Molecular Symmetry: A Structural Property Frequently Present in New Cytotoxic and Proapoptotic Drugs

Carmen Sanmartín*, María Font and Juan Antonio Palop

Department of Organic and Pharmaceutical Chemistry, University of Navarra, Irunlarrea 1, E-31008, Pamplona, Spain

Abstract: In recent years, a large number of new potent symmetrical cytotoxic agents that act through different mechanisms have been described. Apoptosis induction is one of the most representative of these mechanisms. Recent articles have revealed that the activation of apoptosis pathways is the key mechanism by which cytotoxic tumor cells are killed. The present review highlights the importance of the molecular symmetry of several chemical structures and their relation with cytotoxic and apoptotic activity.

Keywords: Cancer, molecular symmetry, cytotoxicity, apoptosis.

1. INTRODUCTION

Cancer encompasses a group of diseases characterized by the excessive and uncontrolled growth of cells that invade and impair tissues and organs and can, ultimately, cause the death of the individual. The World Health Organization [1] estimates that the rate of incidence of such diseases will increase by 50% by the year 2020. For this reason, new and effective drugs are urgently needed. In recent years, a large number of anticancer agents have been discovered that act at different levels [2] and have higher efficacy and lower toxicity than existing treatments. Classically, anticancer drugs were classified into three categories; chemotherapy, hormonal therapy and immunotherapy. Chemotherapy included a number of families [3] defined by both their chemical structure and mechanisms of action: platinum compounds [4,5], topoisomerase I and II inhibitors [6-9], antibiotics [10], alkylating agents [11], antimetabolites [12-15] and mitosis inhibitors [16-18] amongst others. During the last few years, all of these groups have expanded significantly and some belong to classical groups of anticancer drugs whereas others are the first of new families of compounds. For this reason, a new classification has been proposed based on the nature of the target [3]. The new molecules described include a large number of innovative structures where symmetry is frequently a characteristic property. The target may be located at the DNA (either by breaking the helix, interfering with DNA-related proteins or modifying the expression of specific genes), RNA (synthesis) or protein levels. Moreover, new modes of action have been proposed [19-21] for some of these compounds and the disruption of cellular death programs is included owing to its significant activity in tumorgenesis processes [22-29]. There are two types of cellular death; necrosis and apoptosis. It has been demonstrated that apoptosis is inhibited in major tumors and this results in an uncontrolled increase of carcinogenic cellular tissue. This proliferation disorder is not only produced by a significant increase in the mitosis rate but can also be produced by the considerable decrease in cellular death.

*Address correspondence to this author at the Department of Organic and Pharmaceutical Chemistry, Faculty of Pharmacy, University of Navarra, Irunlarrea, 1, E-31008, Pamplona. Spain; E-mail: sanmartin@unav.es

For this reason, an understanding of the biochemistry and molecular apoptotic pathways is extremely important for the research and development of new therapeutic strategies in cancer [30-39]. It is known that the targets of the apoptotic mechanism are complex. Apoptosis [37] may occur through an extrinsic pathway or through intrinsic or mitochondrial pathway. The extrinsic pathway refers to biochemical processes that induce apoptosis and are mediated by members of the tumor necrosis factor (TNF) superfamily of ligands and receptors [37]. Some of the members of this family [TNF-α receptor, CD95/FasL/Apo-1L receptor and TRAIL (TNF-related apoptosis-inducing ligand /APO-2L) receptor] regulate biological functions beyond apoptosis induction, including cell metabolism, proliferation and cytokine production, while others (e.g., TRAIL-R3, -R4, OPG) may be involved in cell proliferation and survival. TRAIL is a cytokine that induces apoptosis in tumor cells but largely spares normal cells. The intrinsic pathway, also known as the mitochondrial pathway, is governed principally by members of proteins encoded by the Bcl-2 superfamily, which includes pro- (Bax, Bak, Bcl-Xs, Bad, Bid) and antiapoptotic proteins (e.g., Bcl-2, BclXl), and acts mainly at the level of the external mitochondrial membrane. Bax acts through different interactions [37] and causes loss of membrane potential, release of apoptogenic factors – including cytochrome c, ATP, SMAC/DIABLO (second mitochondria-derived activator of caspase/direct IAP binding protein with low pI) – and activation of the death signal. Extrinsic and intrinsic pathways converge to a final common pathway involving the activation of a cascade of proteases called caspases (caspase-3 mainly) [40]. These proteases cleave regulatory and structural molecules and this culminates in the death of the cell. Both apoptosis routes are regulated by proteins such as p53, NFκB (necrosis factor kappaB), the ubiquitin proteosome system and the P13 kinase.

This review covers the most recent publications concerning molecules that have a high level of structural symmetry and show cytotoxic activity through a variety of mechanisms, some of which are related to the induction of apoptosis. Symmetry, as employed in this paper, is a broad concept that encompasses a range of molecular structures. This term covers the range from intrinsically symmetrical

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molecules to systems obtained by dimerization. In this way, we consider structures to be symmetrical when they have an element of symmetry (plane or centre) or, alternatively, a chemical group that divides the molecule into two chemically equivalent parts – configurational or conformational considerations apart.

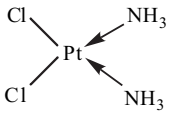

Fig. (1).

