

Using structures to inform the optimization of protein kinase inhibitors

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Strategies based upon knowledge of the 3D structure of a drug-receptor have come to play a significant role in drug design. With several cases of inhibitor and drug design aimed at protein kinases now documented, it is possible to identify how and where structural techniques may play a particular role in targeting this important family of enzymes.

In the process of target validation, structures offer insight into peculiarities of candidate kinases that might make them particularly accessible to specific inhibition. This approach will be described for the consideration of PfPK5 and PfPK7, kinases from *Plasmodium falciparum*, as targets for anti-malarial drug design [1].

In the process of lead optimisation, structural studies of kinases bound to inhibitors have revealed several strategies that may be employed to introduce specificity into kinase inhibition [2]. Whereas some of these depend on the equilibrium structures of the target, others depend on static and dynamic properties of protein kinases. Work aimed at characterising the dynamic properties of CDK2 in complex with cyclin A will be described [3], together with a description of tools that seek to make such dynamic studies accessible to the broader community.

Also in the area of lead discovery and optimisation, a widely used principle is that chemical fragments with modest intrinsic potency can provide a useful array of blocks from which more tightly binding inhibitors may be constructed. Two examples will be described where chemical fragments have been identified from crystallographic binding studies of a drug target in complex with diverse binding partners, and this knowledge has been employed in the discovery or optimisation of lead compounds. Lead discovery will be described for competitors for the ‘‘recruitment site’’ of cyclin A, while lead optimisation will be described for the ATP-binding site of CDK2 [4].

References

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