Arabian Journal of Chemistry (2013) 6, 1–23

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

REVIEW

1st Cancer Update

NSAID's and selectively COX-2 inhibitors as potential chemoprotective agents against cancer

Nitin Kumar [a,*], Sushma Drabu [b], Sambhu Charan Mondal [a]

[a] Department of Pharmaceutical Technology, MIET, NH-58, Bypass Road, Baghpat Crossing, Meerut 250005, UP, India
[b] Maharaja Surajmal Institute of Pharmacy, C-4, Janakpuri, New Delhi 110058, India

Received 20 April 2011; accepted 22 July 2011
Available online 30 July 2011

KEYWORDS
NSAIDs;
COX-2;
Inflammation;
Cancer

Abstract Non-steroidal anti-inflammatory drugs act by inhibiting cyclooxigenase enzyme in the plasma membrane predominantly. Nowadays many researchers have observed a great involvement of these anti-inflammatory drugs in the cure of different types of cancers. This review shows the role of cyclooxigenase inhibitors specifically type-2 in cure or prevention of different types of cancers.

Contents

* Corresponding author. Mob.: +919717893319, +919310497960.
E-mail addresses: nitinvermakr@gmail.com (N. Kumar), sushmadrabu@gmail.com (S. Drabu), sambhu273@yahoo.com (S.C. Mondal).

1878-5352

Peer review under responsibility of King Saud University.
doi:10.1016/j.arabjc.2011.07.020

Production and hosting by Elsevier

1. Introduction

Internationally there are >10 million new cancer cases and >7 million cancer related death reported each year making cancer research a top priority. As per WHO report 1997 cancer continues to be a major health problem in urban areas and during the next 25 years or so cancer alone will contribute 6.3 million annual deaths (Doreswamy and Darshan, 1999). Cancer is a disease of cells characterized by reduction or loss of effectiveness in normal cellular control mechanism which regulates multiplication. Carcinogenesis is a multi-step process as was first described in 1965 by Leslie Foulds, who deduced that there were multiple pathological processes of cancer induction and tumor progression for many human epithelial cancers.

Cancerogenesis is of a three stage process. The first stage is initiation which involves in the mutation by physical, chemical or viral exposure and occurs rapidly with high frequency. The second stage is tumor promotion, a low frequency event that requires sustained chronic exposure to tumor promoters, such as growth factors, hormones or ultraviolet radiation. The third stage is tumor progression in which tumor becomes malignant. Many cancer cells have defects in their progression through the cell cycle or their regulation of cell death. In particular, the distinct feature of tumors is lack of regulation of the cell cycle, resulting in uncontrolled proliferation. Although the goal of cell division is for each daughter cell to inherit a copy of each intact chromosome, defects in this process can lead to aneuploidy, genetic instability and ultimately, metastatic tumorigenesis. A list of various chemotherapeutic drugs is summarized in Table 1 (Goodman and Gilman's, 2001).

In the past, due to poor therapeutic response and high incidence of adverse reactions, chemotherapy was considered as a last resort, after more successful treatments like surgery and radiotherapy had failed. However, even with recent advances, the treatment of cancer continues to be one of the greatest challenges in medicine, as many forms of human cancers still resist effective chemotherapy. A major limitation in cancer therapy is inadequate selectivity of most anti-cancer drugs (Prasanna et al., 2003). COX-2 (also known as prostaglandin H synthase-1) is upregulated in response to inflammatory cytokines, growth factors and tumor promoters (Matthew et al., 2003).

2. Various chronic inflammatory conditions that predispose to cancer

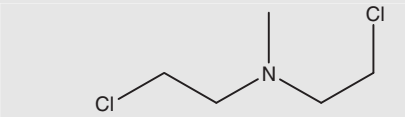
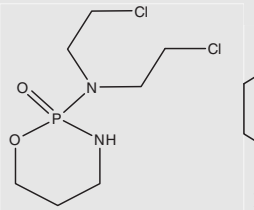
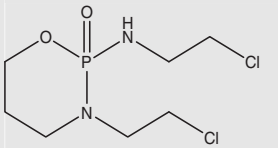
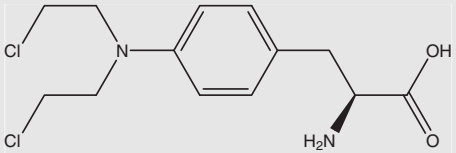
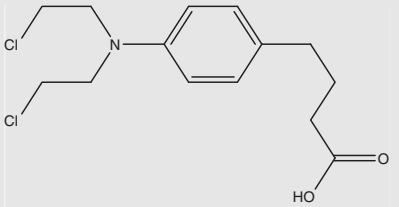
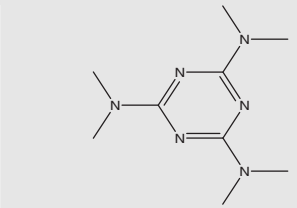
Various chronic inflammatory conditions predispose to the neoplastic transformation. Tumors are mostly of epithelial cell origin (carcinomas). Various cancerous disease associated with inflammatory conditions such as colon carcinoma associated with inflammatory bowel disease (chronic ulcerative colitis and Crohn's disease), esophageal adenocarcinoma associated with reflux esophagitis (Barrett's esophagus), hepatitis predisposing to liver cancer, schistosomiasis causing an increased risk of bladder and colon carcinomas, and chronic *Helicobacter* infection leading to cancer of the stomach. Some increase in the incidence of lymphoma is also seen, particularly mucosa-associated lymphoid tissue (MALT) lymphoma.

2.1. Chronic inflammatory model that leads to progression of tumors

Different animal models demonstrate experimentally that chronic inflammation predisposes to the development of various forms of cancer (Vainio and Boffetta, 1994; Thieblemont et al., 1995). Marmosets have a high incidence of spontaneous colitis and a high incidence of colon cancer as well (Ekbom et al., 1990). For example, the cancer status of parents and grandparents was compared for 48 animals with colon cancer and 58 for controls, all with histological confirmation of ulcerative colitis. Multivariate odds ratios (OR) were calculated using logistic regression. A parental history of colon cancer was associated with risk of colon cancer (multivariate odds ratio, 2.7; 95% confidence interval, 1.1–6.3). Risk also increased as an animal's total number of family members with colon cancer increased (multivariate odds ratio, 1.7 for each increase in the total number of family members with cancer; 95% confidence interval, 1.1–2.8). These results suggested that cotton-top tamarins with ulcerative colitis have a significant increased risk for developing colon cancer if they have a family history of colon cancer (Elizabeth et al., 1998). Skin cancer is induced by administration of carcinogens such as dimethylbenzanthracine (DMBA) followed by repeated administration of tumor promoters such as phorbol myristate acetate (PMA) or benzoyl peroxide, which induces inflammation and the production of various inflammatory mediators (Boone et al., 1992). Plasmacytoma can be induced with high frequency in BALB/c mice by the intra peritoneal introduction of mineral oils (e.g. pristane) and implantation of plastic Lucite discs (Vogelstein and Kinzler, 1993). These types of plasmacytoma have showed that the tumors developed in the peritoneal inflammatory tissue.

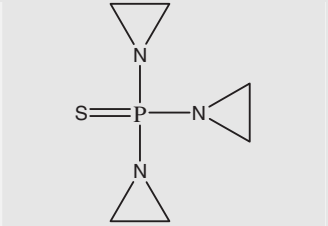
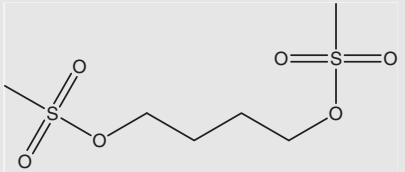
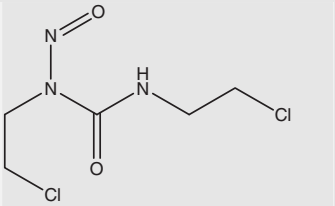
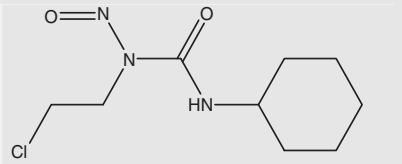
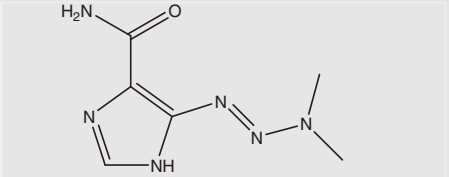
In some cases, there is strong evidence suggesting a genetic basis for the susceptibility to tumor development. For example, in the mouse plasmacytoma model, BALB/c mice were uniquely susceptible to developing plasma cell tumors in response

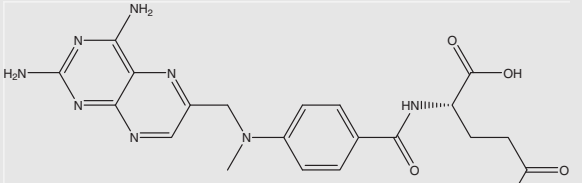
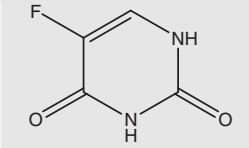
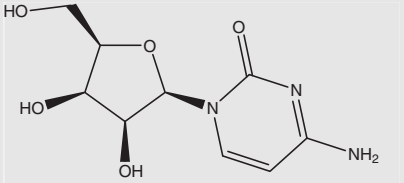
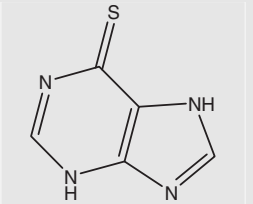
Table 1 List of chemoprotective agents.

