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Synthesis and pharmacological evaluation of substituted 5-[4-[2-(6,7-dimethyl-1,2,3,4-tetrahydro-2-oxo-4-quinoxalinyl)ethoxy]phenyl]methylene]thiazolidine-2,4-dione derivatives as potent euglycemic and hypolipidemic agents

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Abstract—A series of substituted 5-[4-[2-(6,7-dimethyl-1,2,3,4-tetrahydro-2-oxo-4-quinoxalinyl)ethoxy]phenyl]methylene]thiazolidine-2,4-diones were synthesized and their euglycemic and hypolipidemic activities were investigated in Wistar male rats. Based on the in vivo data in rats, compound **4a** was identified as a potent euglycemic and hypolipidemic agent.

1. Introduction

The studies on various analogues of substituted 5-benzyl thiazolidine-2,4-diones having euglycemic activity for the treatment of non-insulin dependent diabetes mellitus (NIDDM) has led to the discovery of a large number of compounds.[1] The best well known treatments for type 2 diabetic patients of NIDDM are generally prescribed as a combination of diet, exercise and a hypoglycemic agent.[2] Since the most commonly used hypoglycemic agent such as sulfonylureas has been known to stimulate insulin secretion for pancreatic β cells, which often led to induce severe hypoglycemia and weight gain, therefore drugs, which can reverse the insulin resistance without stimulating insulin release from β cells fulfill a major medical need in the treatment for NIDDM.[3,4] Since after the pioneering discovery of ciglitazone (**1**), a new class of thiazolidinedione based antidiabetic compounds have been developed to treat diabetic patients that can reverse the insulin resistance in NIDDM of type 2 patients. Among various substituted benzyl-2,4-thiazolidinedione analogues such as troglitazone (**2**), englitazone (**3**), pioglitazone (**4**) and rosiglitazone (**5**) (Fig. 1) has been developed and subjected to clinical testing for the treatment of type 2 diabetes.[5,6] We herein report the synthesis and euglycemic and hypolipidemic activities of 5-[4-[2-(6,7-dimethyl-1,2,3,4-tetrahydro-2-oxo-4-quinoxalinyl)ethoxy]phenyl]methylene]thiazolidine-2,4-diones and related compounds.

2. Chemistry

The preparation of substituted 5-[4-[2-(6,7-dimethyl-1,2,3,4-tetrahydro-2-oxo-4-quinoxalinyl)ethoxy]phenyl]-methylene]thiazolidine-2,4-dione derivatives is outlined in Scheme 1. The starting compound 6,7-dimethyl-1,2,3,4-tetrahydroquinoxalin-2-one **1a** was obtained by cyclization of the corresponding 6,7-dimethyl-1,2-phenylenediamine with α-chloroacetic acid in water as described in earlier reports.[7] Coupling of 4-hydroxybenzaldehyde with 1,2-dibromoethane in presence of a base (potassium hydroxide) gave the corresponding 4-(2-bromoethoxy)benzaldehyde[8] **2a**. Condensation of 4-(2-bromoethoxy)benzaldehyde **2a** with 6,7-dimethyl-1,2,3,4-tetrahydroquinoxalin-2-one in dry dimethylformamide in the presence of sodium hydride yielded the corresponding 4-[2-(6,7-dimethyl-1,2,3,4-tetrahydro-2-oxo-4-quinoxalinyl)ethoxy]benzaldehyde **3a**. 5-[4-[2-(6,7-dimethyl-1,2,3,4-tetrahydro-2-oxo-4-quinoxalinyl)-

