Abstracts

Naff Symposium

Poster Session

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Department of Chemistry

University of Kentucky

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Author Index of Abstracts

AQUEOUS TOXIC HEAVY METAL CAPTURING AND DETECTION USING COLORED SYNTHETIC DITHIOLATES

Authors

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Abstract

The synthetic dithiol molecule B9= N,N'-bis(2-mercaptoethyl)isophthalamide, common name "benzenediamidoethanethiol" has a unique ability, to immobilize heavy metals (Cd, Hg, Pb and As) from water to below the detection limits of ICP-OES and CVAAS through the formation of exceedingly stable, covalent S-M bonds. However, the insolubility of the B9-M compounds precluded structural characterization by single-crystal X-ray crystallography. Thus, a series of new dithithiol molecules was synthesized as derivatives of B9. These include AB9 (carboxylic acid), MB9 (methyl ester) and EB9(ethyl ester). They provide different inductive effects towards the CH2CH2SH, maintain similar bonding possibilities as B9, expanding the solubility for X-ray crystallographic analysis. These new molecules are odorless, have no toxic byproducts, cost-effective, no excess precipitating agent needed, heavy metal removal >60 %. Moreover, the starting materials are resistance to get oxidized, no disulfide bonds formation, and immediate precipitation.

A new class of colored compounds using anthraquinone, anthracene and 2,5-pyridine di-acidchloride were made by performing several modifications to the existing ligands. The interactions between conjugated aromatic system containing pendant thiol groups with metal ion is hypothesized to provide metal ion quantification via colorimetric methods, efficient identification of waste-waters and natural waters contamination and obtaining a crystal structure for L-M.

ELECTROCHEMICAL REDUCTION OF DIAZONIUM SALTS ONTO GLASSY CARBON FOR A MORE ROBUST ELECTROCHEMICAL APTAMER-BASED SENSOR

Authors

Israel Belmonte, Chemistry, University of Cincinnati
Ryan J. White, Chemistry, University of Cincinnati

Abstract

Electrochemical, aptamer-based sensors (E-AB) hold the potential to continuously monitor specific analytes in real-time and in complex media. The point-of-care (POC) application of these E-ABs can replace more expensive, time consuming and complicated methods. E-AB sensors typically employ aptamers, composed of nucleic acids which are singled stranded DNA or RNA sequences, that have been selected to specifically bind a target. Aptamers are capable of being immobilized onto different substrates such as gold, platinum and silver. A common approach to aptamer immobilization is using self-assembled monolayer chemistry on a gold electrode. Unfortunately, the stability of the gold-thiol bond is not ideal for fieldable devices because it is not stable to air drying or significant temperature changes. Additionally, the gold-thiol bond is not stable when stored for long periods of time. Covalent bonding to carbon electrodes, on the other hand, has been shown to be capable of forming strong carbon-carbon covalent bonds and offers rich surface chemistry. The rich chemistry offered by, for example glassy carbon electrodes (GCE), can be exploited by reduction of diazonium salts onto the GCE forming a strong carbon-carbon covalent bond. The carbon-carbon covalent bond can usually only be removed by mechanical polishing and can be stored for several months without breaking. Here, we introduce a diazonium salt and reductively attach it to a glassy carbon electrode. A maleimide group allows for maleimide-thiol coupling chemistry to immobilize thiolated DNA aptamers for E-AB sensor fabrication on GCE. This surface chemistry enables stable performance of folding-based electrochemical sensors.

SYNTHESIS AND PHOTOLUMINESCENCE PROPERTIES OF UPCONVERTING NANOMATERIALS PRODUCED THROUGH LASER ABLATION IN LIQUID

Authors

Rosemary Calabro, Chemistry, University of Kentucky
Dong-Sheng Yang, Chemistry, University of Kentucky
Doo Young Kim, Chemistry, University of Kentucky

Abstract

Upconverting nanomaterials are promising in applications including bioimaging, sensing, photodynamic therapy, drug delivery, and security. Specifically, NaYF4 co-doped with Yb3+ as a photosensitizer and Er3+ as an activator is especially suitable for biological applications because Yb3+ absorbs at 980 nm, in the range of optical transparency for biological tissues. Through the energy-transfer upconversion mechanism, energy is transferred multiple times to Er3+ from Yb3+ before Er3+ emits both red and green photons. One major challenge is producing upconverters that have both high photoluminescence efficiencies and water solubility. Traditional methods, such solvothermal synthesis, fall short with limitations including toxic side products, non-aqueous solubilities, high reaction temperatures, long reaction times, and poor control of phase and morphology. Laser ablation in liquid is a promising alternative for nanomaterial synthesis allowing fast production, fewer chemicals, fewer byproducts, and control over the product by tuning the laser parameters. NaYF4:Yb3+/Er3+ targets are produced through coprecipitation, followed by 532 nm pulsed nanosecond laser irradiation in water. The laser induces formation of smaller particles that are stable in water. The size of the particles is controlled by the laser fluence and the solubility can be tuned by the presence of capping agents in the liquid during laser ablation.

COMPUTATIONAL MODELING OF PURINERGIC RECEPTOR ACTIVATION IN MICROGLIA

Authors

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Darin Vaughan, Chemistry, University of Kentucky
Peter Kekenes-Huskey, Chemistry, University of Kentucky

Abstract

Microglia function is orchestrated through highly-coupled signaling pathways that depend on calcium (Ca2+). In response to extracellular adenosine triphosphate (ATP), transient increases in intracellular Ca2+ can be driven through the activation of purinergic receptors (P2X and P2Y). Their activation is sufficient to promote physiological responses in microglia including cytokine release and morphological changes. Toward improving our understanding of how purinergic receptor activation drives cellular-scale responses, we are developing a minimal computational model fof P2X4/7 P2Y1/6 (Gaq) and P2Y12 (Gai) activation with concomitant changes in intracellular Ca2+. In addition to handling the intracellular cation transients, the model captures the subsequent modulation of intracellular signaling networks including G-protein signaling, the phospholipase C pathway and IP3 receptor activation. These networks ultimately control the release of cytokines associated with microglial function. With this model, we probe the sensitivity of evoking these microglial functions with respect to purinergic receptor expression and their subcellular distribution, which are known to vary across microglia phenotypes.

