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).

0223-5234/$ – see front matter © 2013 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.ejmech.2013.10.005

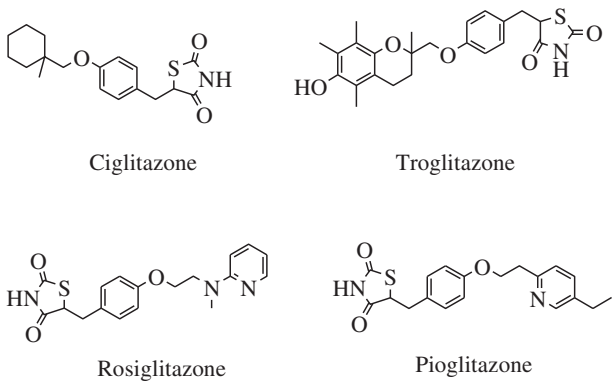


Fig. 1. Structures of some thiazolidinedione drugs.

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.

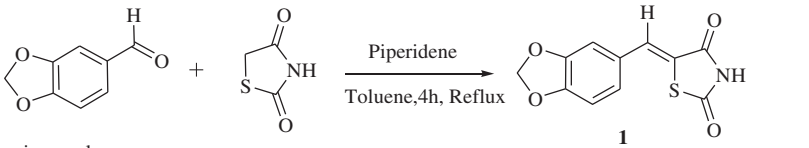
3. Molecular docking studies

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

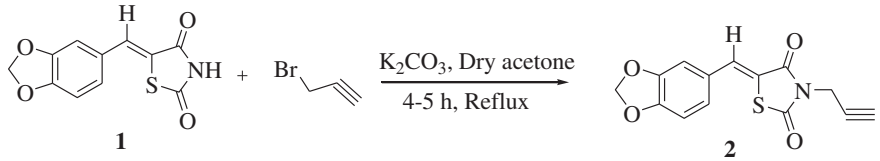
Results of molecular docking on human intestinal α-glucosidase (Table 2 and Fig. 3) showed that compound **3e** (docking score −7.9 kcal/mol and two hydrogen bonds with ARG-647, ASP-649) has similar binding affinity as compared to standard drug

Step 1: Synthesis of 1 (Knoevenagel condensation)



piperonal — thiazolidine-2,4-dione — **1** 5-(benzo[1,3]dioxol-5-ylmethylene) thiazolidine-2,4-dione

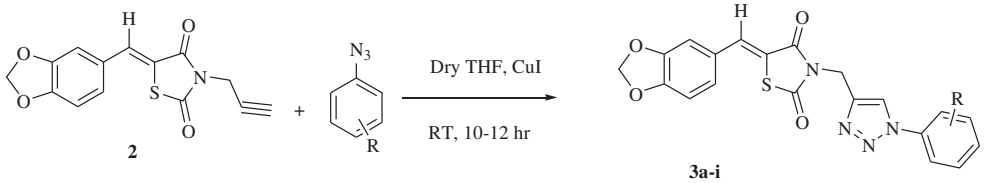
Step 2: Synthesis of 2 (propargylation)



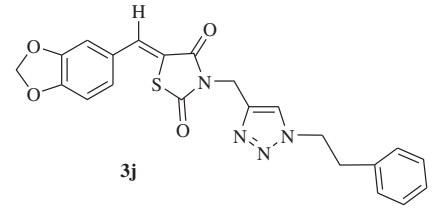
1 5-(benzo[1,3]dioxol-5-ylmethylene)thiazolidine-2,4-dione

2 5-(benzo[1,3]dioxol-5-ylmethylene) -3-(prop-2-ynyl)thiazolidine-2,4-dione

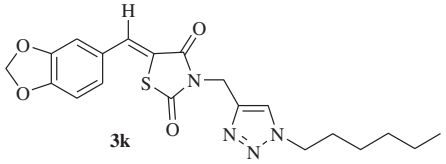
Step 3: Synthesis of thiazolidine-2,4-dione-1,2,3-triazole derivatives



2 — **3a-i**



3j



3k

3a. R=4-F
3b. R=4-Cl
3c. R=2-Cl
3d. R=2-NO_2
3e. R=4-Isopropyl
3f. R=4-CH3
3g. R=3,4-F2
3h. R=3-F,4-Cl
3i. R=2-OCH3,5-CH3

Scheme 1.

