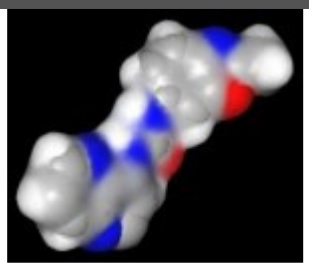
## Rod Porter

**From:** Rod Porter [News@rodporterconsultancy.emailmsg.net] on behalf of rod.porter@rodporterconsultancy.com
**Sent:** 17 June 2013 17:29
**To:** roderick.porter@btinternet.com
**Subject:** Medicinal Chemistry News April 2013





Medicinal Chemistry News from Rod Porter

June 2013 vol 4. no. 3

**Dear Dr Porter,**

### 1. Welcome

Welcome to the June edition of the Medicinal Chemistry newsletter from RodPorterConsultancy.

My thanks to both Cyclofluidic and ChemPharmaServe for sponsoring this issue of the newsletter - this allows me to keep issues rolling out.

Optibrium has announced the release of a new version of their multiparameter optimisation software Stardrop version 5.4 and includes a Bioster™ module for improved search for bioisoteres and the Derek Nexus™ module for enhanced toxicity predictions.

Do have a look at the CompChem Solutions services a range of complementary activities to those of RodPorterConsultancy.

Please forward this newsletter to your colleagues – just follow the link at the bottom of this mail. Any comments, criticisms or suggestions for future articles are very welcome please mail Rod Porter - I am happy to give attribution.

I ran ***in aid of Action Duchenne*** in a team with current and former GSK'ers in the Oxford Town and Gown 10K run (May 12th) in memory of James Kew a friend and former colleague from GSK who died tragically last year. If you wish to donate its not too late please follow the link. The total raised currently stands at about £6,300 - GSK will double the total of all contributions made.

My next mailing is planned for early September 2013.

Wishing you a great summer and every success with your research.

In this issue:



## Cyclofluidic

Cyclofluidic is working with collaborators in the pharmaceutical industry to optimise hits to quality leads using its proprietary CyclOps™ microfluidics platform. CyclOps™ allows biological data to be collected on each compound minutes rather than weeks after it has been designed allowing true integrated data driven medicinal chemistry - saving time and money. A Cyclofluidics scientist will be presenting some of the companies research findings at the 2nd SCI/RSC Symposium on Continuous Processing and Flow Chemistry, 24th/25th September 2013 meeting and for a very recently published example of the companies work please click here. For more information or to discuss evaluation and collaboration opportunities please contact Elizabeth Farrant, Business Development Director at Cyclofluidic.

## ChemPharmaServe

ChemPharmaServe is an innovative chemistry solution provider, established in Cambridge UK in 2004, helping biopharmaceuticals companies to fast-track their drug discovery and development projects. Their core expertise spans preclinical development and cGMP production of drug substances.

One of their most popular services is the provision of metabolites, custom-made compounds and labelled molecules.

They take the risk out of compound supply by investing in the chemistry, solving the technical issues and taking the responsibility for compound delivery to their clients allowing them to focus on drug discovery challenges. The costs are borne by them and they get paid only when products are delivered to our client's satisfaction. For more information and contact details please visit ChemPharmaServe.

## SMR - next meeting

The next Society of Medicines Research meeting Partnerships: future models for drug discovery will take place on 20th June 2013 at Lilly Windlesham. 'This timely meeting explores the new paradigms emerging in drug discovery and development, bringing together senior figures from the worlds of big Pharma, academia, public and charitable institutions. These speakers will highlight opportunities for future models to lead to successful research and development programmes and explore the changing dynamic of interactions between the traditional models of academia, funders and industry.' The 3rd October meeting Kinases: New Horizons will be held at the National Heart and Lung Institute South Kensington.

# 2. State of the industry

## How depressing can things get

I an sure we all take pride in working in pharma research (at least I hope we do) but this generics story - blog from Derek Lowe and the original article - makes depressing reading.

OK so that was generics but now in research - the emerging story of suspected fabricated data from the GSK research group in Shanghai published in Nature Medicine in 2010 with the GSK statement about it and a FierceBiotech comment which inludes a link to In the Pipeline with extensive discussion. Jingwu Zang who headed up the research centre in Shanghai and was a co-author is apparently no longer in the company. It does however, beg the question of how many more examples of this will emerge from that group and how were the checks and balances designed to prevent this sort of thing circumvented. Its important to emphasise however, that the fabrication is suspected as opposed to proven and one of the issues is apparent duplication of images at this stage the Nature Medicine blog does carry a slightly different perspective. In more recent developemts GSK has now (from FierceBiotech) halted a PhI study of an MS drug while there is a little bit of a counter attack from Jingwu Zang - this isn't going to settle down quickly.