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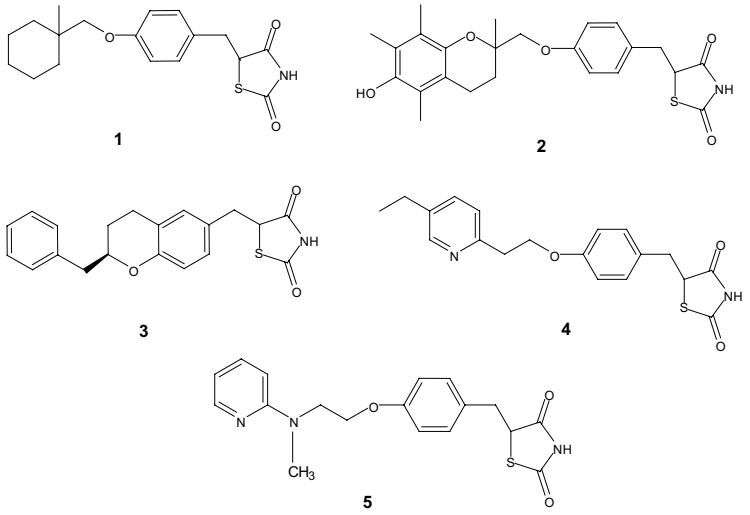
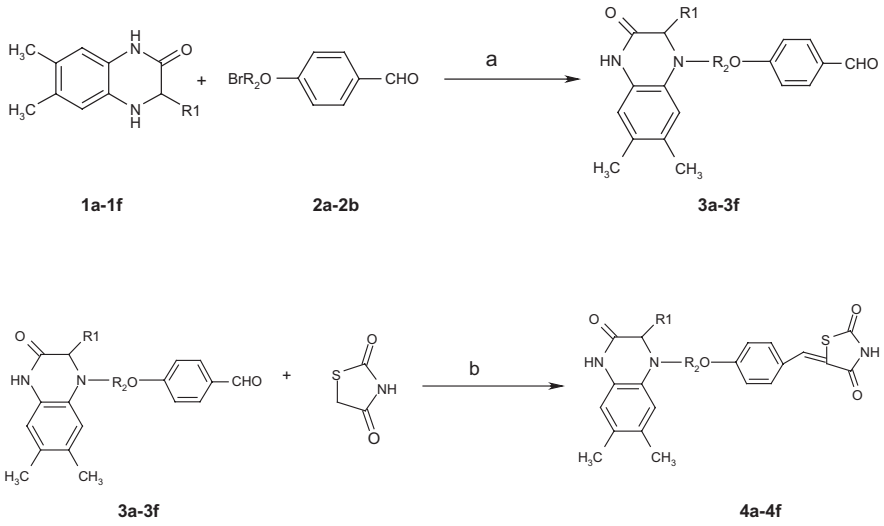


Figure 1.



compds	R_1	R_2
4a	H	$-CH_2CH_2-$
4b	H	$-CH_2CH_2CH_2-$
4c	CH_3	$-CH_2CH_2-$
4d	CH_3	$-CH_2CH_2CH_2-$
4e	C_6H_5	$-CH_2CH_2-$
4f	C_6H_5	$-CH_2CH_2CH_2-$

Scheme 1. Synthesis of compounds **4a**–**f**. Reagents and conditions: (a) sodium hydride, DMF, rt, 24 h; (b) piperidine, benzoic acid, toluene reflux under a Dean and Stark head, 4 h.

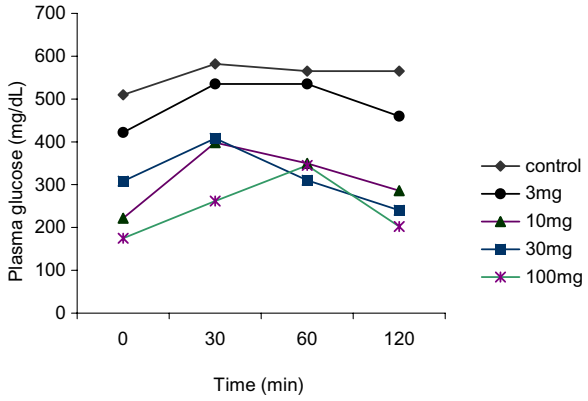
ethoxy]phenyl]methylene]thiazolidine-2,4-dione **4a** was prepared by the Knoevenagel condensation of benzaldehyde **3a** and thiazolidine-2,4-dione in refluxing toluene containing a catalytic amount of piperidinium benzoate with azeotropic removal of water. Compounds **4b**–**f** were prepared in an analogous manner. All thiazolidine-2,4-dione analogues provided satisfactory spectral data (^{1}H NMR, IR and MS and/or elemental analysis).[9]

3. Pharmacologic evaluation

The antidiabetic activities of compounds **4a**–**f** were investigated in male Wistar rats. The test compounds were orally administered at different doses (3, 10, 30, 100 mg/kg) for 14–15 days. Rosiglitazone was used as a standard drug. On the final day blood samples were collected from the tail vein in heparinized tubes. Plasma was separated from whole blood by centrifugation. Plasma

Table 1.