2. CYTOTOXICITY AND SYMMETRY

2.1. Drugs that Target DNA

2.1.1. Platinum Compounds

Since its discovery in 1965 [41], cisplatin (Fig. **1**) has been one of the most widely employed anticancer drugs due to the fact that it is effective in the treatment of testicular, ovarian, small cell lung, bladder, brain and breast tumors. Thousands of platinum complexes have been synthesized and screened for their antitumoral activity, but only cisplatin and carboplatin have received worldwide approval and achieved routine clinical use. Taking these compounds as a reference point, extensive efforts have been made to generate new transition metal complexes with different ligands as potential chemotherapeutic agents. Many of these complexes were designed to interact with DNA by different binding strategies or to react with DNA directly. The strategies proposed to increase the efficacy of these compounds include the preparation of dimeric derivatives. Examples of this affinity include electrostatic binding, hydrophobic binding to the minor groove, and intercalation. Alternatively, these agents may react with DNA directly and this type of action includes oxidative strand cleavage, hydrolytic strand cleavage and oxidative reactions with the DNA bases. It is expected that a bisintercalator may have increased cytotoxicity compared to its corresponding monomer, because DNA binding affinity should be greatly enhanced for a bisintercalator and the biological activity of certain intercalating agents has been correlated with their DNA binding affinity. The structural elements used as ligands for platinum (II or IV) or other transition metals are varied. For example, 6-phenyl-2,2'-bipyridine (Fig. **2**) complexes of Pt(II) [42, 43] showed cytotoxic activity very similar to that of the corresponding monomers despite having higher affinities than the monomer, a square-planar geometry, a

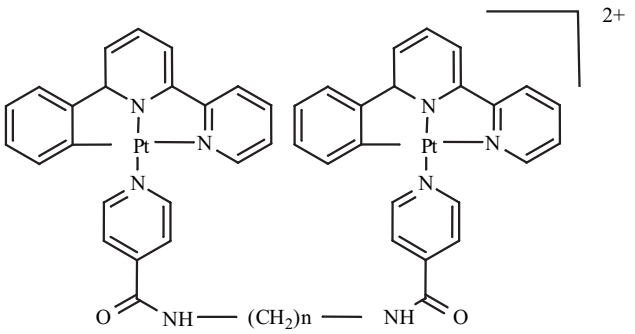

Fig. (2).

cationic charge and aromatic rings – all of which are structural requirements for an intercalator. It is possible that the cytotoxicity of these compounds may not be mediated through DNA binding but may act through a mechanism involving interaction with cellular components other than DNA.

Other ligands include ethylenediamine functionalized with a substituted benzene ring (Fig. **3**, A = substituted benzene ring, L = Cl, H_2O, L' = Cl, OSO_3) [44], acridinylthiourea (Fig. **3**, A = H, L= L' = acridinylthiourea) [45] and dipropionate (Fig. **4**, X = Cl or Br) [46], with the latter ligand complexed with Pt(IV) to give a range of results. In the phenyl derivatives, the best activity was found in the 4-fluorophenyl compound. The platinum acridines are likely to act through a mechanism that differs from that accepted for platinum derivatives. The propionic diesters show poor activity in comparison to the analogous diacetates. This result is due to the different geometries of the complexes – *trans* in the case of propionate and *cis* in the case of acetate.

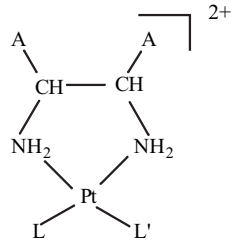

Fig. (3).

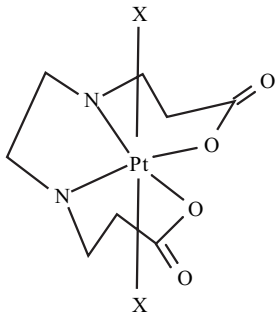

Fig. (4).

Another amine used as a ligand for Pt(II) and Pt(IV) is 1,2-cyclohexanediamine [47-49], which gives rise to compounds related to oxalylplatin. With the aim of increasing the cytotoxicity of these complexes, other modifications have been made to the functionality of the platinum and these include the incorporation of esters [50] and diketones [51], both of which were found to have stronger cytotoxicity than cisplatin. The explanation for this effect is that greater damage is caused to DNA by the latter compounds due to a type of binding caused by the conformation of the compound. The use of carriers such as Lipiodol [52] or the replacement of platinum by tin [53] have been used to increase efficacy. Another platinum compound derived from cisplatin is thioplatin, which is based on the use of sulfur as the complex forming atoms [54].

The antitumoral activity of this compound is pH dependent. A number of analogues of thioplatin have

recently been synthesized [55] with variations in the alkyl group (Fig. **5**). The best results were found for the compounds in which R = isopropyl, ethylpropyl and cyclohexyl.

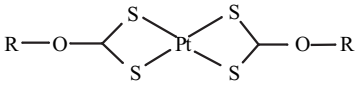

Fig. (5).

The use of bisaminoalkyldiamino anthraquinones (Fig. **6**) [56,57] as linking ligands has been explored and yielded good results for the shortest aminoalkyl chains (n = 2), an observation that reflects the fact that anthraquinones coordinated by platinum are processed through different pathways compared to the uncomplexed anthraquinones.

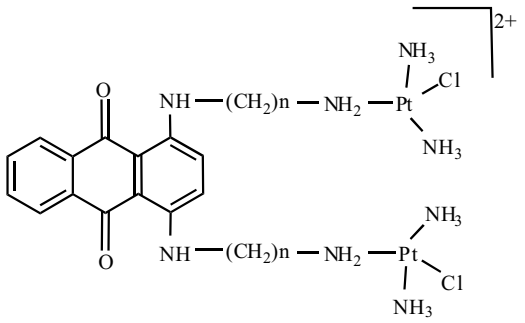

Fig. (6).

Finally, platinum(IV) complexes are more inert than platinum(II) species and have been less widely developed. In terms of the dimers, the most interesting are arguably the estrogen [58] derivatives and adamantylamine [59] systems. The former compounds were designed on the basis of the observation that estrogen receptor-positive cells exposed to the hormone are sensitized to cisplatin. The mechanism of action proposed for this system involves the reducing environment of the cell converting platinum(IV) to platinum(II), thereby releasing cisplatin and two equivalents of estrogen. The results suggest the use of these complexes as target ER (+) malignancies. On the other hand, the adamantylamine complexes are active against cisplatin-resistant cell lines due to their hydrophobicity. These compounds were shown to have a pseudo-first-order rate constant that is one order of magnitude higher than that of cisplatin in the reaction with glutathione. In the search for other active antitumor complexes, various metals have been reported and the most interesting of these are ruthenium [60], cobalt [61], gold [62], iron [63], copper [64] and vanadium [65]. The structure-activity relationships for such systems have not yet been clearly established. In general, the ruthenium compounds are more soluble in water than cisplatin. The cobalt derivatives require the presence of methoxy and/or hydroxy groups in the aryl rings and their cytotoxicity was found to depend on the configuration of the asymmetric carbon atoms. Gold complexes have been studied because gold in the +3 oxidation state is isoelectronic with platinum II. In addition, tetracoordinate gold(III) complexes are found with a square-planar geometry, which is similar to that in cisplatin. Copper and vanadium are apoptosis inducers. Finally, the most recently reported complex is iron with mithramycin [63] and this has a higher cytotoxicity than the drug alone – probably due to its higher DNA-binding and cleavage activity.

