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Review Paper

Chiral discrimination of metal–based chemotherapeutics Co(II), Cu(II) and Zn(II) towards the ultimate drug target–DNA

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Abstract: Understanding the interaction of pharmaceutical agents to DNA is essential for underlying their mode of action, site, sequence and structural specificity of their binding reactions. Chirality of a complex is a pre–requisite criterion for an appropriate model drug design, since usually two enantiomers of the same metal complex have different binding constants and recognition properties. Interaction between small molecules and DNA provides a structural guideline in rational therapeutic drug design regime and to understand the mechanism of action of DNA–targeted drugs. We have described briefly the overview of chiral late 3d–transition metal–based (Co(II), Cu(II) and Zn(II)) chemotherapeutic agents which show enantioselective and preferential binding to inherently chiral DNA molecule.

Introduction

There has been considerable interest in the binding studies of small molecules with DNA [1–6] owing to their diverse applications *viz.,* DNA–target chemotherapeutic agents [7,8], highly sensitive molecular probes for nucleic acids [9–11], enantioselective catalysts [12], etc. Understanding the interaction of pharmaceutical agents to DNA is essential for underlying their mode of action, site, sequence and structural specificity of their binding reactions.

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Interaction between small molecules and DNA provide a structural guideline in rational drug design regime for the synthesis of new, improved chemical drug entities with enhanced or more selective activity, thereby greater clinical efficacy and lower toxicity.

DNA, an inherently chiral molecule has a polymorphic structure with polyanionic nucleotide chains and sugar phosphate backbone [13]. The asymmetric D–ribose and D–2–deoxyribose units contain several stereogenic centers, whose configuration is important in overall DNA structure. It is well known that DNA does not exist in a single three–dimensional structure, but can

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adopt different conformations which are defined both locally and macroscopically by different structural parameters. Double stranded DNA commonly adopts a right–handed helical conformation that of B– and A–form, however, they differ in the conformation of sugar (C2′–endo for B–DNA and C3′–endo for A–DNA, and in helical parameters).

The term 'chirality' or handedness describes the structural property of an object that is non–superimposable on its mirror image. Life is a typical chiral system and chiral phenomena are ubiquitous in nature from the macroscopic to the molecular level, ordinarily, proteins and DNA wind in right handed helixes; left–handed versions are rare and true mirror image versions do not appear in nature. Right and left–handed amino acid molecule exists at different energy levels as a result of the asymmetric weak nuclear force; those in organisms are almost always left–handed. The elementary particle known as neutrino exists only as a left–handed object [14]. Because of the chirality of its key molecules, human chemistry is highly sensitive to enantiomeric differences. Some examples of chiral structures are given in Figure 1.

Chiral drugs are at forefront in pharmaceutical drug research; over one–third of marketed drugs worldwide are chiral, and regulators will now only approve new chiral drugs in single enantiomeric form, preferably with their *in vivo* profile. The introduction of chirality not only enforces stereoselective specific drug interaction but also promotes the formation of active compounds with therapeutic benefit as most of the targets of drugs at the molecular level *viz.,* DNA, RNA and proteins, etc. are chiral in nature. The growing use of enantiomeric drugs is closely related to structure–function relationship. The structure–function relationship in nature is so powerful that when a functional disorder manifests in the form of disease, it can be handled in many cases only by using a molecule of specific chiral structure. The preferential interaction of one enantiomer of a racemate with chiral macromolecules of the body leads to expressed pharmacokinetic and pharmacodynamic effect. The term "eutomer" has been used for more potent isomer and "distomer" for less potent one in terms of their pharmacological effect [15]. Enantiomers can be absorbed, distributed, metabolized and excreted differently. Further, disease states, route of administration, genetic variability and drug–interactions may be stereospecific [16].

Brief Background

The serendipitous discovery of cisplatin–a well known anticancer drug clinically in use, for treating solid tumors [17] has fostered a new discipline of medicinal inorganic chemistry dealing with metal–based drug design. Most of the chemotherapeutic drugs exert their cytotoxic effect and thereby therapeutic effect either by direct interaction with DNA or by inhibition of topoisomerases (preventing DNA relaxation) [18]. Different binding modes process cellular machinery differently at the molecular target, i.e., binding to specific DNA sequence and/or structures. Understanding the features that contribute to enhanced DNA binding by small ligands or metal complexes is crucial for the development of drugs targeted to DNA. Many properties of metal complexes, such as size, oxidation state, geometry and chirality could influence the binding mode.

