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Journal of Pharmacovigilance

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Structure-based Drug Design : Nucleic Acids as anti-cancer drug target

Dr. Prashansa Agrawal
University of Arizona

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Structure-based Drug Design

- Structure-based drug design process involves acquisition of information regarding the three-dimensional structure of **biological 'druggable' target** that plays a key role in the development of the disease, through methods such as x-ray crystallography, NMR spectroscopy or homology modeling.

- Once the target has been identified, a **potential drug candidate** needs to be designed based on the binding affinity and selectivity for its target molecule.

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Approaches for Structure-based Drug Design

- Design new molecules with high affinity for macromolecular receptor (target) whose 3D structure is known (**receptor-based drug design**).

- In addition, the molecular interactions between the target and ligand can be utilized to support the binding of the current prototype into the active site of the receptor (**pharmacophore-based drug design**).

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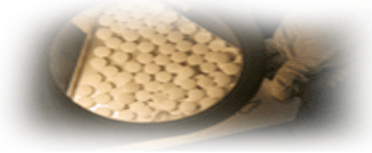

Strategy for Structure-based Drug Design

Identification of the target

↓

Screening a library of compounds

↓

Identification of a compound that binds to target and triggers specific biological actions

↓

Lead optimization

↓

Properties of the lead are tested with biological assays

↓

New molecules are designed and synthesized to obtain the desired properties

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Why Nucleic Acids are an important drug target?

- Nucleic acids play vital roles in genetic information storage, replication, transcription, and translation directing protein synthesis.
- Targeting nucleic acids can selectively interrupt gene expression for treating various diseases including cancers at the genetic level.
- Nucleic acids are the molecular targets of many chemotherapeutic anticancer drugs.
- More than 400 structures of drug-DNA or drug-RNA complexes have been deposited in the structural databases, e.g. PDB bank.

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Driving forces involved in Drug-DNA interactions

- Affinity is controlled by non-directional interactions: hydrophobic interactions

- Specificity is controlled by directional interactions:
  - Van der waals interactions
  - Covalent bonding
  - Hydrogen bonding
  - Electrostatic interactions

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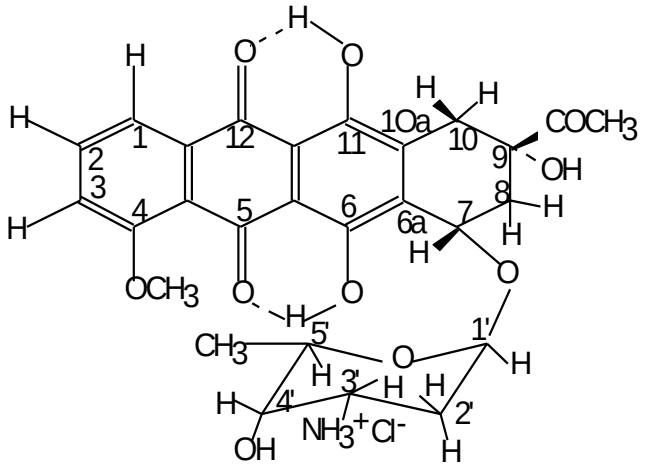
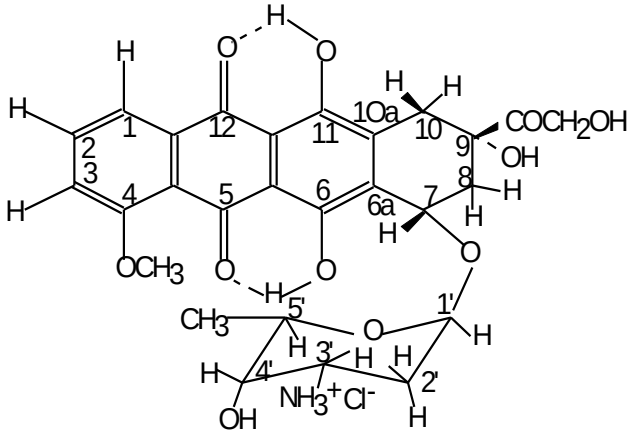
Anthracycline antibiotics are used as potent cancer therapeutics

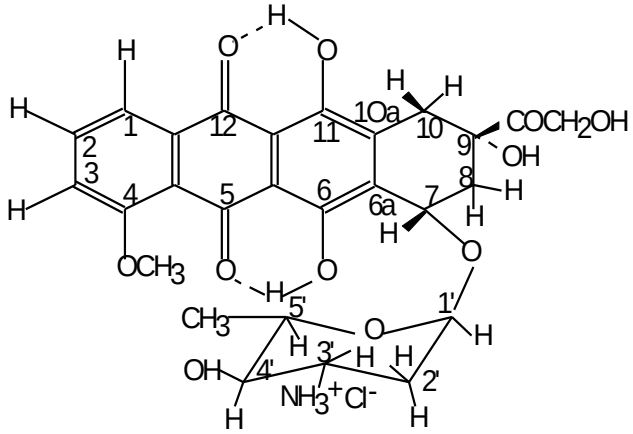
Adriamycin (in which one hydrogen atom of methyl group at carbon position (9$COCH_3$ moiety) of daunomycin is replaced by a hydroxyl group (9$COCH_2OH$), 4'-epiadriamycin, (epimer of Adriamycin and differs at the 4'-position of the daunosamine sugar).



