13	10
P1-b	50	-	9	10	11
	100	8	11	12	13
P1-c	50	7	-	8	-
	100	10	9	10	8
P1-d	50	9	7	-	7
	100	11	9	8	9
P2-a	50	9.5	10	9	10
	100	11	13.5	11	12.5
P2-b	50	8.5	10	11	9.5
	100	11	14.5	14	13
P2-c	50	7.5	8	-	7
	100	11	10.5	-	10
P2-d	50	10.5	8.5	11	-
	100	13	11	13.5	9
P3-a	50	10	9	11	10
	100	13.5	11	14.5	13
P3-b	50	8	-	-	9
	100	11	10	9	11.5
P3-c	50	11	9.5	10	11
	100	14.5	12	13	13.4
P3-d	50	-	-	10	8
	100	8	9	12	10
DMF (control)	----	----	----	----	----

Ciprofloxacin (std.)	22	20	18	23	18

Antifungal Activity

The newly synthesized compounds were screened for their antibacterial activity against *A. nige and C. albicans* by cup plate method. A control was also prepared for the plates in the using solvent DMSO. Activity of each compound was compared with Griseofulvin as standard. Zone of inhibition was determined for all compound and the results are summarized in Table

COMPOUND	CONCENTRATION	ZONE OF INHIBITION(mm)	
	µg/ml	*A. niger*	*C. albicans*
P1-a	50	-	-
	100	-	8
P1-b	50	7	-
	100	9.5	-
P1-c	50	8	7
	100	9	9
P1-d	50	-	7
	100	-	9
P2-a	50	8	7
	100	10	9
P2-b	50	-	9
	100	8	10.5
P2-c	50	7	8
	100	9	10
P2-d	50	7.5	9
	100	11	10.5
P3-a	50	8	8
	100	9.5	11
P3-b	50	-	8
	100	7.5	9
P3-c	50	8.5	7
	100	10	9.5
P3-d	50	7	8
	100	11	9.5
DMF (control)	----	----	----
Griseofulvin (std.)	20	22	21.5

Biological Results

The investigation of antibacterial and antifungal screening data revealed that all the tested compounds and showed moderate to good inhibition at 50-100 µg/ml in DMSO. The compound P1-a, P1-b, P2-a, P2-b, P3-a and P3-c showed comparatively very good activity against all the bacterial strains.

The good activity is attributed to the presence of pharmacologically active phenyl hydrazones and semicarbazone on position 3 on quinoline ring. Presence of phenyl group on the position-1 also increase the antimicrobial activity. The compound P1-a, P2-a, P2-b, P3-a and P3-c showed comparatively good

activity against all the fungal strains. The structure of these compound contain biologically active group like –Ph, -NHNHCONH$_2$.

CONCLUSION

A new series of Substituted 4-Hydroxy quinoline-2-one derivatives have been synthesized.

The research study reports the successful synthesis and antimicrobial activity of new 4-Hydroxy-3-substituted-1-H/Methyl/Phenylquinolin-2-one carrying biologically active groups. Their antimicrobial activity study revealed that all the compounds tested showed moderate to very good antibacterial and antifungal activities against pathogenic strains.

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