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Short communication

Synthesis, antiamoebic and molecular docking studies of furan-thiazolidinone hybrids

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ABSTRACT

In continuation of our previous work, a series of furan-thiazolidinone hybrids was prepared by Knoevenagel condensation of 3-(furan-2-ylmethyl)-2-(phenylimino)-1, 3-thiazolidin-4-one with different aryl aldehydes in presence of strong base. Some members of the series exhibited remarkable antiamoebic activity and cell viability. Three compounds **(3**, **6** and **11)** showed excellent binding energy for *Entamoeba histolytica O*-acetyle-L-serine sulfohydrolase and *Entamoeba histolytica* thioredoxin reductase. These compounds demonstrated significant inhibition of *O*-acetyle-L-serine sulfohydrolase. The promising antiamoebic activity and enzymatic assay of **3**, **6** and **11** make them promising molecules for further lead optimization in the development of novel antiamoebic agents.

1. Introduction

Entamoeba histolytica (*E. histolytica*), the causative agent of amoebiasis has been listed by the National Institute of Health as a category B priority biodefense pathogen in the United States [1]. This water borne pathogen possesses contact-dependent cell killing activity and causes up to 100,000 fatalities per annum worldwide [2,3]. There is currently no vaccine against *E. histolytica* [4]. Metronidazole (MNZ) is the first line medicament against amoebiasis but long term use of the drug produces plenty of perilous side effects [5,6]. Furthermore, resistance to MNZ has been reported and the treatment failure may emerge as a major public health issue [7]. *E. histolytica* O-acetyl serine sulfhydrylase (*Eh*OASS) and *E. histolytica* thioredoxin reductase (*Eh*TrR) are two important enzymes that play crucial role in the life cycle of the parasite. The growth and survival of *E. histolytica* depend upon the cysteine biosynthetic pathway [8]. O-acetyl serine sulfhydrylase catalyzes the last step of the cysteine biosynthetic pathway. Cysteine, which is the product of this pathway, is the only antioxidative thiol in *E. histolytica* and plays significant role in maintaining the redox balance in the organism [9]. *E. histolytica* thioredoxin reductase is also an important enzyme that maintains intracellular redox balance [10]. Thioredoxin reductase (TrR) catalyzes the reversible transfer of reducing equivalents between NADPH and thioredoxin [11,12]. In view of the importance of *E. histolytica* O-acetyl serine sulfhydrylase and *E. histolytica* thioredoxin reductase, these enzymes could be good drug target as both of these enzyme homologues are absent in mammalian hosts.

It has been demonstrated that the additive or even significant synergistic effects can be achieved by molecular hybridization of two or more different medicinally active scaffolds into a single chemical entity [13]. Furan, a well-studied five-membered heterocyclic, has been accounted to display various biological activities such as antibacterial, antiviral, antifungal, antitumor, antiinflammatory and antiglycemic [14]. Furan constitutes the basic core of antiamoebic drug diloxanide furoate (Fig. 1) [15]. In our previous studies, some compounds bearing furan ring in conjugation with other scaffolds have been found to exhibit remarkable antiamoebic activities (Fig. 2) [16]. Recently we have synthesized some novel thiazolidinone derivatives starting from 2-methylpropane-1-amine that demonstrated better growth inhibitory potential against

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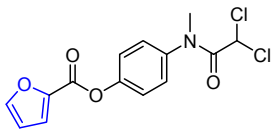


Fig. 1. Antiamoebic drug diloxanide furoate having furan ring.

$IC_{50} = 0.60\mu M$ $IC_{50} = 1.70\mu M$

Fig. 2. Furan based compounds having antiamoebic activity.

E. histolytica (Fig. 3) [17]. Encouraged by the results of the previous studies [16,17] and the fact that the combination of thiazolidinones with other heterocyclic rings produce various biological activities [18], we hypothesized that the thiazolidinone derivatives incorporating a heterocyclic ring might exhibit synergistic effects. Therefore, in this paper, we herein report the synthesis, antiamoebic activity, molecular docking and enzymatic assay of furan-thiazolidinone hybrids (Fig. 4).

