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Synthesis and in vivo antihyperglycemic activity of nature-mimicking furanyl-2-pyranones in STZ-S model☆

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Abstract—Various nature-mimicking pyranones such as 6-(2,5-dimethylfuran-3-yl)-pyran-2-one and 6-(furan-2-yl)-pyran-2-one derivatives were synthesized and evaluated for their in vivo antihyperglycemic activity in sucrose-loaded streptozotocin-induced diabetic rat model. Five of the test compounds showed significant lowering of plasma glucose level in STZ-S model.

Type 2 diabetes is characterized by high level of blood glucose, insulin and impaired insulin action.[1] The remedies available in modern system of medicine for the treatment of type 2 diabetes patients have been focused on dietary management of obesity[2] to improve insulin sensitivity, sulfonylureas[3] to enhance insulin secretion, metformin[4] to inhibit hepatic glucose output, and acarbose[5] to inhibit or reduce the rate of glucose absorption from the gut. In current scenario, the treatment of type 2 diabetes has been revolutionized with the advent of thiazolidinedione (TZD) class of drugs (rosiglitazone, pioglitazone) that ameliorate insulin resistance and thereby normalize elevated blood glucose levels,[6] but are associated with hepatotoxicity, weight gain, and edema.[7] The alarming situation emphasized the need to discover new antihyperglycemic agents with reduced or no hepatotoxicity. One such alternative is to explore antidiabetic leads from traditional sources, identify a pharmacophore-based scaffold, which not only retain blood sugar lowering activity but are also known as hepatoprotectants.

Several indigenous medicinal plants of family Menispermaceae have been used as a tonic, vitalizer, and as traditional remedies for the treatment of metabolic disorders.[8] Studies have shown that aqueous and alcoholic extracts of *Tinospora cordifolia* Miers had caused reduction in fasting blood glucose level and increased glucose tolerance in albino rats.[9] Aqueous and alcoholic extracts of *T. cordifolia* have shown reduction in blood sugar in alloxan-induced hyperglycemic rats and rabbits. The chief constituents of the extracts of *T. cordifolia* were diterpenoid lactones, furanoid diterpene glucoside (Fig. 1, **I** and **II**), sesquiterpenoids, many of them possessing 6-(furan-3-yl)-2-pyranone skeleton.[10] Naturally occurring 2-pyranones functionalized at position 6 with a furan moiety in flexible or rigid conformations, particularly achrocarpins (**III**), are the core skeleton found in

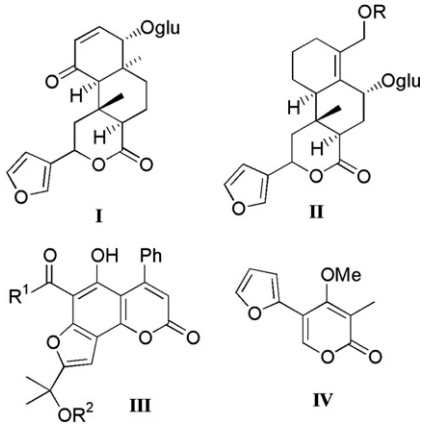

Figure 1. Naturally occurring (furan-3-yl)-2-pyranones (**I**–**III**) and (furan-2-yl)-2-pyranones (**IV**).

