International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 8, Issue 6, 2016

Review Article

DNA TARGETED ANTHRAQUINONE DERIVATIVES: AN IMPORTANT ANTICANCER AGENTS

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Received: 18 Feb 2016 Revised and Accepted: 20 Apr 2016

ABSTRACT

Deoxyribonucleic acid, DNA is the source of various genetic information and is currently one of the most important and studied biological receptor. Lately, a wide range of chemotherapeutic agents are known wherein they affect cell division or DNA synthesis, leading to inhibition of cell growth and cell death. Out of various agents anthraquinone, having a planar tricyclic structure is the backbone of many known antitumor drugs like doxorubicin and mitoxantrone capable of targeting at the molecular/DNA level. This review embraces discussion on DNA-binding molecules with special attention to anthraquinone based compounds having application in anticancer activity by DNA damage mechanism. The review also compiles the work reported on anthraquinone based molecule in molecular imaging.

Keywords: Anthraquinone, DNA, Cancer, Molecular imaging

INTRODUCTION

DNA is a nucleic acid (biomolecule) that contains the genetic instructions specifying the biological development of all cellular forms of life and is frequently stated as the molecule of heredity, as it is responsible for the genetic propagation of all traits [1-3]. During reproduction process, duplex DNA is replicated and transmitted to the offspring and its sequence describes various features from organism type through physical traits to disease susceptibility. DNA sequence is copied (transcription) onto RNA Biomolecules, which are then used in protein synthesis to encode a specific protein sequence (translation). (Bio)chemical sensor technologies that focus on the direct detection of nucleic acids (DNA and RNA) are currently an area of tremendous interest, as they play a major role in forensics, pharmaceutical applications, medical diagnosis, genetic screening etc. [4-7]. Small molecules which are capable of recognizing specific DNA sequences are potent tools for the interpretation of human genome and may serve as valuable therapeutic agents [8]. The structural features of double helix DNA comprises of two anti-parallel, complementary, sugar-phosphate poly-deoxyribonucleotide strands which are connected through hydrogen bonds between nucleotide bases [9]. The backbone of paired strands in DNA describes the helical grooves and within these grooves edges of heterocyclic bases are exposed outside. The structural depiction of DNA is shown in fig. 1 [10].

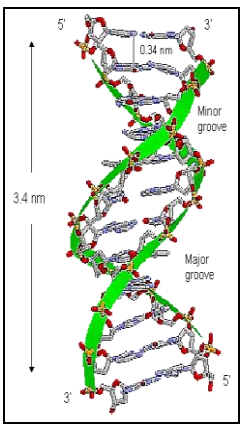

Fig. 1: Structural depiction of DNA (source-wiki books, 2008)

The chemical feature of the molecular surfaces in a given DNA sequence is distinct in either groove (major or minor) and forms the basis for duplex DNA molecular recognition by small molecules and proteins. In this article we have discussed about different modes of DNA binding with special attention to anthraquinone based compounds having application in anticancer activity by DNA damage mechanism. The review compiles the work reported from 1990 to till date on anthraquinone based molecule having application in anticancer activity and molecular imaging.

Interactions of duplex DNA with small organic molecules

The type of chemical interactions between small molecules and DNA is an important tool for the prediction of potential physiological and/or therapeutic consequences of such interactions. Broadly DNA interactions with small molecules can be classified as covalent and non covalent where non covalent interactions can be further classified as intercalation and groove binding.

Covalent interaction of DNA with small organic molecules

DNA alkylating agents are clinically important and are frequently used for the cancer chemotherapy and over the last two decades wide range of alkylating agents has been synthesized. Fig. 2 shows few of the leading examples of DNA alkylating agents. Alkylating agents preferentially reacts with N-7 position of guanine and N-3 of adenine nucleobases present in DNA which inhibits the base pairing of the DNA leading to miscoding of DNA. This alteration in DNA leads to its fragmentation by repair enzymes which replace the alkylated bases of double helix. Another mechanism of DNA damage by alkylating agents is the formation of cross-bridges i.e., bonds formation between atoms present in the DNA that prevents DNA from being separated for synthesis or transcription. The third mechanism of action of alkylating agents causes mispairing of the nucleotides leading to mutations.

The nitrogen mustard was the first DNA alkylating agent used medically, as well as the first modern cancer chemotherapies [11]. Another classic example which is most widely used as a DNA alkylating agent is cyclosporamide. Cisplatin (cis-diammine-dichloro platinum) is a well-known covalent DNA binder used as an anticancer drug which makes an intra/inter strand cross-link with the nitrogen's present on the DNA bases and is extensively used in treatment of testicular, ovarian, head, and neck cancers [12]. The success of cisplatin as an anticancer drug has led to the development of other less toxic derivatives such as carboplatin [13].

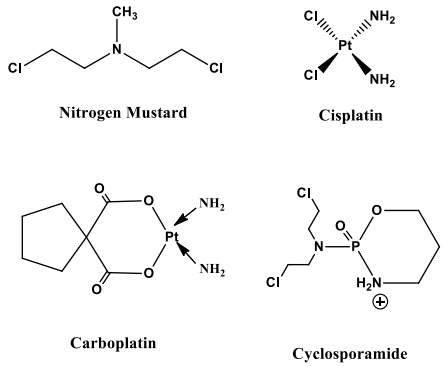

Fig. 2: Examples of DNA alkylating agents

Non-covalent interactions of small molecules with duplex DNA

DNA intercalators

Planar aromatic molecules bind with DNA by a process named as intercalation which is established for a variety of polycyclic aromatic systems termed as intercalators. The DNA intercalation is characterized by insertion of planar aromatic rings between the DNA base pairs and is generally independent of base pair sequence. Intercalation requires changes in the sugar-phosphate torsional angles to accommodate the aromatic compound which is accompanied by other changes in the helical parameters such as unwinding, bending, etc. [14-16]. This interaction is quite strong despite the fact that energy is utilized to unwind the helix and un-stack the base pairs to allow the complex formation. The stability of intercalation complexes is governed by van der Waals, electrostatic and hydrophobic forces. Molecules that bind to double-stranded DNA (ds-DNA) by interactive mode have been significantly used as drugs as shown in fig. 3 [17]. The two major types of intercalation binding modes are: (1) classical intercalation and (2) threading intercalation.

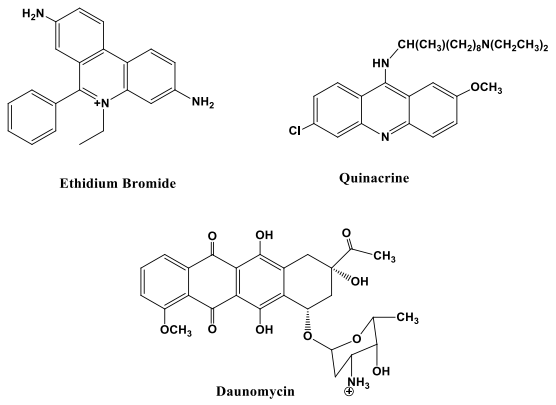

Fig. 3: Chemical structures of some DNA intercalators

DNA stain, Ethidium bromide (EtBr) and antimalarial quinacrine demonstrate intercalating DNA binding by stacking interaction of the respective heteroaromatic rings present in their structure with the DNA base pairs [18]. The cationic side chain present in quinacrine contributes to complex stability by electrostatic interactions with the negative phosphate units of the groove. A number of other classical intercalators are used including the anthracyclines and actinomycin [19]. Intercalation preferentially occurs at G/C-rich sequences, because these sequences get un-stacked easily. Intercalators generally cause more significant distortion of the native conformations of DNA.

