Cyclooxygenases (COX) are rate-limiting enzymes that catalyze the conversion of arachidonic acid to prostaglandins, which are involved in many physiological and pathophysiological responses. COX-2, one of two isoforms of COX, was recently found to play an important role in carcinogenesis in many cell and tissue types. COX-2 inhibitors, which belong to the family of nonsteroidal anti-inflammatory drugs, are believed to be effective in many biological activities such as tumor chemoprevention because of their inhibition of COX-2. However, in the present study we found that both piroxicam, a general COX inhibitor, and NS-398, a COX-2 selective inhibitor, effectively suppressed the activation of transcription factor activator protein 1 (AP-1) induced by ultraviolet B (UVB) or 12-O-tetradecanoylphorbol-13-acetate in mouse epidermal JB6 cells. These COX-2 inhibitors could also inhibit 12-O-tetradecanoylphorbol-13-acetate-induced cell transformation. UVB significantly increased AP-1 activity in Cox-2−/− fibroblasts transfected with an AP-1 luciferase reporter gene, and this increase was blocked by NS-398 or piroxicam. In JB6, Cox-2−/−, or wild-type Cox-2+/+ cells, both NS-398 and piroxicam inhibited UVB-induced phosphorylation of c-Jun NH2-terminal kinases, the kinases that activate the AP-1/c-Jun complex. Based on our results, we propose that the inhibition of AP-1 activity by COX-2 inhibitors NS-398 or piroxicam may occur by a mechanism that is independent of COX-2.

Cyclooxygenases (COX) are rate-limiting enzymes that catalyze the conversion of arachidonic acid to prostaglandins, which are involved in many normal and pathophysiological responses (1–3). Of the two known COX enzymes, COX-1 is expressed in nearly all cells, whereas COX-2 is primarily considered an inducible immediate-early gene product (4). COX-2 inhibitors were reported to inhibit neurons against hypoxia/reperfusion through mechanisms independent of COX (5). We and others have shown that nonsteroidal anti-inflammatory drugs can block mitogen-induced transcription with protein 1 (AP-1) activity and transactivation (6). Considering the important role of AP-1 in tumorigenesis, the inhibition of AP-1 is likely to be one of the major mechanisms involved in nonsteroidal anti-inflammatory drugs chemopreventive effects.

The aim of this study was to determine whether a COX-2 selective inhibitor, N-(2-cyclohexoxy-4-nitrophenyl)methanesulfonamide (NS-398), or a general inhibitor of COX-2, 4-hydroxy-2-methyl-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (piroxicam), is effective in blocking AP-1 activation and whether COX-2 is involved in the inhibitory effects.

MATERIALS AND METHODS

Cell Culture and Reagents—AP-1 luciferase reporter plasmid stably transfected mouse epidermal JB6 P+1−1 cells and the JB6 P+ mouse epidermal cell line, C1 41, were cultured in monolayers at 37 °C, 5% CO2 using minimum essential medium (MEM) containing 5% fetal bovine serum (FBS), 2 mM L-glutamine, and 25 μg of gentamicin/ml. Cox-2+/− murine embryo fibroblasts (MEFs) and wild-type Cox-2+/+ MEFs were kind gifts from Drs. Jeff Reese and Sudhanu K. Dey (University of Kansas Medical Center) (15). The cells were derived from Cox-2 knockout mice supplied by Drs. Joseph E. Dinchuk and James M. Trzaskos (DuPont Merck Pharmaceutical Co.) (16). The cells were cultured in monolayers at 37 °C, 5% CO2 using Dulbecco’s modified Eagle’s medium containing 10% FBS, 2 mM L-glutamine, 0.1 mM MEM nonessential amino acids, and 50 IU/ml penicillin/streptomycin. FBS and MEM were from BioWhittaker, Inc. (Walkersville, MD), TPA, aprotinin, and leupeptin were from Sigma, and the luciferase assay substrate was from Promega (Madison, WI).

