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Optimized Synthesis of Active 5-benzylidine-1,3-thiazolidine-2,4-dione Derivatives

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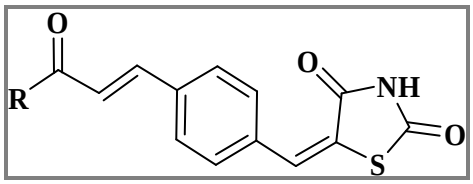
ABSTRACT

The active substrates 5-benzylidine-1,3-thiazolidine-2,4-dione derivatives which are a class of α-glucosidase inhibitors prepared from 4-((Z)-(2,4-dioxothiazolidin-5-ylidene)methyl)benzaldehyde with aromatic/ hetero aromatic ketones in presence of potassium hydroxide with ethanol as solvent. In order to improve the yields the synthesis of 5-benzylidine-1,3-thiazolidine-2,4-dione derivatives(1a-1f) has been optimized by screening different bases and solvents. Finally better conditions for preparation of these derivatives were established by Quality by design. The 5-benzylidine-1,3-thiazolidine-2,4-dione derivatives (1a-1f) were prepared with excellent yield.

Graphical Abstract



Keywords: Thiozolidinedione, α-glucosidase, 5-benzylidine-1,3-thiazolidine-2,4-dione, Derivatives.

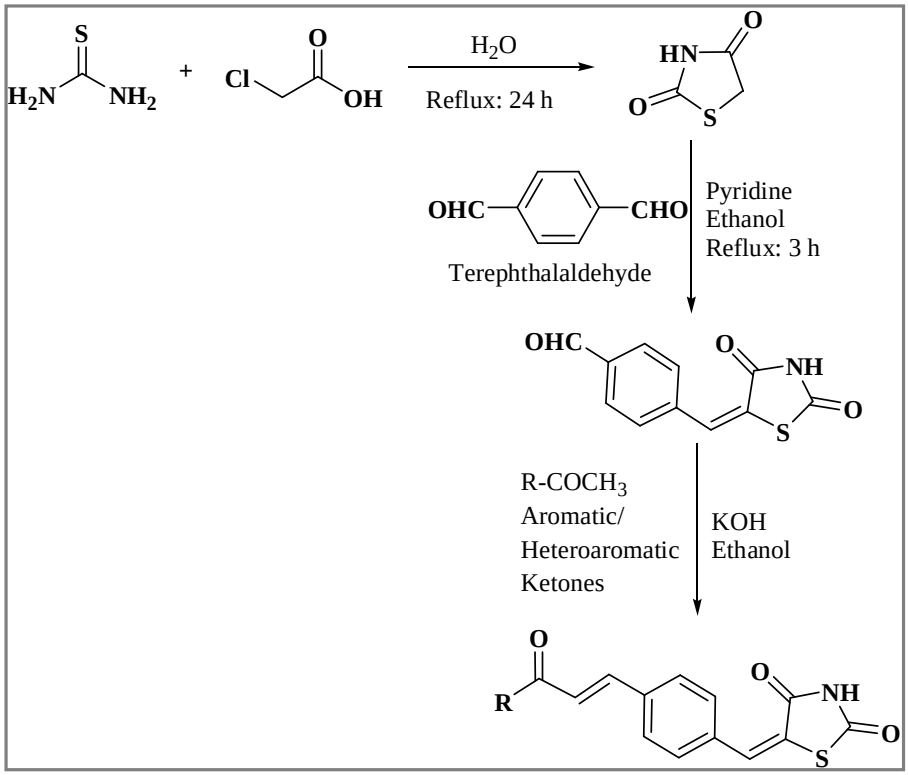
INTRODUCTION

Thiazolidinediones are the derivatives of thiazolidine, which belongs to important group of five membered biologically active hetero cyclic compounds. Thiazolidinediones have one sulphur atom at 1st position , Nitrogen at position 3 and two carbonyl groups each at -2,-4 or -2,-5 or -4,-4 positions respectively [**1**]. In terms of their chemistry, different possibilities of heterocyclic modifications with a wide spectrum of pharmacological properties are the most important grounds for investigations of this interesting class of compounds [**2, 3**]. Primarily 2,4-thiazolidinediones scaffold is extremely versatile and its derivatives, also referred to as glitazones, represent the most promising class of compounds having a wide variety of biological activities [**4**]. Thiazolidinediones are a class of insulin sensitizing drugs, which include Ciglitazone, Pioglitazone, Troglitazone and rosiglitazone [**5**].