BIOPHYSICAL INVESTIGATION OF CYTOCHROME P450 (CYP) IRON STATE STABILITY.

Authors

Catherine Denning-Jannace, Chemistry, University of Kentucky
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Abstract

For catalysis to occur, heme-containing Cytochrome P450s (CYPs) must convert from a ferric to a ferrous state. As the first electron transfer step is rate limiting for turnover, monitoring difference in stability of the Fe(III) and Fe(II) states can be used as a surrogate to investigate changes in Gibbs free energy (ΔG). Specifically, we are interested in studying the impact of iron state on promiscuity of CYPs, which in humans range from being very selective to interacting with a wide array of substrates. P450 BM3, a selective bacterial CYP, was used as a model system as we can mutate it to be highly promiscuous. Our studies demonstrate that the ferric and ferrous states of promiscuous BM3 variants are close in stability unlike the more selective variants. This indicates a smaller energy barrier and therefore a more "ready" state for the promiscuous enzyme. As CYPs all have a similar structure, this finding is important to understanding how CYPs are able to regulate their substrate interactions.

BRAIN REGION SPECIFIC SINGLE-MOLECULE STUDIES SHOW LOW LEVELS OF NICOTINE DRIVE STRUCTURAL CHANGES IN RECEPTOR ASSEMBLY

Authors

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Abstract

Neuronal nicotinic acetylcholine receptors (nAChRs) are cation-selective, ligand-gated ion channels expressed throughout the central nervous system. They form pentameric structures assembled from 9 alpha subunits (α2 to α10) and 3 beta subunits (β2 to β4). Nicotine, the primary addictive compound in tobacco, binds with high affinity to nAChRs. Exposure to nicotine can cause changes in expression, trafficking and stoichiometry of nAChRs, leading to modification in their function. α4β2 receptors, the most abundant nAChRs in the CNS, have two distinct stoichiometries, (α4)2(β2)3 and (α4)3(β2)2, often characterized as high-sensitivity (HS) and low-sensitivity (LS) receptors, respectively. We developed a single molecule technique to monitor changes in the structural assembly of α4β2 receptors in an animal in response to its physiological environment. We used this approach, which utilizes nanoscale vesicles extracted from the brain of an animal, to monitor changes in the distribution in receptor isoforms in specific brain regions. These nanoscale vesicles are composed of the identical cellular membrane in which the receptors originally resided offering similar physiological conditions and maintaining the receptor's structural integrity. The distribution of two isoforms of α4β2 receptors was quantified in the brain as a whole and individually in seven different brain regions from α4-GFP knock-in mice. We used this method to determine the effect of nicotine and withdrawal on the distribution of receptor stoichiometry.

SYNTHESIS, STRUCTURE AND ANTICANCER ACTIVITY OF ORGANOMETALLIC GOLD(III)-DACH COMPLEXES

Authors

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Samuel Awuah, Chemistry, University of Kentucky

Abstract

Novel classes of cyclometalated gold(III) complexes has been prepared by the reaction between (C,N) cyclometalated gold(III) compounds and (1R,2R)-(+)-1,2-Diaminocyclohexane ligand in the presence of different counter ion and their structure determined by X-ray crystallography. The reaction between cyclometalated gold(III) compound 1 ,[Au(C^N)Cl2] yielded a new series of [Au(C^NH)DACH2]+ complexes (3-5) and cyclometalated gold (III) 2, [Au(C^N)Cl2] yielded nitrogen substituted [Au(C^N)(DACH)]2+ complexes (6-8). The in vitro anti-cancer activities of complexes 3-8, cisplatin and auranofin were studied in A2780, OVCaR8, RPE MYC, and MCF7 cancer cell lines by crystal violet assay. Complexes 3-5 exhibited more potency towards A2780 and OVCAR 8 cell lines (IC50 ~ 4.0 μM), while complexes 6-8 were more potent towards MCF7 and RPE MYC (IC50 ~ 4.0 μM). The stability studies in the physiological conditions revealed that these compounds are stable. These complexes do not interact with supercoiled DNA. The cellular uptake of these complexes were low (200-700 picomol /million cells) in OVCAR8 cells. This study proved that tuning the gold(III) center by the DACH ligand can modulate stability and contribute to enhanced anticancer drug discovery.

RU(II) CYP1B1 INHIBITOR PRODRUGS WITH ENHANCED POTENCY

Authors

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Abstract

Cytochrome P450 subfamily 1 (CYP1) comprises three monooxygenases, CYP1A1, 1A2, and 1B1, which have relevance to carcinogenesis. CYP1B1 expression has been found to be higher in tumors compared to normal tissues. Recently, it has been suggested that CYP1B1 might play a key role in cancer progression and enhanced cell proliferation by inducing cell cycle transition and inhibiting cellular apoptosis. CYP1B1 also has been associated with resistance to chemotherapeutics. Therefore, CYP1B1 represents a potential target for anticancer therapy.
The inhibitory effect of natural stilbenoids on CYP1B1 has been known for the last decade.
Based on the rational design, synthesis and biological evaluation of inhibition of cytochromes P450 1B1, 1A1, and 3A4, we identified new selective CYP1B1 inhibitors with up to 10-fold enhanced potency than 2,4,3',5'-tetramethoxystilbene (TMS). The best small molecules were coordinated with Ru(II) scaffolds, yielding new complexes with one and two monodentate ligands. These Ru(II) complexes may be useful for the photoinduced delivery of CYP1B1 inhibitors that provide spatial and temporal control over enzyme inhibition. Chemical modification of a separate scaffold resulted in the most promising molecules, with inhibitory effect on CYP1B1 at picomolar concentrations and selectivity of over 100,000-fold compared to human liver CYPs.

