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Quantum chemistry in drug design

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Abstract - In the past drugs were often discovered by chance or by inferring the properties of their macromolecular receptors from pains-taking structure-activity correlations. Now the structures of receptors are understood in atomic detail both for nucleic acids and a number of important enzymes. It thus becomes possible to design inhibitors and even to start using theoretical calculations to produce desirable selectivity so as to distinguish, for example, between cancerous and normal cells.

Where the enzyme structure is not known quantitative applications of Pauling's idea that enzymes bind transition states are providing an avenue to new inhibitors. Knowledge of transition state structures then offers the promise of designing enzymes with the aid of monoclonal antibodies by producing protein which binds specifically to the transition state. This major goal should be achievable given the recent and imminent advances in computer power such as the transputer.

INTRODUCTION

If we try to design drugs starting with a knowledge of the receptor architecture, then the obvious targets are nucleic acids or enzymes. In the case of DNA interest is being focussed both on intercalating drugs and on groove binders such as the lexitropsins. These latter compounds excite particular interest because they are to a marked degree sequence specific: netropsin, for example, binds preferentially to sequences which are rich in poly(dA) - poly(dT) rather than poly(dG) - poly (dC). Some understanding of this preference may be derived from displays of the electrostatic potential in the minor grooves of model systems. These indicate that the A - T combination gives rise to a potential more attractive to positive species. The hope is that this will be the starting point for the design of drugs which will be specific for precise sequences of bases so that oncogenes could be sought out and switched off, perhaps by methylation.

For proteins there are far more details of the structures of binding sites and a number of physiologically important processes may be blocked by suitable inhibitors. For some years we have been using a modified quantum mechanical method to calculate the binding energies of inhibitors to enzymes (refs. 1,2). Essentially we treat the atoms of the enzyme as point partial charges but treat the small ligand in a full quantum mechanical manner. In this way we have, for example, been able to reproduce the experimental binding energy of the anti-cancer drug methotrexate to dihydrofolate reductase (DHFR) (see Figure 1).

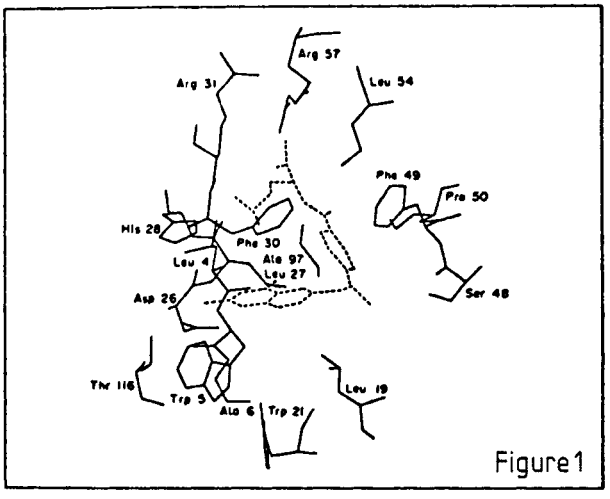

Figure 1

Methotrexate binds strongly to the enzyme, interfering with the metabolism of folic acid and hence killing the cell, so that rapidly proliferating cells are most damaged. However normal cells are also damaged with the result that side-effects are severe.
What is required is a drug which will bind preferentially to cancer cells. A suggestion by Reynolds et al. (Ref. 3) provides a possible avenue; selectivity based on redox potential.

TUMOUR SELECTIVE ANTIFOLATES

Although the target enzyme (DHFR) in normal and tumour cells may be identical, there are other differentiating properties. Solid tumours in particular are hypoxic due to their reduced oxygen supply (Ref. 4). It has been estimated that oxygen tension is reduced from 32 mmHg in normal cells to 0.25 mmHg in solid tumours. This prompted the suggestion (Ref. 3) that it should be possible to design compounds which would bind to and inhibit DHFR when they are in the reduced form but not when oxidized.

Figure 2 shows how the diamino pteridine portion of methotrexate binds to the essentially coplanar Asp 27, Ile 5, Ile 94 and H_2O 635 of methotrexate.

Figure 3 indicates how replacing the amino groups by hydroxyls provides an alternative which is still capable of hydrogen bonding, while the oxidized form (Figure 4) loses this capacity. The design task now becomes one of adjusting the redox potential by means of substituents so as to ensure that the reduced form should be the favoured state in the tumour cells.