DAUNOMYCIN



ADRIAMYCIN



4’-EPIADRIAMYCIN

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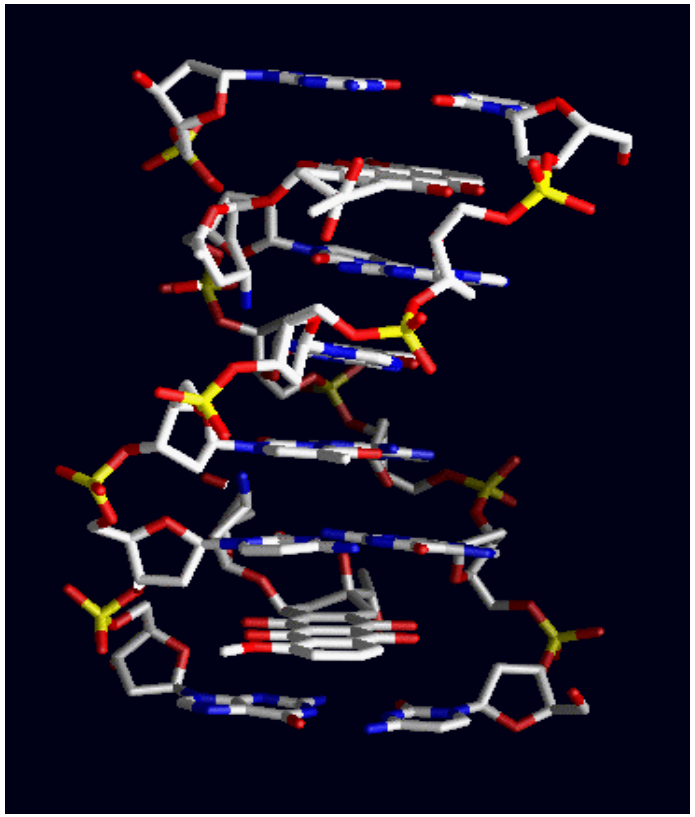
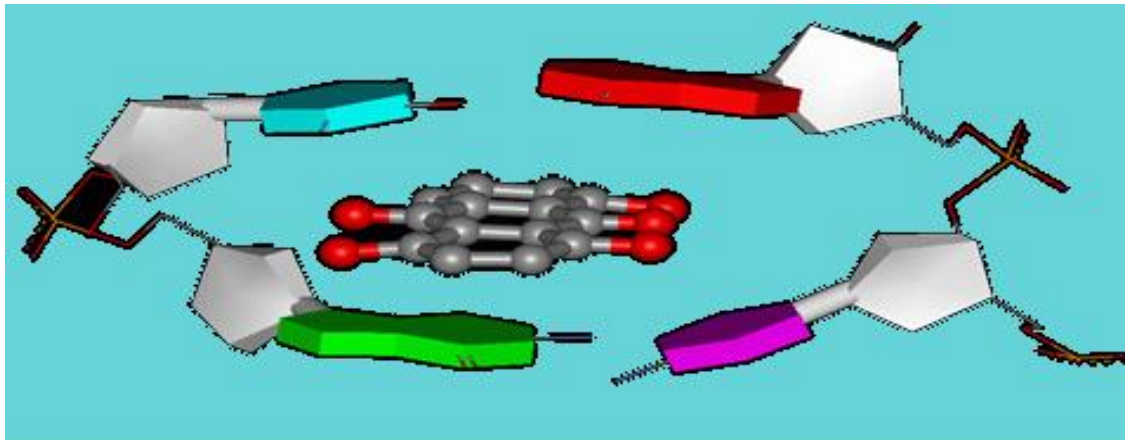
Anthracycline antibiotics are good Intercalators

The intercalation of drug to DNA causes modification in the tertiary structure of DNA leading to inhibition in transcription and cell proliferation.





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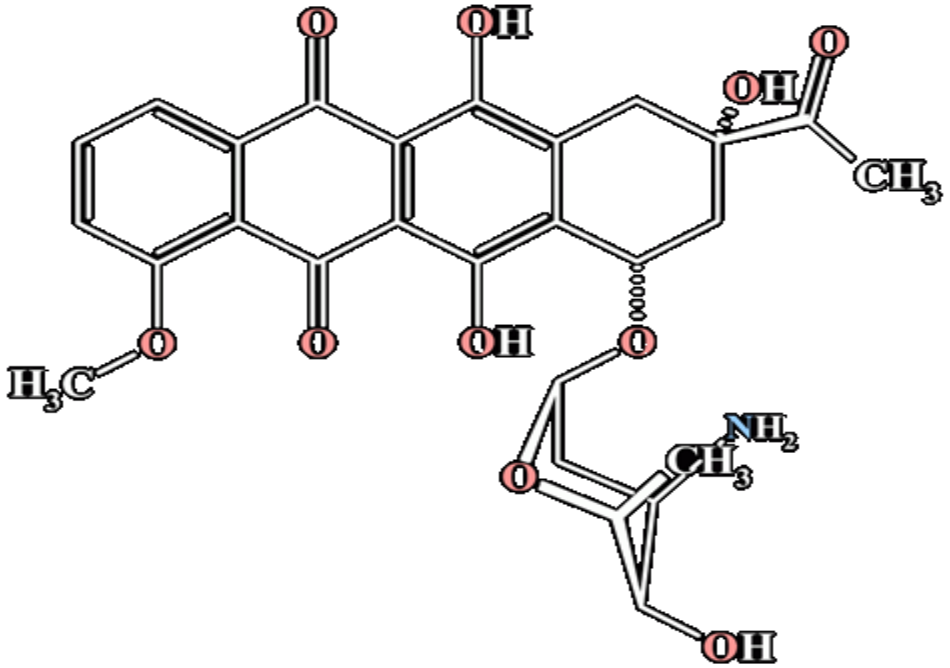
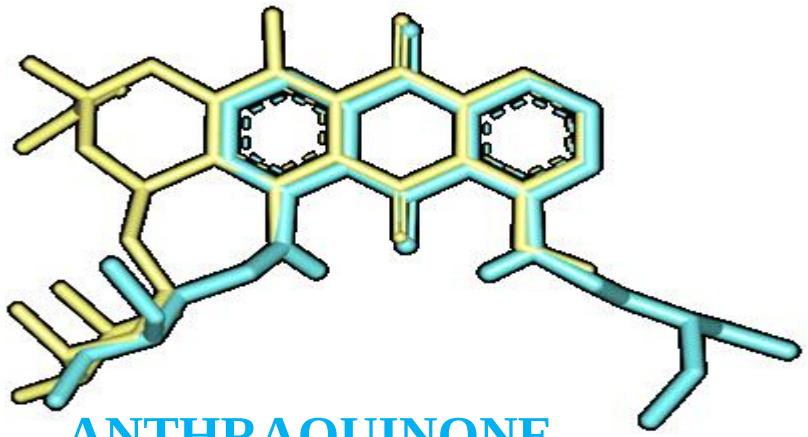
Anthraquinone derivatives were designed on the basis of anthracycline drugs that binds strongly to DNA and show anti-proliferative effects in vitro