POTASSIUM PROMOTED IRON OXIDE CATALYST ON PHOTOCATALYTIC CO_2 REDUCTION

Authors

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Muthu Gnanamani, Center for Applied Energy Research (CAER), University of Kentucky
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Abstract

Photocatalysis by metal doped semiconductor is attracting major attention in regard to enable the reduction of CO_2 (*g*) in the presence of water vapor as a hole scavenger. Such technology has the potential to produce chemical feedstock and simultaneously minimize environmental pollution. Potassium doped iron oxide (α-Fe_2O_3) of varying potassium compositions (100Fe:*x*K, $0 \leq x \leq 5$) are synthesized using incipient wetness impregnation method. The structure, composition, and properties of the catalysts are investigated by X-ray diffraction, nitrogen adsorption-desorption experiments, DSC, TGA, and multiple spectroscopies, including: DRUV-vis, FTIR, Raman, ICP-AES, XPS and UPS, TEM with EDS and SAED. UV-visible light ($\lambda \geq 295$ nm) excited the catalysts uniformly deposited in a cylindrical photoreactor in presence of pure CO_2 or air (400 ppm CO_2), both under a saturated water vapor atmosphere. The maximum production of $CO_{(g)}$ (R_{CO} = 0.5836 μmol g_{cat}^{-1} h^{-1} in pure CO_2 and R_{CO} = 0.4267 μmol g_{cat}^{-1} h^{-1} in air) quantified by GC- TCD-FID corresponds to 100Fe:1K photocatalyst. The surface doped potassium photocatalyst enhances the photocatalytic efficiency by creating a more negative conduction band than the CO_2/CO reduction potential as supported by UPS and DRUV-vis spectroscopies. The photoreduction mechanism and also the effects of other hole scavengers will be reported.

SYNTHESIS AND STRUCTURAL CHARACTERIZATION OF TRICOORDINATE AU(I) COMPLEXES BEARING VARIOUS ANCILLARY LIGANDS

Authors

William Jennings, Chemistry, University of Kentucky
Randall Mertens, Chemistry, University of Kentucky
Sean Parkin, Chemistry, University of Kentucky
Samuel Awuah, Chemistry, University of Kentucky

Abstract

Since the advent of cis-diamminedichloroplatinum(II) (Cisplatin), transition metal complexes have been critical in the effective treatment of a variety of cancers. However, this field has been traditionally dominated by Pt(II) based drugs. The presence of cancer lines resistant to Cisplatin and similar Pt(II) compounds makes the consideration of non-platinum anticancer metal complexes highly important. Recently, Au(I) and Au(III) based complexes have been investigated as potentially effective chemotherapeutics, especially for cisplatin-resistant cancers. However, the physiological stability of gold complexes has typically been problematic. Here, we report the synthesis and chemotherapeutic potential of a class of tricoordinate Au(I) complexes bearing N,N-bidentate and either tertiary phosphine or arsine ligands. X-ray crystallographic studies reveal interesting structural properties of these compounds including variable Au-N bond lengths likely attributable to a second order Jahn-Teller distortion. MTT assays reveal appreciable cytotoxicity which may be related to the unique structural features of this class of compounds. This work provides insights into the relationship between the structure, stability, and cytotoxicity of tricoordinate Au(I) anticancer agents.

EVALUATION OF THE 908 DEVICES MICROFLUIDIC ZIPCHIP FOR CZE-MS ANALYSIS OF ALKALOIDS IN LOBELIA CARDINALIS PLANT CELL CULTURES

Authors

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John Littleton, Psychology, University of Kentucky/Naprogenix Inc.
Trent Rogers, Naprogenix Inc.
Bert Lynn, Chemistry, University of Kentucky

Abstract

Application of the 908 Devices ZipChip™ (ZipChip) for microfluidic capillary zone electrophoresis mass spectrometry (CZE-MS) allows for rapid, in-depth analysis of multiple samples. The ZipChip involves minimal sample preparation and is ideal for small cation analytes, such as alkaloids. Here ZipChip analysis was applied to extracts from Lobelia cardinalis hairy root cultures. These contain the alkaloid lobinaline, an inhibitor of the dopamine transporter (DAT) with potential therapeutic value. By expressing the human (h)DAT in these cultures it was possible to select transgenic mutants for increased hDAT inhibitory activity. Alkaloids that are increased in the selected cultures may represent novel inhibitors. Extracts from wild-type, transgenic, and selected mutant cultures were analyzed by ZipChip and batch processed using the MZmine2 processing software and Prism 8 statistical software. In total 139 features were detected as baseline resolved peaks. Statistical differences in the relative abundance of the primary alkaloid lobinaline ($C_{27}H_{34}N_2$), along with several putative "lobinaline-like" molecules, were further assessed and a narrowed list of possible therapeutic natural product targets was constructed for evaluation of pharmacological activity in the future. Coupling data-processing software with ZipChip data acquisition has enabled comprehensive metabolomic profiles from plant cell cultures to be constructed within a single working day.