2.1.2. Topoisomerase I and II Inhibitors and Intercalating Agents

Topoisomerase type I (topo I) and type II (topo II) represent two classes of the known mammalian DNA topoisomerases. These enzymes can untwist densely packed DNA by generating transient breaks within the DNA strands and allowing topological changes to occur before the breaks are resealed. Topo I and topo II act by creating temporary single-strand and double-strand breaks in DNA, respectively. Many intercalating agents cause DNA strand breaks at very low concentrations and this process usually involves disruption of a topoisomerase enzyme. Some studies concerning structure-activity relationships (SAR) among cytotoxic DNA intercalating agents that act as topoisomerase inhibitors have suggested a positive correlation between cytotoxic potency and the strength of reversible DNA binding [66-68]. However, various dimeric compounds did not improve the activity as much as expected. Several new series of dimeric compounds of acridine, naphthalimide and phenazine derivatives have recently been discovered that show significantly enhanced potencies in cell cultures in comparison to the respective monomers. Clinically useful topoisomerase poisons include an extensive group of molecules such as podophyllotoxin and related compounds, camptothecins, topotecan, irinotecan, some anthracyclines, anthracenediones and acridines.

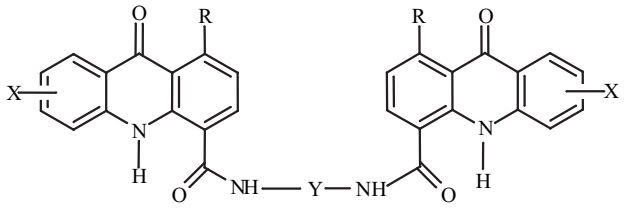

Fig. (7).

2.1.2.1. Acridine Compounds

These compounds have in common the ability to bind tightly but reversibly to DNA by intercalation between the base pairs of the double helix. In some cases, the compounds show an antitumoral profile that is strongly dependent on the nature of the linking chain [69] and this binding is ten times stronger than acridine to DNA when [Fig. **7**, R = NH_2 , X = H and Y = $–(CH_2)_2–N(CH_3)–(CH_2)_3–N(CH_3)–(CH_2)_2–$].

Antonini and Wakelin [Fig. **8**, X = H, OCH_3, Y = $(CH_2)_nN(Me)(CH_2)_nN(Me)(CH_2)_n$, $(CH_2)_n$, $(CH_2)_nN(Me)(CH_2)_n$, R = $CH_2CH_2N(Me)_2$, $CH_2CH_2N(CH_2CH_2)_2O$] [70-72] studied related structures and confirmed that the bisacridone derivatives are more active than the corresponding monomers. Furthermore, the shortest linker gives rise to a lower cytotoxicity and DNA affinity with respect to the longest linker. These results are valid when the acridine possesses a fused pyrazole or pyrimido ring [71]. Furthermore, Wakelin [72] completed the study with semirigid chains (piperazine) as the linker and a morpholino unit in the carboxamide. The conclusion drawn was that these dimeric systems bisintercalate into DNA by a threading mode, in which the 4-carboxamide side chain is located in one groove and the interchromophore linker in the other. The morpholino compounds are 50–80 times more potent than the parental monomer.

Lorente [73] later reported new bisacridines with rigid aromatic chains as linkers. Moreover, some of the aromatic rings contained groups that might facilitate DNA interaction by acting as hydrogen bond acceptors. The interaction between calf thymus DNA and the compounds under investigation seemed to correlate well with the biological activities in the HT-29 cell line. The best results were obtained for the compound in which the link in the 1,3-position is a benzene ring.

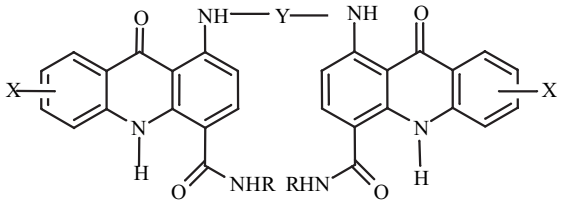

Fig. (8).

The use of monomeric symmetrical 9-anilinoacridines as DNA affinity carriers has been described [74] and these systems are related to the N-alkylating mustard derivatives. The best results were obtained for the compounds in which the alkylating residue is linked to the anilino ring with a short spacer.

2.1.2.2. Bisnaphthalimide Compounds

Bisnaphthalimides are well known cytotoxic DNA intercalating agents and topoisomerase inhibitors. These compounds bear two intercalating tricyclic ring systems connected by a linker of variable length and rigidity and represent the lead in the series of drugs called bisnafide and elinafide (Fig. **9**, X = H, Y = H, Me) [75,76].

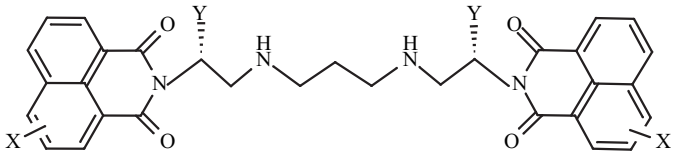

Fig. (9).

In the continued efforts to develop DNA-binding antitumor agents, dimers related to these compounds were synthesized. Bailly [77] reported the synthesis and molecular pharmacology of a furo bisnaphthalimide with a chain linker identical to that in elinafide. A study of the biochemical and biophysical data shows that dimerization reinforces the capacity of the drug to bind to DNA. Indeed, this dimer exhibits an enhanced selectivity toward GC (Guanine-Cytosine) sites compared to elinafide, and this suggests that the furan ring plays a part in the selectivity, possibly through hydrogen bonding interactions with the amino groups of the guanine residues. As a continuation of this work, Braña *et al*. (Fig **10**, X = O,S and Z = $(CH_2)_nNH(CH_2)_nNH(CH_2)_n$ or $(CH_2)_nNMe(CH_2)_nNMe(CH_2)_n$] [78] analyzed the importance on the biological activity of the orientation of the fusion of the heterocyclic ring, the replacement of the oxygen atom by a sulfur atom and the nature of the linker chain. It was found that the introduction of the π-electron rich furan ring oriented toward the *inside* of the molecule, or thiophene ring oriented toward the *outside* led to increases in the activity. A change in the nature of the linker chain of elinafide by methylation of the NH groups led to a decrease in activity.

