Rod Porter

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Sent: 19 July 2012 17:53
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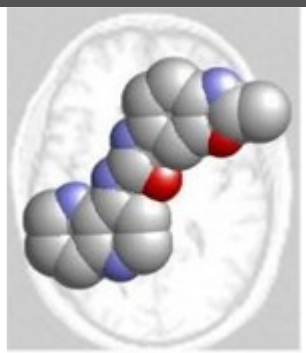
Subject: Medicinal chemistry news May 2012



Medicinal Chemistry News (formerly NiKem News)

May 2012 vol 3. no. 2

Hello,

1. Welcome

Welcome to this slightly delayed Medicinal Chemistry newsletter formerly NiKem News but now brought to you by the same author but now from Rod Porter Consultancy. If you are happy to continue to receive this newsletter from myself, retaining all the usual features, please add the mailing address to safe senders, if you don't want to receive this again please go to the unsubscribe link at the end.

Its been a busy couple of months plus a short holiday visiting my daughter while she was working in Morocco - a lovely break - and my excuse for the delay in getting this to you.

I hope you find this publication useful - any comments, criticisms or suggestions for future articles are very welcome please mail Rod Porter. I am happy to give attribution.

Please feel free to forward this newsletter to your colleagues – just follow the link at the bottom of this mail.

Half Marathon Charity Run

As I have for the past couple of years I have entered the Great North Run half marathon which will take place on the 16th September. I am running on behalf of the Alzheimers Society to support them in their excellent support for patients and carers and in memory of Mum who died of the disease. If you would like to donate please go to my Just Giving page - thank you.

In this issue:

2. In Brief

The decline of pharmaceutical R&D efficiency - a diagnosis

With many recent discussions on how to fix pharma's R&D problems here a paper looking at diagnosis **1**. Firstly meet Eroom's law - the opposite of Moore's transistor law - which states the number of new FDA approved drugs halves per $Bn dollars spent about every 9 years - inflation adjusted. Primary diagnoses identified include, "Better than the Beatles" ie you have to be better than whats already out there, the self explanatory cautious regulator, the throw money at it tendency perhaps more an option in bigger pharma and "basic research - brute force" which covers things like implementation of HTS and focus on high selectivity although there is a trend back to phenotypic screening and the tendency to throw large teams at a problem - when smaller may be more efficient if slightly slower. I also liked the proposal of the Chief Dead Drug Officer a senior level appointment with a remuneration

package largely based on how good his solutions were for fixing Eroom's law 10 years post his detailed report.

A commentary on this paper with some suggested solutions **2** perhaps paints a brighter tone suggesting larger companies suffer from several cultural problems, the "tyranny of the committee", "stagnation through risk avoidance" and continual reorganizing or megamerging that so many companies indulge in. There are additional commentaries linked to this article and some useful discussion associated with it. Proposals from **2** are devolving risk taking and encouraging risk eg with early clinical studies, delayering and finally creating a degree of stability for the scientists concerned.

1. J. W. Scannell et al Nature Reviews Drug Discovery 2012, 11, 191
2. Bruce Booth Forbes

Back to top

Drug Delivery

Intranasal drug delivery to the CNS has been rumbling around for a long time now with discussion extending from, does it really happen (see below) to how to maximise residence time in the nasal cavity - nice topic that one - to how best to optimise the delivery device. So I was interested to see the recent report **1** on the intranasal administration of Neuropeptide S demonstrating anxiolytic effects in mice. The authors also tracked NPS target neurons through out the brain using a fluorophore labelled NPS. Things have clearly moved on downstream as well since I was last directly involved in this field - for example, there is an intranasal Neuropeptide Y clinical trail for PTSD currently recruiting. Also I need to highlight work from the de lange group on Remoxipride **2** showing that about three quarters of the dose absorbed into the brain from intranasal dosing is via the nose the rest is via the systemic circulation. It was also noted that absorption into the ECF was relatively slow compared with drug administered iv.

1. I. A. Ionescu et al Neuropsychopharmacology 2012, 37, 1323
2. S. Stephens et al, Drug Met. Disp., 2011, 39, 2275

Back to top

Abscinazole-E2B, a practical and selective inhibitor of ABA 8'-hydroxylase CYP707A

Its unusual but good to see an item on plant biochemistry in Bioorg Med Chem. - the report of an inhibitor of abscisic acid 8-hydroxylase which improves drought resistance - a splendid irony here in the UK as we have had the wettest April for the last 100 years!

