

# Synthesis, Antidiabetic Evaluation and Bioisosteric Modification of Quinoline Incorporated 2-pyrazoline Derivatives

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## ABSTRACT

**Background:** Diabetes mellitus is a pervasive illness worldwide with many progressively increasing complications day by day. The quinoline nucleus is important heterocyclic moiety with different biological activities. Due to their pivotal role in different biological processes they are well explored as therapeutic agents and some of them have exhibited antihyperglycemic activity. Different substituted pyrazoles have been accounted for their *in vivo* antidiabetic activity, but we concentrated to substituted pyrazoline derivatives in the quest for novel basic classes of medications inhibiting the action of the ATP-K<sup>+</sup> beta cell pancreatic membrane channel, prompting the release of insulin. **Materials and Methods:** In the present study, 1-(4-(7-Chloroquinolin-4-yl oxy) phenyl ethanone and 1-(4-(7-Chloroquinolin-4-yl amino) phenyl ethanone was synthesized by nucleophilic substitution of 4-Chloro of 4,7-dichloroquinoline with substituted 4-hydroxy acetophenone and 4-amino acetophenone in DMF and KOH respectively. The amino linked chalcones and oxo linked chalcones was synthesized by Claisen Schmidt condensation with different substituted aromatic aldehydes. Finally substituted pyrazolines (ACP1-ACP10) was synthesized upon cyclisation of oxo linked and amino linked chalcones with hydrazine hydrate. The structures of the final synthesized compounds were characterized by IR, <sup>1</sup>H NMR and mass spectra. **Results:** The final synthesized compounds were evaluated for their *in vitro* antidiabetic activity by alpha glucosidase inhibition assay. Most of the compounds showed good antidiabetic activity compared to the standard drug acarbose. **Conclusion:** *In-vitro* results revealed that a large number of synthesized compounds having good antidiabetic activity. So these compounds are found to be interesting lead molecules for further synthesis as antidiabetic agents.

**Key words:** Quinoline, Oxo linked, Amino linked, Chalcones, Pyrazoline, Antidiabetic activity.

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## INTRODUCTION

Diabetes mellitus is a pervasive illness disease with numerous complications including neuropathy, cardiac dysfunction, retinopathy, atherosclerosis and nephropathy.<sup>1</sup> The final step in the digestive process of carbohydrate is catalyzed by  $\alpha$ -glucosidase. The inhibitors of  $\alpha$ -glucosidase can postpone the take-up of dietary sugars and smother postprandial hyperglycemia and might be valuable in rewarding patients with diabetes as well as obesity.<sup>2</sup> Quinoline or 1-aza-naphthalene is nitrogen containing heterocyclic

aromatic compound. The quinoline core is significant heterocyclic moiety that is found in numerous naturally occurring quinoline alkaloids, therapeutic and synthetic compounds with wide range of biological activities such as antimalarial, antidiabetic<sup>3</sup> anti-inflammatory<sup>4</sup> antihypertensive and antibacterial agents. Due to their pivotal role in various biological processes, the quinoline derivatives are well explored as therapeutic agents and some of them have displayed antihyperglycemic activity. Literature



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uncovers that there is little data on synthesizing and planning of thiazolidinediones fusing substituted quinolines as a lipophilic tail, 2,4-thiazolidinedione as an acidic head and no carbon chain as a linker. Further, the utility of quinoline derivatives in the preparation of some dyes and pigments has been reported. Pyrazolines are pyrazoles dihydro-derivatives and are well known to contain compounds containing five component nitrogen. Pyrazoline formation have been by the action of nucleophilics such as hydrazine hydrate or phenyl hydrazine using alcohol as a solvent. Pyrazolines are known to exhibit different biological and pharmacological activities like antidiabetic<sup>5</sup> antitubercular<sup>6</sup> anti-inflammatory<sup>7</sup> and anti-depressant. Some different activities are additionally shown by them, for example, anticonvulsant, antitumor<sup>8</sup> pain relieving and antiandrogenic.

