Facile multi-component one-pot synthesis of 4-amidoaralkyl-3-hydroxyquinolines using ZnO NPs: Evaluation of anti-bacterial and anti-diabetic activity

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Abstract

A three-component one-pot synthesis was performed to obtain 4-amidoaralkyl-3-hydroxyquinolines (4a-j), belonging to heterocyclic class of compounds. These derivatives were obtained by the fusion of 3-hydroxyquinoline (1), aromatic aldehydes (2a-j) and amides (3a-j) in the presence of ZnO nanoparticles under solvent free conditions at 40^oC temperature. Using ^{1}HNMR, ^{13}CNMR, FTIR spectral techniques and LC-MS analytical technique, the structural and elemental aspects of the derivatives have been confirmed. Higher yields and less reaction time (1.5 h) were the major outcomes of the protocol and further, greater recoverability of ZnO NPs was observed.

The anti-bacterial activity of the quinoline derivatives (1st cycle) has been evaluated against Staphylococcus aureus and Escherichia coli organisms. Anti-diabetic activity was also tested against insulin as the standard. It was found that the majority of the derivatives (4a-j) possessed greater biological activities in both the performed investigations.

Keywords: Quinolines, ZnO, anti-bacterial activity, anti-diabetic activity.

Introduction

Quinoline based derivatives were synthesized by using Baylis-Hillman reaction[11,13] from 2-chloroquinoline-3-carbaldehyes and olefins containing deactivating groups. These derivatives were reported to display anti-malarial activity of Plasmodium falciparum culture.

The synthesis of thieno[2, 3-b]quinoline adducts helped in anti-bacterial activity. The reaction was conducted in the presence of a non-nucleophilic mild base like DBU (1, 8-diazabicyclo[5.4.0]undec-7-ene) and methyl thioglycolate at room temperature. 8-hydroxyquinolines were synthesized by Mohamed et al[10] which were fused with pyran rings exhibiting anti-bacterial activity against *E. coli*, *S. aureus* and *P. aeruginosa*.

Anti-diabetic activity of 2-hydroxyquinoline, 2-methylquinoline and 2-methyl-8-hydroxyquinoline was tested against α-glucosidase and α-amylase with Acarbose as standard.[12] It was reported that 2-hydroxyquinoline and 2-methyl-8-hydroxyquinoline have shown superior hypoglycemic activity, whereas 2-methyquinoline has not exhibited any activity.

Heterocyclic molecules constructed through metal oxide catalysis have emerged as an alternative to the traditional reaction conditions which were performed in presence of mild bases, inorganic salts, lanthanide halides etc. In this context, metal oxides like TiO_2, ZnO, NiO, Fe_2O_3 etc. have been used in various synthetic protocols. Pertaining to its advantages like low cost, easily availability, thermal stability and heterogeneous nature.[5] ZnO was selected as an efficient nano-catalyst in the present research.

Previously, the ZnO NPs and Zinc ferrite catalysts were used in the synthesis of Imidazo[1, 2-a]pyridine-3-amines and their anti-diabetic activity was investigated.[16] Further, the same catalysts have been incorporated in the synthesis of 6-methoxyimidazo[1, 2-b]pyridazine derivatives and they have performed efficient anti-diabetic activity.[17]

In the view of extending our research towards synthesis of biologically active quinoline derivatives, the present work was designed to synthesize 4-amidoaralkyl-3-hydroxyquinolines in the presence of ZnO NPs through one-pot synthetic approach. Using the substrates 3-hydroxyquinoline, substituted benzaldehydes and amides, it was expected to form a junction connecting these three molecules through C-C and C-N bond formations, simultaneously through condensation. Therefore, it was anticipated that the biological activity of these derivatives would upsurge due to the coupling of the quinoline moiety with the aldehyde and amide. The obtained derivatives were investigated for their anti-bacterial and anti-diabetic activity. The activity of the former was examined against micro-organisms like *Staphylococcus aureus*, *Escherichia coli* and the later was tested against insulin.

