Rod Porter

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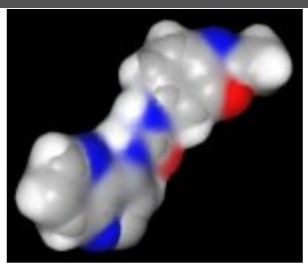

Medicinal Chemistry News from Rod Porter

February 2013 vol 4. no. 1

Dear Dr Porter,

1. Welcome

Welcome to the February edition of the Medicinal Chemistry newsletter from RodPorterConsultancy. I hope 2013 is treating you well - at least so far!

My apologies for a bit of a delay I took on writing a review anticipating January was going to be reasonably quiet, which has turned out not to be the case - not that I am complaining! A couple of weeks typing with four fingers, two thumbs and a slab of plaster did slow me down a bit as well - fortunately now back to normal

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

Just announced is version 5.3 of Stardrop now featuring library enumeration, visual filtering and new clustering tools amongst other features. More details can be found here. The latest Optibrium newsletter discusses the latest ventures to expand Stardrop further.

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.

My next mailing is planned for April 2013. If you would like to make sure you keep receiving this newsletter please add the senders address to your safe senders list.

In this issue:

SMR

The next Society of Medicines Research meeting 'Therapeutic Opportunities in Infectious Diseases' will take place in March. This conference will provide an overview of the current unmet clinical need for new anti-infective agents and will present international speakers from academia and industry with examples of novel approaches and agents including small molecule approaches to the treatment of TB, HCV and HIV and vaccines in clinical trials for the prevention of malaria and meningococcal infection.

Eating Disorders Week

This week is Eating Disorders Awareness week - please visit the b-eat website for more information.

2. State of the industry

The final approval count for 2012 inc in Feb 2013 newsltter

It looks like I was a little out on FDA compound approvals last year, in my December newsletter, with the total now confirmed at

39 the highest since 1996 and with eight approvals in December 1. Encouragingly 18 new mechanisms of action are exploited by these 39 compounds.

Not surprisingly a third of these were in the oncology field and a further tranche for rare diseases. The compounds themselves can be seen here.

While all this is good news a dampener from Thompson Reuters/Deloitte is that while the top 12 pharma have had an increase of a third in approvals of new drugs compared with the previous year the forecast revenues had declined by a third. Of course while some product launches do exceed expectation that is far from true for all. Still the outlook for the same "big 12" companies looks encouraging with a near doubling in forecast value of products in late stage development now compared with the previous year.

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3. In Brief

Functional metabolites

There is something inherently pleasing (to me anyway) that endogenous metabolites often discarded as irrelevant have clear (patho)physiological roles – it seems so elegant. Thus a review **1** on Kynurenines in the CNS caught my eye. The kynurenine pathway is the main metabolic route for tryptophan. It particularly addresses the physiological and path¬ological implications of kynurenine pathway activity in the central nervous system. The pathway has been implicated in neurodegenerative disorders, pain syndromes and autoimmune diseases including Huntington's disease, migraine and mul¬tiple sclerosis. Candidates in preclinical development are also discussed.

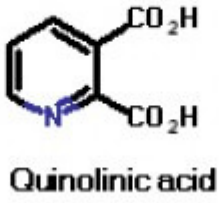
A bit like the London bus joke – another review **2** just in on the role of kynurenine metabolites of tryptophan in the CNS and in regulating the immune system. The review highlights, amongst others, the role of kynurenine in acting on the arylhydrocarbon receptor, quinolinic acid as an NMDA receptor agonist and cinnabirinic acid as a metabotropic glutamate agonist.

Continuing the theme of metabolites the report of metabolites in epigenetic enzyme regulation Class III histone deacetylases are regulated by NAD+ and has been known for some time **3** but now a report **4, 5** of beta-hydroxybutyrate a ketone body generated by calorie restriction or low carbohydrate diets that may be acting as an inhibitor of Class I HDAC's. 1 and 3 and 4. Admittedly IC50 of beta-hydroxybutyrate against HDAC's was in the millimolar range but this is the level achieved during prolonged fasting or in diabetic ketoacidosis.

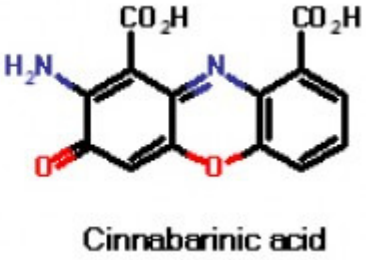
Finally **6** the importance of threonine as a source of cellular glycine and acetyl–CoA and consequently elevated SAM in mouse embryonic stem cells relative to mouse embryonic fibroblasts is discussed 5. The SAM levels reflect the amount of H3K4me3 and consequent epigenetic regulation.

