European Journal of Medicinal Chemistry 70 (2013) 308–314

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis, biological evaluation and molecular modeling studies of some novel thiazolidinediones with triazole ring

Yakaiah Chinthala [a], Anand Kumar Domatti [b], Alam Sarfaraz [c], Shailendra Pratap Singh [b], Niranjan Kumar Arigari [a], Namita Gupta [c], Srinivas K.V.N. Satya [a], Jonnala Kotesh Kumar [a,*], Feroz Khan [c], Ashok K. Tiwari [b], Grover Paramjit [b]

[a] Natural Product Chemistry, CSIR-Central Institute of Medicinal and Aromatic Plants-Research Centre, Boduppal, Hyderabad 500092, A.P., India
[b] CSIR-Indian Institute of Chemical Technology, Uppal Road, Hyderabad 500007, A.P., India
[c] Metabolic & Structural Biology Department, CSIR-Central Institute of Medicinal and Aromatic Plants, Kukrail Picnic Spot Road, Lucknow 226015, U.P., India

ARTICLE INFO

Article history:
Received 8 May 2013
Received in revised form
24 September 2013
Accepted 3 October 2013
Available online 10 October 2013

Keywords:
Thiazolidinediones
1,2,3-Triazoles
Anticancer activity
α-Glucosidase inhibition
Molecular modeling study

ABSTRACT

A new series of thiazolidinedione derivatives were synthesized and evaluated for *in vitro* α-glucosidase inhibition and anticancer activities. Compounds **3d**, **3e** and **3j** showed potential α-glucosidase inhibition with IC_{50} values ranging between 0.1 and 0.3 μg/ml whereas compounds **3i**, **3j** and **3k** have showed better anticancer activity towards human cancer cell lines IMR-32 (neuroblastoma), Hep-G2 (hepatoma) and MCF-7 (breast). Molecular docking studies revealed compounds **3d**, **3e** and **3j** are potent inhibitors of α-glucosidase and also showed compliance with standard parameters of drug likeness.

1. Introduction

Thiazolidinediones (TZDs), also known as glitazones, are a class of insulin sensitizing drugs includes ciglitazone, pioglitazone, troglitazone and rosiglitazone (Fig. 1) etc. TZDs were initially discovered by Takeda Pharmaceuticals, Japan, in 1975 and the lead substance ciglitazone was synthesized in 1980. Although ciglitazone improved gycaemic control in animal models of insulin resistance, but toxicity prevented trials in humans. Rosiglitazone and pioglitazone are currently approved for use for type 2 diabetes under the trade names Avandia™ and Actos™ respectively whereas troglitazone (Rezulin™), the first of the glitazones approved by the U.S.FDA, was recently withdrawn from the market due to hepatotoxicity [1]. Apart from their known antidiabetic activity, the ability of TZDs to contribute to cancer therapy has been evidenced by *in vitro* and *in vivo* studies [2,3]. While TZDs are known to stimulate PPAR-γ (Peroxisome Proliferator Activated Receptor gamma) receptor, they also have showed other significant biological activities, such as antimicrobial [4], analgesic [5], anti-inflammatory [6] and anticancer [7] etc. Similarly, nitrogenous compounds like 1,2,3-triazole also played an important role in agrochemical and pharmaceuticals such as anti-HIV [8,9], antibacterial [10], antiviral [11], antiproliferative [12], insecticidal [13] and fungicidal [14].

The diverse biological potencies of both pharmacophores prompted us to synthesize the title compounds with a presumption that their incorporation in a single structural entity could produce novel compounds with significant antidiabetic as well as anticancer properties. One of the therapeutic approaches for treating diabetes is the inhibition of the enzyme α-glucosidase which delays carbohydrate digestion, causing a reduction in the rate of glucose absorption and consequently blunting the postprandial blood glucose and insulin levels [15]. This paper consists of synthesis of novel TZD's tagged with 1,2,3-triazoles and evaluation of their antidiabetic and anticancer activity profiles. Finally, molecules that showed potential α-glucosidase inhibition were subjected to docking studies using molecular modeling tools.

