Chapter 13. Antineoplastic Agents

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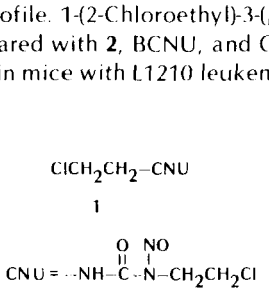
Introduction — A survey of the 1977 literature revealed no truly significant breakthrough in the design or discovery of agents for cancer therapy. With the exception of drugs for enzyme and hormonal therapy, the search for new drugs has continued to rely on antibiotic screening, empirical compound screening, and molecular modifictions of existing agents. One of the most comprehensive treatises on chemotherapy published to date discussed general principles that have led to progress and explained difficulties in achieving a quantum improvement in therapy.[1] The mechanisms of action (MOA) of the various classes of antitumor agents were described, with details covering the most effective in the clinic. General reviews on cancer chemotherapy and immunotherapy[2-6] were published, as well as specific reviews on anthracyclines,[7] antineoplastic agents from plants,[8,9] pharmacokinetics of 5-fluorouracil (5-FU),[10] methotrexate (MTX),[11] levamisole,[12] bleomycin,[13] pyrrole(1,4)benzodiazepine antitumor antibiotics,[14] MOA of DNA synthesis inhibitors,[15] and inhibitors of mercapto enzymes.[16] Clinical results obtained with the most effective adjuvant chemotherapeutic approaches were also reviewed.[18,19] A report detailing cancer survival statistics for patients diagnosed and treated at centers participating in the Cancer Surveillance, Epidemiology and End Results (SEER) program was published by the Department of Health, Education and Welfare (DHEW).[20]

Alkylating Agents and Nitrosoureas — A great deal of research continued to be stimulated by the clinical efficacy of compounds such as cyclophosphamide, L-phenylalanine mustard (L-PAM), *bis*-chloroethyl nitrosourea (BCNU; **1**), and close analogs. With the development of chlorozotocin (**2**) and streptozotocin (**3**) additional work has sought further decreases in toxicity and advantages in activity profile. 1-(2-Chloroethyl)-3-(β-D-glucopyranosyl)-1-nitrosourea (**4**) and **5** were synthesized and compared with **2**, BCNU, and CCNU.[21,22] The % increased life span (ILS) values at the LD_{50} dose (i.p.) in mice with L1210 leukemia were 90 (**4**), 429 (**5**), 332 (**2**), 260 (BCNU), and 364 (CCNU; **6**).



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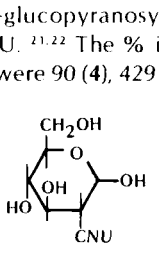

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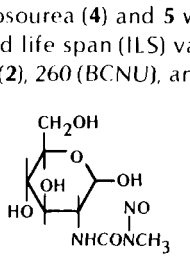

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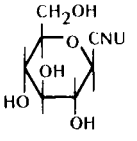

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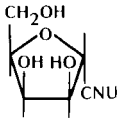

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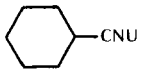

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When compared with BCNU and CCNU, the selective reduction of myelosuppression by **4** and **2** was attributed to the glucose functionality and not the increased water solubility. Support for this hypothesis was obtained by studying the water soluble nitrosourea **7**, which was active against

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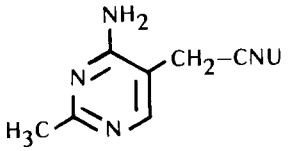
L1210 leukemia (492% ILS), but was also a potent myelotoxin.[23] The mechanism of nitrosourea action remained unclear, as antineoplastic activity did not correlate with carbamoylating



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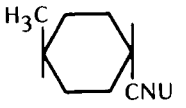

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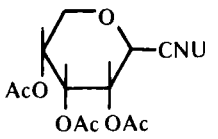

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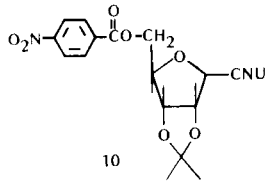
activity, alkylating activity or LD_{10} in mice; however, stability appeared inversely proportional to alkylating activity.



