Solvent free synthesis of active 5-benzylidine-1, 3-thiazolidine-2,4-dione derivatives

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Abstract

Present communication describes the attempts made to improve the yields of thiazolidinedione group of derivatives keeping in view of their anti-cancer activity. 5-benzylidine-1,3-thiazolidine-2,4-dione derivatives were the active substrates belonging to α-glucosidase inhibitor classification. These were prepared by the reaction of 4-((Z)-(2,4-dioxothiazolidin-5-ylidene) methyl) benzaldehyde with aromatic/hetero aromatic ketones in the presence of potassium hydroxide and ethanol as solvent.

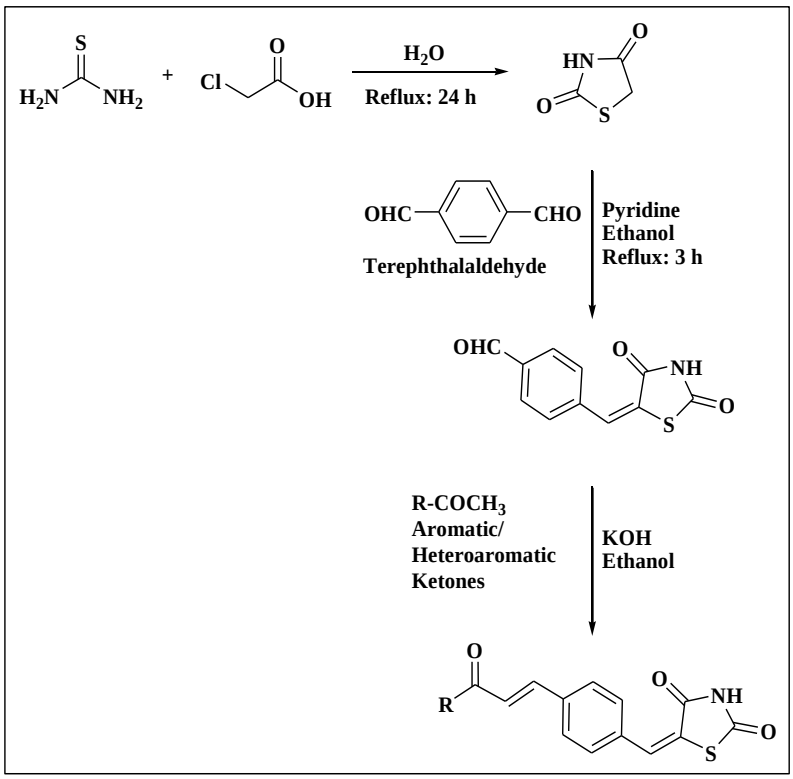
Synthesis of 5-benzylidine-1, 3-thiazolidine-2,4-dione derivatives has been optimized under solvent free condition by screening with different bases in order to achieve the required target (of improving the yields). The solvent free condition has resulted in excellent improvement in yields and reduced the manufacturing cost significantly.

Keywords: Thiazolidinedione, α-glucosidase, 5-benzylidine-1,3-thiazolidine-2,4-dione, synthesis.

Introduction

Thiazolidinediones, biologically active hetero cyclic compounds, are the derivatives of thiazolidine[9]. These contain sulphur at 1st position, nitrogen at 3rd position and two carbonyl groups each at -2, -4 or -2, -5 or -4, -4 positions respectively. These compounds exhibit very good potential pharmacological properties which can be studied further[7]. Primarily 2,4-thiazolidinediones are also known as glitazones which represent the most promising class of compounds with wide variety of biological activities[13]. Thiazolidinediones are said to be insulin sensitizing drugs including ciglitazone, pioglitazone, troglitazone and rosiglitazone[1]. In addition, thiazolidinediones are well established as PPAR-γ receptor stimulators and exhibit numerous PPAR-γ freelance effects[2-6,8,10-12].

Anti-cancer activity of thiazolidinediones is still under examination stage. Various clinical studies are in progress to prove their anti-cancer behaviour along with anti-diabetic activity also. Several 5-benzylidene-1,3-thiazolidine-2,4-diones were prepared and it was found that these compounds possess considerable potential to act as a new class of α-glucosidase inhibitors (Scheme 1). Synthesis of compounds was optimised using base morpholine and acetic acid mixture.



Scheme 1

Material and Methods

General procedure for synthesis: 4-((Z)-(2,4-dio xothiazolidin-5-ylidene) methyl) benzaldehyde was allowed to react with substituted aromatic ketones with a mixture of morpholine base and acetic acid under solvent free conditions in order to improve the yield.

The reaction mixture was maintained at ambient temperature and monitored by thin layer chromatography. It was then quenched with cold water. After completion of reaction, the solid obtained has been filtered.

