European Journal of Chemistry 5 (1) (2014) 144-149

European Journal of Chemistry

Journal homepage: www.eurjchem.com

Synthesis, characterization and in vitro evaluation of some new 5-benzylidene-1,3-thiazolidine-2,4-dione analogs as new class of α-glucosidase inhibitors

Divakara Laxman Somayajulu Nori [a,*], Kasapu Vishnu Veera Venkata Satyanarayana [a], Vasudeva Rao Avupati [b], Bharat Kumar Bugata [c] and Subhash Yenupuri [a]

[a] *Department of Chemistry, Gitam University, Rushikonda, Visakhapatnam-530045, Andhra Pradesh, India*
[b] *Pharmaceutical Chemistry Division, Andhra University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam-530003, Andhra Pradesh, India*
[c] *Department of Biochemistry and Bioinformatics, Gitam University, Rushikonda, Visakhapatnam-530045, Andhra Pradesh, India*

**Corresponding author at: Department of Chemistry, Gitam University, Rushikonda, Visakhapatnam-530045, Andhra Pradesh, India. Tel.: +91.0891.2792928. Fax: +91.0891.2790399. E-mail address: divakarsomu@gmail.com (D.L.S. Nori).*

ARTICLE INFORMATION

DOI: 10.5155/eurjchem.5.1.144-149.925

Received: 10 September 2013
Received in revised form: 18 October 2013
Accepted: 29 October 2013
Online: 31 March 2014

KEYWORDS

α-Glucosidase
Structure activity relationship
Aromatic/heteroaromatic ketone
Thiazolidine-2,4-dione derivatives
Minimum inhibitory concentration
5-Benzylidene-1,3-thiazolidine-2,4-dione

ABSTRACT

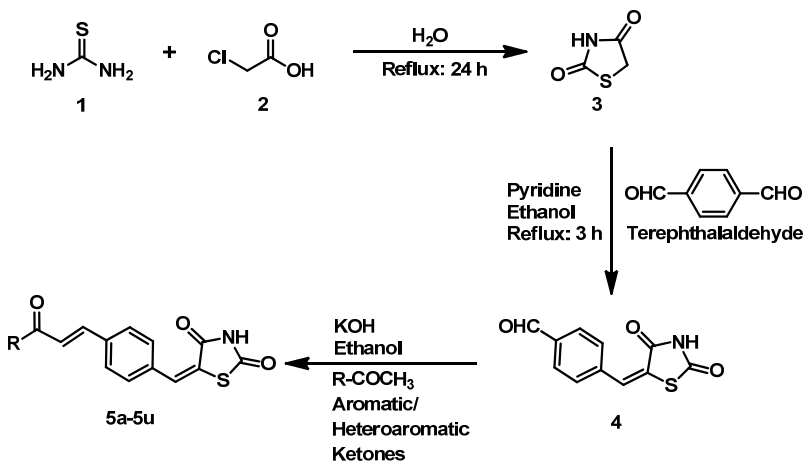
A series of 5-benzylidene-1,3-thiazolidine-2,4-dione derivatives (**5a-u**) were synthesized and tested against α-glucosidase. Preparation of the titled compounds was achieved by reaction of *(Z)*-4-((2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl)benzaldehyde (**4**) and aromatic/hetero aromatic ketone. Among the compounds tested, (**5p**) and (**5o**) were identified as the most active *in vitro* with minimum inhibitory concentration (MIC) of 6.56±0.81 and 8.92±0.21 µg/mL against α-glucosidase, respectively. Evaluation of the structure activity relationship of substituents within these series has followed the discovery of a variety of compounds.

1. Introduction

α-Glucosidases (α-D-glucoside glucohydrolase E.C. 3.2.1.20) are membrane bound exo-acting enzymes, located at the epithelium of the small intestine [1]. They are responsible for catalyzing the final step in the digestive process of carbohydrate metabolism. α-Glucosidases are the key enzymes that hydrolyze O- and S-glycosyl residues, are involved in the biosynthesis and processing of oligosaccharide chains of N-linked glycoproteins in the endoplasmic reticulum (ER) [2]. The most extensively studied are α and β-glucosidases that are known to catalyze the hydrolysis of glycosidic bonds involving a terminal glucose at the cleavage site through α- and β-linkages at the anomeric centre [3]. These two glucosidases differ in how to position their two carboxylic acid side chains during catalysis, one plays the role of a catalytic nucleophile attacking the anomeric centre, and the other acts as an acid catalyst weakening the C-O bond by protonation. Between the two popular glucosidases, α-glucosidase has drawn a special interest of the medicinal chemists because it was shown in earlier studies that inhibition of its catalytic activity resulted in the retardation of glucose absorption and the decrease in post prandial blood glucose level [4]. Several sugar α-glucosidase inhibitors, including acarbose, voglibose and miglitol are clinically used in the effective treatment of type-2 diabetes mellitus. However, such inhibitors, which are of great structural diversity, require tedious multisteps during preparation [5]. Hence, greater attention is focused on non-sugar α-glucosidase inhibitors [6]. The design of glucosidase inhibitors with a high degree of specificity and potency is still needed for exploration of new inhibitors [7]. α-Glucosidase inhibitors are also known to be promising as antiviral, anti-HIV agents, which alter glycosidation of envelop glycoprotein through interference with biosynthesis of N-linked oligosaccharides [8]. Recently, several synthetic ligands have been reported to inhibit α-Glucosidase [9,10].