Luciferase Assay for AP-1 Transactivation—Confluent monolayers of cells were trypsinized, and 8000 viable cells suspended in 100 μl of 5% FBS MEM were added to each well of a 96-well plate. Plates were incubated at 37 °C in a humidified atmosphere of 5% CO2, and 12−24 h later, cells were starved by culturing in 0.1% FBS MEM for 24 h before being treated or not treated with different concentrations of NS-398 or piroxicam for 30 min. The cells were then exposed to UVB (4 J/cm2) or TPA (20 ng/ml) independently. After an additional 12 h (for AP-1 treated with UVB) or 24 h (for AP-1 treated with TPA) of culturing, the cells were extracted with lysis buffer (0.1 M potassium phosphate buffer (pH 7.8), 1% Triton X-100, 1 mM dithiothreitol, 2 mM EDTA), and luciferase activity was measured using a luminometer (Monolight (Molnigh). The results are expressed as relative AP-1 (17).

Anchorage-independent Transformation Assay—The effect of NS-398, piroxicam, or SP600125 on TPA-induced cell transformation was investigated in JB6 C1 41 cells. Cells (8 × 10⁶/ml) were exposed to TPA with or without the chemicals at the concentration indicated in 1 ml of 0.33% basal medium Eagle (BME) agar containing 10% FBS over 3.5 ml of 0.5% BME agar medium containing 10% FBS. The cultures were maintained in a 37 °C, 5% CO2 incubator for 4 weeks, and the cell
NS-398 and Piroxicam Suppress AP-1 Activity

**Fig. 1.** NS-398 or piroxicam suppresses TPA-induced AP-1 activity and cell transformation in JB6 cells. A, 5 x 10⁵ mouse epidermal JB6 C1 41 AP-1 luciferase reporter stably transfected P+1–1 (C1 41 P+1–1) cells suspended in 5% FBS MEM were added to each well of a 96-well plate. After an overnight culture at 37 °C, the cells were starved by replacing the medium with 0.1% FBS MEM for 24 h. The cells were then treated for 30 min with NS-398 or piroxicam at the concentrations indicated before exposure to TPA (20 ng/ml). After another 48 h, AP-1 luciferase activity was measured as described previously. The results are presented as relative AP-1 activity. Each bar indicates the mean and S.D. of triplicate experiments. A significant (*, p < 0.01) inhibition of AP-1 activity was observed compared with TPA treatment and no inhibitor present.

**Fig. 2.** NS-398 or piroxicam suppresses UVB-induced AP-1 activity in JB6 cells in vitro and in vivo. A, C1 41 P+1–1 cells were prepared and serum-starved as in Fig. 1. The cells were then treated with NS-398 or piroxicam for 30 min at the concentrations indicated before exposure to UVB (4 kJ/m²). After another 12 h, the AP-1 luciferase activity was measured as described previously. The results are presented as relative AP-1 activity. Each bar indicates the mean and S.D. of six assay wells from three independent experiments. A significant (*, p < 0.01) inhibition of AP-1 activity was observed in cells treated with UVB plus inhibitors compared with cells treated only with UVB. B, AP-1-luciferase reporter gene-bearing mice were grouped and treated with NS-398 or piroxicam as described under “Materials and Methods.” Each bar indicates the mean and S.D. of the AP-1 activity for each group of 22 mice. A significant (*, p < 0.01) inhibition of AP-1 activity was observed in mice treated with UVB plus inhibitors compared with mice treated only with UVB.