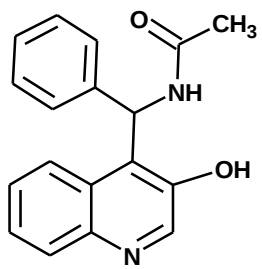
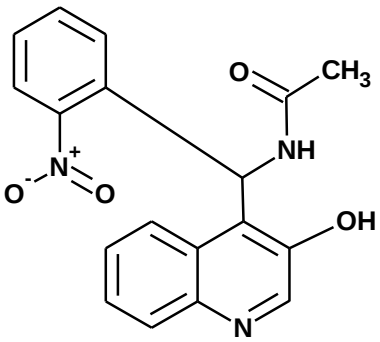
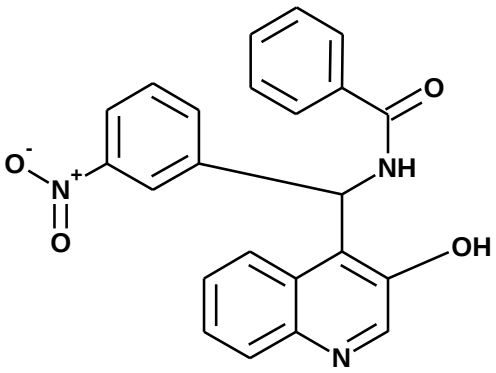
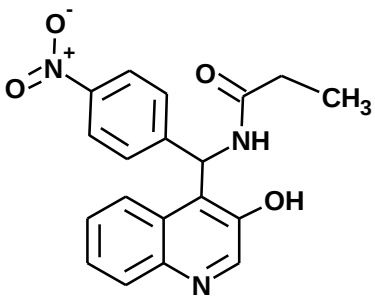
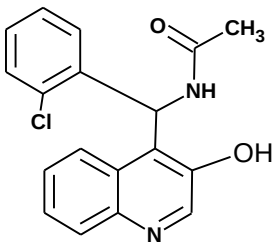
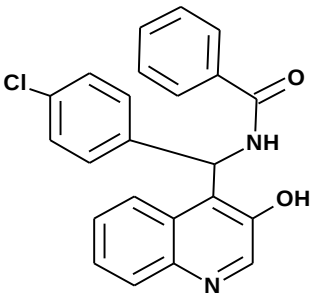
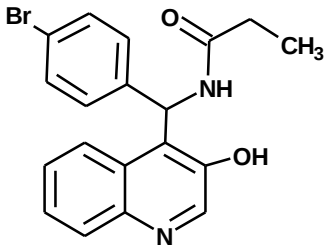
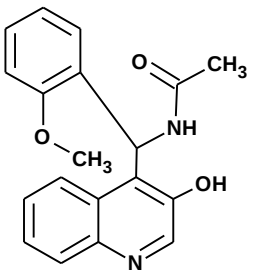
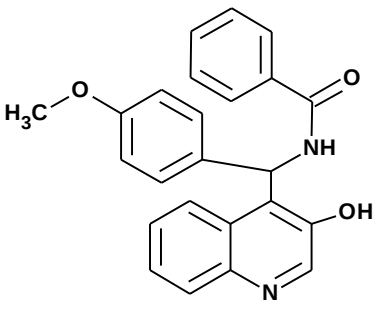
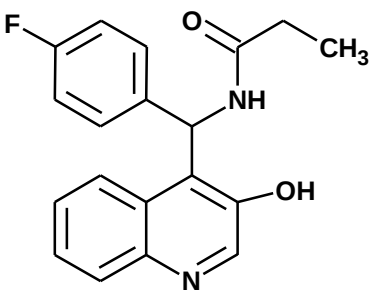
Material and Methods

All the chemicals required for the experimental work were procured from Sigma Aldrich (AR grade, 99 % pure). Melting points were determined in open glass capillaries on a Stuart SMP30 apparatus without further correction. IR spectra were recorded with KBr pellets on a Shimadzu FTIR 8400S spectrophotometer. 1HNMR and 13CNMR (400 MHz and 75 MHz) spectra were recorded on a Bruker DPX 400 spectrophotometer, using tetramethylsilane (TMS) as internal standard. $CDCl_3$ and DMSO-d6 were used as solvents and the signals are reported as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m

(multiplet) and coupling constants in Hertz (Hz). HRMS spectra were recorded on a Xevo QTof mass spectrometer. Silica gel 60 F24 of Merck pre-coated plates were employed for their thin layer chromatography (TLC) analysis to check the progress of the reaction and to analyze the purity of the compounds, the spot being located under UV light and iodine vapors.

Synthesis of 4-amidoaralkyl-3-hydroxyquinolines (4a-j): The synthesis was carried out under solvent free conditions at 40 ºC in the presence of ZnO NPs. Equimolar mixture of 3-hydroxyquinoline (1, 5 mmol), substituted aromatic aldehydes (2a-j, 5 mmol) and amides (3a-j, 5 mmol) was taken in a round bottom flask and 0.01 g of the nano-catalyst was added separately in different experimental set ups. The contents of the flask were subjected to refluxing for 1.5 hours (Scheme 1).

Table 1
Chemical Structures of the 4-amidoaralkyl-3-hydroxyquinolines (4a-j)

 **4a**	 **4b**	 **4c**
 **4d**	 **4e**	 **4f**
 **4g**	 **4h**	 **4i**
 **4j**		

The progress of the reaction was monitored through TLC (thin layer chromatography) using n-hexane: ethyl acetate as the mobile phase. After completion of the reaction, the mass was subjected to cooling, washed with water and dried at room temperature. The crude products (4a-j) obtained were re-crystallized with ethyl alcohol and authenticated by melting point and spectral analysis.

Results and Discussion

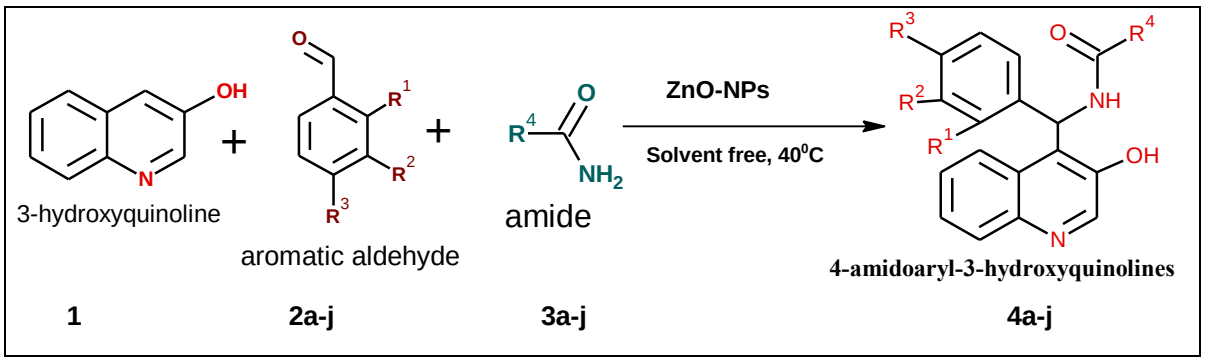
Role of solvents in the synthesis of 4a-j compounds: In order to examine the role of solvent in bringing out the derivatives in good yields, a model reaction was conducted using 3-hydroxyquinoline (1), benzaldehyde (2a) and acetamide (3a) in the presence of few selected organic solvents. In this experiment, many solvents have produced very less or average yields of the derivative 4a.