DAUNOMYCIN

DAUNOMYCIN



ANTHRAQUINONE

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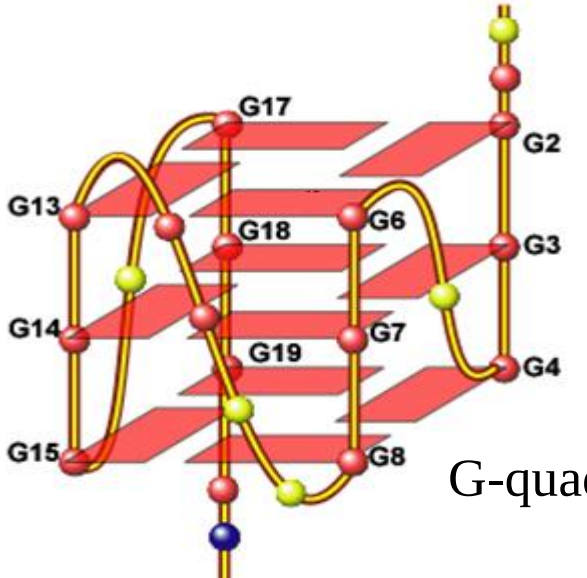
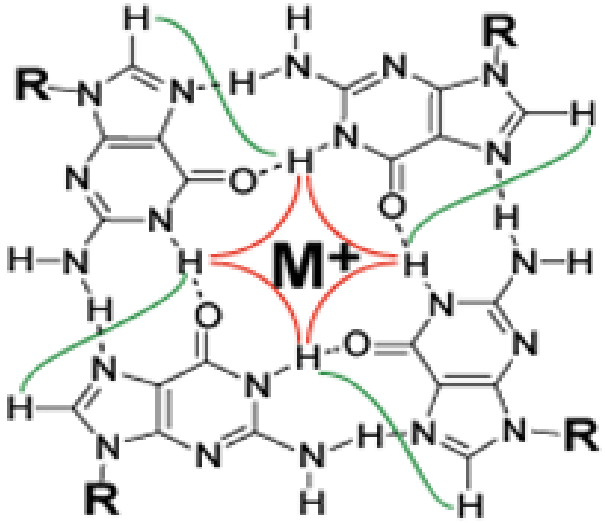
Targeting DNA secondary structures ‘G-quadruplex’

- G-quadruplexes are commonly found in telomere region and the oncogene promoter region which are highly G-rich and dynamic in nature.
- They are formed by stacking of G-tetrads.
- Each G-tetrad has four guanines arranged in square planar manner, stabilized by hoogesten hydrogen bond.



G-quadruplex



G-tetrad

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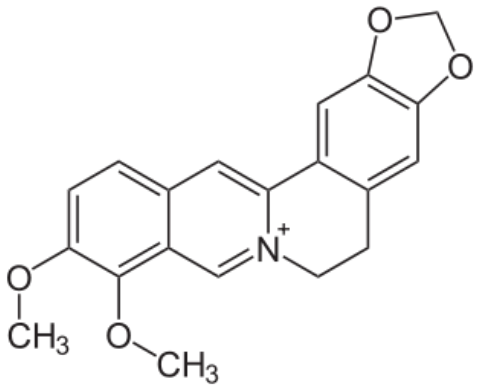
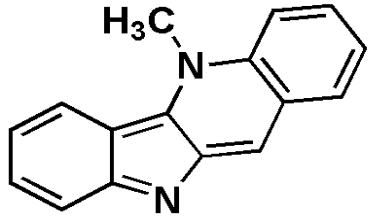
G-Quadruplex-interacting Ligand Design