---

**DNA Binding Studies**—Electrophoretic mobility shift assays were performed essentially as described (21). Nuclear protein extracts were prepared by the modified method of Monick et al. (22). Briefly, cells were harvested and disrupted in 500 µl of lysis buffer (25 mm HEPES, pH 7.8, 50 mm KCl, 0.5% Nonidet P-40, 100 µM dithiothreitol, 10 µg/ml leupeptin, 25 µg/ml aprotinin, and 1 mM phenylmethylsulfonyl fluoride). After centrifugation for 1 min (16,000 × g, 4 °C), the pelleted nuclei were washed once with 500 µl of wash buffer (25 mM HEPES, pH 7.8, 50 mM KCl, 100 µM dithiothreitol, 10 µg/ml leupeptin, 25 µg/ml aprotinin, and 1 mM phenylmethylsulfonyl fluoride). The pelleted nuclei were resuspended in 150 µl of extraction buffer (25 mM HEPES, pH 7.8, 500 mM KCl, 1 mM dithiothreitol, 10 µg/ml leupeptin, 25 µg/ml aprotinin, 1 mM phenylmethylsulfonyl fluoride, and 10% glycerol) and shaken at 4 °C for 30 min. Nuclear extracts were stored at −70 °C. The DNA binding reaction (electrophoretic mobility shift assay) was performed for 30 min at room temperature in a mixture containing 4 µg of nuclear proteins, 1 µg of polydeoxyinosinic-deoxyoctydilic acid (dI-dC), and 15,000 cpm of 3²P-labeled double-stranded oligonucleotide probe. The samples were fractionated through a 5% polyacrylamide gel. The sequence of the AP-1 oligonucleotide probe was 5’-CGGTTGATGAGTCAGCCGGAA-3’. Gels were dried and analyzed using the Storm 840 Phospho-Image System (Molecular Dynamics).

**Western Immunoblotting**—Cells growing in 100-mm cell culture plates were lysed with 0.6 ml radiimmuneprecipitation assay buffer (1× phosphate-buffered saline, 1% Nonidet P-40, 0.5% sodium deoxycholate, 0.1% SDS, and freshly added 100 µg/ml phenylmethylsulfonyl fluoride, 10 µg/ml aprotinin, 1 mM sodium orthovanadate), and the samples for electrophoresis were prepared according to the manufacturer’s instructions (Santa Cruz Biotechnology, Santa Cruz, CA). The
Protein concentration of each sample was determined, and equal amounts of protein were loaded for SDS gel electrophoresis. Immunoblotting for the proteins of COX-2, total JNKs, and phosphorylated JNKs was carried out using antibodies against COX-2 (Upstate Biotechnology, Lake Placid, NY), total JNKs, and the phosphorylated sites of JNKs, respectively (Cell Signaling Technology, Beverly, CA).

**Transient Transfection**—Plasmids of COX-2, COX-2-S516M, and COX-2-S516Q mutants in pOSML were kind gifts from Dr. David L. DeWitt (Michigan State University) (23). The AP-1 luciferase reporter plasmid (p/H1100273/H1100163 collagenase-luciferase) and cytomegalovirus-neo marker vector plasmid were constructed as previously reported (24). Transient transfection was carried out using LipofectAMINE PLUSTM Reagent (Invitrogen) according to the protocol supplied.

**Prostaglandin E2 (PGE2) Assay**—Cells were treated with 30 μM arachidonic acid for 15 min, and PGE2 release in the culture medium was determined using the PGE2 enzyme immunoassay (EIA) system (Amersham Biosciences) according to the protocol provided.

**Kinase Assay**—In vitro phosphorylation of JNK1 and JNK2 by active MKK4 was determined according to the manufacturer’s protocol (Up-FIG.3. NS-398 or piroxicam suppresses UVB-induced JNKs phosphorylation and AP-1 DNA binding activity in JB6 cells. A, CI 41 cells were serum-starved 24 h and then treated for 30 min with NS-398 or piroxicam at the concentration indicated. The cells were then exposed to UVB (4 kJ/m²) followed by culturing for another 30 min. Western immunoblotting for detection of phosphorylation of JNKs was carried out using phospho-specific mitogen-activated protein kinase antibodies against phosphorylated sites of JNKs. Levels of JNKs non-phosphorylated protein indicates equal protein loading. B, CI 41 cells were serum-starved for 24 h and treated or not treated for 30 min with NS-398 or piroxicam at the concentrations indicated. The cells were then exposed to UVB at a dose of 4 kJ/m². After exposure, the cells were cultured for another 8–10 h. The cells were then harvested, and gel-shift assays were performed as described under “Materials and Methods.” Each bar indicates the mean and S.D. of the densitometry analysis of the gels from three independent experiments. A significant (*, p < 0.01) inhibition of AP-1 DNA binding activity was observed. Incubation with an excess of unlabeled probe indicates that the AP-1 DNA binding was specific.