However, under solvent free conditions, 92% yield was produced in 1.5 h of time (Table 2). Hence, it was anticipated that the synthesis of 4-amidoaralkyl-3-hydroxyquinolines (4a-j) was most effective under solvent free conditions which is a major requirement in the field of green chemistry.

Recyclability of ZnO NPs: In order to investigate the effectiveness of the recycled ZnO NPs, the reaction scheme was conducted with the recycled ZnO NPs. The reaction was performed in 3 consecutive runs and the results were presented in table 3. It was noticed that the percentage yield with the 1st recycled form of ZnO NPs was almost nearer to that conducted with their pure form. The percentage yield was average in 2nd recycled form and however, the yields were less with the 3rd recycled form indicating the effectiveness of the ZnO NPs up to 2 cyclic runs. The recycled ZnO NPs were thoroughly washed with EtOH:water mixture in each recycling step.

In organic synthesis, recyclability of heterogeneous catalysts was identified as significant.[17] Metal oxides are generally magnetically active and possess the ability to get easily separable from the reaction mixture.[17]

In the present reaction scheme, the ZnO NPs have shown excellent catalytic activity with the 1st recycled form and the activity has decreased with 2nd and 3rd recycled forms. On recycling, the number of active sites would decrease on the surface of the catalyst resulting in its reduced catalytic role.



Scheme 1: Synthesis of 4-amidoaralkyl-3-hydroxyquinolines (4a-j)

2a: R^1=R^2=R^3=H; **2b**: R^1= -NO_2, R^2=R^3=H; **2c**: R^1=H, R^2= -NO_2, R^3=H; **2d**: R^1=H, R^2= -NO_2, R^3= -NO_2; **2e**: R^1= -Cl, R^2=R^3=H; **2f**: R^1=R^2=H, R^3= -Cl; **2g**: R^1=R^2=H, R^3= -Br; **2h**: R^1= -OMe, R^2=R^3= H; **2i**: R^1=R^2=H, R^3= -OMe; **2j**: R^1=R^2=H, R^3 = -F. **3a**: R^4=H; **3b**: R^4= -Me; **3c**: R^4 = -Ph; **3d**: R^4= -Et; **3e**: R^4= -Me; **3f**: R^4= -Ph; **3g**: R^4= -Et; **3h**: R^4= -Me; **3i**: R^4= -Ph; **3j**: R^4= -Et. **4a**: R^1=R^2=R^3=R^4=H; **4b**: R^1= -NO_2, R^2=R^3=H, : R^4= -Me; **4c**: R^1=H, R^2= -NO_2, R^3=H, R^4 = -Ph; **4d**: R^1=H, R^2= -NO_2, R^3= -NO_2, R^4= -Et; **4e**: R^1= -Cl, R^2=R^3=H, R^4= -Me; **4f**: R^1=R^2=H, R^3= -Cl, R^4= -Ph; **4g**: R^1=R^2=H, R^3= -Br, R^4= -Et; **4h**: R^1= -OMe, R^2=R^3= H, R^4= -Me; **4i**: R^1=R^2=H, R^3= -OMe, R^4= -Ph; **4j**: R^1=R^2=H, R^3 = -F, R^4= -Et

Table 2
Effect of Solvent on the synthesis of 4-amidoaralkyl-3-hydroxyquinolines (4a-j)

Entry	Solvent (0.5 mmol)	Time (h)	Yield (%)[a]
1	Dichloromethane	2.0	12
2.	Ethyl acetate	2.0	23
3.	Tetrahydrofuran	2.0	37
4.	Ethanol	2.0	60
5.	Acetonitrile	2.0	52
6.	None	**1.5**	**92**

[a] Isolated yields; Reaction conditions: 3-hydroxyquinoline (1)= 5 mmol, aldehyde (2a-j) = 5 mmol, amide (3a-j) = 5 mmol, Temperature = 40 ºC, ZnO NPs= 0.01 g.

Table 3
Percentage yields of compounds 4a-j with recycled forms of ZnO NPs

Compound	Trail-1[a]	Trail-2[b]	Trail-3[c]	Trail-4[d]
4a	85	80	77	70
4b	78	75	73	65
4c	89	83	80	73
4d	92	89	81	73
4e	70	66	61	55
4f	88	82	74	62
4g	92	88	82	73
4h	78	74	69	59
4i	90	83	78	67
4j	88	82	78	63

a: Initial form of ZnO NPs; b: 1st recycled form, c: 2nd recycled form, d: 3rd recycled form