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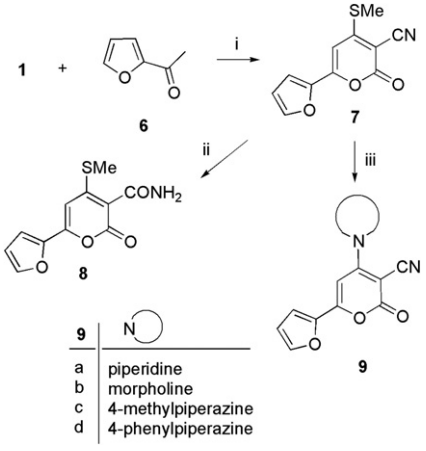
several natural products of biological importance.[11] Molecules embedded with this scaffold have demonstrated diverse interesting activities such as antifungal, antioxidant, anticancer, antidiabetic, etc. In addition, 2-pyranones with furan moiety (**IV**) have been isolated from fruit bodies of the fungus *Ganoderma lucidum*, which is an important constituent of a traditional Chinese drug '*Lin-Chi*' used in the treatment of mild ailments and to promote good health.[12] Studies have also shown that polysubstituted 2-pyranones possess significant hepatoprotective activity. Ram et al.[13] found that 6-furanyl-2-pyranones exhibited 71% and 72% protection in serum glutamate oxaloacetate transaminases (SGOT) and serum glutamate pyruvate transaminases (SGPT), respectively, in rats at 6 mg/kg (po × 7 days). Such informations on furanyl-2-pyranones provided a template for designing new antihyperglycemic agents with hepatoprotective action. Thus, we envisaged that synthesis of repertoire of nature-like 2-pyranones functionalized at position 6 with a furan moiety would be an interesting scaffold to examine the antihyperglycemic activity.

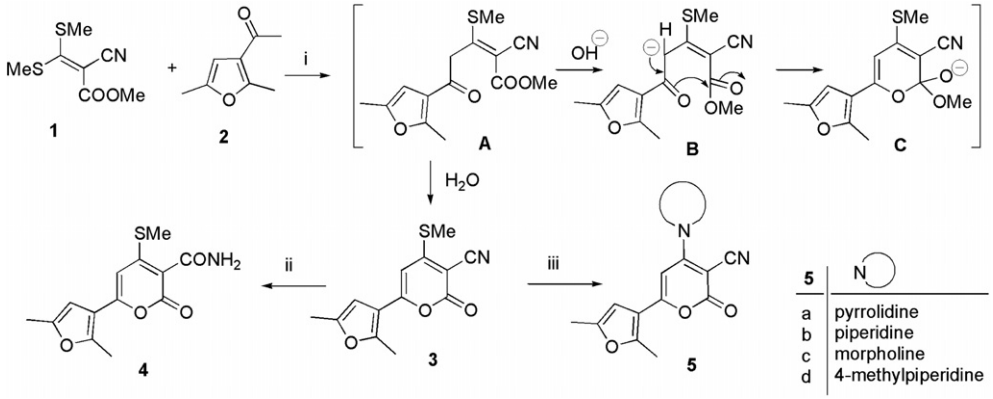
Herein we report synthesis and in vivo antihyperglycemic activity of nature-mimicking 6-(furan-3-yl)-2-pyranone and 6-(furan-2-yl)-2-pyranone derivatives in sucrose-loaded streptozotocin-induced (STZ-S) diabetic model.

Limited synthetic methodologies are available for the preparation of furanyllactones. The most common approaches for the synthesis of furanyl-2-pyranone core skeleton include aldol condensation[14] of 3-furaldehyde and enol silanes or enolates of substituted cyclohexanones and lewis acid catalyzed aldol reactions of 1-trimethylsilyloxycyclohexene with 1-(3-furanyl)-2-nitro-1-propene followed by Baeyer–Villiger oxidation.[15] Our approach for the preparation of functionalized 6-(furan-3-yl)-2-pyranones (**3**, **4**, **5**) is depicted in Scheme 1. The ketene dithioacetal[16] **1** used as a parent precursor was conveniently prepared by methyl cyanoacetate, carbon disulfide, and methyl iodide in presence of a base in good yield. In order to prepare (furan-3-yl)-2-pyranones, a reaction of ketene dithioacetal **1** and 1-(2,5-dimethylfuran-3-yl)-ethanone **2** in the presence of potassium hydroxide in DMSO afforded 6-(2,5-dimethylfuran-3-yl)-4-methylthio-2-oxo-2*H*-pyran-3-carbonitrile **3** in good yield. The reaction is possibly initiated by Michael addition of an enolate of **2** to ketene dithioacetal **1** to form an intermediate A. This intermediate in presence of a base intramolecularly cyclizes to intermediate C, which on elimination of methanol afforded furanyllactone **3**. Acid hydrolysis of **3** furnished 6-(2,5-dimethylfuran-3-yl)-4-methylthio-2-oxo-2*H*-pyran-3-carboxylic acid amide **4** in 84% yield. The methylthio group of 2*H*-pyran-2-one **3** was further replaced by various secondary amines by reacting lactone **3** with a secondary amine in methanol at reflux temperature, which afforded 4-amino-6-(2,5-dimethylfuran-3-yl)-2-oxo-2*H*-pyran-3-carbonitrile **5** in 75–90% yield.

