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Synthesis of Novel Imidazolidine-2,4-dione Derivatives as Potential Antidiabetic Agents

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A series of novel imidazolidine-2,4-dione derivatives were synthesized and their chemical structures were confirmed by ^{1}H NMR and ESI-MS. The preliminary antidiabetic screening results demonstrated that the compound **3b** showed some antidiabetic activity and could acted as lead compound for further design and discovery of antidiabetic agents.

Key Words: Synthesis, Imidazolidine-2,4-dione, Derivatives, Antidiabetic agents.

INTRODUCTION

Type 2 diabetes, previously referred to as non-insulin dependent diabetes mellitus (NIDDM), is a metabolic disorder characterized by hyperglycemia leading to chronic complications such as neuropathy, nephropathy, retinopathy and premature atherosclerosis[1]. Type 2 diabetes accounts for over 90 % of the diabetes cases reported in the Western world and the global incidence of this disease is estimated to increase to over 200 million by the end of the year 2010.

Thiazolidinediones (TZDs) are the major drug class used to improve insulin sensitivity in the treatment of type 2 diabetes. Thiazolidinediones improve glucose utilization without stimulating insulin release. They significantly reduce glucose, lipid and insulin levels in rodent models of non-insulin dependent diabetes mellitus and obesity and recent clinical data supports their efficacy in obese diabetic patients[2].

However, safety concerns on the thiazolidinediones have been a primary focus of pharmacotherapeutics[3]. Thiazolidinediones have several adverse effects, including weight gain and renal and liver toxicity. One of the thiazolidinediones, troglitazone, was withdrawn from the marketing due to severe hepatotoxicity. The hepatotoxicity is caused mainly by the thiazolidinediones scaffold, so more attention is turned to the research of non-thiazolidinediones antidiabetic drugs.

According to the bioisosterism in medicinal chemistry, studies on replacement of the thiazolidine-2,4-dione ring have been carried out in our laboratory. Replacement of the thiazolidine-2,4-dione ring has been tried with imidazolidine-2,4-dione ring.

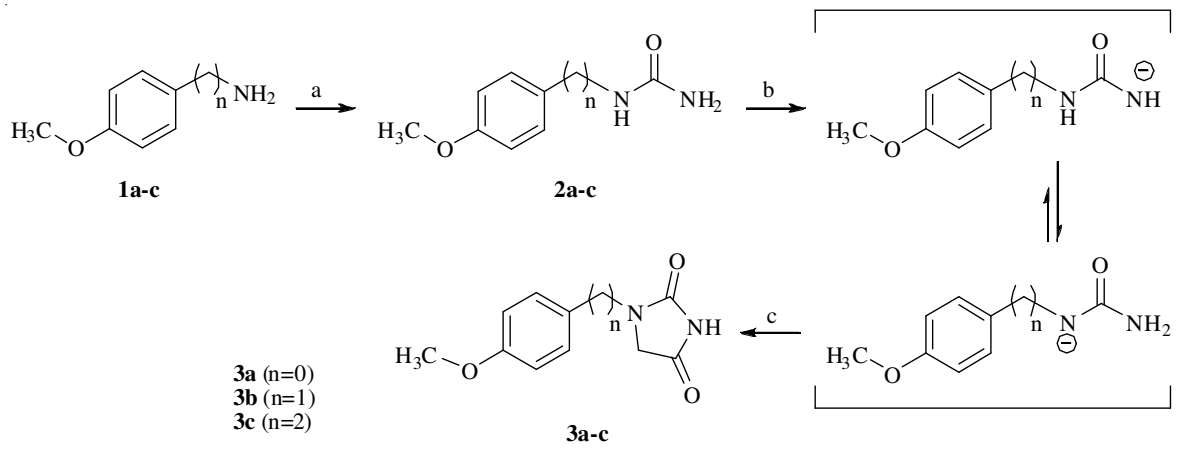
EXPERIMENTAL

N^1-Substituted imidazolidine-2,4-diones and C_5-substituted imidazolidine-2,4-diones were synthesized in our laboratory. Starting from amide as raw material, the N^1-substituted imidazolidine-2,4-diones (**3a-c**) were synthesized *via* acylation and cyclization[4]. Starting from imidazolidine-2,4-dione as raw material, the C_5-substituted imidazolidine-2,4-diones (**6a-b**) were synthesized *via* Knoevenagel reaction and esterification reaction[5]. The synthetic routes of the compounds were shown in **Scheme-I**. The chemical structures of the newly synthesized compounds were confirmed by ^{1}H NMR and ESI-MS. These compounds were further evaluated on mice hyperglycemia model and pioglitazone was used as the standard drug (Table-1).

