Rod Porter1

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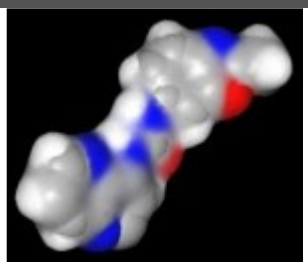
Subject: RPC June 2014 Newsletter

Medicinal Chemistry Newsletter | View Web Version



Medicinal Chemistry News from Rod Porter

June 2014 vol 5. no. 3

Dear Dr Porter,

1. Welcome

Welcome to the June edition of the Medicinal Chemistry newsletter from RodPorterConsultancy. Features this month include; Next generations of medicinal chemists, Drug approvals for 1Q, From boom to bust - Incivek, Megamergers, Early response genes and predicting toxicity, Sex equality- use of both genders in *in vitro* and *in vivo* studies, Metabolite exposure in development, Validity of efficiency metrics part II, calculation of pi-stacking, QED scores reviewing high *v*. low scores, predicting clearance, transport v. passive permeability, long acting injectables, PPI reviews, Don't forget chemistry - a salutory tale of ignoring chemistry, application of CH bond activation and highlighting a review on nickel catalysed chemistry.

If I dont manage to get out another newsletter before the holiday season starts I hope you have a good holiday. We are looking forward to a bit of an adventure travelling the central part of the Silk Road. My Russian is coming along slowly!

As ever 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.

My next mailing is planned for July (or September please bear with me).

Wishing you every success with your research.

In this issue:

1. Welcome

2. State of the industry - pipelines: Next generation, Drug approvals, From boom to bust, Megamergers

3. In Brief: Early response genes, Sex equality, Metabolite exposure

4. Medicinal Chemistry: Efficiency metrics part II, pi-stack, QED, predicting clearance, transport v passive, long acting injectables, PPI reviews, Forgetting chemistry

5. Chemistry: CH activation , nickel

6. Conferences

7. Also of Interest: Cell Press, Lists, Recon 2

8. Rod Porter Consultancy

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.

Optibrium - Stardrop™

Optibrium, has just appointed a director of computational chemistry as part of their expansion.

2. State of the industry

Next generation

An interesting article that I picked up from an article highlighted by Geoff Lawton (INMED) on Linked-In originally from the Life Sci VC blog page looking at the challenges of long term development of trained medicinal chemists in the pharma industry. This is a subject that has been exercising me over the last few years.The article's thesis is that training of a medicinal chemist takes a number of years post academic training to embrace both technical and softer, collaborative skills. These are difficult to learn in a biotech (or realistically in a CRO) where the clock is ticking and the budgets eye wateringly tight and where all the coaching to cover the full range of skills of a "mature" medicinal chemist may not be on site. In contrast big pharma is (or at least was) in a much better position to provide this level of support and training. Herein lies the nub of the problem with big pharma shrinking its research and relying on biotech and outsorucing to fund its pipelines where is the next generation of skilled med chemists going to come from. A couple of solutions offered in the article included more reliance on mid cap pharma to pick up and train new recruits and some of the academic drug discovery groups now well supplied with experienced drug discovery scientists although I am not sure the UK groups are that well-funded to fully support the required level of training. I am not clear if initiatives like GSK's with Strathclyde will provide substantial training for Strathclyde based PhD's. A fair point made in comments on this article is that a mix of experienced and enthusiastic but green new recruits can have a positive impact on productivity – something that sadly got lost in big pharma as recruiting new people dried up over the years.

Drug approvals

Q1Drug approvals are markedly down for 1Q2014 running at half the 1Q2013 level with 6 NME and 2 biologic approvals – interestingly none being oncology targeted. There are 8 products coming up for approval in 3Q2014. I haven'tsee a figure for 2Q.

