Rod Porter

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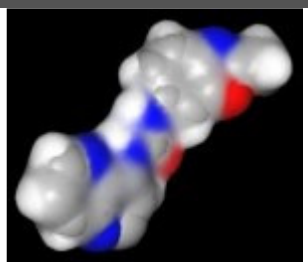
Sent: 23 April 2014 06:01
To: roderick.porter@btinternet.com
Subject: April 2014 Newsletter RodPorterNewsletter



Medicinal Chemistry News from Rod Porter

April 2014 vol 5. no. 2

Dear Dr Porter,

1. Welcome

Welcome to the April edition of the Medicinal Chemistry newsletter from RodPorterConsultancy. Features this month include; some thoughts from Sydney Brenner on the difficulties now of doing the pioneering work that took place in earlier decades, an outlook on schizophrenia, a once weekly dosing of a DPP-4 inhibitor, a brief review of some of the vast kinase literature, progress in peptide chemistry and in evaluating tissue binding and a look at a method for introducing *meta*-substitution.

Tempting though it was I havent revisited protein-protein interactions as there were several more interesting papers in this field looking at a range of interactions showing the increase in confidence in addressing this challenging but in my view critical area of small molecule intervention.

Its still not too late to sponsor my marathon run in aid of the mental health charity Mind completed on 6th April

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 June.

Wishing you every success with your research.

In this issue:

Brighton Marathon running in aid of Mind

The Brighton marathon has been and gone a great experience and a good weekend. So far I have almost £1,000 of donations on my web page, however, it is not too late to donate to Mind the mental health charity that I was running in aid of. To donate please visit my virginmoneygiving page and thank you. If the anonymous donor of £50.00 is a reader of this newsletter a particular thank you to you. Stats - time to complete 3h 43min 59 sec 1595 of 8,900 runners.

If you would rather donate to a different cause I will be running the Great North run half marathon in September in aid of the Alzheimer's Society - web site to follow.

SMR - next meeting

The next meeting of the Society of Medicines Research entitled "Inflammation Research: New Horizons and Translational Challenges" will be the 5th June at the GSK site in Stevenage UK.

Inflammation is one of the most fundamental and well-studied pathological mechanisms which is part of a complex biological response of tissues to stimuli such as pathogens, irritants and damaged cells. Still, after decades of research in both academia and industry there remains a high unmet need for effective anti-inflammatory therapies in a number of diseases. In addition, recent studies have highlighted that in a variety of chronic indications inflammation is not just a mere bystander but an integral part of pathology that is likely to contribute to disease progression and fatality.

One of the major challenges in drug discovery is to harness the available data and generate approaches that have promise to translate from bench to bedside. This meeting will bring together a number of key opinion leaders from both industry and academia to outline the current thinking about inflammatory processes and how they may be tackled to bring benefit to patients. The meeting will be of great interest to anyone involved in inflammation research, or has an interest in new opportunities in drug discovery.

For the full programme please visit here.

Optibrium - Stardrop™

Optibrium, and Integrated Chemistry Design, providers of software solutions and services for drug discovery, recently announced the release of Asteris™, a new iPad app that combines highly intuitive chemistry drawing tools with the most visually informative predictive modelling. Asteris enables creative researchers to rapidly evaluate new compound ideas when and where they want, no longer limited to sitting in an office or in front of a computer.

2. State of the industry

Reasons for complete response letters

The FDA have just published an analysis which has also been summarised of reasons for issuing the 151 complete response rejection letters sent between 2000 and 2012. Interestingly exactly half the 302 applications over this period were approved at first time of asking with 222 (73%) finally being approved within this time frame. For compounds issued complete response letters 87 had been resubmitted with 71 approved mostly at second but 18% at 3rd and 4% after more rounds of review. Best chances of getting an approval was for compounds with safety concerns where 61% were approved on resubmission while efficacy failings were more problematic with only 31% achieving approval on resubmission. Increased mortality was a sure indication that resubmission would lead to rejection again.

Reasons for issuing a complete response letter were lack of efficacy (32%), safety (26%) or failings of both (27%) and perhaps slightly surprising CMC/labelling problems accounted for 15% which seems a tad high to me. Poor dose and end point selection were common problems for efficacy with arguably similar problems of dose where safety was concerned with clinical AE's being most likely to preclude initial approval.