1. L. Vécsei et al Nat. Rev. Drug Disc., 2013, 12, 64
2. T W Stone et al Trends Pharmacol. Sci., 2013, 34, 136
3. S. Imai and L. Guarante Trends in Pharmacol Sci 2010, 31, 212
4. P. Sassone-Corsi Science2013, 339, 148 DOI: 10.1126/science.1233423
5. T Shimzu et al Science 2013, 339. 211
6. N Shyh-Chang et al Science 2013, 339, 222

Kynurenine



Quinolinic acid



Cinnabarinic acid

Predicting human PK

A valuable review of the application of in *silico, in vitro* and *in vivo* PK for the prediction of human PK from AZ **1** is just out. It appears to be targeted to DMPK scientists but it seems pretty handy as a survey of the field to me as a medicinal chemist.

1. K. H. Grime, P. Barton and D. F. McGinnity Mol. Pharmaceutics, Article ASAP DOI: 10.1021/mp300476z Publication Date (Web): January 29, 2013

Screening issues

Another hazard (see Nov 2012 newsletter) for screening is concern over metal impurities in samples **1**. An article from Roche

discusses the problem of zinc contamination that they have had problems with. Recommended solution by the authors runa counter screen in the presence of metal chelator PTEN. OK so that's zinc should we expect problems with very low level concentrations of other metals that may have been used catalytically or stoichiometrically in synthesis perhaps copper or palladium?

. J. C. Hermann, et al ACS Med. Chem. Lett., Article ASAP, DOI:10.1021/ml3003296 Publication Date (Web): December 20, 2012

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4. Medicinal Chemistry

Halogen bonding

A comprehensive review **1** on halogen bonding in medicinal chemistry makes a convincing case that we should forget regarding halogens as simply lipophilic blobs. The key point is the recognition of the anisotropic distribution of electrons in ArHal – excepting fluorine with its extreme electronegativity – in which a positively charged surface, the sigma hole, on the z-axis is available for interaction with a Lewis base. Covered in the review are a consideration of the strength of interactions and their manipulation by additional electron withdrawing substituents on an aromatic ring; interaction geometries and energy boundaries with a comparison of theory and practise – based on crystallography studies; a survey of successful application of halogen bonding and finally a defense of halogen. Halogens have often been regarded as a liability – too lipophilic and adding a lot of molecular weight for very little specific gain in target interaction – "its just a lipophilic effect". The authors argue that affinity gains can be substantial claiming upto 100 fold for ArH – ArI based on an overt halogen bond and that while they are dense their actual contribution to molecular size is much below that of their molecular weight. I have some sympathies with these views although I do beg to differ on the attractiveness of aryliodides - I don't think the authors touched on photostability.

Always good value is a blog from Derek Lowe on this paper and the resultant discussion on halogen bonds again the ambiguity of how to account for the high atomic weight of halogen is a topic for discussion.

. R Wilcken et al J. Med. Chem., Article ASAP Publication Date (Web): January 03, 2013

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Above the neck - species differences, disease, cell lines and *in silico*

Apologies for yet another CNS centric article – but on second thoughts no apology after all CNS drug discovery is only drug discovery in microcosm issues are really little different to those in most other therapeutic area. From a group at UCB **1** comes a valuable review of CNS literature looking in particular at two aspects that rarely get given sufficient consideration. First is a look at species differences in the CNS and second the impact of disease states. Differences in physiological parameters such as CSF production or ECF turnover that affect CNS drug distribution are considered. Differences in BBB transporter levels are also reviewed. Amongst several examples, BCRP is reported to be expressed at substantially higher levels in human brain than in mouse. It is also certain that our picture of differences in expression of transporters inter (and intra) species is incomplete. Examples of documented changes in the CNS in humans with a range of diseases are reviewed with for example impact of age (not much we can do about that) and neurological diseases which of course does beg a cause or effect question. One example of physiological evidence of change in the BBB with therapeutic relevance was the treatment of cerebral meningitis with β-lactam antibiotics which in healthy subjects do not significantly access the CNS. Perhaps one area not considered enough is the impact of induced disease in animal modles and the impact on their BBB behaviour be it disruption of the barrier or changes in transporter protein expression – can these lead to false impressions of efficacy in preclinical species? Quite rightly the authors comment that there is a long way to go getting to grips with all the complexities they raise but its good to see the discussion taking place.

