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Design, synthesis, characterization and biological evaluation of some novel 3, 6-disubstituted-2-pyridinecarboxamide derivatives as antidiabetic agents

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ABSTRACT
Glucokinase catalyzes the phosphorylation of glucose to glucose-6-phosphate and is predominantly expressed in liver and pancreatic β-cells. GK acts as a glucose sensor regulating hepatic glucose metabolism and glucose-dependent insulin secretion. At present a lot of anti-hyperglycemic agents are available in market but they exhibits single mode of action so, select the other targets having multiple action to fulfill the needs to treat type II diabetes, for that we have synthesized some compounds by using moiety 3, 6-disubstituted 2-pyridinecarboxamide through structure activity relationship. Such newly synthesized compounds are elucidated by IR, ^{1}H-NMR and Mass spectroscopy. These synthesized compounds were evaluated for their anti-diabetic activity. Comeouts of in vivo antihyperglycemic activity specified that substitution of pyridine ring at 3rd position with hydrophobic group like methyl group enhances the antihyperglycemic activity shown in compound **5g, 5h and 5i.** The replacement of H from the 4th postion of 1,3-thiazol-2-yl amide nucleus by methyl and ethyl group led to decreased antidiabetic activity. It means that increase the carbon chain on such position decreased antidiabetic activity which can be seen in compounds of **5g, 5h and 5i,** and in compounds **5j, 5k and 5l** respectively.

KEYWORDS: 3, 6-disubstituted 2-pyridinecarboxamide, Diabetes mellitus, Glucokinase activator, Oral glucose tolerance test, Spectroscopy, Structure activity relationship.

1. INTRODUCTION

Pyridinecarboxamide derivatives exhibited lots of therapeutic activities like antitumor[1], antioxidant[2], anti-allergic[3], antihypertensive[4], antibacterial[5], antipsychotic[6], histamine H_3 receptor antagonist[7] and anti-diabetic activity.[8-13] Some other moieties also exhibit anti-diabetic activity.[14-19] Pyridinecarboxamide is a heterocyclic compound containing pyridine ring and $–CONH_2$ group. This compound contains one oxygen atom and two nitrogen atom having formula $C_6H_6N_2O$ and molecular weight is 122.13.

Type 2 diabetes, a disease characterized by hyperglycemia, is becoming more prevalent as a result of the recent dramatic rise in obesity levels. Current antidiabetic drugs to treat this disease include metformin, insulin, thiazolinediones, alpha-glucosidase inhibitors, sulfonylureas and DPPIV inhibitors having side effects. It is difficult to effectively treat T2D by single treatment option in the long term. Hence, to need for the other target for that to develop of new and effective antidiabetic treatment with novel and multiple mode of action. GK activators capability of promising approach for the treatment of type 2 diabetes. Various molecules of glucokinase activators are in pipeline.[8,9]

2. MATERIAL AND METHODS

Chemical used for the synthesis of molecules were of analytical grade. methyl 6-chloro-3-(trifluoromethyl)pyridine-2-carboxylate, methyl 6-chloro-3-methylpyridine-2-carboxylate, methyl 3,6-dichloropyridine-2-carboxylate, 1,3-thiazol-2-amine, 4-methyl-1,3-thiazol-2-amine, 4-ethyl-1,3-thiazol-2-amine, human glucokinase ELISA Kit were obtained from Sigma-Aldrich Bangalore. DMF, potassium carbonate, Lithium hydroxide, Hydrogen peroxide, THF, Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium (HATU), N,N-Diisopropylethylamine (DIPEA), were obtained from was obtained from SD fine Mumbai.

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Thin layer chromatography was performed on ready-made Aluminum backed TLC GF254 plates were used. Melting points were reported by open capillary tube method. IR spectra were done on FTIR on 8400S Shimadzu. ^{1}H-NMR spectra were done on Bruker400 MHz. Mass spectra were done on LC-MS Spectrometer. OGTT model were used to evaluate the biological activity of synthesized compounds as anti-diabetic agents.

