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[7] Crystal data for **3**: $C_{72}H_{96}N_{24}O_{18}Pd_3 \cdot 2CH_3OH$, $M_r = 1968.98$, orthorhombic, space group *Pnma* (no. 62), $a = 27.6315(9)$, $b = 22.1045(7)$, $c = 17.7133(6)$ Å, $V = 10818.9(6)$ Å^3, $Z = 4$, $T = 23.0\,^\circ C$, $\rho_{calcd} = 1.209$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 5.59$ cm^{-1}, $Mo_{K\alpha}$ radiation ($\lambda = 0.71069$ Å), $R = 0.090$, $R_w = 0.253$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-160516. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Directing Topoisomerase I Mediated DNA Cleavage to Specific Sites by Camptothecin Tethered to Minor- and Major-Groove Ligands**

Paola B. Arimondo, Christian Bailly, Alexandre S. Boutorine, Vladimir A. Ryabinin, Alexandre N. Syniakov, Jian-Sheng Sun, Thérèse Garestier, and Claude Hélène*

Hairpin polyamides containing pyrrole– and imidazole–carboxamide units represent convenient tools to target specific sequences in DNA.[1] These compounds form dimeric motifs that fit snugly into the minor groove of B-DNA and recognize defined sequences through the formation of an array of hydrogen bonds and van der Waals contacts. They provide a paradigm for the design of small molecules that regulate genes.[2]

The sequence-recognition properties of hairpin polyamides can be exploited for directing DNA-cleaving and -alkylating agents to particular sequences.[3–7] By analogy, we reasoned that they could also be used to direct the action of DNA-cleaving proteins such as topoisomerases. These ubiquitous

[*] Prof. C. Hélène, Dr. P. B. Arimondo, Prof. A. S. Boutorine, Prof. J.-S. Sun, Prof. T. Garestier
Laboratoire de Biophysique, INSERM U201, UMR 8646 CNRS
Muséum National d'Histoire Naturelle
43 rue Cuvier, 75231 Paris cedex 05 (France)
Fax: (+33) 1-40793705
E-mail: helene@mnhn.fr

Dr. C. Bailly
INSERM U524 and Laboratoire de Pharmacologie Antitumorale
du Centre Oscar Lambret, IRCL
1 Place Verdun, 59045 Lille (France)

Dr. V. A. Ryabinin, Dr. A. N. Syniakov
Institute of Molecular Biology
State Research Center of Virology and Biotechnology "Vector"
Koltsovo, Novosibirsk region, 630559 (Russia)

[**] This work was supported by grants (to C.B.) from the Comité du Nord de la Ligue Nationale Française contre le Cancer. P.B.A. is the recipient of a postdoctoral fellowship from the Ligue Nationale Contre le Cancer.

enzymes regulate DNA topology in cells and therefore are essential for many vital processes, such as replication, transcription, and chromosome segregation.[8] Topoisomerases I and II both represent privileged targets for a number of cytotoxic anticancer drugs.[9] In particular, the camptothecins (CPT), which include the clinically available derivatives topotecan and irinotecan, are the most potent inhibitors capable of stimulating DNA single strand cleavage by topoisomerase I at a variety of sites, essentially at T–G sites.[10, 11]

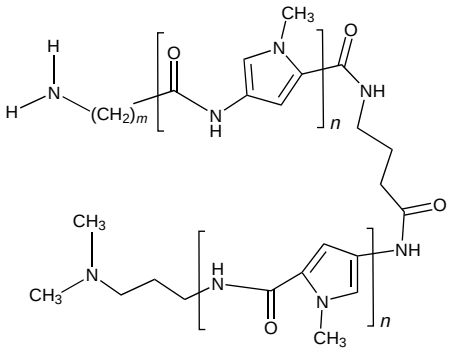
DNA cleavage by topoisomerase I can be targeted to specific sequences by the linkage of topoisomerase inhibitors to sequence-recognition elements, such as oligonucleotides that form triple helices[12–14] or small molecules related to the antibiotics netropsin and distamycin.[3, 15, 16] The limited sequence-recognition properties of these antibiotics and analogues that form 1:1 drug:DNA complexes restrict their use as DNA-cleaving delivery systems. No sequence specificity was reported for the cleavage by the conjugates with the camptothecin derivatives.[15] Here we present an alternative approach to direct camptothecin to specific sites in DNA and to introduce DNA breaks at a precise location by making use of the recognition of the target sequence by hairpin polyamide ligands that bind to the minor groove of DNA in a sequence-specific manner.[1] We have compared these conjugates to camptothecin that is covalently linked to triplex-forming oligonucleotides that bind in the major groove at oligopyrimidine · oligopurine sequences.