Acarbose (docking score −7.9 kcal/mol and eleven hydrogen bonds with ARG-653, ARG-647, TYR-733, ASP-759, GLU-767) within the 4 Å of selection radius. On the other hand compound **3d** (docking score −8.8 kcal/mol and five hydrogen bonds with GLU-658, ARG-647, ARG-653) and **3j** (docking score −8.3 kcal/mol and three hydrogen bonds with ARG-647, GLU-658) showed slightly higher binding affinity than Acarbose.

To analyze oral bioavailability and drug likeness compliance of compounds **3d**, **3e** and **3j** with standard parameters, chemical descriptors of pharmacokinetic properties were calculated. Log *P* value which is a measure of lipophilicity and is the ratio of the solubility of the compound in octanol compared to its solubility in water was calculated. Log *P* and molecular weight of compounds **3d**, **3e** and **3j** were within the standard range limit as per Lipinski's rule of five and comparable with Acarbose, thus indicating high oral bioavailability. The excretion process that eliminates the compound from the human body also depends on Log *P* as well as the molecular weight. Large molecular weight drugs generally have poor absorption pattern due to the presence of polar groups. Moreover, when the TPSA was calculated as a chemical descriptor for passive molecular transport through membranes, results showed lower TPSA value than Acarbose, thus indicates better intestinal absorption of compounds **3d**, **3e** and **3j** (refer Table 1 in Supplementary material).

3.2. Toxicity risk assessment screening

Toxicity risk assessment screening showed that compounds **3d**, **3e** and **3j** have risk of mutagenicity on prolonged usage whereas compound **3d** exhibited risk of tumorogenicity and medium risk of

Table 1
Anticancer and α-glucosidase inhibitory activity of compound **3a**–**3k**.

Compound	α-Glucosidase inhibition	Anticancer activity		
	IC_{50} μg/ml	IMR 32 IC_{50} μg/ml	HepG2 IC_{50} μg/ml	MCF-7 IC_{50} μg/ml
3a	>100	>100	>100	96.21
3b	33.6	>100	>100	>100
3c	40.0	>100	>100	87
3d	0.1	>100	>100	>100
3e	0.3	97.52	66	78
3f	75.5	>100	>100	>100
3g	>100	>100	>100	>100
3h	>100	>100	>100	>100
3i	>100	52.58	45	34
3j	0.3	52.64	31	30
3k	>100	77.58	67	43
Acarbose	12.5	–	–	–
Doxorubicine	–	0.80	0.60	0.87

reproductive or developmental toxicity. Compound **3e** has showed risk of irritation but no risk of tumorogenecity. Compound **3j** showed no risk of tumorogenicity; irritation and reproductive toxicity (refer Table 2 in Supplementary material).

4. Conclusion

Synthesis of a series of novel hybrid molecules, **3a**–**3k**, consisting of biologically important pharmacophores 2,4-thiazolidinediones tagged with 1,2,3-triazoles showed potential antidiabetic properties. α-Glucosidase enzyme inhibition in *in vitro* screening revealed compounds **3d**, **3e** and **3j** were highly potential than the standard Acarbose. These inhibitory results were further optimized by molecular docking studies. Docking studies showed compounds **3d**, **3e** and **3j** have high binding affinity with the α-glucosidase due to the presence of conserved binding site amino acid residues e.g., LEU-640, ARG-647, ASP-649, ARG-653, PRO-676, GLY-766, GLU-767, thus indicating their high stability along with activity potentials similar to control Acarbose.

5. Experimental

5.1. Chemistry

Melting points of all the compounds was recorded on Casia-Siamia (VMP-AM) melting point apparatus and uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR 240-C spectrometer using KBr optics. NMR spectra were recorded on Burker Avance 300 MHz in $CDCl_3$ and DMSO-d_6 using TMS as internal standard. Electron impact (EI) and chemical ionization mass spectra were recorded on a VG Micromass model 7070H instrument. All the reactions were monitored on silica gel precoated TLC plates of Merck and spots were visualized with UV light. Silica gel (100–200 mesh) used for column chromatography was procured from Merck.