2. Results and discussion

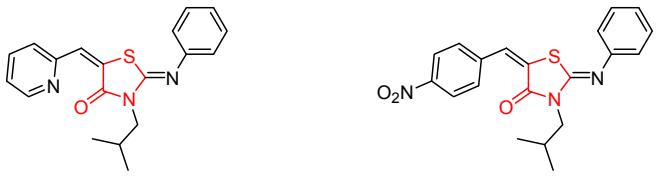
2.1. Chemistry

The synthetic pathway leading to the title compounds (**3**–**17**) is depicted in Scheme 1. 1-(Furan-2-ylmethyl)-3-phenylthiourea (**1**) was synthesized by reacting phenyl isothiocyanate with furfuryl amine in presence of toluene. Sodium acetate assisted cyclization of compound **1** with chloroacetic acid afforded 3-(furan-2-ylmethyl)-2-(phenylimino)-1, 3-thiazolidin-4-one (**2**). Finally, Knoevenagel condensation of compound **2** with different aryl aldehydes in presence of strong base furnished the target furan-thiazolidinone hybrids (**3**–**17**). The structures of all the target compounds (**3**–**17**) were elucidated on the basis of FT-IR, ^{1}H NMR, ^{13}C NMR and ESI-MS. Additional supports for the proposed structure confirmed by X-ray crystallographic studies. The purity of the compounds was confirmed by the elemental analyses.

2.2. Single crystal structure

2.2.1. Single crystal structures of 2, 6, 8, 13 and 15

The asymmetric units of **2, 6, 13** and **15** contain one molecule of furan-thiazolidinone hybrids. The asymmetric unit of 8 contains two molecules of furan-thiazolidinone hybrids and one molecule of cyclohexane. The cyclohexane ring is in a chair form. The furan and phenylimino rings are rotated respect to the carbon atom, C5, and



$IC_{50} = 0.60\mu M$ $IC_{50} = 0.13\mu M$

Fig. 3. Thiazolidinone derivatives with antiamoebic activity.

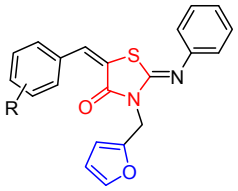
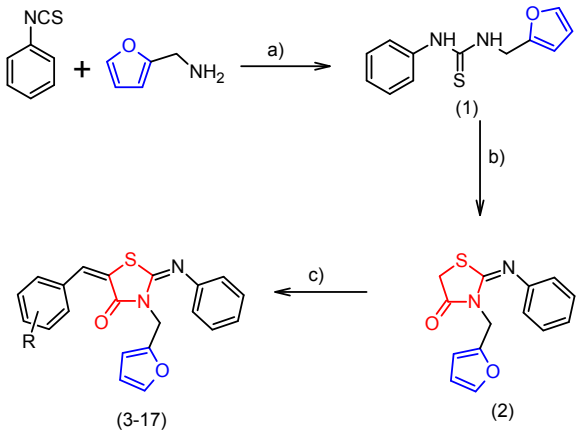


Fig. 4. General structure of Furan-thiazolidinone hybrids (blue and red color depicts Furan and Thiazolidinone respectively).



Scheme 1. Synthesis of Furan-thiazolidinone hybrids (**3**–**17**). **Reagents and conditions:** a) Toluene, room temperature, 1 h. b) Anhydrous sodium acetate, chloroacetic acid, ethanol, reflux, 14 h. c) Piperidine, ethanol, reflux, 12–16 h.

nitrogen atom, N2, respectively, in different forms in the five compounds (Figs. 5–9). Crystal data and details of the data collection and refinement for the compounds **2, 6, 8, 13** and **15** are mentioned in Table 1. Bond lengths and angles are summarized in supplementary data (Table SI1). In **8**, the presence of

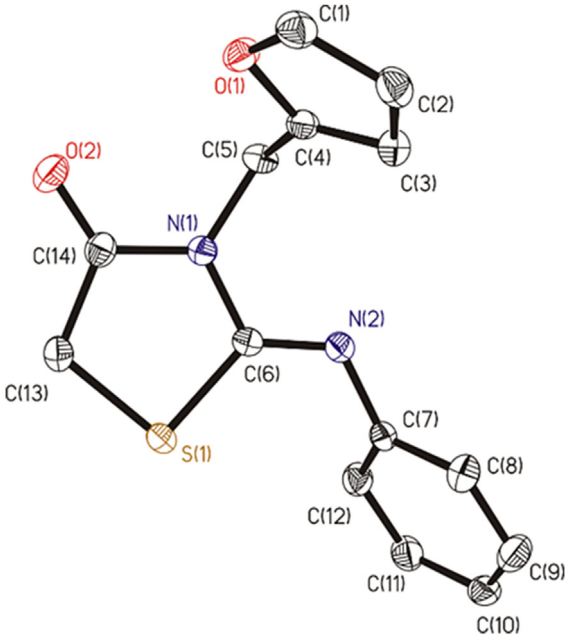


Fig. 5. ORTEP plot of compound 3-(furan-2-ylmethyl)-2-(phenylimino)-1, 3-thiazolidin-4-one (**2**). All the non-hydrogen atoms are presented by their 50% probability ellipsoids. Hydrogen atoms are omitted for clarity.