Introduction

Pancreatic ductal adenocarcinoma is a major cause of cancer-related deaths in developed countries, and it is estimated that in excess of 30,000 new cases will be diagnosed this year in the United States (1). Pancreatic ductal adenocarcinoma is a highly aggressive disease that invariably evades early diagnosis (2, 3). The mean survival time for patients with metastatic disease is only 3 to 6 months, and the 1-year survival time for all pancreatic cancers cases is ~20% to 30%. Several factors are associated with increased risk for pancreatic cancer, and these include chronic pancreatitis, prior gastric surgery, smoking, diabetes, exposure to certain classes of organic solvents, and radiation (4–11). Heritable germline mutations in several genes are also associated with increased risk for pancreatic cancer, and these include Peutz-Jeghers, hereditary pancreatitis, familial atypical multiple melanoma, familial breast cancer 2, and hereditary nonpolyposis colorectal cancer syndromes (3, 12, 13). Several acquired gene mutations have also been identified in sporadic pancreatic tumors (12, 13).

5-Fluorouracil has been extensively used for treatment of advanced pancreatic cancer, and gemcitabine, a deoxyctydine analogue (or antimetabolite), has now partially replaced 5-fluorouracil for pancreatic cancer chemotherapies. Several other drugs for treatment of pancreatic cancer are also being studied in clinical trials, and these include other “antimetabolites,” taxanes, topoisomerase I inhibitors, and various combinations of these drugs, as well as other novel mechanism-based agents (14–20). Research in this laboratory has identified a series of 1,1-bis(3-indolyl)-1-(p-substituted phenyl)methanes (C-DIM), which are being developed for treatment of various cancers, including chronic pancreatitis, familial atypical multiple melanoma, familial breast cancer, and these include Peutz-Jeghers, hereditary pancreatitis, familial atypical multiple melanoma, familial breast cancer 2, and hereditary nonpolyposis colorectal cancer syndromes (3, 12, 13). Several acquired gene mutations have also been identified in sporadic pancreatic tumors (12, 13).

In this study, we investigated the structure-dependent activation of ER stress in pancreatic cancer cells by two C-DIMs that do not activate either PPARγ or Nur77, the ortho, meta, and para-bromo and -fluoro isomers all activated endoplasmic reticulum (ER) stress-dependent apoptosis in pancreatic cancer cells; however, methylation of the indole N group significantly decreased activity, suggesting that a free N was important for activation of ER stress. Both DIM-C-pPhBr and DIM-C-pPhF resembled the classic ER stress inducer thapsigargin in pancreatic cancer cells and activated ER stress markers, such as glucose-related protein 78 and the c-Jun NH2 kinase pathway, resulting in the induction of CCAAT/enhancer-binding protein homologous protein, death receptor 5, and the extrinsic apoptotic pathway. Moreover, DIM-C-pPhBr also inhibited tumor growth in an orthotopic model for pancreatic cancer, demonstrating the clinical potential for this C-DIM compound in pancreatic cancer chemotherapy. (Mol Cancer Ther 2008;7(10):3363–72)
resulting in the induction of CCAAT/enhancer-binding protein homologous protein (CHOP), death receptor 5 (DR5), and the extrinsic apoptotic pathway. These results, coupled with the observed in vivo antitumorigenic activity of DIM-C-pPhBr suggest that C-DIM compounds alone or in combination with other drugs represent a promising new treatment modality for pancreatic cancer.

Materials and Methods

Reagents and Antibodies
C-DIMs were synthesized in this laboratory from the condensation of indole or substituted indole plus a substituted benzaldehyde derivative and confirmed by gas chromatography-mass spectrometry, as previously described (27). Antibodies for poly(ADP-ribose) polymerase (PARP), CHOP, β-tubulin, and GRP78 were purchased from Santa Cruz Biotechnology. Antibodies for cleaved PARP, cleaved caspase-8, cleaved caspase-3, phosphorylated ASK1, ASK1, phosphorylated MKK4, MKK4, and DR5 were obtained from Cell Signaling Technology.

