Chemistry & Biology Interface, 2016, 6, 4, 189-197

RESEARCH PAPER ISSN: 2249 –4820

CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Design, Synthesis and Antidiabetic Evaluation of New Cyanoquinoloxy Benzylidenyl 2,4-Thiazolidinediones

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Received 16 May 2016; Accepted 6 July 2016

Abstract: In search of new antihyperglycemic/antidiabetic agents, hereby following rational approach of drug designing, new (Z)-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) substituted quinoline-3-carbonitriles (**4a-g**) have been synthesized carrying Knoevenagel condensation of new precursors 2-(4-formylphenoxy) substituted quinoline-3-carbonitriles (**3a-g**) and 2,4-thiazolidindione. The required precursors (**3a-g**) were obtained from 2-chloro-3-formyl quinolines (**1a-g**). The compounds (**4a-g**) have been evaluated for *in vivo* antidiabetic activity in sucrose loaded rat model and some of them have displayed moderate antidiabetic activity.

Keywords: Type 2 diabetes mellitus, Quinoline, 2,4-Thiazolidinediones, Antidiabetic agents.

1. Introduction

Non insulin dependent diabetes mellitus (NIDDM) is a complex metabolic disorder with heterogeneous etiologies and is the result of insulin resistant and abnormal insulin secretion leading to hyperglycemia and diabetic complications [1-5]. The complications of this kind of diabetes *viz.* neuropathy, nephropathy, retinopathy, obesity, dyslipidemia, hypertension and other cardiovascular problems are emerging as serious threats [6-12] The clinically used antihyperglycemic drugs for treating type 2 diabetes mellitus include Insulin secretagogues (sulfonylureas, phenylalanine derivatives and glucagonlike peptides); Insulin sensitizers (metformin, thiazolidinediones/TZDs and β-receptor agonists), α-Glucosidase inhibitors (acarbose, miglitol and voglibose), aldose reductase (AR) inhibitors (tolrestat and epalrestat) and DPP-IV inhibitors (gliptins) [13-15]. Thiazolidinediones (TZDs)/glitazones class of insulin sensitizers have been, used widely for management of type 2 diabetes mellitus [16-18]. Clinical agents which were prescribed from this class were like Pioglitazone

1, Rosiglitazone **2**, Troglitazone **3** (**Fig. 1**) and Ciglitazone and are withdrawn because of their severe side effects irrespective of their potential insulin sensitizer property [19, 20]. However, the TZDs, which have been recently withdrawn were developed and allowed to use in clinically at the time when not much scientific data were available on structures and transcriptions of peroxisome proliferator-activated receptors (PPARs), enzymes involved in diabetic mellitus [20].

Recent advances have helped and provided clear understanding of PPARs and therefore medicinal chemists are now keenly focusing their attention on the synthesis of newer analogues of this class by varying lipophilic cyclic tail, incorporating various five/six membered sulphur/nitrogen/ oxygen heterocycles and keeping acid head of the classical TZDs system intact(**Fig. 1**). It is also reviewed that the classical lipophilic tail of the TZDs when replaced by heterocyclic moieties like 2-pyridyl [21], benzoxazolyl [22], thiazolyl and oxazolyl [23], indinonyl [24] and indolyl acetic acid [25] then such TZDs have displayed promising antihyperglycemic activity. The linkers having one or more than one alkyl or alkenyl carbon(s) as pharmacophores have also been found useful in designing TZDs for obtaining better insulin sensitizing property [26-29]. Therefore, medicinal chemists are now paying more attention on designing and generating library of new TZDs [30-36] in search of safe and more effective insulin sensitizers to manipulate and treat type 2 diabetes mellitus and its complications.

Quinoline derivatives are well explored as therapeutic agents because of their pivotal role in various biological processes and some of them have displayed antihyperglycemic activity [37- 39]. Literature revels that there is scanty information on designing and synthesizing of TZDs having substituted quinolines as a lipophilic tail, 2,4-thiazolidinedione as an acidic head and no carbon chain as a linker.