Class	Type of agent	Drugs	Disease	Structure
Alkylating agents	Nitrogen mustard	Mechlorethamine	Hodgkin's disease, non-Hodgkin's lymphomas	 2-chloro-N-(2-chloroethyl)-N-methyl-ethanamine
		Cyclophosphamide, Ifosfamide	Acute and chronic lymphocytic leukemia; Hodgkin's disease, non-Hodgkin's lymphomas; multiple myeloma	 N,N-bis(2-chloroethyl)-1,3,2-oxazaphosphinan-2-amine-2-oxide  N-3-bis(2-chloroethyl)-1,3,2-oxazaphosphinan-2-amide-2-oxide
		Melphalan	Multiple myeloma; breast, ovarian cancer	 4-[bis(chloroethyl)amino]phenylalanine
		Chlorambucil	Chronic lymphocytic leukemia, primary macroglobulinemia, Hodgkin's disease, non-Hodgkin's lymphomas	 4-[bis(2-chlorethyl)amino]benzenebutanoic acid
	Ethylenimines and methylmelamines	Hexamethylmelamine	Ovarian cancer	 N2,N2,N4,N4,N6,N6-hexamethyl-1,3,5-triazine-2,4,6-triamine

(*continued on next page*)

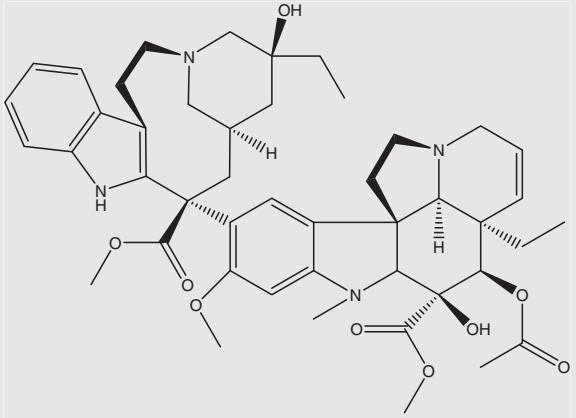
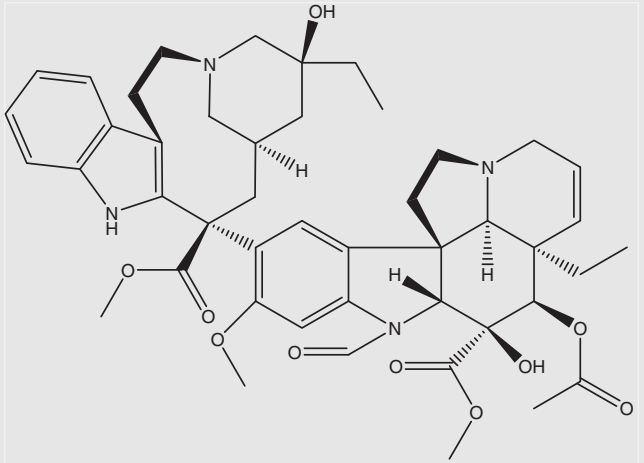
Table 1 *continued*

Class	Type of agent	Drugs	Disease	Structure
		Thiotepa	Bladder, breast, ovarian cancer	 1,1',1''-phosphorothioyltriaziridine
	Alkyl sulfonates	Busulfan	Chronic granulocytic leukemia	 Butane-1,4-diyl dimethanesulfonate
	Nitrosoureas	Carmustine	Hodgkin's disease, non-Hodgkin's lymphomas; primary brain tumors, multiple myeloma, malignant melanoma	 N,N'-bis(2-chloroethyl)-N-nitroso-urea
		Lomustine	Hodgkin's disease	 N-(2-chloroethyl)-N'-cyclohexyl-N-nitrosourea
	Triazenes	Dacarbazine	Malignant melanoma, Hodgkin's disease	 5-(3,3-Dimethyl-1-triazenyl)imidazole-4-carboxamide

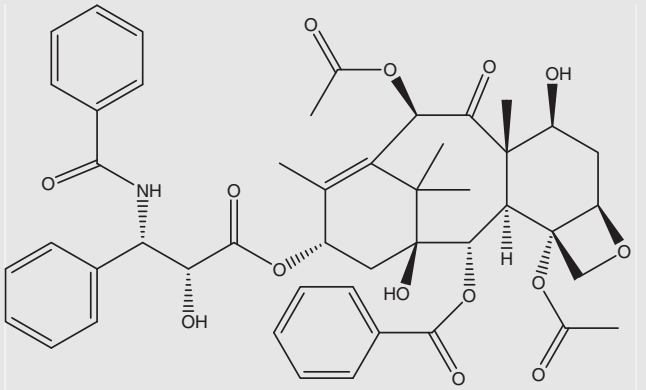
Antimetabolites	Folate antagonist	Methotrexate	Acute lymphocytic leukemia; choriocarcinoma; breast, head and lung cancer	 (2S)-2-[(4-{[(2,4-diaminopteridin-6-yl)methyl](methyl)amino} benzoyl)amino]pentanedioic acid
	Pyrimidine analogs	Fluorouracil	Breast, colon, stomach, pancreas, ovarian, head and neck, urinary bladder cancer	 5-fluoro-1H-pyrimidine-2,4-dione
		Cytarabine	Acute granulocytic and lymphocytic leukemia	 4-amino-1-[(2R,3S,4R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl] pyrimidin-2-one
	Purine analogs	Mercaptopurine	Acute granulocytic and lymphocytic leukemia	 3,7-dihydropurine-6-thione

(*continued on next page*)

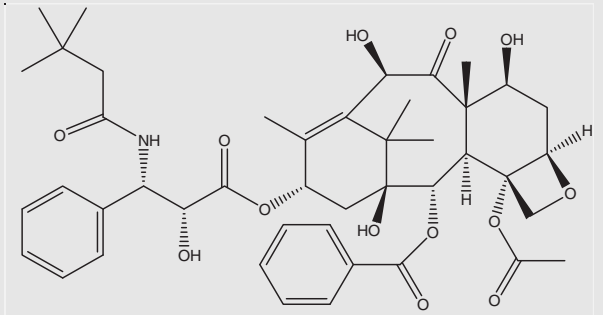
Table 1 (*continued*)

Class	Type of agent	Drugs	Disease	Structure
Natural products	Vinca alkaloids	Vinblastine	Hodgkin's disease, non-Hodgkin's lymphomas, breast and testis cancer	 Dimethyl (2ß,3ß,4ß,5a,12ß,19a)- 15-[(5S,9S)- 5- ethyl- 5-hydroxy- 9-(methoxycarbonyl)-1,4,5,6,7,8, 9,10-octahydro- 2H- 3,7-methanoazacycloundecino[5,4-b]indol- 9-yl] - 3-hydroxy- 16-methoxy- 1-methyl- 6,7-didehydroaspidospermidine- 3,4-dicarboxylate
		Vincristine	Acute lymphocytic leukemia, neuroblastoma, Wilm's tumor	 Methyl (1R,9R,10S,11R,12R,19R)- 11-(acetyloxy)-12-ethyl- 4-[(13S,15S,17S)-17-ethyl- 17-hydroxy- 13-(methoxycarbonyl) - 1,11-diazatetracyclo[13.3.1.04, 12.05,10]nonadeca- 4(12),5,7,9-tetraen- 13-yl] - 8-formyl- 10-hydroxy- 5-methoxy- 8,16-diazapentacyclo[10.6.1.01,9.02,7. 016,19]nonadeca- 2,4,6, 13-tetraene- 10-carboxylate

Taxanes	Paclitaxel, Docetaxel	Ovarian, breast, lung, head and neck, urinary bladder cancer



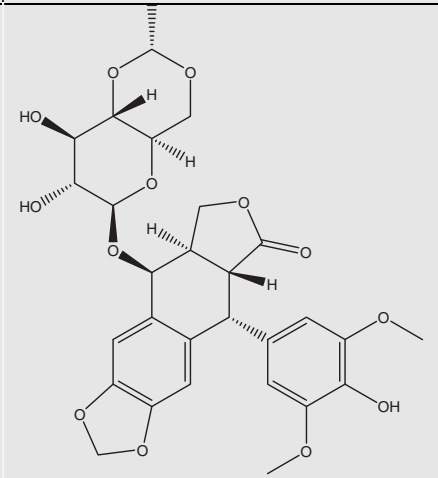
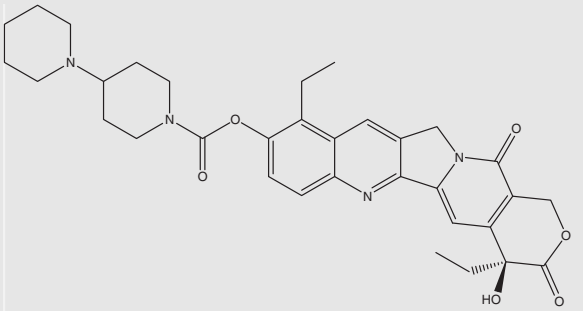
(2a,4a,5ß,7ß,10ß,13a)-4,10-bis(acetyloxy)-13-{[(2R,3S)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoyl]oxy}-1,7-dihydroxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate

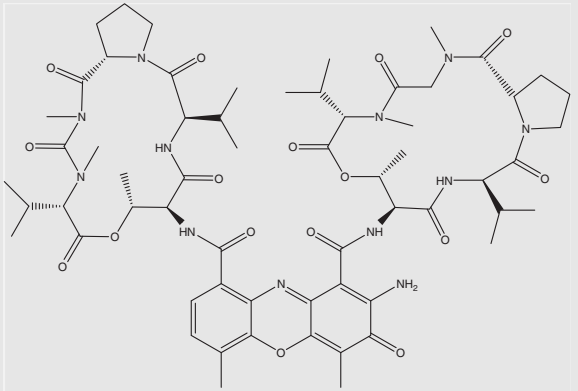
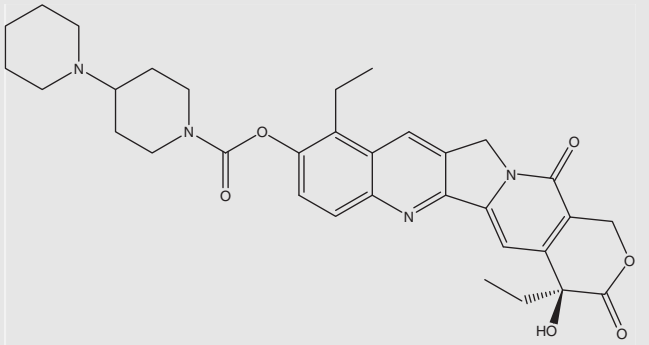