Cell Culture and Treatment
Panc-1, Panc-28, MiaPaCa-2, and BxPC-3 cells (American Type Culture Collection) and L3.6pl cells (kindly provided by Dr. Isaiah Fidler, M. D. Anderson Cancer Center) were maintained in DMEM/Ham’s F-12 (Sigma) supplemented with 20% fetal bovine serum and antibiotics. Panc-1 cells were seeded on Lab-Tek chambered cover glass and allowed to attach overnight. After treatment with the desired compounds, cells were washed with cold PBS twice and incubated with Annexin V conjugate and propidium iodide for 15 min according to the manufacturer’s instruction. The cells were then washed with the Annexin-binding buffer twice and detected for fluorescence with Zeiss LSM 510 confocal microscope (Germany).

Animals and Orthotopic Implantation of Tumor Cells
Male athymic nude mice (NCI-nu) were purchased from the Animal Production Area of the National Cancer Institute, Frederick Cancer Research and Development Center. The mice were housed and maintained under specific pathogen-free conditions in facilities approved by the American Association for Accreditation of Laboratory Animal Care and in accordance with current regulations and standards of the U.S. Department of Agriculture, U.S. Department of Health and Human Services, and NIH. The mice were used in accordance with institutional guidelines when they were ages 8 to 12 wk. To produce tumors, L3.6pl cells were harvested from subconfluent cultures by a brief exposure to 0.25% trypsin and 0.02% EDTA. Trypsinization was stopped with medium containing 10% fetal bovine serum, and the cells were washed once in serum-free medium and resuspended in HBSS. Only suspensions consisting of single cells with >90% viability were used for the injections. Injection of cells into the pancreas was done, as described previously (29, 30). Seven days after implantation of tumor cells into the pancreas of each mouse, five mice were killed to confirm the presence of tumor lesions. Mice were randomized (five per group) to receive by oral gavage control (corn oil) or 25 mg/kg/d DIM-C-pPhBr. Treatments were continued for 4 wk, and the mice were sacrificed on day 35 and subjected to necropsy. Tumor volumes were calculated by using the following formula: 0.5 × (length) × (width)^2. The size and weight of the primary pancreatic tumors were recorded. For immunohistochemistry and histologic staining procedures, tumor tissues were fixed in formalin and embedded in paraffin. Organ and body weights and histopathology on these tissues were determined.

Terminal Deoxynucleotidyl Transferase-Mediated dUTP Nick End Labeling Assay and Histologic Studies
For H&E staining and terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) assay, tumor tissue was fixed in formalin and embedded in paraffin, one section was processed for H&E staining and the others were used for TUNEL assay. TUNEL staining was carried out using DeadEnd Colorimetric TUNEL System (Promega). Paraffin-embedded sections (4–6 μm/μL thick) were processed as per manufacturer’s
protocol. Briefly, sections were deparaffinized in xylene and then treated with a graded series of alcohol [100%, 95%, 85%, 70%, and 50% ethanol (v/v) in double-distilled water] and rehydrated in PBS (pH 7.5). Tissues were then treated with proteinase K solution for permeabilization and then refixed with 4% paraformaldehyde solution. Slides were then treated with recombinant terminal deoxynucleotidyl transferase reaction mix and incubated at 37°C for 1 h. Reaction was terminated by immersing the slides in 2× SSC solutions for 15 min at room temperature. After blocking the endogenous peroxidases activity (by 0.3% hydrogen peroxide), slides were washed with PBS and then incubated with streptavidin horseradish peroxidase solution for 30 min at room temperature. After washing, slides were incubated with 3,3′-diaminobenzidine (substrate) solution until a light brown background appears (10 min) and then rinsed several times in deionized water. After mounting, slides were observed by light microscope.

Results
Previous studies in this laboratory showed that DIM-C-pPhBr and DIM-C-pPhF are cytotoxic to cancer cells but do not activate PPARγ or Nur77 (21, 24, 27). Results in Fig. 1A and B illustrate that both DIM-C-pPhBr and DIM-C-pPhF inhibited Panc-1 cell proliferation with IC50 values of 7.2 μmol/L and 9.3 μmol/L, respectively. Similar results were obtained in Panc-28 cells (Fig. 1C and D); however, the DIM-C-pPhF analogue was slightly less cytotoxic in Panc-28 cells. Higher concentrations of both compounds (10 and 15 μmol/L) caused a considerable increase in floating cells consistent with activation of cell death pathways. Figure 2 summarizes the effects of DMSO, DIM-C-pPhBr, and DIM-C-pPhF on Annexin V and propidium iodine staining in Panc-1 cells after treatment for 18 hours. Positive Annexin V staining indicates the transfer of phosphatidylserine from the inner to outer leaflet of the plasma membrane, whereas negative propidium iodine staining shows membrane integrity. The merged staining results show that both compounds induced apoptosis in this cell line.