From Boom to Bust

An illustration of just one of the risks of drug discovery from Vertex if ever one is needed. Just when you thought good product on the market selling well then a curve-ball comes in to knock you over. Incivek the Hepatitis C medication had sales of over $1.16Bn in 2012 and a healthy $205M for the first quarter of 2013 but a drop to just $3.6M for the first quarter of this year - a 98% fall worse than a compound dropping over the patent cliff. In contrast of course sovaldi had revenues of $2.27Bn this last quarter despite the controversy over Gilead's pricing policy for their Hep C medication.

Megamergers

A comment on megamergers is unavoidable after the AZ/Pfizer talks. I suppose on balance I am happier for all that the merger/takeove didn't occur although I would not be surprised if it all kicks of again in three months driven by AZ shareholders. Certainly AZ are going to need a spectacular run of positive clinical data over the next few months bearing in mind some of the predictions made about the robustness and value of their pipeline. Jobs in all sectors of AZ activity would have been in jepordy within the UK if the merger had taken place no matter any assurance of Pfizer - it was good to see that people were alert to the caveat re subject to due diligence placed by Pfizer. This is perhaps reinforced by this second item from Fiercebiotech. Finally as you might expect commentary from Derek Lowe's in the Pipeline - as usual the comments are also well worth a read. I suppose the upside for me on this has been the wake-up call to HMG that the pharma industry in the UK is rapidly shrinking - and has been doing so for a good many years now. Perhaps a message needs to get through that more to support conversion of academic biology to industry useful assets would be a help - the charitable sector can only do so much and lets face it VC's broadly (although not always) are simply not interested in funding early research.

A review from an AZ group co-authored by Mene Pangalos looking at the trial and tribulations of their pipeline is timely in view of recent events. Here the authors discuss 5 R's the right target, tissue, patients, safety and commercial potential with an interesting sixth the right culture. Perhaps that is meant to help cover the "right" decision making after all at some point decisions will need to be made about an asset where one "right" is so much more right than the others think commercial potential for example. With respect to decision making it as interesting to see acknowledgement that in a few cases projects had been allowed to continue apparently to meet annual metrics. Encouragingly implementing the strategy does appear to be have an impact - in particular a small rise in PhII success heading a bit closer to the industry average. An interesting read and an extension of the the Pfizer "three pillars" approach.

3. In Brief

Early response genes can predict toxicity

A team has reported **1** on a slightly different approach to look at prediction of toxicity based on changes in gene transcription prior to any emergence of visible histopathology which is predictive across both *in vitro* and *in vivo* studies. This approach specifically focused on early response genes only two hours after administration. In a multivariate analysis of the TG-GATEs (Toxicogenomics Project-Genomics Assisted Toxicity Evaluation system) database. It identified four genes—EGR1, ATF3, GDF15 and FGF21—that are induced 2 h after drug administration in both human and rat primary hepatocytes that were predictive for both kidney and liver toxicity *in vivo*. The authors do point out that this data is not absolute and should therefore be used in conjunction with other methods of assessing toxicity but the *in vitro* aspect of this would seem a useful way of prioritising if several compounds are available. I saw no discussion of using an S9 activation arm to the experiments to look for effects of metabolites. For completeness a recent study **2** of 34 acute rat toxicity studies proposed three novel candidate genes (GSTA, ARG1 and HPD) in addition to the established ALT as drug-induced liver injury biomarkers in rats.

1. J. D. Zhang et al Pharmacogenomics J 2014, 14, 208
2. W. J. Bailey et al Toxicol Sci 2012; 130: 229–244.

Sex equality

Following on from earlier discussions in this publication is the report **1** that the NIH is now introducing policy to ensure balanced use of whole animals (and cells) from both sexes. This reflects the growing concern over the general use of male animals in *in vivo* studies and the sometimes unclear sex of the source of cells. This may be hindering the reproducibility of studies – clearly a big issue but also ignores the differences in susceptibility to a condition and the way it is expressed e.g. MS or schizophrenia and differences in response males and females may have to a drug. It has been suggested that one problem that arises using female rats is the variablility of female response based on stage of estrous, however, a meta-analysis suggests that this is not an issue. In my ignorance I had understood that there was a bias to use mail animals as they were cheaper than females but not sure if that difference is all that real.