## EMA 2012 annual report

Hopefully on a more positive note we tend to talk about the FDA but lets not forget the EMA that has recently published its 2012 annual report. A highlight was the approval of the first gene therapy in Europe along with a total of 59 positive opinions for approval. 96 marketing authorisation applications were received of which 19 were for orphan therapies, a 36% increase on 2011. Approximately one third of initial applications are being received from companies defined as SME's with 68% of the orphan designated agents from SME's. For the full report visit the EMA website.

# 3. In Brief

## Nature Focus on epigenetic dynamics

A series of reviews discussing the role of dynamic epigenetic changes in disease and development is available at least short term free of charge. Papers include Regulation of nucleosome dynamics by histone modifications, Determinants of nucleosome positioning, DNA methylation dynamics in health and disease, Epigenetic programming and reprogramming during development, Functional implications of genome topology and Structure and function of long noncoding RNAs in epigenetic regulation.

. Nature Structural & Molecular Biol. 2013. 20, 258 Apologies I could not got this link to work!

## Sleep

A subject close to my heart, sleep, is the topic for discussion in a Nature Outlook Supplement. Discussion covers sleep and circadian rhythms and disease - obesity, mood disorders and neurodegeneration amongst others and the way modern life interferes with our sleep cycles - shift work, jet lag and artificial light. A couple of snippets; amyloid levels fluctuate diurnally decreasing during sleep, red light has a reduced stimulant effect on the suprachiasmatic nucleus relative to blue light - perhaps we should change domestic lights to a more red emitting spectrum. The argument with disease does beg the question of cause and effect so often but there does seem to be a shift (finally) in thinking towards the idea that sleep disruption and circadian rhythm changes can precipitate disease.

## Delaying Alzheimer's

An interesting paper **1** has suggested that environmental enrichment can protect against hippocampal LTP impairment by Aβ oligomers and activate β2 adrenergic receptors. The authors also report that activation of β2 receptors by isoproterenol is also protective. Effects are mediated via the cAMP/protein kinase A pathway and a variety of methods are used to characterise the effects reported including, for example, evidence that Aβ-oligomers reduce levels of β2 receptors and promotes internalisation. Also protective effects of isoproterenol are reported in vivo are reported following 4 week dosing in their drinking water while the antagonist propranolol blocked the beneficial effects of environmental enrichment. One concern to me is that all the small molecule pharmacological tools such as forskolin, "selective" cAMP PKA inhibitors KT5720 or H89, isoproterenol itself and β-adrenergic receptor antagonists used are not particularly selective, furthermore it is difficult to establish a PK/PD relationship using the in vivo dosing protocol required with isoproterenol – how much central β2 receptor stimulation is required and was achieved. This isn't the only report of adrenergic receptor involvement in dementia. Another recent report **2** touches on genetic links and the link of several signalling pathways between AD and β-adrenergic receptor blockade.

Life is of course never simple in the CNS so inevitably there are apparently contradictory reports such as the observation **3** that β-amyloid activates the β2 receptor leading to PKA mediated activation of the AMPA receptor. Activation of AMPA has been shown to lead to neuronal cell death. Finally, in this far from comprehensive tour, a report **4** of epidemiological studies that suggest β-receptor blockade is beneficial in reducing occurrence of Alzheimers in hypertensive patients. However, this was focused on antagonists it would be very interesting to see what epidemiological data there is on the merits of β-receptor agonist dosing and onset of Alzheimers like symptoms and to investigate this phenomenon further with alternative adrenergic receptor ligands.