I have featured quite a lot about predictive models this time and here is another paper **2** looking at predicting efflux ratios and BBB permeation based on chemical structure and combining passive permeability and afflux by P-gp. The authors claim that they can distinguish compounds with high or low efflux ratios as well as CNS+/CNS- compounds although I am a little sceptical what that actually means if it is based purely on defining whole brain:blood ratios. This work may be useful in helping to virtually identify ways of modifying P-gp substrates to minimise (or maximise if desired) efflux transport - not always straightforward in my experience.

An important progression of the hCMEC/D3 human brain endothelial cell line is the report **3** of the quantitative proteomic analysis of transporters and tight junction proteins in that cell line in comparison with primary human brain endothelial cells and in HUVEC's as a non-brain endothelial cell line. Many targets were expressed in both hCMEC/D3 and human brain endothelial cells although exceptions included, amongst others, the transferrin receptor ABCA8 and LAT1. Thus this model does have value but still represents an incomplete picture of transport based permeability across a cultured cell membrane – although it seems to me rather more pertinent than simply looking at cell lines over expressing P-gp

A useful summary **4** of the blood brain barrier interface related to small and macromolecule disposition of compounds outlining some of the tight junction, transport, endocytic and transcytotic mechanisms that could be exploited for xenobiotic, particularly macromolecule access to the CNS.

Finally and just in is a review **5** of methods to measure brain endothelial permeability in humans with some suggestions for simplifying protocols to make it easier to assess changes in permeability clinically as a biomarker or in therapy.

. A. K. Deo, F-P. Theil and J-M. Nicolas Mol. Pharmaceutics, Article ASAP DOI: 10.1021/mp300570z Publication Date (Web):

January 04, 2013
2. E. Dolghih and M. P. Jacobson ACS Chem. Neurosci., Article ASAP DOI: 10.1021/cn3001922 Publication Date (Web): December 11
3. S. Ohtsuki et al Mol. Pharmaceutics, Article ASAP, DOI: 10.1021/mp3004308 Publication Date (Web): December 11, 2012
4. N. Strazielle and J. F. Ghersi-Egea Mol. Pharmaceutics, Article ASAP DOI: 10.1021/mp300518e Publication Date (Web): January 23, 2013
5. Y. Chassidim et al, Fluids and Barriers of the CNS 2013, 10:9 doi:10.1186/2045-8118-10-9 Published 7th Feb

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Peptides = drugs?

Peptides as drugs can be an emotive subject for drug discovery scientists. A recent review **1** highlights recent findings from a variety of fields that are converging on a new understanding of how conformation controls peptide bioactivity and bioavailability. The authors review some examples of peptides with significant oral bioactivity including, amongst others, α-amanitin a relatively rigid bicyclic peptide and the ubiquitous, more flexible, monocycle cyclosporine. Reviewing the case histories the authors conclude that cyclization is the key first step the trick of course being to find the relevant conformation. Refining the structure then follows with natural and unnatural amino macid substitutions and alkylations to optimise target affinity and physcicochemcial properties. However rational approachesa at this stage are limited. One thing that struck me was that often at least bicyclic structures are required - a bit more of a challenge synthetically.

A disappointment to me (also one of my bête noirs) is that the authors do quote data on cell permeability in some instances with dye labelled analogues of a peptide and propose this is evidence of permeability of the peptide - I simply cannot agree with this sort of analysis. All the data is saying is that the dye labelled peptide is cell permeable (probably) not the peptide itself.

One of the big hopes for peptide drug discovery has been stapled peptides as alpha helix mimetics e.g. **2**. However recent data **3** looking at stapled stabilized BimBH3 peptides suggest that this strategy is far from a universal panacea with loss of both target and cell activity on stapling acyclic peptides.

Snake/conotoxin peptides have been recognised for a long time as having some spectacular biological activities therefore a paper **4** on mambalgins, analgesic three finger acid sensing ion channels inhibitors isolated from Black Mamba toxin is timely. Note these mambalgins are highly constrained with four disulfide bridges. Just in case you were thinking where do I buy Black Mamba toxins try Steve at Venomtech – any arachnophobe's – don't watch the video!