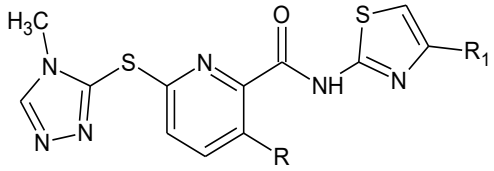
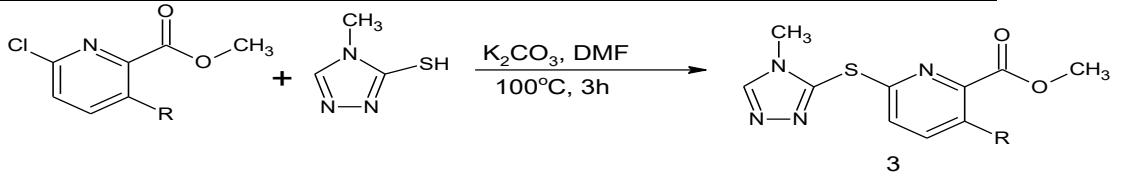


Fig.1: Moiety

Table 1: Melting point and yield of the synthesized compounds 5g – 5l

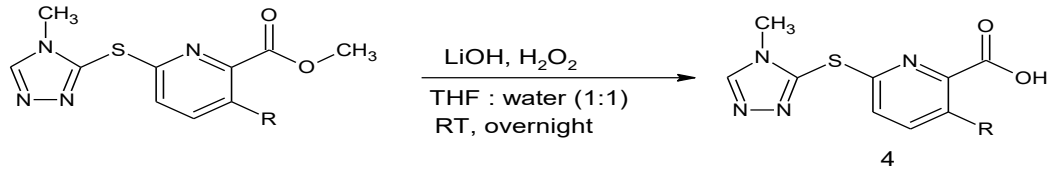
Compound Name	R	R_1	M.P.	% Yield
5g	$-CH_3$	-H	201-204ºC	75%
5h	$-CH_3$	$-CH_3$	207-210ºC	78%
5i	$-CH_3$	$-CH2CH_3$	208-211ºC	80%
5j	-Cl	-H	190-193ºC	77%
5k	-Cl	$-CH_3$	195-198ºC	73%
5l	-Cl	$-CH2CH_3$	196-199ºC	70%



3

3(g-i) - R= CH_3

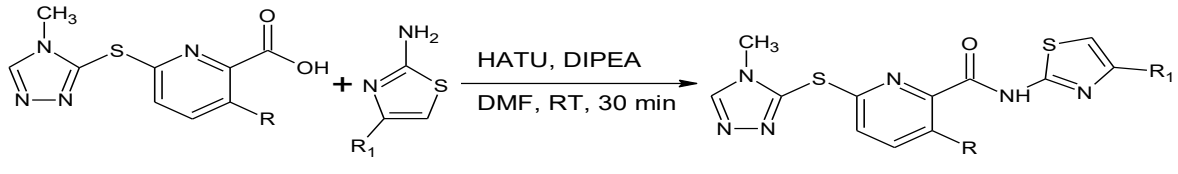
3(j-l) - R= Cl



4

4(g-i) - R= CH_3

4(j-l) - R= Cl



5

5(g-i) - R= CH_3, R_1= H, CH_3, C_2H_5

5(j-l) - R= Cl, R_1= H, CH_3, C_2H_5

Figure 2: Scheme for the synthesis of compounds 5g -5l

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2.1. Synthesis procedure

2.1.1. procedure for the synthesis of methyl 6-((4-methyl-4H-1,2,4-triazol-3-yl)thio)picolinate (3g-3l)

A mixture of methyl 6-chloropicolinate (1a; 16g, 0.08 mol), 4-methyl-4H-1,2,4-triazole-3-thio (9.6 g, 0.09 mol), potassium carbonate (12.4g, 0.09mol), dimethylformamide (72 ml), and water (8ml) is stirred at room temperature (30-35C) for 4-5 h. Dilution of the mixture with water (300ml) then leads to precipitation of a solid which is isolated by suction, dried and purified by column chromatography on silica gel using chloroform and chloroform/methanol (70/30) as eluents. Product 3 is obtained by elution with chloroform/methanol. Compound recrystallized from methanol.

2.1.2. Procedure for the synthesis of 6-((4-methyl-4H-1,2,4-triazol-3-yl)thio)picolinic acid (4g-4l)

The above methyl 6-((4-methyl-4H-1,2,4-triazol-3-yl)thio)picolinate (2.5 g, 7.6 mmol) was suspended in 140 mL of THF in a 500-mL round-bottomed flask. In a separate flask, 2.5 g of lithium hydroxide was dissolved in 140 mL of deionized water. Both mixtures were chilled to 4 °C and combined to form a turbid white mixture. After 1 h of stirring, the mixture had become homogeneous. After 24 h, 50 mL of 3 M HCl was added, and the mixture was allowed to warm to room temperature. Following the addition of a 100-mL portion of saturated aqueous NaCl solution, the mixture was extracted four times with 100-mL portions of EtOAc, and the combined organic layers were evaporated. Yield 2.28 g (7.25 mmol, 95%).