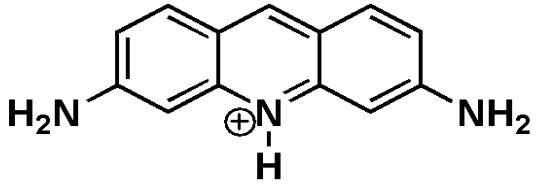
Common DNA intercalators



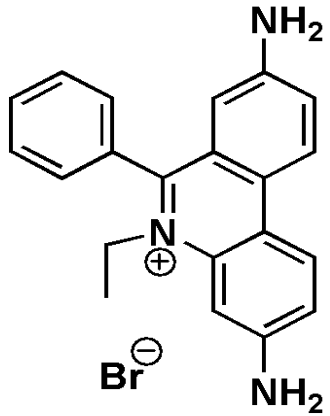
Berberin



Cryptolepine



Proflavine



Ethidium bromide

- DNA intercalators are toxic
- Characterized by large, flat aromatic core, possibly protonated in center
- Need to design ligands selective for G-quadruplex DNA

Chan, A., *et al. J. Med. Chem.* 2005, *48*, 7315-7321.

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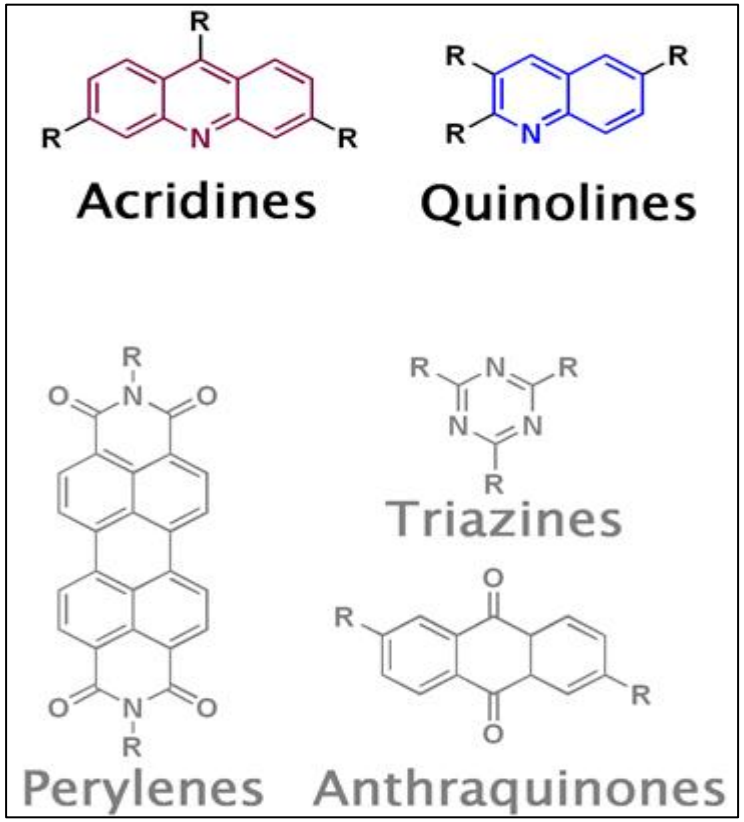
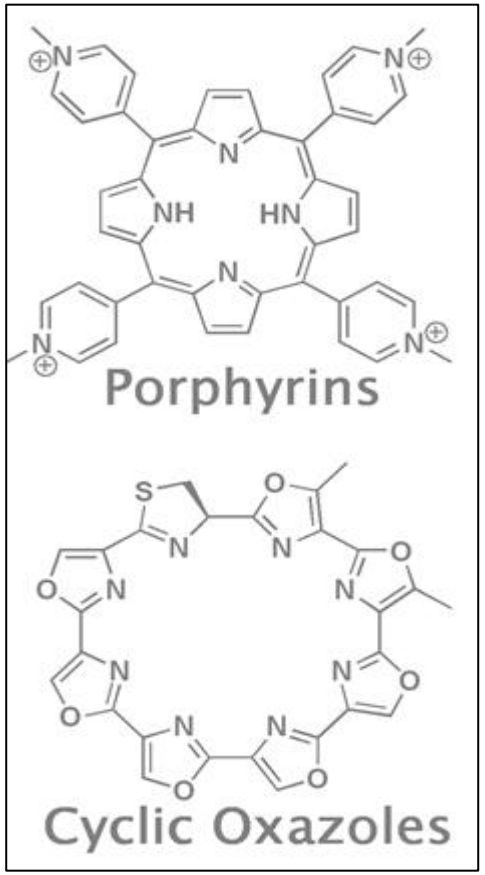
Types of G-Quadruplex-interacting ligands

Polycycles



Macrocycles



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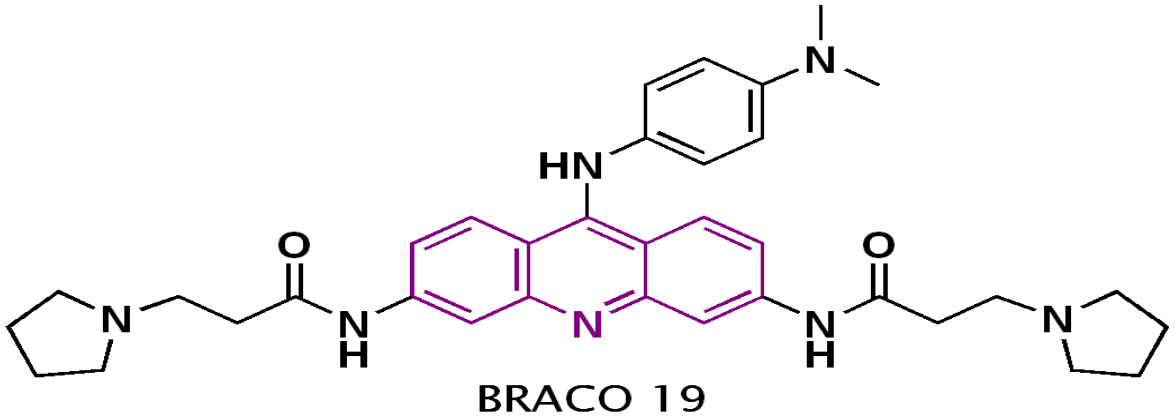
Acridine Derivative



