Hard graft and 'hoopla' – ACS highlights

The *213th American Chemical Society (ACS) National Meeting* was held in mid-April in San Francisco. The Medicinal Chemistry division featured symposia in honor of William S. Johnson and the Team Innovation Award, which was received by the inventors of the antihypertensive losartan at Dupont-Merck. The meeting featured two first-time symposia: Dopamine D_4 Receptor Ligands, and Patents for Molecular Diversity. There was also a media-filled symposium on Strategies for the Treatment of Obesity.

Virtual chemistry

At the William S. Johnson symposium, Professor P. Wender (Stanford University, Palo Alto, CA, USA) described the iterative process of generating pharmacophore hypotheses and subsequent screening of virtual libraries that resulted in the successful design of a simple phorbol mimetic. Phorbol, a well known tumor promoter, mimics the diacyl glycerol activation of protein kinase C (PKC). Because total chemical synthesis cannot provide useful quantities of phorbol, the design and synthesis of simple phorbol analogs will always be gladly embraced. The pharmacophore hypothesis was kept simple – just limited to hydrogen bond donor and acceptor triads – but clearly not too simple, because the resulting mimetic does not resemble phorbol at all (Figure 1). Professor Wender proceeded to illustrate the use of the hypothesis to design a less (but not much less) complicated bryostatin analog (aka Bryolog). Bryolog exhibits 'significant growth-inhibitory activity against all cancer cell lines tested'.

As part of the Team Innovation Award session, Dr J.D. Rodgers (Dupont-Merck, Wilmington, DE, USA) recounted the battle waged between HIV protease affinity and the desirable pharmacodynamic properties of the Dupont-Merck cyclic urea HIV protease inhibitors. The P2/P2′ groups were in the war-zone and were systematically varied to optimize the four 'P's of selection':

- potency,
- profile,
- protein binding and
- pharmacokinetics.

The winning compound was a non-symmetric orally bioavailable amino-indazole containing a cyclic urea (Figure 2).

During the award session Dr M.J. Wythes (Pfizer, Sandwich, UK) summarized the pharmacological evaluation of eletriptan, a 5-HT_{1D}-like partial agonist in Phase III clinical trials for migraine (Figure 3). It appears that eletriptan may overcome the liabilities associated with sumatriptan (Glaxo Wellcome) – slow onset of action and a substrate for monoamine oxidase. The Pfizer group also reported superior tissue selectivity, oral bioavailability, half-life, efficacy rate and headache response rate.

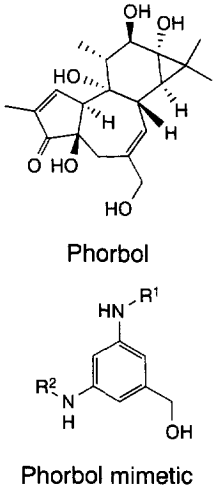

Figure 1. *Phorbol and Wender's phorbol mimetics.*

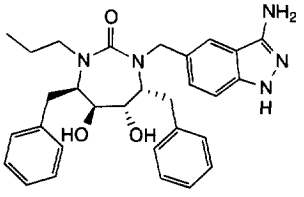

Figure 2. *Cyclic urea HIV protease inhibitor (Dupont-Merck).*

'Rule of 75'

The Dopamine D_4 Receptor Ligands session encapsulated the drug discovery process and the highs and lows associated with this difficult business. It has been postulated that selective dopamine D_4 antagonists may prove to be effective in treating schizophrenia without producing the extrapyramidal symptoms (Parkinsonism) that are associated with typical neuroleptics. Professor P. Seeman (University of Toronto, Canada) suggested that effective treatment of schizophrenia will not be as simple as designing selective D_4 antagonists. Professor Seeman coined the phrase 'rule of 75': for antipsychotic activity 75% occupation of the dopamine D_2 receptors is required. He thought that the atypical antipsychotic clozapine was not an exception to this rule. It may be that what is required is attenuated D_2 affinity with the right balance of D_4 antagonist action. This was the introduction to a series of presentations on the discovery process and preclinical evaluation of selective D_4 antagonists.

Aryl piperazine was the common structural motif in all of the selective D_4 antagonists reported at this session. Most of the lead structures came from high-throughput screening of corporate compound libraries with the exception of Neurogen's aryl piperazine NGD94-1 (Figure 4), which evolved from the benzamide remoxapride. The compounds presented generally showed efficacy in the animal models of schizophrenia without exhibiting the associated extrapyramidal symptoms. Pharmacia &

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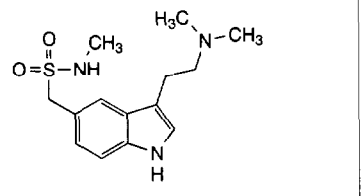
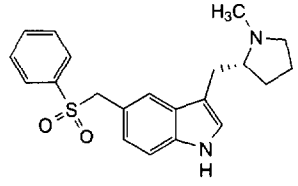
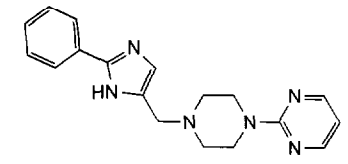


Sumatriptan (Glaxo Wellcome)

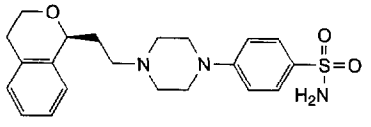


Eletriptan (Pfizer)

Figure 3. *5-HT$_{1D}$-like partial agonists.*



NGD94-1 (Neurogen)



PNU101387G
(Pharmacia & Upjohn)

Figure 4. *Neurogen's selective D$_4$ antagonist NGD94-1 and Pharmacia & Upjohn's clinical candidate PNU101387G.*

Upjohn's D_4 antagonist PNU101387G (Figure 4) is proceeding to Phase II clinical trials. The results from clinical studies of these compounds are eagerly anticipated.