1,7ß,10ß-trihydroxy-9-oxo-5ß,20-epoxytax-11-ene-2a,4,13a-triyl 4-acetate 2-benzoate-13-{(2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoate}

(*continued on next page*)

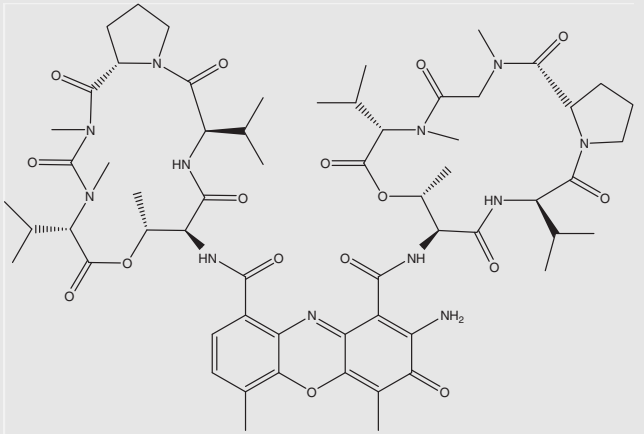
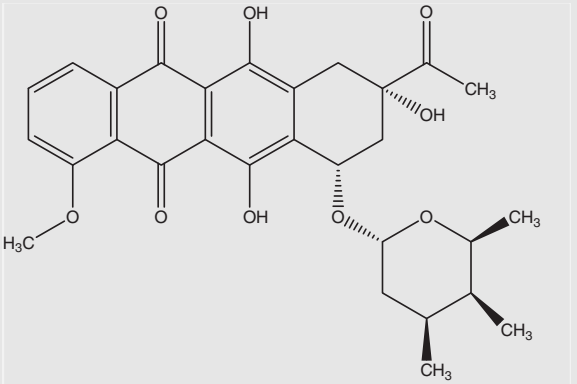
Table 1 (*continued*)

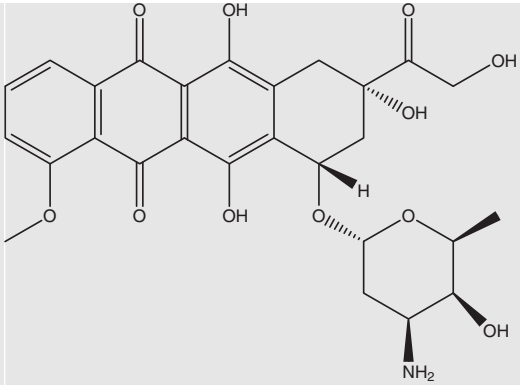
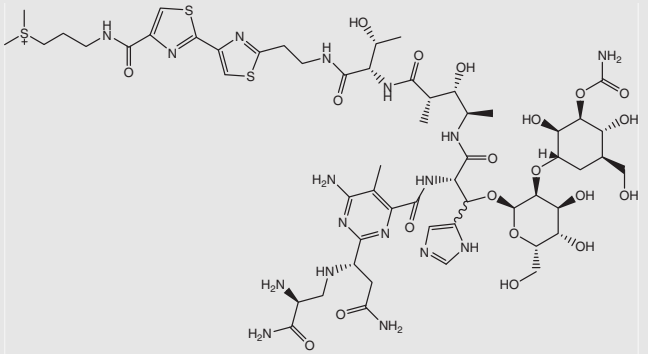
Class	Type of agent	Drugs	Disease	Structure
	Epipodophylotoxins	Etoposide, Teniposide	Testis, small-cell lung, breast cancer; Hodgkin's disease, non-Hodgkin's lymphomas, acute granulocytic leukemia	 4'-demethyl-epipodophyllotoxin 9-[4,6-O-(R)-ethylidene -beta-D-gluco-pyranoside], 4'-(dihydrogen phosphate)
				 (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano [3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate

Camptothecins	Topotecan, Irinotecan	Ovarian cancer, small-cell lung cancer, colon cancer	 2-amino-N,N'- bis[(6S,9R,10S,13R,18aS)-6, 13-diisopropyl- 2,5,9-trimethyl- 1,4,7,11, 14-pentaoxohexadecahydro- 1H-pyrrolo[2,1-i] [1,4,7,10,13] oxatetraazacyclohexadecin - 10-yl]- 4,6-dimethyl- 3-oxo- 3H-phenoxazine- 1,9-dicarboxamide  (S)-4,11-diethyl-3,4,12,14-tetra hydro-4-hydroxy-3,14-dioxo-1H-pyrano [3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate

(*continued on next page*)

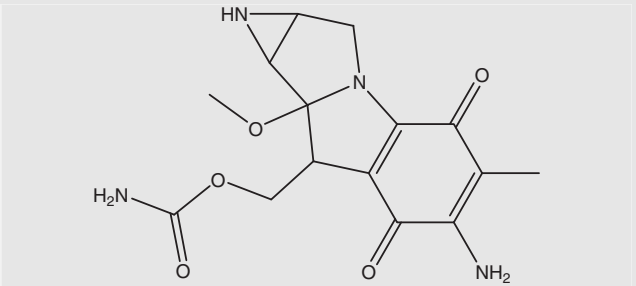
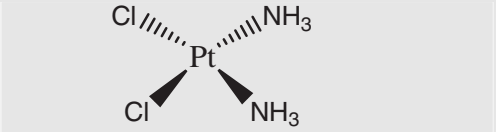
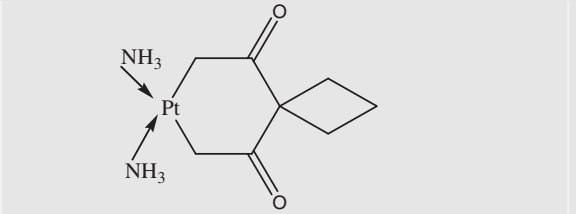
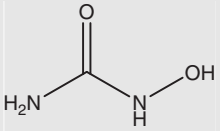
Table 1 (*continued*)

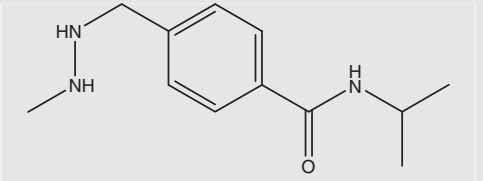
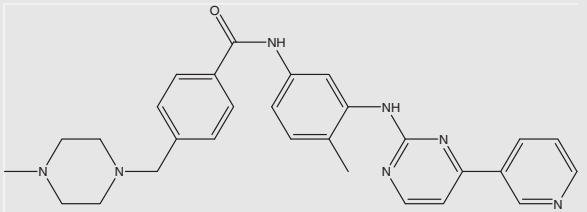
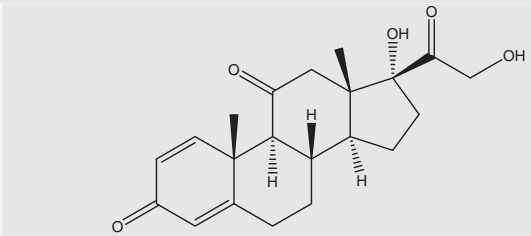
Class	Type of agent	Drugs	Disease	Structure
	Antibiotics	Dactinomycin	Choriocarcinoma, Wilm' tumor, Kaposi's sarcoma	 2-amino-N,N'- bis[(6S,9R,10S,13R,18aS)-6, 13-diisopropyl- 2,5,9-trimethyl- 1,4,7,11, 14-pentaoxohexadecahydro- 1H-pyrrolo[2,1-i] [1,4,7,10,13] oxatetraazacyclohexadecin - 10-yl]- 4,6-dimethyl- 3-oxo- 3H-phenoxazine- 1,9-dicarboxamide
		Daunorubicin	Acute granulocytic and lymphocytic leukemia	 (8S,10S)-8-acetyl-10-[(2S,4S,5S,6S)-4-amino-5-hydroxy-6-methyl-oxan-2-yl]oxy-6,8,11-trihydroxy-1-methoxy-9,10-dihydro-7H-tetracene-5,12-dione

Doxorubicin	Soft-tissue, osteogenic, Hodgkin's disease, non-Hodgkin's lymphomas; breast, thyroid, lung cancer	 (8S,10S)-10-(4-amino-5-hydroxy-6-methyl-tetrahydro-2H-pyran-2-yloxy)-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione
Bleomycin	Testis, skin, lung, head and neck, urinary bladder cancer	 (3-{[(2'-{(5S,8S,9S,10R,13S)-15-{6-amino-2- [(1S)-3-amino-1-{[(2S)-2,3-diamino-3 oxopropyl] amino}-3-oxopropyl] -5-methylpyrimidin-4-yl}-13-[{[(2R,3S,4S,5S,6S)-3-{[(2R,3S,4S,5R,6R)-4-(carbamoyloxy)-3,5-dihydroxy-6- (hydroxymethyl)tetrahydro-2H-pyran-2-yl]oxy} -4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl]oxy} (1H-imidazol-5-yl)methyl]-9-hydroxy-5-[(1R)-1-hydroxyethyl]-8,10-dimethyl-4,7,12,15-tetraoxo-3,6,11,14-tetraazapentadec-1-yl}-2,4'-bi-1,3- thiazol-4-yl)carbonyl]amino}propyl)(dimethyl)sulfonium

(*continued on next page*)

