INHIBITION STUDIES ON A PANEL OF HUMAN CARBONIC ANHYDRASES WITH N1-SUBSTITUTED SECONDARY SULFONAMIDES INCORPORATING THIAZOLINONE OR IMIDAZOLONE-INDOLE TAILS

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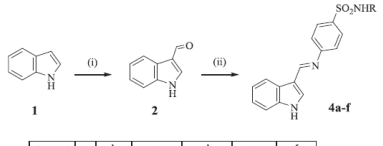
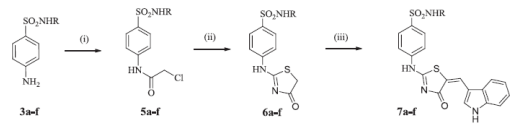
Being the primary sulfonamide among the most efficient zinc binding group (ZBG) to design inhibitors for the metallo-enzymes carbonic anhydrases (CA, EC 4.2.1.1), herein, we propose an investigation on four physiologically important human (h) CAs (hCA I, II, IV, and IX) with N1-substituted secondary sulfonamides incorporating thiazolinone or imidazolone-indole tails. The effect of the functionalisation of the sulfonamide group with five different substitution patterns, namely acetyl, pyridine, thiazole, pyrimidine, and carbamimidoyl, was evaluated in relation to the inhibition profile of the corresponding primary sulfonamide analogues. With most of these latter being nanomolar inhibitors of all four considered isoforms, a totally counterproductive effect on the inhibition potency can be ascribed to N1-functionalisations of the ZBG primary sulfonamide structure with pyridine, thiazole, and pyrimidine moieties. On the other hand, incorporation of less hindered groups, such as sulfonylacetamides and sulfonylguanidines, maintained a certain degree of activity dependent on the tailing moiety, with KIs spanning in the low micromolar range.



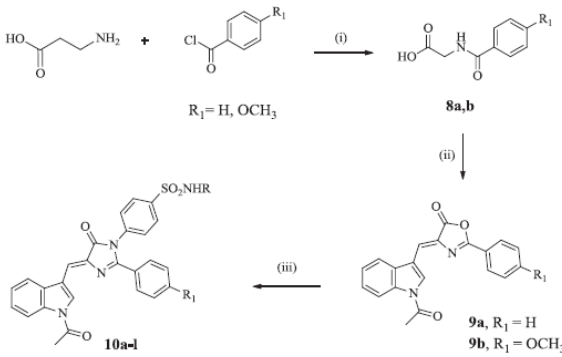
Compound	a	b	c	d	e	f
R	H					

Scheme 1. Synthesis of compounds **4a–f**. Reagents and reaction conditions: i) Phosphorous oxychloride, DMF, 5 °C; (ii) glacial acetic acid.



Compound	a	b	c	d	e	f
R	H					

Scheme 2. Synthesis of compounds **7a–f**. Reagents and reaction conditions: (i) Chloroacetyl chloride, DMF, rt; (ii) Ammonium thiocyanate, absolute alcohol; (iii) Indole-3-carboxaldehyde **2**, fused sodium acetate, glacial acetic acid, reflux.



Compound	a	b	c	d	e	f	g	h	i	j	k	l
R	H						H					
R_1	H	H	H	H	H	H	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3

Scheme 3. Synthesis of compounds **10a–l**. Reagents and reaction conditions: (i) Glycine, 10% sodium hydroxide, ice bath, (0 °C); (ii) Indole-3-carboxaldehyde **2**, acetic anhydride, fused sodium acetate, (100 °C); (iii) The appropriate sulfonamide **3a–f**, glacial acetic acid, fused sodium acetate, (100 °C).