BRACO 19

- Synthesized in 2001 based on parent acridine intercalator
- 45:1 selectivity for G-quadruplex DNA versus duplex DNA
- Phase I/II clinical trial

Read, M. *et al. Proc. Natl. Acad. Sci. U.S.A.* 2001**, *98*, 4844-4849.**

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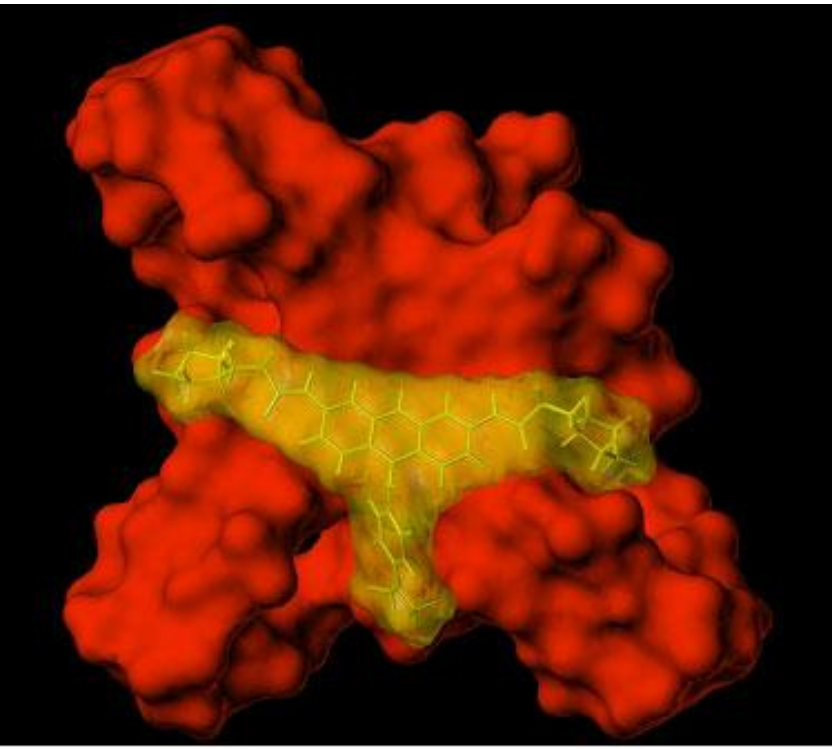
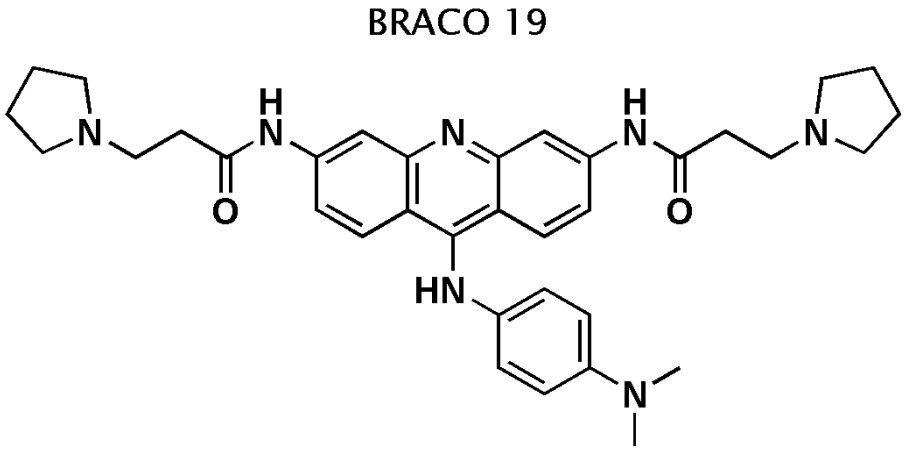
G-quadruplex-interactive molecule BRACO-19 inhibits tumor growth, consistent with telomere targeting and interference with telomerase function