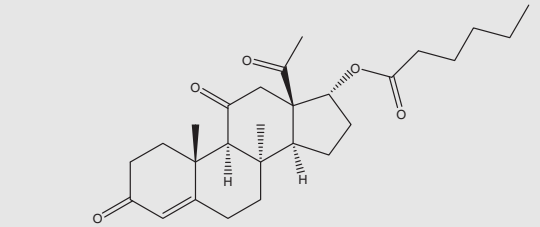
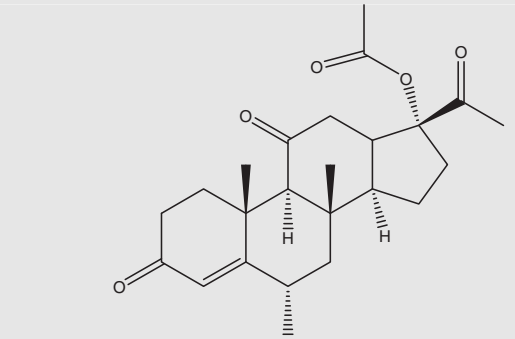
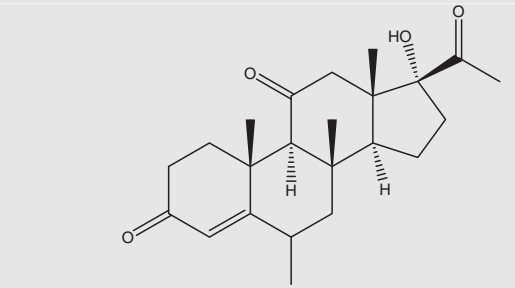
Table 1 (*continued*)

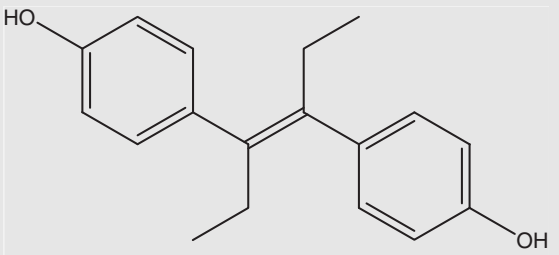
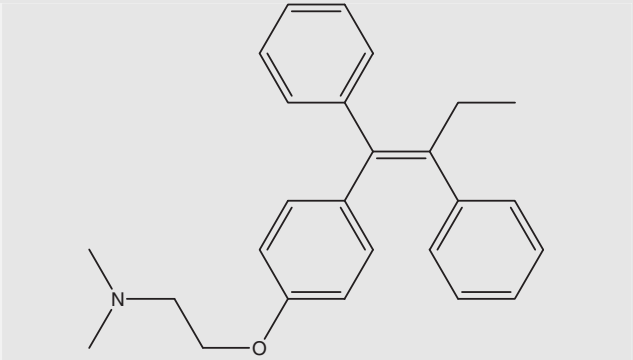
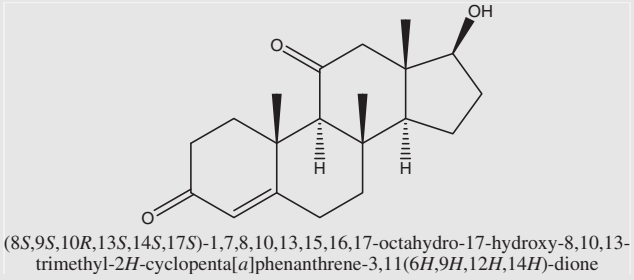
Class	Type of agent	Drugs	Disease	Structure
		Mitomycin	Testis, skin, lung, head and neck and genitourinary tract cancer	 [6-Amino-8a-methoxy-5-methyl-4,7-dioxo-1,1a,2,4,7,8,8a,8b-octahydroazireno[2',3':3,4]pyrrolo[1,2-a]indol-8-yl]methyl carbamate
Miscellaneous	Platinum coordination complexes	Cisplatin, Carboplatin	Testis, ovary, bladder, head and neck, lung, thyroid, osteogenic sarcoma	 (SP-4-2)-diamminedichloridoplatinum
				 cis-diammine(cyclobutane-1,1-dicarboxylate-O,O')platinum(II)
	Substituted urea	Hydroxyurea	Chronic granulocytic leukemia	 Hydroxyurea

	Methylhydrazine derivatives	Procarbazine	Hodgkin's disease	 N-isopropyl-4-[(2-methylhydrazino)methyl]benzamide
	Tyrosine kinase inhibitors	Imatinib	Chronic myelocytic leukemia	 4-[(4-methylpiperazin-1-yl)methyl]-N-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)benzamide
Hormones and antagonist	Adrenocorticosteroids	Prednisone	Acute and chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphomas	 (8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-7,8,13,15,16,17-hexahydro-17-hydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-6*H*-cyclopenta[*a*]phenanthrene-3,11(9*H*,10*H*,12*H*,14*H*)-dione

(*continued on next page*)

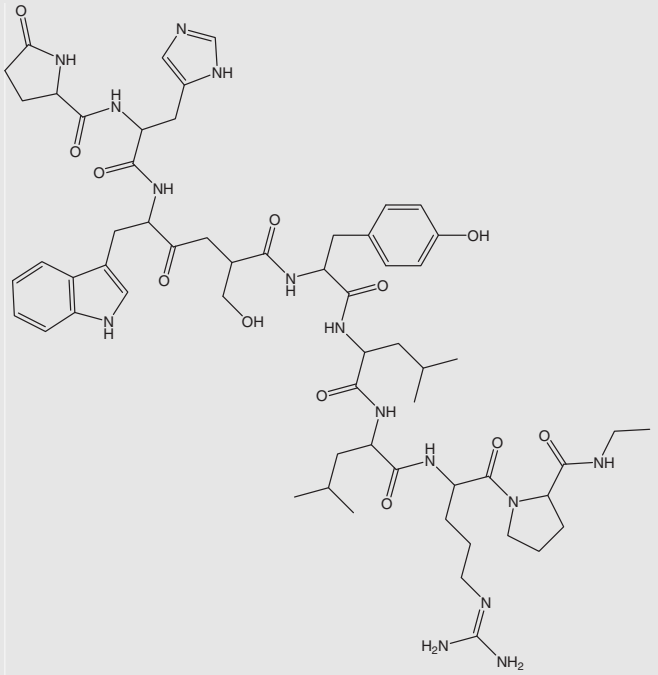
Table 1 (*continued*)

Class	Type of agent	Drugs	Disease	Structure
	Progestins	Hydroxyprogesterone caproate, Medroxyprogesterone acetate, Megestrol acetate	Endometrium, breast cancer	 (8*R*,9*S*,10*R*,13*R*,14*S*,17*R*)-13-acetyl-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-8,10-dimethyl-3,11-dioxo-1*H*-cyclopenta[*a*]phenanthren-17-yl hexanoate  (6*S*,8*S*,9*S*,10*R*,14*R*,17*R*)-17-acetyl-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-6,8,10-trimethyl-3,11-dioxo-1*H*-cyclopenta[*a*]phenanthren-17-yl acetate  (8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-acetyl-1,7,8,10,13,15,16,17-octahydro-17-hydroxy-6,8,10,13-tetramethyl-2*H*-cyclopenta[*a*]phenanthrene-3,11(6*H*,9*H*,12*H*,14*H*)-dione

Estrogens	Diethylstilbestrol	Breast, prostate cancer	 4,4'-(3E)-hex-3-ene-3,4-diyldiphenol
Antiestrogen	Tamoxifen	Breast cancer	 (Z)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-N,N-dimethylethanamine
Androgens	Testosterone propionate	Breast cancer	 (8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-1,7,8,10,13,15,16,17-octahydro-17-hydroxy-8,10,13-trimethyl-2*H*-cyclopenta[*a*]phenanthrene-3,11(6*H*,9*H*,12*H*,14*H*)-dione

(*continued on next page*)

Table 1 (*continued*)

Class	Type of agent	Drugs	Disease	Structure
	Gonadotropin-releasing hormone analog	Leuprolide	Prostate cancer	 N-[1-[[1-[[1-[[1-[[1-[[1-[[5-(diaminomethylideneamino)-1-[2-(ethylcarbamoyl)pyrrolidin-1-yl]-1-oxo-pentan-2-yl]carbamoyl]-3-methyl-butyl]carbamoyl]-3-methyl-butyl]carbamoyl]-2-(4-hydroxyphenyl)ethyl]carbamoyl]-2-hydroxy-ethyl]carbamoyl]-2-(1H-indol-3-yl)ethyl]carbamoyl]-2-(3H-imidazol-4-yl)ethyl]-5-oxo-pyrrolidine-2-carboxamide

to pristane, whereas most other strains were not susceptible. Similarly, SENCAR mice were uniquely susceptible to developing skin tumors in response to DMBA and PMA. On the basis of these results it showed that critical genes and factors contribute to tumor development. Individuals with chronic inflammatory conditions and carcinogen exposure (e.g. smokers) developed cancer while others do not.

The different progenitors of the inflammation are known; which includes chronic bacterial and parasitic infections, chemical irritants and non-digestible particles. Studies showed that any parasitic infection that persists or recurs over many years can predispose to cancer.

2.1.1. Progenitors of inflammation due to bacterial infections lead to cancer

The strongest association between chronic bacterial infection and the development of cancer involved the organism *Helicobacter pylori*, which is associated with at least a twofold-increased risk of adenocarcinoma of the stomach (Slaga et al., 1978 and Potter, 1999). In addition, *H. pylori* infection also increased the incidence of MALT lymphoma (Correa, 1995). *H. pylori* infection is the major risk factor in gastric cancer and the eradication of *H. pylori* can reverse many biochemicals, genetic and epigenetic changes which induce in the stomach leading to the development of gastric cancer (GC). *Helicobacter* infection in humans is always accompanied by mucosal inflammation (gastritis) with an influx of lymphocytes, plasma cells, and neutrophils. The International Agency for Research on Cancer (IARC) in its meeting in 1994 in Lyon, France, concluded that there is sufficient evidence to classify *H. pylori* as "Group 1 = Definite" human carcinogen (IARC Monograph, 1994). The strongest evidence came from control studies based on serological evidence of the *H. pylori* infection. Overall conclusion of six meta-analyses was that *H. pylori* infection was associated with approximately a twofold-increased risk of developing a GC range of pooled odds ratios of 1.92–2.56, all with significant 95% confidence intervals. The strong association between *H. pylori* infection and GC has been obtained in a widely publicized prospective study involving 1526 Japanese patients with duodenal ulcers, gastric ulcers, gastric hyperplasia or nonulcer dyspepsia at entry. After a follow-up period of 7–8 years, GC was detected in 2.9% of *H. pylori* positive patients and not in any participant without *H. pylori* infection. Huang et al. identified 16 qualified studies with 2284 cases and 2770 controls. *H. pylori* seropositivity significantly increased the risk of GC by 2.28 folds. The same study found that an association between *H. pylori* infection and GC was equally strong for intestinal and diffuse cancer [odds ratio 2.49 (95% CI, 1.41–4.43)] with a 2.58 [(95% CI, 1.47–4.53)] (Uemura et al., 2001; Huang et al., 2003; Wong et al., 2004; Forman and Pisani, 2008; Siman et al., 2007) Eradication of *Helicobacter pylori* infection with antibiotics may also eliminate the excess risk for cancer, but this has not yet been established.