The present study explores a new method to synthesize new quinoline incorporated 2-pyrazoline derivatives. Herein an attempt is made towards the incorporation of 2-pyrazoline with quinoline moiety and studying the bioisosteric modification to Probe how biological activity might be influenced by this combination. The study explores the *in vitro* antidiabetic activity of the final synthesized compounds.

## MATERIALS AND METHODS

All the chemicals were of analytical grade: substituted aldehydes, 4,7-dichloroquinoline, 4-hydroxy acetophenone, 4-amino acetophenone, methanol, ethanol, hydrazine hydrate, glacial acetic acid. Melting points were calculated and are uncorrected using an open capillary method. Thin layer chromatography (TLC) checked the purity of the compounds using silica gel G plate. The homogeneity of the compounds was tested using n-Hexane: Ethylacetate (7:3) as solvent coated with silica gel-G plate. All IR spectra were reported using ATR method with Alpha Bruker. <sup>1</sup>H NMR spectra were recorded on Bruker spectrophotometer (400 MHz) in DMSO-d<sub>6</sub> dissolvable utilizing tetra methyl silane (TMS) as an internal solvent. Mass spectra was recorded by LC-MS strategy.

### Synthesis of 1-(4-(7-chloroquinolin-4-yloxy) phenyl)ethanone

The mixture of 4-hydroxy acetophenone (1.5 equiv), 4,7-dichloroquinoline (1.0 equiv) and KOH (1.5 equiv) in DMF was refluxed for 6 h. The reaction mixture was added with the water, the solid started separating out. The separated solid was filtered and recrystallized with ethanol to obtain the white crystals.

### Synthesis of 1-(4-(7-Chloroquinolin-4-ylamino) phenyl)ethanone

The mixture of 4,7-dichloroquinoline (1.0 equiv) and 4-aminoacetophenone (1.5 equiv) in methanol was refluxed for 6 h. Under vacuum, solid mass was obtained by evaporation of solvent. The methanol was used for the recrystallization to obtain the yellow solid.

### General procedure for synthesis of oxo linked chalcones and amino linked chalcones<sup>9</sup> (AC1-AC10)

The aldehydes (1.3 equiv) were dissolved initially in a minimum volume of methanol and then 10% NaOH solution was added to it to give a clear solution. The solution was cooled to 0°C and in about 30 min 1 equiv of substituted quinoline was added dropwise to it. The solution was kept at 0°C for an hour then allowed to stir at room temperature. A solid started separating out after some time. About 1h the solution was further stirred. The solid was filtered out and the methanol or ethanol was used to recrystallize to obtain the crystals of chalcones.

### Synthesis of Substituted Pyrazolines<sup>10</sup> (ACP1-ACP10)

A mixture of substituted oxo liked chalcones (0.1 mol), amino linked chalcones (0.1 mol) and hydrazine hydrate (0.01 mol) in 25 ml ethyl alcohol containing 1-2drops of glacial acetic acid was refluxed for 4-5 hr. TLC was used to monitor the reaction mixture. It was then cooled down and added to the ice cold water. The solid that was precipitated out was filtered and washed with water. It was recrystallized from ethanol. The physicochemical data of quinoline substituted 2-pyrazoline derivatives is given in Table 1.

## EVALUATION OF ANTIDIABETIC ACTIVITY

### *In vitro* alpha-glucosidase inhibition assay<sup>11</sup>

The standard method was used to carry out the Alpha-glucosidase inhibitory activity of the synthesised compounds. Phosphate buffer (50µl, 0.1M, pH-6), alpha glucosidase (10µl, 1unit/ml), varying concentration of the sample (20µl, 10-50µg/ml) was incubated at 37°C for 15min. Then, p-nitrophenanglucopyranoside (20µl, 5mM) was added as substrate and further incubated at 37°C for 20 min. sodium carbonate(50µl, 0.1M) was added to stop the reaction. The absorbance of the released p-nitro phenol was measured at 405nm using multiplate reader. Acarbose was utilized as standard. The

result was expressed in percentage inhibition, which was calculated using formula,

$$\text{Percentage inhibition} = [(A_0 - A_1) / A_0] \times 100$$

Where A1 is absorbance of sample and A0 is absorbance of control

## RESULTS

### Spectral data

#### 1-(4-(7-chloroquinolin-4-yl)amino)phenyl)-3-(4-nitrophenyl)prop-2-en-1-one (AC1)

**IR KBr (cm<sup>-1</sup>):** 1516 (Ar C=C str), 832 (Ar C-H bend), 3028 (Ar C-H str), 1651 (aliphatic C=C str), 1692 (C=O str), 3306 (NH str), 770 (C-Cl str), 1360 (Ar-NO<sub>2</sub>).