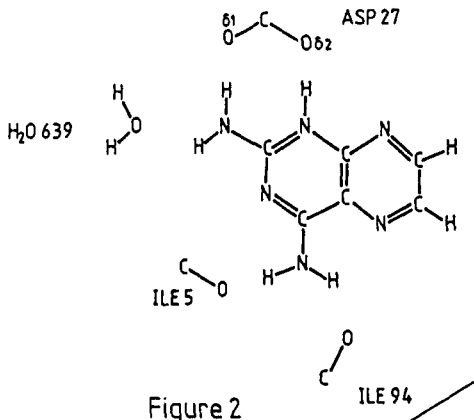

Figure 2

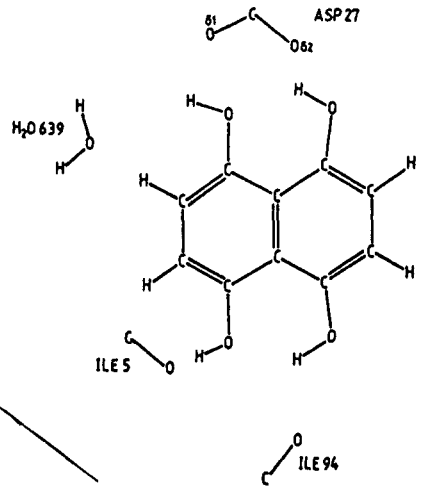

Figure 3

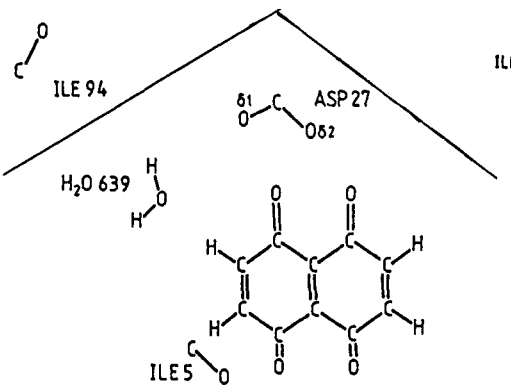

Figure 4 ILE 94

Some support for this approach is provided by the fact that quinonoid molecules such as mitomycin C are used clinically, relying on enzymic reduction to alkylating agents. Our notion is that our designed quinonoid DHFR inhibitors would be administered with compounds thought to reduce oxygen supply. Compounds with the latter property were designed for sickle-cell anaemia patients. The remaining major problem would be the delivery of our compounds given the reduced blood supply to the tumours.

TRANSITION STATE ANALOGUES

If we were limited in designing inhibitors to those enzymes for which crystal structures are available then there would be very limited progress. However the original idea of Pauling (Ref. 5), that enzymes lower the energy of transition states, leads to the conclusion that many enzymes could be blocked by transition state analogues. Such major inhibitors as penicillin or glyphosate exploit this fact.

Since transition states are not classical structures they are not suitable for study by empirically parameterized methods such as molecular mechanics. Quantum chemical calculations, preferably using gradient techniques become essential. Even so massive amounts of computer time may be required when searching for transition states or intermediates on multidimensional surfaces.

Once a transition state has been located the design of an inhibitor demands the synthesis of a stable molecule which mimics the unstable or metastable transitional structure. In order to do this it is helpful to use quantitative measures of how similar any putative inhibitor is to the postulated transition state. Much use has been made of the similarity index introduced by Carbo (Refs. 6,7) which defines the similarity, R_{AB}, between molecules A and B in terms of their charge densities ρ_A and ρ_B by

$$R_{AB} = \frac{\int \rho_A \rho_B dv}{(\int \rho_A^2 dv)^{\frac{1}{2}} (\int \rho_B^2 dv)^{\frac{1}{2}}}$$

(where V is a volume element and integration is over all space)

This index concentrates on similarity of shape of the electron density rather than magnitude (if, for example, $\rho_A = n\rho_B$ the above index would be unity, representing identity). We have proposed an alternative (Ref. 8)

$$R'_{AB} = \frac{2\int \rho_A \rho_B dv}{\int \rho_A^2 dv + \int \rho_B^2 dv}$$

In addition we have used both forms of index not just to compare electron densities but also electrostatic potentials and electrostatic fields. In the case of the latter two properties the index runs from -1 to +1 and we have computed values numerically, taking a grid of points extending 10A around the molecules being compared and excluding the van der Waals volumes of the molecules being compared, since singularities occur at nuclear positions.

The use of similarity measures as a means of designing inhibitors of enzymes can also be used in the reverse fashion - producing enzymes in the form of antibodies.

A long cherished idea has recently proved to be possible (Refs. 9,10). It ought, in principle, to be possible to take a reaction of interest and to compute the transition state. As described above the transition state is then modelled to yield a stable analogue possibly by the use of similarity techniques. The transition state analogue may then be bound to a protein and serve as a hapten against which antibodies may be raised. Since these antibodies are proteins which bind to the transition state of the original reaction they should act as enzymes or 'abzymes' as they have been dubbed (Ref. 11).

CONCLUSIONS

Many of the topics discussed here are perfectly straightforward, in principle, but demand massive computational investment. The advent of the new generation of supercomputers and the impact of the transputer discussed in other parts of this meeting lead to firm confidence that there will be a massive upsurge of activity in the use of quantum chemistry in drug design.

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