Fig. 4. NS-398 or piroxicam suppresses UVB-induced AP-1 activity in Cox-2-null MEFs. 8 × 10⁵ Cox-2⁻/⁻ MEFs transfected with the AP-1 luciferase reporter plasmid were added to each well of a 96-well plate. After an overnight culture at 37 °C, the cells were starved by replacing the medium with serum-free Dulbecco’s modified Eagle’s medium for 12 h. The cells were then treated for 30 min with NS-398 or piroxicam at the concentrations indicated before exposure to UVB (4 kJ/m²). After another 12 h, AP-1 luciferase activity was measured as described previously. The results are presented as relative AP-1 activity. Each bar indicates the mean and S.D. of three assay wells from three independent experiments. A significant (*, p < 0.01) inhibition of AP-1 activity was observed in cells treated with UVB plus inhibitors compared with cells treated with UVB only.

Fig. 5. NS-398 or piroxicam suppresses UVB-induced AP-1 DNA binding activity in Cox-2-null MEFs. Cox-2⁻/⁻ and Cox-2⁻/⁻ MEFs were serum-starved for 6 h and either treated or not treated for 30 min with NS-398 or piroxicam at the concentrations indicated. The cells were then exposed to UVB (4 kJ/m²) or TPA (B). After exposure, the cells were cultured for another 8–10 h. The cells were then harvested, and gel-shift assays were performed as described under “Materials and Methods.”
RESULTS AND DISCUSSION

NS-398 or Piroxicam Inhibits TPA-induced AP-1 Activity and Cell Transformation—Increased AP-1 activity leads to malignant transformation, and thus, the suppression of AP-1 activity is suggested to be involved in the mechanisms of action of many potential chemopreventive agents (25–27). We therefore investigated whether NS-398 or piroxicam could block malignant cell transformation. We used TPA, one of the most potent experimental stimuli used to activate AP-1 activity and tumor promotion in skin, to test the effects of the COX-2 inhibitors on AP-1 activity and cell transformation. NS-398 or piroxicam significantly suppressed both TPA-induced AP-1 activity (Fig. 1A) and TPA-induced cell transformation on soft agar (Fig. 1B) in a concentration-dependent manner. As we have previously reported, increased AP-1 activity is required for tumor promoter-induced transformation (24, 28). Therefore, the inhibition of AP-1 activity may be functionally linked to the anti-cancer effect of these chemicals.

NS-398 or Piroxicam Suppresses UVB-induced AP-1 Transactivation Both in Vitro and in Vivo—Solar UVB is a strong etiological factor in human skin cancer (29). UVB-induced AP-1 and other signal transduction pathways play a role in skin carcinogenesis (23). To determine the effect of NS-398 or piroxicam on UVB-induced AP-1 transactivation, AP-1-luciferase reporter gene-bearing JB6 C141 cells were incubated with the COX-2 inhibitors and then exposed to UVB. Both NS-398 and piroxicam markedly inhibited UVB-induced AP-1 luciferase activity, and the inhibitory effects appeared to be dose-dependent (Fig. 2A). The doses of NS-398 and

![Graph](https://via.placeholder.com/150)

Fig. 6. NS-398 or piroxicam suppresses UVB-induced JNKs phosphorylation in Cox-2-null MEFs. Cox-2−/− and Cox-2+/+ MEFs were serum-starved for 12 h and then exposed to UVB (4 kJ/m2) and harvested at the different time points indicated (A), or the cells were exposed to different doses of UVB as indicated and then harvested 30 min after treatment (B). The cells were also treated for 30 min with NS-398 or piroxicam at the concentrations indicated and then exposed to UVB (4 kJ/m2) followed by culturing for another 30 min (C). Western immunoblotting for phosphorylation of JNKs was carried out using phosho-specific mitogen-activated protein kinase antibodies against phosphorylated sites of JNKs. JNKs non-phosphorylated protein level indicates that an equal amount of protein was loaded.