#### <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ ppm)

δ 6.55 (1H, dd, *J* = 6.6, 0.4 Hz), 7.02-7.20 (8H, 7.17 (ddd, *J* = 8.8, 1.9, 0.5 Hz), 7.12 (d, *J* = 13.9 Hz), 7.09 (d, *J* = 13.9 Hz), 7.05 (ddd, *J* = 8.3, 2.1, 0.5 Hz), 7.08 (ddd, *J* = 8.8, 1.5, 0.5 Hz)), 7.08 (2H, ddd, *J* = 8.3, 1.9, 0.5 Hz), 7.46 (1H, dd, *J* = 8.5, 2.0 Hz), 7.96 (1H, dt, *J* = 2.0, 0.5 Hz), 8.05 (1H, dt, *J* = 8.5, 0.4 Hz), 8.61 (1H, dd, *J* = 6.6, 0.5 Hz).

#### MS (M<sup>+</sup>): 430

#### 7-chloro-4-(4-(5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenoxy)quinoline (ACP1)

**IR KBr (cm<sup>-1</sup>):** 1516 (Ar C=C str), 836 (Ar C-H bend), 3035 (Ar C-H str), 1670 (C=O str), 1520 (C=N str), 3392 (N-H str, Pyrazoline), 772 (C-Cl str), 1360 (Ar-NO<sub>2</sub> str).

#### <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ ppm)

δ 2.95-3.08 (2H, 3.05 (dd, *J* = 6.5, 4.3 Hz), 2.99 (dd, *J* = 8.1, 6.5 Hz)), 5.24 (1H, dd, *J* = 8.1, 4.3 Hz), 6.55 (1H, dd, *J* = 6.6, 0.4 Hz), 6.95 (2H, ddd, *J* = 8.8, 1.7, 0.5 Hz), 7.28 (2H, ddd, *J* = 8.8, 1.8, 0.5 Hz), 7.40-7.54 (5H, 7.43 (ddd, *J* = 8.3, 1.4, 0.6 Hz), 7.47 (dd, *J* = 8.5, 2.0 Hz),

7.51 (ddd, *J* = 8.3, 1.4, 0.6 Hz)), 8.01 (1H, dt, *J* = 2.0, 0.5 Hz), 8.07 (1H, dt, *J* = 8.5, 0.4 Hz), 8.61 (1H, dd, *J* = 6.6, 0.5 Hz).

#### MS (M<sup>+</sup>): 434

#### 7-chloro-4-(4-(5-(3-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenoxy)quinoline (ACP2)

**IR KBr (cm<sup>-1</sup>):** 1510 (Ar C=C str), 838 (Ar C-H bend), 3038 (Ar C-H str), 1676 (C=O str), 1526 (C=N str), 3388 (N-H str, Pyrazoline), 768 (C-Cl str), 3476 (O-H str), 1364 (Ar-NO<sub>2</sub> str).

#### <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ ppm)

δ 3.00 (1H, dd, *J* = 8.1, 6.4 Hz), 3.11 (1H, dd, *J* = 6.4, 4.3 Hz), 5.25 (1H, dd, *J* = 8.1, 4.3 Hz), 6.55 (1H, dd, *J* = 6.6, 0.4 Hz), 6.86-7.05 (5H, 7.01 (ddd, *J* = 7.9, 2.6, 2.5 Hz), 6.98 (ddd, *J* = 2.9, 2.5, 0.5 Hz), 6.95 (ddd, *J* = 8.8, 1.7, 0.5 Hz), 6.90 (ddd, *J* = 8.2, 2.9, 2.6 Hz)), 7.18-7.31 (3H, 7.23 (ddd, *J* = 8.2, 7.9, 0.5 Hz), 7.28 (ddd, *J* = 8.8, 1.8, 0.5 Hz)), 7.47 (1H, dd, *J* = 8.5, 2.0 Hz), 8.01 (1H, dt, *J* = 2.0, 0.5 Hz), 8.07 (1H, dt, *J* = 8.5, 0.4 Hz), 8.61 (1H, dd, *J* = 6.6, 0.5 Hz).