These dimers all show high anticancer activity but they are very insoluble. In an effort to improve solubility, several new N-terminal bisnaphthalimidopropyl-substituted polyamine derivatives were prepared [79,80] and in these cases, the linker chains consist of the natural polyamines spermidine, spermine, putrescine and their corresponding oxy derivatives. These compounds show cytotoxic effects that depend on the length of polyamine linker and also on the number and nature of heteroatoms in the molecules. The best results were obtained for compounds with the shortest polyamine and without oxygen. The introduction of an oxygen atom in the α-position of the naphthalimido ring may have resulted in a loss of recognition of the compounds by the polyamine transporter.

2.1.2.3. Bisphenazine Compounds

Denny [81,82] reported the synthesis and relationships between biological activity and a variety of dicationic linker chain structures for a series of dimers of 9-methylphenazines (Fig. **11**). The length, rigidity and charge density on the chain were varied. There is a negative correlation between absolute IC_{50} and linker length, a trend evidenced by QSAR studies [83]. Recently, XR5944 [81] – one of the most active compounds reported [X = H, Z = $–(CH_2)_2NH(CH_2)_2NH(CH_2)_2–$] – has entered Phase I clinical trials [84] and its exceptional biological activity *in vitro*, *in vivo* and *ex vivo* could be related to a distinct DNA binding mode and, therefore, a novel mechanism of action that differs from topoisomerase I/II inhibition.

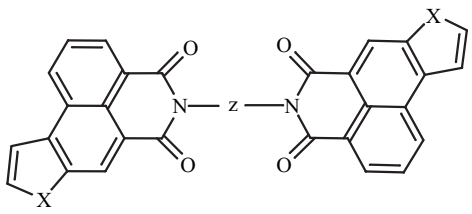

Fig. (10).

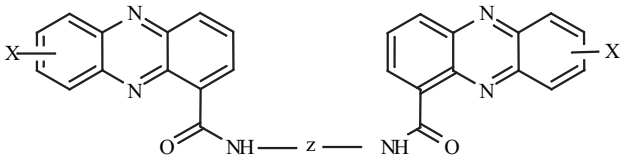

Fig. (11).

A combination of xenografts with 5-fluorouracil or irinotecan in human colon carcinoma cell lines has been investigated [85] and the results show additive activity *in vitro* against HT-29 and HCT-116 colon carcinoma cell lines and *in vivo* activity against HT-29.

2.1.2.4. Other Symmetrical Structures

The exploration of DNA-interactive drugs continued with the preparation of other dimeric derivatives with alternative substituted heterocycles, including phthalazine [86], benzo[*g*]indole [87], benzo[*g*]indazole [88], pyrrolo[2,3-*e*]indole [89] and 10*H*-quindoline [90]. All of these publications are concerned with analyzing the effect of the linker chain (length, flexibility) and/or the substituents in the aromatic rings (chloro, methoxy, dichlorophenyl, N-alkylcarboxamides) on the biological activity. The most active compounds are those that have the central connection $–(CH_2)_n–N(CH_3)–(CH_2)_n–$, where the best value for n is 2 or 3 carbon atoms, and a chloro-substituent in the aromatic unit. Rebeccamycin analogs [91] are microbial metabolites derived from indolocarbazole and these represent an important family of anticancer drugs. Such compounds may inhibit topoisomerase I and/or kinases depending on their chemical structures. In an effort to establish a structure activity relationship, a number of structural modifications were introduced [92] in the imide heterocycle, indole moieties and sugar moiety or by coupling sugar to the second indole nitrogen, preparing an "inverted" rebeccamycin and by replacing indole by azaindole. The conclusion concerning topoisomerase I inhibition is that the presence of a chloro-substituent on the indolocarbazole framework decreases the interaction with DNA and, in terms of inhibition, a variety of substituents can be added to the imide nitrogen. Furthermore, the sugar residue is required and when the indole is replaced by azaindole, the compounds are more selective. Cyclin-dependent kinase structure-activity relationships have also been investigated. More recently, other rebeccamycin derivatives have been evaluated [93] and the preliminary results suggest that there are other cellular targets involved in the biological activity. Other structures with DNA targeting capability are the diphenylcarbazoles [94,95] designed on the basis of other small molecules [96] that can interact selectively with A-T (Adenine-Thymine) base pairs within the minor groove of DNA. The best molecule incorporates two terminal dimethylaminoalkoxy side chains. McPhee [97] described bis(propargylic) sulfone crown ethers as DNA-cleaving agents and explored the complexation of the crown by an alkali metal ion and the importance of this ion on the activity.

Other molecules that interact with DNA have been reported in various studies on systems with peripheral chains containing benzene [98-104], pyridine [105] or naphthalene [106] rings. In order to obtain structure activity relationships, the authors considered the following points; the choice of substituents in the aryl rings and/or the flexibility and rigidity and/or substitution in the linker chain. When the peripheral chains contain benzene rings and the central chains are acyclic, the compounds are weakly cytotoxic. Replacement of the central nucleus by an unsaturated α,β-cyclohexanone ring (with an exocyclic double bond) leads in some cases to an increase in the cytotoxicity, which in some examples is comparable to melphalan (the reference compound) [101]. When this ketone incorporates an N-propenylphenylcarbonyl-4-piperidone [102,103], the compounds display different cell growth inhibition and may exert a selective toxicity against malignant cells. The exploration of a series of other α,β-unsaturated ketones (acyclic and cyclic), such as curcumin analogs, showed anticancer and antiangiogenesis activities that are enhanced by *ortho*-substitution of the aromatic ring [104] and the introduction of heteroatoms in the cyclic ketone unit. The good activity shown by pyridylmethane derivatives is correlated [105] to the presence of a 2-morpholino group on the pyridine moiety and electron-withdrawing substituents on the phenyl ring. Finally, an increase in the rigidity of the periphery of the molecule by the introduction of a naphthyl ring, the presence of an epoxide domain similar to that in azinomycin [106] and a flexible linker of five atoms with a heteroatom between the epoxide subunits are all structural requirements for improved activity.