2.1.3. Procedure for the synthesis of (5g-5l)

Thiazol-2-amine and 6-((4-methyl-4H-1,2,4-triazol-3-yl)thio)picolinic acid (0.5 g, 0.00218 mol 1.0 eq) and substituted thiazol-2-amine was dissolved in dry DMF (10 cm3). The solution was stirred for 10 min at ambient temperature. Acid (1.0 eq) was added, followed by HATU (1.2 eq) and Diisopropyl ethylamine (2 eq). The reaction mass was heated to 45-50 °C for 1-2 hr, the completion of reaction was monitored by TLC.

2.2. Estimation of synthesized compounds as anti-diabetic agents.

2.2.1 In vitro assay of glucokinse enzyme

For this activity human glucokinase ELISA Kit was used for the determination of glucokinase activity of the tested molecules were predicted by using with enzyme glucose-6-phosphate dehydrogenase. All tested molecules (**5g-5l**) were prepared in the solvent dimethyl sulfoxide and make up the final volume 2000 µL then proceed the assay and maintain the temperature at 30^0C and pH=9 containing glucose (10 mM), 2-(4-(2-hydroxyethyl) piperazin-1-yl)ethanesulfonic acid (25 mM, pH 7.4), magnesium chloride (1 mM), potassium chloride (25 mM), Nicotinamide adenine dinucleotide (1 mM), dithiothreitol (1 mM), Adenosine triphosphate (1 mM), glucose-6-phosphate dehydrogenase (2.5 U/mL), glucokinase (0.5 µg). Now, this solution was kept for incubation period 3 minutes. After that absorbance was taken spectrometrically at 340 nm and kept 1 cm light path and calculate the fold activation of the test compounds as compared to control (in control the solvent DMSO only) was considered as 100%).[20-23]

2.2.2. Oral glucose tolerance test (OGTT)

Wistar rats (150-200 g) procured from Deshpande laboratories Pvt. Ltd., Madhya Pradesh, India. Such wistar rats were used for the evaluation of the synthesized test compounds under authority (Approval No. CPCSEA/IAEC/0254/09/20/216). Outcomes of docking study and in vitro GK assay, 5g to 5l selected synthesized derivatives were evaluated by OGTT model in rats. Rats were divided into eight groups and each group containing five animals. First group was the control group, second group of animal was the standard and remaining six groups was the test group (third group to eighth group), by which the biological activity was evaluated of the synthesized compounds (test drug) named as 5g, 5h, 5i, 5j, 5k and 5l. Before experiment all groups of wistar rats were allowed fasted nearly about 8 hours. Glucose (3 g/kg, p.o.) was administered to all the animals of each group. Vehicle only (5% DMSO, p.o.) was administered to all animals of control group (first group), metformin is the standard drug (30 mg/kg, p.o.) was administered to all animals of standard group (second group) and the synthesized compounds 5g, 5h, 5i, 5j, 5k and 5l were administered (50 mg/kg, p.o.) to all the animals of each test groups (third to eighth group) respectively. Loaded animals with glucose (3 g/kg, p.o.) after 30 minutes metformin was administered to the standard group and synthesized compounds 5g to 5l were administered to the test groups respectively. Blood samples were collected from the vein of rat's tail with the help of intravenous injection just prior to drug administration after that blood samples were withdrawn at regular intervals of time that is 0, 30, 60, and 120 minutes. Blood glucose level was measured immediately with the help of blood glucose test strips. Area under the curve was plotted, on x axis blood glucose level was taken and on Y axis control, standard and test compounds were taken.[8-9, 24]

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3. RESULTS AND DISCUSSION

3.1. Structural analysis of synthesized compounds

3.1.1. Compound (5g)

R_f = 0.35, IR peaks (cm^{-1}): (N-H str) 3343.32, (C-H str)-aromatic 3008.82, (C-H str)-aliphatic 2916.37, 2848.86 (C=O str) 1693.50, (C=C str)-aromatic 1656.85, 1546.91, 1492.90, 1427.32, (C-H bending)-aromatic 742.59. NMR spectra in term of δ (ppm): 8.1 (s, 1H), 3.6 (s, 3H), 7.8 (d, 2H, Ar H), 2.3 (s, 3H), 10.4 (s, 1H, NH), 7.6 (d, 2H). ESI Mass *(m/z, %)*: 332 (M^+, 1), 232 (100).

