Dr David C. Horwell *

Recipient of the RSC industrially-sponsored award for medicinal chemistry (Knoll Pharmaceuticals)

PERKIN 1 COVER FEATURE

Career

David Horwell graduated from London University in 1967 and then gained his PhD in organic heterocyclic chemistry with Professor C. W. Rees, CBE, FRS at the University of Leicester in 1970. This was followed by post-doctoral appointments at the National Research Council in Ottawa, Canada (1970), at Gainesville, Florida (1971) and at Imperial College, London with Professor Sir Derek Barton, FRS (1972).

Prior to joining Warner-Lambert (in 1982) he was a senior research chemist with Eli Lilly & Co (UK) (1972–1982). He is the co-author of 100 original scientific papers on the design and synthesis of novel drug candidates for disorders of the central nervous system and gastro-intestinal tract, ranging from compounds derived from ergot alkaloids, alicycles, heterocycles and modified peptides. David is also an inventor on 30 US patents. His research at the Parke-Davis Neuroscience Research Centre has focused on the development of kappa opioid analgesics leading to the clinical candidate CI-977, and the design of 'peptoids' from neuropeptides (*e.g.* cholecystokinin, tachykinins, bombesin) leading to the first ligand based design of a non-peptide CCK-B antagonist, CI-988, developed as an anti-anxiety agent. David received the 1990 Warner-Lambert Distinguished Scientific Achievement Merit Award in recognition of this work. In 1996 David was promoted to Distinguished Research Fellow. He has been a Visiting Professor at the University of East Anglia for 9 years and a member of the Editorial Board of *BioOrganic and Medicinal Chemistry Letters* and *BioOrganic Chemistry and Medicinal Chemistry*. He is also on the Editorial Board of the *Journal of Peptide Research*. His current position is Distinguished Research Fellow, Director of Drug Discovery and Deputy Director of Research at the Parke-Davis Neuroscience Research Centre.

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PD 134308 (CI-988). A CCK-B antagonist:
2-Adoc[*R*]α-MeTrpNHCH$_2$[*R*]CH(NHCO(CH$_2$)$_2$CO$_2$H)Ph

PD 154075 (CI-1021). A substance-P (tachykinin NK-1) antagonist:
(2-Benzofuranyl)CH$_2$OCO[*R*]α-MeTrpNH[*S*]CH(CH$_3$)Ph

PD 165929. A bombesin BB-1 (NMB) antagonist:
(2,6-Diisopropyl)NHCONH[*S*]α-MeTrpNHCH$_2$(2-pyridyl)C$_6$H$_{11}$

Fig. 1 Chemical compounds cited in the text.

Research

My major research interests during the past 16 years at the Parke-Davis Neuroscience Research Centre have focused on the design and synthesis of small non-peptide molecules that are able to mimic the actions of peptides. Such molecules are required as preferred therapeutic agents to circumvent the main limitations of using the hormonal and neurotransmitter peptides themselves. These limitations include their poor oral absorption, short half-life *in vivo*, non-selectivity of their largely pharmacological agonist properties, and high cost of manufacture.

The strategy that I adopted to design these non-peptide molecules, termed as 'peptoids', first involved identification of key constituent amino acid residues required by the peptides to bind to their respective receptors. This was achieved by radiolabelling suitable derivatives of, for example, the peptides cholecystokinin (CCK), substance-P and bombesin, then using these in competitive binding assays with modified peptides where the constituent amino acids were either deleted or replaced by alanine. These assays showed that with CCK the non-continuous amino acid motif Trp---Asp-Phe-, with substance-P the continuous motif Phe(Trp)-Phe-Gly-, and with bombesin the non-continuous motif, Trp---Leu(Phe) served as 'hot-spots' to elicit receptor binding affinity. Further introduction of semi-rigid comformational constraints, such as an α-methyl substituent, identification of preferred chirality, and then modification of the N- and C-terminal substituents gave non-peptide single amino acid derivatives with nanomolar binding affinity to their respective peptide receptors. Ligands produced in this way displayed both agonist and antagonist properties in a wide range of biological paradigms.[1,2]

The first 'peptoid' to be designed by this strategy PD-134308 (CI-988) was found to show both gastrin and CCK-B antagonist and partial-agonist properties (Fig. 1). This compound was progressed to the clinic as a novel type of anti-anxiety agent. The substance-P antagonist PD-154075 (CI-1021) is a powerful anti-emetic which is able to block emesis induced by agents such as cisplatin, and also has a novel profile of pain blocking properties. The bombesin antagonist PD 165929 is selective for the human neuromedian-B sub-type of the bombesin receptor and displays a spectrum of modulatory properties of functions in the central nervous system.[2]

An emerging challenge to medicinal chemists is the design and discovery of small molecules that can mimic protein–protein interactions, which are involved in the pathophysiology of many diseases. The drug design issues relating to this are essentially the same as with 'peptoids', except that protein–protein interactions involve a much larger surface contact area which at first appears to offer less likelihood of discovering small molecules as orally bioavailable surrogates. However, site directed mutagenesis studies with proteins do reveal that amino acid 'hot-spots' can be close in 3-dimensional space due to protein folding. These then may serve as a template from which to design small molecule surrogates. Such small molecules would need to be semi-rigid in order for the side chains to access a range of orientations which allow productive interactions with the receptor to take place. Indeed, in analogy with proteins, they would have the ability to associate and disassociate in order to access a wide range energy minima.

Simple polyfunctional aromatic compounds such as 1,8-disubstituted naphthalenes and 1,2,3-trisubstituted benzenes are examples of small molecules that have the ability to self-organise. I have termed these compounds as 'dendroids' (Greek: *dendron*, a tree).[3] An analogy to the properties of these novel molecules would be likened to the branches of a tree or the unfolding of an umbrella to fill a wide area of space. These molecules are able to be derivatised with the functional groups which correspond to the side-chains of the key amino acids found to contribute to binding affinities of the parent protein. These molecules are then optimised by the introduction of further local conformational constraints and other pharmacophores.[3,4]

The strategies that I have adopted for the design of these peptoids and dendroids have been stimulated by a range of concepts drawn from the fields of synthetic organic chemistry, principles of drug design, and biological concepts relating to the mode of action of therapeutic agents. My hope is that these ideas will serve as a catalyst for further drug discovery concepts that will lead to additional therapeutically useful agents for the future.

References

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