2.1.2. Progenitors of inflammation due to parasitic infections lead to cancer

Several parasitic infections are well known to increase the risk of cancer. Schistosomiasis was prevalent primarily in the third world countries and is difficult to treat and it causes due to contaminated water supplied (Parsonnet, 1995). Chronic schistosomiasis induces cystitis, fibrosis and increases the incidence of carcinoma of the bladder, liver and rectum and follicular lymphoma of the spleen, with different strains of the parasites infecting specific organs and causes various cancers (Konturek et al., 1999). Liver flukes (*Opisthorchis* and *Clonarchis*), introduced by eating raw fish, infect the bile duct and lead to chronic cholangitis associated with an increased incidence of cholangiocarcinoma (Tavani et al., 2000). Chronic infection and inflammatory diseases may also contribute to the development of Hodgkin's disease and non-Hodgkin's lymphoma (Copie-Bergman et al., 1997).

2.1.3. Progenitors of inflammation due to viral infections lead to cancer

Many different viruses cause an increased incidence of cancer. Chronic inflammation associated with the hepatitis B and C viruses, which lead to chronic active hepatitis and hepatocellular carcinoma, Epstein–Barr virus (EBV) is associated with B-cell non-Hodgkin's lymphoma (Bornstein et al., 1995). Other viral infections can also increase the incidence of cancer, but the role of inflammatory mediators is less clear. For example, the human papillomavirus, herpes simplex virus 2, and cytomegalovirus have been implicated in cervical and other carcinomas (Tung et al., 2001). Among RNA retroviruses, the human immunodeficiency virus (HIV) helps in the development of non-Hodgkin's lymphoma, squamous cell carcinomas, and Kaposi's sarcoma while the human T-cell lymphoma virus causes adult T-cell leukemia (Seitz et al., 1998).

Unlike the other parasitic infections described here, viruses implicated in inducing neoplasia directly infect the cells that ultimately undergo neoplastic transformation. Hence, it is difficult to determine whether these agents act by causing a chronic inflammatory condition, by directly transforming the cells that they infect, or both. Most of these viruses induce chronic increased proliferation of the infected cells, thus predisposing to neoplastic transformation. For example, EBV causes sustained proliferation of peripheral B-lymphocytes, but when coupled with a secondary mutation can result in a malignant transformation, such as occurs with the chromosomal translocations that activate the *c-myc* oncogene in Burkitt's lymphoma. The hepatitis viruses are thought to give rise to hepatocellular carcinoma by causing liver damage and regeneration together with the generation of secondary inflammatory mediators (Steenland and Stayner, 1997).

3. Non-infectious causes of chronic inflammation lead to cancer

Various non-infectious agents also cause chronic inflammation associated with an increased risk of cancer. For example, esophageal reflux causes chronic exposure of the esophageal epidermis to irritation by gastric acids. This leads to reflux esophagitis, or Barrett's esophagus, and subsequent development of esophageal carcinoma (Hanahan and Weinberg, 2000). Excess fecal bile acids in patients with primary sclerosing cholangitis and ulcerative colitis are associated with an increased risk of colorectal carcinoma. A recent publication demonstrated that ursodiol, a drug that reduces the colonic levels of deoxycholate and other bile acids (used to treat cholangitis), significantly reduces the incidence of neoplasia (Hennings et al., 1993). Chronic irritation of the liver by alcohol causes cirrhosis and hepatocellular carcinoma (Jackson et al., 1997).

Non-digestible agents such as asbestos, coal and silica dust lead to chronic inflammation in the lung because of the inability of the immune system to remove the substances. Such sterile inflammations increase the incidence of epithelial cancers including mesothelioma and lung carcinoma (Baron and Sandler, 2000). Environmental carcinogen exposure is a requisite for the development of mostly all lung cancers such as asbestos exposure interacts synergistically with tobacco smoke to induce lung cancer. Previous studies have suggested that asbestos was associated with the presence of a k-*ras* mutation in adenocarcinoma of the lung. k-*ras* mutation is strongly associated with adenocarcinoma. There were 84 male patients with available questionnaire-derived work history data and paraffin-embedded tumor tissue for determination of k-*ras* mutation status. Chest radiographic evaluation was done for all of the patients who reported occupational exposure to asbestos. The prevalence of k-*ras* mutation was higher among those with a history of occupational asbestos exposure (crude odds ratio, 4.8; 95% confidence interval, 1.5–15.4) compared to those without asbestos exposure, and this association remained after adjustment for age and pack-years smoked (adjusted odds ratio, 6.9; 95% confidence interval, 1.7–28.6). These data suggest that asbestos exposure increases the likelihood of mutation at k-*ras* codon 12 and that this process occurs independently of the induction of interstitial fibrosis (Nelson et al., 1999). Cigarette smoke is a complex pro-neoplastic agent that may act, in part, by inducing a chronic inflammatory condition. Smoking not only causes chronic bronchitis, but also delivers an array of genotoxic carcinogens (e.g. nitrosamines, peroxides) into the lungs. Definitive evidence that chronic inflammation predisposes to cancer requires identification of the causative inflammatory mediators as well as the agents that prevent neoplastic transformation through inhibition of the inflammatory process. The remainder of this review will focus on the mechanisms whereby inflammatory mediators promote neoplastic transformation.

4. Prostaglandins a mediator responsible for development of cancer

Different evidence from human and animal studies suggests that prostaglandins contribute to the development of cancer (Herschman 1996; Giovannucci et al., 1995). Prostaglandins such as prostaglandin E2 (PGE2) are lipid mediators of the inflammatory immune response and are derived from oxidative metabolism of arachidonic acid. These lipids are synthesized in large quantities by inflammatory cells in response to both acute and chronic inflammatory stimuli. Two different cyclooxygenase (COX) enzymes catalyze the rate-limiting first step in prostaglandin synthesis (Labayle et al., 1991). COX-2 is expressed during inflammation. Its primary site of synthesis is inflammatory monocytes and macrophages, but it is also expressed in noninflammatory cells, such as fibroblasts, epithelial cells, and endothelial cells. Bacterial cell products and inflammatory cytokines induce *in vitro* expression of COX-2. Experimental induction of COX-2 in animal models is accomplished with agents that induce chronic inflammation such as administration of azoxymethane to rats. COX-1 is a constitutive enzyme expressed in most cell types and is associated with regulation of housekeeping functions such as gastric acid secretion.

4.1. Tumorigenesis promotes by prostaglandins

Many different mechanisms have been proposed to explain the mechanisms of tumorigenesis by prostaglandins (Upulescu, 1996). Prostaglandins can stimulate cell proliferation, induce synthesis of cytokines such as IL-6 that serve as tumor growth factors, synthesis of prostaglandins is coupled with formation of DNA-reactive by-products with mutagenic potential; e.g. formation of malondialdehyde (MDA) from prostaglandin G2, and it also can induce angiogenesis, which is required for growth and metastasis of tumors. It has been suggested that these drugs may not be acting entirely through the inhibition of PGE2 synthesis because the addition of exogenous PGE2 fails to overcome the inhibitory effect of the NSAIDs (Sakata et al., 1986). However, the concentrations of NSAIDs required to inhibit prostaglandin-independent angiogenesis *in vitro* are quite high (e.g. 250–500 μM of indomethacin) and are unlikely to be achieved *in vivo*. In contrast, inhibition of prostaglandin synthesis by NSAIDs occurs at concentrations that are achieved *in vivo* (e.g. 1 μM or less for indomethacin) (Carter et al., 1989).

In addition to serving as pro-inflammatory mediators, prostaglandins are also immunosuppressive. By inhibiting the functions of T-cells and macrophages, they may decrease immune surveillance and thereby allow nascent tumor cells to escape detection by the immune system. Prostaglandins may inhibit apoptosis of tumor cells by increasing expression of the anti-apoptotic oncogene *bcl-2* or by removing arachidonic acid, which is thought to be pro-apoptotic. It also stimulates cell signaling through peroxisome-proliferator-activated receptor delta (*PPAR-δ)*, a transcription factor that regulates proliferation-associated genes.

4.2. Cytokines

Inflammatory cells secrete a large number of cytokines and chemokines that can promote the outgrowth of neoplastic cells. These factors are produced in response to pro-inflammatory stimuli such as bacterial lipopolysaccharide. Neoplastic cells have a reduced need for normal metabolic factors, but they often require the presence of specific cytokines in order to proliferate, at least in the early stages of tumor development. Many tumor cells developing in chronically inflamed tissue cultivate a growth advantage by acquiring the ability to proliferate in response to cytokines. They may express growth factor receptors abnormally or alter their response to the factors by undergoing cell division instead of differentiation.

Examples of tumor cell cytokine dependence in human disease are the growth dependence of AIDS- and EBV-associated B-cell lymphomas, B-cell leukemia, and multiple myeloma on the inflammatory cytokines IL-6 and IL-15 and the dependence of malignant mesothelioma on platelet-derived growth factor (Reddy et al., 1987; Yamamoto et al., 1992). Monocytes, macrophages, and T-cells are major sources of cytokines that promote outgrowth of preneoplastic and malignant cells, in addition to autocrine growth factor production by the tumor cells themselves.