Spectral data of compounds 4a-j:
[4a] 4-acetamidobenzyl-3-hydroxyquinoline

Yield/Color	85 %: white solid
Melting point	244- 245 °C
FTIR (KBr: $\bar{\upsilon}_{max}$, cm^{-1})	3591 (O-H str),1345 (C-O str), 3300 (N-H str), 1690 (C=O str), 1500 (N-H str), 2925 (C-H str, benzylic CH_2), 1614, 1506, 1465 (aromatic C=C str) 1086, 1035, 735 (aromatic C-H bend)
^{1}H-NMR (300 MHz; $CDCl_3$): δ ppm:	2.3 (d, -CH_2-Ph); 1.2 (s, acetyl proton); 3.5 (s, Phenolic proton); 6.89 (s, -NH proton); 6.59-7.21 (m, Ar-H, *J*=2.3 Hz)
^{13}C-NMR (75 MHz: DMSO-d_6); δ ppm:	21.42 (**C**H_2-benzylic); 22.21 (**C**H_3, amide), 178.01 (**C**=O); 165.35, 159.10, 151.51 (aromatic carbons);
LC-MS: m/z	292.33184
Elemental analysis, calc. (found) %:	$C_{18}H_{16}N_2O_2$; C: 73. 8 (72.9); H: 5.47 (5.40); N: 9.57 (9. 51); O: 10.94 (10.89).

[4b] 4-acetamido-(2-nitrobenzyl)-3-hydroxyquinoline

Yield/ Color	78 %: Pale yellow solid
Melting point	270- 275 °C
FTIR (KBr: $\bar{\upsilon}_{max}$, cm^{-1})	3591 (O-H str),1345 (C-O str), 3300 (N-H str), 1690 (C=O str), 1500 (N-H str),2925 (C-H str, benzylic CH_2), 1614, 1506, 1465 (aromatic C=C str) 1086, 1035, 735 (aromatic C-H bend), 1510 (N=O str)
^{1}H-NMR (300 MHz; $CDCl_3$): δ ppm:	2.3 (d, -CH_2-Ph); 1.2 (s, acetyl proton); 3.5 (s, Phenolic proton); 6.89 (s, -NH proton); 6.59-7.21 (m, Ar-H, *J*=2.3 Hz); 8.1 (m, *J*=2.1 Hz); 7.51 (m, *J*=1.47 Hz), 7.65 (m, *J*=1.17 Hz).
^{13}C-NMR (75 MHz: DMSO-d_6); δ ppm:	21.42 (CH_2-benzylic); 22.21 (CH_3, amide), 178.01 (C=O); 165.35, 159.10, 151.51 (aromatic carbons); 148.31; 134.71; 129.01; 123.45
LC-MS: m/z	337.3294
Elemental analysis, calc. (found)	$C_{18}H_{15}N_3O_4$; C: 64.03 (65.95); H: 4.44 (4.43); N: 12.45 (12.41); O: 18.97 (18.91)

[4c] 4-benzamido-(3-nitrobenzyl)-3-hydroxyquinoline

Yield/ color	89 %; pale yellow solid
Melting point	247-249 °C
FTIR (KBr: $\bar{\upsilon}_{max}$, cm^{-1})	3591 (O-H str),1345 (C-O str), 3300 (N-H str), 1690 (C=O str), 1500 (N-H str), 2925 (C-H str, benzylic CH_2), 1614, 1506, 1465 (aromatic C=C str) 1086, 1035, 735 (aromatic C-H bend), 1510 (N=O str)
^{1}H-NMR (300 MHz; $CDCl_3$): δ ppm:	2.3 (d, -CH_2-Ph); 1.2 (s, acetyl proton); 3.5 (s, Phenolic proton); 6.89 (s, -NH proton); 6.59-7.21 (m, Ar-H, *J*=2.3 Hz); 8.1 (m, *J*=2.1 Hz); 7.51 (m, *J*=1.47 Hz), 7.65 (m, *J*=1.17 Hz).
^{13}C-NMR (75 MHz: DMSO-d_6); δ ppm:	21.42 (**C**H_2-benzylic); 22.21 (**C**H_3, amide), 167.94 (**C**=O); 165.35, 159.10, 151.51 (aromatic carbons); 148.31; 134.71; 129.01; 123.45
LC-MS: m/z	399.39878.
Elemental analysis, calc. (found)	$C_{23}H_{17}N_3O_4$; C:69.10 (69.05); H: 4.25 (4.21); N: 10.51 (10.49); O: 12.01 (11.89)

[4d] 4-ethanoamido-(4-nitrobenzyl)-3-hydroxyquinoline

Yield/ color	92 %; pale yellow solid
Melting point	238-239 ^{o}C
FTIR (KBr: $\bar{\upsilon}_{max}$, cm^{-1})	3591 (O-H str),1345 (C-O str), 3300 (N-H str), 1690 (C=O str), 1500 (N-H str), 2925 (C-H str, benzylic CH_2), 1614, 1506, 1465 (aromatic C=C str) 1086, 1035, 735 (aromatic C-H bend), 1510 (N=O str)
^{1}H-NMR (300 MHz; $CDCl_3$): δ ppm:	2.3 (d, -CH_2-Ph); 0.89 (t, -CH_3), 1.2 (q, acetyl proton); 3.5 (s, Phenolic proton); 6.89 (s, -NH proton); 6.59-7.21 (m, Ar-H, *J*=2.3 Hz); 8.1 (m, *J*=2.1 Hz); 7.51 (m, *J*=1.47 Hz), 7.65 (m, *J*=1.17 Hz).
^{13}C-NMR (75 MHz: DMSO-d_6); δ ppm:	21.42 (CH_2-benzylic); 35.35 (CH_2); 22.21 (CH_3, amide), 167.94 (C=O); 165.35, 159.10, 151.51 (aromatic carbons); 148.31; 134.71; 129.01; 123.45
LC-MS: m/z	351.35598
Elemental analysis, calc. (found)	$C_{19}H_{17}N_3O_4$; C: 64. 89 (64. 81); H : 4.83 (4.81); N: 11.95 (11.90); O: 18.21 (18.19)