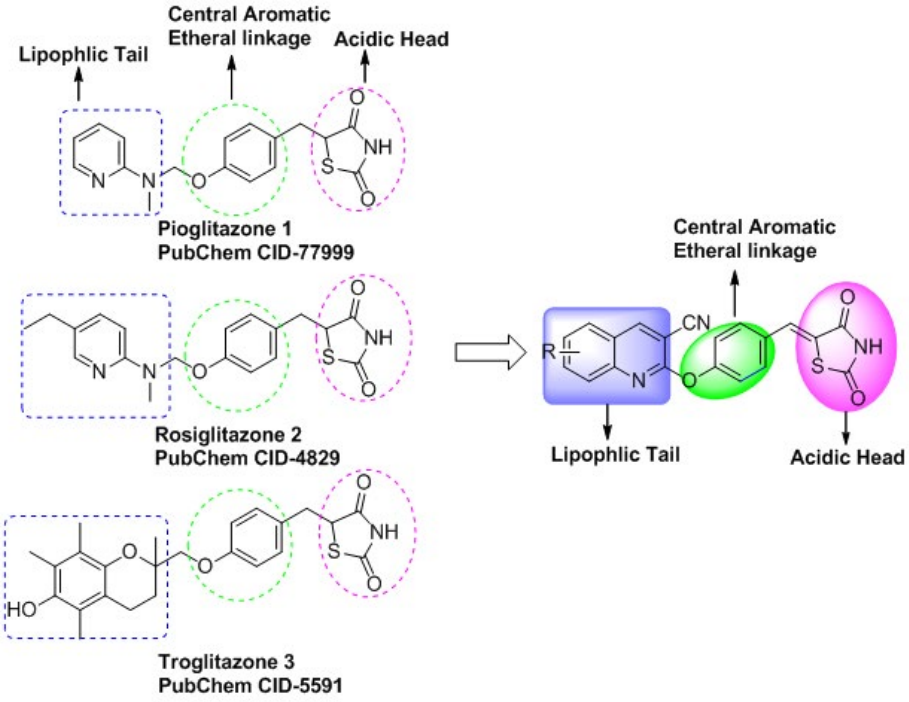


Fig. 1. The structural modification progress of 2,4-thiazolidinediones.

Considering the above facts in mind and in continuation of our search on new antihyperglycemic agents [40-44], here an attempt has been made to design and synthesize new prototypes having pharmacophores like quinolines, 2,4-thiazolidinediones (TZD's) and phenoxy alkyl group as central linker in single molecular architectural framework to achieve the new entities with better antidiabetic activity. Here we report the synthesis of new (Z)-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl) phenoxy)-substituted quinoline-3-carbonitriles, their antihyperglycemic activity.

1. Experimental

General

Chemicals and solvents required were procured from Merck, Spectrochem and S. D. Fine chem. Melting points were determined in open capillary and were uncorrected. IR spectra were recorded on Bruker (FTIR-ATR) instrument, ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance 300 (FT-NMR) and Bruker DRX-300 instrument respectively using $CDCl_3$/ DMSO-d_6 as solvents and TMS as an internal standard, *J* in Hz. Chemical shifts are in δ (ppm). High–resolution mass spectra (HRMS) were recorded on Agilent 6520 (QTOF) ESI-HRMS instrument and mass spectra on JEOL-Accu TOF DART-MS-T 100Lc. The purity of the synthesized compounds was checked by thin layer chromatography (TLC) using Merck silica gel $60F_{254}$ aluminum sheet and hexane: ethyl acetate as eluent. Metformin and STZ were purchased from Sigma Aldrich Co., USA. One touch glucometer and glucostrips were procured from Roche Diagnostics India Ltd.