1. J. E. Bock et al ACS Chem. Biol. 2013 DOI: 10.1021/cb300515u
2. G. L. Verdine and G. J. Hilinski Methods Enzymol. 2012;503:3-33. doi: 10.1016/B978-0-12-396962-0.00001-X.
3. T Okamoto et al ACS Chem Biol., Article ASAP DOI: 10.1021/cb3005403 Publication Date (Web): November 14, 2012
4. S. Diochot et al Nature 2012, 490, 552 and A Fleming Nature Reviews Drug Discovery 2012, 11, 906

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Virtual ADMET modelling

A couple of papers discuss the calculated and physicochemical properties relating to promiscuity. First up **1** is a paper looking at 3D descriptors and promiscuity as measured by successful clinical progression of compounds. The authors suggest that shape-based 3D descriptors such as the radius of gyration and shadow indices discriminate off-target promiscuity of a set nicotinic ligands better than do fraction of sp3 carbon (Fsp3) and the number of stereo centres which others **2** have proposed as key indicators of clinical success. The authors also extended this analysis to show these values were predictors of progress through preclinical and Ph1 development and were also found to be good indicators of solubility. Shadow Index or Fsp3 critieria were generally met (84%) by marketed drugs but were not met by withdrawn or discontinued products. It appears that spherical compounds with few aromatic rings have a better chance of making drugs – does this help explain some of the upsides of macrocycles? I must admit I am not quite convinced about the robust of the arguments over selectivity here.

As a bit of a contrast Keseru **3** emphasises the importance of LogP and basicity in determining selectivity which rather reinforces my feelings against the routine introduction of basic centres to make a compound soluble – there are other ways of doing this – see above – apart from anything else.

A warning comes from Kenny and Montanari **4** that one does have to be careful with data analysis as some strategies can exaggerate the significance of relationships –they introduce a term "correlation inflation". They particularly highlight the risk of analysing binned data and averaging groups of data points before analysis

With respect to promiscuity there is a lot to be said for some targeted screening to look for particular nasties such as hERG or 5-HT2B receptor affinity an approach extolled by a group of authors **5** sharing *in vitro* screening data from four major pharma.

Following the in silico or physicochemical parameters and attrition theme is a paper from Wenlock **6** reviewing the relevance to ADMET behaviour of a range of physicochemical properties including, perhaps what may be considered the usual suspects of, ionization lipophilicity, H-bonding and solubility amongst others – both measured and predicted.

1. D. C. Kombo et al, J. Chem. Inf. Model., Article ASAP DOI: 10.1021/ci300445e Publication Date (Web): January 18, 2013
2. F. Lovering et al J. Med. Chem., 2009, 52, 6752
3. A Tarcsay and G. M. Keserű J. Med. Chem., Article ASAP DOI: 10.1021/jm301514n Publication Date (Web): January 28, 2013
4. P. W. Kenny, C. A. Montanari J. of Computer-Aided Mol. Design Published online 10 January 2013

1. J. Bowes et al, Nature Reviews Drug Discovery, 2012, 11, 909-922 doi:10.1038/nrd3845
2. M. C. Wenlock and P. Barton Mol. Pharmaceutics, Article ASAP DOI: 10.1021/mp300537k Publication Date (Web): January 24, 2013

5. Chemistry

Heck reaction - more progress

The Heck reaction – palladium addition and coupling to create new carbon-carbon bonds has been around since 1968 with many developments since then. Developments still continue with the report **1** of enantioselective Heck arylation of alkenols exploiting redox relay – scheme 1 to generate chiral aryl β, γ or δ alkanones with good enantioselectivity and very respectable chemical yields. Stereochemistry of the starting alkenol dictates stereochemistry of the product with Z-alkenols slightly more efficient than E-alkenols. Aryl ring substitution is limited although both electron withdrawing and electron donating substituents are exemplified albeit all para to the diazonium salt - it would certainly be good to see how ortho-substituted aryldiazonium salts fare. Reaction conditions are mild and while compounds exemplified can generally be made in other ways this is a short and rapid approach to functionally rich products.

1. E. W. Werner et al Science 2012, 338, 1455

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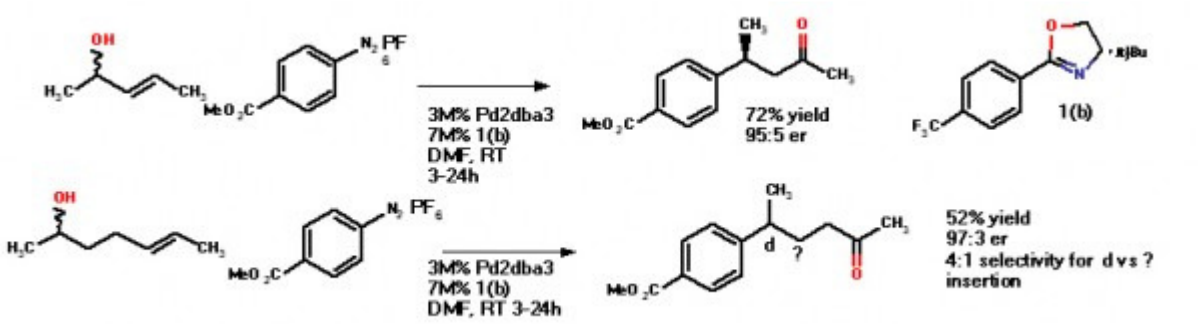

