COVER FEATURE

Professor C. Robin Ganellin FRS *

Recipient of the RSC 1999 Adrien Albert Medal and Lectureship

Career

Robin Ganellin was born in east London, attended Harrow County Grammar School, and then studied at Queen Mary College, London where he received a first class BSc in chemistry and a PhD in 1958 in organic chemistry under Michael Dewar for research on tropylium chemistry. During this time he also collaborated with Dr Rowland Pettit and discovered the oxidative rearrangement of cyclooctatetraene to the tropylium cation. He spent a period in 1960 with A. C. Cope as a research associate at the Massachusetts Institute of Technology (MIT), where he devised the first direct optical resolution of chiral olefins using platinum complexes. He joined Smith Kline & French Laboratories (SK&F) in the UK as a medicinal chemist, and from 1966 collaborated with Sir James Black and led the chemical research for the discovery of the H_2-receptor histamine antagonists. He is coinventor of the drug cimetidine (Tagamet®) which revolutionised the treatment of peptic ulcer disease. He subsequently became Vice-President for Research at the company's Welwyn facility. In 1986 he was awarded a DSc from London University for his published work on the medicinal chemistry of histamine and drugs acting at histamine receptors. In 1986 he was also made a Fellow of the Royal Society and appointed to the SK&F chair of medicinal chemistry at University College London, a position he still holds. He is author or co-author of more than 200 scientific publications and named coinventor on over 160 US patents.

Professor Ganellin has received international recognition as a medicinal chemist, including the RSC Award for Medicinal Chemistry (1977), the Tilden Medal and Lectureship (1982), Le Prix Charles Mentzer de France (1978), the ACS Division of Medicinal Chemistry Award (1980), the Society of Chemical Industry Messel Medal (1988), and the Society for Drug Research Award for Drug Discovery (1989). He has also been elected into the US National Inventors Hall of Fame (1990). He was elected as a Fellow of QMW College, London (1992) and awarded an Honorary DSc by Aston University in 1995.

Robin Ganellin has also been visiting Professor of Medicinal Chemistry at the University of Kent at Canterbury (1979–89), Advisory Tutor in Chemistry at the Polytechnic of North London (1979–83) and Director of the Upjohn Discovery Unit at UCL (1987–94). Together with Dr A. M. Roe he initiated the biennial RSC Summer School in Medicinal Chemistry in 1981 in the format that exists to date and, indeed, he has lectured at every one of them.

He is a past Chairman of the Society for Drug Research and is currently President of the Medicinal Chemistry Section of IUPAC.

Research

The Adrien Albert Medal and Lectureship is awarded in recognition of the application of heterocyclic chemistry to problems of biological interest.

Adrien Albert was an outstanding heterocyclic chemist, publishing over 120 papers on nitrogen heterocycles. He was also an outstanding medicinal chemist who was a pioneer in using physicochemical properties for relating chemical structure to biological activity.[1] His book on this subject grew out of a course of lectures he gave at University College London in 1948, which is a nice coincidence.

Our research at UCL is in medicinal chemistry and is concerned with the design and synthesis of organic compounds as prototype drugs. In this work we have also relied heavily on the use of heterocyclic chemistry and physicochemical properties.

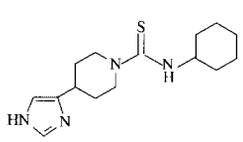
Having been trained as an organic chemist, knowledge of medicinal chemistry had to be acquired "on the job" when I joined SK&F. This is a long learning process but I was very fortunate in that it was accelerated when Dr J. W. Black (now Sir James Black, OM, FRS, Nobel Laureate) arrived to lead the pharmacology. The many discussions we had together introduced me to chemical questions of interest to pharmacologists and gave me a new insight into becoming a medicinal chemist.

The use of the word 'prototype' for a drug implies that a compound can be a useful chemical tool for pharmacologists to help them unravel the mechanistic intricacies of particular physiological processes, often related to disease states, whilst acknowledging that few, if any, such compounds actually become medicines to be used therapeutically.

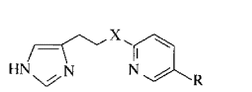
At UCL we collaborate with biochemists and pharmacologists at the frontier of their subject to generate the chemical tools that will be used to definitively characterise a functional cell protein.

Our work has encompassed a wide range of biological applications, from G-protein coupled receptors (for histamine and serotonin), cholecystokinin-inactivating peptidase and HIV-aspartyl peptidase, potassium ion channels, through to phosphatidyl inositol transfer protein (PITP), Transport P and persistent sunscreens.