ANTICANCER EFFECT: STRUCTURE AND MODE OF ACTION DIFFERENCE OF [AU (C^N)(ACAC)CL]

Authors

Jong Hyun Kim, Chemistry, University of Kentucky
Samuel Awuah, Chemistry, University of Kentucky

Abstract

Gold(III) complexes are attractive reagents for several applications including catalysis, electronic materials, and biomedicine. However, their utility is hamstrung by rapid reduction, emphasizing the need for stable complexes with sufficient reactivity. Here, we report a new class of organometallic gold(III) reagents with [C^C^N] configuration within their scaffold. The compounds were synthesized from a reaction of [C^N]-cyclometalated Au(III) complexes with substituted acetylacetonates to generate neutral gold(III) complexes of the type [Au(C^N)(acac)Cl]. These compounds were characterized by NMR, elemental analysis, mass spectrometry, and X-ray crystallography. All compounds showed effective inhibition of cancer cells and selectivity compared to normal cells. A variety of methods were used to investigate mechanism of action: Whole-cell uptake, apoptosis assay, and cell cycle assay. The results reported here indicate that stable gold-acac complexes present the possibility of developing new anticancer drugs and need further studies.

CONFINED VOLUME ELECTROCHEMICAL APTAMER-BASED SENSOR TO MONITOR SINGLE CELL RELEASE OF GLIOTRANSMITTERS

Authors

Robert Lazenby, Chemistry, University of Cincinnati
Ryan White, Chemistry, University of Cincinnati

Abstract

Electrochemical aptamer-based (E-AB) sensors can specifically and reversibly bind to a target molecule and quantitatively measure the concentration. We use a macroscale E-AB sensor that binds to adenosine triphosphate (ATP) to quantify the release of this gliotransmitter from 2D cultures of astrocyte cells. It is shown that ATP released from the 2D cell population increases with cell density, when cells were subjected to stimulus of calcium. We then fabricated E-AB sensors on the microscale, using a recessed and nanostructured gold electrode. We present this as a generic platform to study single cells in a confined environment that restricts the volume of solution between the cell and the sensor to ensure that ATP is detected as soon as it is released from the cell. It is shown that the microscale sensor detects ATP much faster than from the macroscale sensor probing the cell population. This recessed microscale E-AB sensor approach serves as a new methodology to probe single cells with enhanced specificity, temporal resolution and spatial resolution.

SYNTHESIS AND BIOLOGICAL EVALUATION OF CYCLOMETALLATED AU(III) DITHIOCARBAMATES AS A NOVEL CHEMOTHERAPEUTIC

Authors

Tyler Mertens, Chemistry, University of Kentucky
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Samuel Awuah, Chemistry, University of Kentucky

Abstract

Cyclometallated Au(III) complexes have been thoroughly studied as alternative chemotherapeutics to platinum due to their innate cytotoxicity. Although a variety of these class of compounds have been proven to be potent, the lack of stability of Au(III) in biological media has inhibited their practical use. In this work, we employed the [C^N] cyclometallated framework in combination with bidentate sulfur ligands; dithiocarbamates, to synthesize ten (10) drug candidates. These compounds were fully characterized by NMR spectroscopy and structurally characterized by X-ray crystallography. Preliminary cell viability assays show cytotoxicity with nanomolar IC50 values in cisplatin-resistant cells. Furthermore, rigorous biological studies of these compounds have been outlined in future studies. The stability of these complexes towards nucleophilic biomolecules will be explored using UV-VIS and NMR spectroscopy and further studies exploring protein interactions will be performed. Overall, this set of cyclometallated Au(III) complexes has shown promising preliminary results and offers a model framework for expansion.

14

LOCATION OF FADS IN RHODOPSEUDOMONAS PALUSTRIS BIFURCATING ELECTRON TRANSFER FLAVOPROTEIN: SPECTROSCOPY, THERMODYNAMIC AND

Authors

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Abstract

In flavin-based electron bifurcation, flavin adenine dinucleotide (FAD) bifurcates the two electrons coming from NADH to an endergonic and an exergonic electron transfer pathway. Electron transfer flavoproteins (ETFs) possess three domains. In canonical ETFs, a FAD present in domain II is called the electron transfer FAD (ET-FAD) whereas an AMP molecule is present in domain I. In contrast, bifurcating Etfs contain a second FAD molecule in place of AMP. This second FAD is believed to mediate electron bifurcation, and so is called the bifurcating FAD (Bf-FAD). Bf-FAD receives a hydride from NADH and transfers one electron exergonically to ET-FAD, which then reduces the ferredoxin or flavodoxin semiquinone and eventually supports nitrogen fixation in anaerobes. To demonstrate the functions of these FADs individually we used site-directed mutagenesis at the interface between domains I and III to disfavor binding of Bf-FAD's flavin, in the bifurcating ETF of Rhodopseudomonas palustris (RpaETF). The variant protein contained 0.80 □ 0.05 FAD and 1.20□0.04 AMP as in canonical ETFs and was not reduced by NADH, confirming the absence of Bf-FAD. Visible circular dichroism (CD) of FAD present in the variant resembles the signal of ET-FAD of wildtype (WT) RpaETF. That FAD showed a bi-phasic reduction with a midpoint potential of -13 ± 4 mV for reduction to the anionic semiquinone. These results confirm the presence of ET-FAD in domain II. Comparison of structural signatures via quantum chemical calculations was successful in reproducing experimental spectra. The two flavin sites in a modeled structure of RpaETF reproduced the different CD and visible absorbance signatures observed experimentally and confirmed attribution of the ET flavin to domain II. Therefore, we conclude that the Bf-flavin is bound at the interface of domains I and III, as in the prevailing models, and note that this flavin's properties may be coupled to movement of domain I relative to domain III.