Thiazolidinediones (TZDs) are the derivatives of thiazolidine, which belongs to an important group of five-membered biologically active heterocyclic compounds. Thiazolidinediones have an atom of sulfur at position 1, an atom of nitrogen at position 3 and two carbonyl groups each one at -2, -4 or -2, -5 or -4, -5 positions, respectively [11]. 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 [12].

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
http://dx.doi.org/10.5155/eurjchem.5.1.144-149.925



Scheme 1

The positions 3 (-NH- group) and 5 (-CH_2- group) on the TZD ring are relatively more reactive; hence, most of the modifications on the TZD ring are done on these positions to synthesize new molecules [13]. Primarily, 2,4-thiazolidinedione (**3**) scaffold is extremely versatile and its derivatives, also referred as glitazones, represent the most promising class of compounds having a wide variety of biological activities [14]. TZDs are a class of insulin sensitizing drugs, which include ciglitazone, pioglitazone, troglitazone and rosiglitazone [15]. TZDs are known to stimulate PPAR-γ receptor, they also have multiple PPAR-γ independent biological profiles, such as antimalarial [16], antioxidant [17], antitumor [18], cytotoxic [19], anti-inflammatory [20], antimicrobial [21], radical scavenger [22], glycogen synthase kinase (GSK) 3 inhibitor [23], chymase inhibitor [24], aldose reductase inhibitor [25], cholesterol esterase inhibitor [26], thyroid hormone receptor antagonist [27] and neuroprotective [28].

As a part of our ongoing research in systematic investigation of synthesizing some novel bioactive compounds in relation to their α-glucosidase inhibitory activity, we prepared various 5-benzylidene-1,3-thiazolidine-2,4-diones (**5a-u**). However, we have found that 5-benzylidene-1,3-thiazolidine-2,4-diones (**5a-u**) have the considerable potential to act as a new class of α-glucosidase inhibitors, which can be obtained with the efficient methods in organic synthesis (Scheme 1). The novelty of this work is that none of the 5-benzylidene-1,3-thiazolidine-2,4-diones (**5a-u**) synthesized in the present study were earlier not reported to possess any inhibitory activity against α-glucosidase enzyme.

2. Experimental

2.1. Instrumentation

Melting points were taken in open capillary tubes and are therefore uncorrected. Purity of the compounds was checked on silica gel G TLC plates of 2 mm thickness using *n*-hexane and ethyl acetate as solvent system. The visualization of spot was carried out in an iodine chamber. The FT-IR spectra were recorded on Perkin-Elmer spectrometer. The ^{1}H NMR spectra were scanned on a Bruker 400 MHz spectrometer in DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ ppm. The Electronspray Ionisation mass spectra (ESI-MS) were recorded on an Agilent 6100 QQQ mass spectrometer (positive ion mode). The UV-Vis absorption spectra of the compounds were recorded on a Hitachi U-1600 spectrophotometer.

2.2. General procedure for the synthesis of 5-benzylidene-1,3-thiazolidine-2,4-diones (5a-u)

The reaction sequence intended for the preparation of title compounds (**5a-u**) is shown in Scheme 1, and their physical properties are depicted in Table 1. The chief intermediate in the present study *(Z)*-4-((2,4-dioxo-1,3-thiazolidin-5-ylidene) methyl)benzaldehyde (**4**) was prepared by Knoevenagel condensation reaction between terephthalaldehyde and 1,3-thiazolidine-2,4-dione. Further, successive base catalyzed condensation of the (**4**) with appropriate substituted aromatic/ heteroaromatic ketones in the presence of 100% potassium hydroxide solution in ethanol afforded a series of 5-benzylidene-1,3-thiazolidine-2,4-diones (**5a-u**) in good yield. All the newly synthesized compounds were characterized by CHN elemental analysis and spectroscopic methods such as FT-IR, ^{1}H NMR, and LC mass spectral analysis. Eventually all the spectra of the new products (**5a-u**) are in keeping with the predictable structures [29].

(Z)-5-(4-((E)-3-(2-methylphenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5a**): Colour: Yellow. Yield: 79%. M.p.: 137-139 °C. FT-IR (KBr, ν_{max}, 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). ^{1}H NMR (400 MHz, DMSO-d_6, 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]$^+$. Anal. calcd. for $C_{20}H_{15}NO_3S$: C, 68.75; H, 4.33; N, 4.01. Found: C, 67.91; H, 4.34; N, 4.12%.

(Z)-5-(4-((E)-3-(3-methylphenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5b**): Colour: Yellow. Yield: 88%. M.p.: 168-170 °C. FT-IR (KBr, ν_{max}, 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). ^{1}H NMR (400 MHz, DMSO-d_6, 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]$^+$. Anal. calcd. for $C_{20}H_{15}NO_3S$: C, 68.75; H, 4.33; N, 4.01. Found: C, 68.73; H, 4.31; N, 4.11%.

(Z)-5-(4-((E)-3-(2-methoxyphenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5c**): Colour: Yellow. Yield: 91%. M.p.: 238-240 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3124 (N–H), 3027 (C–H, aromatic), 2975 (C–H, aliphatic), 1700 (C=O), 1603 (C=C, aliphatic), 1417 (C=C, aromatic), 713 (C–S), 1171 (C–O–C), 1054 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6, 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]$^+$.

Anal. calcd. for $C_{20}H_{15}NO_4S$: C, 65.74; H, 4.14; N, 3.83. Found: C, 65.79; H, 4.17; N, 3.88%.