5.1.1. Synthesis of 5-(benzo[1,3]dioxol-5-ylmethylene)thiazolidine-2,4-dione ***1*** general procedure

A mixture of Piperonal (40 mmol) and thiazolidine-2,4-dione (40 mmol) with catalytic quantity of piperidine was refluxed in toluene with continuous removal of water using dean stark apparatus for 4 h. The reaction mixture was cooled to 25 °C to obtain a pale yellow solid. The solid was recrystallized from water to get compound **1**, 5-(benzo [1,3]dioxol-5-ylmethylene) thiazolidine-2,4-dione.

5.1.2. Synthesis of 5-(benzo[1,3]dioxol-5-ylmethylene)-3-(prop-2-ynyl)-thiazolidine-2,4-dione ***2*** general procedure

Compound **1** (23.60 mmol) along with potassium carbonate (22 mmol) was dissolved in 10 ml of dry Acetone and later propargyl bromide (23 mmol) was added slowly while stirring. The reaction mixture was refluxed for 4 h and then extracted with ethyl acetate to afford crude 5-(benzo[1,3]dioxol-5-ylmethylene)-3-(prop-2-ynyl)-thiazolidine-2,4-dione **2**. This crude residue was purified by column chromatography over silica gel (100–200 mesh) in 15% ethyl acetate in hexane to get compound **2** in pure state. Yellow solid, yield: 93%, m.p.199-201 °C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.291 (s, 1H), 4.52 (s, 2H), 6.08 (s, 2H), 6.91–6.94 (d, 1H, $J = 8.1$ Hz), 7.06–7.09 (d, 1H, $J = 8.1$ Hz), 7.86 (s, 1H); ^{13}C NMR ($CDCl_3$,75 MHz) δ ppm: 31.03, 72.55, 76.57, 102.39, 109.52, 118.91, 127.22, 127.71, 129.09, 134.94, 149.03, 150.38, 165.56, 167.15; ESI-MS (*m*/*z*): 288.0 (M + 1) observed for $C_{14}H_9NO_4S$.

5.1.3. Synthesis of thiazolidine-2,4-dione triazole derivatives ***3a***–***3k*** general procedure

Compound **2** (1.0 mmol) was dissolved in dry THF (10 ml) and catalytic amount of Copper iodide was added. To this, substituted aromatic azides (1.0 mmol) in dry THF were added slowly while stirring at room temperature under nitrogen atmosphere for 12 h. Later, the solvent was removed under reduced pressure and the residue was diluted with distilled water and extracted thrice with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to get the final product **3a**–**3k**. The crude products were purified by column chromatography with ethyl acetate in hexane.

5.1.4. 5-(Benzo[1,3]dioxol-5-ylmethylene)-3-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione ***3a***

Yellow solid, yield: 85%, m.p.199–201 °C, IR (KBr) cm^{-1} 3156, 2920, 1733, 1683, 1518, 1488. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm):

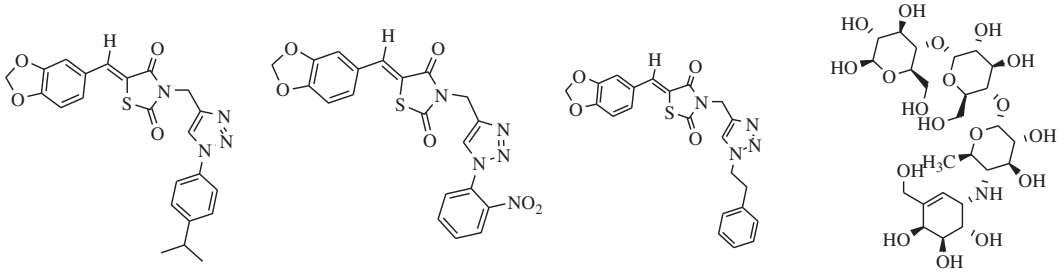


Fig. 2. Structures of most potential α-glucosidase enzyme inhibitors.