Compound		% Decrease in plasma glucose (PG) and triglyceride (TG) level at various drug doses (mg/kg bwt) ($P < 0.01$)			
		3	10	30	100
4a	PG	50.12 ± 3.24	52.63 ± 3.21	69.47 ± 3.84	81.25 ± 1.33
	TG	49.63 ± 01.26	44.20 ± 01.42	49.12 ± 01.82	54.95 ± 02.26
4b	PG	47.65 ± 2.16	49.11 ± 1.66	64.76 ± 2.28	72.33 ± 4.26
	TG	30.36 ± 01.15	38.18 ± 01.08	47.35 ± 00.92	50.10 ± 00.86
4c	PG	43.16 ± 2.12	42.17 ± 3.90	58.48 ± 1.82	69.72 ± 3.21
	TG	23.46 ± 00.65	32.62 ± 02.16	40.00 ± 01.86	43.42 ± 00.55
4d	PG	35.73 ± 0.88	39.21 ± 1.72	49.62 ± 1.08	64.26 ± 1.16
	TG	21.73 ± 02.12	29.69 ± 01.95	28.82 ± 01.92	37.46 ± 01.13
4e	PG	25.24 ± 0.65	21.69 ± 1.73	40.26 ± 1.10	53.96 ± 0.66
	TG	16.87 ± 01.01	20.36 ± 01.20	22.64 ± 04.05	29.73 ± 01.39
4f	PG	18.68 ± 0.45	19.25 ± 2.03	26.42 ± 1.96	38.96 ± 1.46
	TG	10.46 ± 04.26	10.66 ± 01.16	14.73 ± 03.76	22.89 ± 01.73
5	PG	41.60 ± 2.29	47.25 ± 5.74	65.00 ± 5.36	75.50 ± 3.39
	TG	47.00 ± 15.04	35.25 ± 20.42	41.00 ± 17.70	46.00 ± 02.24



Graph 1. The glucose tolerance test was shown by control and compound **4a**.

glucose and triglyceride levels were estimated using commercial kits.[10,11] Oral glucose tolerance test was performed after 14–15 days of treatment. In this parameter, rats were fasted overnight and challenged with glucose (3 g/kg). Blood samples were collected at 0, 30, 60 and 120 min for measuring plasma glucose level. The improvement in glycemic control was calculated as percentage reduction in the area under the plasma glucose content versus time curve (AUC). The AUC was calculated using trapezoidal rule.[12]

4. Results and discussion

The 6,7-dimethyl-1,2,3,4-tetrahydroquinoxalin-2-one derivatives of thiazolidine-2,4-dione **4a**–**f** and rosiglitazone **5** were administered to Wistar rats in the dose range of 3, 10, 30 and 100 mg/kg bwt. Compound **4a**, having two methyl groups in the phenyl ring of 1,2,3,4-tetrahydroquinoxalin-2-one showed a remarkable decrease in glucose and triglyceride levels significantly (all compounds except **4e** and **4f** also showed a notable decrease in glucose and triglyceride level). The dose dependent euglycemic and hypolipidemic activity of rosiglitazone and 6,7-dimethyl-1,2,3,4-tetrahydroquinoxalin-2-one derivatives of thiazolidine-2,4-dione are reported in Table 1. Among these series, the compounds having electron donating substituent methyl group at C-3 position of 1,2,3,4-tetrahydroquinoxalin-2-one showed an appreciable decrease in glucose level and phenyl ring at C-3 position of 1,2,3,4-tetrahydroquinoxalin-2-one exhibit only modest decrease. For all the compounds **4a**, **4c**, **4e** and all the other corresponding compounds **4b**, **4d** and **4e** with an additional CH_2 spacer were also synthesized. Compounds with greater CH_2 spacer showed quite lower euglycemic and hypolipidemic activity as compared to compounds containing lower CH_2 spacer groups.

We also carried out oral glucose tolerance test with **4a** compound after 15 days of treatment. The results are shown in Graph 1.

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9. Structural data for **4a** is IR (KBr) ν cm^{-1}: 3438 (NH), 1730 (CONHCO), 1705 (SCONH), 1669 (NHCO), 1597 (amide II), 1258 ($\nu_{C=S}$). ^1H NMR (DMSO-d_6, 300 MHz): δ 12.30 (br s, 1H, CON*H*CO), 8.17 (br s, 1H, N*H*CO), 7.86 (dd, J = 1.55 Hz, 1H, Ar-*H*), 7.81 (dd, J = 1.60 Hz, 1H, Ar-*H*), 7.72 (d, J = 1.40 Hz, 2H, Ar-*H*), 7.49 (d, J = 1.55 Hz, 2H), 7.42 (t, J = 1.52 Hz, 1H), 7.02 (d, J = 1.51 Hz, 2H), 4.66 (t, J = 1.23 Hz, 2H, OCH_2), 4.41 (t, J = 1.23 Hz, 2H, NCH_2), 4.05 (s, 2H, CH_2), 2.20 (d, J = 7.0 Hz, 3H, CH_3), 2.17 (d, J = 7.0 Hz, 3H, CH_3); MS (EIMS, 70 eV): MS *m/z* 423 (M^+), 422 $(M-H)^+$. Anal Calcd for $C_{22}H_{21}N_3O_4S$: C, 62.39; H, 4.99; N, 9.92. Found: C, 62.28; H, 4.92; N, 9.88.
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