

AUSTRALIAN JOURNAL OF CHEMISTRY

AN INTERNATIONAL JOURNAL FOR CHEMICAL SCIENCE

RESEARCH FRONT: Physiological Targeting in Drug Design

Reviews

Physiological Targeting to Improve Anticancer Drug Selectivity

Trevor W. Hambley

Aust. J. Chem. **2008**, *61*, 647–653.

Physiological differences that exist between solid tumours and the healthy tissues and organs of the body are both an impediment to effective treatment and a potential basis for targeting strategies. In this review, the physiological features that distinguish tumours are outlined. These include hypoxia, acidity, and inhibited transport and the strategies being employed to exploit these differences in order to generate more selective and less toxic anticancer agents are described.

'Clean' or 'Dirty' – Just How Selective do Drugs Need to Be?

Giovanni Abbenante, Robert C. Reid,
David P. Fairlie

Aust. J. Chem. **2008**, *61*, 654–660.

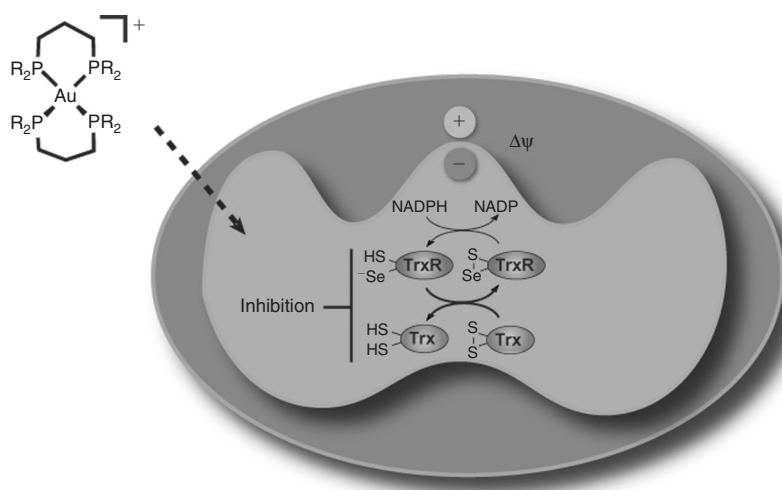
Modern chemotherapy requires increasingly longer timeframes to bring a drug to market, mainly because of more stringent safety standards that need to be met for drug registration. In the face of this growing pressure for 'cleaner' drugs, there has been some debate about the merits of designing new drugs for target selectivity versus target promiscuity. Common drug classes (kinase inhibitors, protease inhibitors, hydroxymethylglutaryl-coenzyme A reductase inhibitors, G protein coupled receptors modulators, non-steroidal anti-inflammatory drugs, antibodies) are used here to highlight this debate in the context of drug development for inflammatory disorders, cancer, cardiovascular, central nervous system, and infectious diseases.

The Design of Gold-Based, Mitochondria-Targeted Chemotherapeutics

Susan J. Berners-Price,
Aleksandra Filipovska

Aust. J. Chem. **2008**, *61*, 661–668.

Mitochondria play a central role in redox regulation and programmed cell death and as a result, they have become attractive targets for cancer chemotherapy. Several strategies have been used to target mitochondria of tumour cells, including the use of delocalized lipophilic cations in an effort to overcome drug resistance and lack of selectivity between normal and cancer cells. Here we discuss the design of gold-based delocalized lipophilic cations that selectively target mitochondria of cancer cells and their redox-regulating system.



Current Chemistry

Photochemotherapy: Targeted Activation of Metal Anticancer Complexes

Nicola J. Farrer, Peter J. Sadler

Aust. J. Chem. **2008**, *61*, 669–674.

Targeted activation of drugs is of crucial importance for improved therapies. The present article highlights recent developments in the design of photoactive anticancer metal complexes. It also considers some of the features required for future improvements.

Drug Delivery Devices and Targeting Agents for Platinum(II) Anticancer Complexes

Anwen M. Krause-Heuer,
Maxine P. Grant, Nikita Orkey,
Janice R. Aldrich-Wright

Aust. J. Chem. **2008**, *61*, 675–681.