Threading intercalators usually have two side chains on the opposite sides of a planar aromatic ring system, and the process of complex formation with DNA is more complicated where one of the side chains of the system slides through the intercalation cavity to form the stable complex. The complex stability of the threading intercalators is due to the favorable interactions of the side chains with both the major and minor grooves. Nogalomycin and Daunomycin are the leading example of the threading intercalators [20].

DNA groove binders

Groove binders are a major class of small molecules that bind to ds-DNA and play an important role in drug development. Small molecules can bind to both the major or minor groove of ds-DNA. Due to the dimensional difference in grooves vastly dissimilar and different shaped molecules are required to target them. Major grooves are the site for binding of many DNA interacting proteins and only limited molecules that bind to the DNA major groove are reported [21, 22].

Major groove binding small organic molecules

Proteins usually bind to DNA by major groove after recognition and reading the sequence information. However, non-peptidyl compounds bind with the minor groove, thus possibly allowing simultaneous major groove recognition by proteins [23]. Therefore, it is desirable to have a major groove binding molecule that could block access to proteins that recognize the same groove. Duplexes made up of polypurine–polypyrimidine sequences can be read by oligomer that bind in the major groove and form hydrogen bond with bases of the purine strand and termed as triplex-forming oligonucleotides (TFOs) [24].

An alternate form of major groove recognition is achieved by peptide nucleic acids (PNAs) which are different from TFOs. The backbone of TFOs are oligonucleotides or their modified analogues, whereas PNAs have a peptide-like backbone secondly TFOs can bind within the existing major groove of DNA, whereas PNAs attack the helix to form a triplex, which then results in the displacement of noncomplementary oligopyrimidine DNA strand, fig. 4 [25, 26]. In order to target the major groove, it is essential to modulate biological processes like, transcription artificially.

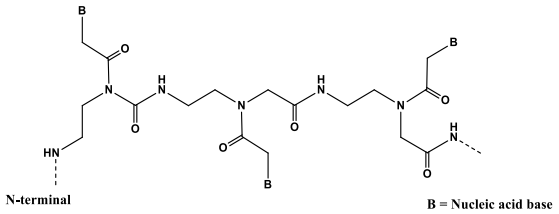

Fig. 4: Chemical structure of peptide nucleic acid (PNA)

Minor groove binding small molecules

Minor groove binders (MGBs) represent an interesting class which has shown highly effective *in vitro* and *in vivo* preclinical tumor models unresponsive to other antineoplastic agents [27-29]. Minor groove binding involves greater binding affinity and higher sequence specificity than that of intercalators binding. DNA minor groove binding is demonstrated for neutral, mono-charged and multi-charged ligands. The dominant forces for small molecule–minor-groove binding interactions are van der Waals, electrostatic, hydrogen and hydrophobic bonding. Sequence specificity is attributed to hydrogen-bonds between the small molecule and base pairs. The design of low molecular mass compounds that can bind with high affinity and specificity to pre-determined DNA sequences (10–16 base pairs long) is of great importance in chemical biology [30]. Minor groove binders frequently show pronounced AT selectivity.

Several factors contribute to preference like-i) AT-rich grooves have higher electrostatic potential than in the GC-filled ones which lead to AT selectivity for the dicationic small molecules, ii) dimensions of the minor groove at AT sites are narrower and deeper than GC

locations. The topology at AT sites allows for easier filling and greater van der Waals contacts by small molecules, the amino group of G in GC locations protrudes into the groove, thus prohibiting van der Waals contacts comparatively to those achievable at the AT sites. The cationic minor groove binders include the natural products Netropsin and Distamycin and the synthetic molecules DAPI and Berenil [31-33]. DNA binding polyamides composed of N-methyl imidazole (Im), N-methyl pyrrole (Py), and N-methyl-3-hydroxypyrrole (Hp) are crescent-shaped molecules that bind to the minor groove as antiparallel dimers. Bhattacharya and co-workers have reported some longer distamycin analogues without the leading amides resulted in high affinity and specificity towards AT-specific stretches of ds-DNA. The synthetic bis-(benzimidazole) derivative Hoechst 33258 is widely used for chromosome staining and also possesses antitumor activity apart from serving as an inhibitor of DNA topoisomerase I [34-36]. Chemical structures of few minor grove binders are shown in fig. 5.

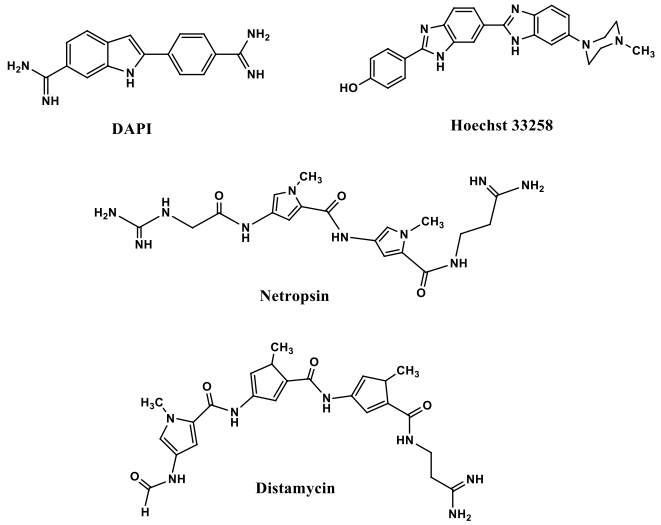

Fig. 5: Chemical structures of DNA minor groove binders

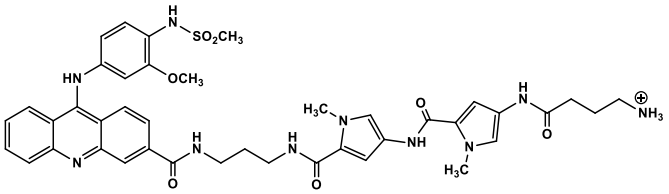

Fig. 6: Structure of net amsa

Intercalator-minor groove binding hybrid molecules

Hybrid molecules commonly bind to DNA by intercalation between the DNA base pairs or through binding in the DNA minor groove.

Hybrid molecules contain both intercalating and minor groove binding functionalities and interact more strongly with DNA than those having either of the individual functionality thereby have a prolonged residence time on DNA allowing them to interfere with DNA processing enzymes [37, 38]. These hybrid molecules are also known as combilexins due to their dual binding mode of action and are usually composed of intercalators based on analogues of ellipticine, amsacrine, anthraquinones and minor groove binders based on analogues of netropsin or distamycin A, etc. The design of DNA threading complexions provides an original way for the development of sequence-specific ligands capable of forming stable complexes with DNA. Combilexins have enhanced DNA sequence specificity compared to mono-intercalators or minor groove binders. The well-known and potent antitumor drug, Net Amsa (structure shown in fig. 6) is a good example of the combilexins which is derived from a covalent combination of the minor groove binder, netropsin and the intercalators, amsacrine. The molecule shows three modes of binding with duplex DNA: (i) sequence-specific recognition of the minor groove of the DNA double helix via the netropsin moiety; (ii) intercalation of the acridine chromophore inside the duplex DNA, and (iii) threading of the methane sulfonanilino group into the major groove.