* Corresponding author. Tel.: +91 40 27201131.
E-mail addresses: koteshkumarj@yahoo.com, koteshnpp@yahoo.co.in (J. Kotesh Kumar).

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http://dx.doi.org/10.1016/j.ejmech.2013.10.005

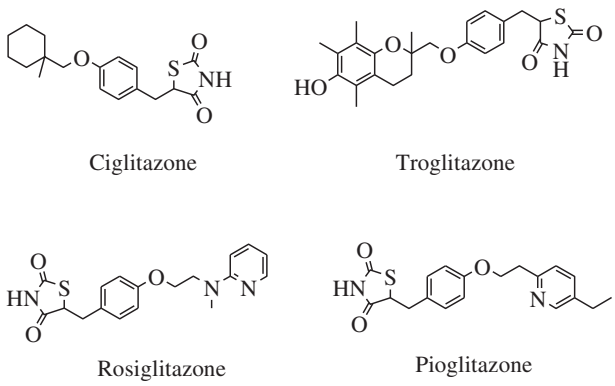

Fig. 1. Structures of some thiazolidinedione drugs.

2. Results and discussion

2.1. Chemistry

A series of 5-(benzo-[1,3]-dioxol-5-ylmethylene)-3-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl) thiazolidine-2,4-diones **3a**–**3k** were synthesized in three steps (Scheme 1). In the first step, 5-(benzo-[1,3]-dioxol-5-ylmethylene)-2,4-Thiazolidinedione **1** was prepared by attempting Knoevenagel condensation reaction between piperonal and 2,4-thiazolidinedione under reflux conditions in the presence of piperidine as catalyst. In the second step, compound **1** was condensed with propargyl bromide in the presence of K_2CO_3 in dry acetone under reflux for 4–5 h to obtain intermediate **2** which was common to all derivatives being synthesized. In the final step, intermediate **2** was condensed with various aromatic azides under click chemistry reaction conditions in presence of copper iodide and dry THF at room temperature for 10–12 h to result in novel TZD's **3a**–**3k** in quantitative yields. All the derivatives were characterized by ^{1}H NMR, IR and ESI-MS spectra. Compounds **3a**–**3k** showed IR absorption bands ranging from 3132 to 3000 cm^{-1} for aromatic C–H stretching, 2960–2900 cm^{-1} for aliphatic C–H stretching's. There were also absorptions due to C=C, C=N stretchings at 1580–1570 and 1505–1480 cm^{-1} respectively. In ^{1}H NMR spectra, the presence of singlet resonances at δ 5.5–6.0 ppm and 6.0–6.5 ppm were attributed to the methylene protons attached to nitrogen and oxygen atoms respectively whereas the corresponding carbon resonances in the ^{13}C NMR spectra were observed at 36.8 and 102.3 ppm respectively. Rest all the protons and carbons resonated at expected regions.

2.2. Anticancer activity

Anti-cancer activity of the synthesized thiazolidinedione derivatives was evaluated in *in vitro* mode using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay [16] on the human cancer cell lines IMR 32 (neuroblastoma), HepG2 (Human hematoma) and MCF-7 (Human breast adenocarcinoma). The assay was dependent on the reduction of tetrazolium salt by the mitochondrial dehydrogenase of viable cells to form a blue formazan product dissolved in DMSO and measured at 570 nm. The results of cytotoxic activity *in vitro* were expressed as the IC_{50} (μg/ml) and doxorubicin was used as positive control (Table 1). The structural diversity in all the derivatives was introduced by varying substitution at 3 position of the triazole ring while keeping the thiazolidinedione moiety intact. As shown in Table 1, most of the compounds were moderately active but, compound **3j** showed better inhibition against HepG2 (IC_{50} 31 μg/ml) and MCF-7 (IC_{50} 30 μg/ml) cell lines respectively.