1. J. A. Clayton and F. S. Collins Nature 2014, 509, 282

Back to top

Metabolite exposure preclinically and clinically

In the recent past both FDA and ICH guidelines on stream of regulatory guidelines on the Safety Testing of Drug Metabolites by the FDA in 2008 and the ICH in 2009 and 2012, have appeared. Since then however few literature accounts have appeared demonstrating how, in practice, a particular strategy or analytical method has been used to qualify drug metabolites during the safety evaluation of a drug during clinical. The AZ Sodertalje group have, however, now just done that

Conclusions were *"Our experience dictates that there is no single strategy for qualifying the safety of drug metabolites in humans; however, all activities should be tied to two unifying themes: first that the exposure to drug metabolites should be compared between species at repeated administration using the relative method or a similar one; and second that the internal regulatory documentation of the metabolite qualification should be agnostic to external criteria (guidelines), indication, dose given, and timing."*

1. J. Haglund et al Chem. Res. Toxicol. 2014, 27, 601−610

4. Medicinal Chemistry

Validity of Ligand Efficiency Metrics

I highlighted papers by Schultz in a previous newsletter **1** questioning the merits of ligand efficiency and its mathematical integrity. Predictably this elicited a response **2** which I find interesting. The response argues that there is mathematical validity in LE specifically "*It is perfectly valid mathematically to divide a real number by an integer*". It then go on to address the fact that the extent of change in LE with each heavy atom depends on the size of the starting molecule which perhaps was one of the things Schultz had issue with. This is one of the problems of applying LE starting with fragments and optimising to more drug sized molecules and has been recognised in the past e.g **3** and introduction of e.g. size independent ligand efficiency (SILE) **4**. There was general agreement about the importance of controlling lipophilicity with the help of metrics such a lipophilic ligand efficiency.

Perhaps the interesting point highlighted was that a target value for a metric will vary depending on the molecular target. This rather begs the question about the analysis of marketed drugs and setting hard cut offs for metrics (of any description) particularly when looking at novel molecular targets. This is reassuring and is falling in line with multiparameter strategies being adopted by companies and as implemented in Stardrop™. It is also consistent with focusing on maintaining or improving efficiency metrics within a chemical series/target rather than needing to achieve a particular obligate minimal value.

Just spotted and I admit I haven't read in full yet, is an article **5** entitled "Ligand efficiency metrics considered harmful". It sets out to provide an overview of LE metrics and a summary of protein ligand binding. The metrics are critically examined and some alternatives for interpreting physicochemical properties suggested for selecting and optimizing leads.

1. Too many optimisation metrics Newsletter 2013 4(5)
2. C. W. Murray et al ACS Med. Chem. Lett., Article ASAP DOI: 10.1021/ml500146d Publication Date (Web): May 09, 2014 Copyright © 2014, American Chemical Society
3. C. H. Reynolds,. J. Med. Chem. 2008, 51, 2432−2438.
4. J. W. M. Nissink, J. Chem. Inf. Model. 2009, 49, 1617−1622
5. P. W. Kenny et al J. Comput. Aided Drug Design 2014 Published on line 5th June DOI: 10.1007/s10822-014-9757-8

Back to top

Quantitative estimate of drug likeness (QED) – high and low scoring marketed drugs

A comparison of QED high and low scoring marketed drugs for which full human PK was available (199 compounds) was undertaken **1**. Bear in mind QED was established **2** as a way of comparing one's own compounds against marketed drugs aggregating and normalising a number of physiochemical properties

The 25 highest scoring compounds had lower molecular weight, lower H-bond donor and acceptor count and PSA and fewer structural alerts and rotatable bonds relative to the 25 lowest scoring. However AlogP and number of aromatic rings were identical for the two sets although the spread particularly for LogP was higher for the low scoring set.