New compounds approved

An interesting survey of numbers of products approved from 2008 – 2013 by pharma companies which placed GSK right out in front of its competitors with 20 new molecular entities compared with the next runner Novartis with 13 and J&J's 9. One slight dampener on this is that the estimated value of these products for GSK by 2018 will be $11.7Bn while J&J are expected to pull in $13.1Bn and Pfizer with their 6 approvals will garner $12Bn. Mind you none of these numbers are too shabby and better with these than Eli Lilly with an anticipated $500Mn from their 2 NME approvals. So perhaps, at least relatively, the much maligned productivity of the research groups of GSK, Pfizer and Novartis haven't been quite as bad as all that. Of course there have been disappointments witness the closure by GSK of their efforts to progress a MAGE-A3 vaccine for lung cancer.

3. In Brief

Models

A paper **1** that I am having some trouble with as it seems so counter intuitive (OK so maybe that sounds like poor science on my part) is the observation that global models to predict an off-target activity is as good as, or better than, a local model built from a coherent range of analogues to quote "In our hands, the local model that best predicts the recent past is seldom the local model that is best at predicting the immediate future. Also, the local model that best predicts the recent past is not systematically better than the global model." The implication of this of course is that making and testing significant numbers of analogues within a series against an off-target is not necessary as a global model will be fine. The caveat is that the global model should be continually updated as new data is generated. The authors do suggest that the type of descriptors eg property v. fingerprint may influence the overall interpretation of global v. local models but it does seem like the need for local models is less than I believed.

1. R. P. Sheridan J. Chem. Inf. Model., Article ASAP DOI: 10.1021/ci500084w, Publication Date (Web): March 26, 2014

Sydney Brenner in conversation

An article picked up by Chris Swain and highlighted on Linked-In of an interview with Nobel laureate Sydney Brenner suggested several issues for young scientists moving into research that perhaps he did not have to face. Amongst various issues he raised were; the apprenticeship type roles of graduate students that he saw particularly in the US where the pressure is to "perform" not necessarily to innovate or work for themselves; to get funding requires preliminary information which means real pioneering work is almost impossible. It seems a bit like the "Catch 22" of great biological hypothesis now go and test it with a compound and then you can access funding. Prof Brenner is clearly not impressed with committee approach to work (lowest common denominator results) or peer review – the latter he really lambasts. He is also unimpressed with the need for scientists to force their work to fit in particular moulds to get published in "prestigious" journals to give a better chance of continuing funding rather than doing the work dictated by the science and then publish. He pointed out that Fred Sanger published very little and not necessarily in peer reviewed journals but the papers were seminal in their field. With a record like that Prof Brenner reckoned Sanger would just not survive these days – a refrain raised by other Nobel laureates over the years.

He is clearly a believer in the benefit of working in areas you are not familiar with – a case of ignorance can be bliss - preconceptions can be very damaging a view I certainly share.

I do recall a worrying account related to me by an academic colleague with whom I was trying to arrange a collaboration. He described work that he had done that he had been unable to get published because the referee's/editors felt the results did not fit with the perceived wisdom of the day - not a healthy way to advance scientific debate.

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ProteomeXchange

ProteomeXchange, is a new website set up to give a single point of entry and is "an EU-funded international consortium of proteomics researchers, data providers and publishers, aims to improve

the integration of public proteomics repositories. By implementing common guidelines, the consortium is greatly facilitating the assessment, reuse, comparative analyses and extraction of new findings from published data." This overcomes problems for both submitters and users of data as to which proteome database suc as PRIDE or peptideAtlas to use

The search function probably needs a bit of work on but as highlighted before in this newsletter having a single point of entry to data sets can only help.

Schizophrenia outlook

Very much personal interest is a recent Nature Outlook feature on schizophrenia looking at; aetiology, some of the issues that arise with speech, the polygenic nature of the condition, progress in identifying animal models, a focus on negative symptoms, signs for early diagnosis and benefits of early intervention and the reality of better outcomes in developing than in developed countries. Unfortunately fewer people in industry are now working on schizophrenia witnessed by rapidly declining numbers of clinical trials reflecting how tough an area this is. 219 drugs have been into schizophrenia trials since 1999 with 8 approvals – all dopamine antagonists and a pretty dismal failure rate. The most recent and deeply disappointing failure being that of bitopertin from Roche which has failed two PhIII studies so far – fingers crossed for studies still to report. Perhaps this is a field where epigenetics can play a significant role in the future and perhaps also where single target therapies may not be the best option. Patient segmentation also remains a challenge for clinical trial selection.

This is a useful survey although perhaps it does paint a slightly more optimistic picture than I would have done.

