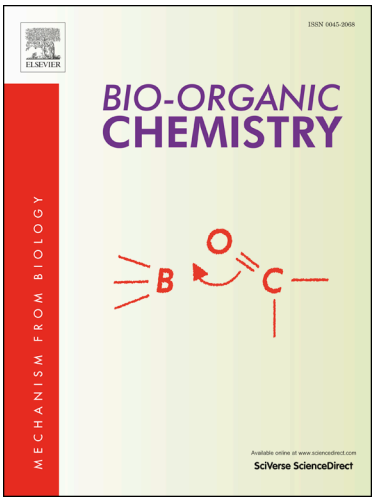

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Synthesis of novel isoindoline-1,3-dione-based oximes and benzenesulfonamide hydrazones as selective inhibitors of the tumor-associated carbonic anhydrase IX.

Alaa A.-M. Abdel-Aziz[a,b*], Adel S. El-Azab[a,c], Mohamed A. Abu El-Enin[b], Abdulrahman A. Almehizia[a], Claudiu T. Supuran[d], Alessio Nocentini[d,*]

[a] *Department of Pharmaceutical Chemistry[a], College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia*

[b] *Department of Medicinal Chemistry [b], Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt*

[c] *Department of Organic Chemistry[c], Faculty of Pharmacy, Al-Azhar University, Cairo 11884, Egypt*

[d] *NEUROFARBA Department, University of Florence, Via Ugo Schiff 6, 50019 Sesto Fiorentino (Florence), Italy.*

Abstract. The synthesis, characterization and biological evaluation of a library of isoindoline-1,3-dione-based oximes and benzenesulfonamide hydrazones is disclosed. The set of hydroxyiminoethyl aromatic derivatives **10-18** was designed to assess the potentiality as zinc-binder for a feebly studied functional group in the field of carbonic anhydrase (CA, EC 4.2.1.1) inhibition. Analogue phenylphthalimmides were linked to benzenesulfonamide scaffold by hydrazone spacers in the second subset of derivatives **20-28** to further investigate the application of the "tail approach" as tool to afford CA selective inhibition profiles. The compounds were assayed for the inhibition of physiologically relevant isoforms of human carbonic anhydrases (hCA, EC 4.2.1.1), the cytosolic CA I and II, and the membrane-bound CA IV and tumor-associated CA IX. The new zinc-binders, both of the oxime and sulfonamide types, showed a striking selective activity against the target hCA IX over ubiquitous hCA I and II, with diverse inhibitory ranges and *ratio* differing the two subsets. With CA IX being a strongly current antitumor/antimetastatic drug target, these series of compounds may be of interest for the development of new, both conventional and unconventional anticancer drugs targeting hypoxia-induced CA isoforms such as CA IX with minimum ubiquitous CAs-related side effects.

Keywords: Isoindoline-1,3-dione; oxime; hydrazone; benzenesulfonamide; carbonic anhydrase inhibition, carbonic anhydrase IX, anti-tumor.

* Corresponding author. Tel.: 00966-53-5991127; fax: 00966-1-4676220; e-mail: almoenes@ksu.edu.sa (A.A.-M. Abdel-Aziz); alessio.nocentini@unifi.it (A. Nocentini)