1.1. *General procedure for the synthesis of 2-chloroquinoline-3-carbonitrile (2a)*

2-Chloroquinoline-3-carbaldehyde (**1a**) (1 mmol) was dissolved in tetrahydrofuron (THF) (5 ml). To this solution aqueous ammonia (6 ml) was added and the solution was stirred for 30 min. To this stirred solution molecular iodine (1.1 mmol) was added in portions and then the reaction mass was at stirred rt. The progress of the reaction was monitored by thin layer chromatography (TLC). After stirring for 4 h the reaction, mixture was treated with aqueous $Na_2S_2O_3$ and the product was then extracted with ethyl acetate (10 ml × 2). The combined organic layers were dried over Na_2SO_4. The solvent from extract was removed under a reduced pressure, and the obtained crude solid residue was crystallized by using ethanol. Similarly the other compounds, (**2b-g**) of the series were synthesized. The melting points and spectral data of these quinilino carbonitriles are in good agreement with those reported in the literature [45].

1.1.1. ***2-Chloroquinoline-3-carbonitrile (2a)***

Compound **2a** White solid, 89 % yield, Mp 140-142 °C. ^{1}H NMR: δ 7.68-8.10 (m, 4H, Ar-H, overlapped spllited peaks), 8.57 (s, 1H, a proton adjacent to CN). DART-MS (ESI^{+}) m/z: 189.3 $[M+H]^{+}$for molecular formula $C_{10}H_6ClN_2$.

1.2. *General procedure for the synthesis of 2-(4-formylphenoxy) quinoline-3-carbonitrile (3a)*

A mixture of *p*-hydroxy benzaldehyde (5 mmol) and anhydrous potassium carbonate (10 mmol) was added to dimethylformamide (DMF) (5 mL) and the reaction was stirred for 30 min. To this mass 2-chloroquinoline-3-carbonitrile **2a-g** (5 mmol) was added and the mixture was heated at 90 °C and the progress of the reaction was monitored by TLC. After heating the reaction mass for 4 h, it was then cooled to room temperature and then poured into chilled water (50 mL) with continuous stirring followed by neutralization with 1.5 N HCl. The obtained solid mass was filtered, washed well with water, dried and crystallized from ethanol. The other compounds, (**3b-g**) of the series were similarly

synthesized.

1.2.1. ***2-(4-Formylphenoxy) quinoline-3-carbonitrile (3a)***

Compound **3a** White solid, 83 % yield, Mp 161-163 °C. ^{1}H NMR: δ 7.50 (d, J =8, 2H, Ar-H,), 7.57-7.86 (m, 4H, Ar-H, overlapped spllited peaks), 7.99 (d, J = 8.1, 2H, Ar-H), 8.59 (s, 1H, a proton adjacent to CN), and 10.04 (s, 1H, aldehydic). ^{13}C-NMR: δ 98.7, 114.8, 122.4, 124.3, 126.9, 128.1, 128.2, 130.1, 131.5, 133.5, 133.8, 146.4, 147, 157.5, 158.2, 191.1 (C=O). HRMS (ESI) $[M+H]^+$ calculated for $C_{17}H_{11}N_2O_2$ 275.0821, found 275.1250.

1.3. ***General procedure for the synthesis of 2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl) phenoxy) quinoline-3-carbonitrile (4a)***

A mixture of 2-(4-formylphenoxy) quinoline-3-carbonitrile (3 mmol) (**3a**), 2-thiazolidinedione (3 mmol) (5) and piperidinium acetate (4.5 mmol) was refluxed in dry ethanol. The progress of the reaction was monitored by thin layer chromatography. After refluxing the reaction mass for 4-5 h, it was allowed to cool to rt. Then, the whole reaction mass was poured on crushed ice. The appeared solid was filtered, washed with ethanol and dried. The crude was crystallized using DMF-Ethanol. Similarly the other compounds, (**4b-g**) of the series have been synthesized.

1.3.1. ***(Z)-2-(4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenoxy)quinoline-3-carbonitrile (4a)***

Compound **4a** Pale yellow solid, 85 % yield, Mp 221-223 °C. ^{1}H NMR: δ 7.50-8.06 (m, 9H, 8 Ar-H and 1 vinylic-H), 9.19 (s, 1H, a proton adjacent to CN), 12.59 (s, 1H, NH, exchangeable with D_2O). ^{13}C-NMR: δ 97.6, 115, 122.6, 123.3, 123.9, 126.5, 127.1, 128.7, 130.4, 130.9, 131.6, 133.5, 146.1, 147.6, 153.7, 158.2, 167.3(C=O), 167.8(C=O). HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{12}N_3O_4S$ 374.0599, found 374.0584 $[M+Na]^+$ for calculated $C_{20}H_{11}N_3O_4S$ Na 396.0419, found 396.0399.