DIMs and C-DIMs activate the extrinsic apoptosis pathway in colon, pancreatic, and ovarian cancer cells through induction of CHOP and CHOP-dependent activation of DR5 (23, 25, 28). Using CHOP as an end point assay, we investigated the induction of this protein by DIM-C-pPhBr (P) and the corresponding ortho (O) and meta (M) bromophenyl C-DIM isomers, as well as the 2-methyl and N-methyl (NMe) derivatives of DIM-C-pPhBr (Fig. 3A). Panc-1 cells were treated with 15 μmol/L concentrations of these compounds for 24 hours, and a significant induction of CHOP was observed in cells after treatment with all

Figure 1. Growth inhibitory effects of C-DIMs. Effects of DIM-C-pPhBr and DIM-C-pPhF on Panc-1 (A, B) and Panc-28 (C, D) cell growth. Panc-1 or Panc-28 cells were treated with 5, 10, or 15 μmol/L C-DIM compounds or control vehicle DMSO (D), and cell growth was determined every 24 h as described in Materials and Methods. Significant (P < 0.05) growth inhibition was observed at all concentrations of DIM-C-pPhBr and 10 and 15 μmol/L DIM-C-pPhF after treatment of 24 h. Results are mean ± SD for at least three replicate experiments for each treatment group.

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compounds except the NMe derivatives of DIM-C-pPhBr. The same series of fluoro-substituted C-DIM analogues was also investigated and, with the exception of the NMe derivative of DIM-C-pPhF, the remaining compounds all induced CHOP in Panc-1 cells. The para-F/Br analogues and the 2-methyl derivatives exhibited the highest activity, whereas 15 μmol/L concentrations of the NMe derivatives did not significantly induce expression of CHOP protein. These structure-dependent effects on CHOP expression show the importance of a free indole N group for maximum activity.

Figure 3B illustrates the concentration-dependent effects (7.5, 12.5, and 15 μmol/L) of some of the same bromo-substituted and fluoro-substituted analogues, and the results show that DIM-C-pPhBr/DIM-C-pPhF (P) and the 2-methyl derivatives induced CHOP at the lowest concentration. Their corresponding ortho-fluoro/bromo-substituted analogues were less active and minimal induction was observed for the NMe derivatives. In these experiments, Panc-1 cells were treated for 24 hours. The time course induction of CHOP in Panc-1 cells (Fig. 3C) by the same set of compounds showed that DIM-C-pPhBr and the 2-methyl analogue induced CHOP within 2-hour after treatment. Maximal induction was observed within 6 to 8 hours, and this was maintained for up to 24 hours. In contrast, the ortho isomer (DIM-C-oPhBr) exhibited a delay in the induction of CHOP (4–6 hours) and induction by the NMe derivative was only observed at later time points and never induced the levels of CHOP protein observed for the C-DIMs containing a free indole group. Moreover, in this study, the concentration of the NMe analogue was increased to 30 μmol/L to see induction of CHOP because lower concentrations did not induce its expression (Fig. 3A and B). The DIM-C-pPhF series of compounds were somewhat less potent as inducers of CHOP than the bromo analogues; however, the structure-dependent differences in the time course induction of CHOP in Panc-1 cells by the fluoro-substituted analogues were comparable with those observed for the bromo compounds.