(Z)-5-(4-((E)-3-(3-methoxyphenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5d**): Colour: Yellow. Yield: 78%. M.p.: 181-183 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3124 (N–H), 3027 (C–H, aromatic), 2977 (C–H, aliphatic), 1700 (C=O), 1605 (C=C, aliphatic), 1457 (C=C, aromatic), 687 (C–S), 1171 (C–O–C), 1054 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6, 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]$^+$. Anal. calcd. for $C_{20}H_{15}NO_4S$: C, 65.74; H, 4.14; N, 3.83. Found: C, 65.72; H, 4.19; N, 3.73%.

(Z)-5-(4-((E)-3-(3-hydroxyphenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5e**): Colour: Yellow. Yield: 77%. M.p.: 179-181 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3445 (O–H), 3124 (N–H), 3015 (C–H, aromatic), 2984 (C–H, aliphatic), 1689 (C=O), 1606 (C=C, aliphatic), 1415 (C=C, aromatic), 676 (C–S), 1054 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.36-8.01 (m, 8H, Ar-H), 7.67 (d, *J* = 15.6 Hz, 1H, HC=CH (H-α)), 8.01 (s, 1H, HC=C), 8.18 (d, *J* = 15.6 Hz, 1H, HC=CH (H-β)), 12.32 (s, 1H, OH), 12.85 (s, 1H, NH). ESI-MS (*m/z*): 352 [M+H]$^+$. Anal. calcd. for $C_{19}H_{13}NO_4S$: C, 64.95, H, 3.73, N, 3.99. Found: C, 64.99, H, 3.71, N, 3.94%.

(Z)-5-(4-((E)-3-(3,5-dihydroxyphenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5f**): Colour: Yellow. Yield: 85%. M.p.: 224-226 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3440 (O–H), 3122 (N–H), 3027 (C–H, aromatic), 2890 (C–H, aliphatic), 1700 (C=O), 1605 (C=C, aliphatic), 1511 (C=C, aromatic), 688 (C–S), 1054 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.21-8.02 (m, 7H, Ar-H), 7.79 (d, *J* = 15.3 Hz, 1H, HC=CH (H-α)), 7.95 (s, 1H, HC=C), 8.03 (d, *J* = 15.3 Hz, 1H, HC=CH (H-β)), 11.52 (s, 2H, OH), 12.89 (s, 1H, NH). ESI-MS (*m/z*): 368 [M+H]$^+$. Anal. calcd. for $C_{19}H_{13}NO_5S$: C, 62.12; H, 3.57; N, 3.81. Found: C, 62.19; H, 3.52; N, 3.82%.

(Z)-5-(4-((E)-3-(4,5-dihydroxyphenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5g**): Colour: Yellow. Yield: 84%. M.p.: 219-221 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3395 (O–H), 3127 (N–H), 3017 (C–H, aromatic), 2989 (C–H, aliphatic), 1686 (C=O), 1615 (C=C, aliphatic), 1545 (C=C, aromatic), 689 (C–S), 1054 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.55-8.03 (m, 7H, Ar-H), 7.83 (d, *J* = 15.3 Hz, 1H, HC=CH (H-α)), 7.95 (s, 1H, HC=C), 8.08 (d, *J* = 15.3 Hz, 1H, HC=CH (H-β)), 9.58 (s, 1H, OH), 10.57 (s, 1H, OH), 12.87 (s, 1H, NH). ESI-MS (*m/z*): 368 [M+H]$^+$. Anal. calcd. for $C_{19}H_{13}NO_5S$: C, 62.12; H, 3.57; N, 3.81. Found: C, 62.17; H, 3.59; N, 3.89%.

(Z)-5-(4-((E)-3-(2-methyl-5-hydroxyphenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5h**): Colour: Yellow. Yield: 85%. M.p.: 185-187 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3440 (O–H), 3122 (N–H), 3021 (C–H, aromatic), 2975 (C–H, aliphatic), 1690 (C=O), 1641 (C=C, aliphatic), 1486 (C=C, aromatic), 678 (C–S), 1054 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.47 (s, 3H, CH_3), 7.62-8.01 (m, 7H, Ar-H), 7.81 (d, *J* = 15.3 Hz, 1H, HC=CH (H-α)), 7.99 (s, 1H, HC=C), 8.08 (d, *J* = 15.3 Hz, 1H, HC=CH (H-β)), 10.52 (s, 1H, OH), 13.01 (s, 1H, NH). ESI-MS (*m/z*): 366 [M+H]$^+$. Anal. calcd. for $C_{20}H_{15}NO_4S$: C, 65.74; H, 4.14; N, 3.83. Found: C, 65.72; H, 4.19; N, 3.86%.

(Z)-5-(4-((E)-3-(2-aminophenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5i**): Colour: Yellow. Yield: 83%. M.p.: 241-243 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3367 (NH_2), 3117 (N–H), 2978 (C–H, aromatic), 2763 (C–H, aliphatic), 1693 (C=O), 1597 (C=C, aliphatic), 1413 (C=C, aromatic), 688 (C–S), 1296 (C–N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.74-8.11 (m, 8H, Ar-H), 7.58 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.95 (s, 1H, HC=C), 8.06 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 10.51 (s, 2H, Ar-NH_2), 12.65 (s, 1H, NH). ESI-MS (*m/z*): 351 [M+H]$^+$. Anal. calcd. for $C_{19}H_{14}N_2O_3S$: C, 65.13; H, 4.03; N, 7.99. Found: C, 65.15; H, 4.07; N, 7.91%.