#### MS (M<sup>+</sup>): 415

#### 7-chloro-4-(4-(5-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenoxy)quinoline (ACP3)

**IR KBr (cm<sup>-1</sup>):** 1512 (Ar C=C str), 838 (Ar C-H bend), 3032 (Ar C-H str), 1676 (C=O str), 1522 (C=N str), 3396 (N-H str, Pyrazoline), 776 (C-Cl str), 1358 (Ar-NO<sub>2</sub> str).

#### <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ ppm)

δ 3.05-3.17 (2H, 3.08 (dd, *J* = 6.9, 4.3 Hz), 3.13 (dd, *J* = 8.1, 6.9 Hz)), 5.24 (1H, dd, *J* = 8.1, 4.3 Hz), 6.55 (1H, dd, *J* = 6.6, 0.4 Hz), 6.95 (2H, ddd, *J* = 8.8, 1.7, 0.5 Hz), 7.28 (2H, ddd, *J* = 8.8, 1.8, 0.5 Hz), 7.38 (2H, ddd, *J* = 8.3, 1.9, 0.5 Hz), 7.47 (1H, dd, *J* = 8.5, 2.0 Hz), 7.95-8.02 (3H, 8.01 (dt, *J* = 2.0, 0.5 Hz), 7.98 (ddd, *J* = 8.3, 1.8, 0.5 Hz)), 8.07 (1H, dt, *J* = 8.5, 0.4 Hz), 8.61 (1H, dd, *J* = 6.6, 0.5 Hz).

**Table 1: Physicochemical data of Quinoline Substituted 2-Pyrazoline Derivatives (ACP1-ACP10)**

Comp. code	X	R	Mol. Formula	Mol. wt	m.p°C	R <sub>f</sub> Value	% Yield
ACP1	O	4-Cl	C <sub>24</sub> H <sub>17</sub> Cl <sub>2</sub> N <sub>3</sub> O	433	178-180	0.70	55
ACP2	O	3-OH	C <sub>24</sub> H <sub>18</sub> ClN <sub>3</sub> O <sub>2</sub>	415	162-164	0.76	60
ACP3	O	4-NO <sub>2</sub>	C <sub>24</sub> H <sub>17</sub> ClN <sub>4</sub> O <sub>3</sub>	444	190-192	0.68	58
ACP4	O	2,3-OCH <sub>3</sub>	C <sub>26</sub> H <sub>22</sub> ClN <sub>3</sub> O <sub>3</sub>	459	196-198	0.60	60
ACP5	O	4-N(CH <sub>3</sub> ) <sub>2</sub>	C <sub>26</sub> H <sub>23</sub> ClN <sub>4</sub> O	442	186-188	0.58	65
ACP6	NH	4-Cl	C <sub>24</sub> H <sub>18</sub> Cl <sub>2</sub> N <sub>4</sub>	432	160-162	0.68	58
ACP7	NH	3-OH	C <sub>24</sub> H <sub>19</sub> ClN <sub>4</sub> O	414	152-154	0.64	62
ACP8	NH	4-NO <sub>2</sub>	C <sub>24</sub> H <sub>18</sub> ClN <sub>5</sub> O <sub>2</sub>	443	178-180	0.66	60
ACP9	NH	2,3-OCH <sub>3</sub>	C <sub>26</sub> H <sub>23</sub> ClN <sub>4</sub> O <sub>2</sub>	458	182-184	0.70	58
ACP10	NH	4-N(CH <sub>3</sub> ) <sub>2</sub>	C <sub>26</sub> H <sub>24</sub> ClN <sub>5</sub>	441	170-172	0.56	60

**MS (M+1): 445**

7-chloro-N-(4-(5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)quinolin-4-amine (APC6)

