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# Ligand-based design, virtual screening, and ADME/T-based profiling on a dataset of 1,3,5-triazine-substituted benzene sulfonamides as carbonic anhydrase inhibitors

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**A quantitative structure–activity relationship (QSAR) analysis was performed on a dataset of 62 (1,3,5-triazine-substituted) benzene sulfonamides as carbonic anhydrase II and IX inhibitors using simulated annealing-based multiple linear regression analysis. The selected QSAR model for carbonic anhydrase II inhibition (cross-validated $Q^2 = 0.689$, $r^2_{pred} = 0.780$, $r^2_m = 0.565$) showed that aromaticity, lipophilicity, electronegativity, and molecular projection in the *XZ* plane influence the activity, whereas that for carbonic anhydrase IX inhibition (cross-validated $Q^2 = 0.767$, $r^2_{pred} = 0.841$, $r^2_m = 0.690$) showed that activity was influenced by hydrophilicity, linker between the aromatic rings, electronegativity, and molecular weight. The QSAR model selected was internally and externally validated to define its predictability. Activity prediction of an external dataset containing nine compounds (within the same sphere of applicability) was performed to prove the models' specificity, selectivity, and sensitivity. The hypothesis in the form of the QSAR model was used for ligand-based virtual screening on the ZINC database to obtain some potential hits. Similarly, docking studies on screened hits showed that the molecules interact and orient at the catalytic site in a way similar to acetazolamide. Additionally, an absorption, distribution, metabolism, excretion, and toxicity screening was also performed, and results showed that most of the compounds that can be possible drug candidates obey the Lipinski rule of five and Jorgensen rule of three. Copyright © 2013 John Wiley & Sons, Ltd.**

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**Keywords:** QSAR; simulated annealing; carbonic anhydrase II inhibitors; carbonic anhydrase IX inhibitors; virtual screening; ADME/T profiling

## 1. INTRODUCTION

Carbonic anhydrases (CA) (EC4.2.1.1) are universal enzymes that catalyze the conversion of $CO_2$ to bicarbonate ions and protons. Zinc ion present in their active site is essential for catalysis. CA enzymes are categorized on the basis of four unrelated gene families, out of which there are 16 human isozymes that differ in their catalytic activity, tissue localization, and distribution and are involved in regulating important physiological and pathological processes [1]. The CAII isozyme increases intraocular pressure, in the anterior uvea of the eye, leading to visual dysfunction (glaucoma). The CAIX isozyme under hypoxic condition leads to acidic pH and tumorigenesis. A crucial problem encountered in the design of CA inhibitors is related to the high number of isoforms and their diffuse localization. Sulfonamide is a versatile functional moiety possessing several therapeutically important applications. Novel sulfonamide derivatives have been reported to show substantial antiglaucoma as well as antitumor activity *in vitro* and *in vivo*, thus constituting interesting leads [2]. One major shortcoming of sulfonamides is their high affinity for all CA isozymes, which leads to a lack of specificity. Recently, a research showed that 1,3,5-triazine-substituted aromatic sulfonamides show enhanced efficacy and specificity for CAII, CAIX, CAXII, and CAXIV isozymes [3]. The present study aims for an understanding to rationalize the physicochemical requirement to modulate biological activity. Similarly, from the hypothesis in the form of QSAR, a virtual screening protocol was devised to screen potential hits from ZINC databases. Moreover, the potential hits obtained were predicted for their binding orientation in the CA enzyme binding pocket and further screened for absorption, distribution, metabolism, excretion, and toxicity (ADME/T) analysis.

## 2. MATERIAL AND METHODS

### 2.1. Dataset

A series of 1,3,5-triazine-substituted benzene sulfonamides containing 62 compounds were selected from the reported literature (Table S1) [3–5]. The inhibition constant values were converted into negative logarithm values in molar units for quantitative structure–activity relationship (QSAR) analysis. The

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