(Z)-5-(4-((E)-3-(3-aminophenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5j**): Colour: Yellow. Yield: 81%. M.p.: 257-259 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3367 (NH_2), 3117 (N–H), 2978 (C–H, aromatic), 2763 (C–H, aliphatic), 1693 (C=O), 1597 (C=C, aliphatic), 1413 (C=C, aromatic), 688 (C–S), 1290 (C–N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.72 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.74-8.11 (m, 8H, Ar-H), 7.94 (s, 1H, HC=C), 8.01 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 10.54 (s, 2H, Ar-NH_2), 12.67 (s, 1H, NH). ESI-MS (*m/z*): 351 [M+H]$^+$. Anal. calcd. for $C_{19}H_{14}N_2O_3S$: C, 65.13; H, 4.03; N, 7.99. Found: C, 65.11; H, 4.13; N, 7.89%.

(Z)-5-(4-((E)-3-(2-nitrophenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5k**): Colour: Yellow. Yield: 84%. M.p.: 247-249 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3122 (N–H), 3024 (C–H, aromatic), 2776 (C–H, aliphatic), 1700 (C=O), 1604 (C=C, aliphatic), 1414 (C=C, aromatic), 688 (C–S), 1529 (N=O), 1291 (C–N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.86-8.18 (m, 8H, Ar-H), 8.05 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.98 (s, 1H, HC=C), 8.35 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 12.72 (s, 1H, NH). ESI-MS (*m/z*): 381 [M+H]$^+$. Anal. calcd. for $C_{19}H_{12}N_2O_5S$: C, 59.99; H, 3.18; N, 7.36. Found: C, 59.92; H, 3.15; N, 7.16%.

(Z)-5-(4-((E)-3-(3-nitrophenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5l**): Colour: Yellow. Yield: 87%. M.p.: 178-180 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3115 (N–H), 3026 (C–H, aromatic), 2775 (C–H, aliphatic), 1700 (C=O), 1599 (C=C, aliphatic), 1412 (C=C, aromatic), 688 (C–S), 1522 (N=O), 1290 (C–N). ^{1}H NMR (400 MHz, DMSO-d_6, 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]$^+$. Anal. calcd. for $C_{19}H_{12}N_2O_5S$: C, 59.99; H, 3.18; N, 7.36. Found: C, 59.91; H, 3.14; N, 7.33%.

(Z)-5-(4-((E)-3-(2-chlorophenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5m**): Colour: Yellow. Yield: 95%. M.p.: 194-196 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3127 (N–H), 3027 (C–H, aromatic), 2893 (C–H, aliphatic), 1689 (C=O), 1597 (C=C, aliphatic), 1450 (C=C, aromatic), 688 (C–S), 786 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6, 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]$^+$. Anal. calcd. for $C_{19}H_{12}ClNO_3S$: C, 61.71; H, 3.27; N, 3.79. Found: C, 61.74; H, 3.22; N, 3.77%.

(Z)-5-(4-((E)-3-(2,4-dichlorophenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5n**): Colour: Yellow. Yield: 92%. M.p.: 227-229 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3124 (N–H), 3018 (C–H, aromatic), 2891 (C–H, aliphatic), 1689 (C=O), 1641 (C=C, aliphatic), 1485 (C=C, aromatic), 691 (C–S), 786 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.65-8.23 (m, 7H, Ar-H), 7.78 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.95 (s, 1H, HC=C), 8.06 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 12.69 (s, 1H, NH). ESI-MS (*m/z*): 405 [M+H]$^+$. Anal. calcd. for $C_{19}H_{11}Cl_2NO_3S$: C, 56.45; H, 2.74; N, 3.46. Found: C, 56.23; H, 2.71; N, 3.42%.

(Z)-5-(4-((E)-3-(2-fluorophenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5o**): Colour: Yellow. Yield: 97%. M.p.: 226-228 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3117 (N–H), 3017 (C–H, aromatic), 2977 (C–H, aliphatic), 1693 (C=O), 1605 (C=C, aliphatic), 1415 (C=C, aromatic), 688 (C–S), 1116 (C–F). ^{1}H NMR (400 MHz, DMSO-d_6, 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]$^+$. Anal. calcd. for $C_{19}H_{12}FNO_3S$: C, 64.58; H, 3.42; N, 3.96. Found: C, 64.55; H, 3.41; N, 3.99%.

(Z)-5-(4-((E)-3-(2,4-difluorophenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5p**): Colour: Yellow. Yield: 84%. M.p.: 189-191 °C. FT-IR (KBr, ν_{max}, 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). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.39-8.31 (m, 7H, 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]$^+$. Anal. calcd. for $C_{19}H_{11}F_2NO_3S$: C, 61.45; H, 2.99; N, 3.77. Found: C, 61.43; H, 2.95; N, 3.76%.

(Z)-5-(4-((E)-3-(furan-2-yl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5q**): Colour: Yellow. Yield: 93%. M.p.: 231-233 °C.

Table 1. Physical characterization and α-glucosidase inhibitory activity data of 5-benzylidene-1,3-thiazolidine-2,4-diones (**5a-5u**).