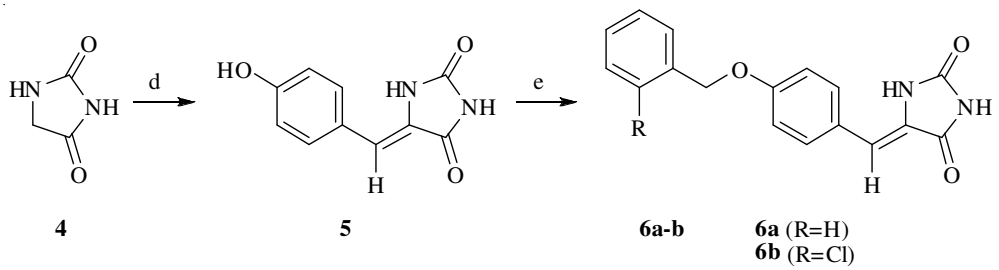
TABLE-1
GLUCOSE INHIBITORY RATE OF IMIDAZOLIDINE-2,4-DIONE DERIVATIVES AND PIOGLITAZONE

Entry	Inhibitory rate (%)	Entry	Inhibitory rate (%)
3a	12	**6a**	22
3b	33	**6b**	13
3c	-40	Pioglitazone	46

Procedure for the synthesis of compounds (2a-c): Compounds **1a-c** (50 mmol) is dissolved in 24 mL of glacial acetic acid and 48 mL of water at 35 ºC. This solution is treated with a solution of 8.1 g (100 mmol) of potassium cyanate in 45 mL of water at 35 ºC. About 5 mL of the potassium cyanate solution is added slowly with stirring until a white crystalline precipitate of the product appears. The rest is then added quickly with vigorous agitation. The rapid separation of the product is



Scheme-I: Reagents and conditions: (a) KCNO, HOAc, H_2O; (b) NaH, DMF; (c) $ClCH_2CO_2CH_2CH_3$



Scheme-II: Reagents and conditions: (d) *p*-hydroxybenzaldehyde, dry piperidine, 130 ºC; (e) benzyl chloride, NaH, DMF

accompanied by a rise in the temperature to 50-55 ºC. The thick, paste-like suspension is stirred for another 10 min, allowed to stand at room temperature for 2-3 h and diluted with 20 mL of water. After cooling to 0 ºC, the material is filtered with suction, washed with water, drained thoroughly and dried. The product is purified by flash column chromatography and **2a-c** is obtained.

Procedure for the synthesis of compounds 3a-c: Compound **2a-c** (10 mmol) is dissolved in 20 mL of DMF and NaH (0.60 g, 25 mmol) is added. The mixture is reacted at room temperature for 1 h and ethyl 2-chloroacetate (1.47 g, 12 mmol) is added dropwise. The solution is stired at room temperature for 20 h, then at 70 ºC for another 1 h. After the reaction is completed, the mixture is filtered and the filtrate is evaporated to give yellow oil. The yellow oil is further purified by flash column chromatography and **3a-c** is obtained.

Procedure for the synthesis of compound 5: To an intimate mixture of 6.11 g (50 mmol) of *p*-hydroxybenzaldehyde and 5.5 g (55 mmol) of hydantoin (**4**), dry piperidine (10 mL) is added. The reaction mixture is heated slowly to 130 ºC and is held at this temperature for 0.5 h; foaming and gentle boiling occur. The reaction mixture is cooled and 200 mL of water at about 60 ºC is added. The mixture is stirred until a clear red solution is obtained. Any traces of tarry material are removed by filtration. The solution is cooled to room temperature, transferred to an Erlenmeyer flask and acidified by dropwise addition of 20 mL of 10M hydrochloric acid. The mixture stands at room temperature a few hours and then the yellow precipitate is collected on a Buchner funnel and washed thoroughly with cold water. The product 5-(*p*-hydroxybenzal)hydantoin (**5**) weighs 8.11 g (79.5 %). It melts at 316-318 ºC and is sufficiently pure for the next step.