A large plethora of chemotherapeutic anticancer agents currently used are targeted to DNA [19,20]. They interact with DNA duplex generally by three different binding

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modes, namely, DNA intercalation [21], covalent binding [22] and non–covalent binding (electrostatic, groove binding and hydrogen bonding) [23,24]. Many classical DNA intercalators have been tested as antitumor drugs, but their use is limited because of the lack of specificity and frequent side effects (non–covalent interactions play a pivotal role in reducing the toxicity as well as to increase the DNA–binding specificity and consequently greater binding strength). The overall handedness of DNA molecule plays a major role in the recognition of DNA by chiral molecules due to two–pole complementary principle [25]. Furthermore, the use of stereochemistry can give clear insight into the mechanism of action allowing the discrimination between unspecific interactions, which are common to both enantiomers and specific contacts that give rise to enantioselectivity. This phenomenon owes importance as many small molecules that interact with DNA *in vitro* do not behave in similar manner *in vivo* and this is one of the major obstacles in the development of drugs based on DNA binding (usually, it is difficult to quantify the differential binding of two enantiomers with DNA as there are subtle differences of binding or repulsive forces) [26].

Chiral molecules play a critical role in the exploitation of three–dimensional space at the target site and regulate stereoselectivity in a highly organised fashion. Consequently, the appropriate design of enantiomeric tumor inhibiting motifs or compounds is well–understood. Chirality in metal complexes can arise by the asymmetry of ligands or in an inherently achiral coordination mode (such as square planar complexes) or by coordination chirality such as Λ or Δ isomers of octahedral complexes of bidentate or terdentate ligands [27].

Relevance of Chirality in Pharmaceuticals

Chirality has a well known relevance in the field of medicine and has played important roles in the quest for new and more efficacious drugs. Both (S)–ibuprofen and (S)–ketoprofen are chiral switch drugs of popular racemates (Figure 2). The use of (S)–enantiomers of these drugs in therapy reduces total dose and toxicity that is associated with (R)–enantiomers. It has been observed that in case of ketoprofen, (S)–(+)–ketoprofen is several times more potent than the racemate. Similarly, omeprazole is a gastric antisecretory proton pump inhibitor. The chiral switch drug esomeprazole which is (S)–(−)–enantiomer of omeprazole has therapeutic benefit than its (R)–enantiomer. Amlodipine, an antihypertensive drug exhibits chirality and receptor binding studies has shown (S)–(−)–isomer of amlodipene has higher L–type calcium channel blocking activity than its (R)–(−)–isomer [28].

Chiral diamines have been used as ligands–mostly ethylenediamine analogs and 1,2–diaminocyclohexane and their efficiency as antitumor drugs have been shown to be dependent on stereochemistry [29]. Most impressive examples in literature are the new drugs derived from (R,R) and (S,S) enantiomers of trans 1,2–diaminocyclohexane (1,2–DACH), which give rise to enantiomeric complexes with metal and labile ligands such as chloride or oxalate. The (R,R)–enantiomer of (1,2–DACH) oxalatoplatinum(II) is more potent as an anticancer drug when compared with (S,S)–analog and has a spectrum of activity and mechanisms of action and resistance different from those of cisplatin and carboplatin exhibiting less toxic effects. For these reasons, the FDA has approved this drug under the generic name oxaliplatin used in several countries for the treatment of

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colorectal cancer which is second leading cause of cancer–related death in the United States [30].

Lippard *et al.* reported structural evidence for the importance of chirality in mediating the interaction between oxaliplatin and duplex DNA [31]. Oxaliplatin has a non–hydrolyzable diaminocyclohexane (DACH) carrier ligand which is maintained in the final cytotoxic metabolites of the drug. Oxaliplatin has shown a wide antitumor effect both *in vitro* and *in vivo*, a better safety profile than cisplatin and a lack of cross–resistance with cisplatin and carboplatin.