[4e] 4-acetamido-(2-chlorobenzyl)-3-hydroxyquinoline

Yield	70 %; white solid
Melting point	235-240^{o}C
FTIR (KBr: $\bar{\upsilon}_{max}$, cm^{-1})	3591 (O-H str),1345 (C-O str), 3300 (N-H str), 1690 (C=O str), 1500 (N-H str),2925 (C-H str, benzylic CH_2), 1614, 1506, 1465 (aromatic C=C str) 1086, 1035, 735 (aromatic C-H bend); 845-560 (C-Cl str)
^{1}H-NMR (300 MHz; $CDCl_3$): δ ppm:	2.3 (d, -CH_2-Ph); 1.2 (s, acetyl proton); 3.5 (s, Phenolic proton); 6.89 (s, -NH proton); 6.59-7.21 (m, Ar-H, *J*=2.3 Hz); 8.1 (m, *J*=2.1 Hz); 7.51 (m, *J*=1.47 Hz), 7.65 (m, *J*=1.17 Hz).
^{13}C-NMR (75 MHz: DMSO-d_6); δ ppm:	21.42 (CH_2-benzylic); 22.21 (CH_3, amide), 167.94 (C=O); 165.35, 159.10, 151.51 (aromatic carbons); 148.31; 134.71; 129.01; 123.45
LC-MS: m/z	326.7769
Elemental analysis, calc. (found)	$C_{18}H_{15}ClN_2O_2$; C: 66.10 (66.02); H : 4.59 (4.51); Cl: 10.86 (10.81); N: 8.56 (8.49); O: 9.79 (9.71)

[4f] 4-benzamido-(4-chlorobenzyl)-3-hydroxyquinoline

Yield/ Color	88 %; white solid
Melting point	224-225^{o}C
FTIR (KBr: $\bar{\upsilon}_{max}$, cm^{-1})	3591 (O-H str),1345 (C-O str), 3300 (N-H str), 1690 (C=O str), 1500 (N-H str),2925 (C-H str, benzylic CH_2), 1614, 1506, 1465 (aromatic C=C str) 1086, 1035, 735 (aromatic C-H bend); 845-560 (C-Cl str)
^{1}H-NMR (300 MHz; $CDCl_3$): δ ppm:	2.3 (d, -CH_2-Ph); 1.2 (s, acetyl proton); 3.5 (s, Phenolic proton); 6.89 (s, -NH proton); 6.59-7.21 (m, Ar-H, *J*=2.3 Hz); 8.1 (m, *J*=2.1 Hz); 7.51 (m, *J*=1.47 Hz), 7.65 (m, *J*=1.17 Hz).
^{13}C-NMR (75 MHz: DMSO-d_6); δ ppm:	21.42 (CH_2-benzylic); 22.21 (CH_3, amide), 167.94 (C=O); 165.35, 159.10, 151.51 (aromatic carbons); 148.31; 134.71; 129.01; 123.45
LC-MS: m/z	388.84628
Elemental analysis, calc. (found)	$C_{23}H_{17}ClN_2O_2$; C: 70.97 (70.90);H: 4.37 (4.32); Cl: 9.12 (9.09);N: 7.20 (7.18); O: 8.22 (8.19)

[4g] 4-ethanoamido-(4-bromobenzyl)-3-hydroxyquinoline

Yield/ Color	92 %; Yellow solid
Melting point	226-227^{o}C
FTIR	3591 (O-H str),1345 (C-O str), 3300 (N-H str), 1690 (C=O str), 1500 (N-H str),2925 (C-H str, benzylic CH_2), 1614, 1506, 1465 (aromatic C=C str) 1086, 1035, 735 (aromatic C-H bend); 680-510 (C-Br str)
^{1}HNMR (300 MHz)	2.3 (d, -CH_2-Ph); 0.89 (t, -CH_3), 1.2 (q, acetyl proton); 3.5 (s, Phenolic proton); 6.89 (s, -NH proton); 6.59-7.21 (m, Ar-H, *J*=2.3 Hz); 8.1 (m, *J*=2.1 Hz); 7.51 (m, *J*=1.47 Hz), 7.65 (m, *J*=1.17 Hz).
^{13}CNMR	21.42 (CH_2-benzylic); 35.35 (CH_2); 22.21 (CH_3, amide), 167.94 (C=O); 165.35, 159.10, 151.51 (aromatic carbons); 148.31; 134.71; 129.01; 123.45
LC-MS: m/z	385.25448
Elemental analysis, calc. (found)	$C_{19}H_{17}BrN_2O_2$; C: 59.18 (59.11); H: 4.41 (4.39); Br: 20.73 (20.69); N : 7.26 (7.21); O : 8.30 (8.21)

