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RESEARCH ARTICLE

# Synthesis and biological evaluation of 5-benzylidenerhodanine-3-acetic acid derivatives as AChE and 15-LOX inhibitors

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**Abstract**

A series of 5-benzylidenerhodanine-3-acetamides bearing morpholino-, 4-arylpiperazinyl-, or 4-benzylpiperidinyl- moieties were synthesized and their inhibitory activities against acetylcholinesterase (AChE) were evaluated. Alteration of amide part and substitution on the benzylidene moiety resulted in change of anti-AChE activity. The most active compound was the 1-benzylpiperidinyl derivative containing 4-(dimethylamino)benzylidene scaffold. Notably, the intermediate compounds, namely 5-arylidene-rhodanine-3-acetic acids (**3**), showed mild inhibitory activity against 15-lipoxygenase (15-LOX), while the final compound **4** showed no activity against 15-LOX.

**Keywords**

2-Thioxothiazolidin-4-one, 15-lipoxygenase, acetylcholinesterase, docking study, inhibitors, rhodanines

**History**

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## Introduction

Rhodanines (2-thioxothiazolidin-4-ones) and their analogues have been known as privileged structures in drug discovery. Compounds containing the rhodanine ring have demonstrated a broad range of biological activities[1]. Particularly, 5-arylidene rhodanines have been reported as small molecule inhibitors of diverse enzyme targets such as β-lactamase[2], hepatitis C virus (HCV) NS3 protease[3], aldose reductase[4], UDP-*N*-acetylmuramate/L-alanine ligase[5], protein mannosyl transferase, JNK-stimulating phosphatase, cyclooxygenase, 5-lipoxygenase[6] and tyrosinase[7].

Historically, rhodanines have become a therapeutic class of compounds since the introduction of epalrestat (*Z,E*-[5-(2-methyl-3-phenyl-allylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid) into clinical use for the treatment of diabetic complications[8]. Epalrestat is a rhodanine-3-acetic acid analogue and acts as an aldose reductase inhibitor[9]. Although, the rhodanine-based compounds are suspected to undergo conjugate addition *in vivo*, they are frequently employed in drug design, as there is no adverse effect (e.g. mutagenicity) correlated to this scaffold[10]. According to a long-term clinical study with epalrestat, the structure can be bioavailable and well-tolerated[11]. Bulic et al. have been described a series of 5-arylidene-rhodanine-3-acetic acids as tau aggregation inhibitors potentially useful in the management of Alzheimer's disease and related dementias[12]. Also, amide derivatives of 5-arylidene-rhodanine-3-acetic acid have been reported as anti-inflammatory agents[13,14].

In view of these facts, although extensive studies on the diverse bioactivity of 5-arylidene-rhodanines have been reported, the anti-acetylcholinesterase (AChE) activities of these prototypes have never appeared in the literature. Accordingly as part of our ongoing studies in developing new anti-AChE agents[15–18], we have synthesized 5-benzylidenerhodanine-3-acetamides and evaluated their inhibitory activity against AChE. Also, the intermediate compounds 5-arylidene-rhodanine-3-acetic acids were screened for 15-lipoxygenase (15-LOX) inhibitory activity.

## Experimental

Carbonyldiimidazole (CDI), dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), hydroxyl benzotriazole (HOBt) and other commercially available reagents were used without further purification. TLC was conducted on silica gel 250 micron, F254 plates. Melting points were measured on a Kofler hot stage apparatus and are uncorrected. The IR spectra were taken using Nicolet FT-IR Magna 550 spectrograph (KBr disks). $^1$H NMR spectra were recorded on a NMR instrument Bruker 500 MHz. The chemical shifts (δ) and coupling constants (*J*) are expressed in parts per million and Hertz, respectively. Mass spectra of the products were obtained with an HP (Agilent Technologies, Santa Clara, CA) 5937 Mass Selective Detector. Elemental analyses were carried out by a CHN-Rapid Heraeus elemental analyzer. The results of elemental analyses (C, H, N) were within ±0.4% of the calculated values.

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