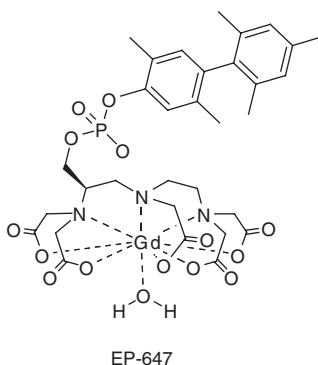
A number of highly potential anticancer drugs have failed to reach commercialization because of their acute toxicity in vivo or undesirable pharmacokinetics. The use of these drugs may now be reconsidered as a result of the recent numerous advances in drug delivery devices, such as cucurbit[*n*]urils, cyclodextrins, calix[*n*]arenes, and dendrimers. Such devices and various targeting methods are highlighted here.

Rapid Communication

A High Relaxivity Magnetic Resonance Imaging Contrast Agent Targeted to Serum Albumin

Stéphane Dumas, Jeffrey S. Troughton,
Normand J. Cloutier, Jaclyn M. Chasse,
Thomas J. McMurtry, Peter Caravan

Aust. J. Chem. **2008**, *61*, 682–686.



Magnetic resonance imaging (MRI) with gadolinium-based contrast is widely used clinically for blood vessel imaging, but recently there have been reports of gadolinium-induced toxicity. EP-647 is a new gadolinium-based contrast agent that binds serum albumin, resulting in increased magnetic resonance relaxation. By using albumin binding to both increase the relaxivity and target the contrast agent to the vascular compartment, high-resolution images of the blood vessels may be achieved at much lower gadolinium doses.

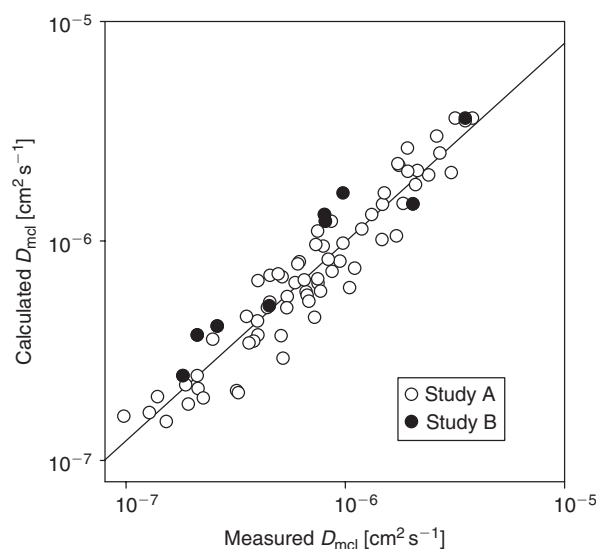
Full Papers

Prediction of Tumour Tissue Diffusion Coefficients of Hypoxia-Activated Prodrugs from Physicochemical Parameters

Frederik B. Pruijn, Kashyap Patel,
Michael P. Hay, William R. Wilson,
Kevin O. Hicks

Aust. J. Chem. **2008**, *61*, 687–693.

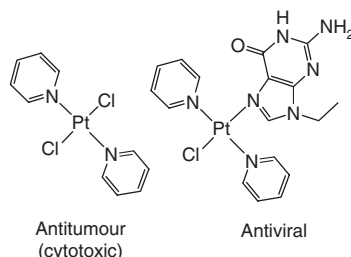
The therapeutic activity of anticancer agents depends critically on their ability to penetrate through tumour tissue to reach their target cells. Here, multicellular layers grown in-vitro from HT29 colon carcinoma cells were used to measure tissue diffusion coefficients (D_{mcl}) of 67 structurally diverse benzotriazine di-*N*-oxides (analogues of the hypoxia-activated prodrug tirapazamine). An algorithm was subsequently developed to predict D_{mcl} from physicochemical parameters.



Comparison of *cis* and *trans*-Platinum Mononucleobase Compounds with DNA and Protein Models

Joseph V. Struikl, Queite A. de Paula,
Xiaohong Yang, Yun Qu,
Nicholas P. Farrell

Aust. J. Chem. **2008**, *61*, 694–699.



Altering the biological properties of platinum compounds from anticancer activity (cytotoxic) to antiviral activity is an important challenge in platinum coordination chemistry. Enhancement of binding preference of platinum agents for protein (sulfur) binding sites rather than nucleic acid (nitrogen) sites may be achieved by suitable complex design. This may allow new target development for specific antiviral activity.