. S. Li et al Neuron, 2013, 77, 929
. K v. q. Luong and L. T. H. Nguyen Am. J. Alzheimers Dis. Other Demen. May 20, 2013 doi: 10.1177/1533317513488924
. D. Wang et al FASEB J 2010, 24, 3511
. J-T Yu et al Brain Res Bull. 2011, 84, 111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## 4. Medicinal Chemistry

## Compound dispensing methods and their errors

An important (and scary) contribution to the literature **1** on screening/SAR generation analysing and following-up on data from two AstraZeneca EphB4 inhibitor patents which reported biological data determined by tip based serial dilution and acoustic dispensing with direct dilution. The scary bit is that there is no correlation (R2 = 0.25) of IC50 data generated using the two methods with ratios of IC50's ranging between about 2 and over 250, nor did compounds even show the same rank order of potency via the two different dispensing methods. Not surprisingly based on these differences, analysis of the data generated by the two methods would send medicinal chemists in very different directions. The acoustic dispensing method gave the lower IC50's and also generated a pharmacophore that closely matched with pharmacophores based on inhibitor bound crystal structures and that successfully predicted activity of additional compounds not in the publications used in the initial analysis. In contrast the tip based serial dilution data gave a pharmacophore lacking two hydrophobic motifs and showed no ability to predict. As the authors highlight it is rare for datasets comparing and contrasting results from two different assay methods to be published – although they do cite a few more. There are no strong correlations of physicochemical properties with activity from either the acoustic or tip based dispensing although it would be good to look at the ratio of the IC50's from the two methods and lipophilicity indices.

Its worth noting one of the authors works for Labcyte with commercial involvement in acoustic dispensing of compounds, however, this by no means reduces the impact of what, to me seems an invaluable analysis of a problem too often ignored. This paper does raise a whole series of concerns over the generation of data and the way it is used – I am thinking here of both screening against targets but also off target and selectivity screening and the generation of ADMET data. How often are the jumps in activity we get so excited about real or an artefact of our assaying? It also raises the concerns over comparing data generated in different labs becoming an increasing issue with the warehousing of large amounts of data in the likes of Chembl and Pubchem.

As this paper deserves there has been some blogging activity and active discussion from for example Derek Lowe and Daniel Evanko in a Nature Methods blog – interestingly no one seems very surprised or is disputing the content. Finally a blog from one of the authors showing the trials and tribulations of getting this manuscript published – over a year after the first submission and after multiple rejections – if at first you don't succeed try, try again.


. S. Ekins et al PLoS ONE 8(5): e62325. doi:10.1371/journal.pone.0062325


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## Predictive modelling of safety

A thought provoking article **1** from AZ global safety assessment critiquing the value of modelling safety related attrition data. The team analysed the progression of AZ compounds through preclinical development PhI and PhII. A particular difference that the authors highlighted was that they did not find the same relationship of cLogP and PSA to toxicity that Pfzer reported **2** for their analysis of preclinical toxicology failures. Indeed the AZ groups analysis suggested that cLogP >3.0 and PSA<75 was the best place to be, a direct contradiction of Pfizer. Clearly datasets are relatively small and some differences in method could account for at least some of the discrepancy.

No connection between Fsp3 as a measure of complexity and toxicity as proposed by Lovering **3** was found nor was a PLS model constructed

by another AZ group **4** found to be especially predictive for tox of basic compounds.

They go on to analyse the 63 small molecule drugs approved between 2009-2012 from Chembl and found that roughly two-thirds therefore had PSA >75 and about the same proportion had a cLogP >3.0. This doesn't of course reveal the full extent of the birth-pangs of each of these molecules – how many had failed on the way to get to these successes? It is worth noting, howeever, that four of the top ten sdelling small molecule drugs have cLogP>3 and PSA <75.

One area where I did disagree with their interpretation was relating to target promiscuity. While the authors argued promiscuity can be good for efficacy and I would agree with that. However, having activity against some specific targets cardiac ion channels or 5-HT2B receptor, for example, is likely going to give rise to problems and I do believe should be screened to exclude such activities at an early stage.

Another comment is that the focus is on cLogP around 3.0 as the authors themselves suggest different ways to measure LogP can give some differences and it might only take small shifts in numbers to potentially significantly change the results as reported here. It would also be interesting to see how this analysis changed with a shift in the cut-off of cLogP – say 3.5 or 4.0. Finally one thing that keeps nagging me is that cLogP is a very blunt instrument, being able to quantify distribution of polarity/lipophilicity sounds like it could be quite revealing as to why some drugs can have higher lipophilicities than seems appropriate but have never seen this done. Of course I still strongly feel that controlling lipophilicity is really important for a project.


. D. Muthas, et al Med. Chem. Commun., 2013, Accepted Manuscript
. J. D. Hughes, et al Bioorg. Med. Chem. Lett., 2008, 18, 4872–4875
. F. Lovering, MedChemComm, 2013, 4, 515–519.
. T. Luker, et al, Bioorg. Med. Chem. Lett., 2011, 21, 5673–5679.