Molecular diversity patents

Without a doubt the most entertaining session of the week was the symposium on Patents and Molecular Diversity – an area that is not normally noted for its entertainment value. The combination of an audience that was looking for guidance and direction on protecting patents in this relatively new area and a collection of opinionated speakers made for an unbeatable combination. This lively session and accompanying round-table discussion, which had to be halted because of time constraints, featured Mr J.W. Caldwell (Woodcock Washburn Kurtz Maciewicz and Norris, Philadelphia, PA, USA), Ms S. Siedman (Brown Martin Haller and McClain, San Diego, CA, USA), Dr B. Elledge (Intellectual Property Law Office, Palo Alto, CA, USA) and Mr J. Kite III (US Patents and Trademarks Office, Arlington, VA, USA). Despite the differences of opinion a common guideline emerged; unfortunately it was the trite 'patent the wheat, not the chaff'. Mr Kite from the Patent Office was able to offer only guidelines, not patent law for the foreseeable future because no court cases are pending. In the end, the patent game remains the same – patent only those compounds with demonstrated utility. Libraries that contain inactive molecules should not be patented because the inactives can be used by a competitor without infringement.

β_3 agonists and obesity

The most entertaining session of the week was followed by the most annoying session: Strategies for the Treatment of Obesity. On the heels of front page newspaper reports of a new 'fat-burning' drug that was going to presented by Dr R.L. Dow (Pfizer, Groton, CT, USA) the lecture hall was filled with cameramen and reporters attempting to establish camera positions with total disregard for the audience caught in the middle of this irresponsible hype-fest. Dr Dow outlined Pfizer's approach to agonizing the β_3 adrenoceptor, which appears to play a role in human energy storage; β_3 agonists may prove to be an effective treatment for obesity. The initial compounds, which had features in common with the well known beta-blockers, were orally bioavailable and very effective in rodent obesity models. This was good for morbidly obese

rats but not for obese humans, because the compounds failed in clinical trials. Subsequent cloning of the human β_3 receptor showed that the original compounds were not as active against the human as the rodent β_3 receptor. Re-screening of the compounds against the human β_3 receptor led to the identification of a new series of closely related beta-blocker-like structures. We must now wait to see how the story unfolds.

In summary, in spite of the β_3 agonist 'hoopla', no significant breakthroughs were reported during the week, just reminders of the difficulties associated with drug discovery and development and the fact that only hard work and the data that result from it will allow us to chemically disrupt biological processes.

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Book review

Molecular Modeling: Basic Principles and Applications

by H-D. Höltje and G. Folkers, VCH, 1996. DM 168 (xii + 194 pages) ISBN 3 527 29384 1

This is the fifth book in the series *Methods and Principles in Medicinal Chemistry* published by VCH. The authors state their intention is 'to provide support for the beginner', and indeed this book provides a fine introduction to many of the techniques used in biomolecular modeling.

The authors begin in Chapter 2 by considering small molecules: issues such as how to generate 3D coordinates and optimize geometries are discussed. Along the way, they interweave discussions of force fields, minimizers, solvent models, charge models and many other 'basic topics' that are a prerequisite for understanding modeling. They then switch to a discussion of somewhat more advanced topics, including electrostatic potentials, grids, comparative molecular field analysis (CoMFA), pharmacophores and superposition. This is a lot of material, but it is well laid out, clearly presented and well supported by figures and tables. Each subchapter reads as a distinct unit, making it easy to read the book in easily digestible instalments. References are given at the end of each section: a very helpful, but sadly uncommon practice.

In Chapter 3, the design of serotonin receptor antagonists is used to exemplify much of the material on small molecule modeling. Chapter 4 then moves on to a different scale and discusses protein modeling, including homology modeling, secondary structure, sequence alignment, distance geometry, etc. Geometry optimization and molecular dynamics are presented, as well as solvent models. Again, many topics are included, and are covered well. A very nice point – often overlooked – that is brought up in this chapter is the validation of protein models: how accurate are they and how can you tell? Chapter 5 illustrates the modeling of protein–ligand complexes with an analysis of antigen presentation by major histocompatibility complex (MHC).

Any introductory text has to avoid two great sins: putting in too much material and not putting in enough. This book tends towards omission (admittedly, the more venial of the two). The meat of the book, ignoring the introduction and the appendices, is only around 150 pages. One might have hoped for somewhat more coverage of certain topics such as docking, *de novo* design, conformational searching for small molecules, and the prediction of ligand–receptor binding affinity. However, the book does cover many current topics in biomolecular modeling.

The one flaw of the book is an advertisement for Tripos software, thinly disguised as a scientific article but with no authors and no references, included at the back (after the appendices and the index). I have never seen such an 'advertorial' in a computational chemistry book before. On the title page is an acknowledgement thanking Tripos for financial assistance. Such advertising, clearly marked as such, is not a problem; book publishers need to make money like everyone else. However, the 'advertorial' is quite another matter; an inexperienced end-user (the target audience for this book) may not be able to discern 'fact from fiction'. This practice raises red flags in many directions; it should be made clear whether other software companies were offered the chance to advertise, whether the content of the book was in any other way influenced by Tripos (there is no evidence for this) and what form the 'sponsorship' took. Book-buyers should be wary of such practices.

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