Importantly, a highly orally available analogue of **MI-63** regresses tumors in multiple xenograft models of human cancer with wild-type p53 at dose-schedules that cause no toxicity to mice.
Conclusions: Our data show that **MI-63** and its potent analogues represent a class of highly promising new anticancer agents and warrant clinical evaluations for the treatment of many different types of human cancers.

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Furan ring-opened 17-hydroxywortmannin analogs as phosphoinositide 3-kinase inhibitors active in human tumor xenograft models

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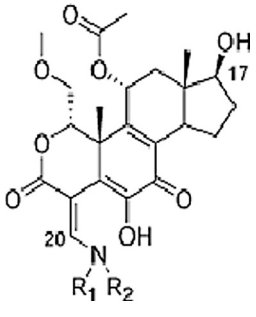
Phosphoinositide 3-kinase (PI3K) is an important target for cancer chemotherapy due to the deregulation of its signaling pathway in a wide spectrum of human tumors. Wortmannin and its analog, 17-hydroxywortmannin (17-HWT), are potent PI3K inhibitors whose therapeutic use has been impeded by inherent defects such as instability and toxicity. Secondary amines react with 17-HWT at the C-20 position to generate furan ring-opened analogs, as shown in the structural formula, with improved properties such as increased aqueous solubility, greater stability, and less toxicity, as evidenced by a higher therapeutic index. 17-HWT is available by the stereoselective sodium borohydride reduction of the natural product wortmannin, available from fermentation. Ring-opened analogs were tested versus the PI3K enzyme (alpha isoform) and in tumor cells deficient in the tumor suppressor gene PTEN (e.g. LNCap). The most potent analogs were then evaluated in human tumor xenograft models in the nude mouse. A variety of different amines (and other nucleophiles) were used containing varying lipophilic and polar groups. Structure activity relationships among these resulting analogs will be presented. In conclusion, ring opening of 17-HWT with secondary amines gives compounds with improved properties (e.g. better stability and reduced toxicity) that are active in human tumor xenograft models in the nude mouse.



166 POSTER

ADME and PK/PD attributes of SB939, a potent orally active HDAC inhibitor

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Histone deacetylase (HDAC) inhibitors are an emerging class of therapeutic agents that induce tumor cell cytostasis, differentiation and apoptosis in various hematological and solid malignancies. They are believed to exert their anti-tumor activity through chromatin remodeling and gene expression modulation that affect cell cycle and survival pathways. In the literature, there is very little information on the ADME attributes of the HDAC inhibitors and their pharmacokinetics in preclinical species. In our HDAC program, *in silico*, *in vitro* and *in vivo* ADME (Absorption, Distribution, Metabolism and Elimination) studies are incorporated in the screening cascade with a view to discovering compounds with optimal ADME properties. These ADME results provided insight to the medicinal chemists in the lead optimization process and led to the identification of SB939 as a promising drug candidate. SB939 exhibits high metabolic stability in human liver microsomes with no major inhibition or induction of major drug metabolizing cytochrome P450 isozymes. The compound has good aqueous solubility and shows high cell permeation in the Caco2 screen. The pharmacokinetic parameters of SB939 were better than the other HDAC inhibitors in clinical trials. In a preclinical tumor model, the superior pharmacokinetic parameters of SB939 correlated well with effects on a pharmacodynamic marker (H-3 acetylation) as well as anti-tumor efficacy.

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A pyrazyne scaffold for the generation of novel inhibitors of B-RAF

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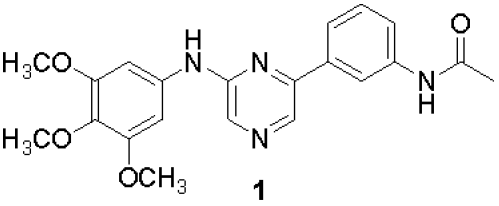
B-RAF is a serine/threonine kinase mutated in 7% of cancers, with a incidence of 70% of melanomas. Mutated B-RAF is oncogenic and expression of the activated mutant V600E leads to increased proliferation and survival of malignant cells. As a result of a Biofocus high-thoughput screen of a 23,000 compound chemical library, 2-(3,4,5-trimethoxy-phenylamino)-6-(3-acetamidophenyl)pyrazine **1** was identified in as a B-RAF inhibitor (IC_{50}(B-RAF) = 3.5 μM). Medicinal chemistry around the trimethoxy phenyl ring identified several sub-micromolar B-RAF inhibitors, for example the 5-oxazolylphenyl analogue **2** (IC_{50}(B-RAF) = 800 nM). The compounds were screened for cellular activity: phospho-ERK inhibition and antiproliferative effects. Valuable SAR data were obtained for the development of this novel class of pyrazine-based compounds as B-RAF inhibitors.



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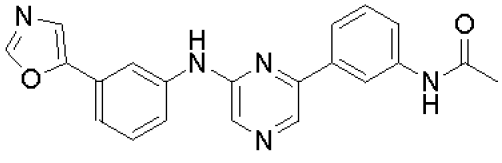

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Design, synthesis and evaluation of novel, selective carbonic anhydrase IX inhibitors as anti-cancer agents

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Carbonic anhydrases (CA's) are a family of Zn-containing isozymes. CA's catalyse the hydration of carbon dioxide to proton and bicarbonate and are primarily involved in pH homeostasis. Of the 15 different isozymes known to date, CAIX has been identified as being tumour-specific, where it is over-expressed in many solid tumours (Zavada, et al, 1992). The role of CAIX in tumour has been attributed to poor prognosis and increased metastasis, which may be due, in part, to the increased acidification of the extra-cellular milieu. It is proposed that selectively inhibiting CAIX decreases the metastastic incidents and increases the uptake of conventional anticancer agents specifically into solid tumours (Stubbs, et al, 2000).
Here, we report synthesis and enzymatic evaluation of a select series of non-toxic, but potent CAIX inhibitors. Initially, a 3D homology model of CAIX was constructed (48% sequence identity) using the Swiss model protocol (Peitsch, et al, 1993). The compounds were then designed based on the skeletal structure of known potent CA inhibitors and on the active site geometry. The synthesised compounds were evaluated using a HTS screen against purified human CAI, CAII and CAIX protein (René, et al, 2005).
Many of compounds synthesised showed good inhibition towards the CAIX protein (micro-molar range). Two compounds, in particular, 2-nitro-N,N-bis(2-chloroethyl)benzenesulfonamide (IC50 [CAI: 776 μM]; [CAII: