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Synthesis and antidiabetic activity of N'-[3-(alkyl/aryl substituted)-4-oxo-1,3 thiazolidin-2-yeidene]-2-(pyrazin-2-yloxy)acetohydrazide

Prabhakar Verma* and Vipan Kamboj

Department of Pharmaceutical Sciences, M.D. University, Rohtak, Haryana-124001, India

Abstract

A series of N'-[3-(4-alkayl/arylsubstituted)-4-oxo-1,3thiazolidin-2-ylidene]-2-(pyrazin-2-yloxy) acetohydrazide was synthesized by the cyclization of various N-substituted thiosemicarbazides using chloroacetic acid and sodium acetate in ethanol. Where N-substituted thiosemicarbazone prepared by the reaction of various alkayl/aryl isothiocyanate with 2-(pyrazin-2-yloxy)acetohydrazide, which was synthesized by amination of ethyl(pyrazin-2-yloxy)acetate with hydrazine hydrate. Ethyl(pyrazin-2-yloxy)acetate was prepared from the 2-hydroxypyrazine by ethylchloroacetate under reflux condition. The purity and homogeneity of compounds synthesized were determined by their sharp melting point, TLC, UV, IR, and NMR spectra. The compound N'-[3-(phenyl)-4-oxo-1,3thioazolidin-2-ylidine]-2-(pyrazin-2-yloxy)acetohydrazides, N'-(pyrazin-2-yloxy)acetohydrazide posses good antidiabetic activity with reduced toxicity.

Keyword: type 2 diabetes, hypoglycaemic, antihyperglycemic, glycaemic, thiazolidinone.

Introduction

A large number of drugs belonging to different categories are presently used as oral antihyperglycemic in the management of non-insulin dependent diabetes mellitus (NIDDM) or type-2 diabetes. Type-2 diabetes is characterized by hyperglycemia, which is mainly due to insulin resistance and impaired insulin secretion and lead to several complications such as neuropathy, nephropathy, retinopathy and atherosclerosis (Porte et al. 1996). Therefore it is important to maintain an appropriate blood glucose level especially during the early stage of disease (The diabetes control and complications trial research group 1993). The most commonly used oral hypoglycemics for the disease are sulfonyl urea, other prominent from them are thiazolidinediones, acrabose and nonsulfonyl ureas secretagogues (Repaglinide and Nateglinide). Although these drugs have helped to control hyperglycemia to a large extent. Their use entails several adverse affects such as skin rashes, dilutional hyponatremia, transient leucopenia, thrombocytopenia, myocarditis severe hypoglycemia increased chances of cardiovascular death of unknown mechanism, lethal lactic acidosis (rare), weight loss, weight gain and edema. Therefore search for more effective and safer hypoglycemic agent have been felt. The literature survey on the thiazolidinone ring revealed that substituted thiazalidinone

***Corresponding author:** vk.kamboj123@gmail.com

derivatives were tested for antidiabetic activity (Bue-Vallesky et al. 1996, Panetta et al. 1997). Thiazolidinones posses diversified pharmacological activity, among them the antidiabetic activity is prominent (Ohuyama et al. 1995). It has been reported that pyridine ring plays an important role to influence the antidiabitic activity of some drugs like Rosiglitazone and Pioglitazone, hence it was planned to introduce pyrazine ring in thiazolidinones to give better antidiabetic activity.

