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Mini Review

Effects of DNA Ordering, Cleavage, and Coordination in Non-Cancer Cells

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Abstract

A series of arylazo sulfones known to cleave NÀS bonds upon exposure to light have been synthesized and their activities studied in the dark and upon irradiation to DNA. Interactions with calf thymus DNA were studied and the observed significant affinities (most likely due to DNA intercalation) were analyzed by in silico molecular docking calculations, suggesting that polar contacts were predominantly through sulfonyl moieties. Incubation with plasmid pBluescript KS II showed DNA cleavage, which was examined over time and concentration. Exposure to UV-A greatly ameliorated DNA damage for most compounds, but the effect was slightly reduced under visible light. As for in vitro experiments, we found that cell death of most compounds was slightly enhanced by irradiation. Photodestructive effect under UV-A irradiation (IC50-13 μM), (IC50-100 μM). These compounds were irradiated in the presence of two non-cancer cell lines and found to be equally toxic only under irradiation but not in the dark. Temporal and spatial control of light may therefore provide opportunities for these new scaffolds to be useful in the development of phototoxic pharmaceuticals.

Keywords: A375 melanoma cells, Molecular docking, Radicals, N–S bond homolysis

INTRODUCTION

A variety of small organic molecules have been designed and tested to interact with structural features of DNA to target the transcriptional machinery of cancer cells, leading to apoptosis. Indeed, DNA modifications can inhibit cancer progression, and this can be achieved through several pathways, including phosphodiester hydrolysis and oxidation of deoxyribose sugars or nucleotide bases **(Crick FH 1958)**. Examine the affinity of small molecules to DNA using spectroscopic analysis. This provides information on changes in DNA content upon interaction with the tested compound. Thus, 'host' intercalation with DNA, binding to the minor and major grooves is revealed, indicating an important physicochemical approach that is a prerequisite for potential effective damage. Although most DNA-cleaving compounds are metal complexes, there have been a considerable number of published studies on artificial organic molecules, also called 'metal-free nucleases', with the aim of identifying differentiated mechanisms of action. Such compounds exhibit very diversified molecular structures, including, among the recent ones, simple oximes and hydroxylamines, coumarin oxime ethers, imidazo-phenanthrolines and their carbohydrate conjugates, indolo- pyridine and naphthoquinone thiazole hybrids and benzothiazole derivatives, bis- and tetrakis-1,2,3-triazole derivatives, naphthalenophanes, selenylated oxadiazoles 2-styryl-4-aminoquinazoline, calixaren and indolyl azaenedienes and the natural product Shishjimicin A The challenge to find DNA binding molecules that do not interfere with the functions of normal cells and/or to overcome multidrug resistance to chemotherapeutics is the most desirable goal **(Haselkorn R et al., 1973)**. Chemotherapy were investigated for the treatment of cutaneous T-cell lymphoma whereas combinations of chemotherapy and photodynamic therapy were applied to study the synergistic effects in various cancer cells and for better therapeutic efficacy in prostate and breast cancer advanced gastric adenocarcinoma etc. In addition, photosensitizers are increasingly being used to inactivate bacteria and other microbes, but scientists believe that the diversity of biological targets in the process makes antibiotics less effective **(Moldave K et al., 1985)**. I

doubt the effectiveness of not reaching a dead end. Within the scope of this manuscript, we were keen to investigate whether the abundant photochemistry of arylazosulfones could affect biomolecules and living cells. For this reason, using established methodology, we synthesized a series of arylazosulfones containing compounds with different electron-donating and electron-withdrawing groups on the aryl group **(Lucas-Lenard JEAN et al., 1971)**. The results were compared to those obtained with compounds with different azo moieties, including arylazosulfides and triazines. The DNA binding profile of the entire set of 17 compounds was examined using calf thymus (CT) DNA and UV-vis and fluorescence spectroscopy and viscosity experiments. DNA cleavage (in the dark) and photocleavage (under UV-A and visible light irradiation) were examined using plasmid DNA pBluescript SK II and visualized by agarose gel electrophoresis **(Davis HP et al., 1984)**. High-grade A375 melanoma cells were the model cells that yielded initial results in cell culture under exposure to darkness, UV-A, and visible light. In addition, two non-cancer cell lines were used as controls for activity. HFL1, a fibroblast cell line isolated from the lungs of white normal embryos, and the HaCaT cell line, an immortalized human keratinocyte **(Crick FH 1958)**.

DNA Experiments

All compounds in 10% or less DMSO solution were incubated with plasmid DNA pBluescript SK II (500 ng). To confirm the stability of the studied compounds in DMSO, NMR experiments were performed in DMSO-d6 and other deuterated media (DMSO-d6/D2O and CD3OD, t = 48 h). The compound was found to be stable in DMSO, the solvent used for storage. Note that the samples were stored in a refrigerator at 4 °C immediately after being prepared with DMSO **(Haselkorn R et al., 1973)**. The concentration chosen for dark experiments was 100 µM, with estimated incubation times of 30 and 150 minutes. According to the protocol used, compounds are incubated for 30 minutes prior to irradiation, followed by irradiation for 2 hours. As can be seen, when the compounds are incubated in the dark for 30 or 150 minutes (for plots of the same color), most compounds show cleavage activity within the first 30 minutes **(Moldave K et al., 1985)**.

