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# Interfacial inhibitors

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ABSTRACT

Targeting macromolecular interface is a general mechanism by which natural products inactivate macromolecular complexes by stabilizing normally transient intermediates. Demonstrating interfacial inhibition mechanism ultimately relies on the resolution of drug-macromolecule structures. This review focuses on medicinal drugs that trap protein–DNA complexes by binding at protein–DNA interfaces. It provides proof-of-concept and detailed structural and mechanistic examples for topoisomerase inhibitors and HIV integrase inhibitors. Additional examples of recent interfacial inhibitors for protein–DNA interfaces are provided, as well as prospects for targeting previously 'undruggable' targets including transcription, replication and chromatin remodeling complexes. References and discussion are included for interfacial inhibitors of protein–protein interfaces.

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Because biological systems consist of macromolecular ensembles that need to move with respect to each other to perform their enzymatic or structural functions, and because such reactions create a spectrum of molecular interfaces between macromolecules, it is understandable how small molecules that bind to such interfaces can interfere with the function of the macromolecular complexes (Fig. 1). Hence, the complexity of macromolecular complexes and their dynamic behavior creates unique opportunities to develop and discover small molecules that bind at such interfaces with high selectivity.

The interfacial inhibitor concept arose from the observation that topoisomerase inhibitors, which are widely used as anticancer drugs, produce topoisomerase-linked DNA breaks that correspond to normally transient catalytic intermediates of the topoisomerase reactions (see below). The hypothesis that topoisomerase-linked DNA breaks were generated by the binding of the topoisomerase inhibitors at the interface of the broken DNA and the enzyme was proposed in the 90s[1–3] but remained unproven for 10 years until the co-crystal structure determination of the natural product derivative topotecan bound to the topoisomerase I (Top1) cleavage complex (Top1cc)[4] and more recently of etoposide bound to the topoisomerase II cleavage complex (Top2cc)[5] (see below and Figs. 2 and 3). Independently, the co-crystal structure of the fungal macrolide brefeldin A bound at the interface of the small GTP-binding protein Arf and its guanine-nucleotide-exchange factor Sec7[6] provided proof of principle that the interfacial concept is not limited to protein–nucleic acid interfaces but also applies to protein–protein interfaces.[7] The term 'interfacial inhibitor'[7] was coined to describe this previously unanticipated mode of inhibition. Since the concept was first proposed, the number of examples of natural product that act as interfacial inhibitors has grown steadily, encompassing cell surface receptors (exemplified by the nicotinic receptor inhibitors), signal transduction molecules (exem plified by the mTOR inhibitors), scaffolding macromolecular complexes (exemplified by tubulin inhibitors), and protein–DNA complexes (exemplified by topoisomerase, polymerase and ribosome inhibitors).[8,9] Recently purely synthetic drugs were found to act as interfacial inhibitors of HIV integrase (see below), thereby opening perspectives for a large number of targets and medicinal chemists. The present review expands our previous reviews on this topic.[7–9]

To illustrate the points described above, the next sections describe specific examples of protein nucleic acid complexes (topoisomerase and HIV integrase inhibitors) and one recent example of interfacial protein–protein inhibitor for the viral cofactor STING.

Topoisomerases are ubiquitous enzymes that alter DNA topology by relieving supercoiling-associated tension in double stranded DNA. Topoisomerases perform their function by transiently cutting one strand (type I topoisomerases including Top1, Top1mt, Top3α and Top3β) or both DNA strands (type II topoisomerases including Top2α and Top2β in humans, and bacterial gyrase and Topo IV).[13,14] The ubiquitous presence and crucial biological roles of topoisomerases explain their prevalence as therapeutic target. Pharmaceutical and medicinal chemistry research efforts have yielded a collection of important antibiotics (e.g., oxolinic and nalidixic acid analogues and quinolone derivatives) and anticancer agents (e.g., irinotecan, topotecan, etoposide,

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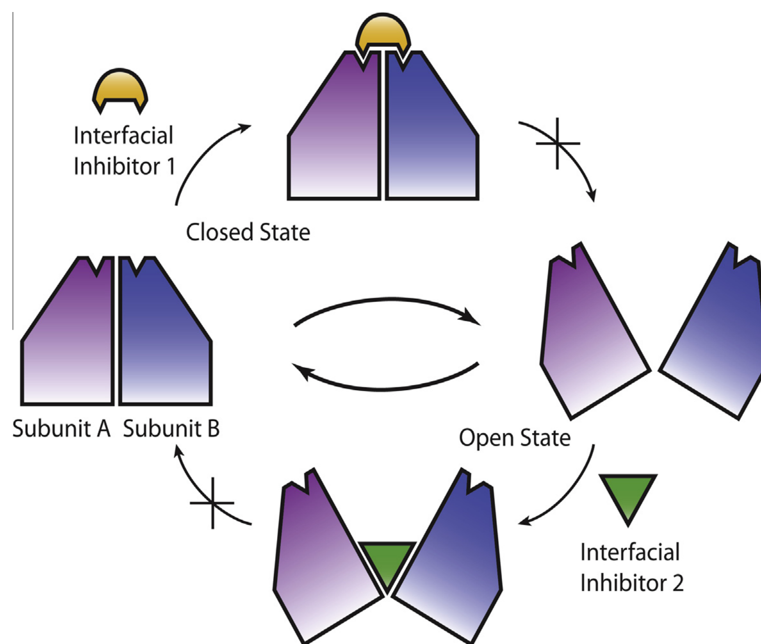