Chiral Transition Metal–based Drug Design and Enantiomeric Disposition for DNA

There has been considerable interest in the DNA properties of a number of ruthenium(II) complexes for developing novel probes of DNA structure or new therapeutic agents. Ruthenium complexes containing planar aromatic ligand can be attached to metal in a controlled manner, exhibit strong visible absorbance due to localized metal–to–ligand charge transfer (MLCT), and strong fluorescence emission making it a convenient to monitor the DNA binding process. The complex $[Ru(phen)_2DPPZ]^{2+}$ (DPPZ=dipyridophenazine), shows two distinct binding stoichometries of Δ and Λ–DPPZ isomers that bind to DNA by classical intercalation and have been validated by florescence energy transfer experiments and relative viscosity measurements [32]. There are however, limited reports on DNA binding and biological properties of enantiomeric pairs of 3d–transition metal ions and understanding their related structure–activity relationship. Copper have been used since antiquity in metal–based therapies. Copper is widely distributed in the biological system and it is the most familiar redox metal serving diverse biological functions [33–35]. It has been demonstrated that copper accumulates in tumors due to selective permeability of the cancer cell membranes [36–38]. Because of this, a number of copper complexes have been screened for anticancer activity and some of them were found active both *in vitro* and *in vivo* [39–41]. Cu(II) complexes are regarded as the most promising alternatives to cisplatin as anticancer drugs. Serum copper levels correlate with tumor incidence, tumor weight, malignant progression, and recurrence in a variety of human cancers: Hodgkin's lymphoma, sarcoma, leukemia and cancer of the cervix, breast, liver and lung [42–45] as well as brain tumors [46,47]. Consistently, the high serum and tissue levels of copper found in many types of human cancers support the idea that copper could be used as a potential tumor–specific target.

Cobalt complexes have received less attention in comparison to other transition metal complexes [32–34] although they exhibit interesting metallo–intercalation and DNA cleavage properties [35,48]. Besides this, cobalt containing complexes offer an exciting possibility for oral delivery of a wide variety of peptide based drugs–most efficient chemotherapeutics. Currently, these peptide–based drugs are given intravenously because of digestion, degradation and poor absorption. They covalently bind to the cobalt containing coenzymes vitamin B_{12} and are readily transported from the digestive system to circulation *via* vitamin B_{12} transport system [49].

Similarly, zinc is second most abundant essential transition metal ion in humans following iron, divalent zinc is an integral part of all biological systems. Zn ions

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possess nutritional features important to human health and health care. Zinc plays important role in genetic stability and function [50,51]. Mechanistically, zinc has significant impact on DNA as a component of chromatin structure, DNA replication and transcription and DNA repair [52]. Zinc enzymes efficiently catalyze the hydrolysis of nucleic acid under physiological condition in the living system. Many proteins possess a Zn–containing motif that serves to bind the DNA embedded in their structure. Structural changes induced by Zn(II) on DNA suggest that this cation can bind to both the nucleobase and the phosphate group [53]. Zinc is vital for recovery of leukemic cells because zinc is required for proper functioning of genetics, immunity, formation of red blood cells, organ, muscle and bone function, cell membrane stability, cell growth, division and differentiation [54]. Zinc has beneficial interactions with several chemotherapy drugs.

In the past decade, our research interest was primarily focused on enantiomeric discrimination of some new chiral transition metal–based antitumor drug entities, which could exhibit improved efficacy against a broader spectrum of tumor phenotypes and also possess fewer side effects as demonstrated by platinum drugs. With this rationale, we have designed some modulated metal–based enantiomeric complexes from organic ligands bearing biologically significant pharmacophore. We have evaluated the effect of chirality in L– and D–enantiomeric complexes towards DNA, which is the ultimate drug target.
Chiral complexes of L– and D–tryptophan and (1R,2R)–(2)–1,2–DACH) of late 3d transition metal ions (Co, Cu and Zn) were synthesized, thoroughly characterized and evaluated as potential chemotherapeutic drug entities (Figure 3) [55].