4.3. Tumor progression mechanisms

Cytokines can contribute to tumor progression by mechanisms other than direct stimulation of cell growth. One such mechanism involves inducing the production of reactive oxygen and

nitrogen intermediates. For example, TNF-alpha is known to enhance the formation of reactive oxygen intermediates by neutrophils and other cells. IL-1-beta, TNF-alpha, and interferon (IFN)-gamma stimulate expression of inducible nitric oxide synthase and the formation of nitric oxide in cholangiocarcinoma. This process has been shown to cause DNA damage and inhibit DNA repair in tumor cells. IL-8 can promote tumorigenesis through two different mechanisms. One involves induction of angiogenesis, possibly through the synthesis of matrix metalloproteinases. In addition, IL-8 recruits inflammatory neutrophils to the site of inflammation and may thereby increase formation of reactive oxygen and nitrogen intermediates. Some cytokines may also promote tumorigenesis by inducing immunosuppression, as is suggested for transforming growth factor-beta.

5. NSAIDs and novel agents

Chronic intake of NSAIDs may reduce carcinogenesis by inhibiting production of prostaglandins, cytokines, and angiogenic factors. Note that NSAIDs do not eliminate inflammation but rather act by reducing the production of selected inflammatory factors. Hence, unlike steroids, they do not suppress elements of the immune response that are necessary for tumor depletion such as T-cells, NK cells, and macrophages. COX-2 selective inhibitors may provide a safer method for chemoprevention than older NSAIDs such as aspirin and indomethacin, which also inhibit COX-1 activity and cause gastric lesions.

NSAIDs exert analgesic, antipyretic, and anti-inflammatory effects through the inhibition of COX-catalyzed biosynthesis of prostaglandin's (Nakadate et al., 1982). Moreover, the ability of these NSAIDs drugs to prevent cancer is thought to be due, in part, to COX inhibition. Currently, there are two known isoforms of COX, both of which catalyze the metabolism of arachidonic acid to prostaglandin H_2, a precursor to prostaglandins (Earashi et al., 1995). The COX-1 isoform is constitutively expressed and produces the prostaglandins important for normal physiological function. COX-2 can be induced by cytokines, growth factors, and tumor promoters and produces prostaglandins at sites of inflammation (Parrett et al., 1997). In carcinogenesis, over expression of COX is thought to deregulate arachidonic acid metabolism and lead to elevated prostaglandin production (Buckmann et al., 1998). The incidence of COX-2 protein expression gradually increases with the development of esophageal lesions, from 75% in metaplasia, to 83% in low grade dysplasia and up to 100% in high-grade dysplasia (Morris et al., 2001). Increased prostaglandin (PG) levels have been observed in human and animal tumors compared with surrounding normal tissue and are thought to contribute to colon carcinogenesis by influencing cell proliferation, tumor promotion, immune response, and metastasis (Marnett, 1992; Kraemer et al., 1996). Increased PG synthesis caused stimulation of cell proliferation and contributed to the development of dysplasia in Barrett's epithelium (Zhang et al., 2001).

The role of arachidonic acid metabolites as modulators in the multi-step process of carcinogenesis, particularly in tumor promotion, has often been postulated with supportive evidence from epidemiological and experimental studies. This notion is strengthened by reports on a reduced mortality and a lower incidence of human colon cancer following chronic consumption of non-steroidal anti-inflammatory drugs (NSAIDs), e.g. acetylsalicylic acid (Puga et al., 1997). Sulindac and indomethacin suppress the number and size of colonic polyps in patients with familial adenomatous polyposis (Vogel et al., 1998; Reddy et al., 1987). Moreover, inhibitors of cyclooxygenase and lipoxygenase activities decrease the tumor promoting effects of various structurally unrelated agents and inhibit the growth of tumor cells *in vivo* and *in vitro*. The impact of arachidonic metabolism on tumorigenesis is based on the following observations: (i) the levels of specific metabolites of arachidonic acid and the expressions of cyclooxygenases and lipoxygenases are enhanced in various human and rodent tumors and (ii) the cyclooxygenase isoenzyme COX-2 is induced in normal tissues by the treatment with tumor promoters, e.g. TCDD and TPA (Levy, 1997). Interestingly, the induction of COX-2 has been observed in pathological processes including tumor promotion. Thus, in a quest for a more mechanistic risk assessment pertaining to tumor promoters such as dioxin-like compounds, the expression of cyclooxygenase activities may provide an important link necessary for this goal (Rubio, 1984).

5.1. Chemoprotection by NSAIDS

A growing body of evidence suggests that anti-inflammatory medications, such as aspirin, NSAIDs and more recently COX-2 selective inhibitors, have a chemoprotective effect against a variety of neoplasms (Rubio, 1986). Coogan et al. found that regular NSAID use (at least 4 days a week for >3 months) reduced the risk of GC in a hospital based control study of 254 patients (OR 0.3; 95% CI, 0.1–0.6). The protective effect was more pronounced among those patients using NSAIDs continually for >5 years (OR 0.2; 95% CI, 0.1–0.7) than for those using NSAIDs for <5 years (OR 0.4; 95% CI, 0.1–0.9) (Coogan et al., 2000). In a large cohort study of 635,031 subjects followed over 6 years, the American Cancer Society demonstrated that regular exposure to aspirin (>16 times/month) exerted a protective effect against GC; aspirin users were found to have approximately 50% the risk of GC compared with nonusers (OR = 0.53; 95% CI, 0.34–0.81) (Yamagata et al., 2002). A recent metanalysis by Abnet et al. found a significant reduction in the incidence of GC in aspirin or non-aspirin NSAID users (OR 0.74; 95% CI, 0.64–0.87 and OR 0.79; 95% CI, 0.71–0.89, respectively) (Abnet et al., 2009). There is compelling epidemiological evidence that the regular or occasional use of aspirin or other NSAIDs drug is inversely related to the risk of cancer (Zimmermann et al., 1999; Wilson et al., 1998). The reduction in the relative risk varies between 50% and 90%. A large study conducted by the American Cancer Society reported a 40% reduction in the risk of cancer in individuals who used aspirin 16 or more time per month compared with those who never used aspirin. In addition a population based case-control study found that current users of aspirin and other NSAIDs have an almost 50% reduction in the risk of developing either adenocarcinoma or squamous cell carcinoma. Beside the epidemiological evidence, experimental and preclinical evidence suggest a possible preventive or therapeutic benefit of aspirin or other NSAIDs in cancer. For example, Li et al. reported that treatment with aspirin resulted in significant growth inhibition of 10 esophageal cancer cell lines (Shamma et al., 2000). This growth inhibition was time and dose dependent and was associated with the induction with apoptosis. Also, Rubio previously showed

that the NSAID indomethacin suppressed the development and delayed the growth of chemically induced esophageal cancer in mice either when given in tandem with NMBA (a potent esophageal carcinogen) or when its delivery was delayed to allow tumor development (Shirvani et al., 2000; Liu et al., 2001). Taken together, the evidence suggests a potential role for aspirin and other NSAIDs in the prevention, and possible treatment, of esophageal cancer. The only well known function of NSAIDs to date is their ability to suppress PG synthesis.

6. COX-2 contributes to cancer: as preclinical evidence

Evidence suggests that COX-2 may contribute to esophageal carcinogenesis. Increased amount of COX-2 is commonly found in adenocarcinoma as well as squamous cell carcinoma of the esophagus (Nasser, 2004 and Eling et al., 1990). In addition, over expression of COX-2 has been observed in premalignant condition of the esophagus, such as squamous dysplasia and Barrett's esophagus (Souza et al., 2000). Shirvani et al. reported a progressive increase in COX-2 expression with increasing histological severity from metaplasia to low-grade and high-grade dysplasia (Li et al., 2001). Increased COX-2 expression has also been associated with decreased survival in patient with esophageal adenocarcinoma. The Approve trial included a randomized multicenter, placebo controlled, double blind trial to investigate whether the chronic use of the coxib (rofecoxib 25 mg daily) would reduce the adenoma recurrence in 2586 patients with a history of colorectal adenomas. Therapy with rofecoxib was associated with a significant reduction in adenoma number and size. An increase in rofecoxib associated cardiovascular adverse events beginning at 18 months was also noted, which led to early study termination (Baron et al., 2006). Similarly, Bertagnolli et al. in a five-year efficacy and safety analysis of the adenoma prevention with celecoxib trial found an inhibitory effect of celecoxib in colorectal adenoma formation but they reported an elevated risk for cardiovascular and thrombotic adverse events [6% (RR, 1.6; 95% CI, 1.0–2.5) and 7.5% (RR, 1.9; 95% CI, 1.2–3.1) in celecoxib 200 and 400 mg twice daily users, respectively, compared to 3.8% in placebo group (Bertagnolli et al., 2009). However, the most direct evidence supporting a cause-and-effect connection between COX-2 over expression and carcinogenesis comes from genetic studies. In a seminal study Oshima et al. reported that knocking out the COX-2 gene significantly reduced the numbers of intestinal polyps in a mouse model of familial adenomatous polyposis. In another study, forced expression of the COX-2 gene in the mammary gland of transgenic mice led to the development of mammary cancer (Langergren et al., 1999). These studies provide the most direct evidence of a cause-and-effect relationship between COX-2 and cancer development.

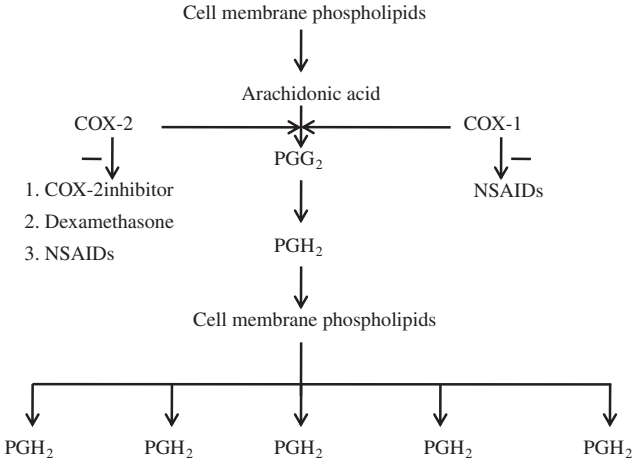


Figure 1 Biosynthetic pathway for eicosanoid derived from arachidonic acid.

