Rod Porter1

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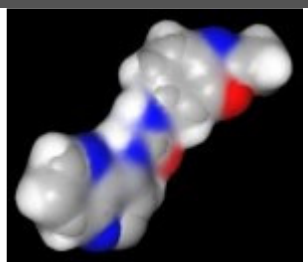
Medicinal Chemistry Newsletter | View Web Version



Medicinal Chemistry News from Rod Porter

July 2014 vol 5. no. 4

Dear Dr Porter,

1. Welcome

Welcome to the Julyedition of the Medicinal Chemistry newsletter from RodPorterConsultancy. I am afraid this is a bit abbreviated this month plenty of papers but afraid there just hasn't been the time to develop the discussions as I would have liked. Topics featured this month include; Big Beasts of the Future, Academy of Sciences report, peptide therapeutics, In vitro toxicology, aromaticity descriptors, Finding binding sites, transporters, disordered proteins, SF5 – good bad or ugly, CNS penetrant ALK inhibitors, Translating P-gp substrates, Synthesis of ArCF2X.

I am looking forward to getting a view of the book chapter I co-wrote with Lee Dawson of Eisai on glycine transporter inhibitors in schizophrenia to be published in Topics in Medicinal Chemistry – Schizophrenia from Springer in the next few days.

Don't forget to have a look at the CompChem Solutions services a range of complementary activities to those of RodPorterConsultancy.

For those hoping to sponsor my Great North Run half marathon in aid of the Alzheimers Society this year I am afraid I have deferred to next year as the build up to the event was just not going to work for me.

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.

My next mailing is planned for September. In the meantime have a great summer.

Wishing you every success with your research.

In this issue:

Society of Medicines Research- next meeting

The next meeting of the SMR, "Personalised Medicine- are we there yet?" will be on 2nd October at the NHLI London

The sequencing of the human the genome, coupled with the explosion of –omics based technology and data analysis capabilities has enabled health care scientists to measure and quantify drug activity at every biological level. The integration of these vast data sets combined with appropriate clinical data from individual patients has the potential to improve patient care by adopting more efficient treatment paradigms tailored to the individual rather than just the clinical diagnosis.

In this one day meeting, we hear about the current UK efforts and progress around the promise of Personalised Medicine in improving the diagnosis and prognosis for patient care. From theory to practice; experts from academia, industry and UK strategy groups will highlight the commitment and progress underway in this exciting and developing field.

For the full programme please visit here.

2. State of the industry

Big beasts of the future

A free report from EvaluatePharma outlines a vision for the future of the industry to 2020. Firstly it comments that 2013 was a bumper year for approvals based on anticipated value in 2018. Secondly it predicts sales will return to growth with an averge 5% annual growth and finally on the upside patent cliffs will look more like rolling hills based on the perception of soft landings for off-patent biologics seen to comprise a higher proportion of companies portfolios. Despite this there is still about a quarter of a trillion dollars of sales at risk from dropping off patent so there is still more pain to be felt. It also suggests that only two of the current top ten pharma companies will still rank in the top 10 in 2020. New entrants to this list are likely to be disease or indeed single product focused perhaps a hint of some thinking behind the deal GSK and Novartis struck re oncology and vaccine products. Oncology is predicted to grow fastest in sales with an 11% annual increase and humira is predicted to be have largest sales. All in all some interesting stuff but as repeatedly noted in this publication predictions are just that – the collected data for 2013 is however worth looking at particularly as it has been normalised.

3. In Brief

Academy of Medical Sciences Report

Picked up from a post by David Fox in the RSC Medicinal Chemistry Centre group forum is a report from The Academy of Medical Sciences on their recent Forum event, the theme of which was "Horizon scanning: Looking ahead to 2025". Key speakers were: An academic perspective: Professor Dame Nancy Rothwell, An industry perspective: Professor Patrick Vallance, An NHS perspective: Professor Sir Malcolm Grant, A regulatory perspective: Sir Gordon Duff. Discussions centred on: skills, open innovation, reducing risk, access to new medicines, increasing collaboration, issues with progressing antibiotics, access to patient data and new technologies/treatment strategies. Perhaps one issue seemed to be the continuing(increasing) focus on single target medication albeit using patient stratification to target the most suitable groups. It seems to me is that for many of our chronic diseases a multitargeted approach is more likely to be successful so understanding targeted polypharmacology or combination dosing regimes for example cf cancer perhaps need more attention. Looking at the attendee list there were certainly a lot of academics present it was a shame that so few industry representatives were there and certainly none from the smaller biotech sector. An interesting read pulling together many themes that we are familiar with.