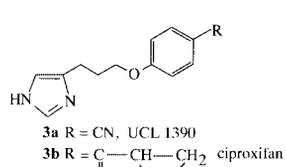
Histamine acts on four subtypes of histamine receptor, and the third subtype H_3, are inhibitory presynaptic receptors which modulate the synthesis and release of histamine at histaminergic neurones in the central nervous system (CNS) and of certain non-histaminergic neurones both in the brain and periphery. Possible therapeutic applications of compounds which block H_3 receptors include various CNS disorders. The prototype H_3 antagonist is thioperamide (**1**) described[2] in 1987,



1 thioperamide



2a X = NH, R = CF_3
2b X = S, R = NO_2 (UCL 1199)



3a R = CN, UCL 1390
3b R = C(=O)—CH(—CH_2—CH_2)—CH_2 ciproxifan

which is potent but was too toxic for clinical study. So far no other antagonist compound has entered beyond phase II clinical trial. We have been collaborating with J.-C. Schwartz and his laboratory at INSERM, Paris, where H_3 receptors were first

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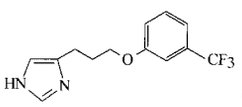
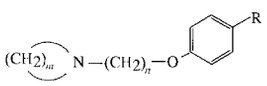
defined, and with W. Schunack in Berlin. Our first approach was to replace the potentially toxic thiourea moiety by amino-heterocycles and open the piperidine ring[3] (**2**). This led to potent phenoxypropylimidazoles[4] which provided several candidate drugs (**3**). We have also obtained isomers (**4**) which are potent agonists and, remarkably do not have basic side chains. We also sought a non-imidazole H_3-receptor antagonist which would have a greater propensity for brain penetration and have recently described[5] *p*-substituted phenoxyalkylamines (**5**); some newer analogues are very potent.



4 UCL 1470



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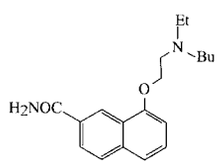
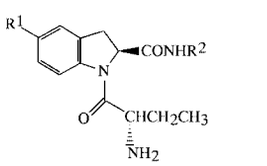
Serotonin acts on at least 14 different subtypes of receptors and we have been interested in ligands acting at the receptor designated 5-HT_1. We have especially investigated naphthalene derivatives (**6**) as 5-HT_{1A} partial agonists; these were also found to act at 5-$HT_{1D\alpha}$ receptors.[6] The latter also provided for an interesting structure–activity analysis whereby blocking potency at 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors correlated with molecular refractivity and the Verloop B_1 size parameter.



6 UCL 1883

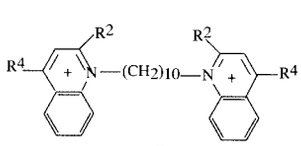


7a butabindide R^1 = H, R^2 = Bu

7b UCL 2000 R^1 = Cl, R^2 = CH_2CF_3

We have designed the first known inhibitor of the enzyme which inactivates the neurotransmitter peptide cholecystokinin-8 (CCK-8). The enzyme had not been fully purified but its activity was isolated from rat brain in the laboratory of J. C. Schwartz in Paris who characterised it as a serine peptidase and assayed the compounds synthesised at UCL. Our approach was to seek a reversible inhibitor since this would be more likely to be selective and non-toxic.[7] This led to the indoline,[8] butabindide (**7a**), a prototype drug which has K_i = 7 nM and is a selective competitive inhibitor which was shown to be active in potentiating the action of CCK-8 and to reduce food intake (satiating effect of CCK-8) in starved mice. Analogues of butabindide have yielded potent inhibitors having K_i as low as 0.4 nM, *e.g.* structure (**7b**).[9]

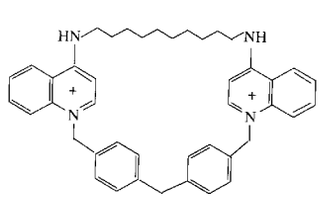
Ion channels selective for K^+ form a large family and we have been synthesizing ligands for calcium-activated potassium ion channels in collaboration with D. H. Jenkinson and P. M. Dunn of UCL Pharmacology for the testing. The small conductance Ca^{2+}-activated K^+ channel (SK_{Ca}) is found in many cell types and selective blockers may have beneficial effects in, for example, myotonic muscular dystrophy, disorders of memory, narcolepsy, and in dismotilities of the gastrointestinal tract. Taking dequalinium (**8**) as a μM lead the pharmacophore



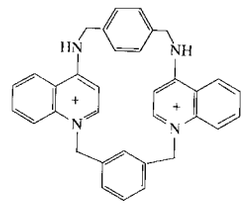
8a dequalinium R^2 = Me, R^4 = NH_2

8b R^2 = H or Me, R^4 = various

was investigated[10] and activity was inversely correlated with the energy of the LUMO.[11] Dequalinium analogues were cyclised to give tetraazacyclophanes and **9** (UCL 1530)[12] provided the first evidence for pharmacological differentiation between the SK_{Ca} channels in liver and neuronal cells; **10** (UCL 1684)