Two hairpin polyamides, each containing two series of three or four *N*-methylpyrrolecarboxamide units that form antiparallel dimers, were synthesized as previously described.[17] Compounds **1** and **3** were linked to 10-carboxycamptothecin through aminoalkyl side chains of different lengths. The two minor-groove binder/camptothecin (MGB–CPT) conjugates **2** and **4** contain the same dimethylaminopropylamino cationic side chain on the C-terminal pyrrole heterocycle and an identical γ-aminobutyrate residue between the two oligopyrrole branches, but they differ in the number of *N*-methylated pyrrole units (2×3 or 2×4 pyrrole rings) and the nature of the alkyl connector (propyl in **2** or pentyl in **4**) between the MGB moiety and the topoisomerase I inhibitor. The coupling procedure recently described for the synthesis of oligonucleotide-aminoalkyl-CPT conjugates was employed.[12, 13] Briefly, the 10-carboxyl group of the camptothecin derivative was first treated with *N*-hydroxysuccinimide in the presence of dicyclohexylcarbodiimide to provide the corresponding active ester, which was then treated with the minor-groove binder **1** or **3**. The resulting MGB–CPT hybrid molecules **2** and **4** were separated from the remaining camptothecin molecules by successive precipitations from a mixture of DMSO and acetonitrile (1:4). The final compounds were characterized by UV spectroscopy and mass spectrometry.

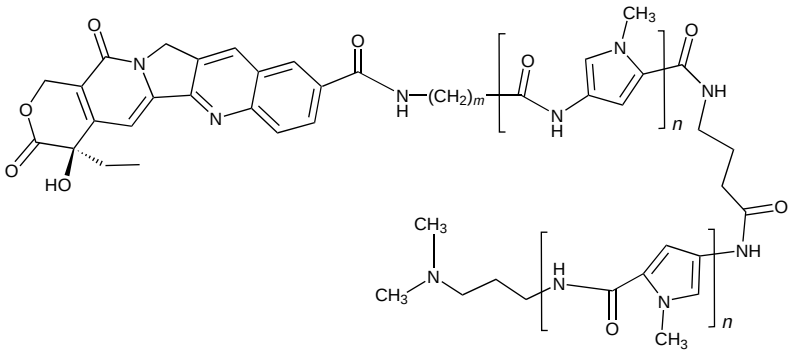
The MGB–CPT conjugates were incubated with a 324 base pair (bp) ^{32}P-labeled DNA fragment prior to the addition of topoisomerase I to initiate the DNA cleavage reactions. Control experiments were performed in parallel with camptothecin alone and with the MGBs **1** and **3**, as well as with the noncovalent association of camptothecin plus each of the two MGBs (CPT + **1** and CPT + **3**). In all cases the DNA samples were treated with sodium dodecylsulfate (SDS) and proteinase K to remove any covalently bound protein and then resolved on an 8% polyacrylamide sequencing gel under denaturing conditions so as to identify the sequence of the drug-induced topoisomerase I cleavage sites. A typical example of a gel is shown in Figure 1a and a summary map showing the position of the main cleavage sites induced by CPT (asterisks) is presented in Figure 2. The positions of the AT-rich MGB-binding sites (boxed sequences in Figure 2) were inferred from DNase I footprinting experiments performed with the same *Eco*RI-*Pvu*II 324-bp restriction fragment (^{32}P-labeled at the 3′-end of the *Eco*RI site) incubated with the untethered polyamides **1** and **3** at 3 μM (data not shown). This particular DNA fragment contains a 24 nucleotide long oligpyrimidine · oligopurine tract used previously for triple helix formation.[12, 13] It was selected because it contained several CPT-sensitive sites, some of which are close to short AT tracts, thus providing exquisite binding sites for oligopyrrole polyamides such as compounds **1** and **3**. In addition it allowed us to compare the cleavage efficacy and selectivity of minor-groove and major-groove ligands conjugated to CPT.

With camptothecin alone, the position of seven cleavage sites (a–g) were determined with nucleotide resolution by various electrophoresis experiments (Figure 2).