Procedure for the synthesis of compounds 6a-b: 5-(*p*-hydroxybenzal)hydantoin (**5**) (2.04 g, 10 mmol) is dissolved in DMF (50 mL), then NaH (0.78 g, 32.5 mmol) and benzyl chloride (9 mmol) are added. The reaction mixture is heated to 70 ºC and is held at this temperature for 4 h. The solution is cooled to room temperature and poured to 100 mL of water, then is extracted by ethyl acetate (50 mL × 5). The organic layers are washed with brine, dried and evaporated to give an yellow oil. The yellow oil is further purified by flash column chromatography and **6a-b** is obtained.

Detection method: 3a: m.p. 198-199 ºC, yield 39 %; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.838 (1H, s, NH), 7.424 (2H, d, *J* = 8.8 Hz, Ar-H), 6.928 (2H, d, *J* = 8.8 Hz, Ar-H), 4.340 (2H, s, CH_2), 3.812 (3H, s, CH_3); MS m/z: 205.1 (M-1).

3b: m.p. 124-125 ºC, yield 37 %; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.154 (2H, d, *J* = 8.8 Hz, Ar-H), 6.857 (2H, d, *J* = 8.4 Hz, Ar-H), 6.280 (1H, s, NH), 5.440 (2H, s, Ar-CH_2), 4.079 (2H, s, CH_2CONH), 3.712 (3H, s, CH_3); MS m/z: 221.2 (M + 1), 441.2 (2M + 1).

3c: m.p. 103-105 ºC, yield 36 %; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.138 (2H, m, Ar-H), 6.840 (2H, t, *J* = 8.4 Hz, Ar-H), 4.241 (1H, s, NH), 3.710 (3H, s, CH_3), 3.406 (2H, t, *J* = 6.8 Hz, CH_2N), 2.750 (2H, m, $ArCH_2$); MS m/z: 235.2 (M + 1), 469.1 (2M + 1).

6a: m.p. 285-288 ºC, yield 9 %; ^{1}H NMR (DMSO-d_6, 400 Hz): δ 10.638 (s, 1H, N_3H), 9.886 (s, 1H, N_1H), 7.500 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.267-7.353 (m, 5H, Ar-H), 6.789 (d, 2H, *J* = 8.8 Hz, Ar-H), 6.505 (s, 1H, =CH), 4.651 (s, 2H, CH_2); MS m/z: 295.0 (M +1), 312.2 (M + NH_4).

6b: m.p. 265-268 ºC, yield 12 %; ^{1}H NMR (DMSO-d_6, 400 Hz): δ 11.135 (s, 1H, N_3H), 10.428 (s, 1H, N1H), 7.594 (d, 3H, *J* = 8.8 Hz, Ar-H), 7.514 (m, 1H, Ar-H), 7.389 (m, 2H,

Ar-H), 7.046 (d, 2H, *J* = 8.8 Hz, Ar-H), 6.381 (s, 1H, =CH), 5.201 (s, 2H, CH_2); MS m/z: 329.0 (M + 1), 346.2 (M + NH_4).

RESULTS AND DISCUSSION

The activity results showed that compounds **3a**, **3b**, **6a** and **6b** could reduce the blood glucose level and were less potent than pioglitazone (Table-1). Compound **3b** was the most potent one with 33 % inhibitory rate. Compound **3c** exhibited negative results with -40 % inhibitory rate, which indicated that **3c** might produce glucose rising effect. Among compounds **3a-c**, **3b** (N_1-benzyl substituted compound) was the most potent one, thus further modification of **3b** at methoxyl position will be performed in our laboratory. In addition, compounds **6a-b** also possess some antidiabetic activities and hydrogenation of **6a-b** probably produce higner antidiabetic activities.

Conclusion

Five novel imidazolidine-2,4-dione derivatives were designed and synthesized. Some of them showed antidiabetic activities and the most potent one was compound **3b**. This research provided valuable information for further design and discovery of antidiabetic agents. Further modification of these compounds were underway in our laboratory.

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