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## Structure and fragment based GPCR drug design

Two papers have recently published taking different approaches to structure based screening for GPCR ligands one from Heptares using a fragment based approach and one using VAST (versatile assembly on stable templates).

Taking the last first **1** the Evotec/Alchemia team used a pyranose based library of ligands to build a model of the MCH-1 receptor binding site. This information was then used to refine a model of the MCH receptor and to run a virtual screen which identified 10 new chemotypes as MCH antagonists with the most potent having IC50's around 100-200nM (Scheme 1, 1, 2). Perhaps the key point here is the design of the pyranose library which is used to act as a tripeptide mimicking motif which the authors propose is sufficient to identify for each GPCR a unique binding motif. The principal is expanded on elsewhere by the same authors **2**. It seems this is a nice example of using tool molecules (the VAST library) to refine a model to then allow more "traditional" virtual screening to take place and avoids the bias of starting with optimising a known structure. This is slightly reminiscent of the excitement (in some quarters) I think going back 20 years now when monosaccharides were being promoted as GPCR antagonist templates and as peptidomimetics but in that case they were being used in an attempt to generate candidates not as stepping stones to develop screening strategies.

In the second approach **3** (commentary **4**) the Heptares StAR technology was used to support SPR screening of a subset of their fragment library against the human β1 adrenergic receptor which led to the identification of two low uM hits (3, 4). These were optimised using both knowledge of the numerous β1 receptor ligands and docking studies which led to (5, 6) The authors subsequently generated crystallographic data for the lead ligands (5, 6) in the turkey β1 StAR receptor. Key features of the approach were the excellent ligand and lipophilic efficiencies observed. Fragment screening has rarely been applied in the GPCR area (although see e.g. **5** cited in **3**) partly because of the challenges of screening low expression level proteins at very high drug concentrations' and partly due to the difficulties of generating isolated protein for application of biophysical screening and structural methods. This is an important contribution to both fragment based and GPCR research, however, it would be good to see this strategy applied where less background ligand information is known and to consider issues of selectivity as the arylpiperaziens identified tend to be promiscuous aminergic receptor ligands. Finally the authors discuss possible differences in functional activity of the optimised ligands (5, 6) but no data was presented it will be interesting to see this discussed in future papers.

To my mind these two papers complement each other nicely the VAST approach being used to increase confidence in the structure of the target GPCR to allow optimisation of fragments' that may have been identified through a range of methods – in silico or wet screening. Arguably the refinement of structural information to support virtual screening would allow more moderate drug concentrations to be assayed – say < 100uM rather than higher concentrations favoured in some screening strategies in the expectation that fragments that have undergone some form of preliminary virtual screen have a better chance of demonstrating at least modest affinity.


. A. Heifetz et al J. Chem. Inf. Model., Article ASAP DOI: 10.1021/ci4000882 Publication Date (Web): April 26, 2013
. G. Abbenante et al J. Med. Chem. 2010, 53, 5576−5586
. J. A. Christopher et al, J. Med. Chem., Article ASAP, DOI: 10.1021/jm400140q Publication Date (Web): April 09, 2013
. B. D. Stevens J. Med. Chem., Article ASAP DOI: 10.1021/jm400561w, Publication Date (Web): April 24, 2013,
. S. P. Andrews et al Med. Chem. Commun. 2013, 4, 52−67.


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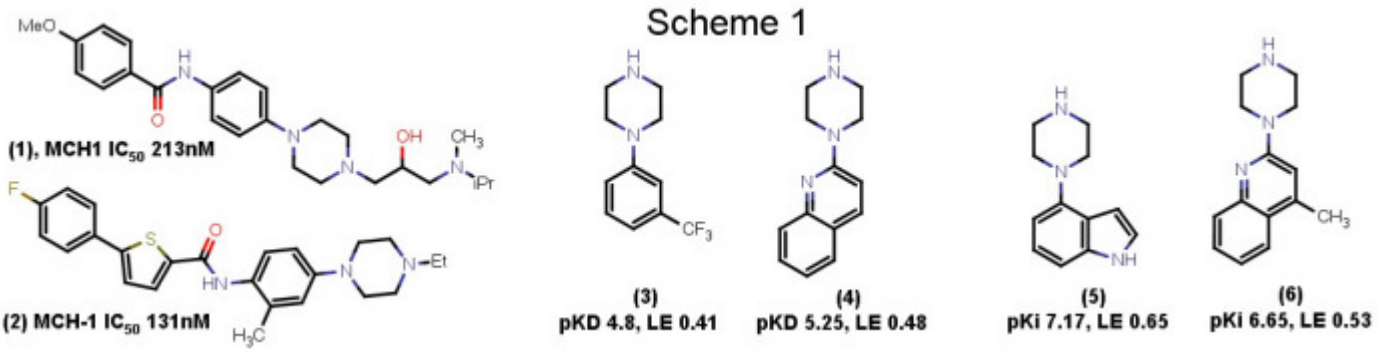