[4h] 4-acetamido-(2-methoxybenzyl)-3-hydroxyquinoline

Yield	78 %; white solid
Melting point	203-206ºC
FTIR (KBr: $\bar{\upsilon}_{max}$, cm^{-1})	3591 (O-H str),1345 (C-O str), 3300 (N-H str), 1690 (C=O str), 1500 (N-H str), 2925 (C-H str, benzylic CH_2), 1614, 1506, 1465 (aromatic C=C str) 1086, 1035, 735 (aromatic C-H bend); 1245 (C-O str, -OMe), 1043 (C-O bend, -OMe)
^{1}HNMR (300 MHz)	2.3 (d, -CH_2-Ph); 1.2 (s, acetyl proton); 3.5 (s, Phenolic proton); 6.89 (s, -NH proton); 6.59-7.21 (m, Ar-H, *J*=2.3 Hz); 8.1 (m, *J*=2.1 Hz); 7.51 (m, *J*=1.47 Hz), 7.65 (m, *J*=1.17 Hz); 3.72 (s, -OMe)
^{13}CNMR	21.42 (CH_2-benzylic); 35.35 (CH_2); 22.21 (CH_3, amide), 167.94 (C=O); 165.35, 159.10, 151.51 (aromatic carbons); 148.31; 134.71; 129.01; 123.45; 55.05 (-OMe)
LC-MS: m/z	322.35782
Elemental analysis, calc. (found)	$C_{19}H_{18}N_2O_3$; C: 70.68 (70.61); H: 5.58 (5.51) ; N : 8.68 (8.61); O : 14.89 (14.81)

[4i] 4-benzamido-(4-methoxybenzyl)-3-hydroxyquinoline

Yield/ Color	90 %; white solid
Melting point	185-186ºC
FTIR (KBr: $\bar{\upsilon}_{max}$, cm^{-1})	3591 (O-H str),1345 (C-O str), 3300 (N-H str), 1690 (C=O str), 1500 (N-H str), 2925 (C-H str, benzylic CH_2), 1614, 1506, 1465 (aromatic C=C str) 1086, 1035, 735 (aromatic C-H bend); 1245 (C-O str, -OMe), 1043 (C-O bend, -OMe)
^{1}HNMR (300 MHz)	2.3 (d, -CH_2-Ph); 1.2 (s, acetyl proton); 3.5 (s, Phenolic proton); 6.89 (s, -NH proton); 6.59-7.21 (m, Ar-H, *J*=2.3 Hz); 8.1 (m, *J*=2.1 Hz); 7.51 (m, *J*=1.47 Hz), 7.65 (m, *J*=1.17 Hz), 3.72 (s, -OMe)
^{13}CNMR	21.42 (CH_2-benzylic); 35.35 (CH_2); 22.21 (CH_3, amide), 167.94 (C=O); 165.35, 159.10, 151.51 (aromatic carbons); 148.31; 134.71; 129.01; 123.45; 55.05 (-OMe)
LC-MS: m/z	384.4272
Elemental analysis, calc. (found)	$C_{24}H_{20}N_2O_3$; C: 74.91 (74.86); H: 5.20 (5.18); N: 7.28 (7.21);O: 12.48 (12.41)

[4j] 4-acetamido-(4-fluorobenzyl)-3-hydroxyquinoline

Yield/ color	88 %; pale yellow solid
Melting point	248-249ºC
FTIR (KBr: $\bar{\upsilon}_{max}$, cm^{-1})	3591 (O-H str),1345 (C-O str), 3300 (N-H str), 1690 (C=O str), 1500 (N-H str),2925 (C-H str, benzylic CH_2), 1614, 1506, 1465 (aromatic C=C str) 1086, 1035, 735 (aromatic C-H bend); 1161-1236 (C-F str, high intense)
^{1}HNMR (300 MHz)	2.3 (d, -CH_2-Ph); 0.89 (t, -CH_3), 1.2 (q, acetyl proton); 3.5 (s, Phenolic proton); 6.89 (s, -NH proton); 6.59-7.21 (m, Ar-H, *J*=2.3 Hz); 8.1 (m, *J*=2.1 Hz); 7.51 (m, *J*=1.47 Hz), 7.65 (m, *J*=1.17 Hz).
^{13}CNMR	21.42 (CH_2-benzylic); 35.35 (CH_2); 22.21 (CH_3, amide), 167.94 (C=O); 165.35, 159.10, 151.51 (aromatic carbons); 148.31; 134.71; 129.01; 123.45
LC-MS: m/z	324.348832
Elemental analysis, calc. (found)	$C_{19}H_{17}FN_2O_2$; C: 70. 29 (70.21); H: 5.24 (5.19); F: 5.85 (5.81); N: 8.63 (8.59); O: 9.86 (9.81)

Evaluation of anti-bacterial activity: The anti-bacterial activity of the synthesized quinoline derivatives (4a-j) was examined against *Staphylococcus aureus* (1) and *Escherichia coli* (2) organisms, with ampicillin as the standard compound. Broth dilution methodology was followed for the studies as recommended by National Committee for Clinical Laboratory (NCCL) standards.[14] Minimum inhibitory concentrations (MIC, g/mL) values were shown in table 4.

From the anti-bacterial studies, it was observed that the compounds 4b, 4d, 4f, 4g, 4h, 4j have displayed excellent activity against the micro-organism (1) with reference to the standard compound Ampicillin. Similarly, the activity

against the micro-organism (2) was superior with the compounds 4b to 4h (except 4a, 4i and 4j). Remaining compounds have shown moderate to less activity.