3.1.2. Compound (5h)

R_f = 0.53, IR peaks (cm^{-1}): (N-H str) 3209.55, (C-H str)-aromatic 3057.17, (C-H str)-aliphatic 2985.81, 2854.65, (C=O str) 1698.78, (C=C str)-aromatic 1608.63, 1546.91, 1492.90, 1355.96, (C-S-C str) 1180.44, (C-N str) 1143.79, (C-H bending)-aromatic 756.10. NMR spectra in term of δ (ppm): 8.1 (s, 1H), 3.6 (s, 3H), 7.8 (d, 2H, Ar H), 2.3 (s, 3H), 10.4 (s, 1H, NH), 6.3 (s, 1H), 2.1 (s, 3H). ESI Mass *(m/z, %)*: 347 (M^+, 1), 232 (100).

3.1.3. Compound (5i)

R_f = 0.42, IR peaks (cm^{-1}): (N-H str) 3262.26, (C-H str)-aromatic 3054.68, (C-H str)-aliphatic 2949.16, 2849.46, (C=O str) 1713.46, (C=N str) 1649.14, (C=C str)-aromatic 1622.13, 1546.91, 1533.41, 1500.62, (C-S-C str) 1178.51, (C-N str) 1116.78, (C-H bending)-aromatic 764.02. NMR spectra in term of δ (ppm): 8.1 (s, 1H), 3.6 (s, 3H), 7.8 (d, 2H, Ar H), 2.3 (s, 3H), 10.4 (s, 1H, NH), 6.3 (s, 1H), 2.5 (t, 3H), 1.06 (s, 2H). ESI Mass *(m/z, %)*: 360 (M^+, 1), 232 (100).

3.1.4. Compound (5j)

R_f = 0.48, IR peaks (cm^{-1}): (N-H str) 3349.35, (C-H str)-aromatic 3044.46, (C=O str) 1643.14, (C=N str) 1620.21, (C=C str)-aromatic 1602.85, 1562.34, 1503.48, 1415.75, (C-S-C str) 1188.15, (C-N str) 1103.28, (C-Cl str) 844.82, (C-H bending)-aromatic 756.10. NMR spectra in term of δ (ppm): 8.1 (s, 1H), 3.6 (s, 3H), 7.8 (d, 2H, Ar H), 10.4 (s, 1H, NH), 2.5 (d, 2H). ESI Mass *(m/z, %)*: 352 (M^+, 1), 232 (100).

3.1.5. Compound (5k)

R_f = 0.62, IR peaks (cm^{-1}): (N-H str) 3290.56, (C-H str)-aromatic 3026.31, (C-H str)-aliphatic 2931.80, 2854.65, (C=O str) 1726.31, (C=N str) 1649.14, (C=C str)-aromatic 1622.13, 1546.91, 1500.62, 1440.83, (C-S-C str) 1178.51, (C-N str) 1116.78, (C-Cl str) 848.68, (C-H bending)-aromatic 758.02. NMR spectra in term of δ (ppm): 8.1 (s, 1H), 3.6 (s, 3H), 7.8 (d, 2H, Ar H), 10.4 (s, 1H, NH), 6.3 (s, 1H), 2.1 (s, 3H). ESI Mass *(m/z, %)*: 366 (M^+, 1), 117 (100).

3.1.6. Compound (5l)

R_f = 0.59, IR peaks (cm^{-1}): (N-H str) 3279.20, (C-H str)-aromatic 3029.06, (C-H str)-aliphatic 2931.60, 2839.66, (C=O str) 1711.46, (C=N str) 1639.14, (C=C str)-aromatic 1622.13, 1536.21, 1512.62, 1440.83, (C-S-C str) 1178.51, (C-N str) 1116.78, (C-Cl str) 842.68, (C-H bending)-aromatic 764.02. NMR spectra in term of δ (ppm): 8.1 (s, 1H), 3.6 (s, 3H), 7.8 (d, 2H, Ar H), 10.1 (s, 1H, NH), 6.3 (s, 1H), 2.5 (t, 3H), 1.03 (s, 2H). ESI Mass *(m/z, %)*: 380 (M^+, 1), 216 (100).

