Cytotoxic activity of 1-phenyl-2-substituted thiourea derivatives

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The 20 thiourea derivatives had been investigated for their cytotoxic activity using MTT assay. Cytotoxic activity was strongly influenced by the substituted alkyl chain length, but not by configuration of C1 and C2. The optimal alkyl chain length for cytotoxicity was C12. The 9 thiourea derivatives showed stronger activity than reference compound, B13. Some of them gave 2−3 times stronger activity than B13.

In vitro Antitumor Activity and Nephrotoxicity of Pt(II) Complexes Containing Diaminocyclohexane

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Platinum(II) coordination complex (cisplatin) has been currently used as one of the most effective compounds in the treatment of various solid tumors. However, its use has been limited by severe side effects such as renal toxicity. Our platinum-based drug discovery program has been aimed at developing drugs capable of diminishing toxicity and improving selective cytotoxicity. We recently synthesized new platinum(II) complex analogs (PC) containing trans-I & cis-diaminocyclohexane (DACH) as carrier ligand and DL-2-hydroxy-3-methylbutyrate (HMB) as a leaving group. A new series of Pt(II)(trans-I/cis-DACH)(HMB):PCs were evaluated its cytotoxic activity on cancer cells and normal kidney tissues. The new platinum complexes demonstrated high efficacy in the cytotoxicity on the various human cancer cell lines. The cytotoxicities of PCs were found quite less than those of cisplatin in normal kidney using MTT assay and [3H]-thymidine uptake tests. Based on the result, Pt(II)(trans-I/cis-DACH)(HMB) were considered as a better valuable lead compounds for improving antitumor activity with low nephrotoxicity in the development of the new clinically available anticancer chemotherapeutic agents.

Selective Cytotoxicity of Novel Platinum(II) Complexes on Gastric Cancer Cell Lines and Normal Kidney Cells

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We recently synthesized new platinum(II) complex analogs containing trans-I and cis-1,2-diaminocyclohexane (DACH) as carrier ligands and L-3-phenyllactic acid (PLA) as a leaving group. Our platinum-based drug discovery program has been aimed at developing drugs capable of diminishing toxicity and improving selective cytotoxicity. These platinum(II) complexes [Pt(II)(trans-I-DACH)(PLA):PC-1]/[Pt(II)(cis-DACH)(PLA):PC-2] are synthesized and characterized by its high performance liquid chromatography, elemental analysis and various spectroscopic techniques (IR, NMR). PC-1 and PC-2 showed acceptable and significant in vitro antitumor activity against MKN-45/P, MKN-45/ADM, and MKN-45/CDP human ovarian cancer cells as compared with that of cisplatin. The cytotoxicity of PC-1 and PC-2 against primary cultured proximal tubular cells of rabbit kidney determined using the MTT assay showed that these novel platinum complexes appear to be a valuable lead compound with high efficacy and low nephrotoxicity.
Effect of DNA methylation on the reactivity of DNA alkylating agents

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In mammalian species, CpG dinucleotides are highly methylated with 60–90% methylation at the 5-position of cytosine. The pattern of DNA methylation in a cell dramatically affects the function of the DNA by switching genes on or off. Abnormal methylation events occur during aging and in the development of many cancers. Methylated CpG was reported recently to affect the reactivity of agents (mitomycin C and benzo[a]pyrene-diol-epoxide) that can form guanine adducts in DNA. It was suggested that the enhanced reactivity is attributed to either a local charge effect, making 2-amino group of guanine more nucleophilic, or to a local conformational change, rendering it more accessible. In this study, we further examined the alkylating reactivity of various DNA alkylating agents at methylated DNA sites by using DNA strand breakage assay. The results suggest different mechanisms of adduct formation at methylated DNA depending upon which groove is attacked by those drug molecules.

[PD1–57] [ 10/17/2002 (Thr) 09:30 – 12:30 / Hall C ]

Anti-angiogenic and anti-tumor activity of 2′-hydroxy-4′-methoxychalcone

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In the previous study, we reported that 2′-hydroxy-4′-methoxychalcone, synthetic chalcone inhibited PGE2 production in TPA–stimulated rat peritoneal macrophages by inhibiting the induction of COX–2 protein. The present study was carried out to clarify whether 2′-hydroxy-4′-methoxychalcone inhibit angiogenesis by the experimental methods in vitro and in vivo. 2′-Hydroxy-4′-methoxychalcone decreased angiogenesis of both chick embryos in the chorioallantoic membrane assay and basic fibroblast growth factor–induced vessel formation in the mouse Matrigel plug assay. 2′-Hydroxy-4′-methoxychalcone also reduced the proliferation of calf pulmonary arterial endothelial (CPAE) cells. and found to possess relatively weak gelatinase / collagenase inhibitory activity in vitro. 2′-Hydroxy-4′-methoxychalcone exhibited a strong anti-proliferative activity and was almost equipotent to that of genistein, a reference drug. 2′-Hydroxy-4′-methoxychalcone, when administered s.c. at a dose of 30 mg/kg for 20 days to mice implanted with murine Lewis lung carcinoma (LLC), caused a significant inhibition of tumor volume by 27.2%. 2′-Hydroxy-4′-methoxychalcone, when treated i. p. at the same dosage for 10 days to ICR mice bearing sarcoma 180, caused a significant suppression in tumor weight by 33.7%.

[PD1–58] [ 10/17/2002 (Thr) 09:30 – 12:30 / Hall C ]

Ligand-Based Virtual Screening for inhibitors of PTP-1B with Antihyperglycemic properties

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Protein–tyrosine phosphatase 1B (PTP–1B), which plays a key role in insulin signaling, is rising as a fascinating target for type 2 diabetes and obesity. Many scientists in structural biology solved the three dimensional X-ray Crystal structure of this type of enzyme, so we could easily get the active site structure of PTP–1B or complex structure with ligand. Our virtual screening study for PTP–1B exactly based on these crystal structures from public database. We collected suitable complex structures and analyzed the critical properties of the binding interaction between active site and ligands. As the next step, we prepared some logical query set which possess above properties. Finally, we conducted the database search with our queries and have got a number of Hits and confirmed to be a potential skeleton of the lead through the enzyme assay.

[PD1–59] [ 10/17/2002 (Thr) 09:30 – 12:30 / Hall C ]