Both enantiomers of complexes bind DNA noncovalently *via* phosphate interaction with slight preference of metal center for covalent coordination to nucleobases. The K_b values of L–enantiomer, however, possess higher propensity for DNA binding in comparison with the D–enantiomeric analogs. Two different enantiomers bind to DNA by a similar non–covalent electrostatic mode; however, the extent of interaction is different which outlines the effect of chirality. *In vitro* anticancer activity of L–enantiomeric complexes were screened against 14 different human carcinoma cell lines of different histological origin, and the results reveal that L–enantiomeric form of copper complex exhibits significant antitumor activity and was particularly selective for MIAPACA2 (pancreatic cancer cell line).

To evaluate the biological preference of chiral drug candidates for molecular target DNA, new potential metal–based chemotherapeutic agents, enantiomeric complexes of late 3d transition metals Ni(II), Cu(II) and Zn(II) derived from (R)– and (S)–2–amino–2–phenylethanol with $–CH_2–CH_2–$ linker were synthesized and thoroughly characterized. Interaction studies of R– and S–enantiomeric complexes with calf thymus DNA in Tris buffer were studied by electronic absorption titrations, luminescence titrations, cyclic voltammetry and circular dichroism. The results reveal that the extent of DNA binding of (R)–enantiomer of copper was highest in comparison to rest of the complexes *via* electrostatic interaction mode. The nuclease activity of (R)– and (S)–copper complex with supercoiled pBR322 DNA was further examined by gel electrophoresis, which reveals that (R)–enantiomeric form of copper complex exhibited a remarkable DNA cleavage activity (concentration dependent) with pBR322DNA, and the

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cleavage activity of (R)– and (S)–enantiomers of copper complex was significantly enhanced in the presence of activators. The activating efficiency follows the order Asc>H_2O_2>MPA for (R)–form, and reverse order was observed for (S)–form, because of the differences in enantioselectivity and conformation. Further, it was observed that cleavage reaction involves singlet oxygen species and superoxide radicals *via* oxidative cleavage mechanism. In addition, (R)–form of copper complex exhibited significant inhibitory effects on the topoisomerase II (topo II) activity at a very low concentration 24 µM, which implicates that R–form of copper complex was catalytic inhibitor of human topo II.

Similarly, a tailored series of Cu(II) and Zn(II) complexes was synthesized from a Schiff base of 2–amino–1–propanol (chiral auxillary) with 2–amino–3–formyl chromones [56]. Chiral Schiff base ligands (R)–/(S)– 2–amino–3–(((1–hydroxypropan–2–yl)imino) methyl)–4H–chromen–4–one (L1 and L2) derived from 2–amino–3–formyl chromone and (R/S)–2–amino–1–propanol and their Cu(II)/Zn(II) complexes (R1, S1, R2 and S2) were synthesized. The DNA binding studies of the complexes with calf thymus were carried out by employing different biophysical methods and molecular docking studies that revealed that complexes R1 and S1 prefers the guanine–cytosine–rich region, whereas R2 and S2 prefers the adenine–thymine residues in the major groove of DNA. The relative trend in K_b values followed the order R1>S1>R2>S2. This observation together with the findings of circular dichroic and fluorescence studies revealed maximal potential of (R)–enantiomeric form of complexes to bind DNA. The cleavage activity of R1 and R2 with pBR322 plasmid DNA was examined by gel electrophoresis that revealed that they are good DNA cleavage agents; nevertheless, R1 proved to show better DNA cleavage ability. Topoisomerase II inhibitory activity of complex R1 revealed that the complex inhibits topo II catalytic activity at a very low concentration (25 µM). Furthermore, *in vitro* antitumor activity of complexes R1 and S1 were screened against human carcinoma cell lines of different histological origin.