Previous studies with C-DIMs have shown their activation of ER stress in pancreatic and ovarian cancer cells (23, 25), but not in colon cancer cell lines (28). Results in Fig. 4A show that, in Panc-1 cells, 15 μmol/L DIM-C-pPhBr and DIM-C-pPhF (P) induced expression of the ER stress protein GRP78, and this was accompanied by enhanced expression of both CHOP and DR5. In contrast, treatment with DMSO (D) and the NMe derivatives (N) did not affect expression of GRP78, CHOP, or DR5 proteins in Panc-1 cells. ER stress-dependent activation of DR5 by DIM-C-pPhBr and DIM-C-pPhF in Panc-1 cells was also accompanied by activation of caspase-8 and caspase-3 and induction of caspase-dependent PARP cleavage consistent with activation of the extrinsic apoptotic pathway. The NMe (N) analogues were inactive as inducers of apoptosis and served as a negative control for these effects. DIM-C-pPhBr induced PARP cleavage at concentrations from...
7.5 to 15 μmol/L, and results of a time course study showed that 15 μmol/L DIM-C-pPhBr and DIM-C-pPhF induced PARP cleavage within 8 hours after treatment (Fig. 4B). Using a similar approach, Panc-28, BxPC-3, L3.6pl, and MIAPaCa-2 pancreatic cancer cells were treated with DMSO, 15 μmol/L DIM-C-pPhBr and DIM-C-pPhF or their NMe analogues (N) for 24 hours, and the structure-dependent induction of GRP78, CHOP, and DR5 (Fig. 4C); caspase activation; and PARP cleavage (Fig. 4D) were also observed in these pancreatic cancer cell lines. This suggests that treatment with DIM-C-pPhBr, DIM-C-pPhF, and related compounds induces comparable ER stress-dependent activation of apoptosis in pancreatic cancer cells, and this is consistent with previous studies in Panc-1 and ovarian cancer cells, which showed that PPARγ-active C-DIM analogues (23, 25) also induce ER stress that is receptor-independent.

C-DIMs also induce JNK phosphorylation in ovarian (25) and colon (28) cancer cells, and in the latter cell line, this response was ER stress-independent. Therefore, we investigated the possible induction of JNK phosphorylation in Panc-1 cells by 15 μmol/L DIM-C-pPhBr/DIM-C-pPhF and their NMe analogues, and the results (Fig. 5A) show that both C-DIMs, but not their NMe analogues, induced phosphorylated JNK. Moreover, 15 μmol/L DIM-C-pPhBr, but not the NMe analogue, also induced phosphorylated JNK in Panc-28, BxPC-3, MiaPaCa-2, and L3.6pl pancreatic cancer cell lines (Fig. 5A), suggesting that this may be a common C-DIM–induced response in pancreatic cancer cells. The effects of C-DIM–induced JNK phosphorylation on downstream responses were determined in Panc1 cells treated with DIM-C-pPhBr and DIM-C-pPhF alone or in combination with the JNK inhibitor SP60015. C-DIM–induced JNK phosphorylation,

Figure 3. Structure-dependent activation of CHOP by DIM-C-pPhBr and DIM-C-pPhF analogues. Structure-dependent (A), dose-dependent (B), and time- (C) activation of CHOP in Panc-1 cancer cells. Cells were treated with either DMSO (D) or 15/30 μmol/L concentrations of the C-DIM derivatives as indicated for 12 h (A, B) or different periods of time (C), and changes in protein expression were determined by Western blot analysis of whole cell lysates as described in Materials and Methods. Protein levels were measured with Image J and normalized to β-tubulin. All experiments were carried out at least thrice and results in A are means ± SD for three replicate determinations and significant (P < 0.5) induction of CHOP is indicated by an asterisk.
JNK and proapoptotic responses in RKO cells, and this was accompanied by induction of the ER stress protein GRP78. Based on the induction of this stress protein, DIM-C-pPhF and DIM-C-pPhBr induce ER stress-dependent apoptosis in pancreatic and ER stress-independent apoptosis in colon cancer cells.

The in vivo anticarcinogenic activity of DIM-C-pPhBr was determined in athymic nude mice in which the L3.6pl pancreatic cancer cells were injected directly into the pancreas. In this orthotopic mouse model for pancreatic cancer, DIM-C-pPhBr (25 mg/kg/d) was given 5 days after injecting the cells and continued for 4 weeks. Results show that DIM-C-pPhBr significantly decreased tumor size (Fig. 6A) and weight (Fig. 6B). No changes in organ or body weights were observed (data now shown), and a comparison of tumors from treated versus untreated animals showed increased TUNEL staining in tumors from mice treated with DIM-C-pPhBr (Fig. 6C). This is consistent with the observed proapoptotic effects of this compound in pancreatic cancer cell lines.

