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COMPARISON OF TLP AND ET-18- OCH_3 IN CHEMICALLY INDUCED AUTOCHTHONOUS RAT TUMORS
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1-Octadecyl-2-methyl-rac-glycero-3-phosphocholine (ET-18- OCH_3) was compared with the newly synthesized 1-hexadecylmercapto-2-methoxymethyl-3-propyl-phosphocholine (TLP) in chemically induced rat tumors. Both compounds were administered at three dosages of 51 to 115 $\mu\text{mol/kg}$ to SD-rats that had been induced with methylnitrosourea (MNU). Therapeutic efficacy was evaluated in terms of tumor inhibition in comparison to controls (T/C%) and in increases of median life span (% ILS) over untreated controls. Toxicity was expressed as percent mortality (%M) and percent body weight difference (% BWD).

At optimal nontoxic doses the following effects were observed in terms of T/C%, %ILS, %M %BWD: ET-18- OCH_3 46, 27, 17, 2.1; TLP 1.2, 40, 13, 2.2; controls 100, 0, 20, 6.4. Comparison of ET-18- OCH_3 and TLP in acetoxymethylmethylnitrosamine (AMMN)-induced colorectal adenocarcinomas displayed no therapeutic activity of either compound. The results indicate a superior antitumor activity of TLP in MNU-induced mammary carcinoma compared to ET-18- OCH_3 . Since both compounds were inactive in AMMN-induced colorectal adenocarcinoma, a highly specific metabolic activation and/or detoxification might be involved.

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Therapeutic efficacy of N-(2-chloroethyl)-N-nitroso-carbamoyl-L-alanine (CNC-ala), CNC-ala-amide ($-\text{NH}_2$), CNC-ala-methylamide ($-\text{NH}-\text{CH}_3$) and their corresponding dipeptide and tripeptide derivatives in autochthonous rat mammary carcinoma.

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Mammary carcinomas were induced with methylnitrosourea in virgin female Sprague-Dawley rats. The substances, dissolved in DMSO, were administered IP in logarithmically spaced dosages once weekly on weeks 1, 2, 4 and 5 following randomisation. Anticancer activity was judged according to therapeutic efficacy (T/C %) and % mortality.

Methylamides were less toxic than their corresponding amides as was shown for instance between the amino acid- and dipeptide- derivatives. The therapeutic efficiency decreased with growing chain-length of the amino acid tail of the molecule from best effect with the amino acids to least effect in tripeptides derivatized as amides and methylamides. This can be impressively shown by the % tumor inhibition observed; for instance, the amino acid CNC-ala- NH_2 was over 90% more effective in inhibiting the tumor growth than the respective tripeptide. Within the series of amino acids the optimal therapeutic efficiency was found for the amidized compounds: CNC-ala- NH_2 had up to a 15 fold increase in antineoplastic activity compared to CNC-ala- $\text{NH}-\text{CH}_3$. After 6 weeks administration of CNC-ala- $\text{NH}-\text{CH}_3$ no mortalities were observed, whilst for CNC-ala- NH_2 50 % mortality occurred for high dosages.

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EXPERIMENTAL STUDIES WITH NEW β -DIKETONATO COMPOUNDS OF TITANIUM, ZIRCONIUM AND HAFNIUM IN AMMN-INDUCED COLONIC TUMORS

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Bis- β -diketonates of the titanium group and their homologous zirconium- and hafnium compounds are being studied for anticancer activity. Variation of the structure resulted in dichloro- and diethoxybis(1-phenylbutane-1,3-dionato) titanium (IV) ($\text{Ti}(\text{bzac})_2\text{Cl}_2$ and $\text{Ti}(\text{bzac})_2(\text{OEt})_2$) as the most active compounds. To test the influence of these compounds on survival times of animals with endoscopically ascertained colonic tumors, animals that had been induced intrarectally with 2 mg/kg AMMN weekly over ten weeks were randomly allocated to the following experimental groups (no. of animals; dosage):

A: $\text{Ti}(\text{bzac})_2\text{Cl}_2$ (25; 10 mg/kg)

B: $\text{Ti}(\text{bzac})_2(\text{OEt})_2$ (25; 10 mg/kg)

C: Dichlorobis(1-phenyl-1,3-butanedionato)-zirconium (30; 12 mg/kg)

D: Dichlorobis(1-phenyl-1,3-butanedionato)-hafnium (30; 14 mg/kg)

All compounds were injected twice a week over a period of ten weeks after diagnosis of tumors. The animals were observed until their normal death from tumor progression. The increase in lifespan (ILS) over untreated controls was (+ significant from controls): A: 4%; B: 46% (+); C: -19%; D: -10%.

In another dose regimen with chemotherapy from week 11-20, 23-24, 27-28, and 31-32, the ILS for $\text{Ti}(\text{bzac})_2\text{Cl}_2$ was: 18% (+) and for $\text{Ti}(\text{bzac})_2(\text{OEt})_2$: 30% (+). Toxicological examination revealed liver toxicity to be the most important side effect. No myelosuppression was observed in therapeutic doses. These data indicate significant activity of the β -diketonato compounds of titanium on the median lifespan of animals bearing AMMN-induced colonic tumors.

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$\text{Mo}(\text{bzac})_2\text{Cl}_2$ AS A STIMULATOR OF THE GROWTH OF AUTOCHTHONOUS CHEMICALLY INDUCED COLORECTAL CANCER IN SD-RATS
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Guided by the efficacy of dichloro- and diethoxy-bis(1-phenylbutane-1,3-dionato)titanium (IV) in the treatment of experimental tumors, the isostructural compound dichloro-bis(1-phenylbutane-1,3-dionato) molybdenum (IV) ($\text{Mo}(\text{bzac})_2\text{Cl}_2$) was synthesized by reaction of MoCl_5 with 1-phenylbutane-1,3-dione in CCl_4 under argon. First experiments on sarcoma 180 (ascitic form) showed distinct prologation of the survival time (T/C %: 200-250) following application of this compound. To evaluate a possible efficacy on slowly growing autochthonous rat tumors, the acetoxymethylmethylnitrosamine (AMMN)-induced colorectal adenocarcinoma was used. Induction of these tumors was performed according to published methods. Treatment of AMMN-induced SD-rats consisted of regular intravenous administration of 6 mg (group I) or 12 mg (group II) $\text{Mo}(\text{bzac})_2\text{Cl}_2/\text{kg}$, twice weekly over ten weeks, starting the week following the induction period, prior to manifestation of tumors. In addition the same dosage was administered after endoscopic diagnosis of tumors (group III and IV respectively). Groups consisted of 20 (I, II) and 22 animals (III, IV) respectively. All animals were sacrificed after treatment and parameters of toxicity and therapeutic effectivity were assessed. The following results in terms of T/C % / % mortality were obtained. Group I: 410/5; group II: 115/10; group III: 170/9; group IV: 155/0. These results show a distinct stimulation of the growth of AMMN-induced colorectal adenocarcinoma by $\text{Mo}(\text{bzac})_2\text{Cl}_2$. Interestingly, lower doses of $\text{Mo}(\text{bzac})_2\text{Cl}_2$ produced larger tumors than those found on treatment with higher doses. Since equimolar dosages of isostructural titanium compounds were associated with significant anticancer activity in this model, this reverse effect is striking.

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