![Graph](https://via.placeholder.com/150)

Fig. 7. Mutants (S516M or S516Q) of COX-2 do not attenuate the inhibitory effects of NS-398 or piroxicam on AP-1 activity. Cox-2−/− and Cox-2+/+ MEFs were transiently transfected with the AP-1 luciferase reporter plasmid. Cox-2−/− MEFs bearing the AP-1 luciferase reporter gene were also transfected with COX-2, COX-2-S516M, or COX-2-S516Q mutant plasmids as described under “Materials and Methods.” A, the transfected cells were treated and assessed for PGE2 production as described under “Materials and Methods.” The asterisks indicate a significantly (p < 0.01) lower production of PGE2 in COX-2 null cells compared with cells having COX-2 gene expression. B, COX-2 protein expression in each cell type was assessed as described under “Materials and Methods.” β-Actin was applied as an inner control of the equal protein volume loaded. C, the transfected cells were also treated with NS-398 or piroxicam 30 min before UVB exposure. The results are presented as relative AP-1 activity. Each bar indicates the mean and S.D. of three assay wells from three independent experiments. The asterisks indicate that a significant (p < 0.01) inhibition of AP-1 activity occurred in cells treated with UVB plus inhibitors compared with cells treated with UVB only.
piroxicam used in the experiment were below the observed cytotoxic range (30, 31).

**NS-398 or Piroxicam Blocks UVB-activated JNKs and AP-1 DNA Binding Activity**—Mitogen-activated protein kinases comprise the most common pathways known to mediate AP-1 function (32). Many reports indicated that JNK, a member of the mitogen-activated protein kinase family, is critical in mediating AP-1 transactivation and malignant transformation (25, 33–36). Inhibition of JNK leads to suppression of AP-1 activity and cell transformation (23). In our results, both NS-398 and piroxicam inhibited UVB-induced phosphorylation of JNKs (Fig. 3A), indicating that the blocking of JNK activation is involved in the inhibitory effects of NS-398 or piroxicam on these signal transduction pathways.

AP-1 functions as a transcription factor by binding to the transactivation promoter region (TPA response elements) of specific genes. To determine whether NS-398 or piroxicam functions through the attenuation of AP-1 binding to its target DNA, we performed electrophoretic mobility shift assay as an indicator of AP-1 DNA binding activity. UVB (4 kJ/m²) induced a significant increase in AP-1 DNA binding activity (Fig. 3B, lane 3) compared with the unexposed control (Fig. 3B, lane 2). The elevated AP-1 DNA binding was suppressed by NS-398 or piroxicam in a dose-dependent manner (Fig. 3B, lanes 4–7). The DNA binding was specific for AP-1 because a 10-fold excess of unlabeled AP-1 probe successfully competed with the labeled probe (Fig. 3B, lane 1).