DNA intercalators as anticancer drugs

Intercalators are one of the most important groups of compounds that interact reversibly with the DNA double helix. Some of them are valuable drugs currently used for the treatment of different cancers like ovarian cancer, breast cancers, and acute leukemias while many others are in different phases of clinical trials. All the intercalating agents share common structural features such as the presence of planar polyaromatic systems which bind by insertion between DNA base pairs, with a preference for 5'-pyrimidine-purine-3' steps. The chromophores are linked to basic chains that might also play an important role in the affinity and selectivity shown by these compounds. It is well established that the antitumor property of intercalators is related to their ability to stabilize the DNA-intercalator-topoisomerase II ternary complex.

Few of the known intercalators are summarized in fig. 7. There are many intercalators reported in literature including (1) naphthalimide and related compounds like Mitonafide and Amonafide that are extensively tested in clinical trials. (2) pyridocarbazole system like Ellipticine and 9-Methoxyellipticine display antineoplastic property, (3) acridine and related compounds like Amsacrine, a drug currently used in the treatment of acute leukemias and malignant lymphomas [39-41].

But anthraquinone based intercalators are the most famous ones with the presence of anthraquinone ring system several antitumor drugs such as, Daunomycin (Daunorubicin), Ametantrone, Mitoxantrone and Doxorubicin (Adriamycin). The antitumor anthracyclines exert their cytotoxic activity involves (i) interaction with DNA, preferentially at 5'-pyrimidinepurine-3' GC-rich sites wherein the planarity of the anthraquinone ring allows an intercalation between base pairs of DNA in the B conformation.

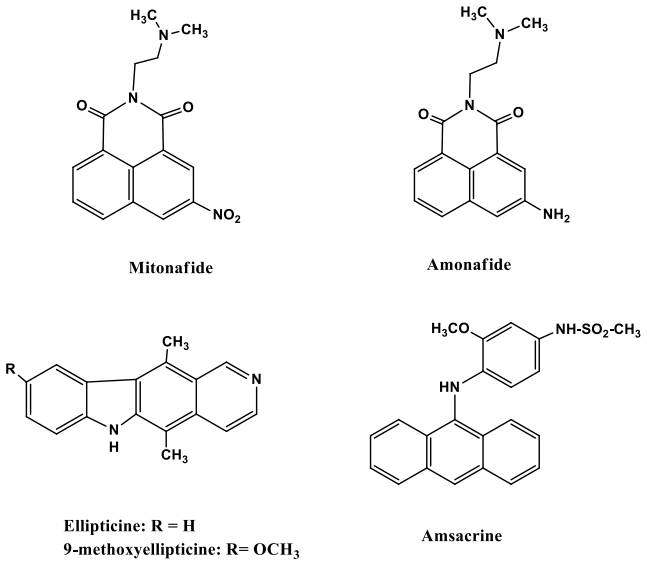

Fig. 7: Structure of well-known DNA intercalators

Anthraquinone as DNA targeting probe

After the structure revelation of DNA by Watson and Crick in 1953 several established therapeutic modalities have been established for targeting DNA like antimetabolites, which deplete nucleotides, eg., methotrexate; alkylating agents, which cause DNA damage, eg., nitrogen mustard and its derivatives; and intercalators which bind to DNA and inhibit the activity of many enzymes which utilizes DNA as a substrate eg., actinomycin. Among the most widely and successfully used anticancer agents are the non-specific DNA damaging chemicals which include topo isomerases inhibitors (TOPO) I and II, alkylating agents, antimetabolites, and agents responsible for covalent modification of DNA (mitomycin C and platinum compounds) [42-44]. Despite phenomenal advances in the understanding of the diseases, cancer still remains the leading cause of death worldwide. Therefore, new strategies for combined diagnostic and therapeutic is imperative for early diagnosis of cancer and appropriate therapeutic strategy [45].

In addition to the surgical removal of tumor tissue, another mode of pretreatment includes chemotherapy, radiotherapy and immuno-therapy. There is continuing interest in the development of new agents in which the small molecule tricyclic anthraquinone structural motif represents an attractive target for the rational design of new anticancer agents due to its central role in the control of cellular proliferation [46, 47]. A wide range of chemotherapeutic agents are known wherein they affect cell division or DNA synthesis leading to inhibition of cell growth and cell death.

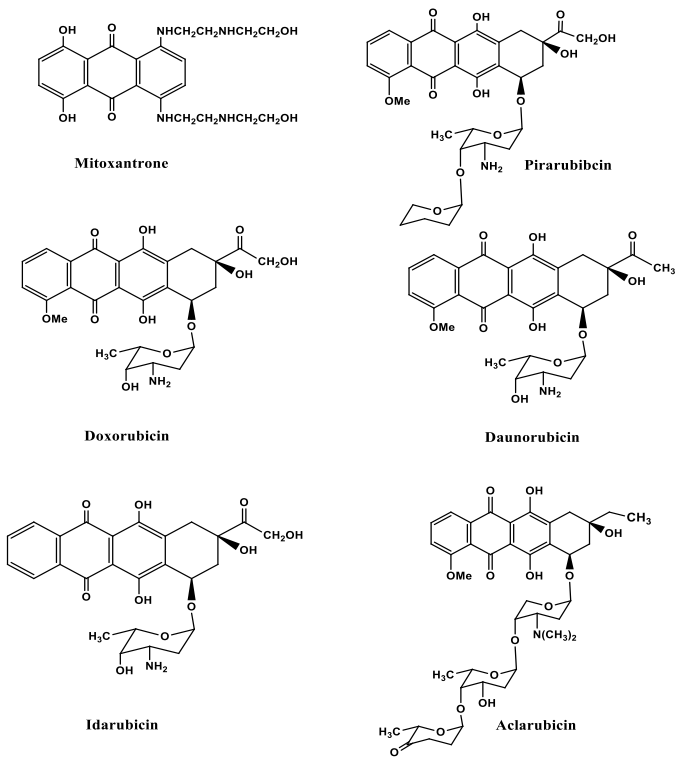

Fig. 8: Structure of anthraquinone-based anticancer drugs

There is a continuing interest for the development of new agents in which anthraquinone base structure represents an attractive target for the design of new anticancer agent due to its strong role in the control of cell proliferation [48-50]. Anthracyclines/anthraquinones from both natural and semisynthetic sources are among the most widely used chemotherapeutic agents and are effective for a broad spectrum of solid tumors and leukemias [51, 52]. Anthraquinone-based compounds occupies a prominent position in cancer chemotherapy, with the naturally occurring aminoglycoside anthracycline doxorubicin and the amino-anthraquinone mitoxantrone both having planar tricyclic structure is the backbone being in clinical use [53]. These and other experimental anthraquinone derivatives are believed to act at the duplex DNA level, probably through the stabilization of a ternary complex with DNA.

They are known for their foremost property of intercalation between the DNA base pairs causing an unwinding of the helix leading to miscoding and possible cell apoptosis. Although the mechanism of action of the antitumor activity of the anthracene-9,10-diones is probably multimodal in nature, a wide range of studies has indicated that an interactive interaction with DNA may be a major cellular event where the planar tricyclic system intercalate into DNA base pairs and interfere in the transcription and replication processes of the cell.

