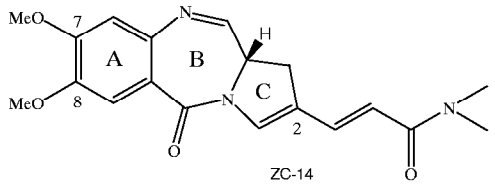

through NMR coupling constants.ZC-14 is remarkably cytotoxic in a number of cell lines with,for example,GI50 values of between 9 and 52 nanomolar in MALME3M, HCT116,SKOV3,SKMEL28,H460 and MCF7 cell lines. The complete synthesis and full *in vitro* evaluation of ZC-14 will be described and compared to a series of closely related analogues.DNA footprinting studies are currently underway to elucidate the effect of the extended C2-acrylamido side chain on sequence-selectivity,and these results will be described.

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Design and optimization of topoisomerase poison conjugates of triple helix-forming oligonucleotides for sequence-specific DNA cleavage

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To achieve a sequence-specific DNA cleavage by topoisomerase I, derivatives of the antitumor drug camptothecin have been covalently linked to sequence-specific DNA ligands, such as triplex-forming oligonucleotides (TFO) and hairpin polyamides (MGB), that bind in a sequence-specific manner to the major and minor groove of double-helical DNA, respectively. The binding of the DNA ligand moiety of the conjugate at the target sequence positions the drug selectively at the target site, thereby stimulating topoisomerase I-mediated DNA cleavage at this site. In a continuous effort to optimize this strategy, a broad set of conjugates consisting of (i) 16-20 bases long oligonucleotides, (ii) hairpin polyamides of different length, (iii) alkyl linkers of variable length, and (iv) camptothecin derivatives substituted on the A or B quinoline ring, were designed and synthesized. Analysis of the cleavage sites at nucleotide-resolution reveals that the specificity and efficacy of cleavage depends markedly on the length of both the triple-helical structure and the linker between the oligonucleotide and the poison. Even though the CPT moiety is brought from the major groove side of DNA by the TFO and from the minor groove side by the MGB, both approaches provide a suitable route to guide a cytotoxic agent to a selected sequence in DNA. The optimized hybrid molecules induced strong and highly specific cleavage. Such rationally designed camptothecin conjugates could provide useful antitumor drugs directed selectively against genes bearing the targeted binding site. In addition, they represent a powerful tool to probe the molecular interactions in the DNA/topoisomerase I complex.

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A-ring Analogues of Oestrone 3-O-Sulphamate as Potent Steroid Sulphatase Inhibitors and Potential Anti-Cancer Agents

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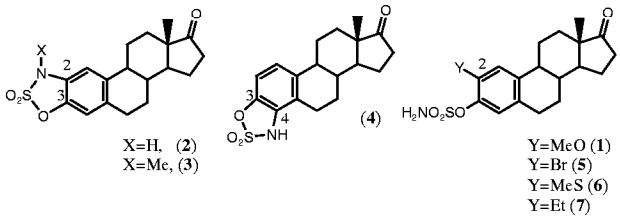
There is strong evidence to suggest that a concomitant inhibition of steroid sulphatase (STS), which converts oestrone (E1) sulphate to E1 and also dehydroepiandrosterone (DHEA) sulphate to DHEA, will further attenuate oestrogenic stimulation to hormone-dependent cancers. E1-3-O-sulphamate (EMATE) was the first potent, orally active, irreversible STS inhibitor developed by us but, unexpectedly, it was found to be also highly oestrogenic. Hence, the challenge has been to design non-oestrogenic STS inhibitors with comparable, or even superior, potency. Whilst there has been success in achieving this goal through the development of the non-steroidal coumarin sulphamates (notably 667COUMATE),1 we have also shown in a series of A-ring modified analogues of EMATE that 2-MeO-EMATE (1) is a highly potent STS inhibitor like EMATE, but in contrast, is devoid of oestrogenicity.2 Here, we further investigate the effects of A-ring modification of EMATE by preparing the 5-ring analogues of EMATE (2 - 4) and a series of 2-substituted EMATE (F, Cl, Br, I, CN, MeS and Et). The most potent STS inhibitor here is 2-Br-EMATE (5) whose IC_{50} of 1.7 nM from a placental microsomes preparation is some 11-fold lower than that of EMATE. Preliminary results from a luciferase reporter gene-expression assay have shown that (5) did not induce oestrogenic activity up to a concentration of 100 nM (c.f. 10 nM for EMATE) indicating that (5) is less oestrogenic than EMATE. A homology model of the human STS has been built from the crystal structure of ASA and the human STS sequence in order to understand the relationship between the binding of these compounds to the active site and their STS inhibitory activities. Although 2-MeS- (6) (IC_{50} = 120 nM) and 2-Et-EMATE (7) (IC_{50} = 820 nM) were found to be less potent than EMATE as STS inhibitors *in vitro*, like (1), these compounds have been shown to induce apoptosis (presumably via tubulin disruptions) in a MCF-7 cells proliferation assay (42%, 53% and 51% inhibition at 1 mM for 1, 6 and 7 respectively). Hence, 1, 6 and 7 are antiproliferative agents with potential applications for treating both hormone dependent- and hormone independent cancers.



This work is funded by Sterix Ltd. LWLW, BVLP, AP and MR are stockholders of Sterix.

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[2] Purohit et.al. (1998) J. Steroid Biochem. Mol. Bio., 64: 269.

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Novel Antineoplastic Complexes of Bismuth(III), Cerium(III) and Lanthanum(III)

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In a search for new lead structures for development of non-platinum antineoplastic metallopharmaceuticals we have identified acetatobis[1-(azepanyl)-4-(2-pyridyl)-2,3-diazapenta-1,3-dien-1-thiolato-N',N3,S]bismuth(III) (KP1255), trans-[aquachlorobis(1,10-phenantroline)cerium(III)] dichloride (KP776) and [tris(1,10-phenantroline)lanthanum(III)] trithiocyanate (KP772) as potent agents among series of related complexes, which have been synthesized in our laboratory.

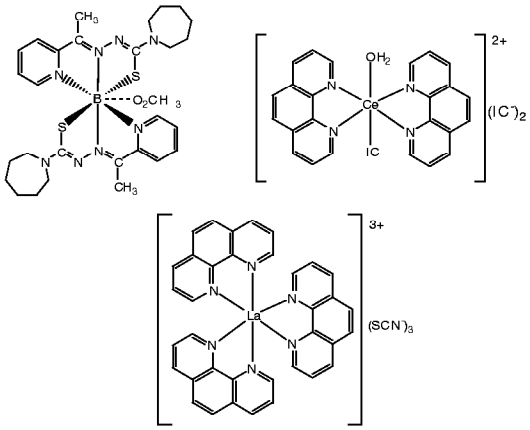

Figure 1. Structures of the bismuth complex KP1255 (top left), the cerium complex KP776 (top right) and the lanthanum complex KP772 (bottom).

Unlike platinum drugs the bismuth complex KP1255 displays rather flat dose-response curves with mean IC_{50} values in the low nanomolar range