

synthesis and recently by xray crystallography. In 1983, we reported that A10 was capable inserting between base pairs in DNA (7). Based upon this observation, we predicted that A10 might compete with certain carcinogens (e.g. arene oxides) for binding to DNA and thus might possess antitumorogenic activity (7). Recent modeling studies and the results of in vivo and in vitro testing are summarized below.

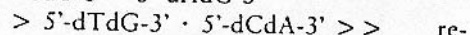
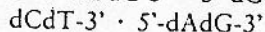
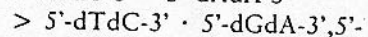
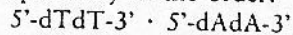
Materials and Methods

The modeling techniques employed in this study were the same as those previously reported (1-6). Corey-Pauling-Koltun (CPK) space filling models, KENDREW skeletal models and silastic polymer models constructed from xray space filling coordinates were used to evaluate the insertion of A10 between base pairs in DNA. Two basic criteria were followed: the stereospecificity of potential donor/acceptor linkages between A10 and DNA (hydrogen bonding domain); the ability of A10 to be accommodated sterically between base pairs (topographical domain). These criteria are consistent with physiochemical parameters considered important for optimization of molecular associations (8).

Results and Discussion

When examined for stereochemical insertion between base pairs in DNA, A10 was found to exhibit reasonable complementarity in several sequences. In each case, A10 was capable of forming a stereospecific hydrogen bond between the imino proton of the piperidinedione ring and a phosphate oxygen on the DNA backbone. A10 exhibited a se-

quence preference but not absolute specificity in the order:



remaining sequences (9). It should be noted that A10 unwound the double helix to a greater extent than classical intercalators e.g. carcinogens or anticancer drugs which are known to bind strongly to DNA. The nature of the insertion suggested that A10 could form weak, reversible, stereospecific complexes with DNA. A10 was also found to be structurally similar to certain known experimental anticancer drugs including 5-cinnamoyl-6-aminouracil whose mode of action is thought to be binding to DNA (9, 11).

Given the above observation of stereochemical complementarity between A10 and DNA, several predictions were made as to its biological activity as summarized in Table 2 (7, 9, 11). The results of a variety of subsequent experiments in vitro and in vivo are summarized in Table 3. Note that the physiochemical properties and biological activities predicted for A10 correlate closely with those observed. Briefly, A10 binds weakly to DNA, is nontoxic and possesses antitumorogenic activity.

We conclude that the predictions based upon stereochemical modeling studies are now supported by experimental evidence. In this regard, the simple modified dipeptide A10 is a promising antitumorogenic drug. Studies in progress involve the working hypothesis that A10 may be an endogenous regulator of tumor cell growth.