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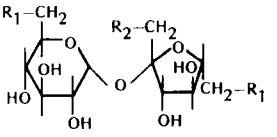
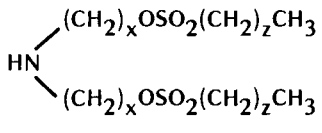


	R_1	R_2
11;	$NHCON(NO)CH_3$	OH
12;	$NHCON(NO)CH_3$	$NHCON(NO)CH_3$

Ribose-containing nitrosoureas **9** and **10** displayed activity against Friend leukemia and L1210, respectively,[24,25] and clinical evaluation of **10** has begun because of its superior therapeutic index (TI ~ 4). Based on reports that the blood-brain barrier prevented access of sucrose to normal brain tissue, but not brain tumors, 6,6'-dideoxy-6,6'-di(3-methyl-3-nitrosoureido)sucrose (**11**) and 1',6,6'-trideoxy-1',6,6'-tri(3-methyl-3-nitrosoureido)sucrose (**12**) were synthesized and tested in mice at doses of 200 mg/kg against both L1210 leukemia [treated/control (T/C) = 137 and 137, respectively] and ependymoblastoma brain tumor (T/C = 148 and 133, respectively).[26] A series of substituted cyclohexyl-CNU derivatives were prepared to investigate the known greater activity of the *trans* configuration of MeCCNU (**8**) versus the *cis*.[27] The compounds were active in L1210 leukemia with little differentiation between *cis* and *trans*, however, against Lewis lung carcinoma[28] it became clear that maximum activity was observed when substituents were at the 4-position of the cyclohexyl and *trans* to the CNU. A structural modification of BCNU, CNU-$(CH_2)_n$-OH (n = 2-4), designed to give a water-soluble alkylating agent, resulted in activity similar to BCNU against Walker carcinosarcoma.[29] A quantitative structure activity relationship (SAR) correlation equation based on lipophilic-hydrophilic balance (R_m) and L1210 activity was obtained for dialkanolamine dialkanesulfonic esters (**13**).[30] The homo-aza-steroidal ester (ASE; **14**) of *p-bis*-(2-chloroethyl)aminophenylacetic acid was active against L1210 and P388 leukemias, while the parent compound, phenestrin, was inactive. This provided the first example of a steroid alkylating agent active in the L1210 system.[31]



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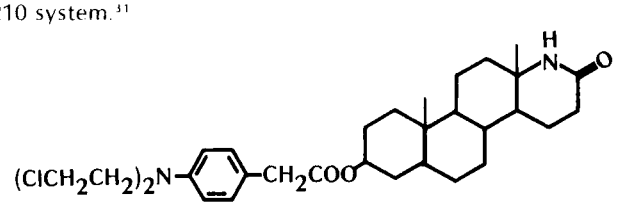

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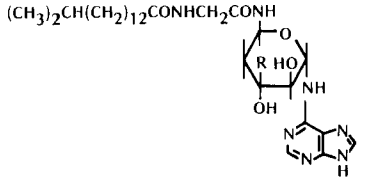
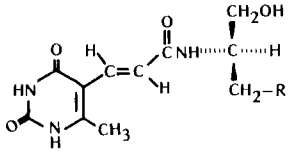
A series of Mannich bases were prepared with and without N-mustard groups and their SAR studied in a variety of tumor systems.[32] Bases with the N-mustard as the amine were particularly active against myeloid leukemia LAJ-1 and Walker 256. Two reports detailed progress toward a chemoimmunotherapeutic approach to cancer, in which an alkylating agent also served as a hapten, thus producing both a cell-mediated response after binding to tumor cells and providing a means for using a cytotoxic antibody generated against the hapten.[33,34] This effect was similar to the observation that EL4 leukemia and Gross-virus induced leukemia displayed new immunogenic properties following treatment with 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (DIC).[35] The absolute configuration of (+)-cyclophosphamide was obtained by x-ray diffraction and will allow determination of the absolute configuration at the phosphorus of all chiral metabolites of cyclophosphamide.[36]

