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Extended Abstract
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MedChem & CADD 2016: Synthesis of novel anthraquinone anti-cancer drugs: Molecular structure, molecular chemical reactivity descriptors and their interactions with DNA

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Background:

Anthraquinones are well-known anticancer drugs. They carry out their cytotoxic activities through interaction with DNA and inhibition of topoisomerase II activity. Anthraquinones (AQ5 and AQ5H) were synthesized and studied with 5-DAAQ by computational and experimental tools.

Aim/Purpose:

The purpose of this study is to shed more light on mechanism of interaction between anthraquinone DNA affinic agents and different types of DNA. This study will lead to gain of information useful for drug design and development.

Methods:

Molecular structures were optimized using DFT B3LYP/6-31+G(d). Depending on intra-molecular hydrogen bonding interactions four conformers of AQ5 were detected within the range of about 42kcal/mol. Molecular reactivity of the anthraquinone compounds was explored using global and condensed descriptors (electrophilicity and Fukui functions). NMR and UV-VIS electronic absorption spectra of anthraquinones/DNA were investigated at the physiological pH. The interaction of the anthraquinones (AQ5 and AQ5H) were studied with different DNA namely, calf thymus DNA, (Poly [dA]. Poly [dT]) and (Poly [dG].Poly [dC]). UV-VIS electronic absorption spectral data were employed to measure the affinity constants of drug/DNA binding using Scatchard analysis.

Anthraquinone is an aromatic organic compound. C14H8O2 is the formula of it. Anthracenedine/ dioxoanthracene are the other names of it. Severa; quinone derivatives are include in isomers. Anthraquinone refers to isomer 9,10-anthraquinone (IUPAC: 9,10-dioxoanthracene), in which the the keto groups are located on the central ring.

It is a building block of many dyes and is used in pulp bleaching for papermaking. It is a yellow solid, very crystalline, sparingly soluble in water but soluble in hot organic solvents. In ethanol, it is almost completely insoluble, near room temperature. But, in 100 g of boiling ethanol, 2.25g will dissolve.

Synthesis

There are several current industrial methods for producing 9,10-anthraquinone: The oxidation of anthracene, a localized reaction at the level of the central ring. Chromium (VI) is the typical oxidant.

The Friedel-Crafts reaction of benzene and phthalic anhydride in the presence of AlCl3 producing o-benzoylbenzoic acid which then undergoes cyclization, forming anthraquinone.

This reaction is useful for producing substituted anthraquinones.

The acid-catalyzed dimerization of styrene to give a 1,3-diphenylbutene, which can then be converted to anthraquinone.

It also occurs via the Rickert-Alder reaction, a retro-Diels-Alder reaction.

Reactions

The hydrogenation gives dihydroanthraquinone (anthrahydroquinone). Reduction with copper gives anthrone. Sulfonation with sulfuric acid gives anthroquinone-1-sulfonic acid, which reacts with sodium chlorate to give 1-chloroanthaquinone.

This work is partly presented at 5th International Conference on Medical Chemistry & Computer Aided Drug Designing and Drug Delivery on December 05-07, 2016 at Phoenix, USA

Synthetic dyes are often derived from 9,10-anthraquinone, like alizarin. The important derivatives are 1-nitroanthraquinone, anthraquinone-1-sulfonic acid and dinitroanthraquinone. Natural pigments that are derivatives of anthraquinone are found, among others, in aloe latex, senna, rhubarb and buckthorn, fungi, lichens and certain insects. 9.10-anthraquinone is used as a digester additive in the production of paper pulp by alkaline processes, such as Kraft, alkaline sulfite or Soda-AQ processes. Anthraquinone is a redox catalyst.

The reaction mechanism may involve a single electron transfer (SET). Anthraquinone oxidizes the reducing end of the polysaccharides in the pulp, i.e. cellulose and hemicellulose, and thus protects it from alkaline degradation (peeling). Anthraquinone is reduced to 9,10-dihydroxyanthracene which can then react with lignin. Lignin is degraded and becomes more soluble in water and therefore easier to wash away from the pulp, while the antraquinone is regenerated.

This process gives an increase in pulp yield, typically from 1 to 3% and a reduction in the kappa index. The first anthraquinone derivative which was discovered in order to have a catalytic effect in alkaline pulping processes, is a Sodium 2-anthraquinonesulfonate (AMS), which is a water soluble anthraquinone.

Medicine

9,10-anthraquinone derivatives include many important drugs (collectively called anthracenediones).

Laxative like dantron, emodin and aloe emodin; rufigallol, which is the anti-material; are included in it. In the treatment of cancer, antineoplastics are utilized like mitoxantrone, pixantrone and anthracyclines; For flow cytometry and fluorescence microscopy, Nuclear DNA stains / counter stains like DRAQ5, DRAQ7 and CyTRAK Orange.

Rhein, emodin, aloe emodin, parietin and chrysophanol, which is extracted from Cassia occidentalis, are the derivative of Anthraquinone. Cassis occidentalis are toxic. Also, in children, they cause hepatyoencephalopathy.

Aloe contains 12 organic compounds called anthraquinones. Aloin, which causes a laxative effect, and emodin help relieve pain and act as antibacterial and antiviral agents.

Anthraquinones are often eliminated from commercial aloe products. Anthraquinones (AQ) are found in rhubarb root, leaves and pods of senna, Cascara, Buckhorn and Aloe, and are widely used in laxative preparations. AQ laxatives include physcion, chrysophanol, aloe-emodin, rhenan and sennosides.

Anthraquinone is used in the manufacture of dyes, in the textile and pulp industries, and as a repellent for birds. On seeds, the 9.10-anthraquinone is utilized as a bird repellant and in satellite balloons, it is utilized as a gas generator. It has also been mixed with lanolin and used as a wool spray to protect flocks of sheep from kea attacks in New Zealand.

Natural anthraquinone derivatives tend to have laxative effects. Prolonged use and abuse results in colonic melanosis. Anthraquinones have been shown to inhibit the formation of Tau aggregates and dissolve paired helical filaments considered essential for the progression of Alzheimer's disease in mouse models and in vitro tests, but have not been studied as a therapeutic agent.

Several other isomers of anthraquinone are possible, including 1,2-, 1,4- and 2,6-anthraquinones. They are of comparatively minor importance. The term is also used in the more general sense of any compound which can be considered an anthraquinone with certain hydrogen atoms replaced by other atoms or functional groups. These derivatives include substances that are technically useful or play an important role in living things.

Safety

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Anthraquinone does not have a registered LD50, possibly because it is so insoluble in water. Many drugs are derivatives of anthroquinone.

In terms of metabolism of substituted anthraquinones, the enzyme encoded by the UGT1A8 gene has glucuronidase activity with many substrates including anthraquinones.

Anthraquinone is not toxic and therefore there would be no cumulative effects expected from common mechanisms of toxicity.

Results:

NMR study confirms qualitatively the drug/DNA interaction in terms of band shift and broadening.

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