3.2. Estimation of synthesized compounds as anti-diabetic agents.

3.2.1. In vitro assay of glucokinse enzyme

Comeouts of in vitro antihyperglycemic activity shown in table 2. In comparison to control the compounds 5g, 5h and 5i exhibited highest fold activation nearly about 2, and the other compounds like 5j, 5k and 5l exhibited mild fold activation nearly about 1.5. Comeouts of in vitro antihyperglycemic activity specified that substitution of pyridine ring at 3rd position with electronegative group like chlorine at 3rd position diminished the antihyperglycemic activity shown in compounds 5j, 5k and 5l. Comeouts of in vitro antihyperglycemic activity specified that substitution of pyridine ring at 3rd position with hydrophobic group like methyl group enhances the antihyperglycemic activity shown in compounds 5g, 5h and 5i. The replacement of H from the 4th postion of 1,3-thiazol-2-yl amide nucleus by methyl and ethyl group led to decreased antidiabetic activity. It means that increase the carbon chain on such position decreased antidiabetic activity which can be seen in compounds of 5g, 5h and 5i, and in compounds 5j, 5k and 5l respectively. Amongst the compounds bearing 3-substituted-pyridin-2-yl ring

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having methyl attached to 1,3-thiazol-2-yl amide nucleus in which 4th position is unsubstituted showed good GK activation (fold activation of 2.42) in compounds 5g. The compounds bearing 3-substituted-pyridin-2-yl ring having methyl attached to 1,3-thiazol-2-yl amide nucleus in which 4th position is occupied with methyl group showed good GK activation (fold activation of 2.05, but less than the compounds 5g) in compounds 5h. The compounds bearing 3-substituted-pyridin-2-yl ring having methyl attached to 1,3-thiazol-2-yl amide nucleus in which 4th position is occupied with ethyl group showed good GK activation (fold activation of 1.85, but less than the compounds 5g and 5h) in compounds 5i. The 3-chloro-pyridin-2-yl ring substituted carboxamide derivatives bearing 1,3-thiazol-2-yl and 4-methyl-1,3-thiazol-2-yl (compounds 5j and 5k) displayed moderate GK fold activation of 1.42 and 1.40 respectively. The 3-chloro-pyridin-2-yl ring substituted carboxamide derivatives bearing 4-ethyl-1,3-thiazol-2-yl (Compound 5l) showed least 1.38 (fold activation). Comeouts specified that substituted the pyridin-2-yl ring at 3rd position with hydrophobic groups showed increased in activity whereas substituted with electronegative group decreased the GK activity.

Table 2: In vitro GK potency and metabolic stability for 5g-5l

S.No.	Compound No.	R	R_1	GK potency EC50 (μM) (*invitro*)	GK activity	Metabolic stability FH (*invitro*)
1	5g	$-CH_3$	-H	0.001	2.42 ± 0.02	100
2	5h	$-CH_3$	$-CH_3$	0.012	2.05 ± 0.09	98
3	5i	$-CH_3$	$-CH2CH_3$	0.023	1.85 ± 0.06	95
4	5j	-Cl	-H	0.046	1.42 ± 0.06	64
5	5k	-Cl	$-CH_3$	0.050	1.40 ± 0.08	81
6	5l	-Cl	$-CH2CH_3$	0.079	1.38 ± 0.09	72

3.2.2. In vivo assay by OGTT model

In vivo antihyperglycemic activity based on evaluation of test compounds by in vitro GK assay and docking studies of selected compounds (5g – 5l). After the results of docking and in vitro of glucokinase assay, OGTT assay was performed to predict the effect of synthesized compounds in rats at the same dose. AUC showed in Figure 3 the blood glucose measured in mg/dL resulted antihyperglycemic activity. At 0 minutes just before the drug (metformin and test) administered the blood glucose of all rats found to be between 78-85 mg/dL. At 30 minutes the glucose level of all the rats found to be between 168-189 mg/dL, but after 60 minutes there was the effect on rat, the tested compounds reduced the glucose level shown in all the groups of rats. Metformin reduced blood sugar level at 144mg/dL compared with compound 5g showed better effect to reduced blood glucose 150 mg/dL. Here, compound 5l showed least effective compound among all. After 120 minutes resulted of metformin showed 110 mg/dL compared to the compound 5g, once again the compound 5g on the top position of potency and exhibited results 122 mg/dL. Overall the compound 5g exhibited better potency as like the Metformin. Here, also 5l is least effective and exhibited blood glucose (145 mg/dL) and no tested compound caused hypoglycemic effect. Compound 5g exhibited satisfactory results as an antihyperglycemic agent after that compound 5h and 5i exhibited appropriate results and