Results and Discussion

The synthesis of N'-[3-(alkyl/aryl substituted)-4-oxo-1,3-thiazolidin-2-ylidene]-2-(pyrazin-2-yloxy) aceto-hydrazine has been carried out following the step down in scheme 1. In the initial step ethyl(pyrazin-2-yloxy)acetate (2) was synthesized in an excellent yield by electrophilic substitution on 2-hydroxypyrazine (1) by ethylchloroacetate under refluxed condition. Compound 2 on amination with hydrazine hydrate afforded 2-(pyrazin-2-yloxy) acetohydrazide (3). Reaction of compound 3 with different alkyl/aryl isothiocynates in ethanol gives corresponding eight N-(substituted alkyl/aryl)-N''(-2-pyrazin-2-yloxy) acetylthiosemicarbazides (4). The reaction of compound 4 with chloroacetic acid in boiling ethanol containing fused sodium acetate afforded the corresponding eight N'-[3-(4-alkyl/aryl substituted)-4-oxo-1,3-thiazolidin-2-(pyrazin-2-yloxy) acetohydrazides. The compounds I-VIII were synthesized by reacting a mixture of triethylamine and 2-hydroxypyrazine, a solution of ethylchloroacetate was added drop wise. The temperature was maintained at 90°c for 1h and then the reaction mixture was stirred for 7-8h. The solid product i.e. compound was recrystallized (yield 70-94%) using chloroform. Further recrystallized product in ethanol (40ml) was refluxed for 12h. The purity of chemical compounds was checked by TLC and elemental analysis. Both analytical and spectral data (H-NMR, IR) of all the synthesized compounds were in full agreement with the proposed structure. In general, infrared spectra (IR) revealed $NHNH_2$, C=O, N-H, C=S peak at 3295, 3210, 3320-3100 and 1360-1270cm^{-1}. In the nuclear magnetic resonance spectra (H-NMR) the signals of the respective protons of the prepared titled compounds were verified on the basis of their chemical shifts, multiplicities and coupling constant.

^{1}HNMR (dimethylsulfoxide (DMSO)-d6): δ2.26 (3H,S) 2.85 (2H,⊤,J=6.5HZ) 4.16(2H,⊤,J=6.5HZ), 5.72(1H ad,J=6.5,4.5HZ). The elemental analysis results were within ±0.4% of the theoretical value.

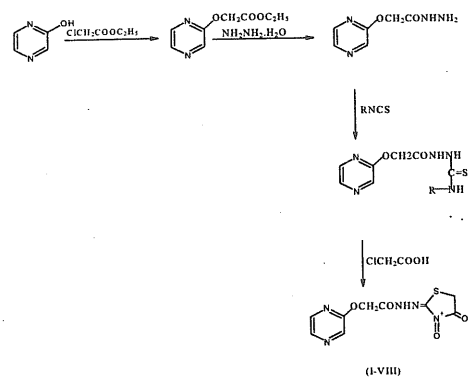
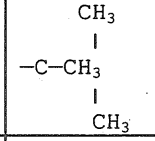
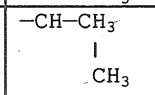
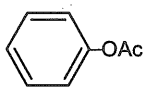
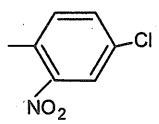
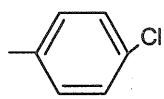
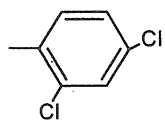


Figure 1. Protocol for the synthesis of N'-[3-(alky/aryl substituted)-4-oxo-1,3-thiazalidin-2-ylidene]-2(pyrazin-2-yloxy)acetohydrazide

Table 1. Physico-chemical studies of the synthesized compounds

Sr No	Comp No	Name of the compound	R	Molecular Formula	Yield (%)	mp (c)	Rf Value	Amax (nm)
1	T1	N'-[3-(phenyl)-4-oxo-1,3-thiazolidin-2-ylidene]-2-(pyrazin-2-yloxy) acetohydrazide	$-C_6H_6$	$C_{15}H_{13}N_5O_3S$	65	84-86	0.72	293
2	T2	N'-[3-(n-butyl)-4-oxo-1,3-thiazolidin-2-ylidene]-2-(pyrazin-2-yloxy) acetohydrazide	$-CH_2CH_2CH_2CH_3$	$C_{13}H_{17}N_5O_3S$	76	124-126	0.69	283
3	T3	N'-[3-(t-butyl)-4-oxo-1,3-thiazolidin-2-ylidene]-2-(pyrazin-2-yloxy) acetohydrazide		$C_{13}H_{17}N_5O_3S$	79	74-76	0.67	310
4	T4	N'-[3-(iso-propyl)-4-oxo-1,3-thiazolidin-2-ylidene]-2-(pyrazin-2-yloxy) acetohydrazide		$C_{12}H_{15}N_5O$	74	144-146	0.62	277
5	T5	N'-[3-(p-ethoxyphenyl)-4-oxo-1,3-thiazolidin-2-ylidene]-2-(pyrazin-2-yloxy) acetohydrazide		$C_{17}H_{17}N_5O_4S$	78	112-114	0.78	305
6	T6	N'-[3-(2-ntro-4-chloro)-4-oxo-1,3-thiazolidin-2-ylidene]-2-(pyrazin-2-yloxy) acetohydrazide		$C_{15}H_{11}N_6O5Cl$	76	102-104	0.84	298
7	T7	N'-[3-(4-chlorophenyl) -4-oxo-1,3-thiazolidin-2-ylidene]-2 (pyrazin-2-yloxy) acetohydrazide		$C_{15}H_{12}N_5O_3SCl$	75	130-132	0.81	311
8	T8	N'-[3-(2,4-dichlorophenyl)-4-oxo-1,3-thiazolidin-2-ylidene]-2-(pyrazin-2-yloxy) acetohydrazides		$C_{15}H_{11}N_5O_5SC_{12}$	72	116-118	0.85	305