1.3.2. ***(Z)-2-(4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenoxy)-6-methoxyquinoline-3-carbonitrile (4b)***

Compound **4b** Yellow solid, 78 % yield, Mp 258-260 °C. ^{1}H NMR: δ 3.84 (s, 3H, OCH_3), 7.05-7.98 (m, 8H, 7 Ar-H and 1 vinylic-H), 9.04 (s, 1H, a proton adjacent to CN), 12.65 (s, 1H, NH, exchangeable with D_2O). ^{13}C-NMR: δ 55.3, 96.1, 110.4, 119.2, 120.1, 123.2, 124.5, 130.1, 130.6, 131.7, 145.8, 147.9, 154.2, 159.9, 163.5, 164.1, 167.4(C=O). 167.5(C=O); DART-MS (ESI^+) m/z: 404.1 $[M+H]^+$for molecular formula $C_{21}H_{14}N_3O_4S$.

1.3.3. ***(Z)-2-(4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenoxy)-6-ethoxyquinoline-3-carbonitrile (4c)***

Compound **4c** Yellow solid, 81 % yield, Mp 251-253 °C. ^{1}H NMR: δ 1.53 (t, J = 8, 3H, OCH_2CH_3) 3.64 (q, J = 8, 2H, OCH_2CH_3), 7.33-8.23 (m, 8H, 7 Ar-H and 1 vinylic-H), 9.12 (s, 1H, a proton adjacent to CN), 12.69 (s, 1H, NH, exchangeable with D_2O). ^{13}C-NMR: δ 19.3, 65.1, 94.1, 109.2, 116.2, 120.3, 122.1, 123.5, 127.5, 128.6, 130.3, 132.6, 134.2, 146.8, 148.8, 156.2, 158.9, 161.5, 162.1, 167.1(C=O), 167.4(C=O). DART-MS (ESI^+) m/z: 418.2 $[M+H]^+$for molecular formula $C_{22}H_{16}N_3O_4S$.

2.3.4. (Z)-2-(4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenoxy)-8-methylquinoline-3-carbonitrile (4d)

Compound **4d** Yellow solid, 83 % yield, Mp 255-257 °C ^{1}H NMR: δ 2.15 (s, 3H, CH_3), 7.34-8.23 (m, 8H, 7 Ar-H and 1 vinylic-H), 9.02 (s, 1H, a proton adjacent to CN), 12.59 (s, 1H, NH, exchangeable with D_2O). ^{13}C-NMR: δ 16.4, 95.3, 114.9, 121.3, 123.1, 123.3, 125.2, 127.4, 127.9, 128.3, 131, 131.7, 143.7, 146.2, 147.3, 154.1, 158.1, 161.9, 167.1(C=O), 167.3 (C=O). DART-MS (ESI^+) m/z: 388.3 $[M+H]^+$ for molecular formula $C_{21}H_{14}N_3O_3S$.

1.1.5. ***(Z)-2-(4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenoxy)-7-methylquinoline-3-carbonitrile (4e)***

Compound **4e** Pale yellow solid, 85 % yield, Mp 259-261 °C. ^{1}H NMR: δ 2.50 (s, 3H, CH_3) 7.45- 7.95 (m. 8H, 7 Ar-H and 1 Vinylic-H), 9.11(s, 1H, a proton adjacent to CN), 12.63 (s, 1H, NH, exchangeable with D_2O). ^{13}C-NMR: δ 21.4, 96.4, 115.2, 122, 122.6, 123.2, 126.4, 128.4, 128.5, 130.4, 130.9, 131.6, 144.5, 146.4, 147.1, 153.8, 158.4, 162.2, 167.3(C=O), 167.7(C=O). HRMS (ESI) $[M+H]^+$calculated for $C_{21}H_{14}N_3O_3S$ 388.0756, found 388.0743 $[M+Na]^+$ for calculated $C_{21}H_{13}N_3O_3S$ Na 410.0575, found 410.0558.