Natural Products and Semi-synthetics — Screening of compounds from fermentation and other natural sources continued to provide the greatest number of new antineoplastic agents. Two antibiotics structurally related to bleomycin, tallysomycin A and B, were identified as having antitumor activity comparable to bleomycin.[37] Antitumor activity (5 mg/kg, i.v.) against an S180 solid tumor in mice was described for a new antitumor antibiotic, sporamycin.[38] A group of fermentation-derived ansamycins, similar in structure to maytansine and active against a broad range of tumor systems, displayed strongest activity against P388 leukemia in mice at daily doses as low as 0.8-25 μg/kg (i.p.).[39] The SAR of septicidin (**15**) and close analogs was investigated by varying the fatty acid, glycine and amino sugar groups attached to the adenine unit. Activity against murine P388 leukemia was observed if the fatty acid contained 12-16 carbons, the amino acid was gycine or β-alanine, and CH_3 or CH_2OH replaced $CHOHCH_2OH$ in the sugar. Septacidin's ability to inhibit nucleic acid syntheses was assumed not to be due to direct attack on DNA because of a negative Ames test.[40] Analogs of sparsomycin (**16**) were compared with the parent compound and found to require the sulfoxide moiety and a D-configuration at the chiral carbon atom for activity against P388 leukemia.[41] However, conflicting with the above data was a report



15; R = $CHOHCH_2OH$

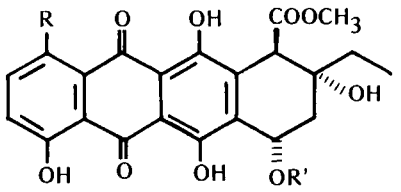


16; R = $-\overset{O}{\overset{\|}{S}}-CH_2SCH_3$
17; R = $-\overset{O}{\overset{\|}{S}}-CH_2CH_2CH_3$

that S-deoxy-S-propyl sparsomycin (**17**) was active against P388 and was a competitive inhibitor of puromycin.[42] Mitomycin C was converted to N-methylmitomycin A, a less acid-sensitive analog, to study the acid catalyzed aziridine ring opening. It gave the same unexpected *cis*-aminoalcohol stereochemistry as mitomycin C and a 180% T/C (3.2 mg/kg/day) against P388 murine leukemia.[43] The total syntheses of mitomycins A and C and porfiromycin were also reported.[44,45] 2-Deaminoactinomycin D was found by a variety of physical measurements to intercalate into DNA as efficiently as the parent compound, but had only 1/100 the ability to inhibit nucleic acid synthesis. The 2-amino group, originally thought necessary for DNA binding, was proposed as slowing displacement by an advancing enzyme during transcription.[46] The antitumor protein, neocarzinostatin, was reported readily purified over earlier isolates and found 2x as inhibitory for human leukemia (CCRF-CEM) cells and 40x for Sarcina lutea.[47] A new quassinoid glycoside, bruceoside-A, was identified and tested against P388 leukemia (156% T/C at 6 mg/kg/day).[48]

Synthetic efforts in the terpene area have focused attention on vernolepin and vernomenin, and a number of synthetic routes to them and their analogs were reported.[49-54] The mechanism for inhibition of nucleic acid synthesis by the sesquiterpenes helenalin and tenulin was studied and proposed as a Michael-type addition of sulfhydryl groups of key regulatory enzymes.[55,56] The synthesis and activity of analogs of podophyllotoxin, an inhibitor of the microtubule system, were investigated to study the dependence of the *trans*-fused ring system on activity, a necessary feature of the parent compound.[57-59] A semisynthetic podophyllotoxin, 4'-demethyl-epipodophyllotoxin 9-(4,6-0-ethylidene-β-D-glucopyranoside), was tried against small cell anaplastic carcinoma (SCAC), and gave a 50% overall response rate after oral dosing, thereby, making it one of the most active single agents against SCAC.[60] In the area of alkaloid research the SAR of vinca alkaloids was studied by correlating LD_{50} data and anti-P388 activity with partition coefficients, pKa, and binding to tubulin.[61] The SAR of 4'-dehydrated vinca alkaloids revealed that a combination of 3',4' double bond and 4-deacetylation in vincristine resulted in a significant increase in TI against B-16 melanoma.[62] In a study of ergot alkaloids, two prolactin inhibitors, Deprenon and ergocryptine, proved to be highly effective against DMBA-induced rat mammary carcinomas.[63] The antitumor SAR of cephalotaxine esters was investigated, and particularly active were methyl (-)-cephalotaxyl itaconate and fumarate. However, there was a lack of correlation between activity and structure of α,β-unsaturated esters, which were 50-100 times less active than the naturally occurring esters.[64] New syntheses were reported for the alkaloids, trilobine, isotrilobine, obaberine,[65] camptothecin,[66] and ellipticine.[67,68]

