

(1, 3), a property shared by several natural products including steroids (4, 5) and thyroid hormones (6). When fitted into DNA, the imino proton of the piperidinedione ring was capable of hydrogen bonding stereospecifically to phosphate oxygens of the DNA backbone. That A10 might form reversible stereospecific complexes with DNA appeared plausible. Because many potent carcinogens such as the aflatoxins and arene oxides are known to intercalate and to form covalent linkages with DNA that can subsequently cause mutations, it was postulated that A10 might compete with certain carcinogens for binding to DNA. Thus, if A10 prevented the formation of such covalent linkages, it might function as an endogenous protector of DNA (1).

Recent animal and clinical testing indicate that A10 does have considerable potential as an antineoplastic agent (7-9). In this and related papers, the authors confirm that A10 is capable of inserting between base pairs in DNA, and that when examined with more advanced modelling technology (5, 10) A10 appears to fit better into certain sequences.

#### Materials and methods

The fit of A10 and related molecules into DNA was evaluated using previously published criteria (5, 10, 11). In short, to be considered a stereochemically complementary fit into DNA, a given molecule must fit between base pairs in two domains: (i) the hydrogen bonding domain - hydrogen bonding functional groups on the molecule are required to form stereospecific linkages to donor/acceptor groups on the DNA; and (ii) the topographical domain - the basic structure of the molecule is required to be accommodated virtually completely between base pairs in unwound DNA at one of the 10 possible sites.

The molecules herein were evaluated using Corey-Pauling-Koltun space filling models, Kendrew skeletal models and silastic polymer models

constructed from X-ray space filling coordinates (10). The data presented in Tables I and II are preliminary data in which the arithmetic sum of the components of fit in both domains are shown. The + symbols in the hydrogen bonding domain reflect the number of hydrogen bonds; the relative fit in the topographical domain is reflected by the numerical score (1.0 poor to 6.0 good). Variations in the fits into DNA in the topographical domain were arbitrarily assigned differential increments of  $\pm 0.5$  units.

#### Results

The fit of A10 into various sequences in DNA is summarized in Table I. Of the 10 unwound sites in DNA which could accommodate A10, the best fit in the topographical domain was in the site 5'-dTdT-3'·5'-dAdA-3' (Fig. 1). The orientation of the molecule when inserted into this site was with the aromatic phenyl ring stacked between the two neighbouring adenines and the piperidinedione ring stacked between thymines. Within this site it was also possible to form a stereospecific hydrogen bond between the imino proton and a phosphate oxygen bordering the cavity. A hydrogen bond between the NH<sub>2</sub> of adenine and the carbonyl oxygen of the peptide linkage was feasible; weak hydrogen bonding involving the NH of the peptide was also possible (denoted in the Table as 1/2). The overall summation of fit for A10 in this sequence was 8.5.

Several additional sites in DNA were capable of accommodating A10. Reasonable fits were observed in the closely related sequences 5'-dTdC-3'·5'-dGdA-3' and 5'-dCdT-3'·5'-dAdG-3' (both 7.5). The site 5'-dTdG-3'·5'-dCdA-3' was an intermediate fit with the remaining sequences having relatively poor fit (<7.0) in comparison with 5'-dTdT-3'·5'-dAdA-3'. Only one hydrogen bond was possible in each of the three sequences 5'-dGdC-3'·5'-dGdC-3', 5'-dGdT-3'·5'-dAdC-3' and 5'-dCdC-3'·5'-dGdG-3'.