Antidiabetic Activity

(A). Cut-off LD_{50}

All the compounds synthesized were tested for acute toxicity test. No toxicity was observed at the dose of 300, 1000, 2000 mg/ kg of body weight. So the animals were further administered the dose of 5000mg/kg of body weight as per the OECD guide line and it was observed that all the animals were died at the dose

of 5000 mg/kg of body weight. Thus for the screening of antidiabetic activity, the dose selected was 200mg/kg of body weight as per the OECD guidelines (Alshamaony et al 1994).

(B) Result of dexamethasone on blood glucose and plasma insulin compared with the controlled shown in Table 2. Effect of the test compounds on the dexamethasone induced hyperglycemia and hyperinsulinemia compared with the control and standard drug (Rosiglitazone) are given in the Table 3 and 4. Compound no. 1 and 2 were found to be most active (155.44% and 124.93%). Compound no. 3,4,5 posses moderate antidiabetic activity (103.14%, 100.46% and 70.52%) while compound no. 6 ,7, 8 were tested antidiabetic activity (33.88%,50.00% and 43.09%) as compared with the standard drug rosiglitazone (145.01%).

Table: 2 Effect of dexamethasone on the blood glucose and plasma insulin level

Sr. No	Blood glucose (mg/dL)		Plasma insulin (mlu/mL)	
	Controlled	Dextreated	Controlled	Dextreated
1	87.60 ± 1.913	257.6 ± 2.015	0.2800 ± 0.011	4.167 ± 0.033

Table: 3 Effect of the different alkyl/aryl substituted thiazolidinone derivatives on the dexamethasone induced hyperglycemia

Compound No	Dose in mg/kg	Mean blood glucose level in mg/dL		Percentage reduction in blood glucose	
		After 1st h	After 2nd h	After 1st h	After 2nd h
1	200	174.7 ± 25.58	101.0±2.082	45.96	155.44
2	200	157.7 ± 22.81	114.7±2.028	61.69	124.93
3	200	178.7 ± 27.76	127.0±14.15	42.69	103.14
4	200	152.0 ± 18.15	128.7±3.383	67.76	100.46
5	200	224.0 ± 1.155	151.3±12.78	13.80	70.52
6	200	236.7 ± 22.58	192.7±10.41	7.73	33.88
7	200	202.7 ± 14.38	172.0±6.110	25.80	50.00
8	200	222.0 ± 21.70	180.3±24.06	14.86	43.09
Rosiglitazone	200	136.0 ± 10.79	105.3±10.65	87.50	145.01

Table: 4 Effect of the different alkyl/aryl substituted thiazolidinone derivatives on the dexamethasone induced hyperinsulinemia

Compound No.	Diabetic vehicle treated	1	2	3	4	5	Rosiglitazone
Plasma insulin (mil/mL)	4.167± 0.033	3.000± 0.057	3.100± 0.057	3.700± 0.57	3.500± 0.057	3.200± 0.057	3.667±0.088

Conclusion

Among the newer derivative compound I and II showed promising antidiabetic activity. It is conceivable that these derivatives showing antidiabetic activity can be further modified to exhibit better potency than the standard drug. These result make novel N'-[3-(4-alkyl/aryl substituted)-4-oxo-1,3-thiazolidin-2-ylidene]-2-(pyrazin-2-yloxy)acetohydrazide and its derivatives, an interesting lead molecule for more

synthetic and biological evaluation. It can be concluded that this class of compound may lead to the development of novel antidiabetic drugs if explored further. Further studies to acquire more information about quantitative structure activity relationships are in progress in our laboratory.

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