As shown in Figure 1, the covalent linkage of a MGB to the CPT chromophore exerts a drastic effect on the sequence



1 $n = 3$; $m = 3$
3 $n = 4$; $m = 5$



2 $n = 3$; $m = 3$
4 $n = 4$; $m = 5$

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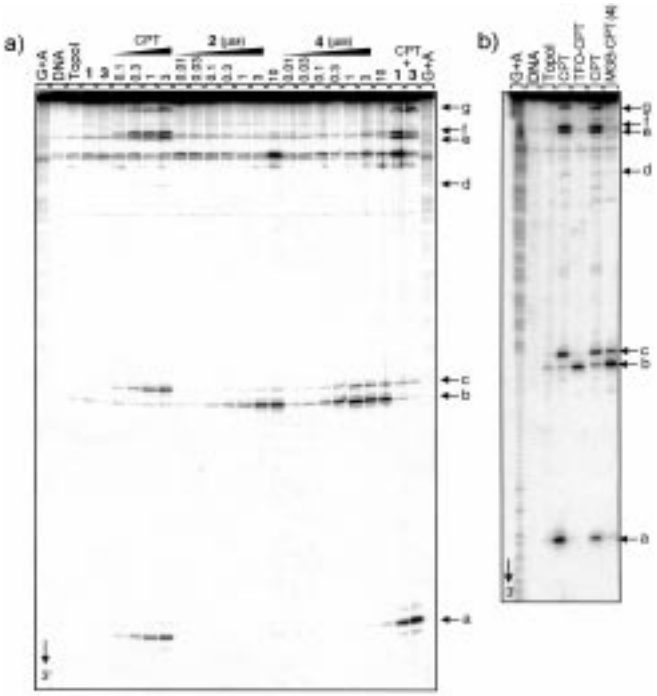

Figure 1. Sequencing of the drug-induced topoisomerase I cleavage sites. The 324-bp DNA fragment, radiolabeled at the 3′-end, was subjected to cleavage by human topoisomerase I in the presence of the test compounds. Cleavage products were resolved on an 8% polyacrylamide gel containing 7 M urea. Purine-specific sequence markers obtained by treatment of the DNA with formic acid followed by piperidine were run in the lanes marked G + A. The lane Topo I refers to the radiolabeled DNA substrate incubated with the enzyme in the absence of any drug. The position of the seven camptothecin (CPT) induced topoisomerase I cleavage sites are pointed out by arrows (sites a – g) and the corresponding sequences are given in Figure 2. Note that the 324 bp DNA fragment contained low amounts of shorter fragments before any DNA cleavage reaction (see lane labeled "DNA"). a) The MGB – CPT conjugates **2** and **4** were added at the indicated concentrations (μM). The nonconjugated MGB **1** and **3** were both used at 3 μM (lanes labeled **1** and **3**). In the lanes marked CPT + **1** and CPT + **3**, both the MGB and camptothecin were used at 3 μM. b) Comparison of the cleavage sites observed with the MGB – CPT hybrid **4** and a triplex-forming oligonucleotide/CPT conjugate (TFO – CPT; 3 μM each). The 10-carboxycamptothecin was covalently attached to the 3′-phosphate group of the 16-nucleotide (-nt) oligonucleotide MPMPMPMPMPPPPPPP through a diaminobutyl linker: 5′**MPMPMPMPMPPPPPPP**3′-NH$(CH_2)_4$-NHCO-CPT.[13] This oligonucleotide, complementary to the oligopyrimidine · oligopurine sequence adjacent to site b, contains both 5-propynyl-2′-deoxyuridines [P] and 5-methyl-2′-deoxycytidine [M] for formation of a stable triple helix.

specificity of DNA cleavage mediated by topoisomerase I. In the presence of the MGB – CPT **2** or **4**, DNA cleavage was strongly enhanced at site b, whereas cleavage at all the other CPT-induced sites were strongly decreased. Very weak cleavage at sites a, e, f, and g was observed only at high concentrations of the conjugates even though these sites were very strong cleavage sites in the presence of CPT alone. Some cleavage at site c was still present with the conjugates. A quantitative analysis of the gels (Figure 3a) revealed that at low concentrations the hybrid **4** (2×4 pyrrole rings) was more efficient than hybrid **2** (2×3 pyrrole rings) at directing cleavage to T – T site b adjacent to a high-affinity site of the MGB moiety of the conjugate. This result is consistent with the higher DNA binding affinity of the dimer of tetrapyrrole rings relative to the dimer of tripyrrole rings. Both conjugates **2** and **4** are more efficient than free camptothecin (Figure 3).