Compound	R	Yield [a] (%)	Molecular weight (g)	Molecular formula	M.p. (°C)	IC_{50} (μg/mL) (mean±SEM) [c]
5a	2-MeC_6H_4	79	349	$C_{20}H_{15}NO_3S$	137-139	33.06±0.25
5b	3-MeC_6H_4	88	349	$C_{20}H_{15}NO_3S$	168-170	15.28±0.15
5c	2-$OMeC_6H_4$	91	365	$C_{20}H_{15}NO_4S$	238-240	38.42±0.52
5d	3-$OMeC_6H_4$	78	365	$C_{20}H_{15}NO_4S$	181-183	49.17±0.14
5e	3-OHC_6H_4	77	351	$C_{19}H_{13}NO_4S$	179-181	29.82±0.12
5f	3,5-diOHC_6H_3	85	367	$C_{19}H_{13}NO_5S$	224-226	23.16±0.27
5g	4,5-diOHC_6H_3	84	367	$C_{19}H_{13}NO_5S$	219-221	19.20±0.37
5h	2-Me,5-OHC_6H_3	85	365	$C_{20}H_{15}NO_4S$	185-187	29.82±0.12
5i	2-$NH_2C_6H_4$	83	350	$C_{19}H_{14}N_2O_3S$	241-243	27.03±0.11
5j	3-$NH_2C_6H_4$	81	350	$C_{19}H_{14}N_2O_3S$	211-213	38.42±0.52
5k	2-$NO_2C_6H_4$	84	380	$C_{19}H_{12}N_2O_5S$	247-249	39.77±0.23
5l	3-$NO_2C_6H_4$	87	380	$C_{19}H_{12}N_2O_5S$	255-257	41.82±0.14
5m	2-ClC_6H_4	95	369	$C_{19}H_{12}ClNO_3S$	194-196	32.11±0.33
5n	2,4-diClC_6H_3	92	404	$C_{19}H_{11}Cl_2NO_3S$	227-229	29.47±0.32
5o	2-FC_6H_4	97	353	$C_{19}H_{12}FNO_3S$	226-228	8.92±0.21
5p	2,4-diFC_6H_3	84	371	$C_{19}H_{11}F_2NO_3S$	189-191	6.56±0.81
5q	Furan-2yl	93	325	$C_{17}H_{11}NO_4S$	231-233	46.41±0.23
5r	Thiophen-3-yl	82	341	$C_{17}H_{11}NO_3S_2$	204-206	48.66±0.31
5s	Pyrrol-2yl	85	324	$C_{17}H_{12}N_2O_3S$	191-193	30.84±0.66
5t	Pyridin-4-yl	83	336	$C_{18}H_{12}N_2O_3S$	201-203	37.39±0.26
5u	Naphthalen-3-yl	87	385	$C_{23}H_{15}NO_3S$	211-213	33.12±0.64
Standard [b]	-	-	-	-	-	0.007±0.27

[a] Crystallization solvent is ethanol.
[b] Acarbose.
[c] SEM = Standard error of the mean.

FT-IR (KBr, ν_{max}, cm^{-1}): 3420 (N−H), 3062 (C−H, aromatic), 3030 (C−H, aliphatic), 1671(C=O), 1591 (C=C, aliphatic), 1453 (C=C, aromatic), 696 (C−S), 1155 (C−O−C), 1053 (C−O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.74 (s, 1H, Ar-H), 6.21 (m, 1H, Ar-H), 7.16-7.50 (m, 5H, Ar-H), 7.62 (d, *J* = 16 Hz, 1H, HC=CH (H-α)), 7.97 (s, 1H, HC=C), 8.06 (d, *J* = 16 Hz, 1H, HC=CH (H-β)), 12.73 (s, 1H, NH). ESI-MS (*m/z*): 326 $[M+H]^+$. Anal. calcd. for $C_{17}H_{11}NO_4S$: C, 62.76; H, 3.41; N, 4.31. Found: C, 62.72; H, 3.44; N, 4.38%.

(Z)-5-(4-((E)-3-oxo-3-(thiophen-3-yl)prop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5r**): Colour: Yellow. Yield: 82%. M.p.: 204-206 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3430 (N−H), 3019 (C−H, aromatic), 2973 (C−H, aliphatic), 1689 (C=O), 1599 (C=C, aliphatic), 1414 (C=C, aromatic), 688 (C−S). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.68 (s, 1H, Ar-H), 6.91 (s, 1H, Ar-H), 7.12 (s, 1H, Ar-H), 7.33-7.58 (m, 4H, Ar-H), 7.76 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.95 (s, 1H, HC=C), 8.02 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 12.68 (s, 1H, NH). ESI-MS (*m/z*): 342 $[M+H]^+$. Anal. calcd. for $C_{17}H_{11}NO_3S_2$: C, 59.81; H, 3.25; N, 4.10. Found: C, 59.84; H, 3.24; N, 4.11%.

(Z)-5-(4-((E)-3-oxo-3-(pyrrol-2-yl)prop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5s**): Colour: Yellow. Yield: 85%. M.p.: 191-193 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3144 (N−H), 3052 (N−H), 3017 (C−H, aromatic), 2973 (C−H, aliphatic), 1695 (C=O), 1615 (C=C, aliphatic), 1414 (C=C, aromatic), 678 (C−S), 1308 (C−N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.46 (s, 1H, Ar-H), 7.44 (m, 1H, Ar-H), 7.55-7.61 (m, 5H, Ar-H), 7.76 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.97 (s, 1H, HC=C), 8.03 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 10.55 (s, 1H, NH), 12.64 (s, 1H, NH). ESI-MS (*m/z*): 325 $[M+H]^+$. Anal. calcd. for $C_{17}H_{12}N_2O_3S$: C, 62.95; H, 3.73; N, 8.64. Found: C, 62.91; H, 3.71; N, 8.66%.

(Z)-5-(4-((E)-3-oxo-3-(pyridin-4-yl)prop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5t**): Colour: Yellow. Yield: 83%. M.p.: 201-203 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3127 (N−H), 3019 (C−H, aromatic), 2931 (C−H, aliphatic), 1689 (C=O), 1604 (C=C, aliphatic), 1417 (C=C, aromatic), 688 (C−S), 1308 (C−N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.98 (d, *J* = 16 Hz, 1H, HC=CH (H-α)), 7.13-7.69 (m, 8H, Ar-H), 7.78 (d, *J* = 16 Hz, 1H, HC=CH (H-β)), 7.97 (s, 1H, HC=C), 12.60 (s, 1H, NH). ESI-MS (*m/z*): 337 $[M+H]^+$. Anal. calcd. for $C_{18}H_{12}N_2O_3S$: C, 64.27; H, 3.60; N, 8.33. Found: C, 64.26; H, 3.66; N, 8.37%.

