SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF NOVEL ANTICANCER OXALIPLATIN ANALOGUES

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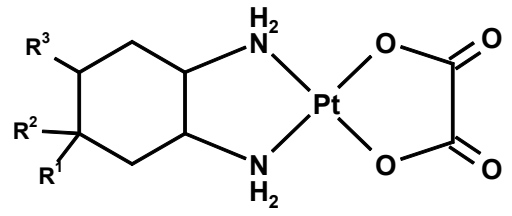
Oxaliplatin, (*trans-R,R*-cyclohexane-1,2-diamine)oxalatoplatinum(II), has recently been approved for combination chemotherapy of metastatic colorectal cancer. Based on the assumption that the steric demand and/or the lipophilicity of the cyclohexane ring are structural requirements for the specific pharmacological properties of oxaliplatin, derivatization of the cyclohexane ring might result in a marked effect on antitumor activity. Following this concept and in order to explore structure-activity relationships, a series of new oxaliplatin analogues has been synthesized and characterized [1, 2, 3]. Their *in vitro* antitumor activity in comparison to oxaliplatin has been tested in different cancer cell lines.



R^1	R^2	R^3
CH_3	H	H
CH_2CH_3	H	H
$CH_2CH_2CH_3$	H	H
C_6H_5	H	H
$C(CH_3)_3$	H	H
CH_3	CH_3	H
CH_3	H	CH_3

Compared to oxaliplatin, potency is increased in subsets of cell lines, particularly in leukemia and some colon carcinoma cells, by introduction of small substituents (methyl, ethyl). Within a panel of five colon carcinoma cell lines, the activity profile of the 4,4-dimethyl-substituted complex most closely resembles that of oxaliplatin, while that of the *cis*-4,5-dimethyl-substituted complex contrasts sharply.

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[2] Galanski, M.; Yasemi, A.; Jakupec, M. A.; Graf v. Keyserlingk, N.; Keppler B. K. Monatsh. Chem., in press.
[3] Galanski, M.; Jakupec, M. A.; Keppler, B. K. Oxaliplatin and derivatives as anticancer drugs – novel design strategies, In Metal Compounds in Cancer Chemotherapy, J. M. Pérez Martín, ed., in press.