Table 2
Binding site residues detected during docking studies of compounds **3d**, **3e**, **3j** and Acarbose on α-glucosidase.

Compound	Interacting amino acid residues (within 4 Å binding site)	Conserved binding site residues
3d	THR-269, GLU-271, GLN-272, GLN-275, TYR-636, THR-639, LEU-640, ARG-647, ASP-649, ARG-653, GLU-658, PRO-676, TYR-733, ILE-734, GLY-766, GLU-767	LEU-640, ARG-647, ASP-649, ARG-653, PRO-676, GLY-766, GLU-767
3e	THR-269, GLU-271, LEU-640, ARG-647, ASP-649, ARG-653, HIS-657, GLU-658, TYR-660, PRO-676, GLY-732, TYR-733, LYS-765, GLY-766, GLU-767	LEU-640, ARG-647, ASP-649, ARG-653, PRO-676, GLY-766, GLU-767
3j	THR-269, GLU-271, TYR-636, THR-639, LEU-640, ARG-647, ASP-649, ARG-653, HIS-657, GLU-658, TYR-660, PRO-676, TYR-733, LYS-765, GLY-766, GLU-767	LEU-640, ARG-647, ASP-649, ARG-653, PRO-676, GLY-766, GLU-767
Acarbose	Tyr-636, THR-639, LEU-640, ARG-643, ARG-647, ASP-649, ARG-653, GLU-658, PRO-676, GLY-732, TYR-737, ILE-734, PRO-736, ASP-759, GLU-763, ALA-764, LYS-765, GLY-766, GLU-767	LEU-640, ARG-647, ASP-649, ARG-653, PRO-676, GLY-766, GLU-767

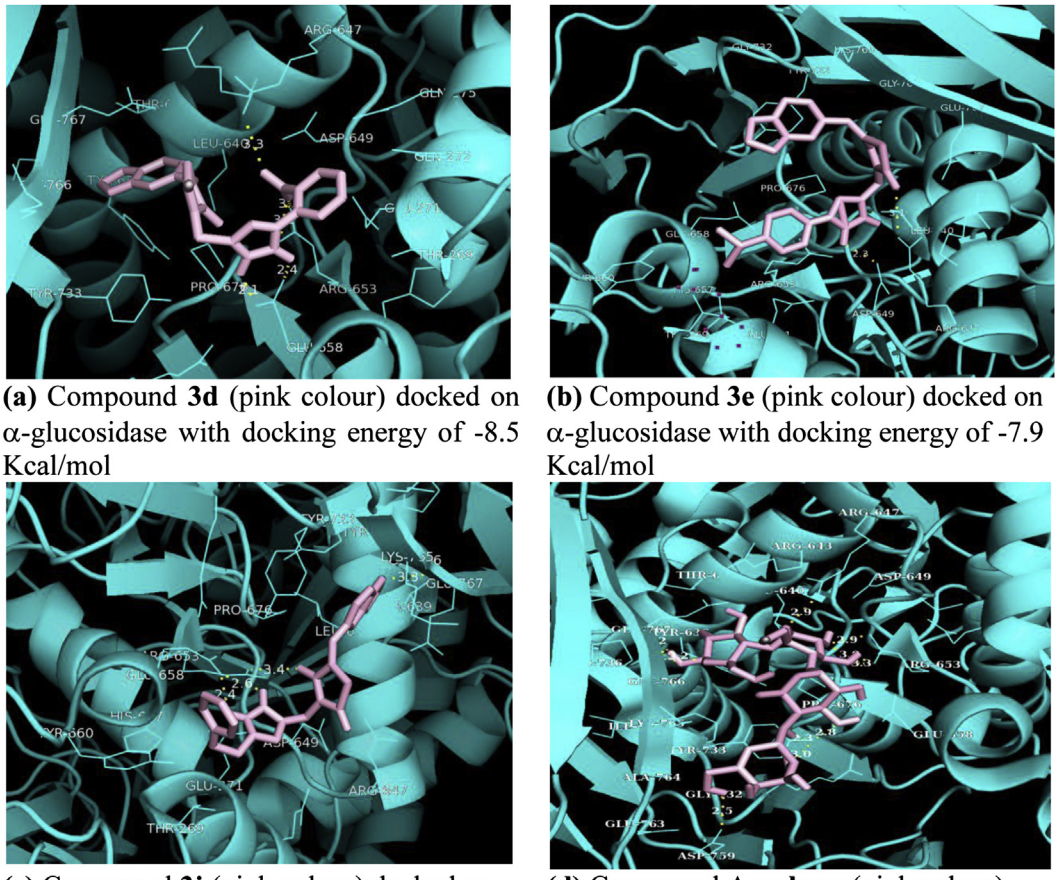
5.14 (s, 2H), 6.07 (s, 2H), 6.91 (d, 1H, $J = 8.1$ Hz), 6.07 (s, 1H), 7.07 (d, 1H, $J = 8.1$ Hz), 7.22 (1H, d, $J = 8.85$ Hz), 7.28 (s, 1H), 7.73–7.69 (m, 2H) 7.85 (s, 1H), 8.04 (s, 1H). ^{13}C NMR ($CDCl_3$,75 MHz): δ (ppm) 36.8, 102.3, 109.5, 116.9, 117.2, 119.11, 122.1, 123.0, 123.1, 127.1, 127.7, 133.6, 134.8, 142.8, 149.0, 150.35, 161.2, 164.5, 166.2, 167.8. ESI-MS (m/z) 425 (M + 1) observed for $C_{20}H_{13}FN_4O_4S$.

