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Unconventional Platinum Anticancer Compounds

Abstract

Contemporary platinum(II) anticancer drugs, such as cisplatin and carboplatin, covalently bind to DNA and exhibit many disadvantages including poor selectivity, acquired resistance, cross-resistance and severe side effects.[1] Our research has focused on the development of unconventional platinum complexes with different biological activities that do not demonstrate these clinical disadvantages. Pt(II) complexes with 1,10-phenantroline-type ligands represent a promising new class of inorganic anticancer drugs. These complexes have the general formula $[Pt(H_L)(A_L)]^{2+}$, where H_L is a heterocyclic ligand such as methyl-functionalized 1,10-phenanthroline and A_L is the *S*,*S* or *R*,*R* isomer of 1,2-DiAminoCycloHexane. Among a series of compounds with different combinations of A_L and I_L moieties, [Pt(1*S*,2*S*-DACH)(5,6-dimethyl-1,10-phenantroline)]$^{2+}$ is the most *in vitro* active demonstrating nanomolar cytotoxicity in human cancer cells. As a consequence of its different chemical structure and mechanism of action with respect to cisplatin, [Pt(1*S*,2*S*-DACH)(5,6-dimethyl-1,10-phenantroline)]$^{2+}$ could represent an different strategy to obtain a wider spectrum of action, also toward tumors resistant to cisplatin and other Pt-based drugs used in the clinics. Pt(IV) derivatives of [Pt(1*S*,2*S*-DACH)(5,6-dimethyl-1,10-phenantroline)]$^{2+}$ have been synthetized and since Pt(IV) complexes are kinetically more inert than their Pt(II) counterparts demostrate a better pharmacokinetic profile. The two extra axial ligands of Pt(IV) allows us to coordinate moieties that can modulate the overall characteristics of these complexes. We can increase lipophilicity or add bioactive molecules, which can provide dual and quad action with synergistic effect.

About the Speaker

Janice Aldrich-Wright obtained her BAppSc (Hons) from University of Technology, Sydney and PhD from Macquarie University, Sydney. She was awarded the Cornforth Medal, for the best PhD in Chemistry in Australia (1993). She is a fellow of the Royal Australian Chemical Institute and of the Royal Society of Chemistry. She investigates platinum anticancer compounds which operate under a mode of action different to current clinical drugs. Her work is internationally recognised in this field where she has patented and published widely. Innovative bioinorganic molecular design, elegant synthesis, comprehensive characterisation and the biophysical analysis of the interactions of these compounds with DNA, exemplify her research while she creates a vibrant, productive and collaborative environment for her research students.

Some Representative Publications from the Past Five Years

1. Pages, B. J.; Sakoff, J.; Gilbert, J.; Zhang, Y.; Hoeschele, J. D.; Kelly, S. M. and **Aldrich-Wright, J. R**. (2017) Combining the platinum(II) drug candidate kiteplatin with 1,10-phenanthroline analogues, *Dalton Transactions*, Accepted: 23/11/2017 DOI: 10.1039/C7DT04108J
2. Petruzzella, E.; Braude, J. P.; **Aldrich-Wright, J. R.**; Gandin, V.; Gibson, D. (2017) A quadruple action Pt^{IV} prodrug with anticancer activity against KRAS mutated cancer cell lines. *Angewandte Chemie, 56(38),* 11539-11544. (DOI: 10.1002/anie.201706739
3. Pages, B. J.; Sakoff, J.; Gilbert, J.; Alison Rodger, A.; Chmel, N. P.; Jones, N. C.; Kelly, S. M.; Ang, D. L.; **Aldrich-Wright, J. R.** (2016) *Chemistry A European Journal*, 22, 1-13. DOI: 10.1002/chem.201601221
4. Ang, D. L.; Harper, B.W.; Cubo, L.; Mendoza, O.; Vilar, R. and **Aldrich-Wright, J. R.** (2016) *Chemistry A European Journal*. 22, 2317-2325 DOI: 10.1002/chem.201503663
5. Pages, B.J.; Sakoff, J.; Zhang, Y.; Li, F. and **Aldrich-Wright, J. R**. (2015), European Journal of Inorganic Chemistry 4167-4175 Cover & feature DOI:10.1002/ejic.201500754
6. Pages, B.; Ang, D.; Wright, E. P. and **Aldrich-Wright, J.R**. (2015) Metal Complex Interactions with DNA. Invited review, Dalton Transactions, 44, 3505-3526 DOI: 10.1039/C4DT02700K