THE SYNTHESIS OF FLUORINATED BENZENESULFONAMIDES BEARING SPECIFIC FUNCTIONAL GROUP AS INHIBITORS OF HUMAN CARBONIC ANHYDRASES

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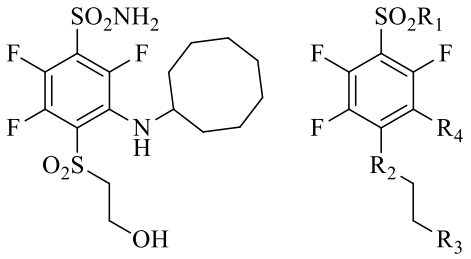
Carbonic anhydrases (CAs) are family of zinc metaloenzymes that catalyze the reversible hydration of CO_2, maintaining various physiological functions in different species of organisms. There are twelve catalytically active CA isoforms in human body. Their overexpression causes numerous diseases including cancer. Isoform CA IX is overexpressed in numerous hypoxic tumors and is thought to be a good target for anticancer drug development. [1]. The most widely known CA inhibitors bear the benzenesulfonamide moiety and a number of drugs used in clinic bear this functional group.

Our research group has successfully designed compounds that inhibit CA IX, with high affinity and selectivity over other CA isoforms. One of them, 3-(cyclooctylamino)-2,5,6-trifluoro-4-[(2-hydroxyethyl)sulfonyl]benzenesulfonamide (VD11-4-2), exhibited subnanomolar affinity for CA IX (K_d = 0.05 nM) [2]. Recently it was discovered that the modification of the *para* tail of VD11-4-2 led to the compound with even higher binding affinity towards CA IX, implying that the tail group made additional contacts with the residues of CA.

The aim of this study is to determine the importance of various moieties for the high affinity towards CA isoforms. For this purpose, we synthesized a series of compounds with modified *para* substituent and sulfonamide group (Fig. 1). Various modifications done to *para* substituent revealed that only benzensulfonamides with specific sulfur oxidation state, particular tail length and exact group significantly increase binding affinity towards CAs.



VD11-4-2

Fig. 1. Compound VD 11-4-2 and schematic representation of modification sites on benzensulfonamide scaffold.

[1] M.Y. Mboge et al. Carbonic Anhydrases: Role in pH Control and Cancer. *Metabolites*. 2018;8(1):19.
[2] V. Dudutienė et al. Discovery and characterization of novel selective inhibitors of carbonic anhydrase IX. J. Med Chem. 2014, 57, 9435