Table 4
Anti-bacterial activity of the compounds 4a-j

Compounds	Anti-bacterial activity MIC (μg/mL)	
	(1)	**(2)**
4a	20	31
4b	**18**	**25**
4c	25	**29**
4d	**19**	**21**
4e	23	**25**
4f	**18**	**23**
4g	**15**	**20**
4h	**18**	**22**
4i	22	35
4j	**15**	33
Ampicillin	**28**	**37**

Evaluation of anti-diabetic activity: The anti-diabetic activity of the synthesized compounds (4a-j) was evaluated against insulin as the standard drug which showed 66.99 % blood glucose lowering activity at 50mg/kg.p.o. Based on the previous reports, the studies were conducted to analyze the anti-diabetic activity.[16,17]

It was observed that almost all the derivatives (4a-j) have exhibited good hypoglycemic activity, when compared with the standard. Compounds 4b (R=2-nitrobenzyl), 4j (R=4-fluorobenzyl) have shown excellent hypoglycemic activity. Remaining all compounds have shown moderate to good hypoglycemic activity and the results were shown in table 5.

Hence, the studies reveal the biological potentiality of the synthesized quinoline derivatives in terms of both anti-bacterial and anti-diabetic activities and the results show the effectiveness of the reaction scheme in bringing out a novel series of 4-amidoaralkyl-3-hydroxyquinolines through ZnO NPs catalysis.

Conclusion

Novel synthesis of 4-amidoaralkyl-3-hydroxyquinolines (4a-j) was reported in the presence of ZnONPs. The compounds were characterized using spectro-chemical instrumental techniques and the presence of the respective substituents and functional groups was confirmed. The compounds were investigated for their anti-bacterial and anti-diabetic activities and the results proved the biological activeness of the compounds and the methodology was unique.

Table 5
Anti-diabetic activity (hypoglycemic) of quinoline derivatives (4a-j)

Treatment (mg/Kg b.w.p.o)	Blood glucose level[a] (mg/dl)			
	Day-0	**Day-3**	**Day-7**	**Hyperglycemic activity (%)**
Control (0.5%CMC)	**347.0 ± 1.44**	**372.4 ± 2.24#**	**379.2 ± 3.21#**	**-**
Insulin	352.23 ± 1.54	213.11 ± 1.09#	116.25 ± 1.22#	66.99
4a	347.29 ± 1.21	221.03 ± 1.12#	121.31 ± 1.12#	65.06
4b	351.03 ± 1.25	219.81 ± 1.15#	119.17 ± 1.31#	66.05
4c	347.19 ± 1.11	220.17 ± 1.11#	125.37 ± 1.05#	63.89
4d	341.21 ± 1.34	225.89 ± 1.12#	120.21 ± 1.12#	64.76
4e	349.12 ± 1.12	215.21 ± 1.02#	115.19 ± 1.19#	67.00
4f	342.19 ± 1.29	225.32 ± 1.12#	120.14 ± 1.11#	64.89
4g	351.04 ± 1.21	210.29 ± 1.25#	122.19 ± 2.01#	65.19
4h	334.27 ± 1.04	215.21 ± 1.32#	119.31 ± 1.87#	64.30
4i	329.19 ± 1.23	219. 30 ± 1.21#	123.19 ± 1.13#	62.57
4j	339.12 ± 1.31	222. 12 ± 1.12#	115.12 ± 1.11#	66.05

a Values are represented as mean ± SEM. Data were analyzed using analysis of variance and group means were compared with the Tukey–Kramer Post ANOVA test. The values were considered when $p < 0.01$. #-$p < 0.001$; Tabulated data are expressed as mean ± SEM; (n = 6).

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References
1. Bandgar B.P., Gawande S.S., Bodade R.G., Totre J.V. and Khobragade C.N., Synthesis and biological evaluation of simple methoxylated chalcones as anticancer, anti-inflamatory and antioxidant agents, *Bioorg. Med. Chem.*, **18**, 1364-1370 **(2010)**

2. Bilker O., Lindo V., Panico M., Etiene A.E., Paxton T., Dell A., Rogers M., Sinden R.E. and Morris H.R., Identifi cation of xanthurenic acid as the putative inducer of malaria development in the mosquito, *Nature*, **392**, 289-292 **(1998)**

3. Chauhan P.M.S. and Srivastava S.K., Present trends and future strategy in chemotherapy of malaria, *Curr. Med. Chem.*, **8**, 1535-1542 **(2001)**

4. Gantier J.C., Fournet A., Munos M.H. and Hocquemiller R., The effect of some 2-substituted quinolines isolated from Galipealongifl ora on Plasmodium vinckei petteri infected mice, *Planta Med*., **62**, 285 – 286 **(1996)**

5. Gopala Krishna D., Satyaveni S. and Purna C.R.G., Green and ecofriendly synthesis of indole-condensed benzimidazole chalcones in water and their antimicrobial evaluations, *Journal of Heterocyclic Chemistry*, **57(3)**, 1201-1210 **(2020)**

6. Hans R.H., Guantai E.M., Lategan C., Smith P.J., Wan B., Franzblau S.G., Gut J., Rosenthal P.J. and Chibale K., Synthesis, antimalarial and antitubercular activity of acetylenic chalcone, *Bioorg. Med. Chem. Lett*., **20**, 942-944 **(2010)**

7. Iwaniuk D.P., Whetmore E.D., Rosa N., Ekoue-kovi K., Alumasa J., De Dios A.C., Roepe P.D. and Wolf C., Synthesis and antimalarial activity of new chloroquine analogues carrying a multifunctional linear side chain, *Bioorg. Med. Chem.*, **17**, 6560-6566 **(2009)**