**IR KBr (cm<sup>-1</sup>):** 1512 (Ar C=C str), 835 (Ar C-H bend), 3018 (Ar C-H str), 1678 (C=O str), 1536 (C=N str), 3388 (N-H str, Pyrazoline), 760 (C-Cl str), 1368 (Ar-NO<sub>2</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ ppm)**

<sup>1</sup>H NMR: δ 2.94-3.02 (2H, 2.99 (dd, *J* = 6.3, 4.3 Hz), 2.98 (dd, *J* = 8.1, 6.3 Hz)), 5.24 (1H, dd, *J* = 8.1, 4.3 Hz), 6.84 (1H, dd, *J* = 5.3, 0.4 Hz), 7.34-7.46 (7H, 7.43 (ddd, *J* = 8.3, 1.4, 0.6 Hz), 7.43 (ddd, *J* = 8.3, 1.8, 0.5 Hz), 7.37 (dd, *J* = 8.3, 1.9 Hz), 7.38 (ddd, *J* = 8.3, 1.1, 0.5 Hz)), 7.51 (2H, ddd, *J* = 8.3, 1.4, 0.6 Hz), 7.86 (1H, dt, *J* = 1.9, 0.4 Hz), 8.37 (1H, dt, *J* = 8.3, 0.4 Hz), 8.73 (1H, dd, *J* = 5.3, 0.4 Hz).

**MS (M+1): 433**

7-chloro-N-(4-(5-(3-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)quinolin-4-amine (APC7)

**IR KBr (cm<sup>-1</sup>):** 1518 (Ar C=C str), 835 (Ar C-H bend), 3022 (Ar C-H str), 1668 (C=O str), 1526 (C=N str), 3380 (N-H str, Pyrazoline), 760 (C-Cl str), 3482 (O-H str), 1368 (Ar-NO<sub>2</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ ppm)** δ 2.90-3.01 (2H, 2.98 (dd, *J* = 6.9, 4.3 Hz), 2.94 (dd, *J* = 8.1, 6.9 Hz)), 5.11 (1H, dd, *J* = 8.1, 4.3 Hz), 6.72 (2H, ddd, *J* = 8.2, 2.2, 0.5 Hz), 6.84 (1H, dd, *J* = 5.3, 0.4 Hz), 7.23 (2H, ddd, *J* = 8.2, 1.0, 0.5 Hz), 7.34-7.46 (5H, 7.38 (ddd, *J* = 8.3, 1.1, 0.5 Hz), 7.43 (ddd, *J* = 8.3, 1.8, 0.5 Hz), 7.37 (dd, *J* = 8.3, 1.9 Hz)), 7.86 (1H, dt, *J* = 1.9, 0.4 Hz), 8.37 (1H, dt, *J* = 8.3, 0.4 Hz), 8.73 (1H, dd, *J* = 5.3, 0.4 Hz).

**MS (M<sup>+</sup>): 414**

7-chloro-N-(4-(5-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)quinolin-4-amine (ACP8)

**IR KBr (cm<sup>-1</sup>):** 1506 (Ar C=C str), 830 (Ar C-H bend), 3022 (Ar C-H str), 1670 (C=O str), 1528 (C=N str), 3382 (N-H str, Pyrazoline), 758 (C-Cl str), 1362 (Ar-NO<sub>2</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ ppm)** δ 2.99-3.10 (2H, 3.02 (dd, *J* = 7.0, 4.3 Hz), 3.06 (dd, *J* = 8.1, 7.0 Hz)), 5.24 (1H, dd, *J* = 8.1, 4.3 Hz), 6.84 (1H, dd, *J* = 5.3, 0.4 Hz), 7.34-7.46 (7H, 7.38 (ddd, *J* = 8.3, 1.9, 0.5 Hz), 7.43 (ddd, *J* = 8.3, 1.8, 0.5 Hz), 7.37 (dd, *J* = 8.3, 1.9 Hz), 7.38 (ddd, *J* = 8.3, 1.1, 0.5 Hz)), 7.86 (1H, dt, *J* = 1.9, 0.4 Hz), 7.98 (2H, ddd, *J* = 8.3, 1.8, 0.5 Hz), 8.37 (1H, dt, *J* = 8.3, 0.4 Hz), 8.73 (1H, dd, *J* = 5.3, 0.4 Hz).