2.1.3. Antibiotics

2.1.3.1. Anthraquinone Derivatives

Anthraquinone-based compounds currently occupy a prominent position in cancer chemotherapy and the anthraquinone mitoxantrone (MX) is an important compound used clinically as an anticancer agent. The planarity of this compound allows intercalation between base pairs of DNA in the conformation, while its redox properties are linked to the production of radical species in biological systems. The biological activity exhibited by anthraquinone compounds is greatly affected by both the position and nature of the different substituents. Huang described the cytotoxicity of a series of symmetrical 1,5- (Fig. **12**, A = SR, OCOR) [107-109] and 1,4- (Fig. **13**, n = 2,3, R= aliphatic chains and aryl or heteroaryl rings) [110,111] bis-substituted anthraquinones. When the subtituents in positions 1 and 5 are acyloxy groups, the highest activity corresponds to the presence of the non-polar butyryl chain in comparison to other chains with more or fewer carbon atoms [107]. The butyryl compound is 100 times stronger than mitoxantrone. This fact suggests that the polarity and the distance may be important; in addition, this compound is a potent antioxidant and protects normal cells from oxidative damage. However, the 1,5-bisthio derivatives [108] are less active compounds and only when R = $CH_2–CH_3$ or 4-$NH_2C_6H_4$ are the values comparable to those of mitoxantrone. A new mechanism of action has been explored for these derivatives and is related to telomerase enzyme inhibition [111,112]. Telomerase is a ribonucleoprotein that contains both an RNA and a protein component for the maintenance of telomere length. The presence of telomerase activity in tumors, combined with its absence in most normal tissue, has generated considerable interest in using telomerase inhibitors as cancer therapeutic agents. The 1,5-bisthio compounds did not exhibit any specific telomerase inhibitory activity and the optimal substituents in the 1,5-bisacyloxy derivatives were propionyloxy, pivaloyloxy and 2,4-dichlorobenzoyl.

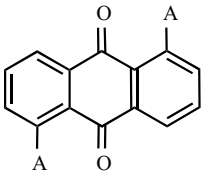

Fig. (12).

Further efforts to obtain compounds related to mitoxantrone led to the synthesis of 1,4-difunctionalized anthraquinones bearing amide groups. The presence of alkylamido groups is crucial to the activity and there are differences between the 1,4- and 1,5-isomers. Although all of the compounds bind through an intercalative mode [110], the 1,5-disubstituted isomers bind with their two side groups occupying adjacent triplex grooves – a situation in contrast with the 1,4-derivatives, which are positioned with both side groups in the same triplex groove. As far as the telomerase [111] activity is concerned, only the compounds with side chains $–(CH_2)_2–NH–(CH_2)_2–OH$ and $–(CH_2)_3–NH_2$ show potent telomerase inhibition and it seems that at least two carbons are required to separate the amine from the core unit in order to obtain good activity.

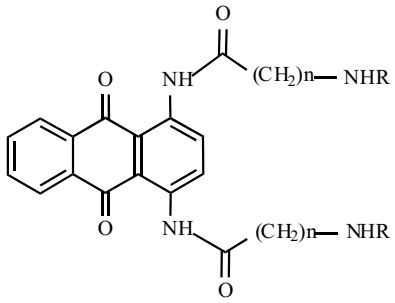

Fig. (13).

2.1.3.2. Quinone Derivatives

The quinone structure is common in numerous natural products that are associated with antitumor, antibacterial, antimalarial and antifungal activities, though few of these compounds are symmetrical. The variable capacity of quinones to accept electrons is due to the electron-withdrawing or -donating substituents on the quinone moiety and these modulate the redox properties. When the substituents are crown ethers, the redox properties are affected and these molecules are classified as redox-switched crown ethers. Although research in this area remains active, a survey of the literature did not reveal any biological data for these redox-switched crown ethers in terms of their antitumor activity. Huang *et al*. [113] observed that the bisnaphthoquinone thiol-crown ethers (Figs. **14** and **15**), with alkyl chains from one to five carbon atoms, are more active than the analogous monomers and represent an increasingly attractive target in the study of new antitumoral agents.

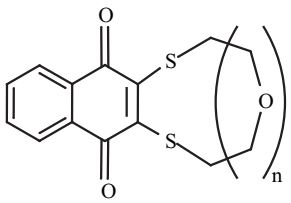

Fig. (14).

2.1.4. Polyamines

During the past twenty years, numerous symmetrical derivatives and analogs of putrescine, spermidine and spermine have been synthesized with the aim of generating a new type of anticancer drug. These natural polyamines are aliphatic cations with multiple functions and are essential for

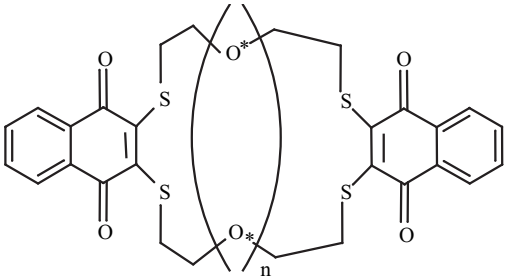

Fig. (15).

cell growth. Numerous ideas have been put forward to explain their mechanism of action [114,115] and these include induction of apoptosis [116], induction of acetylCoA:spermidine N^1-acetyltransferase [117], interaction with nucleic acids [118] (which is one of the more compelling), mitochondriotoxicity [119] and calmodulin antagonism [120] among others. The most widely assayed cytotoxic polyamine analogs have been tetra- or pentamines [121-124] and, more recently, there has been great interest in exploring the antiproliferative activity of their higher homologs [125], such as octamines, decamines, dodecamines and tetradecamines, which are named "oligoamines". These "oligoamines" (Fig. **16**) are more cytotoxic than the polyamines tested previously and the best are tetradecamines and dodecamines.