Rapid Communication

Uncatalyzed Knoevenagel Condensation in PEG-600 at Room Temperature

Babasaheb P. Bandgar, Balaji L. Korbad,
Sachin A. Patil, Sunita B. Bandgar,
Hemant V. Chavan, Baliram S. Hote

Aust. J. Chem. **2008**, *61*, 700–703.

The authors have developed a Knoevenagel condensation reaction of active methylene compounds with aromatic, aliphatic, conjugated and heteroaromatic aldehydes in PEG-600 at room temperature without adding any catalyst, with good to excellent yields.

Full Papers

Synthesis and Characterization of Rutile and Anatase in Air- and Water-Stable Ionic Liquids with and without Isopropanol as a Cosolvent

Mohammad Al Zoubi, Hala K. Farag,
Frank Endres

Aust. J. Chem. **2008**, *61*, 704–711.

In this paper we describe the sol-gel-synthesis of TiO_2 by hydrolysis of some titanium compounds in ionic liquids. By variation of the ionic liquid and of the experimental conditions both rutile and anatase can be obtained independently or as a mixture.

Mg_2Cl_5^- and Mg_3Cl_7^- Superhalogen Anions

Iwona Anusiewicz

Aust. J. Chem. **2008**, *61*, 712–717.

The vertical electron detachment energies of Mg_2Cl_5^- and Mg_3Cl_7^- superhalogen anions were calculated at the outer valence Green function level with the $6-311+G(3df)$ basis sets. These species were found to form rather unusual geometrical structures, each of which corresponds to a stable anionic state exhibiting superhalogen nature. Extremely large electron binding energies of these anions (in the 7–8 eV range) are predicted and discussed.

Synthesis of Novel 3-Alkyl-3',4',5,7-Tetrahydroxyflavones

Raquel S. G. R. Seixas,
Diana C. G. A. Pinto, Artur M. S. Silva,
José A. S. Cavaleiro

Aust. J. Chem. **2008**, *61*, 718–724.

The novel potential antioxidant and pharmacological agents 3-alkyl-3',4',5,7-tetrahydroxyflavones have been prepared. One of the key steps of the synthetic strategy involves a Friedel–Crafts acylation of phloroglucinol, followed by methylation to prepare the appropriate intermediate 1-(2-hydroxy-4,6-dimethoxyphenyl)alkan-1-ones. These compounds were used in the three-step Baker–Venkataraman method to prepare the 3-alkyl-3',4',5,7-tetramethoxyflavones, which were demethylated to afford the expected 3-alkyl-3',4',5,7-tetrahydroxyflavones.

Synthesis, Characterization, DNA Binding, and Photocleavage of $[\text{Ru}(\text{bpy})_2(\text{MFIP})]^{2+}$ and $[\text{Ru}(\text{phen})_2(\text{MFIP})]^{2+}$

Lifeng Tan, Sheng Zhang, Xiaohua Liu,
Yue Xiao

Aust. J. Chem. **2008**, *61*, 725–731.

Binding studies of small molecules to DNA are very important in the development of new therapeutic agents and DNA molecular probes. Varying types or positions of substituents in intercalative ligands may result in differences in the spectroscopic properties and the DNA-binding potential of such complexes, and will be helpful to more clearly understand the binding mechanism of these complexes to DNA. The experimental results suggest that the molecular structure, especially the planarity of the intercalative ligand, has significant effects on the spectral properties and DNA binding behaviour of the complexes.

Synthesis, Characterization, and DNA Binding Studies of Ruthenium(II) Complexes with 2-Pyridyl-1*H*-anthra[1,2-*d*]imidazole-6,11-dione

Yi-Xian Yuan, Yi-Can Wang, Long Jiang, Feng Gao, Si-Min Liang, Cheng-Yong Su, Hui Chao, Liang-Nian Ji

Aust. J. Chem. **2008**, 61, 732–739.

Three novel ruthenium(II) complexes, $[\text{Ru}(\text{bpy})_2(\text{PAIDH})]^{2+}$ **1**, $[\text{Ru}(\text{phen})_2(\text{PAIDH})]^{2+}$ **2**, and $[\text{Ru}(\text{dmp})_2(\text{PAIDH})]^{2+}$ **3**, have been synthesized and characterized. Their DNA binding behaviours were examined by spectroscopic and viscosity measurements. The experimental results suggest that the ancillary ligands of polypyridyl Ru^{II} complexes have significant effects on the DNA binding properties of complexes.

