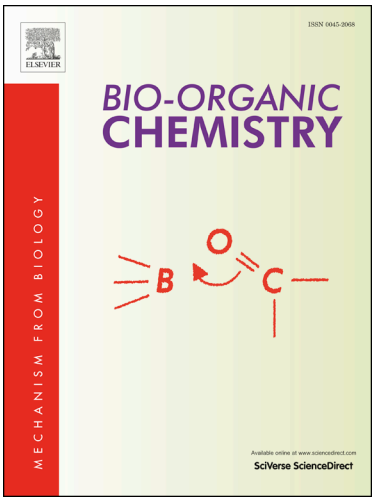

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PII: S0045-2068(18)30785-5
DOI: https://doi.org/10.1016/j.bioorg.2018.09.007
Reference: YBIOO 2504

To appear in: *Bioorganic Chemistry*

Received Date: 29 July 2018
Accepted Date: 7 September 2018

Please cite this article as: W.M. Eldehna, A. Nocentini, S.T. Al-Rashood, G.S. Hassan, H.M. Alkahtani, A.A. Almehizia, A.M. Reda, H.A. Abdel-Aziz, C.T. Supuran, Tumor-associated carbonic anhydrase isoform IX and XII inhibitory properties of certain isatin-bearing sulfonamides endowed with *in vitro* anticancer activity towards colon cancer, *Bioorganic Chemistry* (2018), doi: https://doi.org/10.1016/j.bioorg.2018.09.007

Tumor-associated carbonic anhydrase isoform IX and XII inhibitory properties of certain isatin-bearing sulfonamides endowed with *in vitro* anticancer activity towards colon cancer

Wagdy M. Eldehna[a],* Alessio Nocentini[b], Sara T. Al-Rashood[c], Ghada S. Hassan[d], Hamad M. Alkahtani[c], Abdulrahman A. Almehizia[c], Ahmed M. Reda[e], Hatem A. Abdel-Aziz[f], Claudiu T. Supuran[b,*]

[a]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Kafrelsheikh University, Kafrelsheikh 33516, Egypt.*
[b]*Department of NEUROFARBA, Section of Pharmaceutical and Nutraceutical Sciences, University of Florence, Polo Scientifico, Via U. Schiff 6, 50019, Sesto Fiorentino, Firenze, Italy.*
[c]*Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia.*
[d]*Department of Medicinal Chemistry, Faculty of Pharmacy, Mansoura University, P.O. Box 35516, Mansoura, Egypt.*
[e]*Department of Biochemistry, Faculty of Pharmacy, Egyptian Russian University, Badr City, Cairo, Egypt*
[f]*Department of Applied Organic Chemistry, National Research Center, Dokki, Cairo 12622, Egypt.*

Abstract

Three series of indolinone-based sulfonamides (**3a-f, 6a-f** and **9a-f**) were *in vitro* evaluated as inhibitors of the tumor-associated carbonic anhydrase (CA, EC 4.2.1.1) isoforms hCA IX and XII, using a stopped-flow CO_2 hydrase assay. All the investigated sulfonamides displayed single- or double-digit nanomolar inhibitory activities towards both hCA IX (K_Is: 6.2 – 64.8 nM) and XII (K_Is: 7.1 – 55.6 nM) isoforms. All sulfonamides (**3a-f, 6a-f** and **9a-f**) were *in vitro* examined for their potential anticancer activity against colorectal cancer HCT-116 and breast cancer MCF-7 cell lines. Sulfonamide **9e** was found to be the most potent counterpart against HCT-116 (IC_{50} = 3.67 ± 0.33 µM). Sulfonamide **9e** displayed good selectivity profile for inhibition of the tumor-associated isoforms (CAs IX & XII) over the off-target cytosolic CAs I and II. **9e** was screened for cell cycle disturbance and apoptosis induction in HCT-116 cells. It was found to persuade cell cycle arrest at G_2-M stage as well as alter the Sub-G_1 phase. Also, **9e** induced the intrinsic apoptotic mitochondrial pathway in HCT-116 cells *via* down-regulation of the anti-apoptotic protein Bcl-2 level with concurrent boosting the pro-apoptotic Bax, caspase-9, caspase-3, cytochrome C and p53 levels.