Review

ANTINEOPLASTIC DNA-BINDING COMPOUNDS: INTERCALATING AND MINOR GROOVE BINDING DRUGS

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DNA intercalating and minor groove binding compounds are new weapons in the battle against malignant diseases. These antineoplastic agents target the DNA molecule and interfere with the cell cycle leading to rapidly proliferating cell death. They are mainly derivates of a naturally occurring organic compound derived from a microorganism or plant. Intercalators usually act as topoisomerase I and/or II poisons, while the mechanisms of DNA minor groove binders are a combination of several steps including topoisomerase poisoning. This paper gives an overview of some of the developed DNA intercalating and minor groove binding compounds, as well as an explanation of their chemical structures, origins, and application in chemotherapy.

KEY WORDS: *chemotherapy, DNA intercalator, DNA minor groove binder, organic compounds derivatives*

Cancer or neoplasm is one of the major diseases of modern society, appearing in all age groups. The notion that cancer is a multi-step process involving accrued genetic damage has now been generally well-accepted (1).Cancer is characterised by rapid, abnormal, and uncontrolled specific cell division with increased rate of DNA synthesis and very fast metabolism that requires a high rate of glycolysis (2).

When it comes to the treatment of cancer, nature was the main source of remedies until the middle of the nineteenth century when aspirin, the first synthetic remedy, was made (3). In the last 70 years, more than 175 antitumour drugs have been produced and commercialised, 65 % of which were derived from natural products (4, 5) or were newly-synthesized molecules that contained pharmacophores from natural products (3). Chemicals that alkylate DNA have been used in cancer treatment since 1942 (1). To this day, antineoplastic therapy has been primarily quantitative rather than qualitative because the impact of a therapy is measured through its killing effects and not its specificity. Such therapies are most effective in rapidly dividing tumour cells like lymphomas and leukaemias but also affect normal rapidly dividing cells such as bone marrow cells (6) and various epithelial tissues (7). An ideal anticancer drug should specifically target malignant cancer cells and leave non-malignant cells unaffected (6). Having in mind that the molecular structure of a single tumour type differs between individuals, chemotherapy cannot be considered reliable. Modern antitumour therapeutic

approaches include case individualisation whenever possible as well as the application of modern techniques such as DNA microarrays in order to achieve this individualisation (8).

Molecular studies are showing promise in the development of more efficient antitumour strategies (9). Since the unravelling of the mechanisms behind tumour development, it became clear that DNA is the main driving force in tumourogenesis (10) and the main intracellular target in cancer chemotherapy (11). DNA is a fountain of genetic information with a well-known and studied structure, which makes it a frequent target in drug design. Alterations to gene expression by means of small DNA binding molecules were proposed some time ago and are constantly being improved. Targeting DNA/RNA with small molecules can give rise to versatile therapeutic results (12, 13). The complex created between DNA and a small molecule can modify normal gene expression leading to alterations in the regulation of cell growth (14). The mode of action for most DNA-affecting antineoplastic agents is either the inhibition of DNA synthesis or irreversible and/or reversible DNA damage. DNA-small molecule interactions are driven by two main modes of binding: covalent and non-covalent. The two main models for the most non-covalent DNA-small molecule interaction are intercalation and groove binding (14). This review focuses on compounds belonging to these two groups. DNA minor groove binders (MGBs), one of the most widely studied type of small molecules (4), can be grouped into two functional groups: 1) substances that cause permanent DNA damage and 2) substances that react with DNA solely physically and induce reimbursement inhibition of DNA-dependent function (15). DNA intercalation provokes structural changes in DNA leading to intrusion in the recognition and function of DNA-associated proteins such as polymerases, transcription factors, DNA repair systems, and, especially, topoisomerases (16).