CHARGE EFFECTS AND THEIR ROLE ON PARTICLE TRANSPORT IN POLYMERIC GELS

Authors

Kanthi Nuti, Chemistry, University of Kentucky
Jason DeRouchey, Chemistry, University of Kentucky

Abstract

Biological hydrogels are known to fulfill several important physiological functions, serving as lubricants in joints, acting as barriers against pathogens and serving as selective filters for nutrients, proteins, ions and drugs. All biogels are heterogeneous with varied biophysical properties arrayed on spatially disordered polymer networks. Nanoparticles diffusing in such biogels experience a mixture of complex attractive and repulsive interactions. Using fluorescence correlation spectroscopy (FCS), we have systematically examined the role of probe charge and network charge density on transport and dynamics of probe molecules in polymeric gels. Through a combined theoretical and experimental approach, we have previously shown that particle transport in homogeneously charged dextran gels is highly asymmetric. These dextran gels are low density. In this work, we show increasing the net charge on the probe molecule has large consequences on the transport behavior in attractive gels but minimal effects on transport in neutral or repulsive gels. However, asymmetric transport in the high charge density PVA networks is considerably reduced. Increasing the net probe charge, however, results in nearly identical transport behavior in both low and high charge density polymer networks. Initial results on probe transport in polyampholytic PVA and the dependence of hydrophobic interactions on biotinylated probes will also be presented. Knowledge of polymer-prove interactions could serve as a guideline in the rational design of promising therapeutics that must overcome the significant work required to navigate biological hydrogels in vivo to successfully deliver their payloads.

DISCOVERY OF PARP/PD-L1 DUAL TARGETING SMALL-MOLECULE INHIBITORS

Authors

Samuel Ofori, Chemistry, University of Kentucky
Samuel Awuah, Chemistry, University of Kentucky

Abstract

PARP inhibitors demonstrate synthetic lethality in cells with impaired homologous recombination-mediated DNA repair function, especially BRCA1/2-associated tumors. PD-1/PD-L1 pathway is a checkpoint pathway implied in immunoevasion by tumors. Its blockade reinvigorate T-cells, and the immune system in unison, against tumor cells. Compelling evidence suggests that there is a cross-talk between PARP inhibition and PD-L1 upregulation via GSK3β inactivation.
There is therefore the emergent need to find or design chemical probes that can dually modulate these two pathways. Here, a one-of-a-kind small molecular probes have been developed based on Olaparib, (a PARP inhibitor) and BMS001(a PD-L1) inhibitor. These probes were designed based on results from molecular docking studies. Then synthesized, and their biological activities were validated by cell viability studies, immunoblotting, Flow cytometry. The biological mechanism of these class of dual inhibitors were unravelled by several cellular studies-- cell cycle, and apoptosis. Theses probes are superlatively potent that their individual PARP and PD-L1 inhibitors, and they exhibit synergistic properties of PARP and PD-L1 inhibitors. Additionally, these inhibitors can further be used as probes to fully decode this crosstalk between PARP and PD-L1.

IDENTIFICATION AND QUANTIFICATION OF DNA DAMAGE IN UNCONDENSED AND PROTAMINE-CONDENSED DNA

Authors

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Abstract

The majority of cellular DNA exists in a packaged state. In sperm nuclei, DNA compaction is immensely efficient and fits DNA into a volume about 20 times smaller than in somatic cells. DNA packaging in sperm cells is achieved by replacing histones with arginine-rich proteins called protamines. It is thought that the two primary functions of protamines are to achieve compact nuclei for efficient genetic delivery and protect the paternal genome against damage by mutagens and oxidative species. In recent years, paternal DNA damage in sperm has been shown to not only correlate with infertility but also impact normal embryonic development. Although the processes of sperm chromatin remodeling are considered essential to proper sperm function, our knowledge of the mechanism and degree that protamine packaging alters DNA damage in the sperm nucleus is scarce. Using liquid chromatography-mass spectrometry (LC-MS) and gel electrophoresis (GE) we have investigated DNA damage caused by free radicals to both naked and condensed DNA. A new LC-MS method carried out in HILIC mode (hydrophobic interaction liquid chromatography) on a mixed phase column allows for the simultaneous identification of some DNA damage products. GE after treatment with the DNA repair enzyme formamidopyrimidine [fapy]-DNA glycosylase (fpg) indicates the presence of additional oxidized lesions in DNA. We also show that protamine condensation significantly protects DNA from free radical-mediated damage. Our findings are a preliminary view towards a better understanding of the extent and type of DNA damage events occurring in sperm chromatin structures.

HETEROGENEOUS OXIDATION OF PHENOLIC ALDEHYDES

Authors

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Abstract

Biomass burning emission emits reactive methoxyphenols to the atmosphere, where they are oxidized generating precursors to secondary organic aerosol (SOA) formation. Understanding the mechanisms of oxidation of methoxyphenols on surfaces can contribute to constrain the large uncertainty associated to SOA in climate models. This work explores the heterogenous oxidative processing of three model methoxyphenols: 1) 4-hydroxybenzaldehyde, 2) vanillin, and 3) syringaldehyde by ozone, O3(g), and hydroxyl radical, HO•. Aerosolized 50 µM solutions of each phenol by online electrospray ionization mass spectrometry (OESI-MS) generate microdroplets impinged by O3(g) molecules at mixing ratios between 48 and 5000 ppbv. OESI-MS spectra of methoxyphenols exposed to O3(g) display polyhydroxymethoxyphenol as main products, which implies the participation of in situ generated HO•. As O3 levels increase, the production of polyhydroxymethoxyphenols is favored but new ring fragmentation products are also observed. Fragmentation products include conjugated aldehyde, double bonds, and carboxylic acid functional groups. The interfacial oxidation of the phenols studied is enhanced with an increasing number of methoxy (-OCH3) group: 4-hydroxybenzaldehdye < vanillin < syringaldehyde. The experimental results are explained by two reaction pathways: (1) functionalization of the aromatic ring by HO•, (2) fragmentation of the aromatic ring. Mechanistic schemes explaining the highly oxygenated and low volatility products generated are proposed.