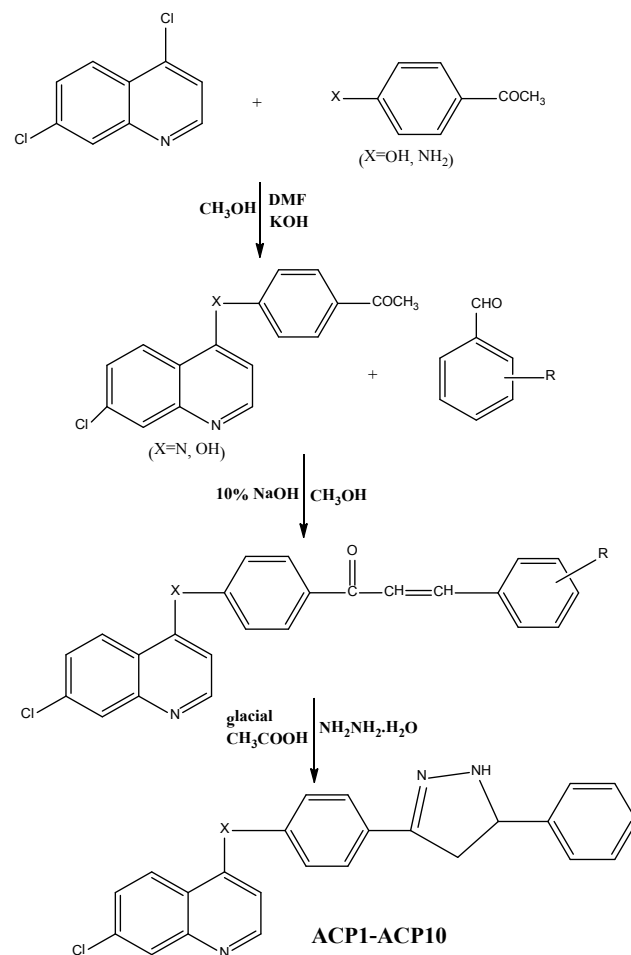
**MS (M+1): 444****DISCUSSION****Chemistry**

Different substituted oxo linked chalcones and amino linked chalcones were prepared as reported in the

literature with different substituted aromatic aldehydes. These compounds were characterized by TLC, melting point and IR spectra that showed characteristic absorption band at 1650 cm<sup>-1</sup> of CH=CH group. The title compounds pyrazoline derivatives (ACP1-ACP10) were prepared as given in Figure 1 upon cyclisation of oxo linked and amino linked chalcones with hydrazine hydrate. The IR spectra of substituted pyrazoline showed characteristic absorption band at 3396 cm<sup>-1</sup> corresponding to N-H of pyrazoline, which was absent in the intermediate chalcones. Similarly the <sup>1</sup>H NMR of the synthesized pyrazoline showed one characteristic signal at δ 2.95-3.08 (2H, 3.05 (dd, *J* = 6.5, 4.3 Hz) which was absent in the <sup>1</sup>H NMR spectra of substituted chalcones. The formation of the title compounds pyrazolines has therefore been confirmed and further established by mass spectra in accordance with molecular formula.

**Antidiabetic activity**

*In vitro* antidiabetic activity of the final synthesised compounds was performed by alpha glucosidase inhibition assay. Compounds ACP1, ACP4, ACP5,