There are numerous articles on chemotherapeutic drugs used in clinical practice. The main goal of this review is to offer a short retrospective of DNA binding/intercalating drugs applied in chemotherapy (Figure 1) according to their mechanism of action and origin. The drugs described in this article are the basis for future generations of anticancer therapeutics focusing on "targeted" small molecule- and protein/antibody-based drugs that will introduce receptor-targeted therapies, downstream effectors, and antiangiogenic compounds (17). Many are already in clinical use and some are promising therapeutics currently under research.

DNA intercalators

DNA intercalators are a group of compounds with diverse structure and the ability to bind firmly but reversibly to DNA by intercalation of a flat, aromatic chromophore between the base pairs (18). The only recognised forces that maintain the stability of the complex, even more than DNA alone, are van der Waals, hydrogen bonding, hydrophobic effects, and/or charge transfer forces (19). Classical intercalators have a straight, heteroaromatic ring which comes in between two neighbouring base pairs. Interaction leads to structural changes of the DNA molecule resulting in the partial unwinding of the DNA molecule and extension of DNA chain by one base pair. Most clinically-used DNA-intercalating compounds are powerful inhibitors of DNA and RNA synthesis and this has been regarded as their primary mode of action.

Their second major biological effect is the provocation of DNA damage, e.g. sister chromatid exchange (20) and micronuclei (21), which is closely correlated with cytotoxicity levels (18). Moreover, DNA damage can originate from the interference of DNA-intercalating agents with topoisomerase II (topo II), an enzymatic protein entrusted with the role of maintaining the correct topological properties of DNA in cells (18). In general, topoisomerase are nuclear enzymes necessary for the maintenance of DNA structure. They are direct participants in the recognition of DNA and the fundamental steps of cellular growth when DNA replication is active, as well as in the S phase of the cell cycle in which topology of DNA plays a significant role. Topoisomerases influence chromatin arrangement in the M phase of the cell cycle indicating that they can be poisoned not only in the S but also in the M phase (19). Topoisomerases can be grouped into two main classes: topoisomerase I (topo I), which breaks only one strand of DNA and topo II, which breaks both strands of the duplex (19). Alterations in DNA topo II have been identified in tumour cell lines selected for resistance to natural products, including etoposide and doxorubicin (18). Actinomycin D, bleomycin, daunorubicin, doxorubicin, elsamicin A, epirubicin, ethidium, m-AMSA, mitoxantrone are just some of the DNA intercalating drugs commonly used today as chemotherapeutics (22-28).

Indolocarbazoles represent a family of natural products with the potential to be used in cancer treatment (29). The natural antibiotic rebeccamycin (Figure 2) isolated from *Saccharothrix aerocoloniegenes* (30) is representative of the indolcarbazole group and is a DNA-binding agent and inhibitor of topo I (31-33).
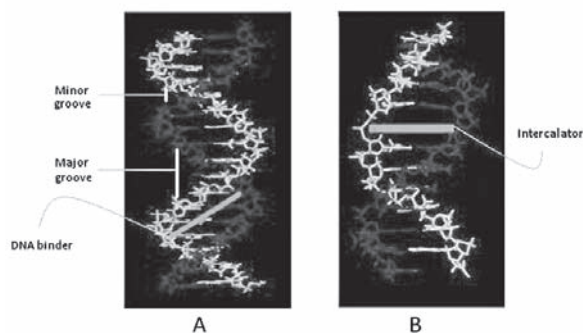

Figure 1 *Schematics showing two distinct models of drug-DNA interaction.*
A) DNA major and minor groove binding – an isohelical drug molecule binds in the minor groove of DNA without inducing significant DNA structural changes; the complex is stabilised mainly with hydrophobic interactions;
B) Intercalation – a planar aromatic chromophore is inserted between two adjacent base pairs in the DNA helix; the complex is stabilised by hydrophobic interactions and van der Waals forces.
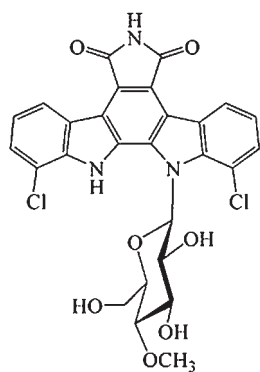

