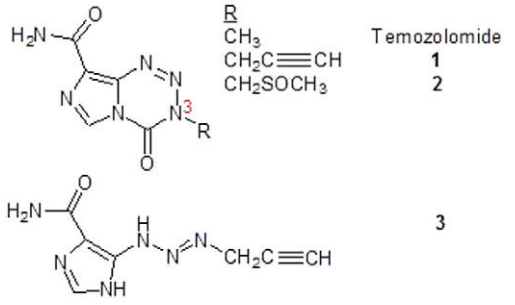
treatment for MGMT positive GBM tumors and possess broader spectrum anticancer activity.



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Amino-carbonyl substituted fused imidazoles: potent, selective and orally bioavailable inhibitors of PI3K

J. Pastor[1], S. Martínez[1], R.M. Álvarez[1], A.I. Hernández[1], C. Varela[1], A.B. García[1], O. Rabal[1], M.T. González-Granda[1], J. Fominaya[1], J.R. Bischoff[1]. [1]*Spanish National Cancer Research Centre, Experimental Therapeutics, Madrid, Spain*

The phosphatidylinositol 3-kinase (PI3K) signaling pathway plays a crucial role in cell growth, proliferation and survival. This pathway is activated in a variety of solid and non-solid tumors. In many instances this is due to either activating mutations in the catalytic subunit of PI3Ka, p110α or inactivating mutations or deletions of the tumor suppressor PTEN.
In addition, persistent signaling through the PI3K/Akt pathway has been shown to be a major mechanism of resistance to therapy. Hence, PI3K, and in particular the p110α subunit of PI3K, is a highly promising candidate for cancer therapy.
Using a rational drug design strategy, we identified a novel fused imidazoles series, with potent activity against PI3Ka. Depending on the C-2 substitution fragment we have observed different isoforms profiles. Here, we describe the exploration and biological characterization of C-2 amino-carbonyl fused imidazoles series, reporting its SAR/SPR (ADME).
We identified lead compounds with a potency in the low nanomolar range *vs.* p110α, b and d and selectivity against other related PIKK family members such as mTOR, DNA-PK or ATR. In general, this series show high selectivity versus a panel of 24 protein kinases. The compounds display cellular activity by blocking PI3K signaling, S473 P-Akt in U2OS cells, in the low nanomolar range.
Finally, we will show in vivo PK data for ETP-992.

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Preclinical characterization of 4SC-202, a novel isotype specific HDAC inhibitor

S.W. Henning[1], R. Doblhofer[1], H. Kohlhof[1], R. Jankowsky[1], T. Maier[2], T. Beckers[2], M. Schmidt[2], B. Hentsch[1]. [1]*4SC AG, Martinsried, Germany;* [2]*Nycomed GmbH, Konstanz, Germany*

Alterations of protein acetylation regulated by histone acetyltransferases (HAT) and histone deacetylases (HDAC) are associated with various types of cancer and thus HDACs have emerged as attractive drug targets for neoplastic disease. The family of HDACs is divided into four classes, of which three consist of Zn^{2+}-dependent enzymes. Several pan-HDAC inhibitors are currently under clinical investigation in a broad range of tumour indications. Based on their chemical structure they can be categorized into hydroxamates, benzamides, cyclic peptides, fatty acid analogs and ketons. While promising, these compounds have exhibited side effects that might limit their clinical potential. It might be possible to reduce some of the toxicity associated with HDAC inhibition by specifically targeting only selected HDAC isoforms.
4SC-202 is a novel orally available class I specific HDAC inhibitor of the benzamide type compound family that harbors additional strong anti-mitotic potential associated with cell cycle arrest and pronounced induction of apoptosis. This HDAC inhibitor shows strong anti-tumoural activity *in vitro* against a broad range of human cancer cell lines with submicromolar activity on tumour cell growth and also *in vivo* after oral application in relevant xenograft animal models. It has been well tolerated in a number of toxicological studies in rodent and non-rodent species. A clinical phase I First-in-Man trial with 4SC-202 in hematological malignancies is currently under preparation and is planned to commence in H2 2010. A comprehensive overview of the preclinical characterization of this novel class I selective HDAC inhibitor and an outlook on the planned first clinical application to man will be presented.