DNA serve as a target of anticancer drug discovery and a variety of compounds have been developed with anticancer activity displayed to target DNA either directly or through inhibition of enzymes that control DNA integrity or provide building blocks for DNA. The rationale for DNA targeting for cancer treatment is based on three facts:

a. 'Broken DNA' in tumor cells (gene mutations);

b. Life cycle of DNA is different in tumor cells from normal cells; and

c. Tumor cells (as compared with normal cells) acquire additional DNA damage, due to higher DNA replication, deficits in checkpoint control and DNA repair process.

Alteration of cellular DNA can be considered for targeted therapy since rapidly proliferating tumor cells depend on upon DNA integrity more than normal quiescent cells. DNA-based cancer therapy is well acceptable but least successful due to-

a. Not effectiveness to cure cancer;

b. Significant adverse side effects; and

c. Cause secondary cancers (cancers not related to primary cancer and appearing 10–15 y after successful elimination of the primary disease).

Therefore, there is an interest in the modification strategy of DNA targeting as an anticancer therapy to achieve two improvements: i) increased specificity towards tumor cells as compared to normal cells by taking advantage of the greater dependence of tumor cells on certain DNA-related processes, and ii) elimination of adverse side effects including secondary cancer, by using compounds that bind to DNA, but do not damage it. Famously used anthraquinone based anticancer drugs structures are shown in fig. 8.

Many anthraquinone based derivatives are reported but particularly the promising clinical activity was observed with 1, 4-bis ((aminoalkyl) amino) anthracene-9,10-diones-substituted anthraquinone; mito-xantrone and ametantrone which led to numerous pharmacological studies [54-62]. Tricyclic core comprising agents like 1,3-dihydroxy-9,10-anthraquinone (DHA), 1-hydroxy-3-(3-alkyl aminopropoxy)-9,10-anthraquinone (MHA) and 3-(3-alkyl aminopropoxy)-9,10-anthraquinone (NHA), pyrrole [2,1-c][1,4] benzodiazepine-anthra-quinone conjugates are potent antitumor agents, which lead to tumor cell apoptosis (structure shown in fig. 9) [63-68].

Substituted anthraquinone derivatives also represent as potential anticancer drugs that target G-quadruplex structures of DNA through its stabilization [69-72]. Anthraquinone derivatives like cationic porphyrin–anthraquinone dyads target the G-quadruplex DNA by π-π interactions whereas the cationic side chains interact with the negatively charged phosphate backbones present in G-quadruplex, as shown in fig. 10 [73].

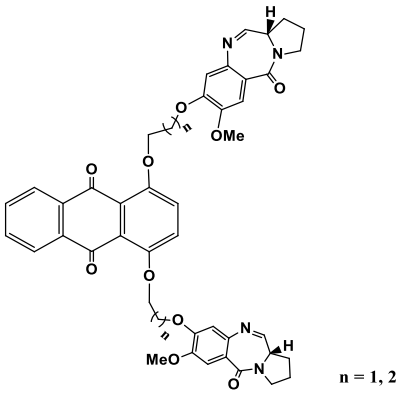

Fig. 9: Structure of benzodiazepine conjugated anthraquinone derivatives [63]

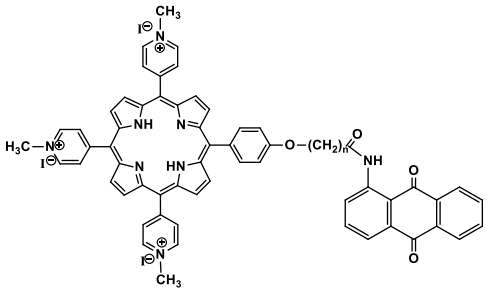

Fig. 10: Structure of cationic porphyrin-anthraquinone dyads [73]

They are also known to stabilize G-quadruplex by acting at the telomeric region of DNA [74]. The 3′-ends of eukaryotic chromosomes consist of poly nucleotides comprising several kilo bases with tandem repeats of the same base sequence (e. g., 5′-TTAGGG in humans) termed as a telomere, ribonucleoprotein in nature and serves to protect the chromosomal termini from end-to-end recombination and attack by exonuclease enzymes. The telomere region of DNA is not conserved during cell division thus led to the hypothesis that the length of the telomere correlates with the capacity of cells to replicate. Most human cells can only divide 50–60 times before senescence occurs and the cells enter a cycle of programmed cell death (apoptosis). Thus, the telomere length is a 'biological clock' capable of determining the proliferative capacity of most human somatic cells. Certain cell types (e. g., germ cells, stem cells and essentially immortal cells such as those found in neoplasms) have been shown to regulate their telomeres to nearly constant length by expressing a specialized RNA-dependent DNA polymerase called telomerase expressed in>85% of cancers, including breast and gastric cancer while the enzyme was not detectable in healthy somatic cells.

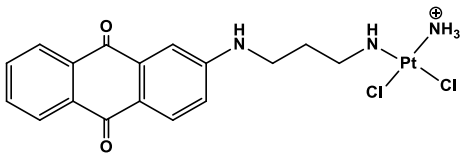

Fig. 11: Structure of Pt-1C3 [76]

Consequently, telomerase became an obligate focus for anti-cancer research as it promised a unique target for chemotherapy without the associated side effects of conventional chemotherapeutics. DNA sequences that are rich in guanines can adopt unusual secondary DNA structural forms. In particular, four guanine bases can associate in a planar, hydrogen bonded assembly called a G-tetrad (or quartet) where each guanine simultaneously accepts and donates two

hydrogen bonds in a reverse-Hoogsteen arrangement. Successive layers of G-tetrads allow such single stranded DNA to adopt a high-order fold-back structure in solution termed a G-tetraplex (or 'quadruplex'). Telomerase requires access to a single-stranded region of telomeric DNA in order to bring about the required elongation and telomere extension by telomerase could be inhibited if agents could be found that acted to stabilize the folded G-tetraplex structure. Derivatives of anthraquinone are also stated as effective inhibitors of c-Met Kinase (product of the MET proto-oncogene) pathway and could be useful for cancer therapy [75].

Interestingly anthraquinone tethered platinum complexes (Pt-1C3) have been shown to accumulate in cancer cell spheroids (useful models for tumors), demonstrating improved cellular accumulation over cisplatin, fig. 11 [76]. Novel esters of chlorambucil with 1,4-dihydroxy-9,10-anthraquinone derivative tested for antitumor activity in mice bearing S-180 ascitic cells as cytotoxic activity against L1210 cells [77]. Cationic anthraquinone derivatives a synthesized through click chemistry are reported, which induces apoptosis in BGC gastric cancer cells which might involve bursting of DNA-damaging ROS disrupting redox homeostasis in cells and activate mitochondrial permeability transition, resulting in a loss of mitochondrial membrane potential (ψ_m) [78,79]. Amino-acyl-hydroxy-anthraquinone bearing glycyl, valyl, lysyl and tryptophanyl residues, 1,4-bis(2-amino-ethylamino) anthraquinone-amino acid conjugates and 1,4-diamido anthraquinone derivatives were reported to exhibit significant DNA binding (intercalation), cytostatic or cytotoxic activities in cancer cells [80-82]. Hydroxy-anthraquinone based derivatives have been identified as the biologically active site within anthracycline-based antitumor therapeutics and are also naturally occurring and extractable from selected plant life.

Biological effects of anthraquinone

Anthraquinones/Anthracycline that has obtained clinical approval includes pirarubicin, aclarubicin, and mitoxantrone. Pirarubicin, a 4-tetrahydropyranyl doxorubicin induces much less cardiotoxicity than doxorubicin in animal models, but clinical studies indicated severe cardiac dysfunction in humans [83-84]. Aclarubicin, a trisaccharide anthracycline is active (with tolerable side effects) in acute myeloblastic leukemia patients [85].

