

Table II Preliminary assessment of fit into DNA of candidate antineoplastic agents and predicted biological activity *t*.

Analogue	Fit in hydrogen bonding domain*	Relative fit in topographical domain	Predicted relative activity**
A10 L-isomer	+ + ½	6.0	8.5
A10 D-isomer	-	2.0	1.0
Phenylacetyl-glutamine	+ + ½	4.0	6.5
Phenylacetyl-isoglutamine	+ + +	5.0	8.0
5-Cinnamoyl-6-aminouracil	+ -	4.0	4.0
PCNU	+ +	5.0	7.0

† Correlations for these agents are with the unwound site 5'-dTdT-3' · 5'-dAdA-3'.

* A minus (-) indicates that a functional group is present which is incapable of forming a hydrogen bond to DNA.

** Sum of components of fit.

An examination of the fits into DNA of compounds structurally related to A10 at the unwound site 5'-dTdT-3' · 5'-dAdA-3' is included in Table II. The D-isomer of A10 constructed from D-glutamine (a compound which apparently does not exist in nature) is a relatively poor fit due to a lack of topographical congruence when inserted into the helix and the absence of possible hydrogen bonds. However, phenylacetylglutamine, the naturally-occurring hydrolysis product of A10, can fit into DNA and form hydrogen bonds to the double helix. Phenylacetylisoglutamine, another product formed upon hydrolysis of A10, fits into DNA in a manner very similar to A10 (rating 8.0). The fits of 5-cinnamoyl-6-aminouracil (12) and PCNU (13), which are related to A10 in structure (3) and which are currently being evaluated as experimental anticancer drugs, were found to have fits of 4.0 and 7.0 respectively.

There are certain inherent limitations of the methodology employed in this study. While the relative fits of A10 and related molecules are clearly demonstrable and are based upon physicochemical principles deemed important for molecular associations (5), the absolute rating scale is subjective. When it becomes possible to assess rigorously the relative energetics of fit which must include, for example, consideration of the details of

the hydration of DNA, more precise quantitative prediction of the biological activity of candidate molecules should become feasible.

Discussion

Peptide and peptide analogues have become well established as regulators of cellular function (e.g., LHRH, insulin, vasopressin, enkephalins, thyroid hormone). Thus the isolation from urine of a modified dipeptide possessing antineoplastic activity is not entirely unexpected. The present findings support the authors' prediction that the mode of action of A10 may involve interaction with DNA. It is interesting that A10 does not appear to be sequence specific in that these models indicate that the parent structure will fit quite well between base pairs at several sites in DNA. The best fits, however, appear to be sequences which contain neighbouring pyrimidines: 5'-dTdT-3' · 5'-dAdA-3', 5'-dTdC-3' · 5'-dGdA-3' and 5'-dCdT-3' · 5'-dAdG-3'. It is interesting that A10 can be accommodated between base pairs at 5'-dTdG-3' · 5'-dCdA-3', a site which accommodates mammalian steroid and thyroid hormones (5, 6, 11).

The comparison of fit into DNA of both A10 enantiomers demonstrates as expected that only the naturally-occurring isomer is stereochemically