in panels of human tumor cell lines. Activities of the cerium complex KP776 and the lanthanum complex KP772 are similar to each other with IC_{50} values mainly in the low micromolar range. In pairs of chemosensitive parental tumor cells and P-glycoprotein- or MRP1-overexpressing cell clones derived from them as *in vitro* models of multidrug resistance collateral sensitivity to the latter two compounds has been observed. All three compounds produce DNA interstrand cross-links, but with much lower efficiency than platinum drugs like cisplatin. The lanthanum complex KP772 induces DNA strand breaks without altering the secondary structure of DNA. For the complexes KP1255 and KP776 neither induction of DNA strand breaks nor alterations of the secondary structure of DNA could be detected. In conclusion, it remains doubtful whether DNA is the critical target site of these novel agents and further possible mechanisms of action are being explored.

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Oxa-aza-benzo[de]anthracenes: design, synthesis and evaluation of a structurally new class of dual topoisomerase inhibitors

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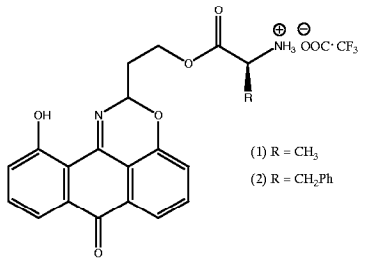
Human DNA topoisomerase I and II are valid targets in cancer therapy and inhibitors of these enzymes include the clinically active doxorubicin (topo II) and the camptothecins topotecan and irinotecan (topo I). The clinical utility of the camptothecin class of compounds is limited by the rapid *in vivo* conversion to inactive metabolites as a result of inherently labile structural features of the active drug molecules and the ease of reversibility of cleavable complex formation. Towards the design of non-camptothecin inhibitors of topo I with increased structural stability, and which also target topo II thereby potentially circumventing acquired drug resistance associated with altered expression of a single topoisomerase, we report the rational design and synthesis of a series of oxa-aza-benzo[de]anthracenes with angular ring systems that do not bind strongly to DNA.



The 2H-3-oxa-1-aza-benzo[de]anthracen-7-ones (1) and (2) are representatives of a new class of dual topo I and II inhibitors with cytotoxic activity against human and animal cell lines *in vitro*; for example the L-alanine conjugate (1) is active against the human leukaemic HL60 cell line (IC_{50} 7μM) and completely inhibited the topo I and topo II-mediated relaxation of supercoiled pBR322 DNA at 50 and 25μM respectively, as shown by changes in the electrophoretic mobility of the plasmid *in vitro*. Furthermore (1) stimulated topo I-mediated DNA cleavable complex formation at 25μM, comparable to camptothecin at 10μM. The chemosensitivity and enzyme inhibitory properties are modulated by the nature of the amino acid sidechain (R-group). Correlations are drawn between chemical structure, cytotoxic potency, DNA binding and topoisomerase I inhibition for this novel class of inhibitor that lacks the structural lability of the camptothecins.

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Synthesis and evaluation of renal dipeptidase inhibitors as biomarkers for colon cancer

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Colon cancer is the second most common cancer in the U.S. and kills more than 50,000 people each year, but it is also one of the most preventable and curable cancers. The best prevention is getting screened on a regular basis. With regular screening, precancerous polyps can be detected early and removed, thus preventing the development of colon cancer in the first place. Current screening tests such as sigmoidoscopy, colonoscopy and detection of fecal occult blood have significant problems which have stimulated the search for more specific non-invasive tests for the early detection of colorectal cancers. In recent serial analysis of gene expression (SAGE) studies carried on normal, adenomatous and cancerous colonic epithelium, the gene renal dipeptidase (RDP) was found to be overexpressed in both benign and malignant tumors compared with normal colonic epithelium. RDP has been extensively analyzed with respect to its catalytic mechanism and inhibition kinetics by variety of synthetic inhibitors. RDP is unique among the dipeptidase in that it can cleave amide bonds in which the COOH terminal partner is a D-amino acid, providing an excellent opportunity for the development of specific probes for its detection *in vivo*. Based on these findings we designed and synthesized alkylaminophosphonic acid derivatives with iodinated aromatic ring as one of the side chains as inhibitors of RDP, in order to use them as biomarkers to detect colon cancer at earlier stage. The Ki values of the substrates were determined using colon cancer lysate *in vitro* and were in the range of 0.6-10 nM. The synthesis of 125iodine alkylaminophosphonic acid is under way. A full update of the enzyme assay results of radiolabelled molecules will be provided at the meeting.

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WP744, a novel anthracycline highly active against STI-571-resistant tumors

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STI-571, a BCR-ABL inhibitor, is effective in chronic myelogenous leukemia, but advanced disease often progresses despite therapy, suggesting that combinations of STI-571 with another agent may be required to control disease progression. We tested one such agent-WP744, a novel anthracycline with greater proapoptotic and cytotoxic properties than its parent compound, doxorubicin (DOX). WP744 has been tested against a panel of DOX-sensitive and MDR-type leukemia and solid tumor cell lines, and has also shown to inhibit colony formation of blasts isolated from fresh bone marrow samples of patients with acute myelogenous leukemia. In this study, we found that WP744 was active not only against the STI-571-resistant cell line K562-R, but also against 4 cell lines (WDT-1, WDT-2, WDT-3, and WDT-4) isolated from peripheral blood of patients with advanced chronic myelogenous leukemia that had progressed after STI-571 therapy. In all of these cell lines, WP744 inhibited cell growth and induced apoptosis to a greater extent than did DOX. These results suggest that WP744 may be effective in treating advanced leukemia that has progressed after STI-571 therapy.

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The synthesis and biological evaluations of n-aminotetrahydropyridines as anticancer agents

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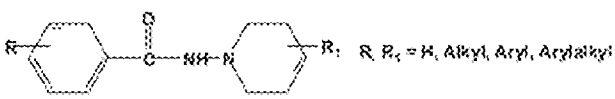
The objective of our research is to develop effective chemotherapeutic agents that can be utilized for the treatment of lung and colon cancers. The role of non steroidal anti-inflammatory agents (NSAIDs) such as aspirin, piroxicam, and sulindac in colon cancer has been well-documented in epidemiological and animal studies. Accumulating evidence indicates that the inhibition of colon tumor development by NSAIDs is mediated through the modulation of arachidonic acid metabolism via the cyclooxygenase enzymes, which in turn inhibit immune responsiveness.



The increased expression of cyclooxygenase-2 (COX-2) enzyme has been reported to correlate with the malignant changes observed in a variety of human cancers, including colorectal, gastric, esophageal, brain, and lung tumors. Our earlier published work established that the N-aminocarbonyl-1,2,3,6-tetrahydropyridine analogs we synthesized were effective non steroidal anti-inflammatory agents with strong cyclooxygenase-1 (COX-1) and (COX-2) inhibitory activities. It was of interest to us to investigate if these analogs showed any anticancer activities. Dry substituted pyridines were reacted with 1-chloro-2,4-dinitro benzene under reflux using acetone and gave invariably crystalline N-(2,4-dinitrophenyl)pyridinium chloride salts. The salts were further reacted with benzoyl hydrazides or benzene sulfonyl hydrazides to furnish an anilino derivative which hydrolyzed in wa-