Mitoxantrone is active in breast cancer, non-Hodgkin's lymphoma, acute promyelocytic and myelogenous leukemias, as well as androgen-independent prostate cancer. Due to diverse molecular effects of anthraquinones, their cytotoxic mechanism involves multiple pathways. The mechanism of anti-angiogenic effects of the anthraquinones responsive of their antitumor properties includes-

1) Intercalation into DNA, leading to inhibited synthesis of macromolecules (DNA, RNA and proteins);

2) Generation of free radicals, leading to DNA damage and/or lipid peroxidation;

3) DNA binding and alkylation;

4) DNA cross-linking;

5) Interference with DNA unwinding or DNA strand separation;

6) Inhibition of helicase activity;

7) Direct membrane effects; and

8) Inhibition of topoisomerase I.

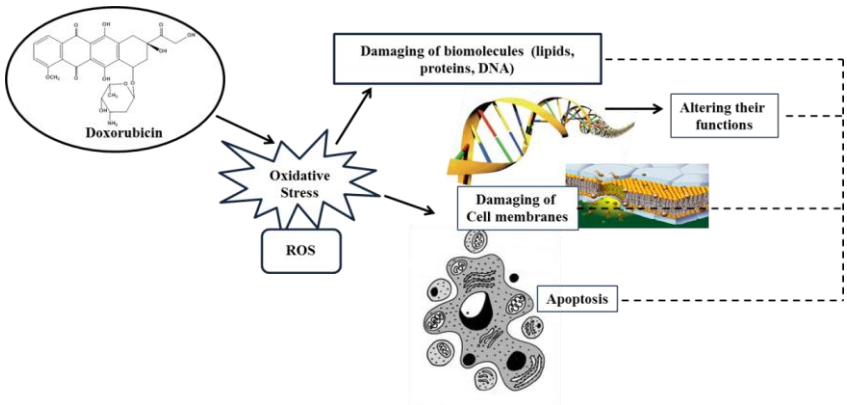

Fig. 12: Biological effect of doxorubicin, an anthraquinone based anticancer drug

There is compelling evidence that cellular DNA is the primary target of anthracyclines. The anthraquinone ring intercalates between DNA base pairs, with its long axis nearly perpendicular to the axis of the double helix. One of the rings acts as an anchor and stabilizes the complex through hydrogen bond interactions as the daunosamine sugar lies in the minor groove. The occurrence of a single positive charge on daunomycin contributes electrostatically to the binding [86]. The concentrations of anthracyclines used in clinical practice caused the formation of protein-associated DNA single and double-strand breaks that were affected by topoisomerase II inhibition. DNA lesions caused by the formation of free radicals and reactivity on the DNA backbone occurred when cells were treated with doxorubicin at concentrations that were too high for patient use [87]. However, at clinically relevant concentrations, anthracyclines do not induce lipid peroxidation in cancer cells [88]. Doxorubicin derivatives can generate reactive oxygen species (ROS). These species can damage cell membranes and bio-molecules, which can, in turn, induce apoptosis, as shown in fig. 12.

Anthraquinone in imaging

Macrocyclic complexes linked with DNA binding agents are started to display sequence selective interaction with DNA depending on the metal ion, nature of the agent and nature of the linker used eg., N-substituted cyclam-amino acid conjugates interacts with DNA in a highly selective manner, fig. 13 [89,90]. The localization of macrocyclic metal complexes on DNA is of interest for a number of reasons. If the metal ion is a radionuclide, increased DNA damage will result, if it is a metal that facilitates phosphate hydrolysis, then DNA cleavage may result and if the metal binds to DNA bases, then sequence-selective binding can occur [91-96].

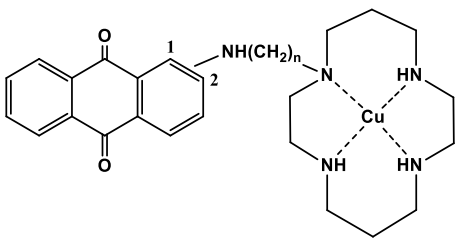

Fig. 13: Cyclam/Anthraquinone macrocycle/intercalators complex [89]

Intercalators bind rapidly and reversibly to DNA and have been shown to increase the rate and extent of DNA binding of a variety of groups including metal complexes. A series of macrocyclic complexes linked to intercalators have been reported in the literature which interacts in a sequence-selective manner with DNA. The sequence selectivity depends on the metal ion, the nature of the intercalator and the nature and position of the link between the macrocycle and the intercalators. In all of these studies the macrocycle employed was the 12-membered ring, cyclen (1,4,7,10-tetraazacyclododecane), a ligand that forces the metal to lie out of the coordination plane promoting interactions with the DNA. Gadolinium complexes of 1,4-and 1,5-diaminoanthraquinone conjugated DOTA based compound are reported to bind with specific DNA sequence open-d(ATCGAGACGTCTCGAT)$_2$ [97-99]. Recently, mono and dimetallic Au (I) triphenylphosphine complexes derived from 1,2-, 1,4-, and 1,8-dialkynyloxyanthraquinone have been synthesized, and their cytotoxicity on cancer cell line (MCF-7) and cell fluorescence imaging have been reported. 1,4-and 1,8-Bis-substituted anthracene dione derivatives inhibit the activity of telomerase [100]. In nuclear imaging, use of stable complexes with radio metal is a crucial factor for the development of metal-based imaging and a therapeutic agent. The lanthanide (trivalent) complexes of poly aza poly carboxylic macrocycle with seven to eight donor atoms such as with DOTA are known for their strong complexation stability, unusually rigid, highly symmetrical structure and adopting same geometry in solution as well as the solid state in comparison with non-cyclic ligands such as DTPA even though both are octa dentate chelate. Though anthraquinone moiety has been much explored for cellular/*in vitro* imaging but *in vivo* studies using, radioisotopes have not yet been exploited in detail. Recently, anthraquinone derivative conjugated with DO3A has been synthesized and labeled with [68] Ga (for PET), [99]^{m}Tc (for SPECT) and exhibited very promising results [101,102].