2.3. α-Glucosidase inhibition

Intestinal α-glucosidase inhibitory activity was determined as per earlier reported methods [17,18]. Rat intestinal acetone powder in normal saline (100:1; w/v) was sonicated properly and the supernatant was used as a source of crude intestinal α-glucosidase after centrifugation. In brief, 10 μL of test samples (5 mg/mL DMSO solution) were reconstituted in 100 μL of 100 mM-phosphate buffer (pH 6.8) in 96-well microplate and incubated with 50 μL yeast α-glucosidase (0.76 U/Ml in same buffer) or crude intestinal α-glucosidase for 5 min before 50 μL substrate (5 mM, p-nitrophenyl-α-D-glucopyranoside prepared in same buffer) was added. Release of p-nitrophenol was measured at 405 nm spectrophotometrically ($Spectra_{MAx}$ $Plus^{384}$, Molecular Devices Corporation, Sunnyvale, CA, USA) 5 min after incubation with substrate. Individual blanks for test samples were prepared to correct back-ground absorbance where substrate was replaced with 50 μL of buffer. Control sample contained 10 μL DMSO in place of test samples. Acarbose was taken as standard reference for α-glucosidase inhibition. All the samples were studied in triplicate. Percentage of enzyme inhibition was calculated as $(1 - B/A) \times 100$ where A represents absorbance of control without test samples, and B represents absorbance in presence of test samples. All the tests were run in duplicate. IC_{50} values were calculated applying suitable regression analysis from the mean inhibitory values. As shown in Table 1, among all the synthesized derivatives, compounds **3d** (IC_{50} 0.1 μg/ml), **3e** (IC_{50} 0.3 μg/ml) and **3j** (IC_{50} 0.3 μg/ml) have shown much better α-glucosidase enzyme inhibitory activity than the standard Acarbose (IC_{50} 12.5 μg/ml). Comparing the α-glucosidase inhibitory activity of compounds **3a**–**3i** with a substituted benzene ring, it was observed that the presence of NO_2 group at *ortho* (**3d**, IC_{50} 0.1 μg/ml) and Isopropyl group at *para*-positions (**3e**, IC_{50} 0.3 μg/ml) showed most potent inhibitory activity than chloro (**3c**, IC_{50} 40 μg/ml) at *ortho*, flouro (**3a**, >100 μg/ml) and methyl (**3f**, 75.5 μg/ml) at *para* positions resulted in dramatically less potential compounds. Similarly, substitution of 1-phenyl ethyl moiety at 3 position of triazole ring (**3j**, IC_{50} 0.1 μg/ml) showed potential enzyme inhibition activity than aliphatic n-hexyl (**3k** $IC_{50} > 100$ μg/ml) substitution.

3. Molecular docking studies

Exploration of mechanism of action and molecular interaction of compound **3d**, **3e** and **3j** was performed through molecular docking studies using AutoDock Vina software [19]. Oral bioavailability and drug likeness parameters screening was performed by evaluating topological polar surface area (TPSA) and Lipinski's rule of five [20]. The toxicity risk assessment at high doses or long term use was performed through OSIRIS program. To study the molecular interaction of compounds, crystallographic data of human intestinal α-glucosidase (EC = 3.2.1.20) (PDB:3L4Y) was retrieved from Protein Data Bank [21]. Retrieved crystal structure of α-glucosidase was cleaned and hydrogen atoms were added. All the heteroatoms were removed before docking study. The chemical samples used in the molecular docking studies were compounds **3d**, **3e**, **3j** and Acarbose (Fig. 2). The 2D structures were sketched using ChemDraw-ultra-v8.0 followed by 3D structure conversion and energy minimization by ChemBioOffice modeling software (Cambridgesoft, UK).

3.1. Exploration of interacting amino acid residues through molecular docking studies

Results of molecular docking on human intestinal α-glucosidase (Table 2 and Fig. 3) showed that compound **3e** (docking score −7.9 kcal/mol and two hydrogen bonds with ARG-647, ASP-649) has similar binding affinity as compared to standard drug