Read, M. *et al. Proc. Natl. Acad. Sci. U.S.A.* 2001**, *98*, 4844-4849.**

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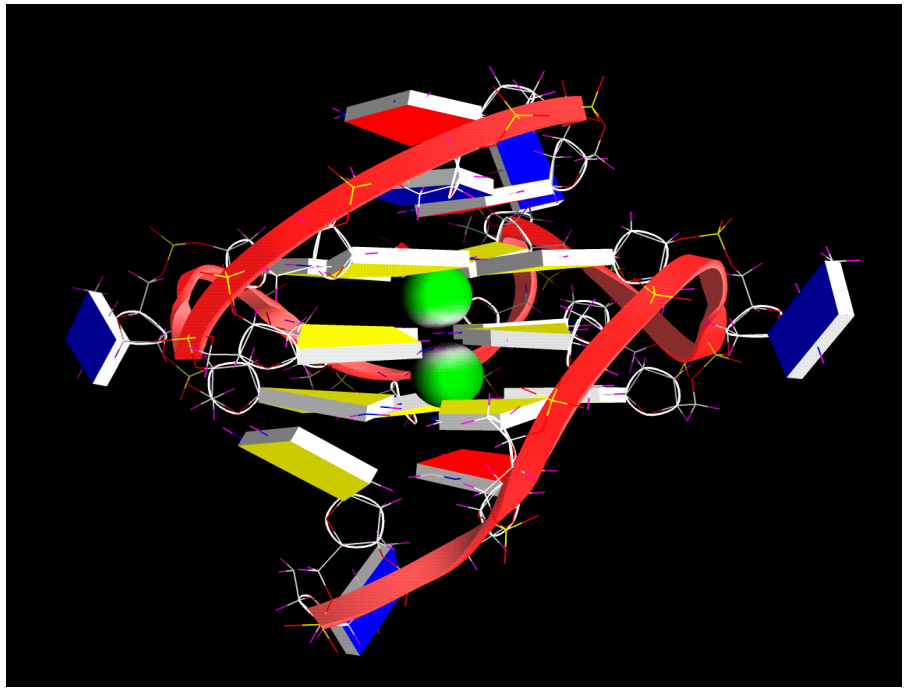
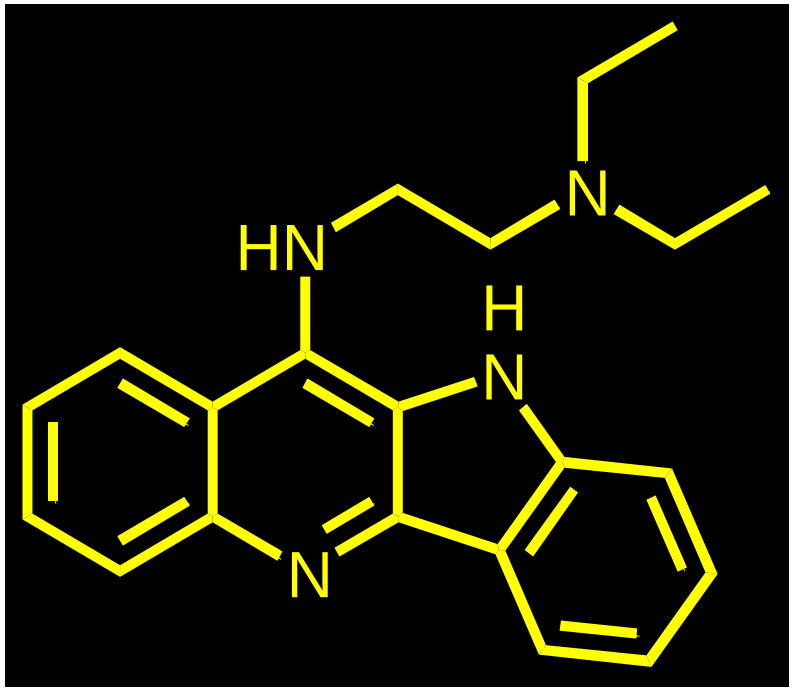
Quindolines

- lower c-myc expression in hepatocellular carcinoma cell line Hep G2 and Burkitt's lymphoma cell line Ramos.



Cmyc G-quadruplex

Ambrus et al. *Biochemistry*, 2005 , 44, 2048



Quindoline

Ou et al. *J. Med Chem.* 2007, 50, 1465

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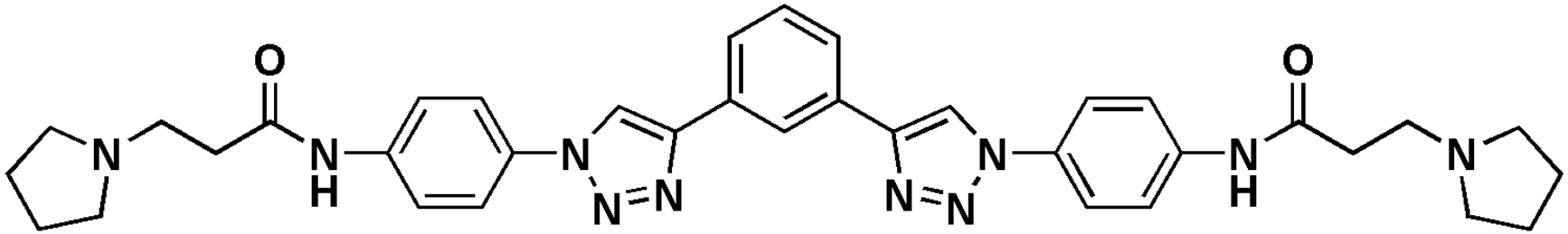
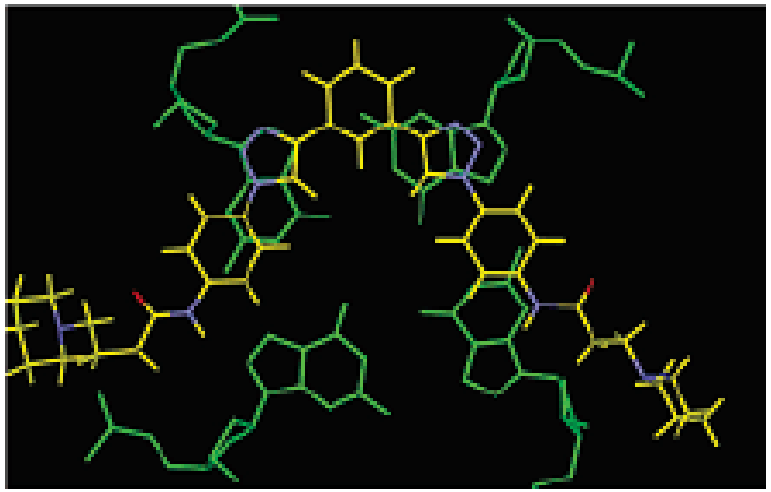
Triazoles





π stacking with guanine bases

Moorhouse, A.D., *et al. J. Am. Chem. Soc.* 2006, *128*, 15972-15973.

