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DEVELOPMENT OF FLUORINATED BENZENESULFONAMIDES AS CARBONIC ANHYDRASE IX INHIBITORS

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Carbonic anhydrases (CA) are zinc metalloenzymes, which catalyze the reversible hydration of carbon dioxide and regulate a broad range of physiological functions. There are 12 active CA isoforms in human which differ in cellular localization, distribution in organs and tissues, expression levels and kinetic properties. The increased activity or expression of different CA isoforms is often associated with various diseases. Isoform CA IX is implicated in cancer since its expression is nearly absent in healthy human but overexpression of CA IX in numerous hypoxic tumors is observed. Design of a selective and high-affinity inhibitor could be developed into an anticancer drug.

Here we investigate fluorinated benzenesulfonamides as CA inhibitors. The fluorine atoms contributed favorably to CA binding. Furthermore, the fluorinated benzenesulfonamides were subject to convenient nucleophilic aromatic substitution reactions which enabled the synthesis of a diversity of fluorinated compounds. A series of 4-substituted-2,3,5,6-tetrafluorobenezenesulfonamides (**2**, **4**, **5**), 2,4-substituted-3,5,6-trifluorobenzenesulfonamides (**3**), 3,4-substituted-2,5,6-trifluorobenzenesulfonamides (**6**), and 3,4,5-substituted-2,6-difluorobenzenesulfonamides (**7**) were synthesized. Some of the fluorinated benzenesulfonamides bearing bulky hydrophobic groups at *ortho* and *meta* positions exhibited high selectivity and picomolar affinity for CA IX as confirmed by the binding assays. Crystallographic analysis showed the position of the compounds bound to CA IX and the effects in 2D and 3D cancer cell culture models of lead compounds showed compound anticancer activity.