The authors go on to compare PK parameters between these high and low QED scoring subsets and apart from initial absorption and oral bioavailability which are a little lower for the low scoring subset other parameters such as metabolic stability or volume of distribution are very comparable. Perhaps reflecting lower absorption of low scoring drugs, doses tended to be higher (though note many of these compounds were antibiotics where achieving high plasma levels is particularly important). Higher scoring drugs do tend to have fewer drug interaction warnings and fewer food interactions. As already noted lower scoring drugs were often eg macrocyclic antibiotics, highly flexible enzyme inhibitors or particularly small polar molecules such as Metformin. High scoring drugs tended to be CNS active where perhaps a greater emphasis on permeability was important

This does seem to support my perspective that overall get LogP and perhaps aromatic ring count in a sensible place then you are in good shape – other factors being perhaps less critical. Of course unmet medical need and where the target is located are some other parameters that need to be considered as the authors highlight. This does also highlight a bit of an issue with parameters like QED established from profiling of marketed drugs – by definition even the low scoring compounds are treating patients so setting some simple cut-off above which it is considered appropriate to progress compounds doesn't seem to work without taking into account several other factors. Perhaps the test would be to establish a parameter based on calculated properties of clinical failures v. marketed compounds cf Wenlock **3** and the (in my view) all important lipophilicity.

1. T. Ritchie and S MacDonald Drug Disc. Today 2014, 19, 489
2. G. R. Bickerton et al Nat. Chem. 2011, 4, 90
3. M. C. Wenlock et al J. Med. Chem., 2003, 46, 1250

π-stacking

A new study **1** looks at calculating pi-stacking of heterocycles using dispersion corrected density functional theory. The authors identified geometric preferences and minimum interaction energies for a range of unsubstituted heterocycles interacting with benzene. Heterocycle centroids were positioned directly over the centroid for benzene with rings stacked in parallel and energies calculated at incremental moves of the heterocycle away from the benzene centroid while simultaneously rotating the heterocycle through 30 degree increments to identify optimal interaction geometry. Electronic properties, as would be expected, are key determinants of interaction. Having an electronegative atom directly over benzene was disfavoured a particular problem for triazine of course. The centroid for the heterocycle was generally displaced about 1.5A from the benzene ring centroid. The dipole of the heterocycle was a good predictor of interaction with better interactions with a greater dipole cf pyridazine/pyrimidine/pyrazine/triazine. This should provide a useful guidance for medicinal chemists although here detailed structural information wold be useful to be able to rapidly identify the most favourable regioisomers of a substituted heterocycle to synthesise. All the work discussed was assessing in plane interactions.

In a similar vein a free chart showing electrostatics of commonly used heterocycles is available from Cresset. You can also create your own using a free download of TorchLite™

1. R. G. Huber, et al J. Chem. Inf. Model., Article ASAP DOI: 10.1021/ci500183u Publication Date (Web): May 09, 2014 Copyright © 2014, American Chemical Society

Back to Top

In silico prediction of route and extent of clearance

A curated human plasma clearance data set of 1003 compounds of which 739 could be assigned to a renal or metabolic route of clearance (included extent of each path) has been put together **1**. Using this data set it was shown that an *in silico* model could achieve excellent prediction of route of metabolism and total clearance in human. About a 90-95% accuracy for the prediction of the primary route of metabolism was achieved. Perhaps not surprisingly robustness of prediction of the extent of human clearance was more modest although results were very comparable to predictions based on monkey *in vivo* data at around the two thirds within two fold of experimental. Extent of

clearance of compounds primarily cleared by the renal route were better predicted than those cleared primarily via the metabolic route.

Others have also made attempts **2-4** to predict clearance from chemical structure alone, however, this latest work has had access to the largest data set to work from and appears to set a bench mark for further work particularly on prediction of extent of clearance.