1. M. Okazaki et al, Bioorg. Med. Chem. 2012, 20, 3162

Back to Top

3. Medicinal Chemistry

Lipophilic efficiency and Compound Quality

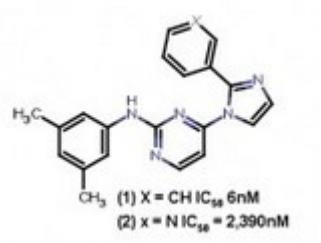
Its fair to say that most (all?) medicinal chemists have bought in to the idea that a measure of lipophilic ligand efficiency (LLE) is a reasonable determinant of compound quality. It is therefore healthy that this is checked every so often as done in a recent report **1** comparing lipophilic ligand efficiency ie LogXC50 - cLogP/D with an alternative measure - lipophilicity corrected ligand efficiency (LELP) - the ratio of LogP and LE. Interestingly the latter measure appears to be a better determinant of good hits and particularly of fragments. It also seemed to be a particularly effective predictor of some - although not all - developability assays and often performs better than LLE eg there is extensive overlap of measured P-gp substate/non-substrate using LLE while LELP gives clear discrimination. The authors conclude that LELP is particularly valuable in the earlier stage of lead optimization with LLE playing a greater role as compounds progress. This study also supports the notion that LLE and LELP support enthalpy driven optimization.

Yet another parameter but well worth consideration in my opinion.

1. A. Tarcsay et al J. Med. Chem. 2012, 55, 1252

Back to top

Matched Molecular Pairs and Activity Cliffs

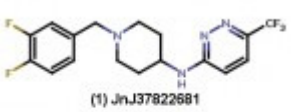


A precis **1** of a longer paper **2** discusses the attributes of oxadiazole regioisomers in particular the substantially greater polarity of 1,3,4-oxadiazoles compared with the other regioisomer. This rather follows on to a paper **3** discussing activity cliffs defined by dramatic differences in activity or selectivity with only minor structural changes - a nice example highlighted by the authors is of the two VEGFR compounds (1) and (2). These themes are combined in a paper due out shortly **4** where activity cliffs are defined using matched pair analysis as opposed to the frequently used and perhaps inappropriate Tanimoto score.

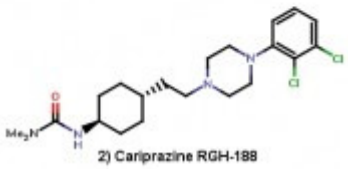
1. K. Muller J. Med. Chem., 2012, 55, 1815
2. J. Bostrom et al, J. Med. Chem., 2012, 55, 1817
3. D. Stumpfe and J. Bajorath J. Med. Chem., 2012, 55, 2932
4. X Hu et al, J. MMP-cliffs: systematic identification of activity cliffs on the basis of matched molecular pairs. J Chem Inf Model, in press

Back to top

Dopamine antagonists



Development of new dopamine antagonists for schizophrenia is continuing with two recent accounts with angles that caught my eye. Firstly from JnJ the Medicinal Chemistry account **1** of their fast dissociating D2 antagonist JNJ-37833681 (1). The focus of their approach was to identify fast dissociating antagonists based on the hypothesis that slower dissociation rates were associated with side effects. In addition (1) had excellent selectivity against a range of unwanted GPCR's such as α, H1 and muscarinic. Factors influencing dissociation rates, particularly lipophilicity and molecular weight are discussed by the same group in a separate paper **2** featured in a previous newsletter.



Slightly different is the account **3** of the identification of Cariprazine (RGH-188) a D2/D3 antagonist (2) the invention of which arose from a lead identified as an impurity during the scale-up of a pyridylsulphonamide D2/D3 antagonist. Sounds like good observation and follow-up to me.

1. X. Langlois et al J. Pharm. Expt. Ther., 2012 April doi: 10.1124/jpet.111.190702
2. G. Tresadern et al, Bioorg. Med. Chem. Lett., 2011, 19, 2231
3. E. Ágai-Csongor Bioorg. Med. Chem. Lett., 2012, 22, 3437

Back to top

GPCR structures, dissociation kinetics, biased ligands and dimers

Something of a blizzard of structures now for GPCR's. First up **1** (see also **2**) the structure of the human M2 muscarinic acetylcholine receptor bound to the antagonist 3-quinuclidinyl-benzilate . The antagonist is in a long aqueous pore extending about two-thirds of the way through the membrane. "The orthosteric binding pocket is formed by amino acids that are identical in all five muscarinic receptor subtypes, and shares structural homology with other functionally unrelated acetylcholine binding proteins from different species". The reason for highlighting this paper is that in parallel appeared a report **3** of the structure of the M3 receptor with the the slow dissociation-rate antagonist Tiotropium. The receptors show many similarities but one possible reason for the slow kinetics of Tiotropium at the M3 receptor is the hypothesis, supported by molecular dynamics, that the drug pauses at an allosteric site on the way to binding at the orthosteric site with a similar trajectory on dissociation.