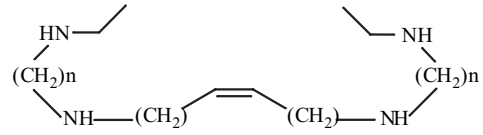

Fig. (16).

In addition, there is a general correlation between the effect of these chains on *in vitro* DNA aggregation and their cytotoxic effects, these results corroborate the hypothesis that the structures of polyamine analogs affect their DNA binding abilities. These interactions with DNA were confirmed by Suda [Fig. **17**, R = $(CH_2)_3NH_2$] [126], who studied 2,7-diaminoalkylamino-1,8-naphthyridine derivatives that bind with the pyrimidinic bases cytosine and thymine by protonation of the nitrogen in the naphthyridine chromophore. This fact may provide a new approach for the design of a molecular element for base recognition.

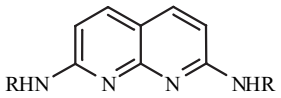

Fig. (17).

2.2. Drugs that Target Proteins

2.2.1. Cyclin-Dependent Kinase Inhibitors

Cancer has been recognized as a disease involving uncontrolled cell proliferation and, as such, the genes that regulate cell proliferation become targets in cancer chemotherapy. The cell cycle consists of a series of highly regulated processes that result in the duplication of a cell and one theory suggests that cell cycle progression is controlled by the sequential activation of a series of cyclin-dependent kinases. The D-type cyclins associated with cyclin-dependent

kinases 4 and 6 are believed to play a critical role, particularly in the G1 phase of the cell cycle. For this reason, compounds that interfere with cyclin-kinases are expected to be promising new therapeutic agents for the treatment of cancer. Some molecules with this mechanism of action are bisindolocarbazoles (Fig. **18**, X = halogen, H, CF_3, OMe, R = H, Me) [127,128], which showed high potency towards CDK4 (cyclin dependent kinase) and CDK2 inhibition and are capable of inhibiting cell growth in human tumor cell lines and some diadamantane derivatives [129].

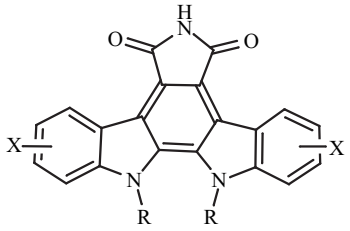

Fig. (18).

2.2.2. Inhibitors of Tubulin

Tubulin contributes to the maintenance of cell shape, intracellular transport and mitosis. The vinca alkaloids, the taxanes and the epothilones act by this mechanism. The most recent bis compound proposed as a microtubule inhibitor is BPR0L075 [130], an indole derivative that inhibits tubulin polymerization through binding to the colchicine site of tubulin. This compound also causes an increase in cyclin B1 levels and a mobility shift of Cdc2 and Cdc25C.

2.2.3. Choline Kinase Inhibitors

Choline kinases play a role in growth promotion or signal transduction in carcinogenesis and are a novel target for the design of antitumor drugs. Choline kinase is generated after mitogenic stimulation by the growth factor phosphorylcholine, which is increased in human tumors. Campos *et al*. [131-135] synthesized and biologically assessed a large number of symmetrical bispyridinium compounds (Fig. **19**, Z = $(CH_2)_n$, benzene, cyclopropane, R = aryl rings, cyclic aliphatic amines] with different linkers to connect the pyridinium cations. The relationship between the antiproliferative activity and the distance between the cationic heads is not clear, but it can be suggested that the enzymatic inhibitory potency is closely related to the size of the spacer, with the higher inhibitory activity found for the 3,3'-biphenyl spacer. The increase in choline kinase inhibition is associated with an increase in antiproliferative activity.

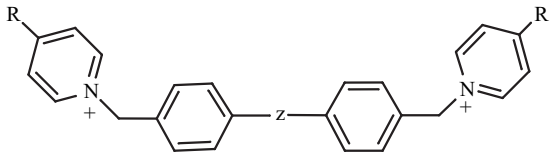

Fig. (19).

3. APOPTOSIS AND SYMMETRY

This section first describes structures in terms of their mechanisms of action, which are related to the aforementioned cytotoxic agents, and then reports a wide variety of other symmetrical structures that induce apoptosis by different mechanisms.

3.1. Metal Complexes

3.1.1. Copper Complexes

The behavior of organic copper complexes depends on the nature of the ligands (Figs. **20** and **21**). When the ligands are quinolines or phenanthroline [136], the compounds are proteasome inhibitors and it has been reported that proteasome inhibitors are tumor cell apoptosis inducers [137]. On the other hand, when the ligands are diarylphosphines, the derivatives are active in the p53 pathway [64]. The p53 pathway is known to arrest the growth of cells and induce apoptosis.

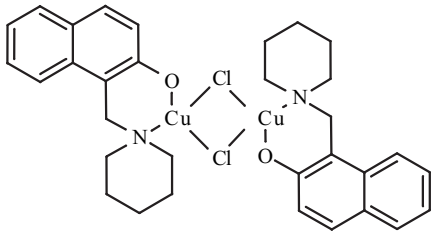

Fig. (20).

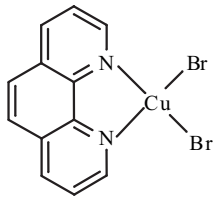

Fig. (21).

3.1.2. Vanadium Complexes

Certain vanadium complexes [65,138] have anticancer activity against human cancer cells *in vitro* (testicular, multiple myeloma, glioblastoma, ovarian, prostate, breast, leukemia). Some of these compounds, particularly when one of the ligands is a phenanthroline derivative [138,139], are new potent apoptosis inducers associated with a loss of mitochondrial transmembrane potential, the generation of reactive oxygen species and depletion of glutathione.

