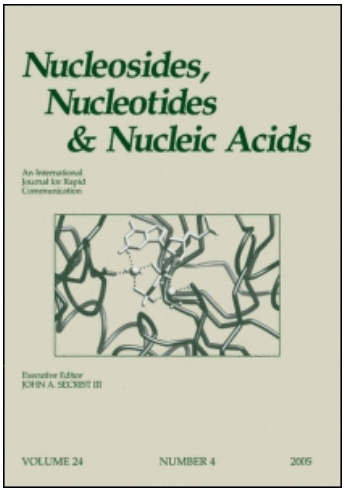

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Sequence-Specific Alkylation of DNA by Duocarmycin A and Its Novel Derivatives Bearing PY/IM Polyamides

Z. F. Tao[a]; T. Fujiwara[a]; I. Saito[b]; H. Sugiyama[a]
[a] Institute for Medical and Dental Engineering, Tokyo Medical and Dental University, Tokyo, Japan [b] Department of Synthetic Chemistry and Biological Chemistry, Faculty of Engineering, Kyoto University, Kyoto, Japan

To cite this Article Tao, Z. F. , Fujiwara, T. , Saito, I. and Sugiyama, H.(1999) 'Sequence-Specific Alkylation of DNA by Duocarmycin A and Its Novel Derivatives Bearing PY/IM Polyamides', Nucleosides, Nucleotides and Nucleic Acids, 18: 6, 1615 — 1616
To link to this Article: DOI: 10.1080/07328319908044799
URL: http://dx.doi.org/10.1080/07328319908044799

NUCLEOSIDES & NUCLEOTIDES, 18(6&7), 1615–1616 (1999)

SEQUENCE-SPECIFIC ALKYLATION OF DNA BY DUOCARMYCIN A AND ITS NOVEL DERIVATIVES BEARING PY/IM POLYAMIDES

Z. -F. Tao[1], T. Fujiwara[1], I. Saito[2], H. Sugiyama[1]*

[1]Institute for Medical and Dental Engineering, Tokyo Medical and Dental University, Tokyo 101-0062, Japan; [2]Department of Synthetic Chemistry and Biological Chemistry, Faculty of Engineering, Kyoto University, Kyoto 606-8501, Japan; CREST, JST.

ABSTRACT: A new class of sequence-specific DNA alkylating agents were developed based on the reactivity of duocarmycin A and the DNA-reading ability of pyrrole-imidazole polyamide. The DNA alkylation sequence specificity by duocarmycin A can be modulated by a variety of pyrrole-imidazole triamides in a predictable manner. Novel hybrids of the segment A of duocarmycin A and pyrrole-imidazole polyamides efficiently and highly selectively alkylated the target base possessing match sequences of Dervan's binding code.

Duocarmycin A (Duo) itself alkylates adenine N3 at the 3' end of A+T-rich sequences in DNA. We recently described that distamycin A (Dist) dramatically modulates alkylation specifity of Duo through a cooperative heterodimer formation between Duo and Dist in DNA minor groove.[1] Methylpyrrole (Py), methylimidazole (Im) polyamides can read DNA in the minor groove according to the binary code: Py/Py recognizes A-T base pairs and Im/Py for G-C pairs.[2] Based on these findings, a new class of sequence-specific DNA alkylating agents can be designed.

At first, we employed a variety of Py/Im triamides as new partners to modulate the sequence specificity of DNA alkylation by Duo. The HPLC and high resolution gel analysis showed that Duo-triamide heterodimers recognized two base pairs of 5' side of the alkylation site as predicted by the pairing rule, e.g. Duo-ImImIm selectively alkylated 5'-CCA-3' sequence. The modulation abilities of triamides on DNA alkylation are in the order: ImImIm, ImPyIm > Dist > PyImIm, PyImPy > PyPyIm, PyPyPy. Secondly, a variety of novel Duo derivatives bearing Im/Py polymides were synthesized. DNA alkylation by these hybrids were evaluated using oligonucleotides and 400 base pair (bp) DNA fragments. All of them efficiently and highly selectively alkylate DNA at the predetermined sequences through side-by-side binding mode. This efficient alkylation was found to occur through a

cooperative heterodimer formation. These results are good in agreement with the previously discovered binary code for the base pair recognition by Py/Im polyamides. For example, **1**-Dist and **2**-Dist heterodimers selectively alkylate 5'-GTG-3' and 5'-(A/T)TG-3' sequences, respectively. A summary of alkylation of octanucleotides by **1**-Dist heterodimer is shown in FIGURE 1. More interestingly, alkylation at predetermined 7-base pair sequence was achieved within 400 bp DNA fragments by hybrids **3** and **4**, namely, **3** and **4** highly efficiently and specifically alkylated 5'-TGTAAAA-3' and 5'-AGTCAGA-3', respectively.

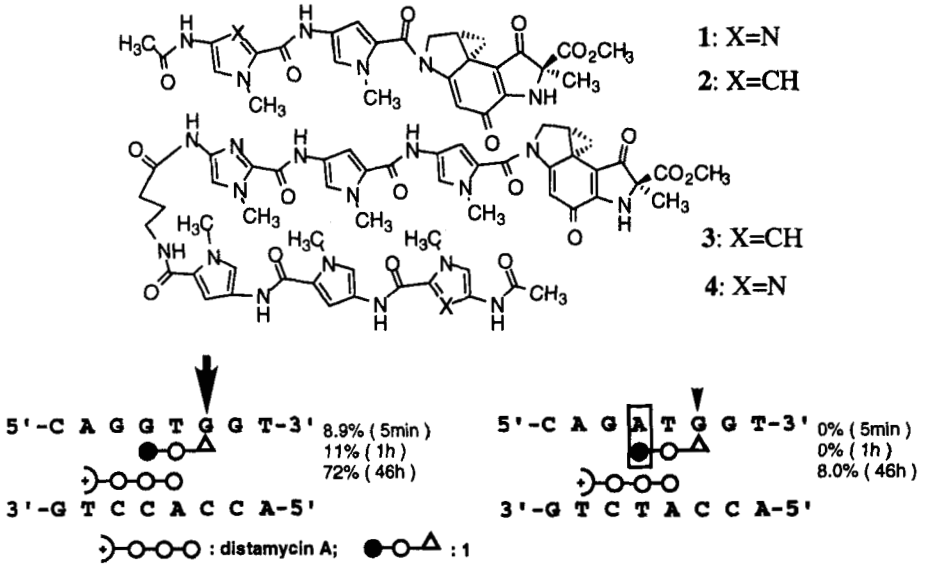

FIGURE 1 Alkylation of oligonucleotides by hybrid **1** in the presence of Dist. The arrows represent the location and the extent of alkylation after the indicated incubation times at 0°C. The imidazole and pyrrole rings are represented by solid and open circles, respectively. Hydrogen-bond mismatches are also highlighted by a box.

In conclusion, the present study reveals that substitutions of Dist Py with Im dramatically modulates the sequence-specificity of Duo in a predictable manner and also shows the highly sequence-specific DNA alkylation by new types of hybrid molecules between the segment A of Duo and the Py/Im polyamides. Results from the present investigation suggest a promising approach for developing a new generation of sequence-specific DNA alkylating agents.

REFERENCES

1. Sugiyama, H.; Lian, C.; Isomura, M.; Saito, I.; Wang, A. H. -J. *Proc. Natl. Acad. Sci. USA* **1996**, 93, 14405.
2. White, S.; Szewczyk, J. W.; Turner, J. M.; Baird, E. E.; Dervan, P. B. *Nature* **1998**, *391*, 468.