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CHEMISTRY ENABLING DRUG DISCOVERY

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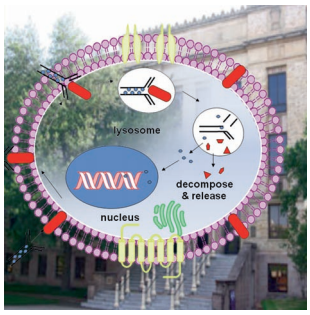
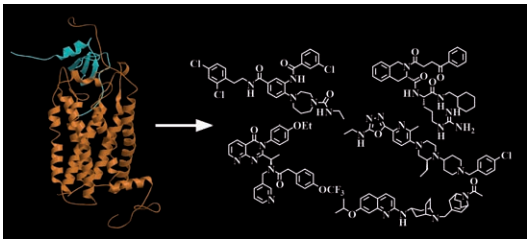
COVER PICTURE



The cover picture shows a schematic representation of the Herceptin–platinum(II) binding complex, which recognizes Her2/neu on the surface of SK-BR-3 cancer cells. The novel platinum(II)-based agents achieve their high binding affinity through Herceptin, which retains its capacity to recognize Her2/neu. The investigated binding complex, Her–*n*LPt^{II}, shows remarkable cancer-cell-specific cytotoxicity toward SK-BR-3 and SK-OV-3 cancer cells. This study highlights an approach that is more practical than the preparation of mAb–drug conjugates, which can be more complex and difficult to develop as drugs. These findings will guide the development of mAb–metal-based drug-targeting entities as a means to treat human cancers and other diseases. For details, see the Full Paper by J. Gao and R. A. Zingaro, et al. on p. 954 ff.

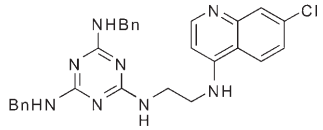
NEWS

MINIREVIEWS



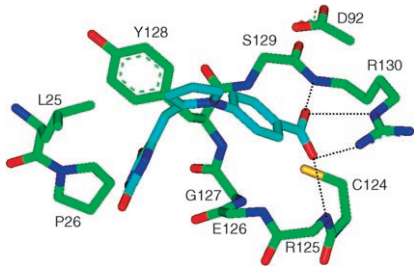
This minireview highlights the postulated therapeutic roles of the CXCR3 chemokine receptor and the nonpeptidergic CXCR3 antagonists and agonists that have been developed in recent years. The use of these molecules in exploring the (patho)physiological roles and putative clinical applications of CXCR3 are discussed.

COMMUNICATIONS

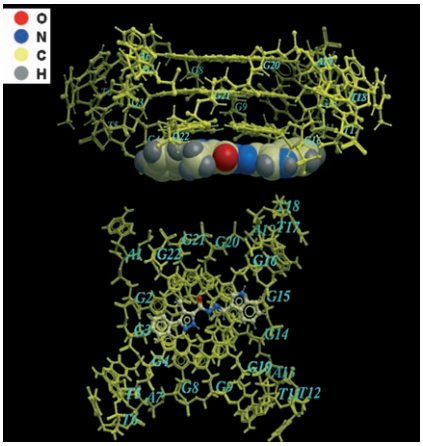


3m IC_{50} (W2) = 32 nM

Managing malaria. Malaria is responsible for two million deaths per year particularly in developing countries, therefore there is great need for the development of cost effective treatment. The synthesis of a library of trisubstituted triazines with potent antimalarial in vitro activity is reported. Among them, five products may be developed as potential leads in the search for new drugs against plasmodial chloroquine-resistant strains.

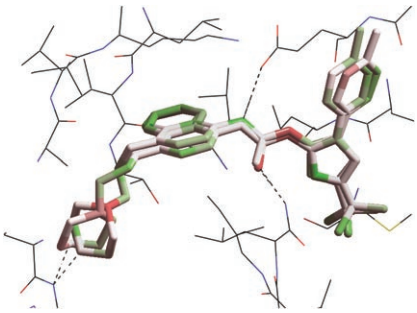


Human VHR phosphatase has been shown to be involved in the regulation of cell-cycle progression and is itself modulated during the cell cycle, indicating that VHR can serve as a therapeutic target for cancer. In the present study, we identify new VHR inhibitors by means of a structure-based drug design protocol involving the virtual screening with docking simulations and in vitro enzyme assay.