1. F. Lombardo al J. Med. Chem., Article ASAP DOI: 10.1021/jm500436v Publication Date (Web): May 06, 2014 Copyright © 2014, American Chemical Society
2. C. W. Yap, et al J. Mol. Graphics Modell. 2006, 24, 383−395.
3. M. J. Yu, . J. Chem. Inf. Model. 2010, 50, 1284−1295.
4. O. Demir-Kavuk et al J. Comput.-Aided Mol. Des. 2011, 25, 1121−1133

Back to top

Transport v. passive permeability - again

The debate continues over different perspectives on the involvement of transporters in drug permeability with a recent review**1**. This review with a large number of well known authors from various academic and industrial groups sets out a series of refutations of the arguments from the Kell group e.g. **2**. The current authors do adopt the view which I do agree with that there is probably both passive permeability and active transport though I suspect there is a lot more involvement of transporters than we currently allow. Certainly it would be good to see more work characterising transporter expression and sensitivity to culture conditions in cell lines commonly used for permeability experiments. Furthermore it would be good to know a bit more about the integrity of PAMPA and indeed cell lines used for passive permeability studies. Finally, recognition of a compound by a transporter does not necessarily mean the transporter is involved in drug disposition – a bit of quantitative data is required. Having said that and being pragmatic most of the time the ideas of passive permeability with an awareness of the possibility of transporter involvement does seem to serve drug discovery reasonably well. I do however believe that this should not discourage groups from rigorously assessing involvement of transporters in drug disposition. Not least to my mind due to the implications of drug interaction with transporters and toxicity and perhaps more speculatively looking at the role of transporters in inducing drug resistance in cancer cell lines/in the clinic.

Following on this theme of permeability are just a couple of the recent papers **3, 4** that have appeared on cell penetrating peptides which seem to largely rely on a concentration of Arg residues and are thought to be endocytosed. Of course with endocytic processes proteins are involved so does this count as transporters or not? Do we also underestimate the amount of endocytosis that goes on albeit as an energy using process it should be detectable. Whatever ones overall impressions of this debate, it is refreshing that general perceptions are getting robustly challenged.

1. D Smith et al Mol. Pharmaceutics, Article ASAP DOI: 10.1021/mp400713v Publication Date (Web): May 06, 2014 Copyright © 2014, American Chemical Society
2. D. B. Kell et al. Drug Discovery Today 2011, 16, 704−714.
3. R. Brock Bioconjugate Chem., Article ASAP DOI: 10.1021/bc500017t, Publication Date (Web): April 11, 2014, Copyright © 2014, American Chemical Society
4. R.Wallbrecher et al Bioconjugate Chem., Article ASAP DOI: 10.1021/bc500107f Publication Date (Web): April 16, 2014 Copyright © 2014, American Chemical Society

Back to top

Long acting injectables and dopamine in cancer

Last time I looked at molecule's with prolonged t1/2's which were seen as suitable for once weekly dosing, now there is a report **1** looking at the strategies that have been used for preparing the six marketed long acting injectable antipsychotics. With these six drugs five different approaches have been used to create an appropriate formulation with others explored and including aqueous suspensions of poorly soluble salts, polymeric microspheres, and new approaches to making prodrugs as well as oily solution of lipophilic drugs. Of course long acting sub-dermal depots and injectable contraceptives have also been around for a while. The report highlights that there have been no concerted strategies for developing long acting/depot formulations and looks at some of the factors involved in helping to develop a long acting injectable. A preferred option proposed by the authors are lipophilic prodrugs rather than, for example, poorly soluble salts It seems to me that the ability to readily create a long acting formulation could assist both patient compliance for Western

diseases but also facilitate drug discovery in the neglected tropical disease area. For the latter I am thinking of the ability to give a single dose to give prolonged effective exposure admittedly perhaps from a slightly more expensive agent but which is perhaps more likely to be efficacious avoiding failed treatment regimes. Of course every compound is different so a single answer is unlikely to emerge for this sort of complex work.