To examine the effect of point of attachment for furan moiety toward biological activity, a series of 6-(furan-2-yl)-2*H*-pyran-2-ones (**7**, **8**, **9a–d**) were prepared as shown in Scheme 2. The reaction of ketene dithioacetal **1** with 2-acetylfuran in presence of KOH afforded **7** in 78% yield. The nitrile group of **7** was further hydrolyzed to corresponding amide **8** in the presence of poly phosphoric acid at 100 °C. The amine-functionalized 2*H*-pyran-2-ones **9a–d** were prepared by replacing methylthio group of **7** with various secondary amines in methanol



Scheme 2. Reagents and conditions: (i) KOH, DMSO, rt; (ii) PPA, 100 °C; (iii) secondary amine, methanol, reflux.



Scheme 1. Reagents and conditions: (i) KOH, DMSO, rt; (ii) PPA, 100 °C; (iii) secondary amine, methanol, reflux.

Table 1. In vivo antihyperglycemic activity of compounds **3**, **4**, **5a–d**, **7**, **8** and **9a–d** at 100 mg/kg dose in STZ-S model

Compound	Blood glucose lowering profile (% change over control)[a]							
	30 min	60 min	90 min	120 min	180 min	240 min	5 h	24 h[b]
3	12.6	16.2	21.2	16.5	2.3	2.5	5.2	04.5
4	13.2	28.8	33.0	29.4	16.3	12.6	11.2	**23.9**
5a	12.5	17.3	20.9	20.9	7.8	1.2	4.5	10.5
5b	8.6	9.4	6.8	8.7	0.8	1.0	5.2	**19.7**
5c	16.6	18.4	24.0	29.0	18.5	20.7	20.3	**29.7**
5d	12.5	16.3	20.9	16.8	2.6	2.8	5.5	4.2
7	11.8	16.5	19.6	19.8	8.1	2.3	6.8	6.7
8	8.5	9.6	6.3	8.9	1.2	1.3	5.52	**19.3**
9a	12.8	17.5	21.1	21.3	7.5	1.4	4.8	10.4
9b	13.1	15.9	19.8	17.4	1.8	5.2	9.8	0.5
9c	12.5	17.5	17.3	22.8	16.8	14.6	12.8	**20.0**
9d	11.8	15.7	20.2	15.9	1.9	3.9	6.1	2.5
Metformin	15.9	18.2	24.5	29.2	18.7	21.1	20.7	**30.0**

[a] Sugar lowering activity was examined at different time intervals after compound treatment.
[b] Values in bold font emphasize significant blood sugar lowering.

at reflux temperature. All the synthesized compounds were characterized by their spectroscopic analyses.[17–19]

Most of the synthesized compounds were evaluated for in vivo antihyperglycemic activity in sucrose-loaded streptozotocin-induced (STZ-S) male Sprague–Dawley diabetic rats.[20] Metformin was taken as a control. Among the 12 screened compounds, five compounds (**4**, **5b**,**c**, **8**, and **9c**) demonstrated good antihyperglycemic activity by showing 19–30% blood sugar lowering at 100 mg/kg dose after 24 h drug treatment (Table 1). The structure–activity profile revealed that 2*H*-pyran-2-ones with amide functionality at position 3 in **4** and **8** showed good sugar lowering activity compared to their nitrile precursors **3** and **7**. It is evident from the activity data of 4-amino-6-(furan-3-yl)-2*H*-pyran-2-ones **5a–d** that compounds having piperidine (**5b**: 19.7%) or morpholine (**5c**: 29.7%) moiety showed good antihyperglycemic activity. Similarly in the series of 4-amino-6-(furan-2-yl)-2*H*-pyran-2-ones (**9a–d**), only 6-(furan-2-yl)-4-(4-methylpiperazin-1-yl)-2-oxo-2*H*-pyran-3-carbonitrile (**9c**) showed 20.0% sugar lowering in Sprague–Dawley diabetic rats. The most active compound **5c** showed 29.7% sugar lowering activity comparable to standard drug metformin (30%).