CONCLUSION

In this article, we have made an attempt to review recent research in drug designing and development for cancer having anthraquinone core. All the DNA binding modes, the biological effect of these drugs on DNA and ongoing research on anthraquinone based compounds having anticancer application has been very well discussed to understand deeply the idea behind designing new DNA-targeted drugs. In conclusion, anthraquinone based molecules are important categories of drugs and can be potentially targeted towards research and development for the treatment and imaging of cancer.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Hannon MJ. Supra molecular DNA recognition. Chem Soc Rev 2007;36:280-95.
2. MacMillan AM. Chemistry of nucleic acids-part 3-preface. Pure Appl Chem 2004;76:14.
3. MacMillan AM. Fifty years of "Watson-Crick". Pure Appl Chem 2004;76:1521-4.
4. Jelly R, Lewis SW, Lennard C, Lim KF, Almog J. Lawsone: a novel reagent for the detection of latent fingermarks on paper surfaces. Chem Commun 2008;30:3513-5.
5. Kranaster R, Marx A. Increased single-nucleotide discrimination in allele-specific polymerase chain reactions through primer probes bearing nucleobase and 2'-deoxyribose modifications. Chem Eur J 2007;13:6115-22.
6. Marras SAE, Tyagi S, Kramer FR. Real-time assays with molecular beacons and other fluorescent nucleic acid hybridization probes. Clin Chim Acta 2006;363:48-60.
7. Werder S, Malinovskii VL, Haner R. Triazolylpyrenes: synthesis, fluorescence properties and incorporation into DNA. Org Lett 2008;10:2011-4.
8. Gottesfeld JM, Neely L, Trauger JW, Baird EE, Dervan PB. Regulation of gene expression by small molecules. Nature 1997;387:202-5.
9. Dickerson RE, Drew HR, Conner BN, Wing M, Fratini AV, Kopka, ML. The anatomy of A-, B-, and Z-DNA. Science 1982;216:475-85.
10. Saenger W. Principles of nucleic acid structure, Biochemical Education, Springer-Verlag, New York; 1984.
11. Bauer GB, Povirk LF. Specificity and kinetics of interstrand and intrastrand bifunctional alkylation by nitrogen mustards at a G–G–C sequence. Nucleic Acids Res 1997;25:1211-8.
12. Hurley LH. DNA and its associated processes as targets for cancer therapy. Nat Rev Cancer 2002;2:188-200.
13. Reedijk J. New clues for platinum antitumor chemistry: kinetically controlled metal binding to DNA. Proc Natl Acad Sci USA 2003;100:3611-6.
14. Panousis C, Phillips DR. DNA sequence specificity of mitoxantrone. Nucleic Acids Res 1994;22:1342-5.
15. Denny WA, Wakelin LPG. Kinetics of the binding of mitoxantrone, ametantrone and analogues to DNA: relationship with binding mode and anti-tumour activity. Anti-Cancer Drug Des 1990;5:189-200.
16. Tanious FA, Jekins TC, Neidle S, Wilson WD. Substituent position dictates the intercalative DNA-binding mode for anthracene-9,10-dione antitumor drugs. Biochemistry 1992;31:11632-40.
17. Denny WA. DNA-intercalating ligands as anti-cancer drugs: prospects for future design. Anti-Cancer Drug Design 1989;4:241-63.
18. Clement B, Jung F. N-hydroxylation of the antiprotozoal drug pentamidine catalyzed by rabbit liver cytochrome P-4502C3 or human liver microsomes, microsomal retroreduction, and further oxidative transformation of the formed amidoximes. Possible relationship to the biological oxidation of arginine to NG-hydroxy arginine, citrulline, and nitric oxide. Drug Metab Dispos 1994;22:486-97.
19. Remers WA. The chemistry of antitumor antibiotics. Wiley, New York; 1979. p. 1.
20. Williams LD, Egli M, Gao Q. Structure of nogalomycin bound to a DNA hexamer. Proc Natl Acad Sci USA 1990;87:2225-9.
21. Neidle S. DNA minor-groove recognition by small molecules. Natural Product Reports 2001;18:291-309.
22. Skibo EB, Xing C, Groy T. Recognition and cleavage at the DNA major groove. Bioorg Med Chem 2001;9:2445-59.
23. Schleif R. DNA binding by proteins. Science 1988;241:1182-7.
24. Jain AK, Bhattacharya S. Groove binding ligands for the interaction with parallel-stranded ps-duplex DNA and triplex DNA. Bioconjugate Chem 2010;21:1389-403.
25. Ganesh KN, Kumar VA. Conformationally constrained PNA analogs: structural evolution towards DNA/RNA binding selectivity. Acc Chem Res 2005;38:404-12.
26. Nielsen PE. Peptide nucleic acids as therapeutic agents. Curr Opin Struct Biol 1999;9:353-7.
27. Bailly C, Chaires JB. Sequence-specific DNA minor groove binders. Design and synthesis of netropsin and distamycin analogs. Bioconjugate Chem 1998;9:513-38.
28. Dervan PB. Molecular recognition of DNA by small molecules. Bioorg Med Chem 2001;9:2215-35.
29. Lown JW, Graham BJ. DNA sequence recognition altered bis-benzimidazole minor groove binders. In: Advances in DNA Sequence-Specific Agents. ed. Graham BJ. JAI Press: Greenwich; 1997. p. 67-95.
30. Dervan PB. The design of sequence-specific DNA-binding molecules. Science 1986;232:464-71.
31. Bhattacharya S, Thomas M. Facile synthesis of oligopeptides distamycin analogs devoid of hydrogen-bond donors or acceptors at the N-terminus: sequence-specific duplex DNA binding as a function of peptide chain length. Tetrahedron Lett 2000;41:5571-5.
32. Eriksson S, Kim SK, Kubista M, Norden B. Binding of 4′6-diamino-2-phenylindole (DAPI) to AT regions of DNA: evidence for an allosteric conformational change. Biochemistry 1993;32:2987-98.
33. Brown DG, Sanderson MR, Skelly JV, Jenkins TC, Brown T, Garman E, *et al.* Crystal structure of a berenil–dodeca-nucleotide complex: the role of water in sequence-specific ligand binding. EMBO J 1990;9:1329-34.
34. Ferguson LR, Denny WA. Microbial mutagenic effects of the DNA minor groove binder pibenzimol (Hoechst 33258) and a series of mustard analogs. Mutat Res 1995;329:19-27.