6.1. Reactions catalyze by COX [Fig. 1]

6.1.1. Insertion of molecular oxygen into arachidonic acid.

6.1.2. Conversion to PGH_2 by the peroxidase activity (Hameeteman et al., 1989).

6.2. Possible mechanism of COX-2 induced carcinogenesis

The effects of COX-2 are attributed by several pathways that are potentially involved in the initiation and progression of cancer, including xenobiotics metabolism, apoptosis, angiogenesis, inflammation and immune surveillance.

6.3. Modification of known indomethacin to improve its specificity for COX-2

The Merck Frosst first reported improving the selectivity of indomethacin for COX-2 by making the larger trichlorobenzoyl analog (Fig. 2). Exchanging the carboxylic acid moiety of indomethacin for a 4-bromophenyle thiazole group (Fig. 3) afforded the highly selective COX-2 inhibitor. It is

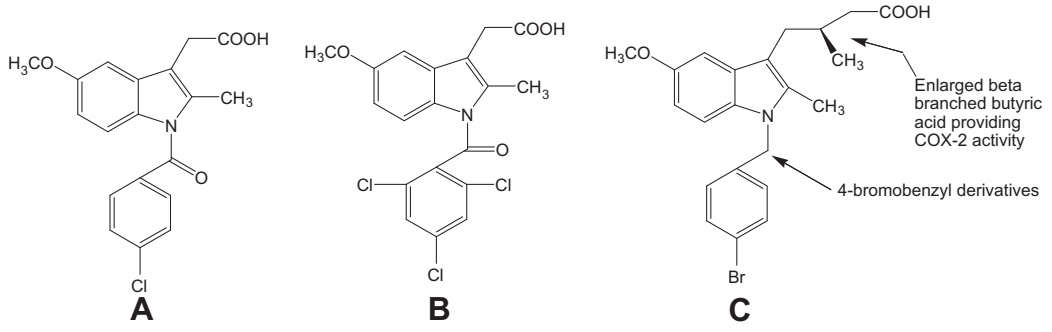


Figure 2 Modification of known indomethacin molecules: (A) indomethacin, (B) trichlorobenzoyl analog and (C) enlarged beta branched and 4-bromobenzyl derivative.

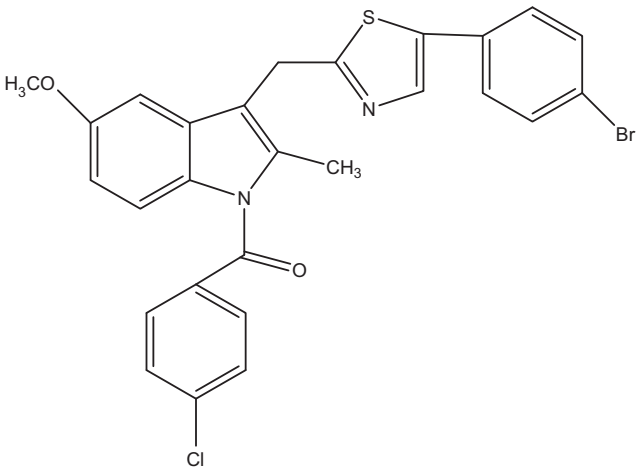


Figure 3 Exchanging with the carboxylic acid moiety of indomethacin with a 4-bromophenyle thiazole group.

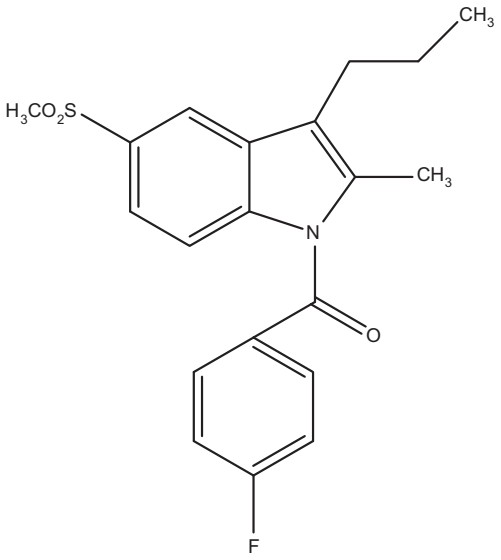


Figure 4 1-Benzoylindole, lacking a side chain at C-3 of the indole nucleus, bind to the active site in COX-2, but in a cell based assay inhibited prostaglandin formation by COX-2.

not known how the 1-benzoylindole (Fig. 4), lacking a side chain at C-3 of the indole nucleus, bind to the active site in COX-2, but in a cell based assay inhibited prostaglandin formation by COX-2 (Kunkel et al., 1986).

6.4. Future direction

The substantial body of experimental and preclinical work reviews shows that a link exists between COX-2 and tumor development or progression. However, the role of COX-2 inhibitor in the prevention or treatment of human tumors remains unsubstantiated. Numerous studies are currently in progress to evaluate both the safety and efficacy of COX-2 inhibitor given either as a chemo preventive agent in patients at a high risk for tumor development or in combination with the standard cytotoxic agent to treat existing malignancies. The present study may lead to discovery of new or better anti-cancer agents (Tsujii et al., 1998).

7. Conclusion

This review will summarize the clinical association between chronic inflammation and cancer and will describe the inflammatory factors and pathways that are thought to be pro-neoplastic agents. Emphasis will be placed on examining the role of the reactive oxygen species, nitrogen intermediates, cytokines and prostaglandins. It also indicates that addition of NSAIDs to conventional anti-cancer therapies may enhance their anti-tumor effect.

References

Abnet, C.C., Freedman, N.D., Kamangar, F., et al., 2009. Nonsteroidal anti-inflammatory drugs and risk of gastric and oesophageal adenocarcinomas: results from a cohort study and a meta-analysis. Br. J. Cancer 100, 551–557.

Baron, J.A., Sandler, R.S., 2000. Nonsteroidal anti-inflammatory drugs and cancer prevention Annu. Rev. Med. 51, 511–523.

Baron, J.A., Sandler, R.S., Bresalier, R.S., et al., 2006. Approve trial investigators. A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas. Gastroenterology 131, 1674–1682.

Bertagnolli, M.M., Eagle, C.J., Zauber, A.G., et al., 2009. Adenoma prevention with celecoxib study investigators five-year efficacy and safety analysis of the adenoma prevention with celecoxib trial. Cancer Prev. Res. 4, 310–321.

Boone, C.W., Kelloff, G.J., Steele, V.E., 1992. Natural history of intraepithelial neoplasia in humans with implications for cancer chemoprevention strategy. Cancer Res. 52, 1651–1659.

Bornstein, J., Rahat, M.A., Abramovici, H., 1995. Etiology of cervical cancer: current concepts. Obstet. Gynecol. Surv. 50, 146–154.

Buckmann, S.Y., Gresham, A., Hale, P., Hruza, G., Anast, J., Masferrer, J., Pentland, A.P., 1998. COX-2 expression is induced by UVB exposure in human skin: implications for the development of skin cancer. Carcinogenesis 19, 723–729.

Carter, C.A., Ip, M.M., Ip, C., 1989. A comparison of the effects of the prostaglandin synthesis inhibitors indomethacin and carprofen on 7,12-dimethylbenz[α]anthracene-induced mammary tumorigenesis in rats fed different amounts of essential fatty acid. Carcinogenesis 10, 1369–1374.

Coogan, P.F., Rosenberg, L., Palmer, J.R., et al., 2000. Nonsteroidal anti-inflammatory drugs and risk of digestive cancers at sites other than the large bowel. Cancer Epidemiol. Biomarkers Prev. 9, 119–123.

Copie-Bergman, C., Niedobitek, G., Mangham, D.C., et al., 1997. Epstein–Barr virus in B-cell lymphomas associated with chronic suppurative inflammation. J. Pathol. 183, 287–292.

Correa, P., 1995. Helicobacter pylori and gastric carcinogenesis. Am. J. Surg. Pathol. 19, S37–S43.

Doreswamy, R., Darshan, S., 1999. Japanese anticancer patents in comparison with currently used plant chemotherapeutics under ipr regime. Indian Drugs 36, 559–567.

Earashi, M., Noguchi, M., Kinoshita, K., et al., 1995. Effects of eicosanoid synthesis inhibitors on the *in vitro* growth and prostaglandin E and leukotriene B secretion of a human breast cancer cell line. Oncology 52, 150–155.

Ekbom, A., Helmick, C., Zack, M., et al., 1990. Ulcerative colitis and colorectal cancer A population-based study. N. Engl. J. Med. 323, 1228–1233.

Eling, T.E., Thompson, D.C., Foureman, G.L., 1990. Prostaglandin H synthase and xenobiotic oxidation. Annu. Rev. Pharmacol. Toxicol. 30, 1–45.

Elizabeth, R.B., Edward, L.G., Norval, W.K.J., Andrew, J.P., Lorna, D.J., 1998. Family history as a risk factor for ulcerative colitis-associated colon cancer in cotton-top tamarin. Gastroenterology 114, 669–674.

Forman, D., Pisani, P., 2008. Gastric cancer in Japan – honing treatment, seeking causes. N. Engl. J. Med. 359, 448–451.

Giovannucci, E., Egan, K.M., Hunter, D.J., et al., 1995. Aspirin and the risk of colorectal cancer in women. N. Engl. J. Med. 333, 609–614.

Goodman and Gilman's, 2001. The Pharmacological Basis of Therapeutics, 10th ed. pp. 1381–1384.

Hameeteman, W., Tytgat, G.N., Houthoff, H.J., 1989. Barrett's esophagus: development of dysplasia and adenocarcinoma. Gastroenterology 96, 1249.

Hanahan, D., Weinberg, R.A., 2000. Cell 100, 57–70.

Hennings, H., Glick, A.B., Greenhalgh, D.A., et al., 1993. Critical aspects of initiation, promotion, and progression in multistage epidermal carcinogenesis. Proc. Soc. Exp. Biol. Med. 202, 1–8.

Herschman, H.R., 1996. Prostaglandin synthase 2. Biochim. Biophys. Acta 1299, 125–140.