## Fluorescently tagged GPCR ligands

A couple of recent reviews highlight some subtleties in preparing fluorescently tagged ligand's for GPCR's. The first **1** focuses specifically on adenosine receptor ligand's while the second **2** covers most GPCR classes. Both emphasise the importance of identifying; the correct ligand, correct point of attachment, the right length (and composition) of the linker and finally the fluorescent tag itself. The linker can have a major impact on the affinity of a ligand for example **1** the adenosine receptor ligand TQO conjugated to a fluorescent tag TQO-C8-X- BODIPY630 TQO (linker **=** CO(CH2)2CONH(CH2)8NH) with an all carbon linker adenosine A3 pKi 7.78. TQO-PEG-X-BODIPY630 (linker = CO(CH2)2CONH((CH2)2O)2(CH2)2NH) with a PEG linker adenosine A3 pKi 9.36. However, the fluorescent tag also influences affinity such that switching from a BODIPY630 to a Cy5 ligand gave about a 300 fold loss in affinity at the A3 receptor.

It is not always clear where the fluorescent tag is disposed relative to the receptor target for example it has been suggested that some tags may sit in the membrane while others may simply be accessing solvent space. As an observation however, the length of some of these linkers is reminiscent of some of the linkers used for designing bivalent GPCR ligand's as for example in a recent report on D2/D3 receptor ligand's **3** or bivalent opioid/chemokine ligand **4**.


. E. Kozma et al Bioorg Med . Chem. Lett. 2013, 23, 26
. A. J. Vernall et al Br. J. Pharmacol., 2013 doi: 10.1111/bph.12265
. S. Gogoi et al ACS. MED. CHem. Lett., 2012, 3, 991
. Y. Yuan et al Med. Chem. Commun., 2013,4, 847-851


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## Transporters and membranes

The debate over the role of lipid membranes in the permeability of drugs into and through cell membranes continues with a new paper **1** from the Doug Kell school of thought that espouses the exclusive role of transporters (influx and efflux) arguing that passive permeability through lipids essentially does not happen. Arguments in favour of their proposal include the modest lipid:protein molar ratios in cell membranes; the already recognised role of some transporters in the distribution of drugs, the role of kinetics in transporter distribution and genetic studies in yeast. The latter system has been developed by the group and allows identification of the transporters in yeast involved in getting drugs into the yeast itself. This to me is some of the more compelling data from the group. A key point that the group make is that there is evidence that a compound may exploit several transporters with specific examples cited – for example Lipitor interacts with at least seven transporters. Equally the converse is true with individual transporters themselves recognising multiple drugs. The authors comment on the blood brain barrier specifically citing literature suggesting the role of transporters in delivering drugs to the CNS has been substantially underplayed. The paper includes an impressive (overwhelming?) 587 references to primary sources or reviews - I will not pretend to having read that many of them!

The counterpoint paper **2** which is dissected by Kell's article is co-authored by a group from various academic and big pharma labs and argues that passive permeability has considerable relevance to permeability of molecules alongside carrier mediated transport. One of many points of dispute is around molar ratios of lipid and protein with figures from the two sides ranging between 1:1 **1** and 40:1 **2** lipid/protein molar ratios the latter would more likely allow for passive permeability although even here one might argue for limited lipid surfaces bearing in mind relative surface areas of lipids and transporter proteins. Perhaps help in resolving at least the extent of lipid surfaces may come from direct characterisation of cell membranes through, for example, nanometre scale secondary ion mass spec **3**.

Assertions are being made on both sides of the arguments in reality more data on more transporters is required to help convince one way or another. A nagging doubt for me is that unless efflux transporters are involved brain free drug concentrations do tend to broadly match free plasma concentrations a bit of a coincidence if only transporters are involved I would have said - see one example **4**. I do still tend to the view that the role of transporters is underestimated and needs a lot more investigation but passive permeability is not dead yet.