Peptide therapeutics current situation

Peptides as therapeutics have a bit of a mixed press but this review **1** from last year that I have only just come across is a timely reminder of the number of therapeutics currently in development that are peptides or that contain peptide motifs for example to facilitate delivery. During 2010 – 2012 three approved drugs per year were peptides – a significant percentage of the total with a total of six in 2012. While most are administered s.c. there are examples of oral, inhaled and i.v.

delivery as well. The diversity of indications tackled is also wide ranging through Cushings disease, various GI indications and anaemia. There is particular interest in peptides for metabolic disorders such as diabetes with GLP-1 agonists a common theme. This is worth a look to emphasise that the non-peptide small molecule is not necessarily the only way to approach a target. Having said that a peptide does not necessarily offer a quick access to a treatment and sometimes moving on from a peptide is appropriate.

Of course cyclic peptides have been around (excuse the pun) on the market for a while **2** as evinced by immunosuppressive peptides such as cyclosporine and of course cyclic peptides and analogous structure's such as stapled peptides are continuing to raise substantial interest.

It does still seem to me that a big gap that remains for us is the ability to easily go from a tool peptide which may be rapidly identified by e.g. phage display synthesis **3** to a peptoid/peptidomimetic which has the drug like properties required for the indication. Perhaps fragment screening could specifically target constrained amino acid fragments. Dleivery of course also remains an opportunity - I continue to read reprots on nasal delivery for the CNS in particular with interest.

1. A A. Kaspar and J. M. Reichert Drug Disc. Today 2013, 18, 807
2. K. Thell et al Drug Disc Today 2014, 19, 645
3. M. Hamzeh-Mivehroud et al Drug Disc Today 2013, 18, 1144

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In vitro Toxicology

While we can focus on getting into preferred physicochemical space to try to reduce attrition we still need methods to evaluate what the toxicological consequences of dosing our compounds is likely to be and any methods to try to steer through the toxicology minefield has to be welcomed. An important paper **1** with summary **2**, looks at the effects of 776 molecules including both environmental and (mostly failed) pharmaceutical compounds on eight human cell culture systems with a range of protein biomarker read-outs. While this is not the first time this or a similar approach has been used (see article in my last newsletter **3**) I think it's one of the larger studies of its kind in terms of both numbers of cell lines and read-outs. "*Computational clustering of the profiling data provided insights into the polypharmacology and potential off-target effects for many chemicals that have limited or no toxicity information. The endpoints measured can be closely linked to in vivo outcomes, such as the upregulation of tissue factor in endothelial cell systems by compounds linked to the risk of thrombosis in vivo. Our results demonstrate that assaying complex biological pathways in primary human cells can identify potential chemical targets, toxicological liabilities and mechanisms useful for elucidating adverse outcome pathways*" This does further increase the appeal of *in vitro* systems for triaging series earlyish in drug discover or perhaps generating toxicology "SAR" to try to reduce liabilities before heading to in vivo studies in a similar way that we look for reactive metabolites or indeed mutagenicity currently.

Complementing this is a report of emerging pattern mining **4** to automatically identify activating features in toxicology data sets to help identify structural alerts. The system has been tested on in vitro mutagenicity and hERG data sets. There have certainly been many predictive in silico approaches to estimating toxicity see for example **5** key is how well such systems can be integrated into a decision making process.

1. C. Westmoreland and P. L. Carmichael Nature Biotechnology 2014, 32, 541
2. N. C Kleinstreuer et al. Nature Biotechnology 2014, 32, 583 doi:10.1038/nbt.2914
3. RodPorter COnsultancy Newsletter 2014, 5 no 3.
4. R. Sherhod, et al J. Chem. Inf. Model., Article ASAP DOI: 10.1021/ci5001828 Publication Date (Web): June 18, 2014 Copyright © 2014, American Chemical Society
5. M. T. D. Cronin and J. C. Madden (editors) In silico toxicology Principles and Application 2010, Issues in Toxicology no 7 RSC Publishing ISBN 978-1-84973-004-4

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4. Medicinal Chemistry

Aromaticity descriptors

A useful review of the various aromatic descriptors that have emerged over the past few years has just published from a couple of the primary exponents of the negative role of too many aromatic rings has on developability.