Figure 2 *Chemical structure of rebeccamycin*

MLN944 (XR5944) (Figure 3) is a novel bis-phenazine originating from a drug development programme aimed at developing new compounds as drugs for the treatment of solid tumours (34). This agent expressed strong cytotoxic activity in a variety of *in vitro* and *in vivo* tumour models. It was designed to target both topo-I and topo-II, but experiments conducted by Sappal et al. (35) showed that the

toxicity of MLN944 was not correlated with the inhibition of topo I and topo II and that treatment induced non-reversible cell cycle arrest in both the G1 and the G2-M phase.
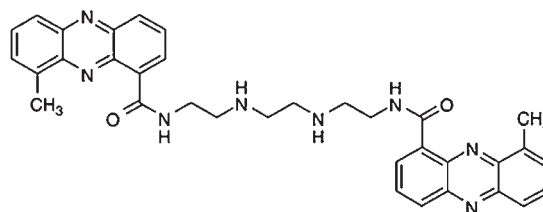

Figure 3 *Chemical structure of MLN944*

Two newly-synthesised drugs, named TAS-103 and DACA (Figure 4), act as dual topo poisons. TAS-103 is a quinoline derivate expressing remarkable activity against subcutaneously-implanted murine and human tumours *in vivo*, as well as various lung-metastatic murine tumours (36). Recent studies on TAS-103 in conjunction with various approved antitumour drugs like cisplatin, if applied simultaneously, expressed a synergistic effect, which may prove beneficial for the treatment of small-cell lung cancer. TAS-103 is therefore a promising anticancer compound and is currently undergoing clinical trials (37). The antitumour activity of DACA was extremely high in certain *in vivo* tumour models (38). For example, DACA was efficient against transplantable Lewis lung adenocarcinoma growing as lung tumour nodules in mice and was more successful than standard drugs in various xenografted cancers (37). DACA is currently in phase I/II clinical trial as an anticancer agent. One of the most interesting facts about DACA is its unusual mode of binding to DNA. It was revealed that the intercalation of the acridine ring was accompanied by a major groove
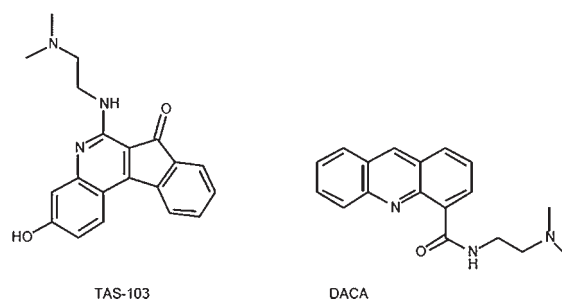

Figure 4 *Synthetic intercalating antineoplastic compounds [adapted from (36)]*

binding of the carboxamide side chain (39). Major groove binding is usually noted with proteins and peptides and infrequently seen in small molecules (37).

Prodiginines (Figure 5) are transformed primary bacteria products with immunosuppressive and anticancer attributes, characterised by a pyrrole dipyrromethane backbone. They act as a dual topo I/II inhibitor. Their antimalignant activity has been shown in several cancer-derived cell lines (breast, lung, stomach, liver, spleen, colon, blood, and chronic myeloid leukaemia) and in mice *in vivo* with a xenografted liver cancer (40). Furthermore, prodiginines show negligible activity in normal cells (31). Prodigiosin, a red pigment produced by numerous strains of the bacterium *Serratia marcescens*, is a prodiginine scanned against dozens of cancer cell lines demonstrating an average inhibitory concentration of 2.1 μmol L^{-1} (41). Obatoclax (GX15-070) is a synthetic derivative of natural prodiginines and the leading candidate for clinical application. Currently, Obatoclax is in multiple phase I and phase II clinical trials for several types of cancer, used both as a single agent and in combined therapies (42, 43).
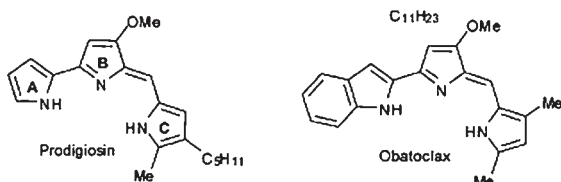