Synthesis (1a): Morpholine (0.56gm, 0.0064) was added to a mixture of 4-((Z)-(2,4-dioxothiazolidin-5-ylidene) methyl) benzaldehyde (1.5 gm, 0.0064mol) 2-Fluoroacetophenone (0.89gm, 0.0064) and acetic acid (0.54g, 0.009) in the temperature range 5-15°C. The mixture was then stirred for 5-6 hours and monitored by thin layer chromatography (silica gel) as described above. Yellow colour solid material with 95% yield was obtained. It was then recrystalized with isopropyl alcohol. Similar procedures were adapted to other compounds (1b-lh) also and were characterized.

Spectral analysis of compounds (1a-h):

(Z)-5-(4-((E)-3-(2-fluorophenyl)-3-oxoprop-l-enyl)benzy lidene)-1,3-thiazoldine-2,4-dione(la): Yellow solid, M.P.: 224-229°C; FT-IR (KBr, νmax, cm^{-1}): 3117 (N-H), 3017(C-H, aromatic), 2977 (C-H, aliphatic), 1693 (C=O), 1605 (C=C, aliphatic), 1415 (C=C, aromatic),1116 (C-F), 688 (C-S). 1H NMR (400 MHz, DMSO-d6, δ, ppm): 7.36-8.03 (m, 8H, Ar-H), 7.55 (d, J=15.2 Hz, 1H HC=CH (H-α)), 7.97 (s, 1H HC=C), 7.82 (d, J=15.2 Hz, 1H, HC=CH (H-β), 12.68 (s, 1H, NH). ESI-MS (m/z): 354 [M+H] +.

(Z)-5-(4-((E)-3-(2-methylphenyl)-3-oxoprop-l-enyl)benz ylidene)-1,3-thiazoldine-2,4-dione (lb): Yellow solid, M.P.: 135-140°C; FT-IR (KBr, νmax, 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, CH_3), 7.43-8.04 (m, 8H, Ar-H), 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 $[M+H]^+$.

(Z)-5-(4-((E)-3-(3-methylphenyl)-3-oxoprop-l-enyl)benz ylidene)-1,3-thiazoldine-2,4-dione (l c): Yellow solid, M.P.: 167-172°C; FT-IR (KBr, νmax, cm^{-1}): 3127 (N-H), 3027 (C-H, aromatic), 2777 (C-H, aliphatic), 1703 (C=O), 1603 (C=C, aliphatic), 1450 (C=C, aromatic), 688 (C-S). 1H NMR (400 MHz, DMSO-d6, δ, ppm): 2.41 (s, 3H, CH_3), 7.38-8.05 (m, 8H, Ar-H), 7.73 (d, J=15.2 Hz, 1H HC=CH (H-α)), 7.98 (s, 1H HC=C), 8.04 (d, J=15.2 Hz, 1H, HC=CH (H-β)), 12.69 (s, 1H, NH). ESI-MS (m/z): 350 $[M+H]^+$.

(Z)-5-(4-((E)-3-(2-methoxyphenyl)-3-oxoprop-l-enyl)ben zylidene)-1,3-thiazoldine-2,4-dione (ld): Yellow solid, M.P.: 235-240°C; FT-IR (KBr, νmax, cm^{-1}): 3124 (N-H), 3027 (C-H, aromatic), 2975 (C-H, aliphatic), 1700 (C=O), 1603 (C=C, aliphatic), 1417 (C=C, aromatic), 1171 (C-O-C), 1054 (C-O), 713 (C-S). 1H NMR (400 MHz, DMSO-d6, δ, ppm): 3.86 (s, 3H, OCH_3), 7.20-8.05 (m, 8H, Ar-H), 7.48 (d, J=15.2 Hz, 1H HC=CH (H-α)), 7.99 (s, 1H HC=C), 8.05 (d, J=15.2 Hz, 1H, HC=CH (H-β)), 12.66 (s, 1H, NH). ESI-MS (m/z): 366 $[M+H]^+$.

(Z)-5-(4-((E)-3-(2-methoxyphenyl)-3-oxoprop-l-enyl)ben zylidene)-1,3-thiazoldine-2,4-dione (le): Yellow solid, M.P.: 180-185°C; FT-IR (KBr, νmax, cm^{-1}): 3124 (N-H), 3027 (C-H, aromatic), 2977 (C-H, aliphatic), 1700 (C=O), 1605 (C=C, aliphatic), 1457 (C=C, aromatic), 1171 (C-O-C), 1054 (C-O), 687 (C-S). 1H NMR (400 MHz, DMSO-d6, δ, ppm): 3.88 (s, 3H, OCH_3), 7.12-8.21 (m, 8H, Ar-H), 7.71 (d, J=15.2 Hz, 1H HC=CH (H-α)), 7.94 (s, 1H HC=C), 8.06 (d, J=15.2 Hz, 1H, HC=CH (H-β)), 12.65 (s, 1H, NH). ESI-MS (m/z): 366 $[M+H]^+$.