3.1.3. Platinum Complexes

Bis(3-aminoflavone) dichloro Pt(II) complexes (Fig. **22**) [140] cause morphological features typical of apoptotic cells,

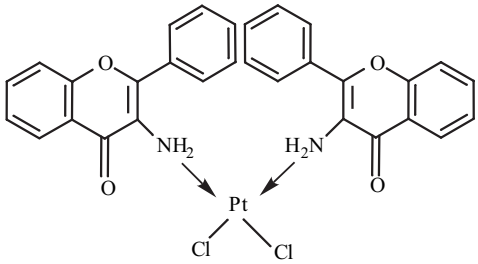

Fig. (22).

such as a decrease in cell size, chromatin condensation and nuclei fragmentation. These compounds are also less toxic than cisplatin. On the other hand, the Pt(IV) complexes with the adamantylamine ligand (Fig. **23**) [59,141] induce apoptosis by modulating the levels of protein p53.

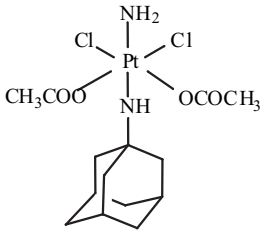

Fig. (23).

3.2. Curcumin Analogs

Fluoride curcumin compounds (Figs. **24** and **25**) [104, 142] induce mitochondrial uncoupling and it is widely accepted that several mitochondrial events control the apoptosis process [37]. These molecules promote the permeability transition pore opening, mitochondrial swelling and release of cytochrome c.

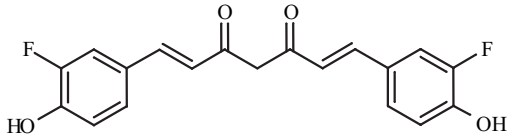

Fig. (24).

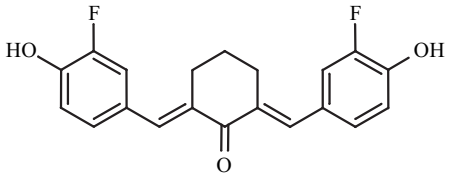

Fig. (25).

3.3. Quinones

The symmetrical quinones have been reported as antitumoral agents [113]. However, our current understanding of the mechanism of action has led to the conclusion that these compounds (Fig. **26**) can induce apoptosis associated with expression of antiapoptotic Bcl-2 protein [143] and p53 protein [144].

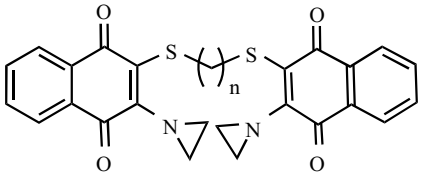

Fig. (26).

3.4. Polyamines

One of the mechanisms of action of polyamines is apoptosis induction [114-116] – either alone [145] or in combination with other drugs [146]. These compounds cause downregulation of the anti-apoptotic Bcl-2 and Bcl-XL proteins and increase the level of pro-apoptotic Bax protein and caspase cascade activation.

3.5. Symmetrical Agents that Target the Extrinsic Pathway

A structural relationship or trend among the molecules whose main mechanism of action is related to the extrinsic pathway has not been found. A bis-benzylidenecyclopentanone derivative was reported (Fig. **27**) [147] that induces apoptosis through a membrane-mediated mechanism. This finding was supported by upregulated expression of Fas (CD95/APO1) (but not Fas L) and by a caspase-8-dependent but mitochondrial caspase-9-independent pathway and upregulation of p53. On the other hand, 1,1-bis(3'-indolyl)-1-(*p*-substitutedphenyl)methanes (Fig. **28**) have been investigated as apoptosis inducers through the modulation of the extracellular signal-regulated kinase and peroxisome proliferator-activated receptor gamma (PPAR-gamma) signaling pathways [148-150]. However, it has recently been reported that these molecules act as Nur 77 agonists [151], activate the nuclear receptor and downstream responses (including decreased cell survival) and induce cell death pathways including tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). On the other hand, these compounds do not affect FasL.

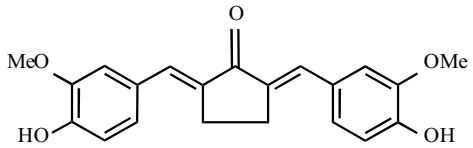

Fig. (27).

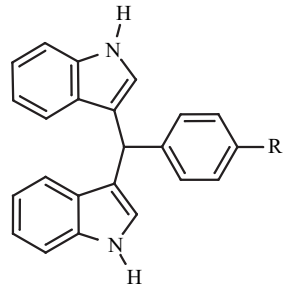

Fig. (28).

3.6. Symmetrical Agents that Target the Intrinsic Pathway

3.6.1. Agents that Target the Mitochondria

Diphenylfuran diamidines (Fig. **29**) represent an important class of DNA minor groove binders [152].

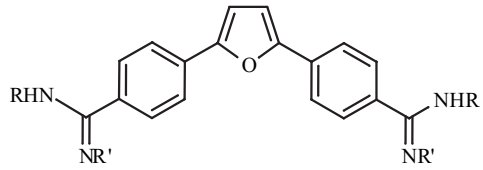

Fig. (29).

To exert their cytotoxic effects, these compounds must first enter into the cell and reach the nuclear compartment, although the forces that drive the drugs into cell nuclei or the influence that the molecular structures have on the cell distribution are not well known. It has been observed that

the introduction of aromatic substituents [153] into diphenylfuran diamidines represents a novel strategy to control the intracellular compartmentalization of these DNA binding agents and directs them to mitochondria. The mitochondria contain a significant proportion of nucleic acids and play a pivotal role in the propagation of the apoptotic signal through which many anticancer drugs kill cells.

3.6.2. Agents that Target SMAC/DIABLO and Bcl-2

Cephalostatin I [154], a bis steroidal marine natural product, selectively induces the intense release of active SMAC/DIABLO without cytochrome c and subsequent apoptosome formation. This compound also changes the mitochondrial morphology and leads to overexpression of the anti-apoptotic protein Bcl-XL. Bisphenol A diglycidyl ether [155] is a peroxisome proliferator-activated gamma-receptor antagonist that stimulates the mitochondrial release of apoptosis inducing factor (AIF) and cytochrome c and is a second mitochondria-derived activator of caspase/direct IAP-binding protein with a low pl value (SMAC/DIABLO).