Thiazolidinediones are well established as PPAR-γ receptor stimulators and also have numerous PPAR-γ freelance effects [**6-18**]. Anti-cancer actions of Thiazolidinediones are in examination. Various clinical studies are establishing their therapy to cancer besides the antidiabetic activity.

Various 5-benzylidene-1,3-thiazolidine-2,4-diones were prepared and found that 5-benzylidene-1,3-thiazolidine-2,4-diones have considerable potential to act as a new class of α-glucosidase inhibitors (Scheme 1). The novelty of this work is that none of the 5-benzylidene-1,3-thiazolidine-2,4-diones synthesized were earlier not reported to possess any inhibitory activity against α-glucosidase enzyme.

In the present work it was optimized the synthesis of these compounds by screening various bases both organic and inorganic, various solvents and established better conditions to improve yields by quality by design experiments.

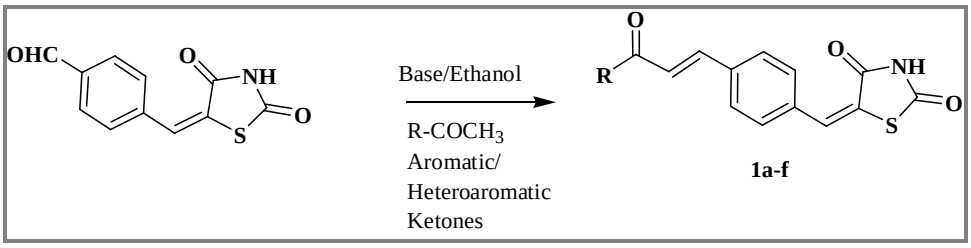


Scheme 1. 5-benzylidene-1,3-thiazolidine-2,4-diones.

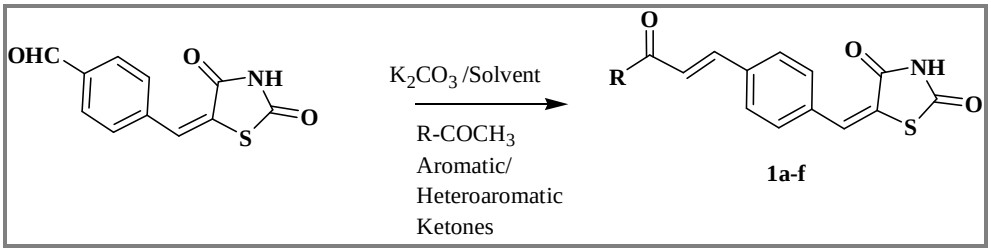
MATERIALS AND METHODS

Synthesis: 4-((Z)-(2,4-dioxothiazolidin-5-ylidene)methyl)benzaldehyde was condensed with substituted aromatic/hetero aromatic ketones by using various bases and solvents to synthesize 5-benzylidene-1,3-thiazolidine-2,4-diones [**19, 20**].

Initially the synthesis was carried by taking ethanol as solvent and screened with different bases.



After the screening process the synthesis was carried out by taking Potassium carbonate as a base and screened with different solvents.



General procedure for Synthesis of 5-benzylidene-1,3-thiazolidine-2,4-dione derivatives: 4-((Z)-(2,4-dioxothiazolidin-5-ylidene)methyl)benzaldehyde was treated with aromatic/ hetero aromatic ketones in the presence of base and solvent. The reaction was maintained at ambient temperature and monitored by Thin layer chromatography. It was then quenched with cold water after completion and filtered the precipitated solid.