Anthracyclines — Adriamycin (ADR) has continued to show dramatic clinical efficacy along with serious toxicity. In spite of the drawbacks, its success against solid tumors has led to a great deal of research centered around the anthracycline nucleus. The design, synthesis and SAR of daunorubicin (DNR), ADR and their new analogs have been carefully reviewed.[7] Labelled DNR and ADR have in the past been prepared by catalytic tritium exchange, which yielded products that readily exchanged during drug distribution studies. This problem was circumvented by synthesis of [14-^{14}C]DNR and [14-^{14}C]ADR using ^{14}C-diazomethane.[69] 4-Demethoxy DNR (i.v.) compared favorably with DNR and ADR (i.v.) against Gross leukemia and S180 tumor bearing mice, however, when given orally (2.55 mg/kg), it was effective (50% reduction in tumor growth and increase in survival time), where ADR and DNR were either ineffective or effective at large multiples of the optimal dose.[70] The importance of stereochemistry at C-9 was demonstrated when 9-deacetyl DNR displayed a 2-fold greater TI over 9-epi-deacetyl DNR against P388 lymphocytic leukemia in mice.[71] Studies on prevention and reversal of ADR associated cardiotoxicity showed that coenzyme Q reduced tachycardia, ECG and histological changes induced in long-term ADR treated rabbits.[72] In a clinical investigation, treatment with digoxin and diuretics reversed ADR-associated cardiac failure.[73] Carminomycin, the 4-demethyl analog of DNR developed in the USSR, has been reviewed and reported not to possess the cardiac toxicity associated with DAR.[74] Recent screening has resulted in a large number of ϵ-pyrromycinone (**18**) and 1-ϵ-deoxypyrromycinone (**19**) analogs with potent L1210 activity.[75-77] Only marginal anti-leukemia activity was observed when deoxy sugar glycosides (**20**) of **19** were synthesized.[78]



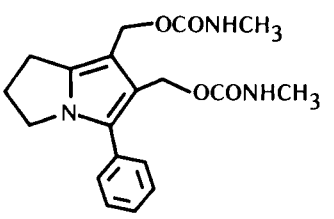
18; R = OH, R' = H
19; R = H; R' = H
20; R = H; R' = deoxysugar

Nucleoside Analogs — Ara-CDP-dipalmitin, after conversion to ara-CMP and phosphatidyl inositol,[79] increased the life of L5187Y leukemia-bearing mice (173% at 50 mg/kg i.p.). Both N^4-behenoyl-1-β-D-arabinocytosine and N^4-stearoyl-1-β-D-arabinocytosine were more active *in vivo* than 1-β-D-arabinocytosine, apparently because the N^4 substituents protected against degradation by cytidine deaminase.[80] New syntheses were reported for ftorafur [1-(2-tetrahydrofuryl)-5-fluorouracil],[81,82] and no differences were seen in biological activities of the R and S isomers. Tumor regression was seen in a Phase I study of advanced gastrointestinal cancer following treatment with ftorafur and mitomycin C or MeCCNU.[83] The chemistry and biology of 5-azacytidine were reviewed.[84] Additional work with 5,6-dihydro-5-azacytidine, the stable analog of 5-azacytidine, demonstrated more efficacy than the parent against cerebral L1210 and had a better TI.[85] Several sulfur-substituted analogs of the α and β anomers of 2'-deoxy-6-thioguanosine had substantial antileukemia activity in mice,[86] but none was as potent as the parent compound.

