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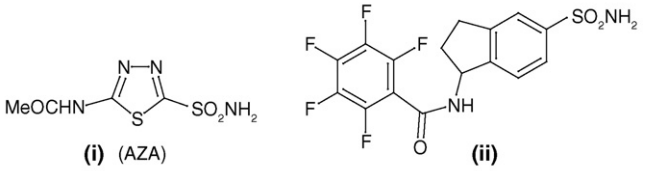
MOLECULES

Novel antitumour agents: indanesulfonamides as selective inhibitors of the tumour-associated isozyme carbonic anhydrase IX

The carbonic anhydrases (CAs) are a family of metalloenzymes involved in the catalysis of CO_2 hydration ($CO_2 + H_2O \rightarrow HCO_3^- + H^+$) and, as a consequence, play an important part in a number of physiological processes such as pH regulation and electrolyte secretion, and in a number of biosynthetic pathways. From the viewpoint of cancer-drug discovery, perhaps the most interesting CA isoform is CA IX; because CA IX has been reported to be prevalently expressed in several human cancer cells but not in their 'normal' counterparts, and high expression levels are related to poor patient prognosis [1]. A further interesting feature of CA IX is that hypoxia in tumours (i.e. low oxygen tension) induces expression of the *CA9* gene via hypoxia-inducible factor-1 (HIF-1), stimulating CA IX to decrease extracellular pH (pH_e); in part, explaining the observation that tumour cells tend to have a lower pH_e than normal cells. Expression of CA IX is also regulated by the von Hippel–Lindau (VHL) tumour suppressor protein.

Previous work in this area has identified small-molecule inhibitors of CA IX [2] such as acetazolamide (AZA; **i**) and sulfonamides, and the indanesulfonamide template has been described as a potent inhibitor of CA I and CA II [3]. Thiry *et al.* [4] have described the synthesis and CA-IX-inhibitory activity of a series of indanesulfonamides containing hydrophobic side-chains, based on a pharmacophore model that was derived from analysis of the CA active site and from the structure of previously reported inhibitors. Evaluation of the inhibitory activities against CA IX compared with isoforms CA I and CA II revealed a number of compounds with potent activity against CA IX and CA II (i.e. low nanomolar K_i) and weak inhibition of CA I. The most selective compound was found to be the pentafluorophenyl derivative **ii**, which was highly potent and selective against CA IX only. The selectivity of compound **ii** for CA IX was rationalized following construction of a CA IX homology model based on the murine CA XIV template, and subsequent active-site-binding studies with **ii** and comparison with a non-selective analogue. The molecular-modelling studies offer the possibility to improve potency and selectivity further for CA IX. Further cellular studies, and the modulatory effect of **ii** in response to chemo- and radio-therapy, are keenly awaited.



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