A slightly awkward segue but there is a report **2,3** that the potent D2 receptor antagonist, haloperidol, a typical antipsychotic available as a long acting injectable has efficacy against brain tumours. This is based on a genome wide shRNA study that showed integrated mitogenic signalling between the dopamine D2 receptor and EGFR in glioblastoma. The authors identified a synergistic effect between D2 antagonists and EGFR inhibitors. *In vivo* an EGFR inhibitor AG1478 or the typical antipsychotic haloperidol alone gave no improved survival in an orthotopic 1123 mouse model with 0% survival after 25-27 days. Combined the two compounds gave 50% survival after 45 days.

1. J. F. Remenar Mol. Pharmaceutics, Article ASAP DOI: 10.1021/mp500070m Publication Date (Web): April 30, 2014 Copyright © 2014, American Chemical Society
2. J. Li et al Oncotarget 2014, 5(4), 882-893.
3. Also E. Mullin FierceBiotech 11 Mar 2014

Protein protein interaction reviews

A special section in Chem Rev "Chemical Biology of protein-protein interactions" **1** caught my comprising five reviews. Topics covered include: cellular incorporation of Unnatural Amino Acids and Bioorthogonal Labeling of Proteins, NMR-Based Approaches for the Identification and Optimization of Inhibitors of Protein–Protein Interactions and Development of a Natural-Product-Derived Chemical Toolbox for Modulation of Protein Function. However the ones of most interest to myself were "Small Molecule Modulators of Protein−Protein Interactions: Selected Case Studies" **2** and "Modulators of Protein–Protein Interactions" **3**. The first of these two reviews focuses on six case histories starting from the molecular PPI target. For example Modulation of HSP90-Related Protein−Protein Interactions by Natural Products and Related Compounds and Small Molecule Modulators of 14-3-3 PPI. The second review briefly looks at screening methods and methods for hit identification followed by an "atomistic-level account of different established and new small molecule stabilizers of PPIs". The authors here argue that stabilization rather than prevention of PPI's is a seriously under investigated strategy for therapeutic intervention. However it is fair to say there is some overlap between these two reviews for example the 14-3-3 PPI modulators.

These are certainly worth a read despite some duplication providing a coherent and pretty comprehensive discussion of progress in the PPI interaction field. The level of discussion of the role of natural products is interesting. I keep meaning to trawl the pdb to look at how natural products interact with proteins – something I have never quite got round to – if anyone knows of a review on that topic I would be grateful to hear from you.

I havent attempted to cover some of the more recent work reported on PPI's not least examples such as "*Discovery of the Fibrinolysis Inhibitor AZD6564, Acting via Interference of a Protein–Protein Interaction*" **4** or "*Discovery of Potent Keap1–Nrf2 Protein–Protein Interaction Inhibitor Based on Molecular Binding Determinants Analysis*" **5**. I am just trying to highlight here how what were consisdered previously to be completely intractable targtes are starting to succumb to the medicinal chemist even if a lot of work remains to be done.

1. Chem Rev 2014, 114, 4621 - 4806
2. M. Aeluri et al Chem Rev 2014, 114, 4640
3. L-G Milroy et al Chem. Rev., Article ASAP DOI: 10.1021/cr400698c Publication Date (Web): April 15, 2014 Copyright © 2014, American Chemical Society
4. L. Cheng, et al ACS Med. Chem. Lett., Article ASAP, DOI: 10.1021/ml400526d Publication Date (Web): February 21, 2014 Copyright © 2014, American Chemical Society
5. Z-Y Jiang, et al J. Med. Chem., Article ASAP, DOI: 10.1021/jm5000529, Publication Date (Web): February 21, 2014 Copyright © 2014, American Chemical Society