5.1.5. 5-(Benzo[1,3]dioxol-5-ylmethylene)-3-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione ***3b***

Yellow solid, yield: 85%, m.p. 180–182 °C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 5.15 (s, 2H), 6.08 (s, 2H), 6.92 (d, 1H, $J = 8.100$ Hz), 6.99 (s, 1H), 7.07 (d, 1H, $J = 8.471$ Hz), 7.29 (s, 1H), 7,45 (d, 2H, $J = 7.912$ Hz), 7.15 (d, 1H, $J = 7.535$ Hz), 7.79 (s, 1H), 7.86 (s, 1H), 8.09 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 168.12, 167.43, 166.22, 150.35, 149.05, 143.50, 138.11, 136.03, 134.90, 131.22, 129.38, 127.77, 127.18, 122.32, 121.96, 121.28, 119.01, 110.62, 109.53, 102.36, 36.84. ESI-MS (m/z) 441 (M + 1) observed for $C_{20}H_{13}ClN_4O_4S$.

5.1.6. 5-(Benzo[1,3]dioxol-5-ylmethylene)-3-((1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione ***3c***

Yellow solid, yield: 83%, m.p.179–180 °C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.15 (s, 2H), 6.05 (s, 2H), 6.89 (d, 1H, $J = 8.120$ Hz), 6.97 (s, 1H), 7.04 (d, 1H, $J = 8.120$ Hz), 7.42–7.46 (m, 2H) 7.55–7.61 (m, 2H) 7.83 (s, 1H), 8.08 (s, 1H). ESI-MS (m/z) 441 (M + 1) observed for $C_{20}H_{13}ClN_4O_4S$.



(a) Compound **3d** (pink colour) docked on α-glucosidase with docking energy of -8.5 Kcal/mol

(b) Compound **3e** (pink colour) docked on α-glucosidase with docking energy of -7.9 Kcal/mol

(c) Compound **3j** (pink colour) docked on α-glucosidase with docking energy of -8.3 Kcal/mol

(d) Compound **Acarbose** (pink colour) docked on α-glucosidase with docking energy of -7.9 Kcal/mol

Fig. 3. Molecular insight of compounds **3d**, **3e**, **3j** and Acarbose docked on human intestinal α-glucosidase.