It is noteworthy that the targeting of cleavage at site b was only observed when CPT was covalently attached to compound **1** or **3**, but not when the inhibitor was mixed with an equimolar amount of the MGB (Figure 1a). The cutting profiles observed with CPT + **1** or CPT + **3** were almost identical to those observed with CPT alone. Only a diminished cleavage at site d was observed, which is in agreement with the binding of the MGB to this AT-rich site and thus reducing the access of topoisomerase I to this particular site. Controls were also performed with the two hairpin polyamides **1** and **3** to show that without CPT they do not stabilize topoisomerase I/DNA cleavage complexes.

Interestingly, the cutting profiles observed with the MGB – CPT hybrids **2** and **4** are similar, but not identical. Both the gel in Figure 1 and the histogram in Figure 3b show clearly that cleavage at site c is decreased less with conjugate **4** than with conjugate **2**. It is likely that upon binding of the MGB moiety to the adjacent $A_7 \cdot T_7$ tract, access of the appended CPT molecule to site c is still possible when the alkyl connector between the CPT and the MGB units is longer, as in conjugate **4**.

The results reported here parallel those recently obtained with a CPT-conjugate of a triplex-forming oligonucleotide (TFO) that binds to the major groove of DNA and was shown to direct DNA cleavage mediated by topoisomerase I to the same site b (Figure 1b).[13] The MGB – CPT and TFO – CPT conjugates are equally potent at targeting the enzyme to a

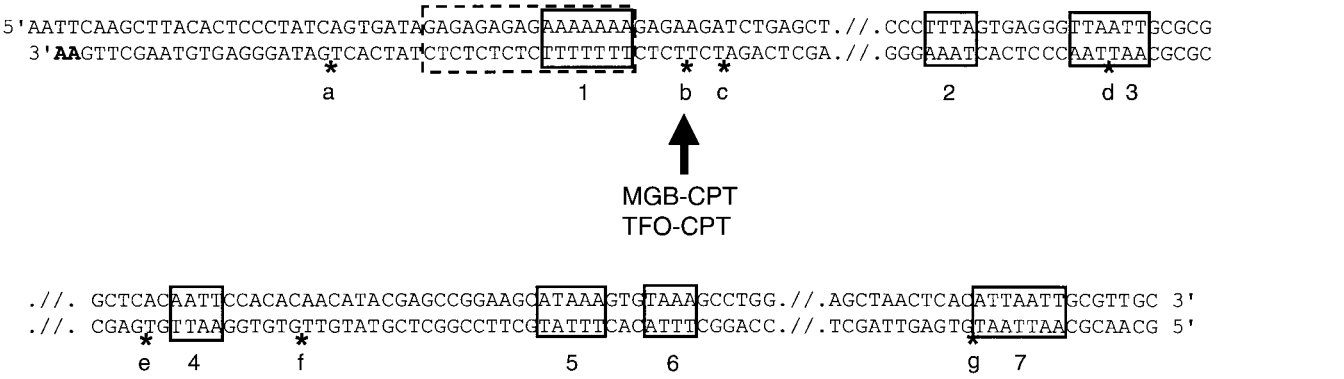

Figure 2. Partial sequence of the DNA fragment used to locate the toposiomerase I cutting sites induced by CPT (asterisks). The site selected by MGB – CPT and TFO – CPT conjugates is indicated by an arrow. The positions of the MGB binding sites at AT tracts (boxed sequences) were inferred from DNase I footprinting experiments (data not shown). The dotted box indicates the binding site of the TFO described in Figure 1b.