(Z)-5-(4-((E)-3-(naphthalen-3-yl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione (**5u**): Colour: Yellow. Yield: 87%. M.p.: 211-213 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3115 (N−H), 3019 (C−H, aromatic), 2931 (C−H, aliphatic), 1689 (C=O), 1604 (C=C, aliphatic), 1417 (C=C, aromatic), 688 (C−S). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.62-8.33 (m, 11H, Ar-H), 7.89 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.99 (s, 1H, HC=C), 8.26 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 12.71 (s, 1H, NH). ESI-MS (*m/z*): 386 $[M+H]^+$. Anal. calcd. for $C_{23}H_{15}NO_3S$: C, 71.67; H, 3.92; N, 3.63. Found: C, 71.65; H, 3.94; N, 3.68%.

2.3. Enzyme inhibition assay

The α-glucosidase inhibitory potential of the synthesized compounds (**5a-u**) was determined by α-glucosidase inhibition assay as described by Pierre *et al*. [30]. α-Glucosidase activity was assessed using 50 mM phosphate buffer at pH = 7.0, and the appropriate PNP (p-nitrophenyl) glycoside (at 1 mM) were used as substrates. The concentration of the enzyme was specified in each experiment. Compounds (**5a-u**) at the designated concentration was added to the enzyme solution and incubated at 37 °C for 30 min, and the substrate was then added to initiate the enzyme reaction. The enzyme reaction was carried out at 37 °C for 30 min. Product (PNP) was monitored spectrophotometrically by measuring the absorbance (λ = 400 nm). One unit of α-glucosidase is defined as the amount of enzyme liberating 1.0 μmol of PNP per minute under the assay conditions specified. The enzyme reaction was performed in the above reaction conditions with inhibitors of various concentrations. Inhibition types for the compounds were determined by Lineweaver–Burk plots and its replot of slope versus the reciprocal of the substrate concentration. The characterization of secondary structure of α-glucosidase in the buffer solution with or without inhibitors was examined with CD spectroscopy. The data obtained from the experiments were dealt with the professional software secondary structure estimation and Origin 6.0. The result for the test compound was compared with the positive control Acarbose. The results of α-glucosidase inhibition study are given in Table 1.

3. Results and discussion

3.1. Synthesis

The IR spectrum of all the compounds (**5a-u**) exhibited the characteristic absorptions at various frequencies correspondingly at 3310-3110 and 1640-1715 cm^{-1} suggesting the presence of a secondary amine group and α,β-unsaturated carbonyl group respectively. In the ^{1}H NMR spectra of 5-benzylidene-1,3-thiazolidine-2,4-diones (**5a-u**), a singlet integrating for one proton characteristic of the HC=C group was

observed in between δ 7.71-8.15 ppm and a singlet integrating for one proton of the NH group was observed in between δ 12.2-13.4 ppm as a broad signal indicating the presence of characteristic features of basic scaffold. Further, The geometry of all 5-benzylidene-1,3-thiazolidine-2,4-diones (**5a**-**u**) were assumed to be *(Z)*-isomer as observed from the previously reported literature [31-34]. As seen in case of compound **5a**, the IR spectrum of **5a** exhibited characteristic −C=C− (aliphatic) and −C=C− (aromatic) stretching bands at frequencies 1645 and 1513 cm^{-1} respectively. The other IR absorptions at various frequencies correspondingly at 3155 and 1688 cm^{-1} suggesting the presence of a secondary amino group and α,β-unsaturated ketone group respectively. The 400 MHz ^{1}H NMR spectrum of the compound **5a** in DMSO-d_6 as solvent with TMS as an internal standard exhibited characteristic peaks of H_α and H_β protons of α,β-unsaturatedketone bridge appeared as two doublets, one doublet at δ 7.78 ppm (H_α, J = 15.2 Hz) and the other one at δ 8.01 ppm (H_β, J = 15.2 Hz). The large J value 15.2 Hz of both the protons clearly reveals the *trans* geometry at the double bond. The distinguishing peaks of 5-benzylidene (HC=C) and NH protons appear as two singlets, one singlet at δ 7.98 ppm and the other singlet at δ 12.74 ppm. The ESI mass spectrum (positive ion mode) of **5a** revealed a $(M+H)^+$ ion at *m/z* 350. Based on the above spectral information the structure of the compound **5a** was confirmed as (*Z*)-5-(4-((*E*)-3-(2-methylphenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione.

