## IN BRIEF

ANTIBACTERIAL DRUGS

### A convergent enantioselective route to structurally diverse 6-deoxytetracycline antibiotics.

Charest, M. G. *et al*. *Science* **308**, 395–398 (2005)

Many antibiotics are based on natural products, such as the tetracyclines. However, the complexity of natural product structures is a major obstacle to synthesizing novel derivatives with the aim of enhancing their usefulness as drugs. Charest *et al.* report a short and efficient route for synthesizing a range of tetracycline derivatives that could be studied as potential new candidates for combating the widespread problem of antibiotic resistance.

G-PROTEIN-COUPLED RECEPTORS

### GPCR antitarget modeling: pharmacophore models for biogenic amine binding GPCRs to avoid GPCR-mediated side effects.

Klabunde, T. & Evers, A. *ChemBioChem* **6**, 876–889 (2005)

G-protein-coupled receptors (GPCRs) that bind biogenic amines such as dopamine, serotonin and adrenaline have proved to be excellent drug targets. However, the key role that such GPCRs have in cell signalling can pose a risk for new drug candidates that show 'side affinities' for them. The authors present pharmacophore models that can rationalize the affinity of numerous drug candidates for various key GPCRs that bind biogenic amines, which could be valuable in developing drugs with improved safety profiles.

COMPUTATIONAL CHEMISTRY

### "*In situ* cross-docking" to simultaneously address multiple targets.

Sotriffer, C. A. & Dramburg, I. *J. Med. Chem.* **48**, 3122–3125 (2005)

In standard 'docking' approaches for investigating ligand–protein interactions, separate calculations are needed for each protein target of interest, which is time-consuming, both in terms of computing time, and also with respect to set-up and analysis of multiple runs. Sotriffer and Dramburg present an approach in which multiple proteins can be addressed in a single docking run, which might help in more efficiently addressing issues such as selectivity and protein flexibility.

ALZHEIMER'S DISEASE

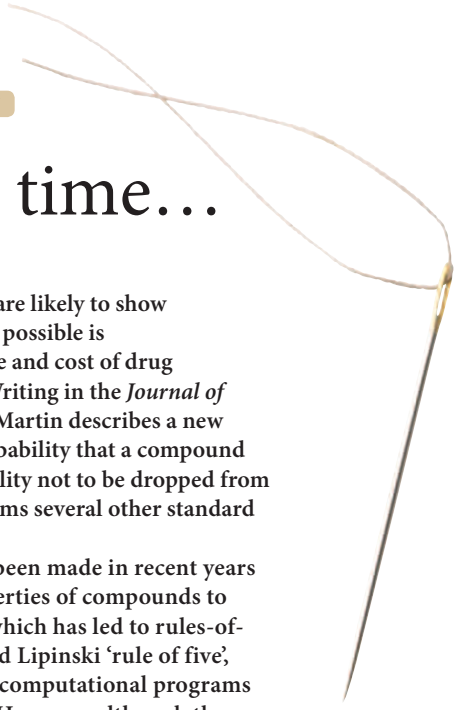
### Diverse compounds mimic Alzheimer disease-causing mutations by augmenting Aβ42 production.

Kukar, T. *et al. Nature Med.* **11**, 545–550 (2005)

Increased production of the 42-amino-acid form of amyloid-β (Aβ42) has been linked to the development of Alzheimer's disease. Some commonly used painkillers have been shown to inhibit the production of Aβ42, but Kukar and colleagues now identify a number of compounds, including cyclooxygenase 2 (COX2)-selective agents such as celecoxib and the antilipidaemic agent fenofibrate, that raise Aβ42, which suggests that studies to investigate the effects of such agents on the pathogenesis of Alzheimer's disease are warranted.

COMPUTATIONAL CHEMISTRY

# A stitch in time…



**Filtering out compounds that are likely to show poor bioavailability as early as possible is important in reducing the time and cost of drug discovery and development. Writing in the *Journal of Medicinal Chemistry*, Yvonne Martin describes a new method for predicting the probability that a compound will have sufficient bioavailability not to be dropped from development, which outperforms several other standard such methods.**

**Considerable efforts have been made in recent years to use physico-chemical properties of compounds to predict their bioavailability, which has led to rules-of-thumb, such as the widely used Lipinski 'rule of five', and also many more complex computational programs for making such predictions. However, although there are examples in which the consideration of physico-chemical properties has been useful in optimizing bioavailability within a specific series of compounds, the generalization of such studies to diverse molecules has not been convincingly shown.**

**Using rat bioavailability data for ~500 diverse compounds for a range of therapeutic targets that had been collected over a number of years at Abbott, Martin first examined properties that have traditionally been considered to be associated with bioavailability, such as molecular mass, octanol–water log *P*, log *D*, polar surface area and the number of rotatable bonds. Analysis of the ability of various methods to generate a probability that a compound will have a bioavailability, *F*, >10% in the rat on the basis of these properties revealed that none could successfully categorize the compounds.**

**To explore further the lack of predictivity of established methods, the author investigated whether they fail for certain classes of compounds, and ionic state was one of the classifications considered. Interestingly, the results of this investigation indicated that the physical properties that govern the bioavailability of compounds that are negatively charged at pH 6–7 differ from those that govern the bioavailability of compounds that are uncharged or positively charged at this pH. For negatively charged compounds, the key property is polar surface area, whereas for the other compounds the rule of five has predictive ability.**

**On the basis of these observations, a bioavailability score (ABS) was developed that assigns a probability that a compound will have *F* >10% in the rat. This same categorization also distinguishes compounds that are poorly permeable from those that are permeable in Caco-2 cells, and poorly and well-absorbed compounds tested in humans. So, ABS could be a valuable tool for filtering compounds before experimental screening and for selecting compounds for purchase.**

***Peter Kirkpatrick***

**References and links**

**ORIGINAL RESEARCH PAPER** Martin, Y. C. A bioavailability score. *J. Med. Chem.* 5 Apr 2005 (doi:10.1021/jm0492002)

**FURTHER READING** Van de Waterbeemd, H. & Gifford, E. ADMET *in silico* modelling: towards prediction paradise? *Nature Rev. Drug Discov.* **2**, 192–204 (2003)