Synthesis (1a): 4-((Z)-(2,4-dioxothiazolidin-5-ylidene)methyl)benzaldehyde (1.5 gm, 0.0064 mol) is treated with1-o-tolylethanone (0.86 g, 0.0064)in presence of Potassium carbonate (0.89 g, 0.0064 mol) and acetone(5 volumes) as solvent. The reaction mixture was stirred for 5-6 h at ambient temperature and monitored by thin layer chromatography (silica gel). The reaction mass was quenched by cold water and then filtered the precipitated yellow color solid material which gave 92% yield. Similarly the other compounds 1b-1f were prepared and characterized.

Quality by design: Finally by DOE (Design of experiments) using Fusion pro soft ware which is completely aligned with Quality by Design principles, better reaction conditions were established to improve yields (Table 1 and 2).

Table 1. Study variable settings

Name	Units	Range/Levels
Potassium carbonate	(g)	0.90 <= Potassium carbonate <=1.1
Acetone	(v)	4.0 <= Acetone <= 6.0
Temperature	(degrees)	25.0 <= Temperature <= 40.0

Global ordering settings: Ordering strategy; Standard matrix array, Renumber rows; -.

Design wizard settings: Design type; 2-level–full factorial, Design model; Quadratic, Generate design option; New, Number of design runs, 11

Replication/Degrees of Freedom settings: Number of centre points; 3, Number of non-centre points to be repeated; 0

Replicate Group	Run No.
1	2
	8
	9

Table 2. Experimental Design matrix

Run No.	Potassium carbonate (eq.)	Acetone (v)	Temperature (degrees)
1	1.10	6.0	40.0
2	1.00	5.0	32.5
3	0.90	4.0	40.0
4	1.10	6.0	25.0
5	1.10	4.0	40.0
6	0.90	4.0	25.0
7	0.90	6.0	40.0
8	1.00	5.0	32.5
9	1.00	5.0	32.5
10	1.10	4.0	25.0
11	0.90	6.0	25.0

Spectral data analysis of some selected compounds

Compound 1a: FT-IR (KBr, vmax,cm^{-1}):3155 (N−H), 3031 (C−H, aromatic), 2884 (C−H, aliphatic), 1688 (C=O), 1645 (C=C, aliphatic), 1513(C=C, aromatic), 689 (C−S). 1H NMR (400 MHz, DMSO-d6, δ, ppm): 2.32 (s, 3H, CH3), 7.43-8.04 (m, 8H, ArH), 7.78 (d, J=15.2 Hz, 1H, HC=CH (H-α)), 7.98 (s,1H, HC=C), 8.01(d, J=15.2 Hz, 1H, HC=CH (H-β)), 12.74 (s, 1H, NH). ESI MS (m/z): 350 $[M+H]^+$

Compound 1b: FT-IR(KBr,vmax,cm-1):3122(N−H),3021(C−H,aromatic),2884(C−H,aliphatic),1693 (C=O),1605(C=C, aliphatic),1415(C=C, aromatic), 688(C−S),1114(C−F). 1HNMR (400MHz,DMSO-d6, δ, ppm): 7.39-8.31 (m,7H,Ar-H), 7.76 (d,J=15.2Hz, 1H, HC=CH (H-α)), 7.94 (s, 1H, HC=C), 8.08 (d, J=15.2 Hz, 1H, HC=CH (H-β)), 12.69 (s, 1H, NH). ESI-MS (m/z): 372 $[M+H]^+$.

RESULTS AND DISCUSSION

The compounds 1a-1f were synthesized by choosing ethanol as solvent and screened bases are Triethylamine, Piperidine and Potassium carbonate and the corresponding yields were tabulated. The results show that the use of potassium carbonate as base was advantageous than other bases. Hence Potassium carbonate was selected for screening different solvents (Table 3).