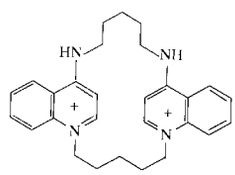
9 UCL 1530



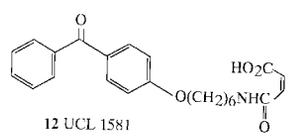
10 UCL 1684

was the first non-peptidic nanomolar inhibitor[13] (IC_{50} = 3 nM) and further developments have yielded an interesting series of bisalkane quinolinium cyclophanes, typified by **11** (UCL 1848) (IC_{50} = 2 nM).[14]

Interest in a persistent sunscreen led us to combine known protective chromophores with a group that would react with the keratin cysteine residues in skin. Thus (**12**) is a Michael base which would accept a thiol group and form a covalent bond, and hence it would bind and it also possesses a UV and visible light absorbing chromophore based on 4-methoxybenzophenone.[15]



11 UCL 1848



12 UCL 1581

References

1 A. Albert, S. D. Rubbo, R. J. Goldacre, M. E. Davey and J. D. Stone, *Br. J. Exp. Pathol.*, 1945, **26**, 16. See also A. Albert, Selective Toxicity, *The Physico-chemical Basis of Therapy*, 7th edn., Chapman and Hall, London, 1985.

2 J.-M. Arrang, M. Garbarg, J.-C. Lancelot, J.-M. Lecomte, H. Pollard, M. Robba, W. Schunack and J.-C. Schwartz, *Nature* (*London*), 1987, **327**, 117.

3 C. R. Ganellin, S. K. Hosseini, Y. S. Khalaf, W. Tertiuk, J. M. Arrang, M. Garbarg, X. Ligneau and J.-C. Schwartz, *J. Med. Chem.*, 1995, **38**, 3342.

4 C. R. Ganellin, A. Fkyerat, B. Bang-Andersen, S. Athmani, W. Tertiuk, M. Garbarg, X. Ligneau and J.-C. Schwartz, *J. Med. Chem.*, 1996, **39**, 3806.

5 C. R. Ganellin, F. Leurquin, A. Piripitsi, J.-M. Arrang, M. Garbarg, X. Ligneau, W. Schunack and J.-C. Schwartz, *Arch. Pharm. Pharm. Med. Chem.*, 1998, **331**, 395.

6 K. Y. Wong, PhD Thesis, University of London, 1997. Design and Synthesis of 5-HT_{1A} Receptor Ligands.

7 C. R. Ganellin, P. B. Bishop, R. B. Bambal, S. M. T. Chan, J. K. Law, B. Marabout, P. Mehta Luthra, A. N. J. Moore, O. Peschard, P. Bourgeat, C. Rose, F. Vargas and J.-C. Schwartz, *J. Med. Chem.*, 2000, **43**, 664.

8 C. Rose, F. Vargas, P. Facchinetti, P. Bourgeat, R. B. Bambal, P. B. Bishop, S. M. T. Chan, A. N. J. Moore, C. R. Ganellin and J.-C. Schwartz, *Nature* (*London*), 1996, **380**, 403.

9 C. Rose, J.-C. Schwartz, F. Vargas, Y. Chen, C. R. Ganellin, S. Samad and L. Zhao, Tripeptidylpeptidase Inhibitors. Patent PCT WO 99/33801 (1999).

10 D. Galanakis, J. A. D. Calder, C. R. Ganellin, C. S. Owen and P. M. Dunn, *J. Med. Chem.*, 1995, **38**, 3536.

11 D. Galanakis, C. A. Davis, C. R. Ganellin and P. M. Dunn, *J. Med. Chem.*, 1996, **39**, 359.

12 (*a*) J. Campos Rosa, D. Galanakis, C. R. Ganellin and P. M. Dunn, *J. Med. Chem.*, 1996, **39**, 4247; (*b*) P. M. Dunn, D. C. H Benton, J. Campos Rosa, C. R. Ganellin and D. H. Jenkinson, *Br. J. Pharmacol.*, 1996, **117**, 35.

13 J. Campos Rosa, D. Galanakis, C. R. Ganellin, P. M. Dunn and D. H. Jenkinson, *J. Med. Chem.*, 1998, **41**, 2.

14 J.-Q. Chen, D. Galanakis, C. R. Ganellin, M. Dunn and D. H. Jenkinson, *J. Med. Chem.*, 2000, **43**, 3478.

15 B. E. Davison, B. C. N. M. Jones, C. R. Ganellin, P. B. Bishop and D. Jack, Compounds containing a Michael acceptor linked to a chromophore and their use in long lasting sunscreen compositions. Patent PCT WO 95/30646 (1995).