Figure 5 *Prodigiosin and his derivative Obatoclax [adapted from (43)]*

Anthracyclines act as topo II inhibitors. Doxorubicin and daunomycin are representatives of this group, as is aclacinomycin A, a dual topo inhibitor with the ability to kill cells in the exponential and plateau phase by a non-selective mechanism (37). Doxorubicin (Figure 6) is an anthracycline antibiotic with antineoplastic activity. It acts as a topo II poison and is used for treating breast and ovarian cancer, lung cancer, gastric (stomach) cancer, testicular cancer, bladder and thyroide cancer, Hodgkin's and non-Hodgkin's lymphoma, soft tissue sarcoma, acute leukaemia, Wilm's tumour and neuroblastoma (44). Since 2007, doxorubicin and bortezomib have been used in combined therapy for treating multiple myeloma (45). Epirubicin is also an anthracycline antibiotic. It expresses reduced myelosuppression

and cardiotoxicity and has produced high response rates in early breast cancer compared to doxorubicin (46). Mitoxantrone is an anthraquinone derivate structurally and functionally very similar to doxorubicin: it acts as an intercalator and topo II poison. It is used in the treatment of prostate cancer, acute myelogenous leukaemia (AML), breast cancer, and Non-Hodgkin's lymphoma (47).
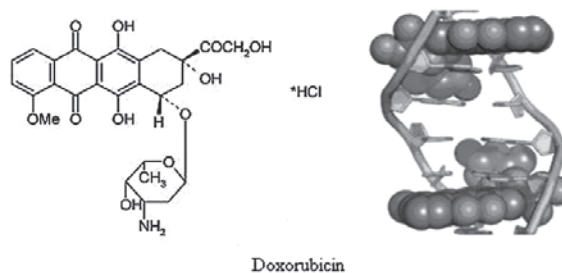

Figure 6 *Doxorubicin chemical structure and 3D intercalating model [adapted from (44)]*

DNA groove binders

Minor groove DNA binding compounds are a new family of antineoplastic drugs with representatives already in the process of clinical testing. The structure of these molecules is characterised by several connected aromatic rings that allow freedom of movement and torsion. Binders usually have a characteristic curved shape compatible with the DNA minor groove. The formed complex is stabilised with hydrophobic interactions (Figure 1A). Furthermore, DNA binders do not cause significant structural changes in the DNA molecule and no change to the DNA free energy structure (22). One of the most prominent characteristics of DNA minor groove binding compounds is their preferable binding to AT rich regions due to good hydrophobic interaction between the aromatic ring of the compound and second C atom of adenine. On cell level, DNA minor groove binders stop the cell cycle in its G2-M phase (48).

MGBs are especially interesting because of their possible effect on gene expression, pronounced affinity, and selective binding. In the last decade, many synthetic and natural analogues like distamycin A, netropsin (49), CC-1065 (50), and Hoechst 33258 (51) were tested for their antineoplastic impact. Some possessed fluorescent attributes, with antibacterial, antifungal, and antiviral properties. They can be used in combination with other drugs for cytotoxic enhancement with an aim to reduce the applied drug

concentrations. For example, distamycin A in combination with duocarmycin A enhanced the cytotoxicity of duocarmycin A by 10 times in comparison with duocarmycin A alone (52).