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Allelic loss on p16, BRCA1, BRCA2, PTEN and p53 genes in sporadic invasive ductal carcinomas

C. Park[1], S. Choi[1], S. Cho[2]. [1]*Hallym University Kangdong Hospital, Surgery, Seoul, Korea;* [2]*Hallym University Kangdong Hospital, Pathology, Seoul, Korea*

Background: Breast cancers show various molecular and genetic alterations in its development and progression. The major tumor suppressor genes (TSGs) such as p16, PTEN and p53 may play important roles in cell cycle regulation, apoptosis and the regulation of the expression of other genes as well as tumor suppression. BRCA1 and BRCA2 genes are TSGs involved in familial breast cancer. Loss of heterozygosity (LOH), novel mechanisms of carcinogenesis, has been known to be a useful prognostic factor in many kinds of malignant tumors. LOH is related to the allelic loss of various TSGs. This study was planned not only to evaluate LOH of 5 TSGs in sporadic invasive ductal carcinomas (IDCs) and correlate these results with the clinicopathological factors, but also to investigate the role of BRCA1 and BRCA2 TSCs.
Material and Methods: LOH analysis was carried out using a polymerase chain reaction with 20 polymorphic microsatellite markers (including D9S162, TP53, D13S290, D17S1323, D10S541, etc) of 5 TSGs in 50 surgically resected tumors and their non-tumorous counterparts. IDC case having three or more LOH was grouped as LOH-H.
Results: There was no detectable LOH in normal tissue. At least one LOH was detected in 88% of 50 cases of IDCs. LOH results detected on all chromosomes showed statistical discrimination between benign tumor and malignant tumor. LOH rates of p16, BRCA1, BRCA2, p53 and PTEN TSGs were detected in 38%, 32%, 42%, 56 and 48%, respectively. Especially, LOH rates on D13S290, D17S1323 markers were 25.0% and 30.2%, respectively. LOH of p16, BRCA1 and PTEN TSGs inversely correlated with tumor grade 1. Low LOH detection rate on BRCA2 gene was measured in T1 tumor and stage I. LOH of p53 and PTEN TSGs correlated well with the lymph node metastasis and stage. The LOH-High results correlated well with the tumor size, lymph node metastasis and stage.
Conclusions: These results suggest that LOH of BRCA1, BRCA2 as well as 3 major TSGs may contribute to the development and invasion of IDCs. Also combined use of various LOH markers and application of LOH-H concept may help in deciding prognosis of IDCs.

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Is sorafenib effective in colorectal cancer?

C. Schimanski[1], M.M. Markus Moehler[1]. [1]*University of Mainz, First Dept of Internal Medicine, Mainz, Germany*

Background: We initiated this preclinical study in order to analyze if tyrosine kinase inhibitor sorafenib might be an effective therapeutic option in human colorectal cancer.
Material and Methods: The expression status of *VEGFR1−3*, *PDGFRα/β* and *EGFR1* was analysed in 100 colorectal cancer samples and in 4 different CRC cell lines. Expression was correlated with clinico-pathologic parameters. The K-ras, Raf, PI3K and PTEN mutation status of cell lines was obtained by PCR-RFLP or sequencing, respectively. The effect of increasing sorafenib doses on proliferation, apoptosis, migration and invasion was analysed *in vitro*. In addition, we analysed the efficacy of sorafenib monotherapy and different combination therapies (sorafenib + 5-FU, Irinotecan or oxalipaltin) *in vitro* and *in vivo* in a xenograft tumor mouse model.
Results: The majority of colorectal carcinoma samples revealed a *VEGFR1* (92%), *PDGFRα* (83%), *EGFR1* (88%) and *PDGFRβ* (62%) expression, whereas *VEGFR2* (51%), VEGFR3 (50%) were expressed only in half of all samples. Expression of VEGFR3 and *PDGFRα* significantly correlated with lymphatic metastatic disease ($P = 0.01$ and $P = 0.05$, respectively), whereas VEGFR3 did correlate with distant metastases ($P = 0.05$). Human colorectal cancer cell lines revealed varying expression levels of TKs. In vitro, sorafenib did impact on growth of SW480 and HT29 cells but not on SW620 or Caco2 cells. Migration was decreased in all cell lines analysed, while sorafenib did not modulate invasion in any cell line. Combination of sorafenib and 5-FU, irinotecan or oxalipaltin was not superior to a sorafenib mono-therapy and even seemed to stimulate proliferation in some cell lines. Similarly, the combination of 5-FU and sorafenib was inferior to a 5-FU or sorafenib monotherapy, in an *in vivo* mouse model. Response did not correlate with the mutation status of K-ras, Raf, PTEN or PI3K. Nor did we observe any evident association of response with the expression of pPI3K/PI3K, pAKT/AKT, mTOR/pmTOR or pMEK/Mek. However, responsive cell lines (SW480 and HT29) decreased AKT expression upon sorafenib exposition, which was not observed in resistant cell lines (Caco2, SW620).