1.1.6. ***(Z)-2-(4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenoxy)-6-methylquinoline-3-carbonitrile (4f)***

Compound **4f** Pale yellow solid, 79 % yield, Mp 241-243°C. ^{1}H NMR: δ 2.41 (s, 3H, CH_3), 7.38-8.15 (m, 8H, 7 Ar-H and 1 vinylic-H), 9.13 (s, 1H, a proton adjacent to CN), 12.67 (s, 1H, NH, exchangeable with D_2O). ^{13}C-NMR: δ 20.4, 96.3, 116, 122.3, 122.9, 123.6, 124.3, 126.4, 127.5, 128.4, 131.2, 131.7, 144.7, 146.8, 147.6, 156.1, 158.5, 163.2, 167.4(C=O), 167.6 (C=O). DART-MS (ESI^+) m/z: 388.2 $[M+H]^+$ for molecular formula $C_{21}H_{14}N_3O_3S$.

1.1.7. ***(Z)-2-(4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenoxy)-7-methoxyquinoline-3-carbonitrile (4g)***

Compound **4g** Yellow solid, 82 % yield, Mp 245-247 °C. ^{1}H NMR: δ 3.87(s, 3H, OCH_3) 7.05-7.96 (m, 8H, 7 Ar-H and 1 vinylic-H), 9.04 (s, 1H, a proton adjacent to CN), 12.63 (s, 1H, NH, exchangeable with D_2O). ^{13}C-NMR: δ 55.9, 94.1, 106.4, 118.9, 119, 122.7, 123.3, 130, 130.4, 131.6, 146.5, 148.8, 153.8, 159.1, 162.2, 163.6, 167.3(C=O), 167.7(C=O). HRMS (ESI) $[M+H]^+$ calculated for $C_{21}H_{14}N_3O_4S$ 404.0705, found 404.0689.

1.3. ***Experimental protocol for antidiabetic activity***

2.4.1. Procurement and selection of animals

Male albino rats of Sprague Dawley strain (8 to 10 weeks of age: body weight 150 ± 20 g) were procured from the animal colony of the Central Drug Research Institute, Lucknow. Research on animals was conducted in accordance with the guidelines of the committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) formed by the Government of India in 1964. Rats were always placed in groups of five in polypropylene cages and provided standard environmental conditions. The animal had free access to pellet diet and tap water unless stated otherwise.

2.4.2. Effect in sucrose loaded rat model

Male albino rats of Sprague Dawley strain were selected for this study. Fasting blood glucose level of each animal was checked by glucometer using glucostrips (ACCU-CHEK) after 16 h starvation. Animals showing blood glucose level between 60 to 80 mg/dl at 0 min were finally selected and divided into groups of five animals in each. Rats of experimental group were administered the suspension of the test sample orally prepared in 1.0 % gum acacia (vehicle) at desired dose levels i.e. 100 mg/kg body weight of compounds and standard antidiabetic drug i.e. glybenclamide. Animals of control group were given an equal amount of 1.0 % gum acacia and termed as sham control. An oral sucrose load of 10 g/kg body weight was always given to each animal exactly after 30 min post administration of the test sample/ vehicle. Blood glucose profile of each rat was again determined at 30, 60, 90 and 120 min post administration of sucrose by glucostrips and Area under curve (AUC) determined. Food but not water was withheld from the cages during the course of experimentation. Comparing the AUC of experimental group with that to control

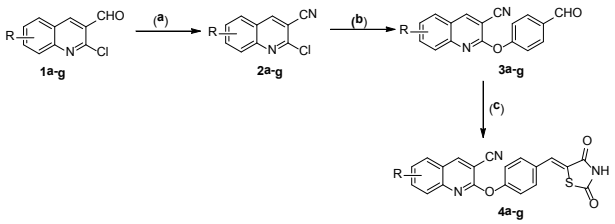
group determined the overall improvement of oral glucose tolerance by the compound. Statistical analysis was made by Dunnett's test (Prism Software) [46].

2. Results and discussion

3.1. *Chemistry*

The titled compounds have been synthesized starting from freshly prepared 2-chloro-3-formyl quinolines in three successive steps. Freshly prepared 2-chloro-3-formyl quinolines (**1a-g**) [47] were allowed to interact with ammonia and molecular iodine in THF at room temperature and obtained 2-chloroquinoline-3-carbonitriles (**2a-g**). The melting points of the 2-chloroquinoline-3-carbonitriles (**2a-g**) are in good agreement with those in reported [45]. The carbonitrile quinolines (**2a-g**) were then condensed with 4-hydroxy benzaldehyde in DMF in the presence of potassium carbonate to get the required 2-(4-formylphenoxy) quinoline-3-carbonitriles (**3a-g**) with moderate to better yields. The physical data of (**3a-g**) is incorporated in (**Table 1**). (Z)-2-(4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenoxy)substituted quinoline-3-carbonitriles (**4a-g**) were then synthesized by carrying the Knoevenagel condensation of 2-(4-formylphenoxy)quinoline-3-carbonitriles (**3a-g**) and 2,4-thiazolidinedione in dry ethanol in presence of piperidinium acetate (**Scheme 1**). The physical data of the new compounds, (**4a-g**) is recorded in (**Table 2**).

All the synthesized intermediates and titled compounds have been characterized using their ^{1}H NMR, ^{13}C NMR and HRMS spectral data. The ^{1}H NMR spectrum of compound **4g** displayed characteristics singlet peak at δ 3.87 ppm for methoxy protons, singlet at δ 9.04 ppm, corresponds to deshielded aromatic proton due to withdrawing effect of nitrile functional group. A singlet peak at δ 12.63 ppm has also been recorded for N-H labile proton of the 2,4-thiazolidinedione ring. The presence of three characteristic carbon signals are observed at δ 55.9, 167.3 and 167.7 ppm in ^{13}C NMR spectrum of compound **4g** owing to carbons of O-CH_3, and two C=O groups, respectively, confirming the presence of a 2,4-thiazolidinedione ring in **4g**. The HRMS spectrum of compound **4g** further strengthen the structure as it displays $[M+H]^+$ ion peak at *m/z* 404.0689 in consistent with its molecular formula $C_{21}H_{14}N_3O_4S$.



Reagents and conditions : (a) Aqueous NH_3, I_2, THF, rt. Stirr 3-4 h; (b) *p*-hydroxy benzaldehyde, K_2CO_3, DMF, 90 ^{o}C, 4 h; (c) 2,4-TZD, Piperidinium acetate, EtOH, reflux 4-5 h.
Scheme 1. Synthesis of (Z)-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) substituted quinoline-3-carbonitriles.

Table 1. Physical data of 2-(4-formylphenoxy) quinoline-3-carbonitriles (**3a-g**)[a].

Compounds	R	Melting points (°C)[c]	Yield (%)[b]
3a	H	161-163	83
3b	6-OCH_3	231-233	82
3c	6-OC_2H_5	221-223	78
3d	8- CH_3	181-182	79
3e	7-CH_3	167-169	83
3f	6-CH_3	201-203	81
3g	7-OCH_3	175-177	80

Reaction conditions: substituted 2-chloroquinoline-3-carbonitriles (**2a-g**) (5 mmol), *p*-hydroxy benzaldehyde (5 mmol), anhydrous potassium carbonate (10 mmol) in dimethylformamide (DMF) (5 mL) heated at 90 °C for 4-5 h [a]. Isolated yields [b]

Table 2. Physical data of (Z)-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) substituted quinoline-3-carbonitriles (**4a-g**) [a].

Compounds	R	Melting points (°C)	Yield (%)[b]
4a	H	221-223	85
4b	6-OCH_3	258-260	78
4c	6-OC_2H_5	251-253	81
4d	8- CH_3	255-257	83
4e	7-CH_3	259-261	85
4f	6-CH_3	241-243	79
4g	7-OCH_3	245-247	82

Reaction conditions: Substituted 2-(4-formylphenoxy) quinoline-3-carbonitriles **(3a-g)** (3mmol), 2-4-TZD (3 mmol), piperidinium acetate (3 mmol), ethanol (10 ml), refluxed for 4-5 h[a]. Isolated yields [b]

3.2. Antidiabetic activity

3.2.1. Antihyperglycemic activity evaluation.-

The compounds (**4a–g**) were evaluated for their antihyperglycemic activity in sucrose loaded model Sprague Dawley strain male albino rats.