4. Medicinal Chemistry

Once weekly dosing

DPP-4 inhibitors are making big waves in the diabetes field with several compounds on the market and others striving to get a foot hold. Merck now report on omaragliptin **1** – currently in phase 3 as a once weekly DPP-4 inhibitor. Sitagliptin (1) was a key starting point that evolved to aminopyrans such as (2). However these were readily oxidised to the corresponding pyrrolopyrimidines – also DPP-4 inhibitors but with reduced selectivity against other DPP-4 family members. Focusing on the heterocycle a range of 6,5 and 5,5-fused systems were investigated leading to pyrazolopyrroles (3) which were both potent and selective and importantly were not oxidised. The 2R,3S,5R sulphonamide (4) (omaragliptin) showed improved PK properties with t1/2 of 11h (rat) and 22h (dog) and 100% oral bioavailability coupled with low clearance and low volume of distribution. In man omaragliptin (4) has a t1/2 120h. Omaragliptin has excellent selectivity over other proteases, negligible CV ion channel activity and good selectivity over other targets screened against. Omaragliptin behaves itself *in vivo* giving robust responses in oral glucose tolerance tests and a concentration dependent increase in GLP-1

I must admit I am not convinced about advantages of patient dosing once weekly for most inidcations. I would have enough trouble remembering to take medication once daily let alone once weekly perhaps this would be where smart technology would be exploited to send messages to remind patients to take their medicine

1. T. Biftu, et al J. Med. Chem., Article ASAP DOI: 10.1021/jm401992e Publication Date (Web): April 02, 2014 Copyright © 2014, American Chemical Society

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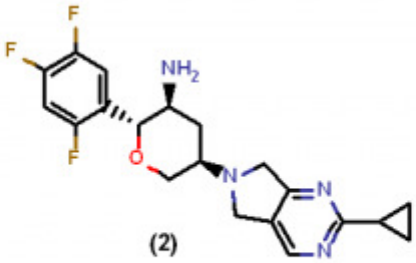
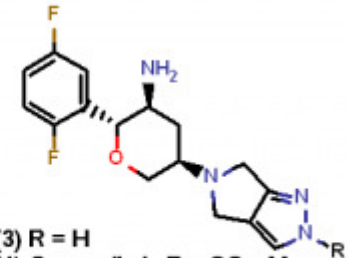
(1) Sitagliptin IC_{50} 18nM



(2)



(3) R = H
(4) Omaragliptin R = SO_2Me
IC_{50} 1.6nM

Kinases

I don't often cover kinases and certainly not individual stories of kinase inhibitors – there are just too many - but this useful looking review on Type III or allosteric kinase inhibitors **1** that bind to a site proximal to the ATP binding site, caught my eye as a useful background to this approach to kinase inhibition. The focus of the article is on allosteric inhibitors of non-small cell lung carcinoma particularly those that have reached the clinic. Another review **2** looking at non-ATP competitive inhibitors covers Type III, Type IV (allosteric site distal to the ATP binding site and Type V bisubstrate/bivalent inhibitors has also recently appeared. Advantages offered by these approaches are well documented but perhaps a key one is that common mutations of the ATP binding site can reduce the efficacy of ATP competitive compounds with use of new chemical space another clear advantage.