(Z)-5-(4-((E)-3-(2-Chlorophenyl)-3-oxoprop-l-enyl)benz ylidene)-1,3-thiazoldine-2,4-dione (lf): Yellow colour solid, M.P.: 193-198°C; FT-IR (KBr, νmax, cm^{-1}): 3127 (N-H), 3027 (C-H, aromatic), 2893 (C-H, aliphatic), 1689 (C=O), 1597 (C=C, aliphatic), 1450 (C=C, aromatic), 786 (C-Cl), 688 (C-S). 1H NMR (400 MHz, DMSO-d6, δ, ppm): 7.60 (d, J=15.2 Hz, 1H HC=CH (H-α)), 7.62-8.24 (m, 8H, Ar-H), 7.78 (d, J=15.2 Hz, 1H, HC=CH (H-β)), 7.88 (s, 1H HC=C), 12.65 (s, 1H, NH). ESI-MS (m/z): 370 $[M+H]^+$.

(Z)-5-(4-((E)-3-(2-Nitrophenyl)-3-oxoprop-l-enyl)benzy lidene)-1,3-thiazoldine-2,4-dione (lg): Yellow solid, M.P.: 245-250°C; FT-IR (KBr, νmax, cm^{-1}): 3115 (N-H), 3026 (C-H, aromatic), 2775 (C-H, aliphatic), 1700 (C=O), 1599 (C=C, aliphatic), 1522 (N=O), 1290 (C-N), 1412 (C=C, aromatic), 688 (C-S). 1H NMR (400 MHz, DMSO-d6, δ, ppm): 7.55-8.39 (m, 8H, Ar-H),7.86 (d, J=15.2 Hz, 1H HC=CH (H-α)), 7.98 (s, 1H HC=C), 8.06 (d, J=15.2 Hz, 1H, HC=CH (H-β)), 12.73 (s, 1H, NH). ESI-MS (m/z): 381 $[M+H]^+$.

(Z)-5-(4-((E)-3-(2,4-Difluorophenyl)-3-oxoprop-l-enyl)b enzylidene)-1,3-thiazoldine-2,4-dione (lh): Yellow solid, M.P.: 187-192°C; FT-IR (KBr, νmax, cm^{-1}): 3122 (N-H), 3021 (C-H, aromatic), 2884 (C-H, aliphatic), 1693 (C=O), 1605 (C=C, aliphatic). 1415 (C=C, aromatic), 1114 (C-F), 688 (C-S). 1H NMR (400 MHz, DMSO-d6, δ, ppm): 7.39-8.31 (m, 8H, Ar-H), 7.76 (d, J=15.2 Hz, 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

Preparations of these dione derivatives were done using solvents like DMF and strong base like sodium hydroxide. In the present study a solvent free green synthesis has been developed in order to increase the rate of reaction. The results are presented in table 1.

The reactions showed excellent progress by maintaining the ratio of morpholine and acetic acid at 1: 1.4 equivalents.

Solvent free synthesis has several benefits which include safe reaction profile, high yields, shorter reaction times, high selectivity and easy to work up compared to classical synthetic methods. Moreover, results of the current study showed that the use of morpholine as base under solvent free condition is advantageous than the conventional methods.

Conclusion

It can be concluded that an efficient and simple green synthetic method has been developed for the preparation of 5-benzylidene-1,3-thiazolidine-2,4-diones for better yields of the reaction with the combination of morpholine and acetic acid under solvent free conditions.

Acknowledgement

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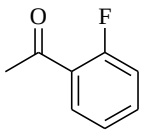
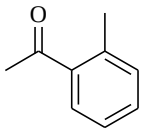
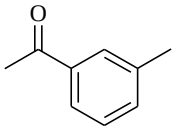
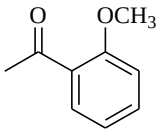
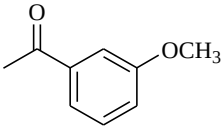
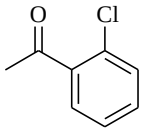
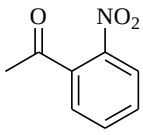
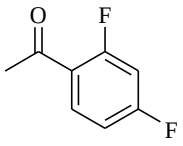
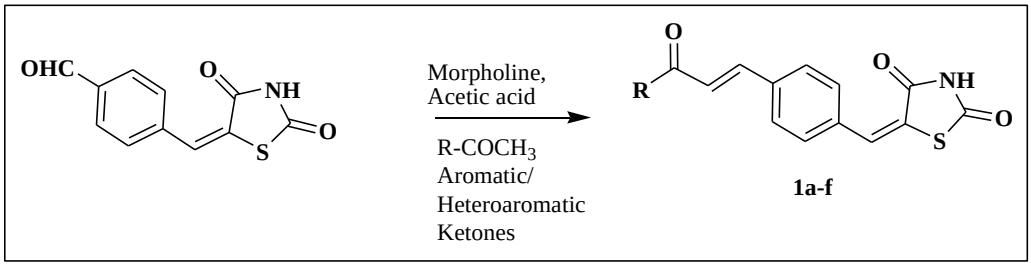
Table 1
Yield data

Compound	R	Yield (%)
1a		95.0
1b		89.0
1c		92.0
1d		93.0
1e		86.2
1f		93.0
1g		89.4
1h		89.7

Synthesis:



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