5.1.7. 5-(Benzo[1,3]dioxol-5-ylmethylene)-3-((1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione ***3d***

Yellow solid, yield: 83%, m.p. 202–205 °C, IR (KBr) cm^{-1} 3155, 2923, 1733, 1675, 1585, 1456. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.13 (s, 2H), 6.04 (s, 2H), 6.89 (d, 1H, J = 9.042 Hz), 7.60 (d, 1H, J = 7.15 Hz), 7.71 (d, 1H, J = 7.535 Hz), 7.77 (d,1H, J = 8.66 Hz), 7.83 (s, 1H), 7.97 (s, 1H), 8.08 (d, 1H, J = 8.66 Hz). ESI-MS (m/z) 452 (M + 1) observed for $C_{20}H_{13}N_5O_6S$.

5.1.8. 5-(Benzo[1,3]dioxol-5-ylmethylene)-3-((1-(4-isopropylphenyl)-1H-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione ***3e***

Yellow solid, yield: 79%, m.p. 142–146 °C, ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.29 (s, 6H), 2.93–3.02 (m, 1H), 5.12 (s, 2H), 6.05 (s, 2H), 6.88–6.91 (d, 1H, J = 8.30 Hz), 6.97 (s, 1H), 7.03–7.06 (d, 1H, J = 8.3 Hz), 7.33–7.36 (d, 2H, J = 8.3 Hz), 7.59–7.62 (d, 2H, J = 9.0 Hz), 7.83 (s, 1H), 8.02 (s, 1H). ESI-MS (m/z) 449 (M + 1) observed for $C_{23}H_{20}N_4O_4S$.

5.1.9. 5-(Benzo[1,3]dioxol-5-ylmethylene)-3-((1-p-tolyl-1H-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione ***3f***

Yellow solid, yield: 79%, m.p.155–158 °C, ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.28 (s, 3H), 5.16 (s, 2H), 6.08 (s, 2H), 6.92 (d, 1H, J = 8.10 Hz), 6.99 (s, 1H), 7.08 (d, 1H, J = 7.53 Hz), 7.64 (d, 1H, J = 7.91 Hz) 7.73–7.81 (m, 2H), 7.86 (s, 1H), 8.00 (s, 1H), 8.11 (d, 1H, J = 7.91 Hz). ESI-MS (m/z) 421 (M + 1) observed for $C_{21}H_{16}N_4O_4S$.

5.1.10. 5-(Benzo[1,3]dioxol-5-ylmethylene)-3-((1-(3,4-difluorophenyl)-1H-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione ***3g***

Yellow solid, yield: 85%, m.p.182–184 °C, ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.11 (s, 2H), 6.05 (s, 2H), 6.90 (d, 1H, J = 8.477), 6.96 (s, 1H), 7.05 (s, 1H), 7.30 (d, 1H, J = 11.86 Hz), 7.58–7.64 (m, 2H), 7.85 (d, 1H, J = 2.63 Hz) 7.83 (s, 1H) 8.02 (s, 1H). ESI-MS (m/z) 443 (M + 1) observed for $C_{20}H_{12}F_2N_4O_4S$.

5.1.11. 5-(Benzo[1,3]dioxol-5-ylmethylene)-3-((1-(4-chloro-3-fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione ***3h***

Yellow solid, yield: 80%, m.p.174–175 °C, IR (KBr) cm^{-1}: 3156, 2926, 1736, 1685, 1588, 1451. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.14 (s, 2H) 6.08 (s, 2H), 6.92 (d, 1H, J = 8.10 Hz), 6.98 (s, 1H), 7.07 (d, 1H, J = 8.10 Hz),7.33 (d, 1H, J = 8.28 Hz), 7.61–76 (m, 1H), 7.83 (d, 1H, J = 2.637 Hz), 7.85 (s, 1H), 8.06 (s, 1H). ESI-MS (m/z) 459 (M + 1) observed for $C_{20}H_{12}ClFN_4O_4S$.

5.1.12. 5-(Benzo[1,3]dioxol-5-ylmethylene)-3-((1-(2-methoxy-4-methylphenyl)-1H-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione ***3i***

Yellow solid, yield: 82%, m.p. 200–205 °C, ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.25 (s, 3H), 2.414 (s, 3H), 5.12 (s, 2H), 6.04 (s, 2H), 6.88–6.91 (d, 1H, J = 8.12 Hz), 6.97 (s, 1H), 7.03–7.06 (d, 1H, J = 9.63 Hz), 7.28–7.31 (d, 2H, J = 8.3 Hz), 7.56–7.59 (d, 2H, J = 8.3 Hz), 7.83 (s, 1H), 8.01 (s, 1H). ESI-MS (m/z) 451 (M + 1) observed for $C_{22}H_{18}N_4O_5S$.