Interesting observations of marketed versus patented compounds included the fact that only 14% of marketed drugs compared with 63% of patented compounds had more than two aromatic rings. Furthermore Ar- sp3 (the number of aromatic atoms – the number of sp3 atoms in a molecule) stays fairly constant over time with marketed drugs – varying with the ionisation state. Namely acidics had a (high) value of 4.05, bases 0.73, neutal molecules -0.22 and zwitterions -1.48. Possibly this reflects issues around solubiity for neutral and zwitterionic compounds. Amongst the other developability characteristics of a compound solubility does seem to be influenced significantly by aromaticity (above and beyond any change in lipophilicity there may be) – cf a following discussion on predicting solubility.

A useful addition to the supplementary material is a .csv spreadsheet which can be used to calculate a range AROM, Fsp3, Ar-sp3, Ar/HA, and PFI from any SMILES string molecule input if JChem for Excel is installed. Apart from this aid, this is a useful review of the various ways that have so far emerged for assessing impact of aromaticity on drug design and the developability of compounds and as such is well worth a read. Bottom line really seems to be keep control of aromatic rings and don't use an aromatic when an sp3 motif will do - the odd chiral centre is no bad thing by all accounts in helping survive development.

1. T. Ritchie and S. Macdonald J. Med. Chem Article ASAP DOI: 10.1021/jm500515d Publication Date (Web): June 03, 2014 Copyright © 2014, American Chemical Society

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Finding binding sites

An interesting attempt to try to unravel binding sites which caught my eye **1** although perhaps I am not best placed to say if this adds real benefit but it brings to mind some of the recent work I have been reading for personal benefit relating to some epigenetic targets where "gold standard" crystallographic data is failing to identify intact binding sites due to the crystallisation of protein constructs rather than whole proteins. Which of course then brings to mind the dangers of trying to assess druggability of a binding site based solely on published (often incomplete) protein structures or indeed protein complexes. Perhaps looking more holistically so called poorly druggable sites are more druggable than initially thought if whole protein or whole protein complexes were considered. This was I believe some of the point behind the work Cellzome was involved with in assessing target protein in a whole cell environment rather that as expressed proteins – HDAC as a target springs to mind where selectivity of compounds in isolated enzyme systems was very different to that in the whole cell due to the impact of other proteins on the target enzyme.

1. H.Pradeep and G. K. Rajanikant J. Chem. Inf. Model., Article ASAP DOI: 10.1021/ci500243h Publication Date (Web): July 07, 2014 Copyright © 2014, American Chemical Society

Predicting Solubility

While predicting/calculating any property is tricky predicting solubility has proved particularly problematic over time. It has been argued that the problem is really due to the relatively poor quality of the data sued to generate models. However a new report suggests that the real problem is that the most appropriate properties to include in models have not yet been identified. The approach used was to compare models built with a collation of literature solubility data versus a set of compounds for which solubility as carefully measured to a high degree of confidence. The conclusion was that no matter which set of data was used the models generated were equally unreliable – back to the drawing board for the modellers!.

1. D. S. Palmer and J. B. O. Mitchell Mol. Pharmaceutics, Article ASAP, DOI: 10.1021/mp500103r Publication Date (Web): July 09, 2014 Copyright © 2014, American Chemical Society

Transporters

A series of papers on transporters has published in Drug Discovery Today Technology **1** particularly looking at assay methodology, taxonomy and assay ontologies. Perhaps of more particular interest for the medicinal chemists are items on computational models for predicting compound interaction with transporters **2**, using transporters to reduce tissue exposure – specifically the brain **3** and intriguingly a review of small molecule chaperones to help refold misfolded transporter proteins **4**.