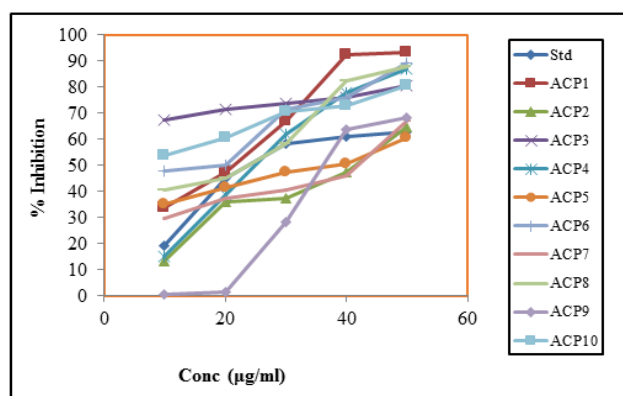


**Figure 1: Scheme for synthesis of 2-pyrazoline derivatives.**



**Table 2: Antidiabetic activity by alpha-glucosidase inhibition assay of 2-pyrazoline derivatives**

		Concentration ( $\mu\text{g/ml}$ )					
% inhibition	Sample Code	10	20	30	40	50	IC <sub>50</sub>
	Standard	19.32	45.21	58.23	61.2	62.69	17.47
	ACP1	34.06	47.25	67.03	92.30	93.40	29.1
	ACP2	13.18	36.26	37.36	47.25	64.83	148.75
	ACP3	67.39	71.73	73.91	76.06	80.43	144.79
	ACP4	15.12	38.63	61.9	78	86.76	26.94
	ACP5	35.16	41.75	47.25	50.54	60.43	180.53
	ACP6	47.82	50	71.73	76.08	89.13	31.12
	ACP7	29.67	37.36	40.65	46.15	67.03	126.36
	ACP8	40.65	45.05	58.24	82.41	87.91	32.56
	ACP9	0.58	1.76	28.52	63.82	68.52	31.18
	ACP10	53.63	60.54	70.54	72.81	80.45	62.22

**Figure 2: Antidiabetic activity of 2-Pyrazoline derivatives (ACP1-ACP10) by alpha glucosidase inhibition assay.**

ACP8 and ACP9 have shown good antidiabetic activity when compared to the standard acarbose as given in Table 2 and Figure 2. The presence of electron releasing groups like methoxy, dimethyl amino and electron withdrawing groups like nitro and chloro resulted in increased antidiabetic activity. The antidiabetic activity in oxo linked 2-pyrazoline derivatives was good compared to amino linked 2-pyrazoline derivatives.

## CONCLUSION

In this study, the successful synthesis of 2-pyrazoline derivatives from cyclisation of quinolinyl chalcones have moderate yields and most synthesized compounds have shown promising antidiabetic activity.

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## CONFLICT OF INTEREST

The authors declare that there was no conflict of interest.

## ABBREVIATIONS

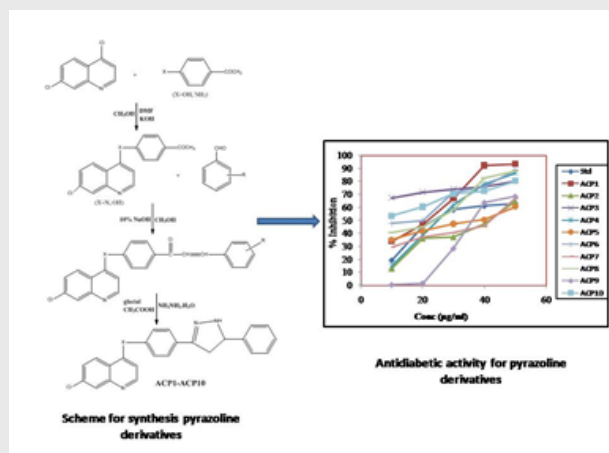
**ATP-K<sup>+</sup>**: Adenosine triphosphate sensitive potassium; **DMF**: Dimethylformamide; **KOH**: Potassium hydroxide; **IR**: Infrared; **<sup>1</sup>H NMR**: Proton nuclear magnetic resonance; **<sup>13</sup>C NMR**: Carbon-13 nuclear magnetic resonance; **TLC**: Thin layer chromatography; **UV**: Ultraviolet; **ATR**: Attenuated total reflection; **equiv**: Equivalent; **h**: hour; **%**: Percentage; **NaOH**: Sodium hydroxide; **°C**: Degree celsius; **min**: Minute; **mol**: mole; **m.p**: melting point; **R<sub>f</sub>**: Retardation factor;  $\mu\text{l}$ : Microliter; **M**: Molar;  $\mu\text{g}$ : Microgram; **mM**: Millimolar; **ml**: Millilitre; **nm**: Nanometre; **str**: Stretching; **KBr**: Potassium bromide; **MHz**: Megahertz; **CDCl<sub>3</sub>**: Deuteriochloroform; **d**: Doublet; **MS**: Mass spectroscopy; **J**: coupling constant; **dd**: doublets of doublet; **dt**: doublet of triplets; **ddd**: doublet of doublets of doublets.