ADVANCED INSIGHTS INTO MECHANISMS OF CHEMOTHERAPY INDUCED COGNITIVE IMPAIRMENT ("CHEMOBRAIN") INVOLVING TNF-A

Authors

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Daret St. Clair, Toxicology and Cancer Biology, Radiation Medicine & Markey Cancer Center, Univ. of Kentucky
D. Allan Butterfield, Chemistry, Markey Cancer Center, Sanders-Brown Center on Aging, University of Kentucky

Abstract

A large fraction of cancer survivors demonstrate cognitive dysfunction and associated decreased quality of life both shortly, and often long-term, after chemotherapy treatment. The etiologies of chemotherapy induced cognitive impairment (CICI) are complicated, made more so by the fact that many anti-cancer drugs cannot cross the blood-brain barrier (BBB). Chemotherapy induced, oxidative stress-mediated tumor necrosis factor-alpha (TNF-α) elevation was considered as one of the main candidate mechanisms underlying CICI. In the present study, we used TNF-α null (TNFKO) mice to investigate the role of TNF-α in Doxorubicin, a reactive oxygen species (ROS)-generating chemotherapeutic agent, -induced, oxidative stress-mediated alterations in brain. We report that Dox-induced oxidative stress in brain is ameliorated and brain mitochondrial function is preserved in brains of TNFKO mice. Further, we show that Dox-decreased the level of hippocampal choline-containing compounds and brain phospholipases activity are partially protected in TNFKO group in MRS study. Our results provide strong evidence that Dox-targeted mitochondrial damage and levels of brain choline-containing metabolites, as well as phospholipases changes decreased in the CNS are associated with oxidative stress mediated by TNF-α. The results are discussed with reference to our identifying a potential therapeutic target to protect against cognitive problems after chemotherapy.

INVESTIGATING THE PROTEIN-PROTEIN INTERACTIONS OF CYP1B1 THROUGH BIOPHYSICAL TECHNIQUES

Authors

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Kimberly Stevens, Chemistry, University of Kentucky
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Edith Glazer, Chemistry, University of Kentucky

Abstract

Cytochrome P450s are a family of mono-oxygenases that are known to catalyze a variety of endogenous and exogenous substrates. While Cytochrome P450 1B1 (CYP1B1) is typically found in extrahepatic tissues, it is rarely expressed in normal tissues and more commonly present in disease states. CYP1B1 is involved in the activation of procarcinogens and plays a role in deactivating chemotherapeutics. Using single molecule total internal reflection fluorescence (TIRF) microscopy, the protein-protein interactions of CYP1B1 can be elucidated. We are specifically interested in investigating the dimerization of the protein as the monomer-dimer equilibrium could play a role in the activity of the enzyme. Substrates and inhibitors of CYP1B1 have the potential to shift this equilibrium, affecting the activity and stability of the enzyme. CYP1B1 stability can be approximated by studying overall global structure, through pulse proteolysis, as well as the presence or absence of heme, through UV-Vis spectroscopy. Various CYP1B1 mutants are involved in both cancer and congenital glaucoma, and have a range of activities within the cell. Elucidating the protein-protein interactions as well as the stability of these variants compared to wild type will add to current understanding of how CYP1B1 contributes to the mechanism of disease development.

TRIDENTATE RUTHENIUM(II) N-HETEROCYCLIC CARBENE COMPLEXES AS PHOTOTOXIC AGENTS

Authors

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Abstract

Since the initial success of platinum-based antineoplastic drugs, there has been substantial focus on developing new metal-based chemotherapeutics with improved efficacy and decreased side effects. Ruthenium-based chemotherapeutics have drawn considerable attention due to their long, ~ 1 μs, excited state lifetimes and ability to act as photosensitizers. These properties are highly desirable for photodynamic therapy (PDT), which functions by activating an inert photosensitizer with light to generate cytotoxic singlet oxygen in a spatially controlled region of the tumor. The efficiency of PDT agents is associated with the agent having a sufficiently long triplet excited state to allow for sensitization of oxygen to singlet oxygen. While Ru(II) tris-bidentate polypyridyl complexes can effectively sensitize oxygen, bis-tridentate complexes containing ligands analogous to 2,2';6',2"-terpyridine (tpy) have extremely short excited state lifetimes of ~ 250 ps, making them ineffective for PDT. To increase the excited state lifetime of tridentate complexes for use as PDT agents, tridentate N-heterocyclic carbene (NHC) ligands were evaluated as tpy replacements. NHCs were selected to study due to their strong sigma-donating characteristics which can tune photophysical properties, such as excited state lifetime. This study will report the synthesis, photophysical properties, and biological activity of three Ru(II) tridentate NHC complexes.

INTRAMOLECULAR SYN DIAMINATION: A NOVEL APPROACH TOWARDS LOLINE ALKALOIDS TOTAL SYNTHESIS

Authors

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Abstract

Loline alkaloids are a group of nitrogen-containing natural products that are produced by fungal endophytes. They provide a remarkable range of survival benefits to the host plants. The saturated pyrrolizidine ring in lolines contains a 1-exo amino group and an ether bridge between C2 and C7. Various substituents on the 1-amino group define different lolines, and the oxygen bridge causes the tricyclic to be strained. Despite their simple structure and intriguing biological activities, only a few total syntheses have been reported to date. Their strained structure and presence of four contiguous stereogenic centers in the heterotricyclic skeleton makes synthesis of lolines challenging. In our retrosynthetic analysis, bond cleavage between C3 and N in loline tricyclic lead us to a bicyclic 1,2-diamine intermediate with N and O atoms in each ring. We hypothesized that this intermediate might be produced by intramolecular *syn* diamination across the double bond of a dihydrofuran.