. D. Kell et al Drug Discovery Today 2013, 18, 218
. L. Di et al. Drug Discovery Today 2012, 17, 905
. J. F. Frisz et al PNAS 2013 110, E613-E622
. J. Watson et al Drug Met. and Disp , 2009 37:753–760


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## Transport(ers) at altitude

Not wishing to look fixated on transporters but an interesting article **1** looks at changes in ocular transporter expression levels under hypoxic conditions – a stimulus of neovascularisation and subsequent retinopathies. Rats kept under hypobaric hypoxic conditions for 2 weeks showed >1.5 fold changes in 29 of 84 trasnporters examined at the mRNA level. Functional effects were also observed.

Clearly if it is assumed that drugs are only distributed by transporters this could have significant consequences for the ability to deliver drug to diseased or compromised tissues and supports the importance of using relevant (diseased) tissues for testing. One wonders also at the consequences of living at high altitude and the consequent chronic hypoxia on transporter expression – a literature I have never got into

. R. S. Kadam et al, Mol. Pharmaceutics, 2013, 10 (6), pp 2350–2361

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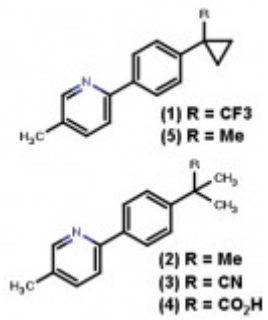
## Isosteres

A *tert*-butyl isostere with improved metabolic stability has been reported – namely the cyclopropyl trifluoromethyl group as in (1). Typically this seems to increase metabolic stability as measured by t1/2 in rat liver microsomes by generally more than four fold and a little less in human liver microsomes relative to the corresponding *tert*-butyl analogue (2). Examples of both aryl *tert*-butyl and *tert*-butyl amide replacements are given. In direct comparison with, for example, 2-substituted-2-methyl-propionitriles (3) or 2-substituted-2 methyl-propanoic acid (4) the cyclopropyl trifluoromethyl group seems to give superior metabolic stability and offers another alternative to the *tert*-butyl group. The cyclopropyl methyl analogue (5) was marginally less stable than a *tert*-butyl group. This new group is about 0.1 log units more polar than the tert butyl group (Chemaxon v 6.0) but as expected is about 0.5 log units less polar than 2-substituted-2-methyl-propionitriles.




. L. Bell et al ACS Med. Chem. Lett., Article ASAP DOI: 10.1021/ml400045j

## Measurement of intracellular unbound drug concentrations

Estimation of intracellular drug concentrations and more particularly pharmacologically, toxicologically, or metabolically relevant free drug concentrations has been a bit problem over the years. Thus an approach to address this problem is very welcome **1** in this case focusing on HEK293 cells considered to lack transporters and metabolizing enzymes. However the authors did extend the study beyond HEK293 cells to include hepatocytes although not perhaps more directly disease relevant cell lines. The approach uses a combination of determination of total cell concentration at steady state (Kp) and intracellular drug binding (Fu, cell) to allow estimation of intracellular unbound drug accumulation ratio Kpu,u. The authors argue that the approach circumvents the issues around assuming free intracellular drug equates with free plasma drug concentration as cells can achieve substantial free drug concentration gradients due to transporter effects – vide supra! Indeed liver cells have been cited to manage upto 500 fold increased concentrations based on transporter effects. Furthermore the authors demonstrate that plasma protein binding tends to be lower than binding to HEK293 cell components presumably reflecting the fact that plasma protein represents a more limited set of binding components for a compound in particular missing membrane. However there is a better correlation of HEK293 cell binding with binding to hepatocyte cells albeit needing a small correction thought to be due to increased lipid and protein in mature hepatocytes relative to HEK293 cells.

As expected increased lipophilicity increased intracellular binding as did shape and amount of hydrogen bonding. Charge also had an influence as did intracellular pH. For example decreasing lysosomal pH by treatment with quinidine increased binding of basic compounds but acidic and neutral compounds showed no effect. This does raise the issue of course of what is the pH of the cell and its organelles when looking at disease model cells. This approach is reminiscent of the work done a few years ago now, particularly by groups at Pfizer and GSK looking at estimating free drug concentrations in brain tissue based on total brain concentrations and a brain fraction unbound.