Discussion

The unfolded protein response or ER stress is an important pathway that responds to ER dysfunction due to accumulation of misfolded proteins and other stressors, including inappropriate nutrients, abnormal calcium levels, and induced alterations of cellular homeostasis (32). The ER stress response involves coordinate induction of chaperone protein synthesis, activation of an ER-associated degradation pathway to remove proteins from the ER, and decreased protein translation to limit ER processing of
proteins. Failure to respond to ER stress results in activation of cell death pathways and removal of severely damaged cells. There is evidence that tumors which grow under hypoxic conditions have an elevated ER stress response, and GRP78, an important marker for ER stress, is up-regulated in many cancers and is a prognostic factor for cancer recurrence and poor rates of survival (33). It has been suggested that because GRP78 has antiapoptotic properties and contributes to cancer progression, metastasis agents that target this protein may be effective for cancer chemotherapy (33).

In contrast, drugs that activate ER stress and GRP78 expression are also being developed for clinical treatment of cancer alone or in combination with other therapies (34). For example, bortezomib (PS-341, Velcade) alone induces ER stress and apoptosis in pancreatic and human non–small lung cancer cells and also sensitizes cells to the apoptotic effects of other chemotherapeutic drugs and the death receptor ligand TRAIL, which is also being developed for treatment of some tumors (34). Several reports show that other ER stress inducers sensitize cancer cells and tumors to TRAIL-induced apoptosis, and this combination is dependent, in part, on up-regulation of DR5 and/or decreased expression of the cellular FLICE inhibitory protein (34–39).

Previous studies show that in several different cancer cell lines, 20 μmol/L DIM alone does not induce activation of caspase 8 or apoptosis but enhances the activity of TRAIL by down-regulation of cellular FLICE inhibitory protein (36). However, in Panc-1 and Panc-28 cells, 20 μmol/L DIM induced DR5 and the extrinsic pathway of apoptosis (23, 25). Our recent studies in colon cancer cells show that DIM-C-pPhF and DIM-C-pPhBr induce CHOP, DR5, and apoptosis, but this is not accompanied by induction of the ER stress marker GRP78 (28). The results suggest that induction of apoptosis in colon cancer cell is due to ER stress-independent activation of the JNK pathway. In contrast, PPARγ-active C-DIM compounds induce ER stress in ovarian and pancreatic cancer cells through enhanced expression of CHOP, which in turn induces DR5 and activation of the extrinsic apoptotic pathway, which is dependent on the induction of CHOP and activation of JNK (23, 25). In this study, we used DIM-C-pPhF and DIM-C-pPhBr, which are not PPARγ agonists, to further investigate the structure-dependent activation of ER stress and apoptosis in pancreatic cancer cells and to determine the in vivo potency of DIM-C-pPhBr as an anticancer agent.

Treatment of Panc-1 or Panc-28 cells with DIM-C-pPhBr or DIM-C-pPhF inhibited cell proliferation and induced

Figure 5. Activation of stress-dependent JNK and pro-apoptotic pathway. A, activation of JNK pathway in Panc-1 and other pancreatic cancer cells. PanC-1, Panc-28, BxPC3, MIAPaCa-3, and L3.6pl cells were treated with DMSO (D), 15 μmol/L DIM-C-pPhBr and DIM-C-pPhF (P), or the NMe analogues (N) for 24 h, and whole cell lysates were analyzed by Western blots as described in the Materials and Methods. B, effects of SP600125. Panc1 cells were treated with DMSO, 30 μmol/L SP600125, and 15 μmol/L DIM-C-pPhBr alone or in combination with SP600125 for 24 h. Whole cell lysates were analyzed by Western blots as described in Materials and Methods. Comparative activation of apoptosis and stress in Panc-1 cells (C) and activation of kinases in Panc-1 and RKO cells (D). Cells were treated with DMSO (D), 15 μmol/L DIM-C-pPhBr (Br), 15 μmol/L DIM-C-pPhF (F), 5 μmol/L Tg or 5 μg/mL Tm for 24 h, and whole cell lysates were analyzed by Western blots as described in Materials and Methods. β-Tubulin served as a loading control, and blots illustrated in A–D were observed in two or more experiments.
apoptosis (Figs. 1 and 2). Structure-activity studies among a series of C-DIM analogues gave results (Fig. 3) which were similar to those observed in colon cancer cells (28). DIM-C-pPhBr, DIM-C-pPhF, and their 2-methyl analogues (15 μmol/L) were the most active inducers of CHOP in Panc-1 cells, and CHOP expression was induced within 2 to 4 hours after treatment. There were structure-dependent differences among the ortho, meta, and para DIM-C-PhBr and DIM-C-PhF isomers, however, the most striking differences were observed for the NMe analogues, which induced minimal CHOP expression and only at higher concentrations (30 μmol/L; Fig. 3), indicating that maximal activity required a free indole group. The structure-dependent pattern of CHOP induction by DIM-C-pPhBr and DIM-C-pPhF was also observed for induction of DR5 and cleaved PARP, caspase-8, and caspase-3 in Panc-28, BxPC-3, L3.6pl, and MIAPaCa-2 cells (Fig. 4). Moreover, in this study, we also showed that, in Panc1 cells, inhibition of C-DIM-induced JNK phosphorylation with SP600125 decreased the induction of CHOP, DR5, and PARP cleavage, indicating that JNK plays a major role in mediating ER stress responses.

