SYNTHESIS AND EVALUATION OF HYDRAZONE COMPOUNDS AS CARBONIC ANHYDRASE INHIBITORS

Liucija Urbelytė[1], Martynas Bagdonas[2], Birutė Grybaitė[1], Rita Vaickelionienė[1], Daumantas Matulis[2], Asta Zubrienė[2], Vytautas Mickevičius[1]

[1]Department of Organic Chemistry, Kaunas University of Technology, Kaunas, Lithuania

[2]Department of Biothermodynamics and Drug Design, Institute of Biotechnology, Life Sciences Center, Vilnius University, Saulėtekio 7, Vilnius, Lithuania

birute.grybaite@ktu.edu

Introduction

Carbonic anhydrases (CAs) are enzymes implicated in a wide range of diseases, including epilepsy, obesity, glaucoma and cancer. Benzenesulfonamide based compounds are effective in inhibiting tumor cell growth in vitro and in vivo. Selective inhibition of CAs by synthetic inhibitors-drugs could be used for the treatment of CA-related diseases. Primary sulfonamides are the most important class of CA inhibitors [1–3]. In this study a group of 4-substituted-benzensulfonamides bearing hydrazone moieties (Fig. 1) was synthesized and compound binding affinity to CA isozymes was evaluated.

Synthesis of substituted benzenesulfonamides

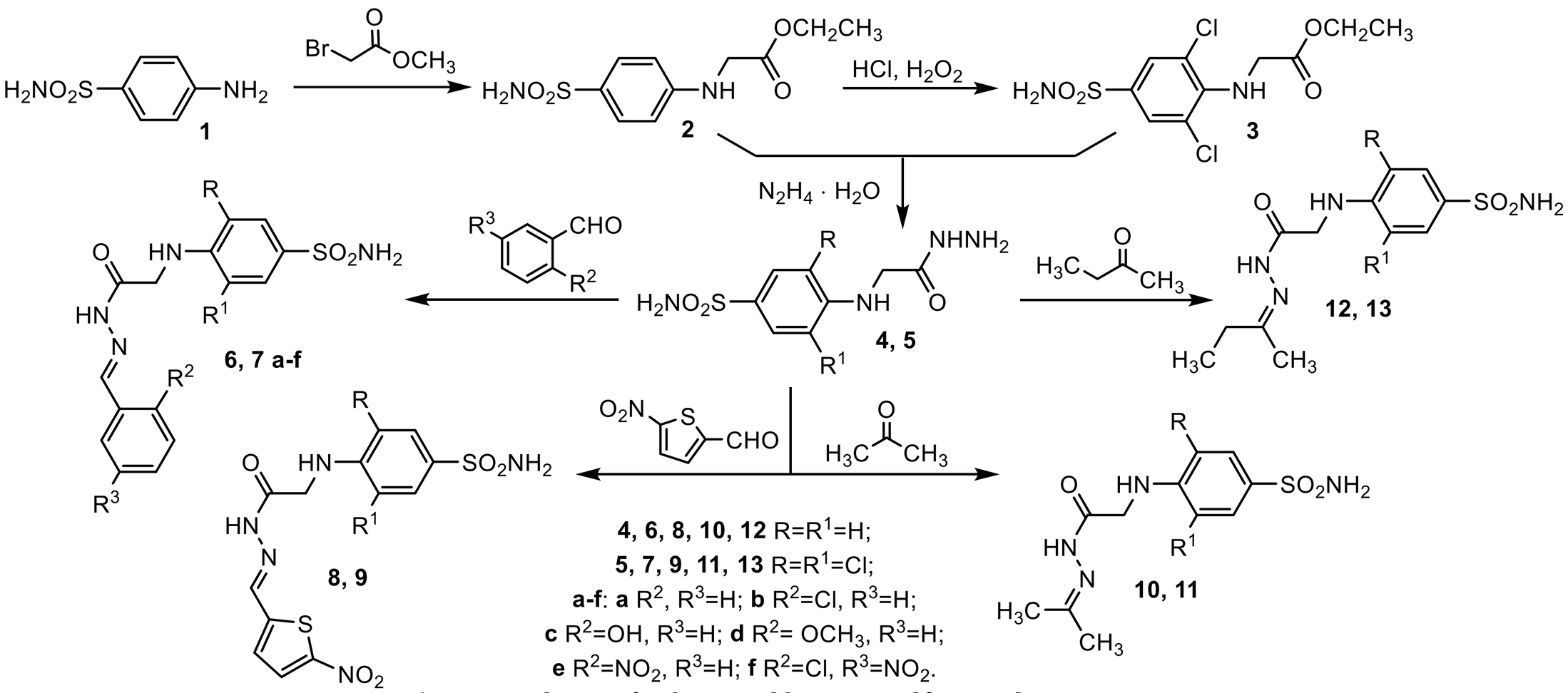

Fig. 1. Synthesis of substituted benzenesulfonamides **2-13**

Binding studies

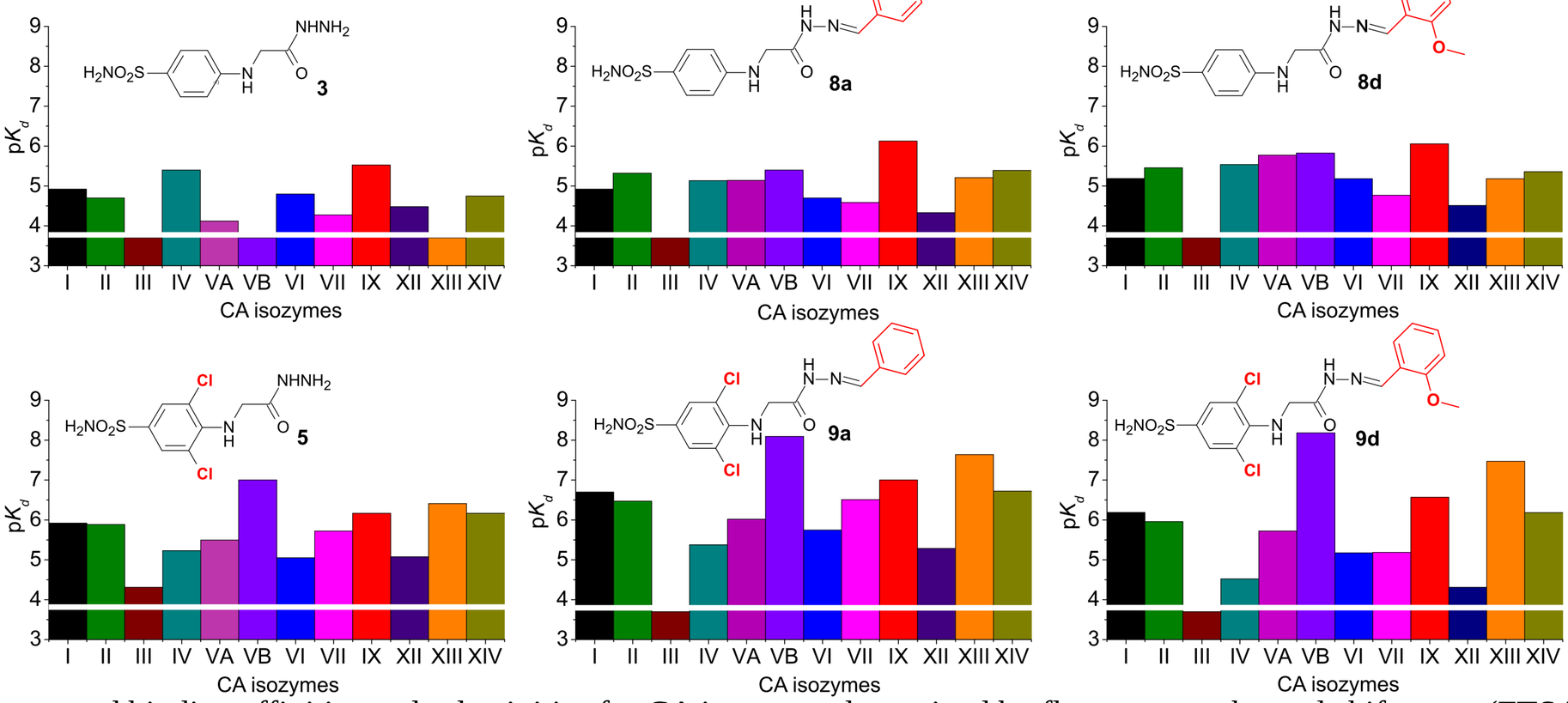

Fig. 2. Compound binding affinities and selectivities for CA isozymes determined by fluorescence thermal shift assay (FTSA)

References

1. Linkuvienė V, Zubrienė A, Manakova et al. *Quarterly Reviews of Biophysics*. 2018. **51**. e10.
2. Frost S., McKenna R. (Ed.) Subcellular Biochemistry. 2014. Springer Netherlands, p. 430.
3. P. A Colinas, *Expert Opinion on Therapeutic Patents* **23**, 761–763 (2013).

Conclusions

- Compounds with chlorine attached to the 3,5-positions of benzenesulfonamide bound stronger to all CA isozymes than their non-chlorinated analogues.
- Compounds **9a**, **9d** and **12** bound to mitochondrial CA VB with a single – digit nanomolar dissociation constant and showed more than 10-fold selectivity towards CA VB over remaining 11 catalytically active human CAs.