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Structural optimization of new class of selective carbonic anhydrase inhibitors: QSAR approach

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Quantitative structure activity relationship studies have been conducted on a series (24 compounds) of sulfonamide derivatives with selective carbonic anhydrase inhibitory activity using ChemOffice v.8.0 software. The best predictions have been obtained for hCA-II enzyme inhibition activity ($Q^2 = 0.552$, $r^2 = 0.724$) and with hCA-VII enzyme inhibition activity ($Q^2 = 0.501$, $r^2 = 0.704$). Both equations are validated by a test set of compounds and give satisfactory predictive r^2 values of 0.434 and 0.608, respectively. The equations selected emphasized the importance of LogP (octanol/water partition coefficient), Highest Occupied Molecular Orbital (HOMO) and Radius of gyration (Rgy) on biological activity i.e.; hydrophobic groups, presence of electron donating groups, size and shape of molecule might be influencing the selective carbonic anhydrase inhibitory activity.

Keywords: Sulfonamide, carbonic anhydrase, antiglaucoma, anticancer, quantitative structure activity relationship

Carbonic anhydrases (CAs, EC 4.2.1.1) are zinc-containing metalloenzymes that catalyze the reversible hydration of carbon dioxide to bicarbonate with discharge of a proton, thus playing important physiological and pathophysiological functions. Till date, sixteen different carbonic anhydrase isozymes with different distribution have been described in higher vertebrates, including humans, some of them have been considered as important targets for inhibitors with therapeutic applications viz; topically acting antiglaucoma, anticancer, antiobesity, anti-thyroid and antihyperglycemic agents. Some sulphon-amides also find applications as diagnostic tools, in positron emission tomography (PET) and magnetic resonance imaging (MRI)[1].

Carbonic anhydrase inhibitors (CAIs) are of two types: (i) metal complexing anions, (ii) Unsubstituted sulfonamides. Both of these bind to the Zn(II) ion of the enzyme either by substituting the non-protein zinc ligand or adding to the metal coordination sphere, generating trigonal-bipyramidal species. Clinically useful sulfonamide derivatives as carbonic anhydrase inhibitors like; acetazolamide, methazolamide, ethoxzolamide, dichlorophenamide, dorzolamide topiramate, zonisamide, and brinzolamide, bind in a tetrahedral geometry of the Zn(II) ion (**Figure 1 A**), in deprotonated state with the nitrogen atom of the sulfonamide moiety coordinated to Zn(II) and an extended network of hydrogen bonds, involving residues Thr199 and Glu106, also participating to the anchoring of the inhibitor molecule to the metal ion. Anions may bind either in tetrahedral geometry of the metal ion or as trigonal-bipyramidal adducts (**Figure 1B)**, (ref. 2). The aromatic/heteroaromatic part of the inhibitor (R) viz; sulfonamide/sulfamate/sulfamide interacts with hydrophilic and hydrophobic residues of CA-I, CA-II and CA-IV. In deprotonated state as -SO_2NH^--; it is coordinated to Zn(II) ion of the enzyme, and its –NH- moiety participates in a hydrogen bond with the Oγ of Thr199, which in turn is engaged in another hydrogen bond to the carboxylate group of Glu106. One of the oxygen atoms of the -SO_2NH- moiety also participates in a hydrogen bond with the backbone –NH- moiety of Thr199 (refs. 2-9).

Carbonic Anhydrase VII isozymes are less studied and understood among the cytosolic CA's. Montgomery *et al.*[10], isolated it from a human genomic library in 1991; showing 50, 56, and 49% identity with hCA-I, hCA-II and hCA-III isozyme respectively. Later Tashinan's group carried out purification, characterization and kinetic studies on the mouse isozyme, mCA VII, and concluded that this enzyme is also inhibited by sulfonamides with high