Recently, we prepared L–/D–penicillamine based enantiomeric Zn(II) complexes of 1,10–phenanthroline in our lab [57] and structural elucidation was done by various spectroscopic techniques. The interactions of the complexes with CT DNA have been explored by absorption, fluorescence and CD measurements, revealing that both the complexes interact with DNA *via* electrostatic binding. All the corroborative results indicated the enantiopreferential selective binding of L–form of the complex over the D–form. A gel electrophoretic pictogram of the L– and D–forms of complexes demonstrates their ability to cleave pBR322 DNA through hydrolytic process; validated by T4 religation assays; furthermore, the L–form of the complex exhibited more pronounced cleavage than the D–form. However, both complexes preferred the minor groove of the DNA double helix. Interaction studies with mononucleotides revealed that both the enantiomers possess high affinity towards the A–T base pairs of DNA, consistent with the previous reports on stereospecific selectivity of Zn(II) complexes. These studies were further supported by molecular docking studies and the resulting binding energy of docked metal complexes1a and 1b were found to be –306.4 and –289.1 $KJmol^{-1}$, respectively. The more negative relative binding energy of L–form of complex suggests greater propensity for DNA than the D–enantiomer.

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Copper–based potential chemotherapeutic drug entities (R)– and (S)–enantiomers were designed, synthesized and evaluated for *in vitro* DNA binding, cleaving capability and *in vivo* genotoxicity [58]. The structural elucidation of complexes was done using elemental and spectroscopic data while the (R)–enantiomer of Cu(II) complex was studied by single crystal diffraction (Figure 4).

In vitro DNA binding profiling of both (R)– and (S)–enantiomers of complexes was carried out to evaluate their enantioselectivity, exhibiting a remarkable degree of enantioselectivity in their interaction with DNA, with the (R)–enantiomer exhibiting greater DNA binding propensity. Interaction between complexes and pBR322 DNA was evaluated by agarose gel electrophoresis assay; both the (R)–enantiomeric complexes exhibit effective DNA cleavage and proceed *via* an oxidative pathway. Furthermore, the *in vivo* genotoxicity of the (R)–enantiomer of complex was evaluated by micronucleus testing on bone marrow cells and comet assay in peripheral blood lymphocytes. These results support our contention that the (R)–enantiomer of complex was a suitable chemotherapeutic drug candidate showing reduced toxic effects on normal cells as compared to cisplatin and an antioxidant (EVOO).

Conclusion

The emerging market of enantiopure drugs has awakened the researchers in medicinal chemistry to design and synthesize enantiomerically pure form of drugs. Since, drugs are targeted mostly to bio–macromolecules *viz.,* DNA and proteins which are inherently chiral in nature, therefore, the interaction of metal–based drug entities with DNA has proven to be highly sensitive to enantiomeric differences and thus can promote formation of better, efficacious drugs with improved therapeutic potential at the molecular level. In this review, we have briefly described the profound role of chirality in enantiomeric forms of transition metal–based drug entities {(Cu(II) and Zn(II)} which are aimed to act as antitumor chemotherapeutic drugs. This review will help to unravel the subtle differences in behavior of enantiomeric complexes towards their molecular target DNA and their structure–activity relationship.

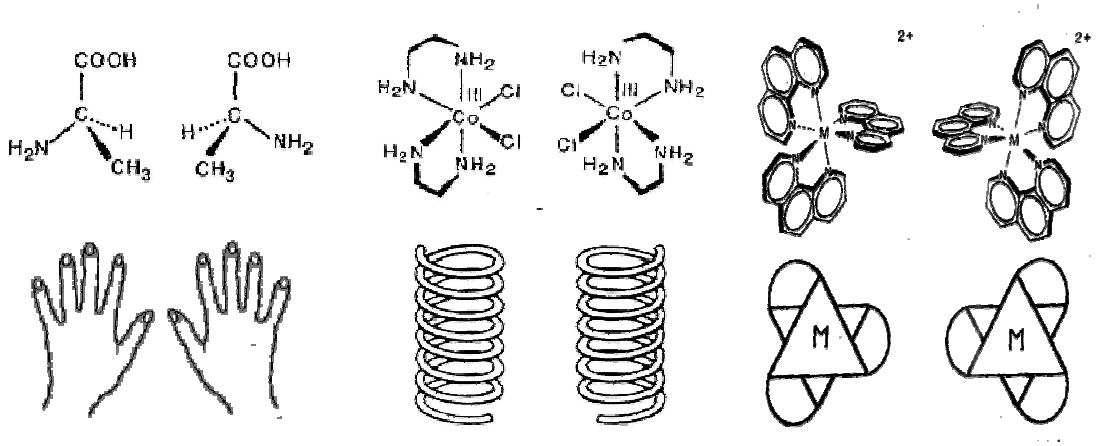

Figure 1. Depiction of enantiomeric pairs.