Opioid receptors have submitted to crystallisation with both a dimeric kappa receptor with the selective antagonist JDTic bound **4** and the mu **5** structures being reported. Analysis of the binding of JDTic and SAR based on modelling and site directed mutagenesis generated some hypotheses on generating selective kappa ligands. The mu receptor also crystallised as a dimer through helices 5 and 6. (see also commentary **6**). All intriguing stuff I have written in the past on possible drug intervention at dimer interfaces. Another example **7**, albeit not a crystal structure, of a possible physiological role of GPCR dimers with a report of heterodimerisation of the Growth Hormone Secretagogue receptor 1a GHSR1a and the dopamine D2 receptor influencing dopamine induced Ca2+ mobilization.

Some structural work is discussed **8** on the structural origins of receptor bias using NMR to track 19F labelled cysteine residues at the intracellular ends of helices 6 and 7. The study showed that the helices are in equilibrium between two different conformations in the ligand free state with the relative populations changing on binding of agonists.

Finally and really starting to pull everything together the review **9** from the Heptares group using all this structural information to explore the druggability of GPCRs. This is nicely complemented by the report on structure based drug screening for GPCR's **10**.

1. K. Haga et al Nature 2012, 482, 547 doi:10.1038/nature10753
2. R. L. Kow and N. M. Nathanson Nature 2012, 482, 480
3. A. J. Kruse et al Nature 2012, 482, 552
4. H. Wu et al Nature 2012 published on line 21st March doi:10.1038/nature10939

A. Manglik et al 2012 published online 21st March doi:10.1038/nature10954
L. Buchen Nature 2012, 483, 383
A. Kern et al Neuron 2012, 73, 317
J. J. Liu et al Science 2012, 335, 1106 See also S. R. Sprang and J. C. Elk Science 2012, 335, 1055
J. S. Mason et al Trends in Pharmacol. Sci., 2012, 33, 249
B. K. Shoichet and B. K. Kobilka Trends in Pharmacol. Sci., 2012, 33, 268

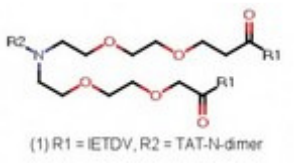
Protein-Protein Interactions - PDZ domains

Returning to a favourite topic of mine – PDZ domains and some interesting reports highlighting efficacy in stroke models with a monomeric PSD95 inhibitor **1**, a report of a highly potent PDZ domain inhibitory dimer **2** and compounds active in oncology models **3**. PSD95 is a synaptic scaffolding protein tethering NMDA receptors and nNOS via their PDZ binding motifs. The first compound TAT-NR2B9c – the nine C-terminal residues of the NMDA receptor linked to TAT as a delivery vector improved functional outcomes and reduced tissue damage as determined by MRI, histology and transcription capacity in the primate. Profiling in lower species has been reported elsewhere see **1**. Drug was delivered at low mg/kg doses by iv infusion. The dimeric agent (1) targets both the NMDA and nNOS PDZ domains simultaneously giving very high target potency the delivery vector is again TAT and efficacy in a mouse stroke model at 3nmol/g iv. Finally on PDZ domains another chemically modified peptide **3** targeting the PDZ domain of GIPC as an approach to treat cancer though I must admit these compounds arent the highest affinity in the world. Here an 8-mer with an N-terminal myristoyl tail to assist cell exposure and two bromobenzamide modified lysines (thought to extend the interaction domain of the peptide – how far could one go while reducing the length of the peptide?) give cell permeable compounds with activity in animal models of pancreatic and breast cancer. So these are peptides and oral activity is highly unlikely which of course brings us back to more medicinal chemistry in an underexploited area or delivery strategies.

Continuing the PPI theme briefly, a nice summary has appeared **4** of some of the success stories emerging in PPI research and some of the continuing issues. Trying to address some of those issues comes from Blundell and colleagues **5** looking at structural biology and PPI's and of course fragments.