Back to top

Don't forget the chemistry

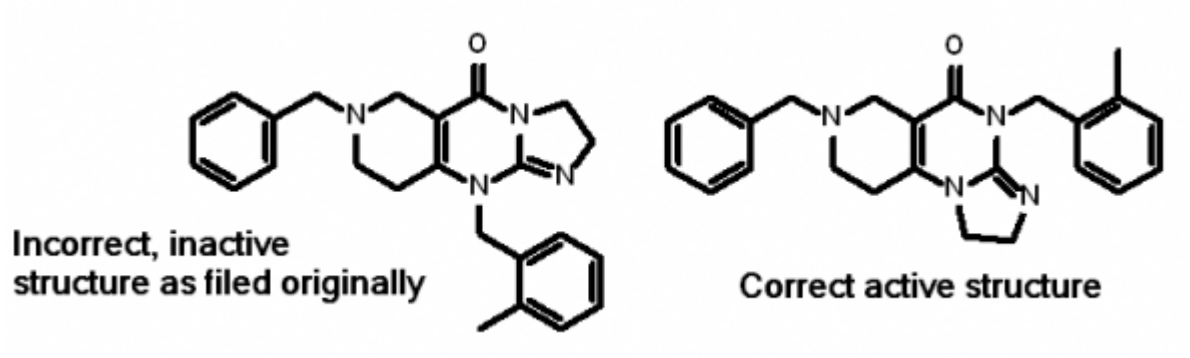
In a bit of a whoopsie it has come to light **1** that a compound TIC10, a stimulator of gene expression for TRAIL and in PhI/II clinical trials has in fact got an incorrect structure or rather the compound that was protected in the patent was assigned the incorrect structure. It was patented in

a single compound patent **2** – which might ring alarm bells for some - were they really that confident they had the best compound. A quick look at the patent revealed large amounts of *in vitro* work but none *in vivo* again begging the question how good is this single compound. The compound had been identified by a group at Pennsylvania State University and licensed to Oncoceutics from screening of the NCI compound collection but the team, as reported, only attempted structural characterisation by MS. This would be unlikely to differentiate regioisomers which is what the problem turns out to be. It does however seem strange that the patenting error was not detected during resynthesis and scale-up for progression to the clinic. The error was picked up when a group from the Scripp's **3** who synthesised the patented compound but found it inactive while they found the NCI batch to be active. They characterised the patented (inactive) and non-patented (active ex NCI) structures by crystallography and total synthesis. The corrected structure has now been patented by the Scripps group and licensed to Sorrento.

Of course this is all a bit embarrassing for those concerned but also more seriously could end up with extensive patent litigation, wasting money and discouraging investors from supporting the work until the patent situation is clarified causing delay in progressing the asset. Please please talk to medicinal chemsist early in a project this one looks like no one did which has led to an expensive mistake.

1. S. Borman Chem Eng News 2014, May 26 page 7
2. US Patent US8673923
3. N. T. Jacob et al Angew. Chemie. Int. Ed., Article first published online: 18 May 2014 DOI: 10.1002/anie.201402133

Back to top



5. Chemistry

Applying CH bond activation

I have featured CH-bond activation several times now in this newsletter as I see it as a great way of changing the way we apply synthetic chemistry in medicinal chemistry, in particular the regio- and stereo-selective introduction of more polar functionality. Thus I was pleased to see the publication of a collation of catalytic methods for the rapid diversification of simple starting materials including natural products some examples are shown in scheme 1 with obvious implications for drug discovery. It would be good to see this methodology directly exploited in a medicinal chemistry project in the future.

In yet another approach to synthesis built on CH bond activation and perhaps particularly relevant for drug discovery is the report of synthesis of strained nitrogen heterocycles **2** namely aziridines and β-lactams. The method uses a (currently fairly hindered) secondary amine Scheme 2 (1) and a palladium catalyst to generate a highly unusual 4-membered ring palladacycle (2) which is then functionalised to target either via oxidation to give an aziridine (3) or via carbonylation to give a β-lactam.