6. Conferences

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

- SMR Therapeutic Opportunities in Infectious Diseases 14th March London
- SciNovo Unlocking the value of drug candidates 23rd April, Stevenage Biocatalyst
- 24th Symposium on Medicinal Chemistry in Eastern England, Hatfield 25th April 2013

Meetings Attended

I have not been preparing extended meeting reports as I have done on occaision in the past links below will get you to the agendas for meetings attended - if any item catches your eye 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. Meetings attended during December and January; RSC BMCS Symposium 14th Dec. Chemistry Dept Cambridge. RSC BMS, PPINET MGMS and SCI International Protein-Protein interaction meeting 16th/17th Jan 2013 Royal Society London

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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.

Interactive chemical space visualisation

A mapplet for the interactive visualisation of chemical space defined by principal component planes of 42 dimensional Molecular Quantum Numbers has just been introduced. Databases used for this purpoose are Drugbank, GDB-13 (near 1 billion molecules), GDB-11, Pubchem and Chembl. The graphic below illustrates the whole Chembl database, any molecule can be identified along with nearest neighbours. Zooming in allows selection of each molecule (not in GDB-13) otherwise each pixel may represent multiple molecules for which an average structure is displayed in the average molecule box. More information is available on the

Reymond group website and in the reference **1**.

. M. Awale et al J. Chem. Inf. Model., Article ASAP DOI: 10.1021/ci300513m Publication Date (Web): January 22, 2013
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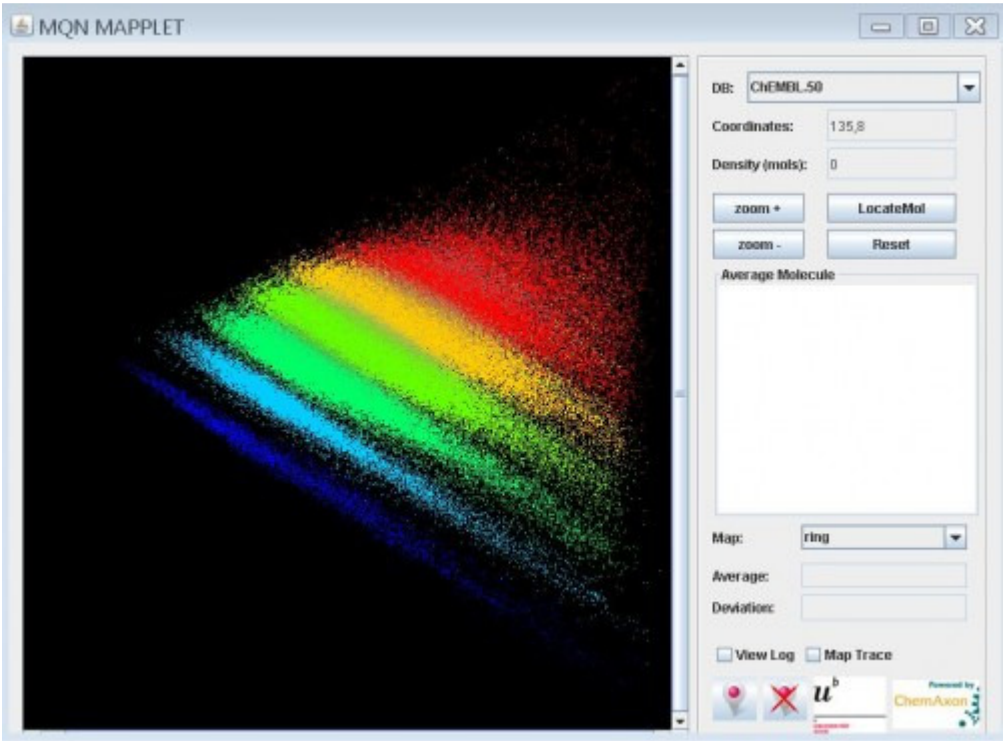

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Wishing you every success with your research.

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.

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