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IN VITRO BIOLOGICAL EVALUATION OF *(Z)*-5-(4-(*(E)*-3-(PHENYL)-3-OXOPROP-1-ENYL) BENZYLIDENE)-1, 3-THIAZOLIDINE-2, 4-DIONE AS POTENIAL 5-LIPOXYGENASE (5-LO) INHIBITOR

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ABSTRACT

In the present study a 1,3-thiazolidine-2,4-dione derivative (*Z*)-5-(4-((*E*)-3-(phenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione **(1)** has been studied for its inhibitory potential against 5-lipoxygenase (5-LO) enzyme. The results clearly state that this compound is a potent inhibitor of potato 5-LO enzyme. This observation is remarkable starting point to develop potential inhibitors of 5-LO enzyme.

Keywords: 1, 3-Thiazolidine-2, 4-dione, 5-lipoxygenase (5-LO)

INTRODUCTION

Lipoxygenases are a class of non-heme, iron-containing enzymes that catalyze the incorporation of molecular oxygen into 1,4,-*cis,cis*-pentadiene-containing fatty acids (e.g. linoleic and arachidonic acids) to form hydroperoxide products [1]. The human isozymes, 5-, 12- and 15-Lipoxygenases are associated with different disease states, which suggests that selective inhibition may be important in targeting them for therapeutic purposes. 5-Lipoxygenase (5-LO), which was first discovered in 1976, plays an essential role in the biosynthesis of leukotrienes (LTs) that exert a large number of different biological activities mediated by specific G-protein coupled receptors. LTB_4 is a typical proinflammatory mediator that recruits and activates leukocytes, whereas cysteinyl-leukotrienes C_4, D_4 and E_4 cause vascular permeability and smooth muscle contraction. In view of these properties, development of drugs with 5-LO inhibitory activity have been hypothesized to possess therapeutic potential for treatment of asthma, allergic disorders and other inflammatory diseases [2].

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Based on the mechanism of action, the lipoxygenase inhibitors have been classified into four distinct classes: (i) iron chelating inhibitors, (ii) competitive reversible inhibitors, (iii) inhibitors of the 5-LO activating protein (FLAP) and (iv) anti-oxidative [3].

Intensive discovery efforts in the development of clinically useful drugs from the inhibitors of 5-LO enzyme have led to one marketed drug; Zileuton (A-64066) and others, namely MK-3000, MK-886, MK-0591, ZM 211965, AKBA, BW A4C, LDP-977, Bay-X-1005, and Abt-761, which are evaluated at different stages of drug development [2,3].. As a part of our ongoing research in systematic investigation for identifying some novel bioactive compounds in relation to their 5-LO inhibitory activity, we have selected *(Z)*-5-(4-((*E*)-3-(phenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione **(1)**.

EXPERIMENTAL

Chemical synthesis

The compound (*Z*)-5-(4-((*E*)-3-(phenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione **(1)** was procured from Pharmaceutical Chemistry Research Labs, AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, as gift sample.

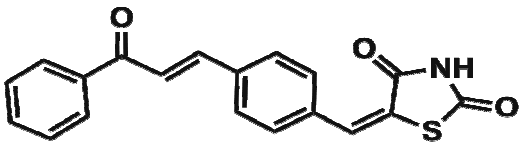

Figure 1: Chemical structure of (*Z*)-5-(4-((*E*)-3-(phenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione **(1)**

Enzyme 5-LO Inhibition Assay

The 5-LO inhibitory potential of the (*Z*)-5-(4-((*E*)-3-(phenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione **(1)** was determined by 5-LO inhibition assay (UV-Kinetic method) as described by Sircar *et al*. [4]. For the evaluation of 5-LO inhibitory activity, the enzymatic activity of 5-LO was measured spectrophotometrically using potato 5-LO [5] and an incubation mixture containing 80 mM linoleic acid and 50 mM sodium phosphate buffer (pH = 6.3). The reaction was initiated by the addition of an enzyme buffer mix to substrate (Linoleic acid) and the enzyme activity was monitored as an increase in rate of absorbance at 234 nm on a UV/visible spectrophotometer (Varion Cary-50 UV-Visible spectrophotometer) for 120 sec. Each experiment was conducted by incubating along with control at various concentrations of the test substances with enzyme buffer mix for 2 min before addition of the substrate. The percentage inhibition was calculated by comparing slope or increase in absorbance of test substance with that of control enzyme activity. The assay was performed in triplicate and mean values were used for the calculation. The IC_{50} values were obtained using fenny probed analysis software. The result for the test compound was compared with the positive control abietic acid (LI01020) [6].

RESULTS AND DISCUSSION

Chemical synthesis

The chemical synthesis, physical and spectroscopic characterization of the selected compound (Z)-5-(4-((E)-3-(phenyl)-3-oxoprop-1-enyl) benzylidene)-1,3-thiazolidine-2,4-dione **(1)** was earlier reported by one of the authors Dr. A. Vasudeva Rao *et al*.[7]

Enzyme 5-LO inhibition assay

From the analysis of *in vitro* 5-LO inhibitory activity screening data discovered that the compound (Z)-5-(4-((E)-3-(phenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione **(1)** demonstrated comparatively the most effective inhibitory activity, with IC_{50} values of 8.37 ± 1.16 µg/mL in comparison with the standard drug (Abietic acid, IC_{50} : 4.11 ± 0.23 µg/mL). The 5-LO inhibitory activity is significantly affected by substituents at position 1 and 3 of α,β-unsaturatedketone system.

CONCLUSION

In conclusion we could evaluate the 5-LO inhibitory potential of (Z)-5-(4-((E)-3-(phenyl)-3-oxoprop-1-enyl)benzylidene)-1,3-thiazolidine-2,4-dione **(1)** and it was appeared to be a good inhibitor of potato 5-LO enzyme.

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