35. Bhattacharya S, Chaudhuri P. Medical implications of benzimidazole derivatives as drugs designed for targeting DNA and DNA-associated processes. Curr Med Chem 2008;15:1762-77.
36. Holmquist G. Hoechst 33258 fluorescent staining of Drosophila chromosomes. Chromosoma 1975;49:333-56.
37. Bourdouxhe C, Colson P, Houssier C, Henichart JP, Waring MJ, Denny WA, *et al*. Design of composite drug molecules: mutual effects on binding to DNA of an intercalator, amsacrine, and a minor groove binder, netropsin. Anticancer Drug Des 1995; 10:131-54.
38. David-Cordonnier MH, Hildebrand MP, Baldeyrou B, Lansiaux A, Keuser C, Benzschawel K, *et al.* Design, synthesis and biological evaluation of new oligopyrrole carboxamides linked with tricyclic DNA-intercalators as potential DNA ligands or topoisomerase inhibitors. Eur J Med Chem 2007;42:752-71.
39. Llombart M, Poveda A, Forner E, Martos CF, Gaspar C, Muñoz M, *et al.* Phase I study of mitonafide in solid tumors. Invest New Drugs 1992;10:177-81.
40. Rosell R, Carles J, Abad A, Ribelles N, Barnadas A, Benavides A, *et al.* Phase I study of mitonafide in 120-hour continuous infusion in non-small cell lung cancer. Invest New Drugs 1992;10:171-5.
41. Arlin ZA. A special role for amsacrine in the treatment of acute leukemia. Cancer Invest 1989;7:607-9.
42. Jackson TC, Verrier JD, Kochanek PM. Anthraquinone-2-sulfonic acid (AQ2S) is a novel neurotherapeutic agent. Cell Death Dis 2013;4:1-24.
43. Lown JW. Anthracycline and anthracene dione-based anticancer agents. In: Bioactive Reviews; Elsevier: Amsterdam, Netherlands; 1988;6:1-753.
44. Lown JW, Morgan AR, Yen SF, Wang YH, Wilson WD. Characteristics of the binding of the anticancer agents mitoxantrone and ametantrone and related structures to deoxyribonucleic acids. Biochemistry 1986;24:4028-35.
45. Danhier F, Breton AL, Preat V. RGD-based strategies to targ*et al.* pha (v) Beta-integrin in cancer therapy and diagnosis. Mol Pharm 2012;9:2961-73.
46. Kohn KW. DNA as a target for anticancer drug action. In: Anticancer Drugs. Tapiero, Robert J, Lampidis TJ. Eds. Colloque Inserm/John Libbey Eurotext Ltd.; 1989. p. 77-86.
47. Kizek R, Adam V, Hrabeta J, Eckschlager T, Smutny S, Burda JV, *et al*. Anthracyclines and ellipticines as DNA-damaging anticancer drugs: recent advances. Pharmacol Ther 2012;133:26-39.
48. Routier S, Bernier JL, Catteau JP, Riou JF, Bailly C. Synthesis, DNA binding, topoisomerase II inhibition and cytotoxicity of two guanidine-containing anthracene-9,10-diones. Anticancer Drug Des 1998;13:407-15.
49. Huang HS, Chiou JF, Fong Y, Hou CC, Lu YC, Wang JY, *et al.* Activation of human telomerase reverse transcriptase expression by some new symmetrical bis-substituted derivatives of the anthraquinone. J Med Chem 2003;46:3300-7.
50. Perry PJ, Read MA, Davies RT, Gowan SM, Reszka AP, Wood AA, *et al.* 2,7-Disubstituted amido fluorenone derivatives as inhibitors of human telomerase. J Med Chem 1999;42:2679-84.
51. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacol Rev 2004;56:185-229.
52. Johnson RK, Zee-Cheng RKY, Le WW, Acton EM, Henry DW, Cheng CC. The experimental antitumor activity of amino-anthraquinones. Cancer Treat Rep 1979;63:425-39.
53. Skladanowski A, Konopa J. Mitoxantrone and ametantrone induce interstrand cross-links in DNA of tumor cells. Br J Cancer 2000;82:1300-4.
54. Zee-Cheng RKY, Cheng CC. Structure-activity relationship study of anthraquinones: 1,4-dihydroxy-5, & bis((2-(2-hydroxyethoxy) ethyl)amino)-9,10-anthracenedione, an analog of an established antineoplastic agent. J Pharm Sci 1982; 71:708-9.
55. Zee-Cheng RKY, Cheng CC. Antineoplastic agents. Structure-activity relationship study of bis (substituted amino alkylamino)-anthraquinones. J Med Chem 1978;21:291-4.
56. Zee-Cheng RKY, Podrebarac EG, Menon CS, Cheng CC. Structural modification study of bis (substituted amino-alkylamino) anthraquinones. An evaluation of the relationship of the (2-(2-hydroxyethyl)amino)ethyl)amino side chain with antineoplastic activity. J Med Chem 1979;22:501-5.
57. Huang HS, Chiu HF, Lee AR, Guo CL, Yuan CL. Synthesis and structure-activity correlations of the cytotoxic bifunctional 1,4-diamidoanthraquinone derivatives. Bioorg Med Chem 2004;12:6163-70.
58. Murdock KC, Child RG, Fabio PF, Angier RB, Wallace RE, Durr FE, *et al*. Antitumor agents. 1,4-bis-((aminoalkyl)amino)-9,10-anthracenediones. J Med Chem 1979;22:1024-30.
59. Johnson MG, Kiyokawa H, Tani S, Koyama J, Morris-Natschke SL, Mauger A, *et al.* Antitumor agents CLXVII. Synthesis and structure-activity correlations of the cytotoxic anthraquinone 1,4-Bis-(2,3-Epoxypropylamino)-9,10-anthracenedione and of related compounds. Bioorg Med Chem 1997;5:1469-79.
60. Gatto B, Zagotto G, Sissi C, Cera C, Uriarte E, Palu G, *et al.* Peptidyl anthraquinones as potential antineoplastic drugs: synthesis, DNA binding, redox cycling, and biological activity. J Med Chem 1996;39:3114-22.
61. Huang HS, Huang KF, Li CL, Huang YY, Chiang YH, Huang FC, *et al.* Synthesis, human telomerase inhibition and antiproliferative studies of a series of 2,7-bis-substituted amido-anthraquinone derivatives. Bioorg Med Chem 2008;16:6976-86.
62. Hua DH, Lou K, Battina SK, Zhao H, Perchellet EM, Wang Y, *et al.* Syntheses, molecular targets and antitumor activities of novel triptycene bisquinones and 1,4-anthracenedione analogs. Curr Med Chem 2006;6:303-18.
63. Kamal A, Ramu R, Tekumalla V, Khanna GB, Barkume MS, Juvekar AS, *et al.* Synthesis, DNA binding, and cytotoxicity studies of pyrrolo[2,1-c][1,4]benzodiazepine-anthraquinone conjugates. Bioorg Med Chem 2007;15:6868-75.
64. Routier S, Cotelle N, Catteau JP, Bernier JL, Waring MJ, Riou JF, *et al.* Salen-anthraquinone conjugates. Synthesis, DNA-binding and cleaving properties, effects on topoisomerases and cytotoxicity. Bioorg Med Chem 1996;4:1185-96.
65. Hsin LW, Wang HP, Kao PH, Lee O, Chen WR, Chen HW, *et al.* Synthesis, DNA binding, and cytotoxicity of 1,4-bis(2-amino-ethylamino)anthraquinone–amino acid conjugates. Bioorg Med Chem 2008;16:1006-14.
66. Teng CH, Won SJ, Lin CN. Design, synthesis and cytotoxic effect of hydroxy and 3-alkylaminopropoxy-9,10-anthraquinone derivatives. Bioorg Med Chem 2005;13:3439-45.
67. Wu M, Wan B, Perchellet EM, Sperfslage BJ, Stephany HA, Hua DH, *et al.* Synthetic 1,4-anthracenediones, which block nucleoside transport and induce DNA fragmentation, retain their cytotoxic efficacy in daunorubicin-resistant HL-60 cell lines. Anti-Cancer Drugs 2001;12:807-19.
68. Cheng CC, Zee-Cheng RKY. The design, synthesis and development of a new class of potent antineoplastic anthraquinones. Prog Med Chem 1983;20:83-118.
69. Zagotto G, Sissi C, Moro S, Dal Ben D, Parkinson GN, Fox KR, *et al.* Amide bond direction modulates G-quadruplex recognition and telomerase inhibition by 2,6 and 2,7 bis-substituted anthracene dione derivatives. Bioorg Med Chem 2008;16:354-61.
70. Cairns D, Michalitsi E, Jenkins TC, Mackay SP. Molecular modeling and cytotoxicity of substituted anthraquinones as inhibitors of human telomerase. Bioorg Med Chem 2002;10:803-7.
71. Wang Y, Perchellet EM, Ward MM, Lou K, Hua DH, Perchellet JP. The rapid collapse of mitochondrial transmembrane potential in HL-60 cells and isolated mitochondria treated with anti-tumor 1,4-anthracenediones. Anti-Cancer Drugs 2005;16:953-67.
72. Perchellet EM, Wang Y, Weber RL, Sperfslage BJ, Lou K, Crossland J, *et al.* Synthetic 1,4-anthracenedione analogs induce cytochrome c release, caspase-9,-3, and-8 activities, poly(ADP-ribose) polymerase-1 cleavage and internucleosomal DNA fragmentation in HL-60 cells by a mechanism which involves caspase-2 activation but not Fas signaling. Biochem Pharmacol 2004;67:523-37.
73. Zhao P, Xu LC, Huang JW, Fu B, Yu HC, Ji LN. Cationic porphyrin–anthraquinone dyads: modes of interaction with G-quadruplex DNA. Dyes Pigments 2009;83:81-7.
74. Hurley LH, Wheelhouse RT, Sun D, Kerwin SM, Salazar M, Fedoroff OY, *et al.* G-quadruplexes as targets for drug design. Pharmacol Ther 2000;85:141-58.