3.2. α-Glucosidase inhibitory activity

From the analysis of *in vitro* α-glucosidase inhibitory activity screening data (Table 1) discovered that the compounds **5p** and **5o** demonstrated comparatively the most effective inhibitory activity, with IC_{50} values of 6.56±0.81 and 8.92±0.21 μg/mL, respectively. It is remarkable to note that the compounds **5b** and **5g** also showed appreciable inhibitory activity with IC_{50} values of 15.28±0.15 and 19.20±0.37 μg/mL, respectively. The other compounds such as **5f**, **5i**, **5n**, **5e**, **5h**, **5s**, **5m**, **5a**, **5u**, **5t**, **5c**, **5j** and **5k** showed reasonable activity at concentrations (IC_{50}) ranging from 23.16±0.27 to 39.77±0.23 μg/mL. The remaining compounds **5l**, **5q**, **5r** and **5d** exhibited less activity with IC_{50} values ranging from 41.82±0.14 to 49.17±0.14 μg/mL in comparison with the standard drug (Acarbose, IC_{50} : 0.007±0.27 μg/mL). On the basis of the obtained data we could develop interesting structure-activity relationships [35-36]. The α-glucosidase inhibitory activity is significantly affected by substituents at position 1 of α,β-unsaturatedketone system. For instance, the compounds **5p** (2,4-di-F-C_6H_3, IC_{50}: 6.56±0.81 μg/mL) > **5o** (2-F-C_6H_4, IC_{50}: 8.92±0.21 μg/mL) > **5n** (2,4-di-Cl-C_6H_3, IC_{50}: 29.47±0.32 μg/mL) > **5m** (2-Cl-C_6H_4, IC_{50}: 32.11±0.33 μg/mL) having halogen substituents either at *ortho* or *meta* or *para* positions considerably improved the activity and the most potent derivative of the series was obtained. Among the diverse functionalities taken into consideration, when the substituted phenyl ring was replaced with some other aromatic/hetero aromatic ring systems, as indicated by its activity order as **5s** (Pyrrol-2yl, IC_{50}: 30.84±0.66 μg/mL) > **5u** (Naphthalen-3-yl, IC_{50}: 33.12±0.64 μg/mL) > **5t** (Pyridin-4-yl, IC_{50}: 37.39±0.26 μg/mL) > **5q** (Furan-2yl, IC_{50}: 46.41±0.23 μg/mL) > **5r** (Thiophen-3-yl, IC_{50}: 48.66±0.31 μg/mL) moieties, respectively. The activity was sustained when the compounds substituted with electron releasing groups, the activity order was **5b** (3-Me-C_6H_4, IC_{50}: 15.28±0.15 μg/mL) > **5i** (2-NH_2-C_6H_4, IC_{50}: 27.03±0.11 μg/mL) > **5a** (2-Me-C_6H_4, IC_{50}: 33.06±0.25 μg/mL) > **5c** (2-OMe-C_6H_4, IC_{50}: 38.42±0.52 μg/mL) > **5j** (3-NH_2-C_6H_4, IC_{50}: 38.42±0.52 μg/mL) > **5d** (3-OMe-C_6H_4, IC_{50}: 49.17±0.14 μg/mL), respectively. On the other hand a trend of activity was followed, when hydroxyl group substituted at different positions on the phenyl ring A of α,β-unsaturatedketone was found to be biologically significant i.e. (**5g** (4,5-diOH-C_6H_3, IC_{50}: 19.20±0.37 μg/mL) > **5f** (3,5-diOH-C_6H_3, IC_{50}: 23.16±0.27 μg/mL) > **5e** (3-OH-C_6H_4, IC_{50}: 29.82±0.12 μg/mL) > **5h** (2-Me, 5-OH-C_6H_3, IC_{50}: 29.82±0.12 μg/mL), respectively. It is of interest to note that the introduction of a nitro group *ortho* or *meta* to the phenyl ring A of α,β-unsaturated ketone particularly unfavorable for the activity as seen in case of compounds such as **5k** (2-NO_2-C_6H_4, IC_{50}: 39.77±0.23 μg/mL) > **5l** (3-NO_2-C_6H_4, IC_{50}: 41.82±0.14 μg/mL).

4. Conclusion

A series of new class of α-glucosidase inhibitors is reported, the synthesis of which is achieved by conventional methods. During this study, we have identified a number of 5-benzylidene-1,3-thiazolidine-2,4-diones (**5a**-**u**) exhibiting significant α-glucosidase inhibitory properties. Structure activity relationship studies revealed that substitution at position 1 of α,β-unsaturatedketone is important to modulate the activity. Further studies determining the *in vivo* antidiabetic activity of these compounds are under progress.

Acknowledgements

One of the authors Divakara Laxman Somayajulu Nori is thankful to Gitam University, Visakhapatnam, for providing necessary facilities to carry out research work.