**The Inhibitory Effects of NS-398 or Piroxicam on AP-1 Are Independent of COX-2**—Although we have observed that both NS-398 and piroxicam could efficiently block AP-1 activation, whether the effects of the COX-2 inhibitors on AP-1 occurred through their inhibition of COX-2 is important to determine because of the key role that AP-1 plays in tumorigenesis. Cells transfected with the AP-1 luciferase reporter gene showed that an increase in AP-1 activity could also be induced by UVB exposure in Cox-2−/− MEFs (Fig. 4). NS-398 and piroxicam suppressed the UVB-induced increase in AP-1 activity in these MEFs (Fig. 4). We observed that similar to Cox-2−/− cells, either UVB irradiation or TPA exposure could still induce a significant increase in AP-1 DNA binding in Cox-2−/− MEFs (Fig. 5, A and B), and NS-398 and piroxicam suppressed the increases in AP-1 DNA binding in these cells (Fig. 5, A and B). These results indicated that COX-2 is not required in the signaling pathways mediating UVB-induced AP-1 activation because the COX-2 inhibitors NS-398 and piroxicam suppressed AP-1 activity by mechanisms independent of their inhibition of COX-2. To further investigate whether the absence of COX-2 affects JNK activation, we exposed Cox-2−/− MEFs to different doses of UVB irradiation and harvested the cells at different time points after UVB treatment. The results showed that UVB activated JNKs in Cox-2−/− as well as in Cox-2+/− MEFs in a time (Fig. 6A) and dose (Fig. 6B)-dependent manner, and both NS-398 and piroxicam effectively blocked UVB-induced JNK activation in both cell types (Fig. 6C). These results indicated that COX-2 is not involved in the inhibitory mechanism of NS-398 or piroxicam affecting UVB-induced AP-1 activity. Some reports suggest that JNKs and the downstream AP-1 were required in mediating COX-2 expression (37, 38), but whether COX-2 is involved in the regulation of JNKs or AP-1 activation is still unclear.

COX inhibitors block the catalysis of arachidonic acid to PGE₂ (39–41). Several studies suggest that PGE₂ signals through AP-1 and, thus, may play a definitive role in tumor development (42–44). To elucidate whether NS-398 or piroxicam blocks AP-1 activation by attenuating PGE₂ production,
we transfected two acetylation active site mutants of COX-2, SS16 M and S516Q, together with the AP-1 luciferase reporter gene into Cox-2−/− cells. The two mutant cell lines did not produce PGE2 (Fig. 7A), although they could encode the COX-2 protein (Fig. 7B). NS-398 and piroxicam blocked UVB-induced AP-1 activation in both COX-2 mutant-transfected Cox-2−/− cells (Fig. 7C). The results indicated that PGE2 production was not the major effect involved in the inhibition of AP-1 by NS-398 or piroxicam.

The Blocking of JNK Kinase Activation Inhibits TPA-induced Cell Transformation—Although COX-2 has been well recognized as an important target for therapy/prevention of cancer and COX-2 selective inhibitors are already applied as an approach for prevention or treatment of cancer, many reports suggest that some tumors can still occur or grow in COX-2-negative mice or cell lines. COX-2 inhibitors exhibit identical tumor growth inhibitory effects on either Cox-2−/−, Cox-2+/−, or Cox-2+/+ mice or cell lines (45–48), indicating that alternative pathways exist. So far in this paper, we have demonstrated that NS-398 or piroxicam inhibits AP-1 transactivation independently of COX-2, and blocking of JNK kinase phosphorylation likely plays a role in the function of the chemicals. However, we still don’t know if JNKs are really important in mediating mitogen-induced cell transformation. To answer the question we utilized a highly selective JNK inhibitor, SP600125, to observe its effect on TPA-induced JB6 cell transformation (Fig. 8A), indicating that the activation of JNKs is required in the signaling pathway leading to cell transformation. Similar observations have also been reported previously (23). However, further investigation revealed a synergistic inhibition when both SP600125 and NS-398 or piroxicam were included with TPA on soft agar (Fig. 8B). The results indicated that although JNKs might be a major target of COX-2 inhibitors, other molecules may play a role in the mechanisms of COX-2 inhibition of cell transformation.