Bisamidines are a group of compounds used as a base for the synthesis of new compounds with minor alterations in structure. The biological effects of bisamidines presumably originate from their inhibitory effects on transcription and replication (53). Hoechst 33258 and 33342 are representatives of the *bis*-benzimidazole group and probably one of the most studied DNA binding compounds (Figure 7).
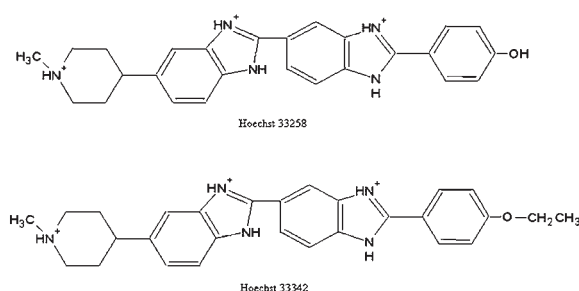

Figure 7 *Chemical structure of DNA binding dyes Hoechst 33258 and 33342 used in fluorescent microscopy for DNA visualisation and detection*

Hoechst 33258, known as pibenzimol, is a fluorescent reagent with a head-to-tail *bis*-benzimidazole structure that initially showed activity against L1210 murine leukaemia (54). In human phase I clinical trials, it exhibited mild suppressive reaction in pancreatic cancer. However, phase II did not show any objective responses (54). Since Hoechst 33258 possesses strong DNA binding power, many chemists have used it as a backbone for new compounds with different radicals and substituted groups or atoms. Not long ago, Liu et al. (55) have pinpointed Hoechst 33342 and 33258 as delegates of a class of human topo I poisons that display cytotoxic behaviour in numerous cancer cell lines. These drugs bind to the minor groove of AT-tract duplex DNA. Nevertheless, this binding mode by itself does not seem adequate to reveal biological activity as a topo I poison, because other AT-specific, minor groove-directed ligands, such as netropsin, 4´,6-diamidino-2-phenylindole (DAPI), berenil, and distamycin A were proven to be powerless or inert poisons of human topo I (56). Therefore, minor groove binding by itself, even though probably required, is not sufficient to poison topo I (56). However, Hoechst 33258 has uncommon DNA

binding properties. Besides settling into the minor groove of AT sequences (57), the drug can intercalate into GC-rich sequences (58). Analogue DNA sequence-dependent binding modes have been exhibited with DAPI and berenil and diphenylfuran derivatives. Hence, inactivation of topoisomerase I by Hoechst 33258 may, to a certain extent, rely on the intercalative binding mode rather than the DNA minor groove complex formation (37). Hoechst 33342 is more lipophilic than 33258 and is commonly applied for histochemical staining and flow cytometric analysis of DNA content in viable cells (59, 60). Curiously, Hoechst 33342 generated protein-DNA cross links and DNA strand breaks in cultured mammalian cells. G2-phase arrest and chromosome end reduplication were also pronounced effects of Hoechst 33342 treatment (61).

Terbenzimidazoles are a group of synthetic ligands that poison the human topo I enzyme and contribute to cancer cell death (49). One of its representatives is the 5-phenylterbenzimidazole derivative (5PTB), which poisons human topo I and is lethal to tumour cells that overexpress the multi-drug resistance protein (MDR) (49).

