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INTRINSIC STRUCTURE-THERMODYNAMICS CORRELATIONS OF FLUORINATED BENZENSULFONAMIDES AS INHIBITORS OF HUMAN CARBONIC ANHYDRASES

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The carbonic anhydrases are established as therapeutic targets. There are 12 catalytically active CA isozymes in human body. At least 30 CA sulfonamide inhibitors have been used as drugs to treat glaucoma, epileptic seizures, altitude sickness, and as diuretics. However, most of them exhibit poor selectivity towards target isozymes and result in various side effects.

In this study a class of 4-substituted-benzensulfonamides and 4-substituted-2,3,5,6-tetrafluorobenzensulfonamides as inhibitors of CA is reported [1]. Isothermal titration calorimetry was used for direct measurement of observed thermodynamic parameters, such as change of Gibbs free energy ΔG, enthalpy ΔH, and entropy ΔS. To confirm enzyme inhibition and binding affinity, stopped-flow CO_2 hydration and fluorescent thermal shift assays were applied. The combined use of these methods provided a detailed picture of enzyme-inhibitor interactions [2].

Changes in the protonation of enzyme, inhibitor and buffer affect the observed thermodynamic parameters of binding. Each binding reaction should be dissected in order to determine the intrinsic thermodynamic parameters that are independent on experimental conditions. Intrinsic structure-thermodynamics correlations showed that several fluorinated compounds bind selectively to carbonic anhydrase I with strongly exothermic enthalpy and extremely high affinity [3].

References

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