1. G. Eckers Drug Discov Today Technol. 2014 Jun;12 e35-6 doi: 10.1016/j.ddtec.2014.04.002
2. M. Pinto Drug Discov Today Technol. 2014 Jun;12 e-69-79 DOI: 10.1016/j.ddtec.2014.03.007
3. S. Bagal and P. Bungay Drug Discov Today Technol. 2014 Jun;12 e79-85 DOI: 10.1016/j.ddtec.2014.03.008
4. E. Rudashevskaya et al Drug Discov Today Technol. 2014 Jun;12 e87-95 DOI: 10.1016/j.ddtec.2014.03.009

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Disordered proteins

Perhaps there is a bit of a tendency to think of proteins as generally reasonably well ordered perhaps driven by our looking at elegant crystal structures – forgetting the omitted loops and other sections too mobile to give useful co-ordinates. A full issue of Chemical reviews **1** has been dedicated to Intrinsically disordered proteins with sections introducing the field and systems of classification. There are also, amongst others, sections on looking at free energy landscapes using NMR, multisteric regulation by structural disorder in modular signalling proteins **2**, short linear motifs as diverse protein interaction modules involved in cell regulation **3**, looking at conditionally and transiently disordered proteins and a new 'omic – pathological unfoldomics of uncontrolled chaos. Perhaps this really highlights the dangers of over interpreting crystallographic data certainly during target evaluation and at least in some cases when using structure based lead optimisation.

1. V. N. Uversky Chemical Reviews 2014, 114 (13) 6557, DOI: 10.1021/cr500288y
2. P. Tompa Chem. Rev., 2014, 114 (13), 6715–6732, DOI: 10.1021/cr4005082
3. K. Van Roey et al Chem. Rev., Chem. Rev., 2014, 114 (13), 6733–6778

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SF5 good, bad or ugly

It's quite a while since I considered neglected aromatic substituents but am revisiting this now with a long running thread on Linked-In on the SF5 substituent – is it good or bad or just ugly? As expected opinion is a little divided with the high molecular weight and large increase in lipophilicity with one contributor pointing out that relative to an ArMe group ArSF5 increases mol. Wt. by 112 and cLogP +2.4. While the former may be neither here nor there the latter must be a concern. Former colleague Daniele Andreotti at Aptuit (a fan of SF5) does highlight the electronic properties of SF5 relative to CH3 or CF3 and cites references of his experience 1. A couple of points are that synthetic routes are not readily available at present and an interesting point raised was that if so metabolically stable itself what happens to it in the environment – segueing back to the earlier discussion on toxicology. In my view at present with a big caveat on the lipophilicity implications and impact on metabolism remote to the SF5 group it is perhaps too early to say good or bad perhpas just ugly.

You may need to be a member of the Linked-In Medicinal Chemistry and Drug Discovery group to see the discussion

1. F. Micheli et al Bioorg. Med. Chem. Lett. (2010), 20 (15), 4566-8.

CNS penetrant macrocyclic ALK inhibitors

I don't often feature case histories trying to focus on more generally interesting (hopefully) topics. However a nice paper has just come out from Pfizer reporting invention of a macrocyclic analogue of Crizotinib, PF-06463922 a CNS penetrant non P-gp substrate ALK inhibitor also having activity against ALK mutants particularly to target brain metastases **1**. As expected from the La Jolla Pfizer group LipE feature heavily in their design strategy.

SBDD was also used heavily to help design macrocycles in which the ring components not only helped hold the molecule in a preferred conformation but also contributed directly to binding leading to PF-06463922. Macrocyclic compounds did tend to show good translation of isolated enzyme activity into cellular activity

The team identify that to reduce P-gp liabilities low molecular weight, not too low lipophilicity and reducing number of H-bond donors is preferred as is avoiding basic centres. Macrocycles also tended to show reduced P-gp substrate liability as argued by the authors possibly reflecting the compactness of the macrocycle structure effectively reducing the number of rotatable bonds. PF-06463922 had an AUC CSF/free plasma ratio of 0.31 indicative of being able to achieve effective brain concentrations. This paper provides an interesting discussion of some of the merits of macrocycles although there were some synthetic challenges to be overcome to get to the target macrocycles that I haven't discussed.

