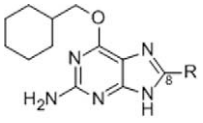
quantum mechanical energy calculations to identify suitable C-8 groups. Addition of a 2-methylphenyl or 2-chlorophenyl group at C-8 restored the potency of this series of 'reverse' binding mode compounds to that of NU2058, providing a novel starting point for inhibitor design. The synthesis, biological evaluation and structural biology of these CDK2 inhibitors will be discussed.



1; R = H
2; R = $CH(Me)_2$

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Optimisation of tetrahydroisoquinoline based microtubule disruptors as anti-cancer agents

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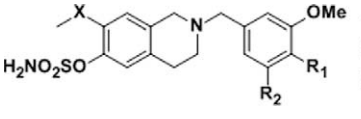
We outline the discovery and optimisation of new microtubule disruptors with *in vivo* anti-tumor activity. Translation of the SAR from a steroidal series of microtubule disruptors led us to identify a series of tetrahydroisoquinoline (THIQ) based systems which exhibit a similar activity profile. Of this new series, 2-(3′,4′,5′-Trimethoxybenzyl)-7-methoxy-6-*O*-sulfamoyl THIQ 1 proved especially potent in both *in vitro* (GI_{50} [DU-145] 297 nM) and *in vivo* experiments. Herein, we describe the results of optimisation at C-6 and C-7 of the THIQ core and assessment of other polymethoxylated *N*-benzyl systems.
Variations at the N-2 and C-6 positions were achieved by alkylation, esterification and etherification. Friedel Crafts acylation of C-7 and functional group interconversion allowed access to various C-7 alkyl and alkoxy derivatives. The various dimethoxybenzyl compounds proved similar in activity to the lead compound 2 (GI_{50} 2.1 mM) in the *N*-mono-methoxybenzyl series while, apart from the 3′,4′,5′-trimethoxybenzyl compound 1, only 2′,4′,5′-trimethoxybenzyl substitution delivered sub-micromolar activity. Investigations of the effect of C-6 substitution proved more fruitful. In contrast to the SAR observed for 2 where the sulfamate group is essential for activity, the 6-OH, with the 6-*O*-acyl and 6-*O*-mesyl derivatives of 1 displayed similar or improved activity to the parent compound (GI_{50}s range from 650 to 220 nM). The 6-*O*-methyl derivative, in contrast, proved completely inactive, highlighting the importance of a H-bond donor directly attached to C-6 or a H-bond acceptor projecting further out from this position. The most pronounced improvement in activity was obtained from exploration of C-7 substitution. In the 3′,4′,5′-trimethoxybenzyl series isosteric replacement of methoxy with ethyl delivered a 7-fold improvement in activity (3 GI_{50} 41 nM). Intriguingly, the corresponding phenol proved significantly active suggesting different binding modes operate for the phenol and sulfamate derivatives since the H-bond acceptor properties of the C-7 substituent of the former are clearly important. Incorporation of a C-7 ethoxy group meanwhile proved detrimental for both sulfamate and phenol derivatives. The same transformations were made to 2, though no improvement in activity was obtained.
In order to establish the potential of these compounds as anti-tumor agents their activity in the RPMI-8226 multiple myeloma xenograft model was assessed. The >75% inhibition of tumor growth observed (3 p.o. 40 mg/kg, 28 d) in this preliminary study augers well for the development of this class of anti-cancer agents.



1 X = O, R_1 = R_2 =OMe
2 X = O, R_1 = R_2 = H
3 X = CH_2, R_1 = R_2 =OMe

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Stereoisomerism significantly impacts on the anticancer activity of novel oxaliplatin analogues in vitro and in vivo

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Background: Aim of this study was to compare the anticancer properties of two oxaliplatin derivatives (KP1537, KP1691) in vitro and in vivo which differ only in the orientation of the methyl substituent at the cyclohexane ring (equatorial and axial, respectively).
Methods: Cytotoxic/antiproliferative effects were tested against selected human cancer cell lines by MTT analysis. Platinum accumulation was determined by ICP-MS. For in vivo experiments, cells were transplanted i.p. (leukemic) into immuno-competent or immuno-deficient mice.
Results: In vitro both oxaliplatin analogues exerted cytotoxic/cytostatic activity with IC_{50} values in the low μM range, with those for KP1691 beeing significantly lower in comparison to oxalipaltin. In contrast, KP1537 was moderately less active. KP1691 accumulated in tumour cells to the same extend as oxaliplatin. Surprisingly, KP1537 was taken up more rapidly and accumulated over time to 3-fold higher intracellular concentrations. However, the distribution between nuclear and cytosolic compartments was similar between all three platinum drugs. Remarkably, first in vivo experiments demonstrated that both novel substances were less toxic than oxaliplatin resulting in an altered therapeutic window. Generally, all compounds tested prolonged the survival of leukemia-bearing mice, but to different extents. KP1691 was least active, whereas oxaliplatin treatment resulted in an increase in life-span (ILS) by about 100% and 1/5 long-term survivor (LTS). Unexpectedly, the in vitro less active compound KP1537 induced a stronger ILS (>300%) and 3/5 LTS. Furthermore, the impact of the immune system was tested. As known for oxaliplatin, the novel compounds were more active in an immuno-competent background.
Conclusion: Taken together, these findings demonstrate that small sterical changes can have major impacts on the activity of anticancer metal complexes. Thus, the axial methylated KP1691 is more active in vitro but obviously does not efficiently reach its molecular target in vivo. In contrast, the equatorial methylated KP1537, which is less active in vitro, exerts very promising anticancer properties in vivo. Several aspects, including the higher accumulation rates, less adverse effects and the higher in vivo anticancer activity of KP1537 as compared to oxaliplatin, suggests further (pre)clinical development of this novel oxaliplatin analogue.
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Regulation of uridine phosphorylase-2 redox-control mechanism to improve capecitabine selectivity

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The key for a successful chemotherapy agent is the selectivity and specificity for tumor tissue sparing the surrounding normal tissues from toxic anti-proliferative effects. Few agents have been designed to be selectively activated in tumor tissue, one of them is the 5-fluorouracil (5-FU) pro-drug Capecitabine. Capecitabine undergoes a 3-step activation process, initially hydrolysis of the carbamate side-chain by the hepatic carboxylesterases and eventually metabolized from 5′-deoxy-fluorouridine to 5-FU mainly in the tumor tissue that presents an increased phosphorolytic activity due to an elevated presence of the two phosphorolytic enzymes: uridine and thymidine phosphorylases. Several organs and tissues, including liver, express the same two phosphorolytic enzymes resulting in the activation to 5-FU with consequent toxic effects.
In mammalians Uridine Phosphorylase (UPP) is present in two isoforms: UPP1 and the more recently characterized UPP2. Human UPP2, a 317 aa. protein of 35 kD molecular mass, is 60% identical to human UPP1, while murine UPP2 is 85% identical to human UPP2. UPP-2 has broader substrate specificity than UPP1. In addition to uridine and deoxyuridine, UPP-2 utilizes thymidine as substrate. However, no phosphorolytic activity was detected when the enzyme was incubated with adenosine, cytidine, guanosine, deoxyadenosine, deoxycytidine or guanosine. In humans the protein is expressed in kidney, liver and spleen while in mouse UPP2 is present in liver and in much less amount in kidney and brain.
We have completed the crystallographic structure determination of hUPP2, having collected a 1.5Å dataset at SSRL and phased the data using Molecular Replacement, searching with a homology model of hUPP2 constructed