NS-398 and Piroxicam Block JNK Phosphorylation in Vitro—To further confirm that the COX-2 inhibitors act on JNK function, we studied the effect of NS-398 or piroxicam on active MKK4-induced JNK1/2 phosphorylation in vitro. Our results indicated that the COX-2 inhibitors effectively suppressed JNK1/2 phosphorylation in vitro (Fig. 9A). In another investigation as to whether the COX-2 inhibitors target mediators other than JNKs existing in the pathway, we used N-terminal c-Jun fusion protein-bound glutathione-Sepharose beads to pull down the JNK proteins from UVB-irradiated cells and incubated them with ATP at the presence of NS-398 or piroxicam in vitro. Piroxicam at the high concentration of 10 μM in vitro had a weak inhibitory effect on active JNK-activated phosphorylation of c-Jun, the downstream oncogene target of JNKs and a component of AP-1, whereas NS-398 had little effect (Fig. 8B). This result combined with the observation that NS-398 or piroxicam blocks JNK phosphorylation, indicates that the chemicals may work on JNK signaling from within the JNKs themselves.

In summary, our data indicated that the COX-2 “selective” inhibitors NS-398 or piroxicam effectively blocked UVB-induced AP-1 activity both in vitro and in vitro. They could also suppress TPA-induced AP-1 activity and cell transformation. The blocking of JNK activation by the chemicals appears to be involved in their inhibition of AP-1 activity. We further demonstrated that the inhibition of AP-1 by these compounds was COX-2-independent. Considering the critical role that AP-1 plays in tumorigenesis, these results may supply some novel insights regarding the mechanism of COX-2 inhibitory effects and provide a biological basis for the development of new chemopreventive agents for cancer.
38. Yang, T., Huang, Y., Heasley, L. E., Berl, T., Schnermann, J. B., and Briggs, J. (2000) J. Biol. Chem. 275, 23281–23286
39. Thun, M. J. (1994) Cancer Metastasis. Rev. 13, 269–277
40. Marnett, L. J. (1992) Cancer Res. 52, 5575–5589
41. Kopp, E., and Ghosh, S. (1994) Science 265, 956–959
42. Simonsen, M. S., Herman, W. H., and Dunn, M. J. (1994) Exp. Cell Res. 215, 137–144
43. Dendorfer, U., Oettgen, P., and Libermann, T. A. (1994) Mol. Cell. Biol. 14, 4443–4454
44. Won, J. S., Suh, H. W., Kim, Y. H., Song, D. K., Huh, S. O., Lee, J. K., and Lee, K. J. (1998) Mol. Brain Res. 60, 203–214
45. Waskewich, C., Blumenthal, R. D., Li, H., Stein, R., Goldenberg, D. M., and Burton, J. D. (2002) Cancer Res. 62, 2029–2033
46. Masferrer, J. L., Leahy, K. M., Koki, A. T., Zweifel, B. S., Settle, S. L., Woerner, B. M., Edwards, D. A., Flickinger, A. G., Moore, R. J., and Seibert, K. (2000) Cancer Res. 60, 1306–1311
47. Williams, C. S., Watson, A. J., Sheng, H., Helse, R., Shan, J., and DaBois, R. N. (2000) Cancer Res. 60, 6045–6051
48. Blumenthal, R. D., Waskewich, C., Goldenberg, D. M., Lew, W., Flefleh, C., and Burton, J. B. (2001) Clin. Cancer Res. 7, 3178–3185
49. Bennett, B. L., Sasaki, D. T., Murray, B. W., O'Leary, E. C., Sakata, S. T., Xu, W., Leisten, J. C., Motiwala, A., Pierce, S., Satoh, Y., Bhagwat, S. S., Manning, A. M., and Anderson D. W. (2001) Proc. Natl. Acad. Sci. U. S. A. 98, 13681–13686

NS-398 and Piroxicam Suppress AP-1 Activity
NS-398 and Piroxicam Suppress UVB-induced Activator Protein 1 Activity by Mechanisms Independent of Cyclooxygenase-2
Guangming Liu, Wei-Ya Ma, Ann M. Bode, Yiguo Zhang and Zigang Dong

J. Biol. Chem. 2003, 278:2124-2130.
doi: 10.1074/jbc.M202443200 originally published online November 13, 2002

Access the most updated version of this article at doi: 10.1074/jbc.M202443200

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 49 references, 32 of which can be accessed free at http://www.jbc.org/content/278/4/2124.full.html#ref-list-1