In summary, we have demonstrated synthesis and in vivo antihyperglycemic activity of a new class of nature-mimicking furanyl-2*H*-pyran-2-ones with donor-acceptor functionalities, which are promising candidates for the development of antidiabetic agents. Among various screened compounds, furanyllactone **5c** showed 30% blood sugar lowering at 100 mg/kg dose in STZ-S induced male Sprague–Dawley diabetic rats. Further exploratory work on furanyllactone template is currently in progress.

Sucrose challenged low dosed streptozotocin-induced diabetic rats (STZ-S):[20] Male albino rats of Sprague–Dawley strain of body weight 140 ± 20 g were selected for this study. Streptozotocin (Sigma, USA) was dissolved in 100 mM citrate buffer, pH 4.5, and calculated amount of the fresh solution was injected to overnight fasted rats (45 mg/kg) intraperitoneally. Blood was checked 48 h later by glucostrips and animals showing blood glucose values between 8 and 15 mM were included in the experiments and termed diabetic. The diabetic animals were divided into groups consisting of five to six animals in each group. Rats of experimental groups were administered suspension of the desired test samples orally (made in 1.0% gum acacia) at 100 mg/kg dose. Animals of control group were given an equal amount of 1.0% gum acacia. A sucrose load of 2.5 g/kg body weight was given after 30 min of drug administration. After 30 min of sucrose load, blood glucose level was again checked by glucostrips at 30, 60, 90, 120, 180, 240, 300 min and at 24 h, respectively. Food but not water was withheld from the cages during the experimentation. Comparing the AUC of experimental and control groups determined the percent antihyperglycemic activity.