1,2-[Bis(1,2-benzoisoselenazolone-3-(2*H*)-ketone)]ethane (Fig. **30**) is a novel organoselenium compound [156,157] that inhibits the growth of prostate tumoral cells and induces apoptosis with a decrease in the expression of Bcl-2 but an increase the levels of bax.

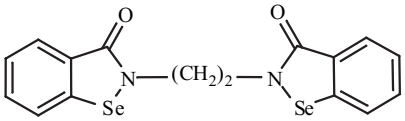

Fig. (30).

Another compound that modulates the expression of Bcl-2 is the triazine derivative 12459 [158], which induces a delayed apoptosis that causes overexpression of the Bcl-2 protein. Finally, 2,5-bis[4-(3-dimethylaminopropoxy)styryl]-1,3,4-thiadiazole [159] induces an apoptotic reaction by downregulation of Bcl-X(L) expression, upregulation of bax expression and an increase in caspase-3 activity.

3.7. Agents that Target Modulators of the Apoptosis Pathways

3.7.1. p53

1,4-Bis(1-naphthyl)-2,3-dinitro-1,3-butadiene [160] induces apoptosis through upregulation of the p53 oncosuppressor-protein.

3.8 Agents that Target the Common Pathway: Caspase Activators

3.8.1 Synthetic Activation of Caspases

Caspase-activating agents, which are also known as death switches, can be produced by the fusion of one or more chemically inducible dimerization domains. These drugs lead to protein aggregation inside the cell and this induces caspase activation and downstream apoptosis. Molecular symmetry is an important property for this mechanism. Recently were described (Figs. **31** and **32**) [161,162] a number of symmetrical derivatives as apoptotic inducers by caspase-3 activation.

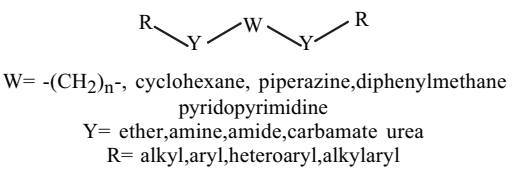

Fig. (31).

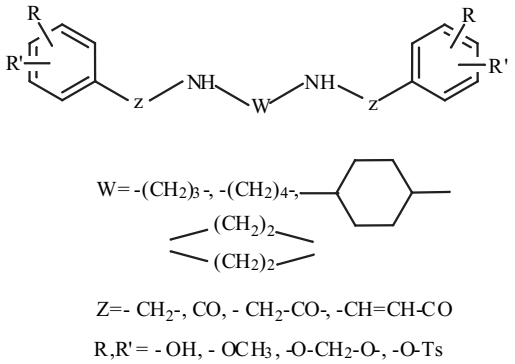

Fig. (32).

Lin [163] described 1,6-diaryl-3(*Z*)-hexen-1,5-diynes and their derivatives as caspase-3 activators and related these properties to the presence of heteroatoms close to the C-1 and C-6 positions of enediyne domains.

3.9. Other Apoptosis Mechanisms

Other types of symmetrical structures included in this category are bisphosphonates [164], which act by an as yet undetermined mechanism – although the apoptosis is probably related to the induction of the expression of factors such as growth transforming factor-β or cell cycle regulating factors.

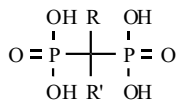

Fig. (33).

4. CONCLUSION

The present work reveals a clear trend in our studies on new molecules with antitumoral properties, most of which have molecular symmetry as a structural characteristic. This review only includes references published since 2002 and this is due to the ever-increasing amount of work carried out in this area. The mechanistic relationship between symmetry and cytotoxicity or apoptosis is yet to be demonstrated but in many cases, this activity cannot be attributed to random action. However, establishing any type of relationship between molecules that possess symmetry and their mechanisms of action is an extremely difficult and complex task. In some cases, such as drugs that interact with DNA (e.g., platinum compounds, acridines, bisnaphthalimides, bisphenazines, benzoindoles, benzoindazoles, anthraquinones and polyamines), the interest in bifunctional compounds originally stemmed from the possibility of enhancing the binding constant to DNA (in comparison to that of the

corresponding monomers) and slowing dissociation rates from DNA. Hydrogen bonding and stacking interactions usually play a crucial role in determining DNA sequence-specific reading for bisintercalators. On the other hand, increasing the overall volume occupied by the ligand could afford greater opportunities for sequence selectivity. In addition, the bisanthraquinones are potent antioxidants and protect normal cells from oxidative damage. In the case of the polyamines, it has been suggested that DNA is probably the primary target, although another biochemical target of these bis derivatives could be the natural polyamine metabolism. In relation to apoptosis and symmetry, the majority of authors do not establish structure activity relationships. One of the mechanisms involved in apoptosis is the activation of caspases, which is probably the most significant type of action given that all the apoptotic routes converge on one of these enzymes (caspase-3). All of the caspases are synthesized in the form of inactive precursors (proenzymes) that are subsequently activated by self-proteolysis (autocatalytic cleavage) or other proteases [165]. It can therefore be assumed that a series of adaptative molecules exist, which interact with a specific point of the amino-terminal prodomains of the procaspases. If two proenzymes that carry these adaptive structures meet each other within an appropriate distance, they are able to aggregate together. This aggregation is sufficiently strong that a self-activating internal self-proteolysis process can occur, with the two large units and the two small units released. These four units associate with each other to form a heterotetramer, which is the active form of the caspase. At the same time, this active form of caspase can act on other procaspases, thereby initiating what is known as a caspase cascade – an amplifying system of the apoptotic signals and a direct result of the original signal. For this reason, molecular symmetry could help in the interaction between two proenzymes and activate the caspase cascade. In many other compounds, the possible biological role of symmetry in the cytotoxic activity has not been described, although these do represent good candidates for antitumoral drugs and further studies to better understand the mechanism of action are needed. For example, drugs that target proteins, such as cyclin-kinase inhibitors, are competitive inhibitors that are capable of inhibiting cell growth in the human tumor cell lines. They are also selective inhibitors of the phosphorylation of serine 780 on pRb. As well, in a similar way to tubulin and choline kinase inhibitors, these behavior are not explained in terms of symmetry. Finally, it is important to highlight the structure/activity correlation found in a number of these antitumoral compounds that provides evidence of the importance of molecular symmetry.

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