Bioorganic & Medicinal Chemistry Letters 26 (2016) 5867–5870

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and carbonic anhydrase inhibitory properties of novel chalcone substituted benzenesulfonamides

Tayfun Arslan [a,*], Emir Alper Türkoğlu [b], Murat Şentürk [c,*], Claudiu T. Supuran [d,*]

[a] Technical Sciences Vocational School, Giresun University, 28049 Giresun, Turkey
[b] Ağrı İbrahim Çeçen University, Department of Pharmaceutical Technology, 04100 Ağrı, Turkey
[c] Ağrı İbrahim Çeçen University, Science and Art Faculty, Chemistry Department, 04100 Ağrı, Turkey
[d] Universitá degli Studi di Firenze, Dipartimento Neurofarba, Sezione di Scienze, Polo Scientifico, Via Ugo Schiff 6, 50019 Sesto Fiorentino, Florence, Italy

ARTICLE INFO

Article history:
Received 10 October 2016
Revised 4 November 2016
Accepted 7 November 2016
Available online 9 November 2016

Keywords:
Chalcone
Sulfonamides
Carbonic anhydrase
Inhibitors

ABSTRACT

Carbonic anhydrases (CAs, EC 4.2.1.1) are crucial metalloenzymes involved in many bioprocesses, through catalysis of the reversible hydration/dehydration process of CO_2/HCO_3^-. The inhibition of human CA isoforms I and II with a new series of sulfonamide derivatives incorporating substituted chalcone moieties were studied in this study. All these newly synthesized sulfonamides demonstrated important inhibitory profiles to these CA isoforms with K_Is in the range of 9.88 to 55.43 nM, making these compounds interesting leads, with potential applications in medicinal chemistry.

Carbonic anhydrases (CAs, EC 4.2.1.1) are essential metalloenzymes involved in many biochemical/physiological processes.[1] By catalyzing the hydration of carbon dioxide (CO_2) to bicarbonate (HCO_3^-) and protons (H^+), they are deeply involved in pH regulation and biosynthetic processes in which bicarbonate or carbon dioxide are substrates.[2] CAs are present in all living creatures from Bacteria to Eukaria,[3] being encoded by seven phylogenetically unrelated gene families.[4] 15 CA isoenzymes belonging to the α-CA gene family are expressed and were described in humans.[5] Some human (h) CA isoenzymes (hCA I, II, III, VII and XIII) are cytosolic, four forms (hCA IV, IX, XII and XIV) are membrane-bound, two of them, i.e., hCA VA and VB are mitochondrial forms and one form (hCA VI) is secreted in the saliva and milk.[6] The last three forms (hCA VIII, X and XI) are a catalytic proteins.[7]

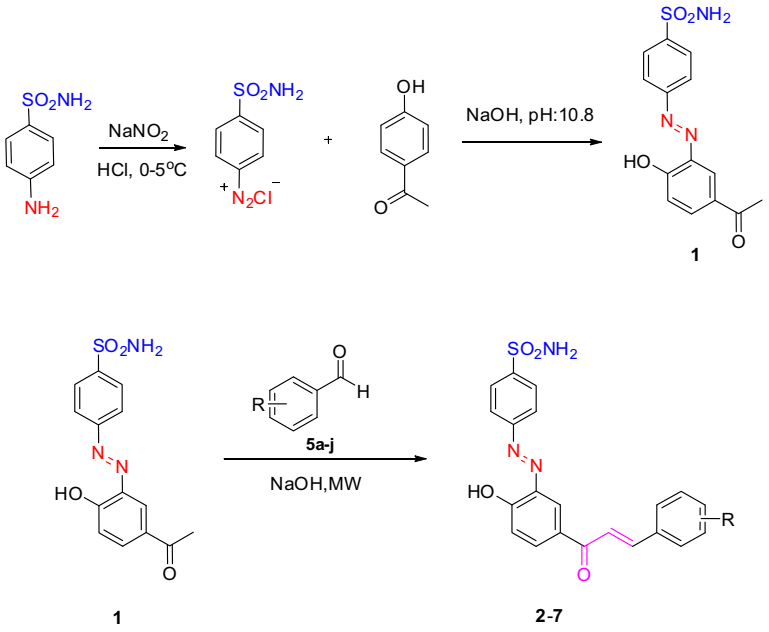
The studies related to inhibition and activation of the CA activity seem to be essential for the treatment of many diseases in which the activity of some isoforms is upregulated. The inhibitors of the two major cytosolic CA forms (hCA I and II) are used as drugs for the treatment of glaucoma and epilepsy for decades.[7] Novel CA inhibitors (CAIs) were designed as potential pharmacological agents for other conditions such as tumors, obesity or as antiinfectives.[8] To date, many compounds have been shown to inhibit hCAs, among which (i) anions,[4c] (ii) bischalcones,[9] (iii) coumarins,[10] (iv) thioureas,[11] (v) nitro compounds,[12] (vi) uracil derivatives,[13] (vii) bromophenols,[14] (viii) sulfamates,[15] etc. An important class of drugs is constituted by the primary sulfonamides, which were proved to inhibit the catalytic activity of all hCAs, by coordinating as anions to the zinc ion from the enzyme active site.[16]