3.2.2. Improvement of test samples on normoglycemic rats.-**Table 3** shows the effect of various (**4a-g**) compounds on improvement of oral glucose tolerance of sucrose loaded rat model. The standard antidiabetic drug i.e. metformin was taken as positive standard. It is evident from the results that compounds **4a**, **4b**, **4c**, **4d**, **4e**, **4f**, and **4g** have shown moderate improvement of oral glucose tolerance of sucrose loaded rats. In Sucrose loaded normoglycemic rats, at a dose of 100 mg/kg, compounds **4a**, **4b**, **4c**, **4d**, **4e**, **4f**, and **4g** showed improvement on oral glucose tolerance to the tune of 4.68 ($p<0.05$), 5.12 ($p<0.05$), 7.55 ($p<0.05$), 3.22 ($p<0.05$), 0.40 ($p<0.05$), 6.82 ($p<0.05$) and 9.40 ($p<0.05$) % respectively during 0-120 min. The standard drug metformin showed around 19.1 ($p<0.01$) improvement in oral glucose tolerance in Sucrose loaded rat model at the tested dose i.e. 100 mg/kg p.o. (**Fig. 2)**

Table 3. Effect of compounds **4a-g** and Standard drug Metformin on improvement of oral glucose tolerance of sucrose loaded rats and docking simulations.

Compounds	Dose (mg/ kg)	% improvement in oral glucose tolerance (0-120 min)
4a	100	4.68
4b	100	5.12
4c	100	7.55
4d	100	3.22
4e	100	0.40
4f	100	6.82
4g	100	**9.40***
Metformin	100	**19.1****

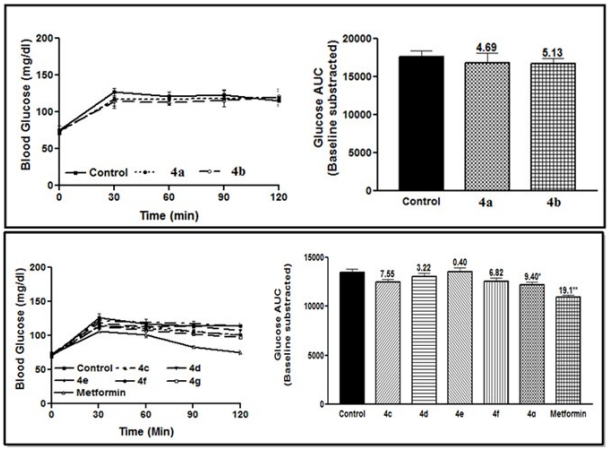


Fig. 2. Effect of compounds **4a-g** and Standard drug metformin on improvement of oral glucose tolerance of sucrose loaded rats.

2. Conclusion

A synthetic route for new (Z)-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) quinoline- 3-carbonitriles (**4a-g**) has been developed using 2-chloro-3-formyl quinolines (**1a-g**) as a starting material. This route gives

overall moderate yield of the titled compounds and has Knoevenagel condensation as a key step. An unique Knoevengel condensation of 2-(4-formylphenoxy) quinoline-3-carbonitriles (**3a-g**) and 2,4-thiazolidinedione has been carried in the presence of base, piperidinium acetate in ethanol. This route is scalable and some of the compounds from this series have displayed moderate antidiabetic activity compare to metformin.

Acknowledgements

Authors are thankful to Professor D. B. Ingle for his invaluable discussions and guidance. Authors are also very much grateful to CSIR-CDRI, Lucknow, India for providing scanning and screening data of newly synthesized compounds. One of the authors ARD is also grateful to Wockhardt Research Centre, Aurangabad and Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, India for awarding research fellowship.

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