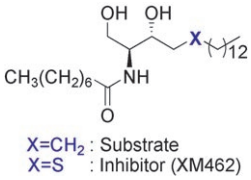


A new G-quadruplex binding ligand, namely 1*H*-pyrazole-3-carboxy-4-methyl-5-phenyl-(1*H*-indol-3-ylmethylene)hydrazide, was identified from a database of 100 000 drug-like compounds by in silico high-throughput docking. This compound was demonstrated experimentally to be an effective stabilizer of G-quadruplex DNA; it exhibits high selectivity for G-quadruplex over duplex DNA.

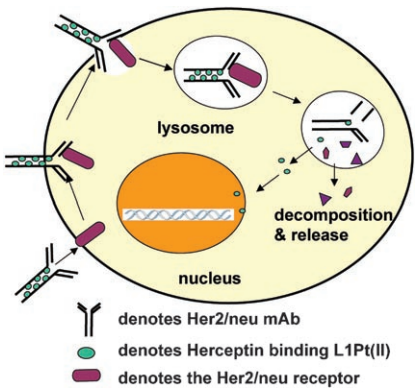
FULL PAPERS



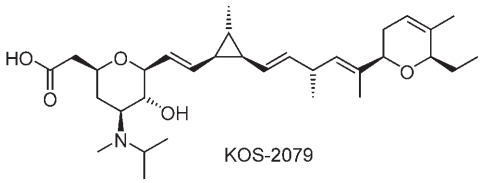
HYDE is a new empirical scoring function for the evaluation of protein–ligand complexes that estimates binding free energy based on two terms for dehydration and hydrogen bonding only. In contrast to other scoring functions, HYDE accounts for destabilizing dehydration effects in a consistent manner, thereby decreasing the rate of false positive hits in virtual screening.



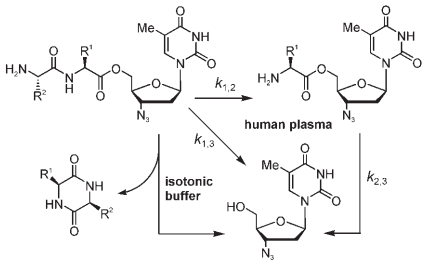
Rational design considering both mechanistic aspects of enzymatic desaturation and structural features of reported fatty acyl-CoA desaturase inhibitors led to the dihydroceramide desaturase inhibitor XM462. The design, synthesis, and biological activity of this compound both in vitro and in Jurkat A3 human leukemia cells are reported.



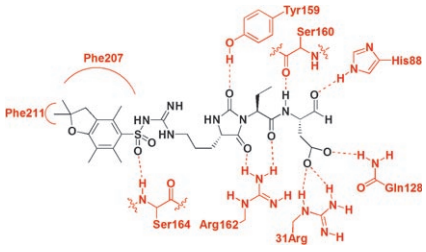
Specificity and toxicity. A new series of Herceptin–platinum(II) binding complexes, Her–*n*LPt^{II}, were investigated and show remarkable cancer-cell-specific cytotoxicity toward Her2/neu-overexpressing cancer cells (SK-BR-3 and SK-OV-3). This study suggests a new approach for the development of mAb–platinum(II)-based targeting agents for the treatment of human cancers.



Potent antifungals: A study of the amine region of the ambruticin VS series resulted in compound KOS-2079, which has excellent potency and oral bioavailability, and which showed efficacy in an in vivo mouse model.



5′-*O*-Dipeptide ester prodrugs of AZT were prepared and found to be good substrates for hPEPT1. They exhibit anti-HIV activity similar to that of AZT, yet are less cytotoxic. The prodrugs release AZT through an elimination–cyclization pathway in aqueous buffer and by the action of amino- and diaminopeptidases in human plasma, as shown in the scheme.



Apoptosis induction: Novel scaffold molecules for the inhibition of caspase-3 have been developed. These compounds have an overall attenuated negative charge and show similar IC_{50} values for both recombinant and human endogenous caspase-3. This could provide the basis for a new strategy for the discovery of potent and more druglike inhibitors of caspase-3.

BOOKS

SERVICE

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