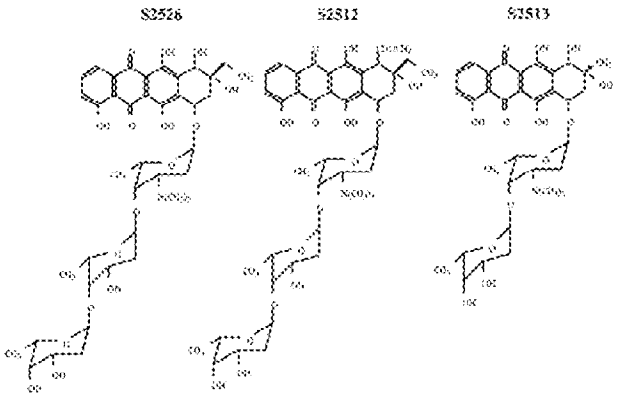

The structure-activity data of the novel compounds suggest that the 10-carbomethoxy moiety plays a role in the inhibition of topoisomerase II and arresting the cell cycle at G1. Additionally, we observed that the lack of an amino sugar residue resulted in diminished topoisomerase inhibition. Preliminary *in vitro* cytotoxicity tests revealed three compounds, S2512, S2513 and S2526, that were comparable with the clinically used anthracyclines daunorubicin, doxorubicin and aclarubicin. These drug candidates were further analysed in a broader panel of cancer cell lines. One of the compounds, S2512, showed particularly high activity against all the cell lines *in vitro*, whereas another one, S2513, was more active *in vivo* against mouse leukaemia and solid tumours.

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Application of combinatorial chemistry for the identification of pyran-4-one and thiopyran-4-one inhibitors of DNA-dependent protein kinase

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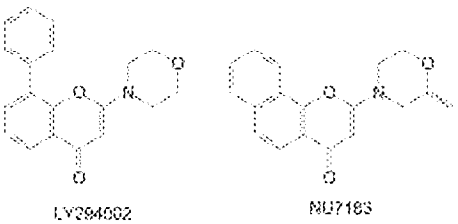
DNA-dependent protein kinase (DNA-PK) detects and initiates repair of DNA double strand breaks (DSBs), and therefore inhibitors of this enzyme are potential radio- and chemo-potentiators in the treatment of cancer. Utilising the non-specific inhibitor LY294002 (DNA-PK; IC_{50} = 1.0 μM, PI-3 K; IC_{50} = 2 μM) as the structural basis for a pharmacophore mapping approach, chromen-4-ones and pyrimidoisoquinolinones have been developed, which are more potent and selective as DNA-PK inhibitors than the lead compound. Thus, the benzochromenone NU7163 has been found to exhibit excellent selectivity for DNA-PK (IC_{50} = 0.2 μM) over the related kinases ATM (IC_{50} = 100 μM) and PI-3 K (IC_{50} = 20 μM) (Griffin et al, Proc Amer Assoc Cancer Res, 43:4210, 2002). Further refinement of the pharmacophore model has resulted in the identification of pyran-4-one and thiopyran-4-one inhibitors, which retain the potency and selectivity of the analogous chromen-4-ones. These include the pyran-4-one NU7074 (DNA-PK; IC_{50} = 0.2 μM, PI-3 K; IC_{50} = 18 μM). To assist the rapid development of structure-activity relationships for these new templates, we have employed multiple parallel synthesis to prepare small chromenone and thiopyranone libraries bearing a range of substituents.



These studies have led to the identification of interesting novel compounds in both series, and have provided an insight into structural requirements for inhibitors of the PI-3 kinase family of enzymes.

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4-Alkoxy-2,6-diaminopyrimidine derivatives: inhibitors of cyclin dependent kinases 1 and 2

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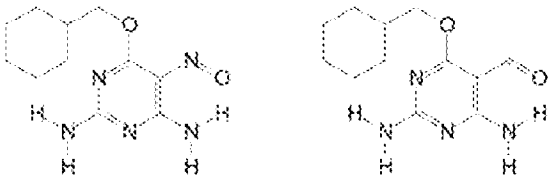
The cyclin-dependent kinases (cdks) are a family of serine-threonine kinases that play a crucial role in cell cycle control. Progression of cells through the cell cycle is strictly regulated by the sequential activation and deactivation of cdks, and loss of cell cycle control, through aberrant cdk activity, leads to unrestrained proliferation. Hence, the identification of potent and selective cyclin dependent kinase inhibitors is of interest in the search for novel potential anti-cancer agents. The cdk inhibitor NU6027, 4-cyclohexylmethoxy-2,6-diamino-5-nitrosopyrimidine (IC_{50} vs. cdk1/cyclinB1 = 2.9 $\pm$ 0.1 μM and IC_{50} vs. cdk2/cyclinA3 = 2.2 $\pm$ 0.6 μM), was used as the foundation for the design of a series of 4-alkoxy-2,6-diamino-5-nitrosopyrimidine derivatives. We have successfully synthesised and evaluated a series of pyrimidines as potential inhibitors of cdks 1 and 2; and probed structure-activity relationships relative to NU6027. The introduction of simple alkoxy- or cycloalkoxy- groups at the O4-position was tolerated, with the 4-(2-methylbutoxy)-derivative (IC_{50} vs. cdk1/cyclin B1 = 12 $\pm$ 2 μM and cdk2/cyclin A3 = 13 $\pm$ 4 μM) retaining activity. Substitutions at the N6-position were not tolerated, and replacement of the 5-nitroso substituent with ketone, oxime and semicarbazone groups effectively abolished activity.



Surprisingly, NU6055 (2,6-diamino-4-cyclohexylmethoxy-pyrimidine-5-carbaldehyde), where the 5-nitroso group of NU6027 is replaced by an isosteric 5-formyl substituent, was significantly less active than the parent compound (IC_{50} vs. cdk1/cyclinB1 = 35 $\pm$ 3 μM and cdk2/cyclinA3 = 43 $\pm$ 3 μM). A comparison of the crystal structures of NU6027 and NU6055 bound to monomeric unphosphorylated CDK2, revealed differences in the binding orientations of the two inhibitors. Notably, while an intramolecular H-bond occurs between the 5-nitroso and 6-amino groups of NU6027, the corresponding interaction is not observed with the 5-formyl substituent of NU6055. Thus the parent compound, NU6027, still remains the optimal basis for future structure-activity studies for cdk inhibitors in this series.

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Studies on the cellular uptake and cleavage of nucleoside analogues conjugated to motexafin gadolinium

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Introduction: Motexafin gadolinium (MGd, Xcytrin®) has been shown to enhance the efficacy of radiation in animal tumor models and is currently in advanced stage clinical development as an adjuvant to radiation therapy. MGd selectively localizes in tumors and has recently been demonstrated to enhance the effectiveness of the redox active drugs bleomycin and doxorubicin in preclinical models. On the basis of these data, we have investigated further possible synergy between MGd and other antineoplastic agents. One such compound, 5-fluorouracil (5-FU), is an important agent in the therapy of selected solid tumors. However, the therapeutic effect of 5-FU is limited due to the high clearance of the drug, with only 5% to 10% entering anabolism into active compounds such as the nucleoside 5-fluoro-2′-deoxyuridine (FdUrd). We have attempted to improve the biolocalization of FdUrd, and thus enhance its therapeutic index, by conjugating it with MGd through an enzymatically cleavable phosphodiester linkage.