. A. Mateus et al, Mol. Pharmaceutics, Article ASAP DOI: 10.1021/mp4000822 Publication Date (Web): May 15, 2013

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## Detecting intramolecular H-bonds

Exploiting intramolecular H-bonds may be a way of extending permissible chemical space through masking and unmasking (depending on the environment) of polar functionality modulating physicochemical properties, interactions with proteins and PK/PD. The involvement of intramolecular H-bonds in drug design was examined in some detail a few years ago **1**. However, it is not always easy to predict the propensity of a structure to form intramolecular H-bonds an issue which has now been approached **2** through use of ΔLogP oct/toluene for a compound and its difference from ΔLogP oct/toluene for a closely related compound incapable of forming an intramolecular H-bond. Newly developed experimental protocols and development of predictive software specifically taking into account 3D considerations in intramolecular H-bond formation are reported. As a rule of thumb two guidelines were identified briefly:-

- if ΔLogP oct/toluene of a control compound > than ΔLogP oct/toluene of the target compound the compound has a high likelihood of invoking an intramolecular H-bond (Category I)
- if ΔLogP oct/toluene of a control compound < than ΔLogP oct/toluene of the target compound the compound has a low likelihood of invoking an intramolecular H-bond (Category II). The predictive software could be used for both control and target compounds.

To highlight relevance particularly for CNS drug design the reader is referred to e.g. **3** although it's worth remembering that a lot of this goes back much earlier than that – see for example work from old colleagues of mine **4** who used ΔLogPoct/hexane for estimating (whole) brain:blood ratios.


. B. Kuhn et al J. Med. Chem., 2010, 53, 2601−2611.
. M. Shalaeva et al J. Med. Chem., 2013 DOI: 10.1021/jm301850m Publication Date (Web): May 27, 2013.
. M. H. Abraham et al . J. Pharm. Sci., 2010, 99, 2492−2501.
. R. C. Young et al J. Med. Chem., 1988, 31, 656.


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## 5. Chemistry

### Enantio and diasterodivergent dual catalysis

With some analysis suggesting that chirality and increased sp3 character can be beneficial for overall drug properties e.g. **1** new methods for introducing chirality are always welcome. In particular a recent paper from Carreira's group **2** (commentary **3**) outlines a highly efficient (chemical, enantio- and diasteroselective) method for generation of two contiguous stereocentres. The work centres on using two different chiral catalysts (each available as both enantiomers) to independently activate each of the two reagents to control the formation of the two stereocentres. The approach has been termed stereodivergent dual catalysis and is illustrated with α-allylation of branched aldehydes with an allylic alcohol using a chiral amine to activate the aldehyde and a chiral iridium catalyst to activate the allyl alcohol – scheme 1. Clearly there are many potential extensions of this strategy.


. T. J. Ritchie and S. J. F. MacDonald Drug Discovery Today 2009, 14, 1011
. S. Krautwald et al Science 2013, 340, 1065
. C. S. Schindler and E. N. Jacobsen Science 2013, 340, 1052


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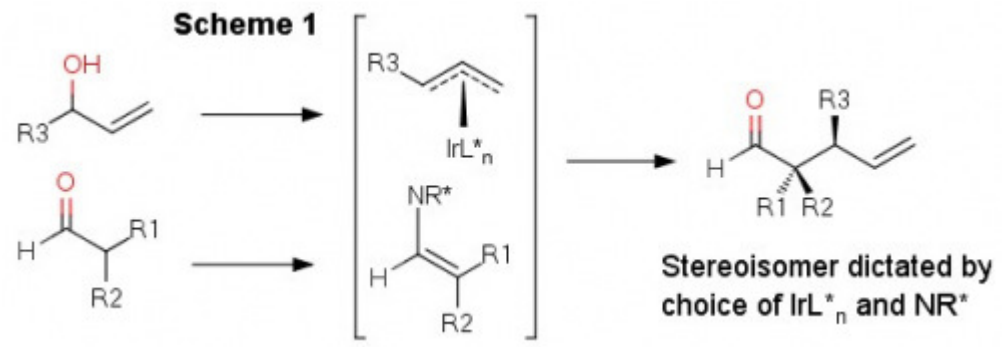
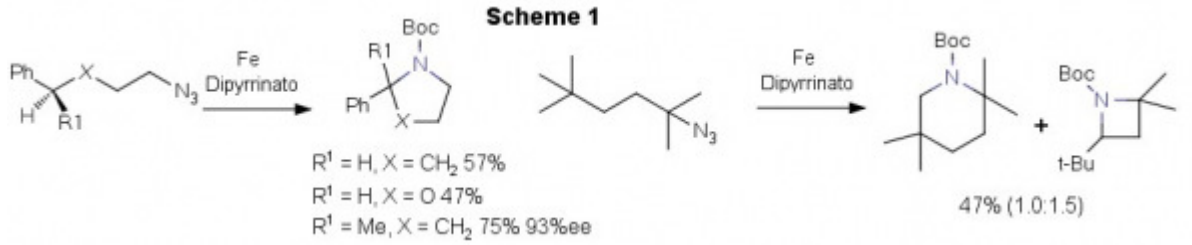