## REFERENCES

- Sowers JR, Epstein M, Frohlich ED. Hypertension and cardiovascular disease: An update. *Hypertension*. 2001;37(1):1053-105.
- Toeller M.  $\alpha$ -Glucosidase inhibitors in diabetes: Efficacy in NIDDM subjects. *Eur J Clin*. 1994;24(Suppl 3):31-5.
- Desai NC, Kotadiya GM, Trivedi AR. Studies on molecular properties, prediction, antitubercular and antimicrobial activities of novel quinoline based pyrimidine motifs. *Bioorg Med Chem Lett*. 2014;24(14):3126-30.
- Tseng CH, Tung CW, Peng SI, Chen YL, Tseng CC, Cheng CM. Discovery of pyrazolo[4,3-c]quinoline derivatives as potential anti-inflammatory agents through inhibiting of NO production. *Molecules*. 2018;23(5):1036.
- Faidallah HM, Al-Mohammadi MM, Alamry KA, Khan KA. Synthesis and biological evaluation of fluoropyrazolesulfonyl urea and thiourea derivatives

- as possible antidiabetic agents. J Enzyme Inhib Med Chem. 2016;31(Suppl 1):157-63.
6. Ali MA, Yar MS, Kumar M, Pandian GS. Synthesis and antitubercular activity of substituted novel pyrazoline derivatives. Nat Prod Res. 2007;21(7):575-9.
  7. Amir M, Kunar H, Khan SA. Synthesis and pharmacological evaluation of pyrazoline derivatives as new anti-inflammatory and analgesic agents. Bioorg Med Chem Lett. 2008;18(3):918-22.
  8. Karabacak MK, Altinop MD, Ciftci HI, Koga R, Otsuka M, Fujiba M. Synthesis and evaluation of new pyrazoline derivatives as potential anticancer agents. Molecules. 2015;20(10):19066-84.
  9. Kotra V, Ganapaty S, Adapa SR. Synthesis of a new series of quinolinyl chalcones as anticancer and anti-inflammatory agents. Indian J Chem. 2011;41B:1109-16.
  10. Chovatia YS, Gandhi SP, Gorde PL, Bagade SB. Synthesis and antibacterial activity of some pyrazoline derivatives. Orient J Chem. 2010;26(1):275-8.
  11. Telagari M, Hullatti K. *In-vitro* alpha amylase and alpha glucosidase inhibitory activity of *Adiantum caudatum* Linn. and *Celosia argentea* Linn. extracts and fractions. Ind J Pharmacol. 2015;47(4):425-9.

## PICTORIAL ABSTRACT



## SUMMARY

- Diabetes mellitus is a common disease worldwide with many progressively increasing complications day by day. Despite the fact that there are so many synthetic and herbal drugs available, there is no proper treatment for diabetes.
- This inculcated the need for discovering newer and better molecules to treat diabetes in terms of controlling blood glucose as well as to reduce the complications in order to improve the quality of life.
- In the present study, 1-(4-(7-Chloroquinolin-4-yl oxy) phenyl ethanone and 1-(4-(7-Chloroquinolin-4-yl amino) phenyl ethanone was synthesized by nucleophilic substitution of 4-Chloro of 4,7-dichloroquinoline with substituted 4-hydroxy acetophenone and 4-amino acetophenone in DMF and KOH respectively.
- The oxo linked chalcones and amino linked chalcones was synthesized by Claisen Schmidt condensation with different substituted aromatic aldehydes. Finally substituted pyrazolines (ACP1-ACP10) was synthesized upon cyclisation of oxo linked and amino linked chalcones with hydrazine hydrate.
- The final synthesized compounds were evaluated for their *in vitro* antidiabetic activity by alpha glucosidase inhibition assay. Few compounds showed good antidiabetic activity compared to the standard drug acarbose.

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