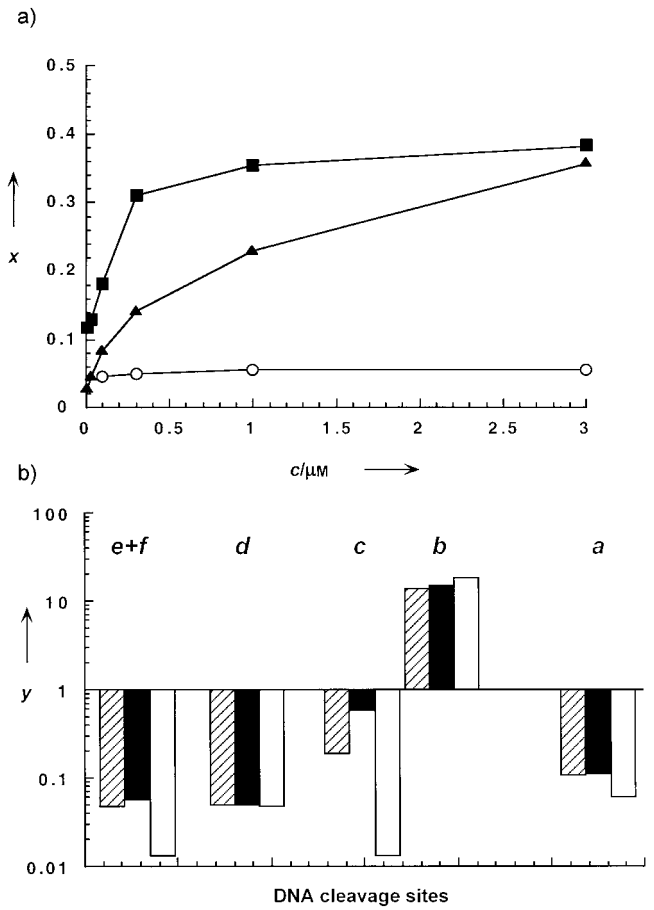

Figure 3. a) Quantification of the intensity of topoisomerase I mediated cleavage (x) at site b is reported as a function of the concentration (μM) for free camptothecin (○), hybrid **2** (▲), and **4** (■). x = fraction of cleaved DNA. b) Intensities of the cleavage observed in the presence of conjugates MGB–CPT **2**, **4**, and TFO–CPT (3 μM each) are indicated by hatched, black, and white bars, respectively. The extent of the topoisomerase I mediated cleavage refers to the ratio between the intensity of the cleavage in the presence of the conjugate and that in the presence of free CPT (y) and is reported on a logarithmic scale. The position of the cleavage sites is indicated. y = ratio of cleavage intensity for conjugated drug versus free drug.

single site in the DNA fragment; cleavage at all the other sites disappeared upon conjugation of the CPT to the DNA ligand. Some cleavage at site c was still observed, since we used conjugate **4** for the comparison, which is in contrast to the conjugate TFO–CPT. It should be noted that the linkers were different for the two conjugates (Figure 1b). However, even though the CPT moiety is brought from the major-groove side of DNA by the TFO and from the minor-groove side by the MGB, both approaches provide a suitable route to guide a cytotoxic agent to a selected sequence in DNA (Figure 3b). The main advantage of MGB–CPT over TFO–CPT conjugates is that the binding of MGBs is not restricted to oligopyrimidine·oligopurine DNA sequences as observed with TFOs. In addition, MGBs are expected to be more cell permeable than TFOs and, therefore, might be more suitable for cell studies.

In summary, prominent cutting at site b attests that the covalent linkage of a hairpin polyamide to camptothecin provides an efficient system to direct DNA cleavage mediated by topoisomerase I to specific sites. Hairpin polyamide/camptothecin conjugates represent a new category of single-strand-breaking artificial nucleases that could provide a basis for potential therapeutic applications.

Experimental Section

Synthesis of the CPT–MGB conjugates: 10-Carboxycamptothecin (0.005 mmol) was activated with a small excess of *N*-hydroxysuccinimide (0.007 mmol) in the presence of dicyclohexylcarbodiimide (0.007 mmol) for 8 h at room temperature in dry dimethylformamide (DMF). The camptothecin ester was then precipitated by diethyl ether, dissolved in DMF, and added to a solution of **1** or **3** (at 0.001 mmol) and triethylamine (4 μL) in dimethyl sulfoxide (DMSO; 50 μL) and left to stand at room temperature in the dark for 8 h. The product was isolated by precipitation with deionizied water (1.5 mL). The pellet was dried, dissolved again in DMSO, and precipitated twice with 80% acetonitrile, then dried, and then dissolved in DMSO for subsequent biochemical experiments.

The resulting conjugate **2** or **4** was characterized by UV spectroscopy and by mass spectrometry. The A_{379}:A_{310} ratio demonstrated a 1:1 stoichiometry of camptothecin to the minor groove binder in the conjugate. MS (matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF)): found: 1381.7 (calcd: 1382.6) for **2**.

DNase I footprinting experiments: The protocol previously described was used.[18] A 324-bp 3′-end radiolabeled DNA fragment was prepared as described in ref. [13]. The DNA was incubated with the conjugate at room temperature for 6 h.

Topoisomerase I cleavage assays were performed using the calf thymus enzyme at room temperature as described in refs. [13, 14].

Received: May 21, 2001 [Z17143]

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