Metal Complexes — With the clinical utility of *cis*-platinum diamminodichloride (PDD) repeatedly reinforced,[87,88] work has continued toward establishing the MOA of this compound and the growing number of cytotoxic, heavy metal complexes. PDD was found to be synergistic with cyclophosphamide in L1210 leukemia[89] and with 2,2'-anhydro-1-β-D-arabinofuranosyl-5-fluorocytosine in L1210 and P388 systems resistant to 5-FU or MTX.[90] A series of *cis*-dichlorobis(1-methyl-imidazole-2-thiol)Pt (II) and Pd (II) compounds were complexed with nucleosides to determine the binding properties of the metals. IR and NMR were used to show Pt and Pd bound to N^7 in guanosine and adenosine and N^6 in cytidine.[91] Acetylacetonate-1,5-cyclooctadienerhodium(I) (AC) and *cis*-dichlorotetrakisdimethylsulfoxide ruthenium(II) (CR) compared favorably with PDD *in vivo* against Ehrlich ascites carcinoma, however, only AC and PDD were effective in L1210.[92] Cyclic and polymeric amino phosphazenes have been reacted with K_2PtCl_4, resulting in water-soluble complexes with cytostatic activity in mouse P388 leukemia and Ehrlich ascites tumor regression systems.[93] Partition coefficients for rhodium(II) carboxylates were correlated with activity in mice bearing the Ehrlich ascites tumor. The data showed increases in lipophilicity gave increases in %ILS and TI, until steric factors or too little water solubility lessened the effects.[94] Evidence has been obtained for cytotoxic copper and rhodium complexes reacting with enzymes containing essential -SH groups.[95,96] Concentrations of rhodium carboxylates that will inhibit -SH enzymes have been correlated with maximal survival times of mice bearing Ehrlich ascites tumors.[97]

Miscellaneous Agents — Anti-L1210 leukemia activity was correlated with a lipophilic-hydrophilic balance for a series of 4'-(9-acridinylamino)alkanesulfonanilides.[98,99] Acridines substituted in the 3-position with lipophilic groups were found more active when further substituted with hydrophilic groups. *In vivo* reduction of nitro derivatives of 4'-(9-acridinylamino)methanesulfonanilide (AMSA) had been postulated to explain the activity of these weakly basic compounds, however, 3- and 4-aza analogs of AMSA had similar base strength and were equally active.[100] Joining two acridine rings at the 9-amino position by a varying number of methylene units yielded a series of *bis*-intercalating diacridines, shown to have an inverse correlation between %ILS (P-388) and agglutination involving S180 cells treated with Con-A.[101] The SAR of a group of N-protected amino acids converted to their vinyl, 1,2-dihaloethyl and cyanomethyl esters was reported; particularly active against Ehrlich ascites carcinoma were the esters of N-carbobenzoxy-L-phenylalanine, glycine, and leucine.[102,103] 1,8-Di-N-*bis*-(*n*-butyloxycarbonylaminomethyl)-L-citrulline was shown to be orally effective against rats implanted with AH 41C ascites hepatoma (i.v.).[104] In a study concerned with homocysteine metabolism in neoplastic tissue, arachidonoyl homocysteine thiolactone (HCT) amide decreased growth, and oleoyl HCT amide increased growth of A-10 mammary adenocarcinoma.[105] 1-Formylpyridine thiosemicarbazone has been

shown to have the E-configuration,[106] and in a series of 5,6-dihydro-8(7H)-quinoline thiosemicarbazones, investigation of structural requirements revealed that the E-isomers were slightly more active than the Z-isomers against P388 leukemia.[107] 4-Methyl-5-amino-1-formylisoquinoline thiosemicarbazone (i.p.) significantly increased survival time in mice bearing S180, L1210 and P388 leukemia, B16 melanoma or Lewis lung carcinoma.[108] Analogs of **21** and **22**, structurally similar to mitomycins and pyrrolizidine alkaloids, were found effective against P388 *in vivo*.[109,110] 5,5-*Bis*(4-chlorophenyl)-1,3-dichlorohydantoin was the most active (190% T/C) of a group of hydantoins tested against P388 leukemia.[111]



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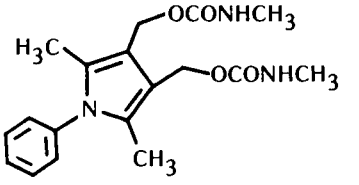