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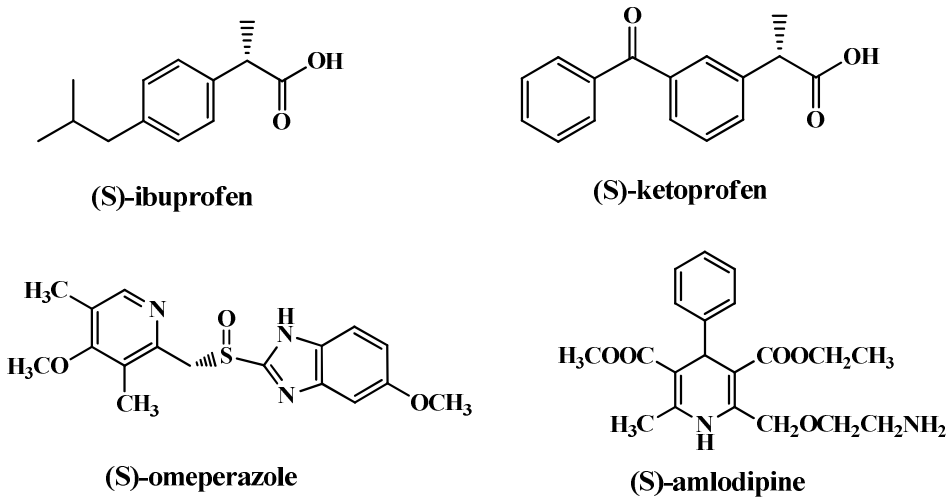

Figure 2. Some chiral switch drugs.

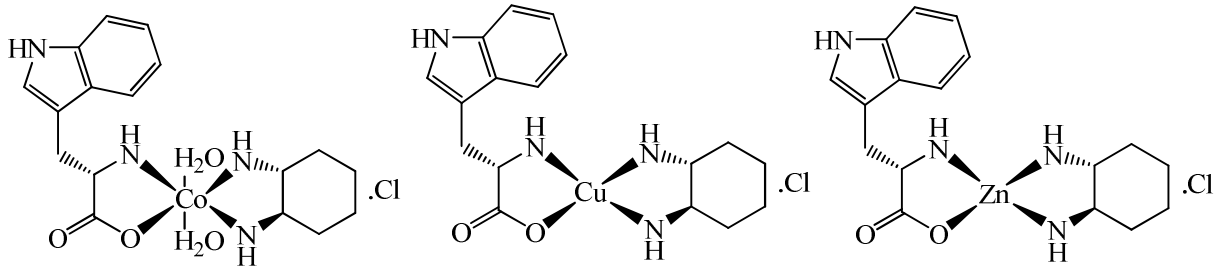

Figure 3. Proposed structure of complexes derived from L– and D–tryptophan and (1R,2R)–(2)–1,2–DACH).

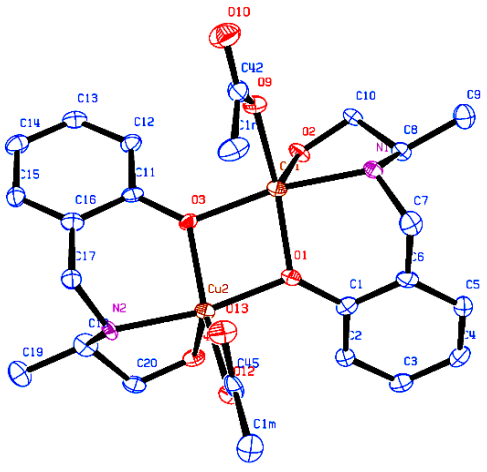

Figure 4. One unit of labeled ORTEP view of (R)–enantiomer of copper complex with atom numbering scheme. H atoms and H_2O molecules were omitted for clarity

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