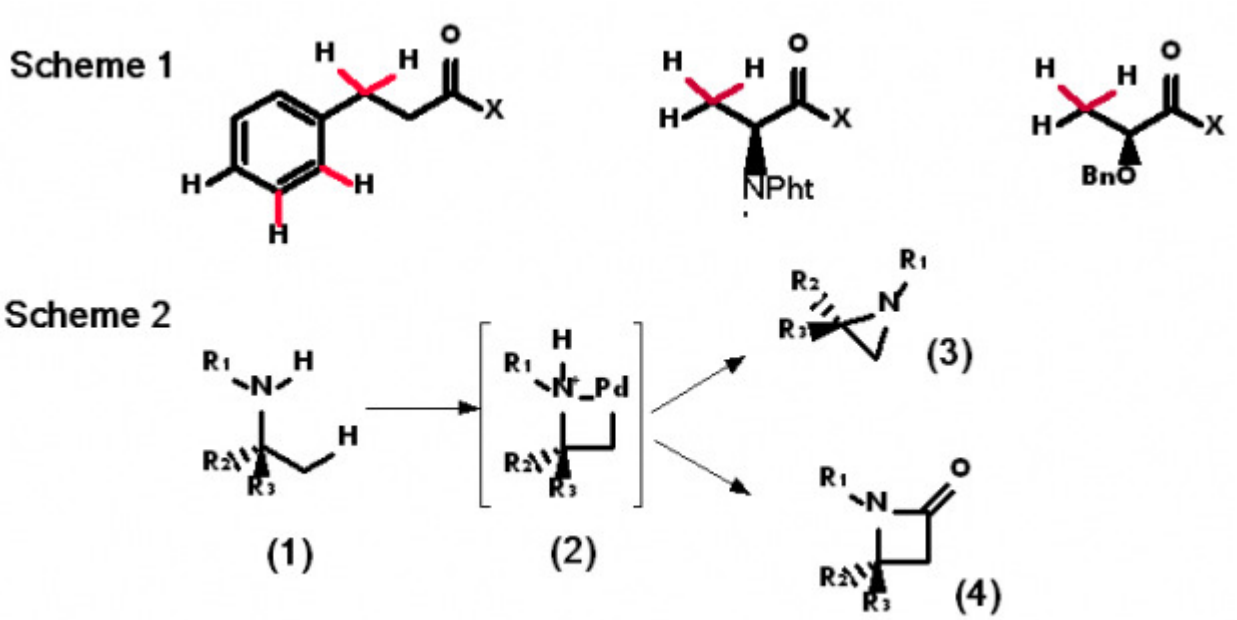
1. M. E. Farmer et al Bioorg. Med. Chem. 2014 doi.org/10.1016/j.bmc.2014.05.031
2. A. McNally et al Nature (2014), doi:10.1038/nature13389 Published online 28 May 2014

Nickel

A good review of the use of homogeneous catalysis using nickel covering a wide range of cross couping reactions, reductive cross couplings, CH-activation, Heck couplings and reductive coupling has appeared. While nickel may not be the ideal metal to have as a putative heavy metal contaminant it does allow some powerful research phase synthesis.

1. S. Z Tasker et al Nature 2014, 509, 299

Back to Top



6. Conferences

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

- 15th Tetrahedron Satellite meeting 24th June 2014

Meetings Attended

I have attended several meetings over the last few weeks. The 25th Symposium on Medicinal Chemistry in Eastern England held on 24th April again had a series of excellent talks. The Drugs of the Future report on the SMR meeting "Reducing Attrition through Early Assessment of Drug Safety" has now published. The SMR's Inflammation Research: New Horizons and Translational Challenges 5th June GSK Stevenage gave a lot of valuable information I learnt a lot about this core area of research. 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.

Back to top

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.

Cell Press Reviews

A useful resource for reviews from Cell Press compiling reviews from their stable of journals into a one-stop shop. They also highlight free access reviews although most will unfortunately need a subscription to the relevant journal.

Lists

The latest compilation of Science Directs greatest hits articles is now available with the usual range of categories.

Recon 2 – metabolic reconstructon network

A website of a metabolic network reconstruction focused on the systems biology of metabolism with 7440 reactions (~1/3 transport), 5,063 metabolites, 2,626 unique metabolites and can be used for example to look for prediction of e.g. Inborn errors of metabolism, exometabolites, drug actions, cellular differences.

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

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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Back to top