### CH Bond amination

I have written a couple of times now about CH bond activation and without apology here is another example **1** this time of CH bond activation and amination to give cyclic secondary amines – generally trapped with a protecting group. It seems to me that (increasingly predictable) CH bond activation has enormous potential in drug discovery to generate complex materials rapidly from simple precursors functionalise molecules at a late stage and perhaps speculatively be able to generate putative metabolites rapidly via CH-oxidation. Back to amination – 4-, 5- and 6-membered rings can be formed although larger rings are not while some hetero atom substitution is tolerated – scheme 1. Yields are moderate to good although only a few isolated yields are quoted.


. E. T. Hennessy and T. A. Betley Science 2013, 340, 591


## 6. Conferences

Conferences Rod Porter Consultancy will be attending - click on the links for the agenda.

- Partnerships: future models for drug discovery SMR Lily Horsham, 20th June
- ELRIG Manchester 3rd, 4th September
- RSC Medicinal Chemistry Symposium Cambridge 8th-11th Sept
- Kinases: New Horizons, SMR NHLI London, 3rd Oct

**Meetings Attended**

Meetings attended during APril and May included SciNovo Unlocking the value of drug candidates, Stevenage Biocatalyst, 23rd April, 24th Symposium on Medicinal Chemistry in Eastern England, Hatfield 25th April 2013, Blood brain barrier club Kings College London (invitation only), Target Validation Workshop RSC Burlington House 30th April, Choosing the Right Target in Drug DIscovery, SCI London 15th May. If you spot any items from these meetings that you would like to know more about I should be able to supply some notes to you. Of course nothing compares with actually attending the meetings and speaking with old and new friends.

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## 7. Also of interest

Using the web, all sorts of interesting resources appear. If you come across any resources that you would like to share please contact Rod Porter.

### Royal Society of Chemistry - BMCS

Good news for RSC Bioorganic and Medicinal Chemistry Section members - we now have free access to MedChemComm - spot the papers now being cited from this journal below! To access a paper click on the interested article title which will send you to a log in page with a greyed out PDF link - fill it in with your RSC membership number (username) and your RSC password Log in (Subscriber Access) the PDF isno longer greyed out for that session and you can view in html or pdf format.

These sites are featured because has found them of interest - featuring these sites does not reflect any endorsement or accountability for their use from Consultancy

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## 8. About RodPorterConsultancy

Established in 2009 RodPorterConsultancy offers medicinal chemistry consultancy services to a widening client base of small biotechs, academic and charitable bodies. Services offered include assistance with or proposal of medicinal chemistry strategies, with a particular interest in CNS targets, independent, expert review of ongoing programmes and projects, review, critique and refereeing of research proposals, third party due diligence and more. If I can't help you perhaps my informal network of contacts can. Visit the RodPorterConsultancy website, see my linked-in page or contact Rod Porter directly for more information.

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## About CompChemSolutions

CompChem Solutions offers computational chemistry & computational biology services to academic and industrial researchers involved in drug discovery and development. Established in 2004 and based in Cambridge, UK, CompChem Solutions has a wealth of experience across the range of chemoinformatic and computational chemistry disciplines, having worked extensively in many therapeutic areas, particularly oncology, inflammation and pain. Recent publications from CompChem Solutions have exemplified the use of in silico methodology for target validation and identification, particularly within the context of phenotypic screening. Services can be provided in virtual screening, rational ligand design, protein homology modelling, library design, ADMET property prediction, and many other areas.

We are currently offering fixed-price virtual fragment screening services for a limited period. Please contact Susan Boyd at CompChem Solutions for more details on any aspect of CompChem Solutions services.

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