Acknowledgments

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17. *Synthesis of 6-furanyl-4-methylthio-2-oxo-2H-pyran-3-carbonitrile (***3** *and* **7***):* A mixture of methyl 2-cyano-3,3-di(methylthio)acrylate **1** (10 mmol), acetylfuran (**2** or **6**, 12 mmol), and powdered KOH (15 mmol) in dry DMSO (25 mL) was stirred at room temperature for 15–18 h. After completion, the reaction mixture was poured into ice water with constant stirring. The precipitate thus obtained was filtered and purified on a silica gel column using chloroform as eluent. Compound **3**: yellow solid; yield: 85%; mp: 250–252 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.29 (s, 3H, Me), 2.61 (s, 3H, Me), 2.64 (s, 3H, SMe), 6.15 (s, 1H, CH), 6.21 (s, 1H, CH); IR (KBr) 1718 (CO), 2213 cm^{-1} (CN); MS (ESI) 262 (M^++1); ^{13}C NMR (200 MHz, $CDCl_3$): δ 13.86, 15.18, 23.27, 94.41, 104.48, 114.52, 118.19, 123.92, 151.36, 152.90, 156.38, 160.81, 165.49. Compound **7**: yellow solid; yield: 78%; mp: 208–210 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.70 (s, 3H, SMe), 6.66 (s, 2H, 2CH), 7.24 (d, J = 3.4 Hz, 1H, CH), 7.66 (d, J = 1.1 Hz, 1H, CH); IR (KBr) 1718 (CO), 2214 cm^{-1} (CN); MS (ESI) 234 (M^++1).
18. *Synthesis of 6-(2,5-dimethylfuran-3-yl)/(furan-2-yl)-4-methylthio-2-oxo-2H-pyran-3-carboxylic acid amide (***4** *and* **8***):* Compound **3** or **7** (10 mmol) was heated at 90–100 °C for 8–10 h. After completion, the reaction mixture was poured into ice water with constant stirring. The precipitate thus obtained was filtered and purified on a silica gel column using chloroform as eluent. Compound **4**: yellow solid; yield: 84%; mp: 214–216 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.29 (s, 3H, Me), 2.45 (s, 3H, Me), 2.62 (s, 3H, SMe), 5.56 (br s, 1H, NH), 6.18 (s, 1H, CH), 6.41 (s, 1H, CH), 8.70 (br s, 1H, NH); IR (KBr) 1664 (CO), 1711 (CO), 3181 (NH), 3398 cm^{-1} (NH); MS (ESI) 279 (M^+). Compound **8**: yellow solid; yield: 85%; mp: 232–234 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.51 (s, 3H, SMe), 5.60 (br s, 1H, NH), 6.58–6.62 (m, 1H, CH), 6.84 (s, 1H, CH), 7.19 (d, J = 3.40 Hz, 1H, CH), 7.61 (d, J = 1.1 Hz, 1H, CH), 8.70 (br s, 1H, NH); IR (KBr) 1660 (CO), 1708 (CO), 3187 (NH), 3428 cm^{-1} (NH); MS (FAB) 252 (M^++1); ^{13}C NMR (200 MHz, $CDCl_3$): δ 17.40, 73.21, 98.33, 113.53, 115.36, 145.83, 146.65, 167.25, 171.26.
19. *Synthesis of 6-(2,5-dimethylfuran-3-yl)/(furan-2-yl)-4-sec.amino-2-oxo-2H-pyran-3-carbonitrile (***5a**–**d** *and* **9a**–**d***):* A mixture of compound **3** or **7** (10 mmol) and secondary amine (12 mmol) was refluxed in methanol (20 mL) for 6–8 h. After completion, methanol was evaporated under vacuum, and reaction mixture was washed with ice-cooled water. Crude was purified on a silica gel column using chloroform as eluent. Compound **5a**: white solid; yield: 89%; mp: 224–226 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.00–2.11 (m, 4H, $2CH_2$), 2.25 (s, 3H, Me), 2.54 (s, 3H, Me), 3.58–3.62 (m, 2H, CH_2), 4.05–4.09 (m, 2H, CH_2), 5.84 (s, 1H, CH), 6.08 (s, 1H, CH); IR (KBr) 1704 (CO), 2208 cm^{-1} (CN); MS (ESI) 285 (M^++1); ^{13}C NMR (200 MHz, $CDCl_3$): δ 16.59, 17.85, 28.38, 54.99, 95.09, 103.08, 114.49, 119.10, 123.85, 151.73, 153.90, 