USING MICROBIAL CYTOLOGICAL PROFILING AS A PRIMARY SCREEN FOR IDENTIFYING THE MECHANISM OF ACTION OF METAL-BASED ANTICANCER

Authors

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Abstract

One of the main obstacles in cancer drug discovery is determining the mechanism of action of new compounds. For this reason, we developed a microbial cytological profiling technique. While bacteria as a model organism lacks the complexity of mammalian cells, this can actually be an advantage. Our technique offers a rapid and uncomplicated method to characterise the mechanism of action of novel compounds; the phenotypic changes seen in Escherichia coli allow for the classification of anticancer compounds with similar or related mechanisms of action. There is a strong rationale supporting this application, as key processes in the central dogma have been implicated as mechanistic targets for anticancer agents in mammalian systems based on the response of E. coli. We have used this technique to determine how the mechanism of action of different metal-based compounds targeting different cellular processes manifests phenotypically in E. coli. The test group included platinum compounds, other DNA damaging agents, antitumor antibiotics, antimetabolites, oxidising agents, and related compounds. This characterization serves as a time-saving, preliminary mechanistic indicator to point researchers in the right direction and expedite the transition of anticancer agents into clinical chemotherapeutics.

DETERMINING THE SOLUBILITY OF POTENTIAL NON-AQUEOUS REDOX FLOW BATTERY MATERIALS USING A QUANTITATIVE STRUCTURE-PROPERTY RELATIONSHIP MODEL

Authors

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Abstract

In screening active materials for redox flow batteries (RFBs), we are modifying redox-active organic molecules to optimize (increase) the solubility and stability without compromising other properties such as redox potential. However, predicting the solubility and stability of active materials across all states of charge is a challenging task. We hope to change our approach to materials development by better predicting properties in advance. Using the quantitative structure-property relationship (QSPR), we have shown that the properties of unknown organic molecules can be predicted when the experimental properties of a training set of related compounds are provided. Herein, we sought to expand this approach to predict the solubility of a different redox core, phenothiazines, which we have evaluated as posolyte candidates for RFBs. We measured the solubility of about a dozen phenothiazine derivatives – in both relevant states of charge (neutral, radical cation and dication) – in a nonaqueous electrolyte. The structure of these derivatives included variations in the number, type, and position of substituents to offer a diverse training set. We used our experimental values and the results of density functional theory calculations to develop a QSPR model for the phenothiazine core, following which we synthesized and measured the solubility of a new set of phenothiazines. Here we will report on the degree of success of our model for solubility prediction.

MOLECULAR BASIS OF CALMODULIN-DEPENDENT CALCINEURIN ACTIVATION

Authors

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Abstract

Calcineurin (CaN) is a phosphatase involved in a wide range of physiological processes. CaN is activated by Calmodulin (CaM), which is an important Ca2+ binding protein found in all eukaryotic cells. While there has been valuable knowledge yielded from previous studies, the molecular mechanism of CaN's activation by CaM is still lacking mainly due to the intrinsically disordered nature of CaN's long regulatory domain (RD). In this study, by combining protein-protein docking and extensive molecular dynamic simulation, we explored and identified an interaction surface between a motif in CaN's RD domain and CaM. This motif, referred as 'distal helix' thereafter, has been shown in experimental studies that it's interaction with CaM is indispensable for CaN's activation. Computational mutagenesis of residues within this site shows impaired binding affinity, which are correlated with measured reduced activities in a related CaM target, implying the fidelity of the prediction. We believe this characterization of binding site between distal helix and CaM provides a potential structural basis of CaN's activation. It may also shed insights into the CaM-dependent activation of many another proteins.

ELECTROCHEMICAL STUDIES OF CATION CONDENSATION AND COLLAPSE OF SURFACE-BOUND DNA

Authors

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Abstract

We demonstrate the ability to control, and electrochemically monitor, short nucleic acid conformation by inducing DNA collapse of short, surface-bound oligonucleotides (between 7 and 28 nucleotides). More specifically, we monitored changes in electrode-bound DNA structure via changes in the faradaic current related to the reduction/ oxidation of a 3'-terminal-appended redox moiety. DNA collapse was induced by cation condensation achieved by either changing the dielectric constant of the interrogation solution or by the addition of multivalent cations including the polyamine spermidine (3+). We observe significant collapse of the DNA structure when the fraction neutralization of the DNA phosphate backbone is >88% consistent with previous reports.

DETERMINING THE STRUCTURE OF THERMOELECTRIC LA3-XTE4-NI COMPOSITES USING HIGH-RESOLUTION TEM

Authors

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Abstract

A NASA incentive is to utilize thermoelectric materials (TE) in radioisotope thermoelectric generators to convert heat generated from radioactive decay to electrical power. Lanthanum telluride (La3-xTe4), is a TE with a figure of merit (zT) of 1.1 (1275 K) which can be increased by 30% when nickel (Ni) nanoparticle (NP) inclusions are introduced. Our goal is to characterize the structures of these high-efficiency TE with atomic-resolution at ambient and elevated temperatures in high-vacuum. We hypothesize that coherent interfaces between LaTe1.46/Ni permit low electrical resistivity and these interfaces are spread out sufficiently to maintain a low thermal conductivity. These interfaces must likely be a key factor determining the stability and performance of the LaTe1.46-Ni composites, but their role and nature are not well understood. We postulate that the presence of a reaction layer at the interface can cause this enhancement in zT. The characterization of these TE materials is extremely challenging due to high oxidation of La3-xTe4 which can interfere with the characterization of the interface with Ni. Here, we show the sample preparation methods and high-resolution structural characterization of LaTe1.46-Ni and their interfaces at high-vacuum and ambient temperature conditions, using Transmission Electron Microscopy (TEM) and Energy Dispersive X-ray Spectroscopy (EDS).