The compounds [1a-1f] were synthesized by choosing potassium carbonate as base and screened the solvents Isoproprylalcohol, Methanol, Acetone. The results show that the use of Acetone as solvent was advantageous than other solvents. Table 3 shows that the combination of Acetone, Potassium carbonate resulted better yield. So this combination of these selected for Quality by design.

Experiments were designed by taking equivalents of Potassium carbonate, Volumes of Acetone and temperature of reaction by 2 level-full factorial design. Table 4 shows the DOE results of the experiments by using Acetone as solvent and Potassium carbonate as base for preparing the compound 1b which is the better active substrate among all the synthesized compounds. The yield was better by performing the reaction with 1.1 equivalents of base, 6 volumes of Acetone and maintaining the reaction temperature at 40°C.

Table 3. %Yield with different bases

Compound	R	Solvent	Base used	Yield (%)	Solvent	Base used	Yield (%)
1a	2-MeC_6H_4	Ethanol	KOH	79.0		Ethanol	85.0
			Triethlamine	62.0	Potassium	Isopropylalcohol	83.0
			Piperidine	78.0	carbonate	Methanol	81.0
			Potassium carbonate	85.0		Acetone	92.0
1b	2,4-diFC_6H_3	Ethanol	KOH	84.0	Potassium	Ethanol	88.0
			Triethlamine	65.0	carbonate	Isopropylalcohol	86.0
			Piperidine	76.0		Methanol	82.0
			Potassium carbonate	88.0		Acetone	91.0
1c	3-$OMeC_6H_4$	Ethanol	KOH	78.0	Potassium	Ethanol	89.0
			Triethlamine	64.0	carbonate	Isopropylalcohol	85.0
			Piperidine	79.0		Methanol	83.0
			Potassium carbonate	89.0		Acetone	92.0
1d	3-OHC_6H_4	Ethanol	KOH	78.0	Potassium	Ethanol	87.0
			Triethlamine	68.0	carbonate	Isopropylalcohol	87.0
			Piperidine	75.0		Methanol	80.0
			Potassium carbonate	87.0		Acetone	90.0
1e	2-$NO_2C_6H_4$	Ethanol	KOH	84.0	Potassium	Ethanol	86.0
			Triethlamine	69.0	carbonate	Isopropylalcohol	87.0
			Piperidine	85.0		Methanol	79.0
			Potassium carbonate	86.0		Acetone	93.0
1f	Thiophene-3-yl	Ethanol	KOH	82.0	Potassium	Ethanol	85.0
			Triethlamine	68.0	carbonate	Isopropylalcohol	84.0
			Piperidine	81.0		Methanol	78.0
			Potassium carbonate	85.0		Acetone	89.0

Table 4. Results of DOE

Run No	Potassium carbonate (eq.)	Acetone (v)	Temperature (degrees)	Yield (%)
1	1.10	6.0	40.0	94.0
2	1.00	5.0	32.5	91.0
3	0.90	4.0	40.0	89.0
4	1.10	6.0	25.0	90.0
5	1.10	4.0	40.0	93.0
6	0.90	4.0	25.0	88.0
7	0.90	6.0	40.0	90.0
8	1.00	5.0	32.5	91.0
9	1.00	5.0	32.5	92.0
10	1.10	4.0	25.0	89.0
11	0.90	6.0	25.0	88.0

APPLICATION

This is simple and convenient synthetic method which gives good yield of target molecule. The Thiazolidinediones are of great interest due to their pharmacological properties. The synthesized compounds are active substrates for α-glucosidase inhibition. The main purpose of the present work is to optimize the best conditions for the synthesis of these active substrates. It also ensures the use of Quality design in establishing better conditions for synthesis after optimization. This is simple and convenient synthetic method which gives good yield of target molecules.

CONCLUSION

An efficient and simple method for the preparation of 5-benzylidene-1,3-thiazolidine-2,4-diones was developed by improving the yields of the reaction. It can be concluded that the combination of potassium carbonate, Acetone with reaction temperature at 40°C resulted in excellent yield.

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