5.1.13. 5-(Benzo[1,3]dioxol-5-ylmethylene)-3-((1-phenethyl-1H-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione ***3j***

Yellow solid, yield: 86%, m.p. 166–165 °C, IR (KBr) cm^{-1}: 3122, 2924, 1744, 1684, 1591, 1506. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.44–3.49 (t, 2H), 4.81–4.86 (t, 2H), 5.27 (s, 2H), 6.35 (s, 2H), 7.18–7.20 (d, 1H, J = 8.12 Hz), 7.32–7.37 (m, 3H), 7.50–7.59 (m, 4H) 7.62 (s, 1H), 8.01 (s, 1H). ESI-MS (m/z) 435 (M + 1) observed for $C_{22}H_{18}N_4O_4S$.

5.1.14. 5-(Benzo[1,3]dioxol-5-ylmethylene)-3-((1-octyl-1H-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione ***3k***

Yellow solid, yield: 81%, m.p. 95–98 °C, ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.84–0.89 (t, 3H), 1.25–1.30 (s, 6H), 1.85–1.90 (t, 2H), 4.28–4.33 (t, 2H), 5.03 (s, 2H), 6.05 (s, 2H), 6.88–6.91 (d, 1H, J = 8.12 Hz), 6.96 (s,1H), 7.02–7.05 (d, 1H, J = 8.12 Hz), 7.60 (s, 1H), 7.81 (s, 1H). ESI-MS 415 (m/z) (M + 1) observed for $C_{20}H_{22}N_4O_4S$.

Acknowledgments

Authors thank Director, CSIR-CIMAP, Lucknow, India, and SIC, CSIR-CIMAP-RC, Hyderabad, India for their constant encouragement and support. Author Yakaiah thanks CSIR-New Delhi for granting Senior Research Fellowship. Also, Author Sarfaraj thank 'Council of Science and Technology, Uttar Pradesh' (CST, UP), Lucknow for the award of fellowship.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.10.005.