DNA Photo Experiments

All compounds at a concentration of 100 µM were mixed with pBluescript SK II, incubated for 30 minutes and then irradiated with 365 nm or visible light for 120 minutes **(Lucas-Lenard JEAN et al., 1971)**. Each set of three same-colored charts shows the average number of %ss and %ds (pictured) cleavage. The latter is always at the top of the SS plot and is shown in red]. The second column of each triad shows the results of UV-A irradiation for each compound in the group, and the third column is the results of visible light irradiation **(Lengyel P 1969)**. The first column was added to compare the dark effect at the same concentration and exposure time. Agarose gel electrophoresis images of representative experiments for each compound under UV-A and visible light illumination. UV-A irradiation appears to cause more DNA photocleavage than visible light for most compounds (Group A compounds, Group B compounds, and all Group C and D compounds) **(Weissbach H 2012)**. This may be due to the compound's significant absorption in the UV-A region and the higher energy provided by UV-A irradiation compared to visible light. The nitro derivative turned out to be so effective that it had to be tested at lower concentrations. Fortunately, compound 100 in particular proved to be highly active even at a concentration of 25 µM, cleaving 50% of the plasmid between 10 and 25 µM **(Loftfield RBet al., 1972)**.

MATERIALS AND METHODS

All commercial reagent grade chemicals and solvents were used without further purification. Trisodium citrate, NaCl, CT-DNA, and EB were purchased from Sigma-Aldrich Co. and all solvents were obtained from Chemlab. DNA stock solution by diluting CT-DNA in buffer (pH 7.0 containing 150 mM NaCl and 15 mM trisodium citrate), vigorously stirring at 4 °C for 3 days, and keeping at 4 °C for >1 week. The CT-DNA stock solution has a ratio of UV absorbance at 260 nm and 280 nm (A260/A280) of approximately 1.90, indicating that the DNA is free of protein contamination. DNA concentration per nucleotide was determined by UV absorbance at 260 nm.

We synthesized the supercoiled plasmid pBluescript SK II and confirmed the absence of nicked or linear chains. All samples containing pBluescript SK II were illuminated with a Philips 2 × 9W/10/2P UV-A lamp at 365 nm or an OSRAM DULUX S BLUE white light at pH 6.8. NMR spectra were obtained on Agilent 500/54 (500 MHz for 1H) (Agilent Technologies, Santa Clara, Calif., USA) and Bruker (300 MHz for 1H) spectrometers using DMSO-d6, DO, CDCl3 and CD3OD as absorbers solvent. UV-Vis spectra were recorded with a Hitachi U-2001 dual-beam spectrophotometer (Hitachi, Tokyo, Japan). Viscosity experiments were performed using an ALPHA L Fungilab rotational viscometer (Fungilab, Barcelona, Spain) equipped with an 18 mL LCP spindle and measurements were performed at 100 rpm. Fluorescence spectra in solution were recorded on a Hitachi F-7000 fluorescence spectrophotometer.

Molecular Studies

The organic compounds are fully optimized at the B3LYP/6-31g* level of theory, with the LanL2DZ basis set for iodine for compounds implemented in the Gaussian 09 suite of programs (revision B.01). increase. The crystal data for the B-DNA dodecamer d(CGCGAATTCGCG)2 (PDB 1D: 1BNA) was downloaded from the Protein Data Bank. Docking analysis was performed with the AutoDock Vina program. DNA was prepared for docking by removing water molecules and polar hydrogen atoms, and Gasteiger charges were added by Autodock. A 60 x 80 x 114 grid box with 0.375 Å spacing was used to surround all DNA. A rigid docking protocol and 100 rounds of Lamarck's genetic algorithm were run to search for

ligand conformations. PyMOL was used to visualize docking results and DNA-compound interactions.

CONCLUSIONS

A series of arylazosulfone derivatives were synthesized and their biological characterization was investigated with respect to their strong UV-A and visible light absorption and NÀS bond instability. Their ability to photocleavage DNA and their cytotoxic effects on highly malignant A375 melanoma cells and two non-cancer cell lines were investigated. The affinity of sulfones for bovine thymus DNA was studied, demonstrating the ability of sulfones to interact with biomaterials through polar contacts and van der Waals forces. The interaction of the compound with CT-DNA revealed that it strongly binds to CT-DNA via partial intercalation. We found that m-substitution (for NO2 and Cl derivatives) resulted in higher DNA binding constants. Molecular docking calculations show moderate energy bonds and polar contacts in most of the compounds. Incubation of compounds with plasmid DNA revealed some derivative DNA cleavage, but exposure to light resulted in substantial DNA photocleavage, especially in the UV-A region. The derivatives that showed the highest photocleavage activity were compounds, most of which had nitro or halo aromatic substituents. Cell cultures containing melanoma cells showed that the derivatives exhibited chemical activity with an IC50 of approximately 100 µM. On the other hand, only compounds and exhibited photochemical activity, with IC50 values of approximately 13, 100 and 100 µM, respectively. The same was evident for two non-cancer cell lines. Derivatives, especially naphthyl, had little effect on cells in the dark, but killed them at concentrations as low as 100, 100, and ~13 µM, respectively. They may therefore be lead compounds for the development of novel derivatives that act under photodynamic effects and can be used in the development of phototoxic drugs.

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