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showed the activity as antihyperglycemic agents. The compound 5j, 5k and 5l exhibited moderate antihyperglycemic agent. Compound 5l is least effective compound. Comeouts of in vivo antihyperglycemic activity specified that substitution of pyridine ring at 3rd position with hydrophobic group like methyl group enhances the antihyperglycemic activity shown in compounds 5g, 5h and 5i. The replacement of H from the 4th postion of 1,3-thiazol-2-yl amide nucleus by methyl and ethyl group led to decreased antidiabetic activity. It means that increase the carbon chain on such position decreased antidiabetic activity which can be seen in compounds of 5g, 5h and 5i, and in compounds 5j, 5k and 5l respectively. Results of the in vivo GK assay exhibited the potency of the synthesized compounds were found in this order 5g, 5h, 5i, 5j, 5k and 5l.

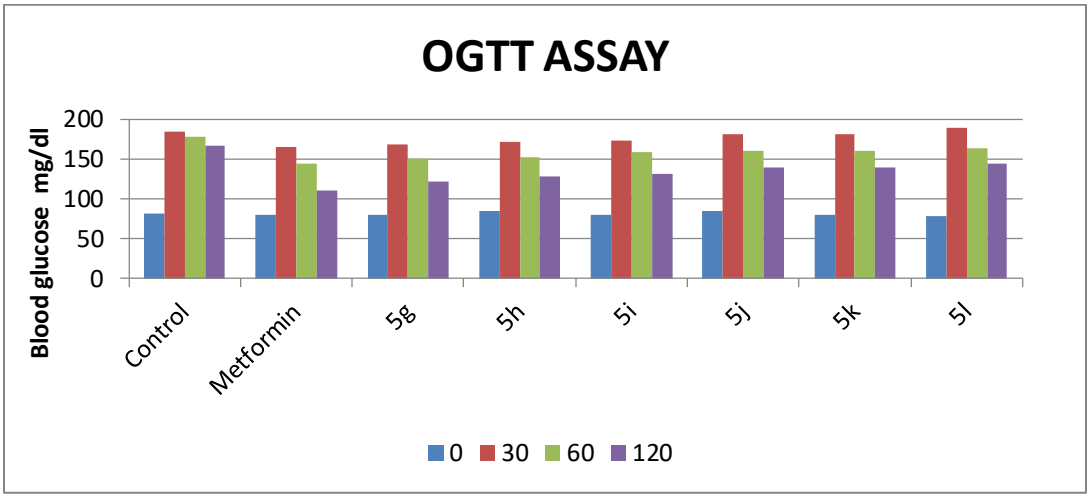

Figure 3: AUC of compounds 5g, 5h, 5i, 5j, 5k and 5l in rat OGTT model.

4. CONCLUSION

From the present experimental study, it was observed that 3, 6-disubstituted 2-pyridinecarboxamide moiety gives better anti-diabetic activity. Comeouts of in vivo antihyperglycemic activity specified that substitution of pyridine ring at 3rd position with hydrophobic group like methyl group enhances the antihyperglycemic activity shown in compounds 5g, 5h and 5i. Comeouts of in vitro antihyperglycemic activity specified that substitution of pyridine ring at 3rd position with electronegative group like chlorine at 3rd position diminished the antihyperglycemic activity shown in compounds 5j, 5k and 5l. The replacement of H from the 4th postion of 1,3-thiazol-2-yl amide nucleus by methyl and ethyl group led to decreased antidiabetic activity. It means that increase the carbon chain on such position decreased antidiabetic activity which can be seen in compounds of 5g, 5h and 5i, and in compounds 5j, 5k and 5l respectively. Results of the in vivo GK assay exhibited the potency of the synthesized compounds were found in this order 5g, 5h, 5i, 5j, 5k and 5l. These compounds further can be taken for evaluation of other studies.

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Certificate of Interest:

The article entitled Design, synthesis, characterization and biological evaluation of some novel 3,6-disubstituted-2-pyridinecarboxamide derivatives as antidiabetic agents is herewith submitted for publication in Journal of cardiovascular disease research. It has not been published before, and it is not under consideration for publication in any other journal (s). I/We certify that I/We have obtained written permission for the use of text, tables, and/or illustrations from any copyrighted source(s), and I/We declare no conflict of interest.

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