References

[1] J.P. Ye, Challenges in drug discovery for thiazolidinedione substitute, Acta Pharm. Sin. B 1 (2011) 137–142.
[2] C. Blanquicett, J. Roman, C.M. Hart, Thiazolidinediones as anti-cancer agents, Cancer Ther. 6 (A) (2008) 25–34.
[3] P. Vijay, T. Kalpana, M.M. Sonali, R. Mohan, C.S. Ramaa, Synthesis and primary cytotoxicity evaluation of new 5-benzylidene-2,4-thiazolidinedione derivatives, Eur. J. Med. Chem. 45 (2010) 4539–4544.
[4] X.F. Liu, C.J. Zheng, L.P. Sun, X.K. Liu, H.R. Piao, Synthesis of new chalcone derivatives bearing 2,4-thiazolidinedione and benzoic acid moieties as potential antibacterial agents, Eur. J. Med. Chem. 46 (2011) 3469–3473.
[5] A. Garg, P. Chawla, D. Panjvani, S.A. Saraf, Synthesis of some novel 5-substituted arylidine 2,4-thiazolidinediones as bioactive agents, Int. J. Pharm. Sci. Nanotechnol. 4 (2011) 1373–1378.
[6] V.S. Jain, D.K. Vora, C.S. Ramaa, Thiazolidine-2,4-diones: progress towards multifarious applications, Bioorg. Med. Chem. 21 (2013) 1599–1620.
[7] A. Galli, E. Ceni, T. Mello, S. Polvani, M. Tarocchi, F. Buccoliero, F. Lisi, L. Cioni, B. Ottanelli, V. Foresta, G. Mastrobuoni, G. Moneti, G. Pieraccini, C. Surrenti, S. Milani, Thiazolidinediones inhibit hepatocarcinogensis in hepatitis B virus-transgenic mice by peroxisome proliferator-activated receptor γ-independent regulation of nucleophosmin, Hepatology 52 (2010) 493–505.
[8] M. Whiting, J.C. Tripp, Y.C. Lin, W. Lindstrom, A.J. Olson, J.H. Elder, K.B. Sharpless, V.V. Fokin, Rapid discovery and structure activity profiling of novel inhibitors of human immunodeficiency virus type 1 protease enabled by the copper(I) catalyzed synthesis of 1,2,3,-triazoles and their further functionalization, J. Med. Chem. 49 (2006) 7697–7710.
[9] M.J. Giffin, H. Heaslet, A. Brik, Y.C. Lin, G. Cauvi, C.H. Wong, D.E. McRee, J.H. Elder, C.D. Stout, B.E. Torbett, A copper(I)-catalyzed 1,2,3-triazole azide-alkyne click compound is a potent inhibitor of a multidrug-resistant HIV-1 protease variant, J. Med. Chem. 51 (2008) 6263–6270.
[10] H. Bektas, N. Karaali, D. Sahin, A. Demirbas, S.A. Karaoglu, N. Demirbas, Synthesis and antimicrobial activities of some new 1,2,3-triazole derivatives, Molecules 15 (2010) 2427–2438.
[11] G.P. Dorota, B. Jan, E.G. Iwona, Design, synthesis, antiviral and cytostatic evaluation of novel isoxazolidine nucleotide analogues with a 1,2,3-triazole linker, Eur. J. Med. Chem. 47 (2012) 501–509.
[12] S.G. Agalave, S.R. Maujan, V.S. Pore, Click chemistry: 1,2,3-triazoles as pharmacophores, Chem. Asian J. 6 (2011) 2696–2718.
[13] I.K. Boddy, G.G. Briggs, R.P. Harrison, T.H. Jones, M.J. O'Mahony, I.D. Marlow, B.G. Roberts, R.J. Willis, R. Bardsley, J. Reid, The synthesis and insecticidal activity of a series of 2-aryl-1,2,3-triazoles, Pest Manage. Sci. 48 (1996) 189–196.
[14] N.G. Aher, V.S. Pore, N.N. Mishra, A. Kumar, P.K. Shukla, A. Sharma, M.K. Bhat, Synthesis and antifungal activity of 1,2,3-triazole containing fluconazole analogues, Bioorg. Med. Chem. Lett. 19 (2009) 759–763.
[15] S.A. Ross, E.A. Gulve, M. Wang, Chemistry and biochemistry of type 2 diabetes, Chem. Rev. 104 (2004) 1255–1282.
[16] T. Mossman, Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays, J. Immunol. Methods 65 (1983) 55–63.
[17] K.S. Babu, A.K. Tiwari, P.V. Srinivas, A.Z. Ali, B.C. Raju, J.M. Rao, Yeast and mammalian α-glucosidase inhibitory constituents from Himalayan rhubarb

Rheum emodi Wall. Ex Meisson, Bioorg. Med. Chem. Lett. 14 (2004) 3841–3845.
[18] G.J. McDougall, F. Shpiro, P. Dobson, P. Smith, A. Blake, D. Stewart, Different polyphenolic components of soft fruits inhibit α-amylase and α-glucosidase, J. Agric. Food Chem. 53 (2005) 2760–2766.
[19] O. Trott, A.J. Olson, AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading, J. Comput. Chem. 31 (2010) 455–461.
[20] D.K. Yadav, A. Meena, A. Srivastava, D. Chanda, F. Khan, S.K. Chattopadhyay, Development of QSAR model for immunomodulatory activity of natural coumarinolignoids, Drug Des. Dev. Ther. 4 (2010) 173–186.
[21] L. Sim, K. Jayakanthan, S. Mohan, R. Nasi, B.D. Johnston, B.M. Pinto, D.R. Rose, New glucosidase inhibitors from an ayurvedic herbal treatment for type 2 diabetes: structures and inhibition of human intestinal maltase-glucoamylase with compounds from *Salacia reticulate*, Biochemistry 49 (2010) 443–451.