Pyrrolobenzodiazepines (PBDs) are a group of naturally occurring alkylating antitumour antibiotics. They are a class of sequence-selective DNA binding agents obtained from the thermophilic actinomycete *Streptomyces refaineus* (62), which includes DC-81, tomaymycin, and anthramycin (63). Anthramycin was isolated in 1963 and in spite of good antineoplastic activity against different types of tumours (Ehrlich solid carcinoma, sarcoma 180, epidermal carcinoma no.3 and leukaemia L1210 cells), the clinical application of anthramycin is limited because of its high cardio toxicity and possible appearance of acute necrosis at the site of drug application (62). SJG-136 is a new member of the PBD group. This compound exhibited significant *in vivo* potential for leukaemia treatment. The first phase of clinical evaluation finished in 2010 (64). The tripyrrole peptide distamycin A is a naturally occurring antibiotic agent obtained from the cultures of *Streptomyces distallicus* (62). It binds exclusively to the minor groove of DNA with high selectivity for the AT rich region (65). Distamycin A (Figure 8) is a potent inhibitor of Werner and Bloom syndrome helicases and a dual inhibitor of topo I and II. It inhibits RNA polymerase II transcription by blocking chain elongation as well as intensifying transcription at natural RNA polymerase II pause sites (66). One significant representative among distamycin
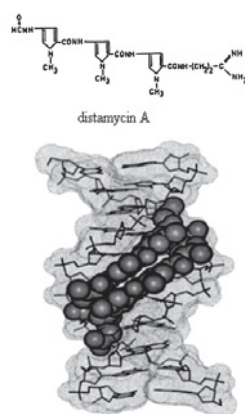
Figure 8 *Distamycin A chemical structure and 3D overview of binding in side of a DNA molecule*
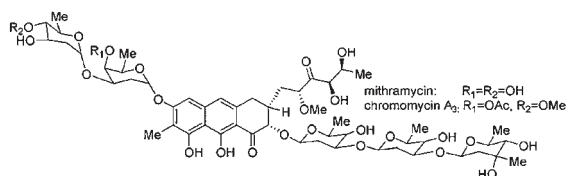

Figure 9 *Aureolic acid group of antineoplastic compounds [adapted from (66)]*

A derivatives is tallimustine (TAM) (67). Until recently, TAM was the only clinically developed derivative (68). TAM passed phase I of clinical trials but was halted in phase II (69, 70), because it showed severe myelotoxicity (68). Netropsin (71) acts in the same way as distamycin A, inhibiting Werner and Bloom syndrome helicases and dually inhibiting topo I/II.

Other relatively frequently used drugs include the natural antibiotic duocarmycin SA, member of the CC-1065 family (72), which is a tremendously powerful cytostatic compound against different cancer cell lines and hence one of the most powerful anticancer agents known so far (73). Mithramycin (MTR) and chromomycine (Figure 9) have a similar mode of binding to GC-rich DNA sequences in the minor groove and belong to the aureolic acid group of anticancer drugs (66).

CONCLUSION

The substances listed in this article are just some of the most frequent chemotherapeutic drugs and their forerunners. The mechanism of their action is specific, but they have no particular selectivity toward malignant cells. The medicine of tomorrow will need to implement a personalised approach with tailored therapy for specific patient transcription/genotype profiles. Acquisition of effective substances through gene profiling in combination with proficiency gained through applied antimalignant therapy is the future recipe for successful treatment.

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Sažetak

DNA-VEZUJUĆI ANTITUMORSKI SPOJEVI – INTERKALIRAJUĆI I MALI UTOR-VEZUJUĆI LIJEKOVI

Novo oružje u borbi protiv zloćudnih bolesti su spojevi koji se umeću u dvolančanu strukturu deoksiribonukleinskih kiselina (DNA) ili se vezuju na mali utor DNA. Navedene skupine kemoterapeutika primarno ciljaju molekulu DNA te utječu na stanični ciklus što vodi do smrti brzo dijelećih stanica. Uglavnom su derivati organskih spojeva prirodnog podrijetla, izoliranih iz mikroorganizama ili biljaka. DNA umetnuti spojevi uglavnom djeluju kao otrovi enzima topoizomeraza I i/ili II a spojevi koji se vezuju na mali utor DNA imaju kombinirani mehanizam djelovanja pri čemu je jedan od koraka i otrovanje topoizomeraza. U ovom preglednom članku dajemo pregled nekih od spojeva koji se umeću u molekulu DNA ili vezuju na mali utor DNA, a koji se primjenjuju u kemoterapiji, njihova podrijetla i kemijske strukture.

KLJUČNE RIJEČI: *derivati organskih spojeva, kemoterapija, mali utor DNA vezujući spojevi*

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