SYNTHESIS AND CHARACTERIZATION OF POLYAMPHOLYTE POLYMERS FOR ENHANCED IN VIVO GENE DELIVERY

Authors

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Abstract

Despite the promises of gene therapy to treat serious inherited and acquired diseases, clinical success has been hindered due to safety concerns or lack of efficiency of various gene delivery systems. While viral vectors account for majority clinical trials due to inherent nature, they suffer from significant safety concerns such as immunogenicity, oncogenicity and concerns commercial production. Synthetic non-viral vectors has the potential to overcome immune responses, but to date, have suffered from low efficiency and biocompatibility; especially in vivo. To address these issues, we produced zwitterion-like derivatives of polyethylenimine via succinylation (zPEI) with 9-55% of the amines modified. Characterization of polymer/DNA interactions revealed that this modification decreased the protonation constant of zPEI resulting in decreased buffering capacity, tunable particle stability and exhibited decreased aggregation in serum. Serum-free transfections with zPEI/DNA exhibited slightly improved transgene expression compared to unmodified PEI/DNA, but in serum, we observed zPEI 9-25% increased transgene expression up to 51-fold compared to unmodified PEI/DNA. Gene delivery mediated by zPEI 9/DNA polyplexes in serum was equal to or greater than unmodified PEI/DNA polyplexes out of serum. Lastly, we'll discuss our current effort to synthesize and more fully characterize polyampholytic polymer designed for enhanced in vivo gene delivery.

COLLOIDAL SILVER NANOPARTICLES: A MORE EFFECTIVE BACTERICIDAL AGENT THAN CHLORINE AGAINST WATERBORNE GRAM-NEGATIVE BACTERIA

Authors

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Abstract

The main aim of this study was to study the antimicrobial and bactericidal activity of unfunctionalized, silver nanoparticles (eAg) against well-established water indicator organisms: Escherichia coli, Klebsiella variicola, and Pseudomonas aeruginosa. This was achieved by determining the Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) of eAg, which were synthesized electrochemically, size-elected, concentrated, and purified by tangential flow filtration (TFF). The MIC values for E. coli, K. variicola, and P. aeruginosa were 0.75-4.02, 1.09-4.08, and 1.55-5.39 mg/L, respectively. The MBC values for the same bacteria were 1.51-3.96, 1.55-5.39, and 2.18-4.99 mg/L, respectively. When tested against chlorine, the MIC values increased by factors of 1000, 2000, and 2000, respectively for the bacteria. The MBC values increased by factors of 1000, 1500, and 1500, respectively. CytoViva hyperspectral imaging will be performed to confirm the proposed mechanistic aspects associated with the attachments of eAg to the cellular membrane and its subsequent disruption.

ELECTROCATALYTIC MECHANISM BETWEEN DNA-TETHERED METHYLENE BLUE AND FREELY DIFFUSING FERRICYANIDE

Authors

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Abstract

Electrochemical DNA (E-DNA) sensors with ultrasensitivity are highly desirable in fields such as clinical diagnostic, forensics, and environmental monitoring. However, E-DNA sensors often require performance of polymerase chain reaction (PCR) to amplify target DNA prior to electrochemical detection. To circumvent the need for PCR target amplification, alternative biomolecule am-plification and signal amplification strategies have been developed. Examples include utilization of the electrocatalytic reaction between intercalated/covalently tethered methylene blue (MB) and freely diffusing ferricyanide (Fe(CN)63-) to develop DNA-mediated charge transport-based (DNA-CT) sensor platforms. Distinguished from previous DNA-CT platforms employing MB and relatively immobile DNA, in this manuscript, we explore the effects of DNA dynamics using the electrocatalytic reaction be-tween DNA-tethered MB (T) and freely diffusing Fe(CN)63-, as the difference in dynamics of the DNA pre- and post-hybridization is often postulated as the fundamental sensing mechanism for numerous E-DNA sensors. Through both cyclic voltammetry (CV) and square wave voltammetry (SWV) studies, we validate that the electrocatalytic reaction between DNA-tethered MB(T) and freely diffusing Fe(CN)63- can be used to differentiate probe dynamics of electrode-bound nucleic acid. This is demonstrated by both the potential difference (ΔE) between the catalytic peak induced by the presence of Fe(CN)63- and the reduction peak of MB(T), and the observation that the percent signal increase (% SI) obtained based on the catalytic current in the presence of Fe(CN)63- de-creases with decreasing probe dynamics. Since the electrocatalytic reaction between DNA-tethered MB(T) and freely diffusing Fe(CN)63- can be used to indicate DNA dynamics differences, and DNA dynamics alters after hybridization, thus we believe, the electrocatalytic platform is highly promising for providing an alternative strategy to achieve desirable sensitivity in structure-switching electrochemical nucleic-acid based sensing.

CLOSED BIPOLAR ELECTRODES FOR APTAMER-BASED SENSORS

Authors

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Abstract

Electrochemical aptamers based (E-AB) sensors, with high specificity and affinity, easy modification and functionalizations, and low cost, have become one of the research hotspots in the fields of chemistry, biochemistry, materials science and so on. In this paper, we have developed a closed bipolar electrode (C-BPE) for colorimetric aptamers-based sensors, which can be detected the TARGETs for deformation of the aptamer. In a closed bipolar electrode, the anode is modified to a target and the cathode has a reducing substance, such as Prussian White (PW). According to the reported potassium ferricyanide (K) can catalysed leucomethylene blue (LB) to methylene blue (MB), the electrons are lost from the C-BPE by PW and this cycle is achieved. Results demonstrate the K and target concentration could be known in this time. So the color change signal from the BPE can more directly and reliably reflect the nature of the E-AB sensor. The results show that C-BPE with aptamers based sensors provides a convenient way for non-professionals to perform further tests on E-AB sensors. Therefore, our bipolar electrodes will enable future applications to label catalysts, enzymes and E-AB sensors.