References

[1]. Fujisawa, T.; Ikegami, H.; Inoue, K.; Kawabata, Y.; Ogihara, T. *Metabolism*. **2005**, *54*, 387-390.
[2]. Sou, S.; Takahashi, H.; Yamasaki, R.; Kagechika, H.; Endo, Y.; Hashimoto, Y. *Chem. Pharm. Bull*. **2001**, *49*, 791-793.
[3]. Liu, Y.; Zou, L.; Ma, L.; Chen, W. H.; Wang, B.; Xu, Z. L. *Bioorgan. Med. Chem*. **2006**, *14*, 5683-5690.
[4]. Pandey, J.; Dwivedi, N.; Singh, N.; Srivastava, A. K.; Tamarkarb, A.; Tripathi, R. P. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 1321-1325.
[5]. Look, G. C.; Fotsh, C. H.; Wong, C. H. *Acc. Chem. Res*. **1993**, *26*, 182-190.
[6]. Roth, J.; Ziak, M.; Zuber, C. *Biochimie*. **2003**, *85*, 287-294.
[7]. Kaushal, G. P.; Pastuszak, I.; Hatanaka, K. I.; Elbein, A. D. *J. Biol. Chem*. **1990**, *265*, 16271-16279.
[8]. Hammond, C.; Braakman, I.; Helenius, A. *Proc. Natl. Acad. Sci. U. S. A*. **1994**, *91*, 913-917.
[9]. Alonso, J. M.; Santa-Cecilia, A.; Calvo, P. *Eur. J. Biochem*. **1993**, *215*, 37-42.
[10]. Takeda, Y.; Totoni, K.; Matsuo, I.; Ito, Y. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 5357-5359.
[11]. Momose, Y.; Meguro, K.; Ikeda, H.; Hatanaka, C.; Oi, S.; Sohda, T. *Chem. Pharm. Bull*. **1991**, *39*, 1440-1445.
[12]. Bruno, G.; Costantino, L.; Curinga, C.; Maccari, R.; Monforte, F.; Nicolo, F.; Ottana, R.; Vigorita, *Bioorgan. Med. Chem*. **2002**, *10*, 1077-1084.
[13]. Jung, S. H.; Park, S. Y.; Kim-Pak, Y.; Lee, H. K.; Park, S. Y.; Shin, K. H.; Ohuchi, K.; Shin, H. K.; Keum, S. R.; Lim, S. S. *Chem. Pharm. Bull*. **2006**, *54*, 368-371.
[14]. Liu, X. F.; Zheng, C. J.; Sun, L. P.; Liu, X. K.; Piao, H. R. *Eur. J. Med. Chem*. **2011**, *46*, 3469-3473.
[15]. Zuping, X.; Christian, K.; Jian, M.; Zanna, M.; Beharry, C. M.; Wenxue, W.; Andrew, S. K.; Charles D. S. *J. Med. Chem*. **2009**, *52*, 74-86.
[16]. Patil, V.; Tilekar, K.; Munj, S. M.; Mohan, R.; Ramaa, C. S. *Eur. J. Med. Chem*. **2010**, *45*, 4539-4544.
[17]. Bonde, C. G.; Gaikwad, N. J. *Bio. Org. Med. Chem*. **2004**, *12*, 2151-2161.
[18]. Fan, Y. H.; Chen, H.; Natarajan, A.; Guo, Y.; Harbinski, F.; Iyasere, J.; Christ, W.; Aktasa, H.; Halperina, J. A. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 2547-2550.
[19]. Jeon, R.; Park, S. Y. *Arch. Pharm. Res*. **2004**, *27*, 1099-1105.
[20]. Hafez, H. N.; ElGazzar, A. R. B. A. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 4143-4147.
[21]. Madhavan, G. R.; Chakrabarti, R.; Reddy, K. A.; Rajesh, B. M.; Balraju, V.; Rao, P. B.; Rajagopalan, R.; Iqbal, J. *Bioorgan. Med. Chem*. **2006**, *14*, 584-591.
[22]. Sambasivarao, S. V.; Soni, L. K.; Gupta, A. K.; Hanumantharao, P.; Kaskhedikar, S. G. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 512-520.
[23]. Wu, Y.; Tai, H. H.; Cho, H. *Bio. Org. Med. Chem*. **2010**, *18*, 1428-1433.
[24]. Komatsu, T.; Hirano, T.; Songkram, C.; Kawachi, E.; Kagechika, H. *Bio. Org. Med. Chem*. **2007**, *15*, 3115-3126.
[25]. Hu, B.; Ellingboe, J.; Gunawan, I.; Han, S.; Largis, E.; Li, Z.; Malamas, M.; Mulvey, R.; Oliphant, A.; Sum, F.; Tillett, J.; Wong, V. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 757-760.

[26]. Koide, Y.; Tatsui, A.; Hasegawa, T.; Murakami, A.; Satoh, S.; Yamada, H.; Kazayamaa, S.; Takahashia, A. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 25-29.
[27]. Li, Q.; AlAyoubi, A.; Guo, T.; Zheng, H.; Sarkar, A.; Nguyen, T.; Eblen, S. T.; Grant, S.; Kellogg, G. E.; Zhang, S. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 6042-6046.
[28]. Peyrot, V.; Leynadier, D.; Sarrazin, M.; Briand, C.; Rodriquez, A.; Nieto, J. M.; Andreu, J. M. , *J. Biol. Chem.* **1989,** *264*, 21296-21301.
[29]. Vasudeva, R. A.; Rajendra, P. Y.; Annapurna, A.; Girija, S. G.; Bhagya, R. D.; Venkata, R. V.; Suvarna, R. A.; Lakshmana, S. A.; Aruna, K. V. *Bioorg. Med. Chem. Lett*. **2012**, *22*, 6442-6450.
[30]. Pierre, C.; Roland, R.; Tremblay, D. *J. Clin. Chem*. **1978**, *24*, 208–211.
[31]. Peyrot, V.; Leynadier, D.; Sarrazin, M.; Briand, C.; Menendez, M.; Laynez, J.; Andreu, J. M. *Biochemistry* **1992,** *31*, 11125-11132.
[32]. Assia, S.; Kaddour, L.; Mahieddine, M.; Nouara, Z.; Paul, M. *Eur. J. Chem*. **2011**, *2(3)*, 311-313.
[33]. Mohammed, R. A.; Mohammed, H. R. K.; Vedula, G. S.; Nasreen, B.; Syed, A.; Yejella, R. P. *Eur. J. Chem*. **2012**, *3(2)*, 186-190.
[34]. Mohammed, S. B.; Aly, A. A.; Ashraf, F. W.; Marwa, M. R. *Eur. J. Chem*. **2013**, *4(2)*, 92-97.
[35]. Ashutosh, B.; Malleshappa, N.; Niharika, S.; Vishnu, D. G.; Gaurav, B. *Eur. J. Chem*. **2011**, *2(3)*, 388-393.
[36]. Du, Z. Y.; Liu, R. R.; Shao, W. Y.; Mao, X. P.; Ma, L.; Gu, L. Q.; Huang, Z. S.; Chan, A. S. *Eur. J. Med. Chem*. **2006**, *41(2)*, 213-218.