158.38, 161.35, 162.81. Compound **5b**: white solid; yield: 78%; mp: 188–190 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.65–1.85 (m, 6H, $3CH_2$), 2.26 (s, 3H, Me), 2.56 (s, 3H, Me), 3.74–3.78 (m, 4H, $2CH_2$), 5.96 (s, 1H, CH), 6.09 (s, 1H, CH); IR (KBr) 1704 (CO), 2209 cm^{-1} (CN); MS (ESI) 299 (M^++1); ^{13}C NMR (200 MHz, $CDCl_3$): δ 13.65, 15.01, 24.30, 26.71, 51.14, 94.04, 104.44, 109.98, 114.43, 118.08, 151.74, 153.98, 158.42, 161.38, 162.83. Compound **5c**: white solid; yield: 76%; mp: >250 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.26 (s, 3H, Me), 2.57 (s, 3H, Me), 3.78–3.90 (m, 8H, $4CH_2$), 5.93 (s, 1H, CH), 6.08 (s, 1H, CH); IR (KBr) 1712 (CO), 2214 cm^{-1} (CN); MS (ESI) 301 (M^++1); ^{13}C NMR (200 MHz, $CDCl_3$): δ 13.38, 14.85, 50.12, 52.61, 94.45, 104.85, 114.59, 118.81, 124.48, 151.36, 152.90, 156.38, 160.19, 163.49. Compound **5d**: white solid; yield: 77%; mp: 184–186 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.01 (d, 3H, J = 6.0 Hz, Me), 1.29–1.39 (m, 2H, CH_2), 1.81–1.91 (m, 3H, CH and CH_2), 2.26 (s, 3H, Me), 2.56 (s, 3H, Me), 3.11–3.28 (m, 2H, CH_2), 4.26–4.37 (m, 2H, CH_2), 5.96 (s, 1H, CH), 6.09 (s, 1H, CH); IR (KBr) 1686 (CO), 2208 cm^{-1} (CN); MS (ESI) 313 (M^++1); ^{13}C NMR (200 MHz, $CDCl_3$): δ 13.61, 14.96, 21.74, 30.99, 34.75, 50.38, 94.16, 104.48, 114.45, 118.09, 151.73, 153.90, 158.39, 161.36, 162.81. Compound **9a**: white solid; yield: 80%; mp: 184–186 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.77–1.81 (m, 6H, $3CH_2$), 3.80–3.84 (m, 4H, $2CH_2$), 6.43 (s, 1H, CH), 6.54–6.61 (m, 1H, CH), 7.10 (d,J = 3.4 Hz, 1H, CH), 7.55 (J = 1.1 Hz, 1H, CH); IR (KBr) 1708 (CO), 2216 cm^{-1} (CN); MS (FAB) 271 (M^++1); ^{13}C NMR (200 MHz, $CDCl_3$): δ 24.25, 26.78, 51.31, 72.04, 113.29, 114.53, 117.86, 146.03, 146.23, 152.58, 160.68, 162.37. Compound **9b**: white solid; yield: 78%; mp: 248–250 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.88 (s, 8H, $4CH_2$), 6.40 (s, 1H, CH), 6.56–6.62 (m, 1H, CH), 7.12 (d, J = 3.4 Hz, 1H, CH), 7.56 (d, J = 1.1 Hz, 1H, CH); IR (KBr) 1686 (CO), 2208 cm^{-1} (CN); MS (FAB) 273 (M^++1); ^{13}C NMR (200 MHz, $CDCl_3$): δ 51.78, 53.25, 92.37, 112.29, 114.53, 116.51, 146.97, 147.03, 152.68, 161.58, 163.81. Compound **9c**: white solid; yield: 80%; mp: 172–174 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.37 (s, 3H, NCH_3), 2.56–2.65 (m, 4H, $2CH_2$), 3.85–3.94 (m, 4H, $2CH_2$), 6.41 (s, 1H, CH), 6.54–6.62 (m, 1H, CH), 7.11 (d, J = 3.4 Hz, 1H, CH), 7.55 (d, J = 1.1 Hz, 1H, CH); IR (KBr) 1706 (CO), 2214 cm^{-1} (CN); MS (FAB) 286 (M^++1); ^{13}C NMR (200 MHz, $CDCl_3$): δ 37.87, 52.25, 53.81, 92.58, 112.29, 114.86,

116.51, 146.53, 147.63, 153.08, 161.37, 162.78. Compound **9d**: white solid; yield: 82%; mp: >250 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.39–3.47 (m, 4H, $2CH_2$), 4.04–4.20 (m, 4H, $2CH_2$), 6.47 (s, 1H, CH), 6.58–6.64 (m, 1H, CH), 6.91–7.00 (m, 3H, ArH), 7.15 (d, J = 3.4 Hz, 1H, CH), 7.28–7.38 (m, 2H, ArH), 7.59 (d, J = 1.1 Hz, 1H, CH); IR (KBr) 1700 (CO), 2218 cm^{-1} (CN); MS (FAB) 348 (M^++1); ^{13}C NMR (200 MHz, $CDCl_3$): δ 49.97, 66.93, 73.11, 92.45, 113.47, 115.11, 117.52, 145.83, 146.53, 153.15, 161.48, 161.78.

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