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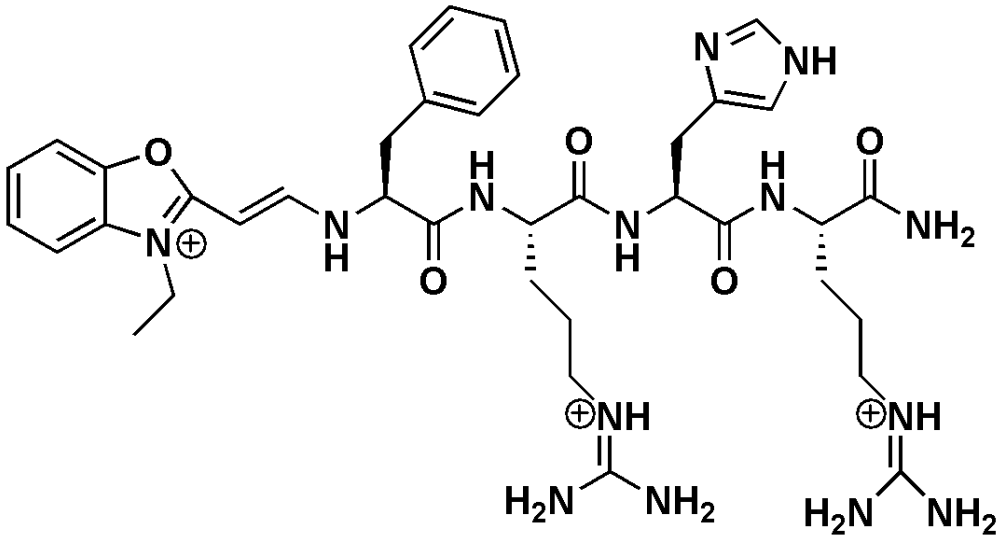
Heterocycle-Peptides



- greater than 50:1 selectivity for G-quadruplex DNA versus duplex DNA

Schouten, J.A., *et al. J. Am. Chem. Soc.* 2003, *125*, 5594-5595.
Green, J.J., *et al. J. Am. Chem. Soc.* 2006, *128*, 9809-9812.

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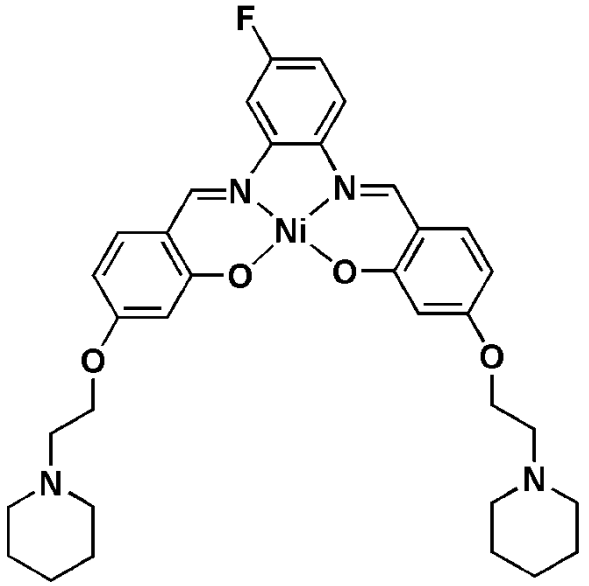
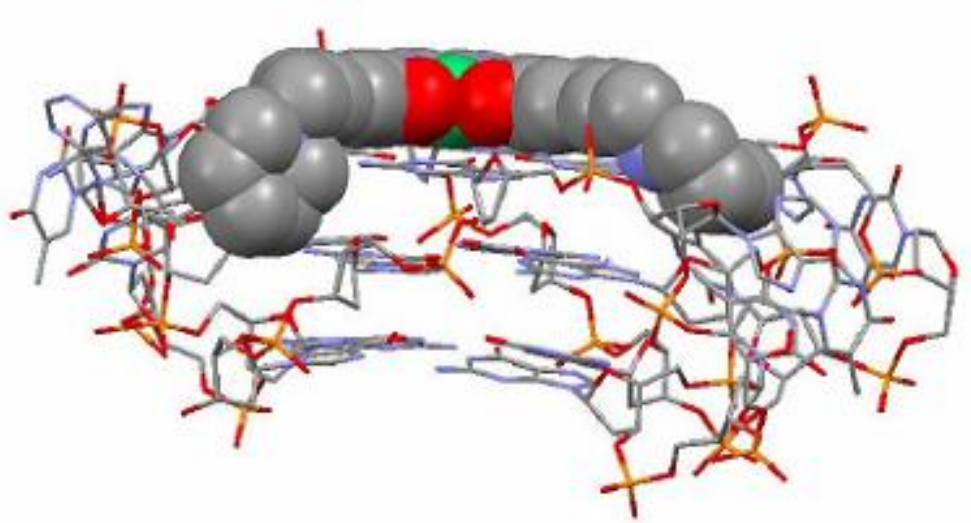
Metal Complexes





- Ni(II) forces planarity, resulting in π stacking
- Piperidine interaction with phosphate backbone

Reed, J.E., *et al. J. Am. Chem. Soc.* 2006, *128*, 5992-5993.