8. Kumar Ch. N.S.S.P., Srihari E., Ravinder M., Pranay Kumar K., Murthy U.S.N. and Jayathirtha Rao V., DBU Promoted Facile Synthesis of New Thieno[2,3-b]pyridine/quinoline Derivatives and Their Antimicrobial Evaluation, *Journal of Heterocyclic Chemistry*, **50(51)**, 131-135 **(2013)**

9. (a) Michael J.P., Quinoline, quinazoline and acridone alkaloids, *Nat. Prod. Rep*., **14**, 605 – 618 **(1997)**

(b) Michael J.P., Quinoline, quinazoline and acridone alkaloids, *Nat. Prod. Rep*., **22**, 627-646 **(2005)**

(c) Michael J.P., Quinoline, quinazoline and acridone alkaloids, *Nat. Prod. Rep*., **24**, 223-246 **(2007)**

10. Mohamed R., Omar B., Younes L., Khadija O. and Brahim L., Synthesis, Characterization and Biological Activity of new Pyran Derivatives of 8-Hydroxyquinoline, *Eurasian Journal of Analytical Chemistry*, **13(6)**, 19-30 **(2018)**

11. (a) Narender P., Srinivas U., Gangadasu B., Biswas S. and Jayathirtha Rao V., Anti-malarial activity of Baylis – Hillman adducts from substituted 2-chloronicotinaldehydes, *Bioorg. Med. Chem. Lett.*, **15**, 5378-5381 **(2005)**

(b) Narender P., Gangadasu B., Ravinder M., Srinivas U., Swamy G.Y.S.K., Ravikumar K. and Jayathirtha Rao V., Baylis – Hillman adducts between pyridine carboxaldehyde derivatives and cyclic enones, *Tetrahedron*, **62**, 954-959 **(2006a)**

(c) Narender P., Srinivas U., Ravinder M., Anand Rao B., Ramesh Ch., Harakishore K., Gangadasu B., Murthy U.S.N. and Jayathirtha Rao V., Synthesis of multi-substituted quinolines from Baylis - Hillman adducts obtained from substituted 2-chloronicotinaldehydes and their antimicrobial activity, *Bioorg. Med. Chem*., **14**, 4600-4609 **(2006b)**

(d) Narender P., Ravinder M., Sadhu P.S., China Raju B., Ramesh Ch. and Jayathirtha Rao V., Synthesis of substituted 1,8-naphthyridine-3-carboxylates from Baylis - Hillman adducts of substituted 2-chloronicotinaldehydes, *Helv. Chim. Acta*, **92**, 959-966 **(2009)**

12. Narwal S., Kumar S. and Kumar Verma P., Synthesis and therapeutic potential of quinoline Derivatives, *Res Chem Intermed*, **43**, 2765-2798 **(2017)**

13. (a) Ravinder M., Sadhu P.S. and Jayathirtha Rao V., Simple, facile and one-pot conversion of the Baylis – Hillman acetates into 3,5,6- trisubstituted-2-pyridones, *Tetrahedron Lett*., **50**, 4229-4232 **(2009)**

(b) Ravinder M., Sadhu P.S., Santhoshi A., Narender P., Swamy G.Y.S.K., Ravi Kumar K. and Jayathirtha Rao V., Synthesis of new aminonicotinate derivatives from acetylated Baylis – Hillman adducts and enamino esters via a consecutive [3 + 3]-annulation protocol. Synthesis, **41**, 573-578 **(2010)**

14. Soma Sekhar R. and Paul Douglas S., Evaluation of Anti-microbial activity of graphene oxide-TiO2 nanocomposites with variable compositions, *Res. J. Chem. Environ.*, **25(10)**, 80-83 **(2021)**

15. Suryawanshi S.N., Chandra N., Kumar P., Porwal J. and Gupta S., Chemotherapy of leishmaniasis Part-VIII: synthesis and bioevaluation of novel chalcones, *Eur. J. Med. Chem.*, **43**, 2473 – 2478 **(2008)**

16. Tata Veereswara Rao K., Hima Bindu G. and Paul Douglas S., Green synthesis, characterization and anti-diabetic activity of 2-substituted aryl/alkyl-N-aryl/ alkyl Imidazo[1,2-a] pyridine-3-amine derivatives, *Asian Journal of Chemistry*, **30(7)**, 1531-1536 **(2018)**

17. Tata Veereswara Rao K., Hima Bindu G. and Paul Douglas S., Synthesis, characterization and antidiabetic activity of 6-methoxyimidazo[1,2-b] pyridazine derivatives, *Journal of the Chinese Chemical Society*, **66(6)**, 630-637 **(2019)**

18. Tomar V., Bhattacharjee G., Kamaluddin Rajakumar S., Srivastava K. and Puri S.K., Synthesis of new chalcone derivatives

containing acridinyl moiety with potential antimalarial activity, *Eur. J. Med. Chem.*, **45**, 745-751 **(2010)**

19. Venkatesan P. and Sumathi S., Piperidine mediated synthesis of N -heterocyclic chalcones and their antibacterial activity, *J. Heterocycl. Chem.*, **47**, 81-84 **(2010)**

20. Vlahov R., Parushev St., Vlahov J., Nickel P. and Snatzke G., Synthesis of some new quinoline derivatives – potential antimalarial drugs, *Pure Appl. Chem.*, **62**, 1303-1306 **(1990)**.

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