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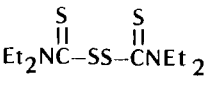
Immunotherapeutics — No new significant immunotherapeutic agents have been reported, but the approach has been accepted as clinically useful, and BCG, MER, C. *parvum*, and levamisole usage continued to grow. The general subject was comprehensively reviewed,[3,112] as well as the specific topics, MER-BCG,[113] levamisole,[12] and clinical trials of immunotherapy in man.[114] The mechanism of macrophage activation by BCG was studied with respect to lysosomal enzymes and the presence of intracellular free radical species.[115] A vaccine of BCG plus x-irradiated L10 hepatocarcinoma cells eliminated a disseminated tumor burden in guinea pigs.[116] This approach has been extended to the clinic where good results against acute lymphoid leukemia have been observed after chemotherapy followed by active immunotherapy with BCG.[117] C. *parvum* (i.v.) was found more effective than BCG in reducing incidence of regional lymph node metastases after surgery of adenocarcinoma in rats.[118] The mechanism of C. *parvum* antimetastatic activity has been explained as mediation by macrophages with T-cell cooperation[119] and a T-cell independent activation.[120] Various combinations of C. *parvum* given s.c., i.v. and i.p. increased survival of Fischer 344 rats bearing 13762 adenocarcinoma.[121] Pulmonary, peritoneal, and splenic macrophages from these animals were cytotoxic toward target 13762 tumor cells *in vitro*. An objective response was seen in human ovarian cancer with C. *parvum* and a program of Cytoxan, adriamycin, and 5-FU, where conventional therapy had failed.[122] Levamisole was reported to inhibit s.c. malignant neurinoma growth in 80% of treated rats.[123] Skin tests, E-rosettes, and cAMP levels have been measured in patients with malignant melanoma and squamous cell cancer of the head and neck, and improved values correlated with responders to levamisole therapy.[124]

Drug Delivery — There has been a persistent effort in increasing selectivity of antitumor agents by altering physical, chemical and biochemical parameters.[125-127] Emulsions[128,129] have been applied to delivery of agents to lymphatics, and liposomes have been used to enhance the action of nitrogen mustard,[130] specific tumor cell antibody[131] and a variety of cytotoxic agents.[127] The proposed lisosomal membrane alteration of target cells has been extended to Amphotericin B (AMP B), which is known to alter membrane permeability.[132,133] AMP B has enhanced BCNU uptake into tumor cells and stimulated host response to killed cells.[134] Objective clinical responses were observed when AMP B was used during combination chemotherapy.[135,136] Macromolecular species such as BSA, IgG, poly amino acids,[137] and Con A[138] have been used as carriers of antitumor agents to increase specificity and TI. MTX covalently coupled to tumor associated antibodies (ab) was shown to be more effective against C3H murine ovarian carcinoma thanthe agent

alone or a simple mixture of ab and MTX.[139] Specificity has also been sought by incorporating alkylating groups on hydantoin,[140] pyrimidine[141] and isoquinoline[142] pharmacophores.

Anticarcinogens — Published reports concerning compounds inhibiting tumors induced by carcinogens have continued to grow. Dithiocarbamates such as disulfiram (**23**) and diethyldithocarbamic acid prevented 1,2-dimethyl hydrazine (DMH)-induced large bowel tumors in mice.[143] Selenium supplementation of diet decreased colon cancer induction in rats by DMH.[144] Similarly, incidence of rat intestinal and bladder tumors induced by bracken fern was decreased by addition to the diet of BHA, PVP, calcium chloride, and disulfiram.[145] The most studied class of compounds in this area has been the retinoids, thought to act via control of epithelial cell growth. Retinyl methyl ether was found superior to natural retinyl acetate for inhibition of DMBA-induced mammary cancer in rats.[146] Invasive cancer was prevented or delayed in rats treated with 13-*cis*-retinoic acid following induction of preneoplastic lesions with either N-methyl-N-nitrosourea or N-butyl-N-(4-hydroxybutyl)nitrosamine.[147-149] Systemic use of the aromatic retinoid, Ro 10-9359, (**24**) successfully treated DMBA-induced skin papillomas in Swiss mice.[150]



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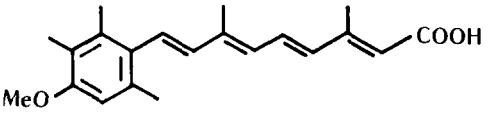

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