Aryl-Diazonium Analogues as Potent DNA Cleavage Agents for Treating Cancer and Bacterial Infections

Potent, specific, modular, cost-effective, and synthetically-accessible agents for cytotoxic DNA cleavage.

Technology

NYU researchers in the Diao Lab have designed and synthesized a range of novel small molecule compounds featuring aryl diazonium functional groups to cleave DNA for a variety of therapeutic applications, including cancer and infectious disease. These diazonium salts are synthetically accessible, modular, and possess advantageous activation properties. Diazonium analogues can be activated *via* red-light irradiation providing spatial and temporal selectively and reduced off-target effects. Additionally, the diazonium compounds can be activated in reducing environments, such as by cysteine. In proof-of-concept studies (unpublished), diazonium salts were tested for DNA cleavage activity by incubating them with purified DNA, irradiating the mixtures with red light or adding cysteine, and analyzing the DNA in the reactions by gel electrophoresis. Upon photoredox or redox activation, these analogues generated aryl multiradicals that cleaved DNA with high potency; the most potent compound had an EC_{50} of 6-8 nM, which is comparable to the EC_{50} of calicheamicin γ1 (≈ 10 nM). Together, these novel diazonium salts are promising early-stage cytotoxic agents for further development as potent, specific, cost-effective, synthetically accessible, targeted warheads for the treatment of cancer, as well as bacterial infections.

Background

DNA cleavage, the process of breaking phosphodiester bonds within the DNA molecule, plays a critical role in combating harmful DNA, such as those found in cancerous, viral, and bacterial cells. Natural products like calicheamicin γ1 and its analogues have been utilized for their DNA-cleaving abilities in antitumor antibody-drug conjugates (ADC) like Mylotarg and Besponsa. However, the complex structure of these natural products presents challenges in efficiently and economically synthesizing and preparing derivatives to enhance binding affinity and selectivity. Moreover, Mylotarg and Besponsa exhibit substantial hepatotoxicity, attributed to the uptake of the drug by hepatic sinusoidal endothelial cells. Therefore, there is an unmet challenge to develop synthetic alternatives with similar and/or enhanced potency (low nanomolar EC_{50}), better selectivity towards cancer cells, but with more efficient and cost-effective synthesis routes.

Development Status

The team has presently developed diazonium salts with EC_{50} ranges from 6-600 nM. The next step is to design and synthesize analogues with additional diazo functional groups to further improve potency. The cytotoxicity of the optimized compounds will be tested using cell viability

Technology ID

DIA01-02

Category

Life Sciences/Biochemicals & Small Molecules
Life Sciences/Therapeutics/Antibacter
Doug Brawley
Life Sciences/Research tools/Oncology

Authors

Tianning Diao, PhD

View online

assays. The compounds will then be linked to antibodies to form ADCs, whose efficacy and specificity in inducing cytotoxic DNA damage will be examined using cell survival assays. If the results show promise, the team will pursue *in vivo* studies with mouse models.

Applications

- Diazonium salts could be used in the following therapeutic and research contexts:
  - **General chemotherapy:** With or without light-dependent activation or tumor-specific targeting
  - **Broad-spectrum antibacterial:** Could be selectively targeted to bacteria to cleave their foreign DNA
  - **Photo- and redox-responsive cytotoxic research tool:** Could be used as reagents to kill DNA-containing cells in response to light or reducing conditions

Advantages

- **Synthetically accessible compound family:** Easy and economical synthesis and derivatization using commercially available starting materials
- **Similar potency to standard-of-care:** Displays low-nanomolar potency comparable to calicheamicin γ1
- **Modular:** The adjustable potency of the payload provides another dimension of optimizing the ADC's therapeutic index
- **Targetable agent:** Diazonium salts can be linked to small molecules or antibodies for cell-, tissue-, and/or organism-specific targeting cancer cells
- **Photoresponsive activity:** Red-light irradiation can trigger DNA cleavage providing spatiotemporal selectivity with reduced off-target effects
- **Tunable activation:** Some diazonium salts can also be activated in reducing environments (without light) or under standard physiological conditions

Intellectual Property

NYU has filed a U.S. provisional patent application covering the composition of matter for aryl diazonium salts, their method of activation, and their applications in treating human diseases.