Our groups studied the inhibition of some chromone incorporating sulfonamide moieties, which showed low micromolar/submicromolar inhibitory profile on the activity of some CA isoenzymes, notably hCA I and II.[17] We have extended our earlier results in this study, reporting here a new series of such sulfonamide. This class of pharmacological agents shows many types of bioactivities and are widely used drugs for several clinical applications.[17] In this study, we have purified hCA I and hCA II from human fresh blood and performed *in vitro* inhibition studies using the esterase activity of CA with the newly synthesized sulfonamides ⟨**1** –**7**⟩.

The rationale of investigating sulfonamides as CA inhibitors (CAIs) is due to the fact that the simple benzenesulfonamide ($PhSO_2NH_2$) has been shown to be a competitive inhibitor with both CO_2 and 4-nitrophenyl acetate as substrates for many CAs.[6–8] Sulfonamides bind to CAs by coordinating to the Zn(II) ion from the enzyme active site and thus substituting the fourth, non-protein ligand, a water molecule or hydroxide ion. Acetazolamide (**AZA**), a clinically used compound since 1954, has been crystallized in

* Corresponding authors.
E-mail addresses: tayfunars28@hotmail.com (T. Arslan), senturkm36@gmail.com (M. Şentürk), claudiu.supuran@unifi.it (C.T. Supuran).

http://dx.doi.org/10.1016/j.bmcl.2016.11.017
0960-894X/

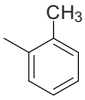
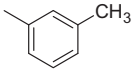
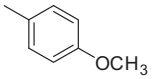
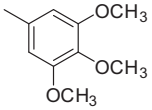
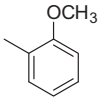
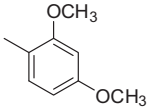
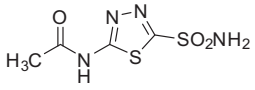


Scheme 1. General synthesis of benzenesulfonamides derivatives.

adducts with many CA isoforms and shows this typical inhibition mechanism.[7]

Inhibition mechanism of CA inhibitors may be understood with X-ray crystal structure. For instance, in the adduct process of hCA II with sulfamide,[18] it is showed that the ligand binds to CA by anchoring its NH functional group to the zinc ion of the CA active site, whereas a network of hydrogen bonds to the NH amide and OH moiety of Thr199 residue, an amino acid found in all α-CAs and essential for the catalytic cycle of CA enzymes, further stabilized the adduct.[18] Only recently, our group performed the

Table 1
hCA I and II inhibition data with sulfonamides **1–7** and clinically used inhibitör (AZA), and the selectivity ratio hCA I over hCA II.

Compound	R	Yield (%)	M.p. (°C)	K_I (nM)		Selectivity ratio (hCAII/hCAI)
				hCA I	hCA II	
1	–	52	155–157	19.10	42.30	2.21
2		64	160–162	24.40	18.25	0.75
3		56	168–170	13.25	20.7	1.53
4		27	202–204	13.05	55.43	4.25
5		45	210–212	21.88	52.17	2.38
6		40	181–183	14.47	31.76	2.19
7		45	175–177	9.88	20.05	2.03
AZA		–	–	250[a]	12.00[a]	0.05

Errors in the range of 2–5% of the shown data, from three different assays.
[a] From Ref. 7.