1. T. W. Johnson et al J. Med. Chem., Article ASAP DOI: 10.1021/jm500261q Publication Date (Web): June 03, 2014

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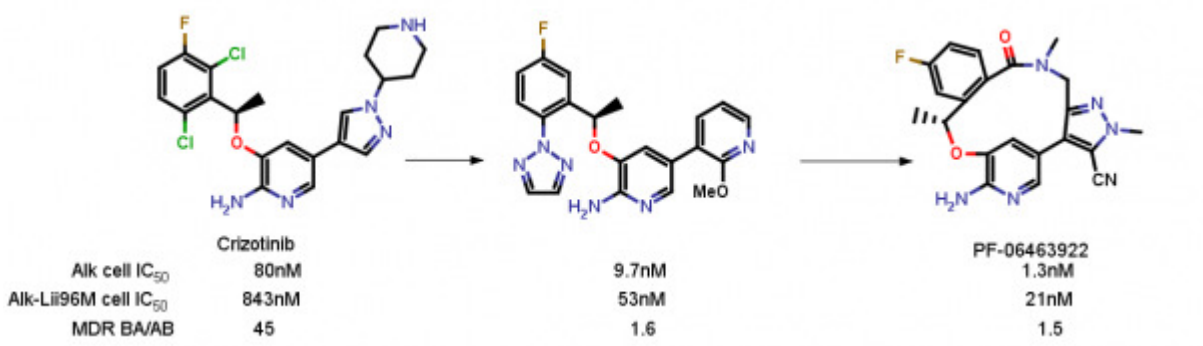

P-gp substrates and translation to man

In an extension of earlier work in the mouse **1** the Terasaki group have reported **2** on reconstruction of distribution of P-gp substrates in the cynomolgus monkey brain to help increase confidence in translation of CNS drugs into man. "*this study experimentally demonstrated that the Kp brain and Kp,uu,brain values of P-gp substrates and non-substrate can be reconstructed by integrating in-vitro P-gp transport activity, P-gp protein expression levels, and the unbound fractions in plasma and brain based on BBB PPx. These results also demonstrate that in-vivo P-gp transport function at the BBB can be reconstructed based on in-vitro P-gp transport activity and P-gp protein expression levels*. The key points is that expression (and activity) levels of P-gp are much closer (ratio <1.5) between cynomolgus monkey and human relative to rodent/human and that Fuplasma varies substantially across species. The team also use pH adjusted Fubrain **3** to try and more accurately reflect the *in vivo* situation. This gives an *in vitro* method for helping to give an improved estimate of effective exposure in man particularly when working with compounds with evidence for efflux liability

Fu brain was broadly similar for mouse and monkey general differing by only two fold although indinaivr did show a three fold variation which is consistent with earlier data showing a broad conservation of Fubrain while Fu plasma is more variable across species.

1. Y. Uchida et al J Pharmacol Exp Ther 2011, 339, 579-588
2. Y. Uchida et al J. Pharmacol. Expt. Ther 2014 Published online before print June 19, 2014, doi: 10.1124/jpet.114.214536
3. Friden et al Drug Metab Dispos 2011, 39, 353-362

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5. Chemistry

Synthesis of ArCF2X

Complementing the discussion above on SF5 are a couple of reports of transition metal, palladium **1** and more recently nickel mediated synthesis **2** of ArCF2X compounds from arylboronic acids and BrCF2X where X is CONHR1R2, P(O)(OEt)2 or CO2Et. As the authors point out and I have discussed previously this functionality has significant potential in medicinal chemistry but certainly in part access has been hampered by lack of decent synthetic methodology to introduce the group. Features of this approach are described as "*high generality, excellent functional-group compatibility, low-cost nickel-catalyst, and practicality for gram-scale production*".

1. Z. Feng et al Angew Chem Int Ed Engl. 2014 Feb 3;53(6):1669-73. doi: 10.1002/anie.201309535
2. Y. L Xiao et al Angew Chemi. Int Ed. 2014, doi: 10.1002/anie.201405653 Article first published online: 17 JUL 2014

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6. Conferences

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

- The Secrets of Success: CRO views of successful outsourcing SCI, London 30th September
- Personalised Medicine- are we there yet? SMR, London, 2nd October

Meetings Attended

A couple of meetings reently attended 15th Tetrahedron Satellite meeting 24th June 2014 which was really rather good. It was interesting that only one of the (several) academic speakers made the link between academic research and patient benefit. Also excellent was the Cresset user group meeting held in Cambridge and my thanks to theCresset team for their hospitality. If you are interested in finding out more about any of the talks at these meetings please contact me I may be able to send you some notes.

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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.

None this month

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

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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.

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

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.

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