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RESEARCH PAPER

Carbonic anhydrase inhibitory activity of phthalimide-capped benzene sulphonamide derivatives

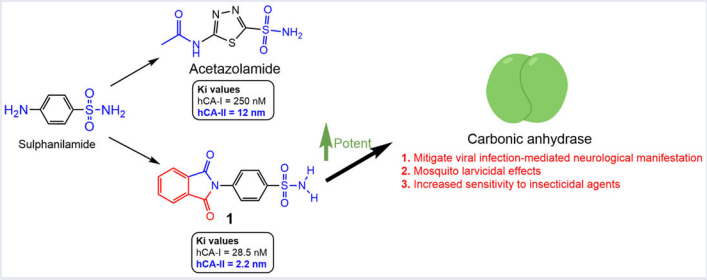
Deepak Shilkar[a], Mohd Usman Mohd Siddique[b], Silvia Bua[c], Sabina Yasmin[a,d], Mrunali Patil[b], Ajay Kumar Timiri[a], Claudiu T. Supuran[c] and Venkatesan Jayaprakash[a]

[a]Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Ranchi, India; [b]Department of Pharmaceutical Chemistry, Shri Vile Parle Kelavani Mandal's Institute of Pharmacy, Dhule, India; [c]Neurofarba Department, Section of Pharmaceutical and Nutraceutical Sciences, University of Florence, Firenze, Italy; [d]Department of Pharmaceutical Chemistry, College of Pharmacy, King Khalid University, Abha, Saudi Arabia

ABSTRACT

A series of phthalimide-capped benzene sulphonamides (**1**–**22**) reported by our group for dengue protease inhibitory activity have been evaluated for their carbonic anhydrase (hCA, EC 4.2.1.1) inhibitory activity against hCA I, hCA II. Compounds **1**, **3**, **10**, and **15** showed hCA I inhibition, whereas **1**, **4**, and **10** showed hCA II inhibition at nanomolar concentrations. Among these compounds, **1** displayed potent inhibitory activity against the hCA I (Ki = 28.5 nM) and hCA II (Ki = 2.2 nM), being 10 and 6 times more potent than acetazolamide, a standard inhibitor (Ki = 250 nM and 12 nM), respectively. Furthermore, this compound displayed 14-fold selectivity towards the hCA II isoform compared to hCA I. Molecular docking and MD simulations were performed to understand the atomic level interactions responsible for the selectivity of compound **1** towards hCA II.

GRAPHICAL ABSTRACT



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Introduction

Carbonic anhydrases (CAs) are metalloenzymes that contain Zn^{2+} and are involved in regulating CO_2 levels and many other physiologic processes in living organisms[1]. Eight distinct evolutionarily unrelated gene families of CAs exist: α-CAs, β-CAs, γ-CAs, δ-CAs, η-CAs, θ-CAs and ι-CAs. Among the eight subtypes, only the α-CAs are present in human cells, with 15 different isoforms identified up until now[2,3]. CAs catalyse the reversible hydration of CO_2 to bicarbonate and protons. Several CA isoenzymes are involved in critical physiological processes, such as biosynthetic reactions[4], acid–base regulation, gluconeogenesis, bone resorption/calcification, electrolyte secretion, and tumourigenicity[5]. Therefore, they have been well-established therapeutic targets for years. Any deregulation or dysfunction in CA activity can cause various disorders such as obesity and cancer[3,4]. Currently, several CA isoforms are essential targets for treating various disorders, including CA II, IV, XII, and XIV, which are targets for diuretics; CA II, IV, and XII for treating glaucoma and CA IX and XII isoforms as anticancer targets[5,6].

All CA families catalyse the reversible hydration of carbon dioxide. The active site of α-CAs consists of a zinc ion coordinated to three histidine residues and a water molecule. The water molecule acts as a nucleophile and attacks the carbon dioxide molecule, forming bicarbonate and a proton. The proton is then released into the solvent through a network of hydrogen bonds involving other amino acid residues such as glutamate and asparagine. The active site of carbonic anhydrase is highly conserved among different isoforms and species, indicating its functional importance[7]. Human carbonic anhydrase II (hCA II), one of the most extensively investigated isoforms, possesses an active site comprising a zinc ion (Zn^{2+}) coordinated to three histidine residues (His94, His96, and His119) and a water molecule or hydroxide ion[8]. In coordination with these residues, the zinc ion coordinated water/hydroxide serves as a nucleophilic catalyst for enzymatic activity. Apart

CONTACT Venkatesan Jayaprakash drvenkatesanj@gmail.com Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Ranchi, India; Claudiu T. Supuran claudiu.supuran@unifi.it Neurofarba Department, Section of Pharmaceutical and Nutraceutical Sciences, University of Florence, Firenze, Italy

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