The structure-dependent induction of CHOP, DR5, and PARP cleavage by DIM-C-pPhBr, DIM-C-pPhF, and related compounds were comparable in colon and pancreatic cancer cells; however, there were important differences in their mechanism of action. The effects of DIM-C-pPhBr and DIM-C-pPhF in pancreatic cancer cells were similar to those observed for the classic ER stress inducers Tg and Tm. These compounds induce the classic ER stress markers GRP78 and also enhance expression of phosphorylated ASK-1 (Figs. 4 and 5), which is downstream from

![Figure 6](image-url)
inostiol-requiring enzyme 1 and is responsible for ER stress-dependent activation of JNK (40). In contrast, DIM-C-pPhBr and DIM-C-pPhF did not enhance phosphorylation of ASK-1 in colon cancer cells (Fig. 5D; ref. 28), whereas activation of MKK4, which is upstream from JNK, was increased in both colon and pancreatic cancer cells. Thus, in pancreatic cancer cells, DIM-C-pPhBr and DIM-C-pPhF induced JNK phosphorylation through the classic ER stress pathway, whereas in colon cells JNK phosphorylation was ER stress-independent (Fig. 5D) and required activation of MKK4 through other pathways (Fig. 6D), which are currently being investigated.

We also determined the in vivo effects of DIM-C-pPhBr in an orthotopic model of pancreatic cancer, in which L3.6pl pancreatic cells (29, 30) are injected directly into the pancreas. The results (Fig. 6) clearly show that DIM-C-pPhBr (25 mg/kg/d) inhibited pancreatic tumor growth, and these effects were not accompanied by changes in body or organ weights or histopathology, as previously observed for C-DIMs in other in vivo studies in mice (21, 24, 25). In addition, an increase in TUNEL staining was observed in tumors from mice treated with DIM-C-pPhBr compared with mice treated with the vehicle control, demonstrating activation of apoptotic cell death in vivo, which complements results obtained after treatment of L3.6pl cells in culture with DIM-c-pPhBr (Fig. 4C and D).

In summary, this study shows that DIM-C-pPhBr and related compounds activate ER stress pathways in pancreatic cancer cells leading to up-regulation of DR5 and induction of apoptosis. Previous studies show that activation of this pathway is an important element for overcoming TRAIL resistance (34–39); however, our results show that DIM-C-pPhBr alone is a highly effective inhibitor of pancreatic cell and tumor growth, and this compound and other C-DIMs exhibit minimal toxicity in in vivo mouse models (21, 24, 28). Current studies are focused on the development of C-DIMs as a novel class of anticancer drugs for clinical treatment of pancreatic cancer, either alone or in combination with other agents including TRAIL.

Disclosure of Potential Conflicts of Interest

S. Safe acts as a consultant for Plantacor, a company that has licensed the C-DIM compounds. The other authors reported no potential conflicts of interest.

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ER stress-dependent apoptosis in pancreatic cancer

In the article on ER stress-dependent apoptosis in pancreatic cancer in the October 2008 issue (1), the second to last author’s name was spelled incorrectly. The author’s name should have appeared as Xinyi Liu.

Reference
Molecular Cancer Therapeutics

Structure-dependent activation of endoplasmic reticulum stress-mediated apoptosis in pancreatic cancer by 1,1-bis(3′-indoly)-1-(p-substituted phenyl)methanes

Ping Lei, Maen Abdelrahim, Sung Dae Cho, et al.


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