D. J. Cook et al Nature 2012, 483, 213
A. Bach et al Proc. Natl Acad. Sci. USA, 2012, 109, 3317
C. R. Patra et al ACS Chemical Biology 2012, 7, 770
A. Mullard Nature Rev. Drug Disc., 2012, 11, 173-175
H. Jubb et al Trends Pharmacol Sci 2012, 33, 241

Back to top



4. Synthetic chemistry

CH bond activation and functional group insertion

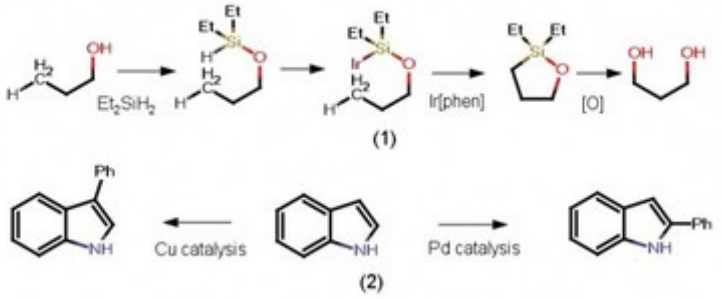
I have discussed this topic a couple of times now – but no apologies for revisiting it as the potential impact on medicinal chemistry is to my mind substantial. Firstly a short review **1** from one of the significant contributors to the field Christina White. A brief history of the field is followed by a summary of the White groups work using Fe(PDP) for selective oxidation using hydrogen peroxide/acetic acid as oxidant. A key finding has been the predictably of the regiochemistry of reaction based on the same rules that dictate reactivity of "traditional" functional groups.

Following on from this is the report **2, 3** of catalytic functionalisation of unactivated primary C-H bonds directed by an alcohol. The procedure is based on silane insertion to a gamma carbon of a hydridosilyl ether and subsequent oxidation (1) - an iridium-phenanthroline catalyst is required.

A different aspect of functionalisation of CH bonds – amongst others – with subsequent introduction of additional functional groups is considered in the review by Hickman and Sanford **4** of the use of catalytic high valent copper and palladium in synthesis. An interesting section of the review contrasts some of the differences – often subtle – between Cu and Pd catalysts as in for example arylation of indoles (2).

M. C. White Science 2012, 335, 807
E. M. Simmons and J. F. Hartwig Nature 2012, 483, 70
For News and Views commentary D. M. Schultz and J. P. Wolfe Nature 2012, 483, 42
A. J. Hickman and M. S. Sanford Nature 201, 484, 177

Back to top



5. Conference Reports

The last couple of months have been fairly quiet on the conference front- just picking up in the last week. Consequently I havent had time to prepare any reports - possibly for next time. In the meantime if you would like to find out a little more about any of the individual talks please do contact Rod Porter at the least I can mail my notes/hieroglyphics to you. The agendas can be seen by following the links to the conference descriptions below.

- The UKQSAR meeting hosted by Novartis at Horsham
- 23rd symposium on Medicinal Chemistry in Eastern England hosted by Eisai at Hatfield.

To at least bring you one conference report, if not written by myself, see this blog report on the 7th Fragment Based Drug Design conference organised by CHI in San Diego

Back to top

6. 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.

More databases

I havent had a chance to explore this search engine crossing over several databases – simple searching is free closely as yet but it looks interesting One irritation is that it is currently optimised for Google Chrome and Mozilla browsers. There is also a discussion on in Chug (Chembl User group Linked-in group) you will need to be a member of the group to access it.

This looks a good one as well an extensive compilation of modelling software - certainly some of which is freely downloadable to all although I havent had a chance to check more than a couple as yet.

FBDD

Have I mssed something or is it that proponents of Fragment based drug design seem to be particularly enthusiastic bloggers - this site has caught my eye in the recent past and is regularly updated and commented on.

Protein methyltransferases poster

Nature Chemical Biology presents a poster highlighting the human protein methyltransferase families, the small molecules known to target them and the prospects for PMT-focused drug development

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

Back to top

Just a reminder that any feedback on the content or suggestions for new content will be gratefully received please e-mail Rod Porter

Wishing you every success with your research.

7. About Rod Porter Consultancy

Established in 2009 Rod Porter consultancy 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 network of contacts can

See my linked-in page for more background or contact Rod Porter.

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Back to top

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