**Figure 1.** Schematic illustration of interfacial inhibition. The normal cycle of enzyme mechanical interconversion from 'closed' state to 'open' is interrupted by use of the interfacial inhibitors. The cycle is stalled at the 'open' state by a 'wedge'-like inhibitor (green triangle) analogous to inhibition of Top2 catalyzed DNA relegation step by etoposide. The stabilization of the 'closed' state is achieved by use of a 'lock'-like inhibitors (yellow), similar to dexrazoxane trapping of the closed state of Top2 ATP binding subunits.

doxorubicin, aclarubicin, dexrazoxane and mitoxantrone).[15] A dozen of topoisomerase inhibitors are in common clinical practice worldwide for treating bacterial infections and a broad range of cancers. Structural and biochemical studies have unambiguously demonstrated that topoisomerase inhibitors are interfacial inhibitors.[4,5,16–18] Their binding at the subunit or protein–DNA interfaces interferes with the topoisomerase catalytic cycle by preventing the rapid conversion of enzyme-DNA configurations required for the topoisomerase reactions (Fig. 1).[13–15,19,20]

Topoisomerase-mediated DNA supercoil removal is a three-step process. First, the topoisomerases cut one (type I) or two (type II) strands of double-stranded DNA, forming a covalent binary topoisomerase–DNA complex, which is referred to as a cleavage complex (Top1cc for Top1 and Top2cc for Top2). For Top1 (type IB), the subsequent step of supercoil removal occurs via rotation when the clamp-like structure of the topoisomerase encapsulating the DNA allows the rotation of the free DNA end around the intact strand.[21,22] For type IA (Top3α and Top3β in humans and Topo I in bacteria) and type II topoisomerases (Top2α and Top2β in humans or gyrase and Topo IV in bacteria), supercoils are removed through strand passage and the overall process is orchestrated by subunit rearrangements within homodimers (Top2) or tetramers (gyrase and Topo IV). Type IB topoisomerases (Top1 and Top1mt) change the DNA linking number in steps of one as the DNA swivels (rotates) around the enzyme covalently bound to DNA. By contrast, topoisomerization reactions for type IA and type II topoisomerases proceed by strand passage (gate mechanism) for each catalytic cycle, changing the linking number in steps of 1 (Type IA enzymes) or 2 (type II enzymes). In the final step of the reaction, topoisomerases (and their covalent bond to DNA) are released by nucleophilic attack of the free DNA end at the break site toward the topoisomerase–DNA covalently bound catalytic tyrosine.[13,14]

Human Top1 (type IB) is an essential enzyme targeted by the two FDA-approved anticancer drugs topotecan and irinotecan. Together structural, biochemical, and mutation analyses[23] revealed the critical importance of drug interaction with both the cleaved DNA and the enzyme, highlighting its interfacial nature. When bound to the Top1–DNA complex, camptothecin or its synthetic analogues intercalate into the DNA at the site of Top1-induced nick, and at the same time form a network of direct and water-mediated hydrogen bonds.[4,24] It was shown that DNA sequence preference differs across chemical classes of Top1 inhibitors demonstrating the impact of π–π stacking interactions between drug and DNA nucleobases on the binding and selectivity of inhibitors.[25] Additionally, it was observed that Top1 mutations at residues R364, D533 and N722 confer resistance towards camptothecin-based inhibitors.[23] These residues were later found to play key roles in drug binding to Top1–DNA complex (Fig. 2B).[24]

Upon inhibitor binding, the ends of the cut DNA strand are spatially separated to a distance of ~11 Å, preventing their religation. Remarkably, the binding site of camptothecins (PDB IDs: 1K4T, 1T8I), of the non-camptothecin indenoisoquinolines in clinical development (PDB IDs: 1SC7, 1TL8) and of indolocarbazoles (PDB ID: 1SEU) determined via crystallographic studies could not be observed in the cleavage complex alone (PDB ID: 1K4S).[4,16] The binding site of Top1 inhibitors and its interfacial nature became apparent only when the structure of the Top1-DNA complex trapped by inhibitors was crystallographically resolved. Figure 2 shows structural alignment of the binary Top1–DNA cleavage complex and the Top1–DNA-topotecan ternary complex. Such alignment reveals the required alteration of the structure of the complex in order to form the binding site that accommodates topotecan. The DNA double helix on the 5′-end of the cut strand adopts a new position relative to the binary complex (Fig. 2). In addition, the position of some Top1 loops is altered, but the overall fold of the enzyme as determined by X-ray crystallography remains the same.

Top2 inhibitor-stabilized cleavage complexes also involve the trapping of type II topoisomerases: topoisomerase IV from Streptococcus pneumonia and human Top2β.[5,26,27] In the case of Top2β, each monomer of the Top2 dimer accommodates one inhibitor molecules of the Top2–DNA cleavage complex (Top2cc) (Fig. 3).[5] Similar mode of binding is observed in the case of the topoisomerase IV complex with the formation of a binding pocket

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