Huang, J.Q., Zheng, G.F., Sumanac, K., Irvine, E.J., Hunt, R.H., 2003. Meta-analysis of the relationship between cagA seropositivity and gastric cancer. Gastroenterology 125, 1636–1644.

IARC Monograph on the Evaluation of Carcinogenic Risks to Humans, 1994. Schistosomes, Liver Flukes and Helicobacter pylori, vol. 61. International Agency for Research on Cancer, Lyon, France.

Jackson, J.R., Seed, M.P., Kircher, C.H., et al., 1997. The codependence of angiogenesis and chronic inflammation. FASEB J. 11, 457–465.

Konturek, P.C., Bielanski, W., Konturek, S.J., et al., 1999. Helicobacter pylori associated gastric pathology. J. Physiol. Pharmacol. 50, 695–710.

Kraemer, S.A., Arthur, K.A., Denison, M.S., 1996. Regulation of prostaglandin endoperoxide H synthase-2 expression by 2,3,7,8,-tetrachlorodibenzo-p-dioxin. Arch. Biochem. Biophys. 330, 319–328.

Kunkel, S.L., Wiggins, R.C., Chensue, S.W., 1986. Regulation of macrophage tumor necrosis factor production by prostaglandin E2. Biochem. Biophys. Res. Commun. 137, 404.

Labayle, D., Fischer, D., Vielh, P., 1991. Sulindac causes regression of rectal polyps in familial adenomatous polyposis. Gastroenterology 101, 635–639.

Langergren, J., Bergstrom, R., Lindgren, A., 1999. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N. Engl. J. Med. 340, 825.

Levy, G.N., 1997. Prostaglandin H synthases, nonsteroidal anti-inflammatory drugs and colon cancer. FASEB J. 11, 234–247.

Li, M., Wu, X., Xu, X., 2001. Induction of apoptosis by cyclooxygenase-2 inhibitor NS398 through a cytochrome C-dependent pathway in esophageal cancer cells. Int. J. Cancer 93, 218.

Liu, C.H., Chang, S.H., Narko, K., et al., 2001. Over expression of cyclooxygenase-2 is sufficient to induce tumorigenesis in transgenic mice. J. Biol. Chem. 276, 18563.

Marnett, L.J., 1992. Aspirin and the potential role of prostaglandins in colon cancer. Cancer Res. 52, 5575–5589.

Matthew, R.Y., Yang, H.S., Nancy, H.C., 2003. Promising molecular targets for cancer prevention: AP-1, NF-κB and Pdcd4. Trends Mol. Med. 9, 36–41.

Morris, C.D., Armstrong, G.R., Bigley, G., Green, H., Attwood, S.E., 2001. Cyclooxygenase-2 expression in the Barrett's metaplasia-dysplasia-adenocarcinoma sequence. Am. J. Gastroenterol. 96, 990–996.

Nakadate, T., Yamamoto, S., Iseki, H., et al., 1982. Inhibition of 12-O-tetradecanoylphorbol-13-acetate-induced tumor promotion by nordihydroguaiaretic acid, a lipoxygenase inhibitor, and p-bromophenacylbromide, a phospholipase A2 inhibitor. Gann 73, 841–843.

Nasser, A., 2004. J. Surg. Res. 117, 114–120.

Nelson, Heather H., Christiani, David C., Wiencke, John K., Mark, Eugene J., Wain, John C., Kelsey, Karl T., 1999. k-*ras* mutation and occupational asbestos exposure in lung adenocarcinoma asbestos-related cancer without asbestosis. Cancer Res. 59, 4570–4573.

Parrett, M.L., Harris, R.E., Joarder, F.S., et al., 1997. Cyclooxygenase-2 gene expression in human breast cancer. Oncology 10, 503–507.

Parsonnet, J., 1995. Bacterial infection as a cause of cancer. Environ. Health Perspect. 103 (Suppl. 8), 263–268.

Potter, M., 1999. Indomethacin inhibition of pristane plasmacytomagenesis in genetically susceptible inbred mice. Adv. Exp. Med. Biol. 469, 151–156.

Prasanna, A.D., Shirodkar, P.Y., Panikkar, K.R., 2003. Synthesis of new 4-aryl/alkyl-1-(5', 5'-diphenyl- 4'-oxo-1'-H-4' 5'-dihydro-imidazolidin-2'-yl)-3-hydroxy-1,2,4-triazolidine-5-thi one derivatives as potential anti-cancer agents. Ind. J. Chem. 42B, 690–694.

Puga, A., Hoffer, A., Zhou, S., et al., 1997. Sustained increase in intracellular free calcium and activation of cyclooxygenase-2 expression in mouse hepatoma cells treated with dioxin. Biochem. Pharmacol. 54, 1287–1296.

Reddy, B.S., Maruyama, H., Kelloff, G., 1987. Dose-related inhibition of colon carcinogenesis by dietary piroxicam, a nonsteroidal antiinflammatory drug, during different stages of rat colon tumor development. Cancer Res. 47, 5340–5346.

Rubio, C.A., 1984. Antitumoral activity of indomethacin on experimental esophageal tumors. J. Natl. Cancer Inst. 72, 705.

Rubio, C.A., 1986. Further studies on the therapeutic effect of indomethacin on esophageal tumors. Cancer 58, 1029.

Sakata, T., Hasegawa, R., Johansson, S.L., et al., 1986. Inhibition by aspirin of A'-[4- < 5-Nitro-2-furyl)-2-thiazolyl] formamide initiation and sodium sac charin promotion of urinary bladder carcinogenesis in male F344 rats. Cancer Res. 46, 3903–3906.

Seitz, H.K., Poschl, G., Simanowski, U.A., 1998. Alcohol and cancer. Recent Dev. Alcohol 14, 67–95.

Shamma, A., Yamamoto, H., Doki, Y., et al., 2000. Up-regulation of cyclooxygenase-2 in squamous carcinogenesis of the esophagus. Cancer Res. 6, 1229–1238.

Shirvani, V.N., Ouatu-Lascar, R., Kaur, B.S., et al., 2000. Cyclooxygenase-2expression in Barrett's esophagus and adenocarcinoma: ex vivo induction by bile salts and acid exposure. Gastroenterology 118, 487–496.

Siman, J.H., Enstrang, L., Berglund, G., Forsgren, A., Floren, C.H., 2007. Helicobacter pylori and CagA seropositivity and its association between gastric and esophageal carcinoma. Scand. J. Gastroenterol. 42, 933–940.

Slaga, T.J., Lichti, U., Hennings, H., et al., 1978. Effects of tumor promoters and steroidal anti-inflammatory agents on skin of new born mice *in vivo* and *in-vitro*. J. Natl. Cancer Inst. 60, 425–431.

Souza, R.F., Shewmake, K., Beer, D.G., 2000. Selective inhibition of cyclooxygenase-2 suppresses growth and induces apoptosis in human esophageal adenocarcinoma cells. Cancer Res. 60, 5767–5772.

Steenland, K., Stayner, L., 1997. Silica, asbestos, man-made mineral fibers, and cancer. Cancer Causes Control 8, 491–503.

Tavani, A., La Vecchia, C., Franceschi, S., et al., 2000. Medical history and risk of Hodgkin's and non-Hodgkin's lymphomas. Eur. J. Cancer Prev. 9, 59–64.

Thieblemont, C., Berger, F., Coiffier, B., 1995. Mucosa-associated lymphoid tissue lymphomas. Curr. Opin. Oncol. 7, 415–420.

Tsujii, M., Kawano, S., Tsuji, S., et al., 1998. Cyclooxygenase regulate angiogenesis induced by colon cancer cells. Cell 93, 705.

Tung, B.Y., Emond, M.J., Haggitt, R.C., et al., 2001. Ursodiol use is associated with lower prevalence of colonic neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. Ann. Intern. Med. 134, 89–95.

Uemura, N., Okamoto, S., Yamamoto, S., et al., 2001. Helicobacter pylori infection and the development of gastric cancer. N. Engl. J. Med. 345, 784–789.

Upulescu, A., 1996. Prostaglandins Leukot. Essent. Fatty Acids 54, 83–94.

Vainio, H., Boffetta, P., 1994. Mechanisms of the combined effect of asbestos and smoking in the etiology of lung cancer. Scand. J. Work Environ. Health 20, 235–242.

Vogel, C., Schuhmacher, U.S., Degen, G.H., et al., 1998. Modulation of prostaglandin H synthase-2 mRNA expression by 2,3,7,8-tetrachlorodibenzo-p-dioxin in mice. J. Arch. Biochem. Biophys. 351, 265–271.

Vogelstein, B., Kinzler, K.W., 1993. The multistep nature of cancer. Trends Genet. 9, 138–141.

Wilson, K.T., Fu, S., Ramanujam, K.S., et al., 1998. Increased expression of inducible nitric oxide synthase and cyclooxigenase-2 in Barrett's esophagus and associated adenocarcinomas. Cancer Res. 58, 2929.

Wong, B.C., Lam, S.K., Wong, W.M., et al., 2004. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA 291, 344–346.

Yamagata, R., Shimoyama, T., Fukuda, S., Yoshimura, T., Tanaka, M., Munakata, A., 2002. Cyclooxygenase-2 expression is increased in early intestinal-type gastric cancer and gastric mucosa with intestinal metaplasia. Eur. J. Gastroenterol. Hepatol. 14, 359–363.

Yamamoto, S., Jiang, H., Otsuka, C., et al., 1992. Involvement of prostaglandin E_2 in ornithine decarboxylase induction by a tumor promoting agent, 7-bromomethylbenz[α] anthracene, in mouse epidermis. Carcinogenesis 13, 905–906.

Zhang, F., Altorki, N.K., Wu, Y.C., Soslow, R.A., Subbaramaiah, K., Dannenberg, A.J., 2001. Duodenal reflux induces cyclooxygenase-2 in the esophageal mucosa of rats: evidence for involvement of bile acids. Gastroenterology 121, 1391–1399.

Zimmermann, K.C., Sarbia, M., Weber, A.A., et al., 1999. Cyclooxygenase-2 expression in human esophageal carcinoma. Cancer Res. 59, 198.