75. Liang Z, Ai J, Ding X, Peng X, Zhang D, Zhang R, *et al.* Anthraquinone derivatives as potent inhibitors of c-met kinase and the extracellular signaling pathway. ACS Med Chem Lett 2013;4:408-13.
76. Gibson D, Binyamin I, Haj M, Ringel I, Ramu A, Katzhendler J. Anthraquinone intercalators as carrier molecules for second-generation platinum anticancer drugs. Eur J Med Chem 1997;32:823-31.
77. Jin GZ, You YJ, Kim Y, Nam NH, Ahn BZ. Esters of chlorambucil with 2-substituted 1,4-dihydroxy-9,10-anthraquinones as multi-functional anticancer agents. Eur J Med Chem 2001;36:361-6.
78. Wang S, Wang Q, Wang Y, Liu L, Weng X, Li G, *et al.* Novel anthraquinone derivatives: synthesis via click chemistry approach and their induction of apoptosis in BGC gastric cancer cells via reactive oxygen species (ROS)-dependent mitochondrial pathway. Bioorg Med Chem Lett 2008;18:6505-8.
79. Tu H, Huang A, Teng C, Hourb T, Yang S, Pu, Y, *et al.* Anthraquinone derivatives induce G_2/M cell cycle arrest and apoptosis in NTUB1 cells. Bioorg Med Chem 2011;19:5670-8.
80. Gatto B, Zagotto G, Sissi C, Palumbo M. Preferred interaction of D-peptidyl-anthraquinones with double-stranded B-DNA. Int J Biol Macromol 1997;21:319-26.
81. Zagotto G, Sissi C, Gatto B, Palumbo M. Aminoacyl-analogues of mitoxantrone as novel DNA-damaging cytotoxic agents. Arkivoc 2004;5:204-18.
82. Zagotto G, Supino R, Favini E, Moro S, Palumbo M. New 1,4-anthracene-9,10-dione derivatives as potential anticancer agents. Il Farmaco 2000;55:1-5.
83. Koh E, Ueda Y, Nakamura T, Kobayashi A, Katsuta S, Takahashi H. Apoptosis in young rats with adriamycin-induced cardiomyopathy-comparison with pirarubicin, a new anthracycline derivative. Pediatr Res 2002;51:256-9.
84. Niitsu N, Yamazaki J, Nakayama M, Umeda M. Pirarubicin-induced myocardial damage in elderly patients with non-Hodgkin's lymphoma. Nippon Ronen Igakkai Zasshi 1998;35:358-62.
85. Wojnar J, Mandecki M, Wnuk-Wojnar AM, Holowiecki J. Clinical studies on actinomycin A cardiotoxicity in adult patients with acute nonlymphoblastic leukemia. Folia Haematol 1989;116:297-303.
86. Rabbani A, Finn RM, Ausio J. The anthracycline antibiotics: antitumor drugs that alter chromatin structure. Bioessays 2005;27:50-6.
87. Gewirtz DA. A critical evaluation of the mechanisms of action proposed for the antitumor effects of the anthracycline antibiotics adriamycin and daunorubicin. Biochem Pharmacol 1999;57:727-41.
88. Kiyomiya K, Matsuo S, Kurebe M. Mechanism of specific nuclear transport of adriamycin: the mode of nuclear translocation of the adriamycin-proteasome complex. Cancer Res 2001;61:2467-71.
89. Ellis LT, Perkins DF, Turner P, Hambley TW. The preparation and characterisation of cyclam/anthraquinone macrocyle/ intercalator complexes and their interactions with DNA. Dalton Trans 2003;13:2728-36.
90. Venkata Ramana A, Watkinson M, Todd MH. Synthesis and DNA binding ability of cyclam–amino acid conjugates. Bioorg Med Chem Lett 2008;18:3007-10.
91. Kimura E, Kikuta E. Why zinc in zinc enzymes? From biological roles to DNA base-selective recognition. J Biol Inorg Chem 2000;5:139-55.
92. Gibson D, Mansur N, Gean KF. Preparation, characterization, and antitumor properties of cis-$PtCl_2$ complexes linked to anthraquinones through position number 2. J Inorg Biochem 1995;58:79-88.
93. Whittaker J, McFadyen WD, Wickham G, Wakelin LP, Murray V. The interaction of DNA-targeted platinum phenanthridinium complexes with DNA. Nucleic Acids Res 1998;26:3933-9.
94. Perrin LC, Prenzler PD, Cullinane C, Phillips DR, Denny WA, McFadyen WD. DNA targeted platinum complexes: synthesis, cytotoxicity and DNA interactions of cis-dichloro platinum (II) complexes tethered to phenazine-1-carboxamides. J Inorg Biochem 2000;81:111-7.
95. Shionoya M, Ikeda T, Kimura E, Shiro M. Novel "multipoint" molecular recognition of nucleobases by a new zinc (II) complex of acridine-pendant cyclen (cyclen = 1,4,7,10-tetraazacyclododecane). J Am Chem Soc 1994;116:3848-59.
96. Kimura E, Kikuchi M, Kitamura H, Koike T. Selective and efficient recognition of thymidylylthymidine (TpT) by bis(ZnII-cyclen) and thymidylylthymidylylthymidine (TpTpT) by tris(ZnII-cyclen) at neutral pH in aqueous solution. Chem Eur J 1999;5:3113-23.
97. Jones JE, Pope SJ. Sensitized near-IR lanthanide luminescence is exploiting anthraquinone-derived chromophores: syntheses and spectroscopic properties. Dalton Trans 2009;39:8421-5.
98. Jones JE, Amoroso AJ, Dorin IM, Parigi G, Ward BD, Buurma NJ, *et al.* Bimodal, dimetallic lanthanide complexes that bind to DNA: The nature of binding and its influence on water relaxivity. Chem Commun 2011;47:3374-76.
99. Jones JE, Kariuki BM, Ward BD, Pope SJ. Amino-anthraquinone chromophores functionalised with 3-picolyl units: structures, luminescence, DFT and their coordination chemistry with cationic Re(I) di-imine complexes. Dalton Trans 2011;40:3498-509.
100. Balasingham RG, Williams CF, Mottram HJ, Coogan MP, Pope SJA. Gold (I) complexes derived from alkynyl oxy-substituted anthraquinones: Syntheses, luminescence, preliminary cytotoxicity, and cell imaging studies. Organometallics 2012;31:5835-43.
101. Adhikari A, Datta A, Chuttani K, Rawat H, Shukla A, Mishra AK. Preliminary evaluation of an anthraquinone conjugated DOTA derivative as SPECT agent. Int J Pharm Pharm Sci 2015;7:85-9.
102. Adhikari A, Datta A, Adhikari M, Chauhan K, Chuttani K, Saw S, *et al.* Preclinical evaluation of DO3A-Act-AQ: A poly aza macro-cyclic monomeric anthraquinone derivative as a theranostic agent. Mol Pharm 2014;11:445-56.