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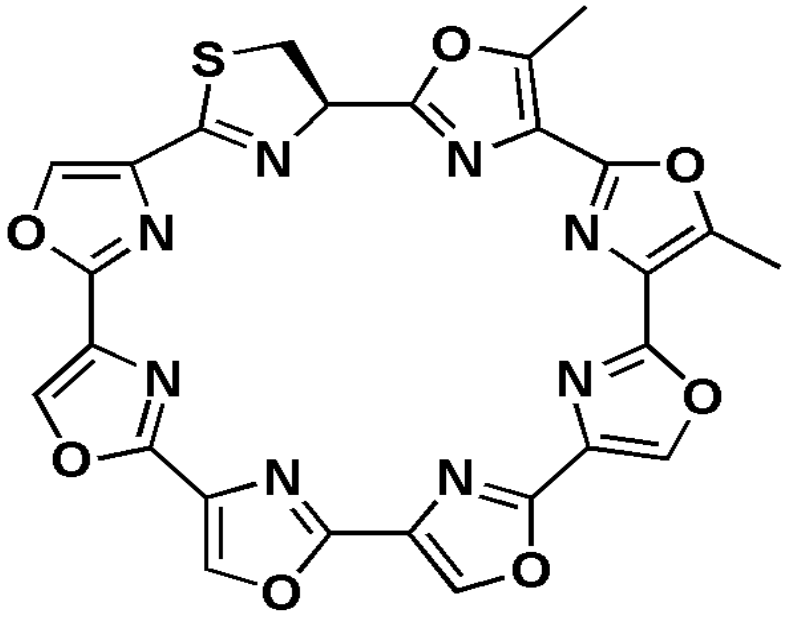
Cyclic Oxazoles



Telomestatin

- IC_{50} 5 nM
- First isolated in 2001 from *Streptomyces anulatus*
- Total synthesis finished in 2006, 21 steps, <1% overall yield
- First *natural product* shown to bind selectively to G-quadruplex DNA

Shin-ya, K., *et al. J. Am. Chem. Soc.* 2001, *123*, 1262-1263.
Doi, T., *et al. Org. Lett.* 2006, *8*, 4165-4167.

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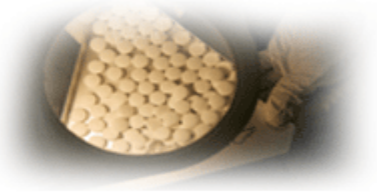
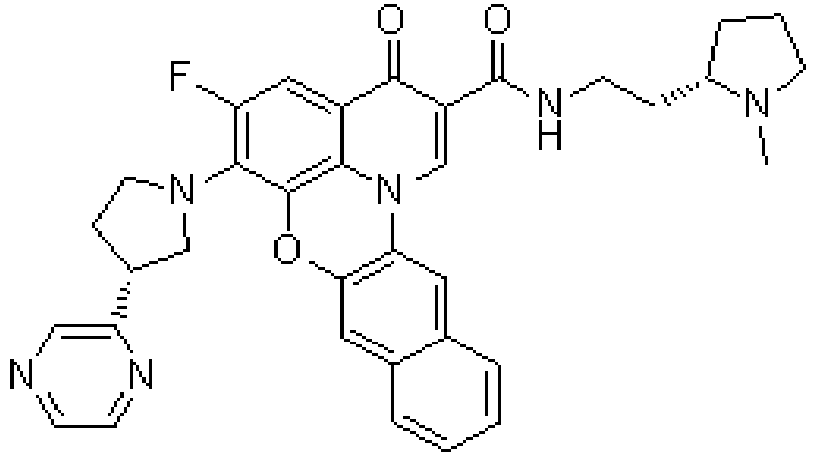


Fluoroquinolone Derivative



Quarfloxin

- Quarfloxin shows antineoplastic activity.
- Quarfloxin disrupts the interaction between the nucleolin protein and G-quadruplex DNA in the ribosomal DNA (rDNA) template, a critical interaction for rRNA biogenesis that is overexpressed in cancer cells.
- This may result in inhibition of ribosome synthesis and tumor cell apoptosis.
- Phase I/II clinical trial.

Balasubramanian, S. *Nat Rev Drug Discov.* 2011, 10, 261–275.

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Future Directions on Structure-based Drug Design

- Learning from the past experience.
- Need deeper understanding of identifying suitable hits/ligands to prevent them from failing during clinical trials.
- Toxicity and safety issues needs to be addressed in order to reduce the attrition rate.
- Developing efficient methods to gain understanding at the atomic level of the target-ligand interaction and use that information in drug design.

Pharmacovigilance Related Journals

- Journal of Clinical Trials
- Advances in Pharmacoepidemiology & Drug Safety
- Journal of Drug Metabolism & Toxicology

Pharmacovigilance Related Conferences

- 5th International Conference and Exhibition on Pharmaceutics & Novel Drug Delivery Systems
- 5th World Congress on Bioavailability and Bioequivalence: Pharmaceutical R&D Summit
- 3rd International Conference and Exhibition on Pharmacovigilance & Clinical Trials

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