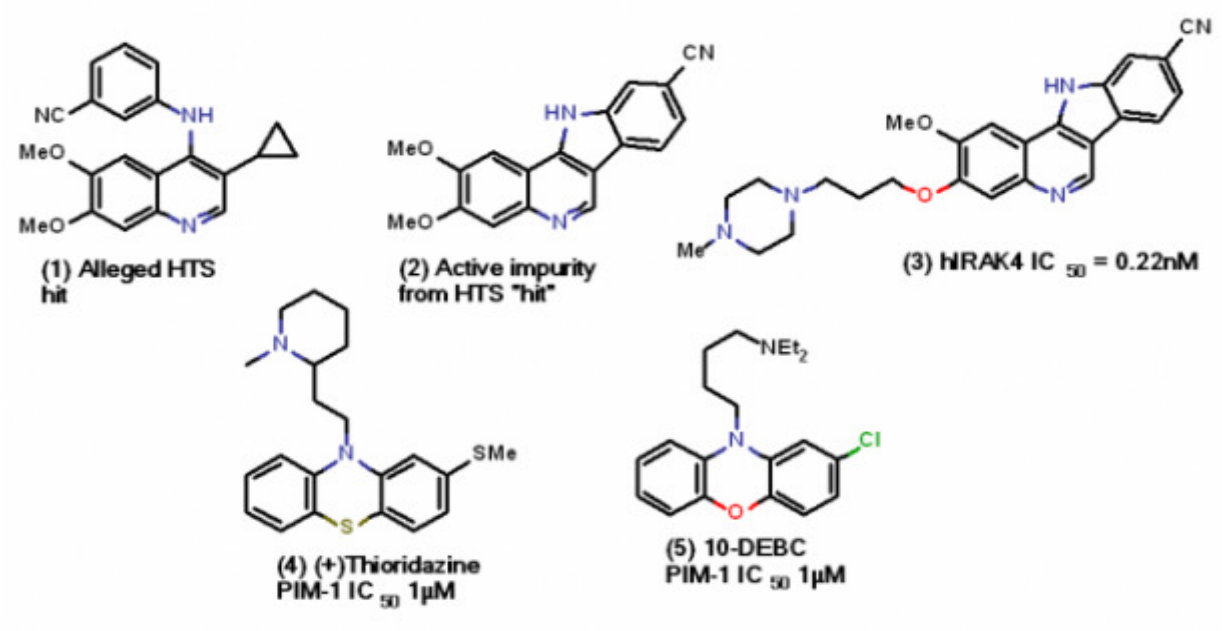
Following the kinase theme a nice example **3** of some detective work to follow up an HTS "hit". Compound (1) was identified as a hit IRAK4 inhibitor. IRAK4 is responsible for initiating signalling from Toll-like receptors (TLRs) and members of the IL-1/18 receptor family. However subsequent work showed that the real hit was an impurity (2) which was optimised to the more soluble (3) although (3) had only poor PK – removing the basic centre gave improve kinetics. Notwithstanding (3) could be dosed to achieve levels of drug equivalent to those that were efficacious in *ex vivo* whole blood assays and demonstrated inhibition of LPS induced TNFα in a murine model.

An interesting report on the structure and regulation of the membrane associated phosphatidylinositol 4-kinase IIα **4** discusses the role of palmitoylation, amonst other modulatory influences on the activity of this kinase. Interestingly the authors suggest that the protein is associated with cell membranes via hydrophobic residues rather than through the palmitoyl group. However, the palmitoylation does have a key role in regulating the phosphatidylinositol binding site and therefore the activity of the enzyme. Addition of cholesterol – decreasing membrane fluidity also affected/increased kinase activity and is perhaps a caution on assay systems but also – at least with respect to palmitoylation – an alternative approach to regulate the kinase by inhibition of palmitoyl transferase

Finally anti-psychotics as ATP competitive kinase inhibitors **5** – not the most potent perhaps but structurally rather different to standard heterocyclic ATP competitive inhibitors. Thioridazine (4), a dopamine D2 receptor antagonist, has been shown to be a PIM-1 kinase inhibitor with crystallography studies to back it up. Potency is modest and interestingly the basic centre can be removed and the activity is essentially retained. However 10-DEBC (5) a known "selective" AKT inhibitor shows a significant increase in target activity thought to be due to the basic centre wrapping round to improve an interaction with D128 – see PDB 4MED.

Just as I was completing this commentary the ACS released a collection of 24 kinase inhibitor papers collated from J. Med. Chem, ACS Med. Chem. Lett, Biochemistry and ACS Chemical Biology.

1. M. Fsano et al Expert Opin Investig Drugs. 2014 Mar 28. [Epub ahead of print]
2. V. Lamba and I. Ghosh Curr Pharm Des. 2012, 18, 2936.
3. L. N. Tumey et al Bioorg. Med. Chem. Lett 2014 http://dx.doi.org/10.1016/j.bmcl.2014.03.056
4. Q Zhou et al Nature Comm., 2014, 5, doi:10.1038/ncomms4552
5. W. Li et al MedChemComm 2014, 5, 507



Peptides

Upto 30'ish residue peptides can be reasonably synthesised using conventional peptide synthesis but one limitation is the reagent contact time. Hence its interesting to see a report **1** of use of lab automated flow chemistry to reduce cycle times to 2 min – the trick being a preheat of the individual amino acid building block. The short contact time and use of flow minimises side reactions and maximises conversion. The same team used the technique to couple peptides together to make DARPin pE59 and BaRNase **2**. These peptides had the same activity as the recombinant proteins. Furthermore exploiting the flow technology the team were able to rapidly optimise reaction conditions to minimise side reactions.

No mention of making cyclic peptides was made in these two papers but that doesn't stop me highlighting a useful recap **3** on the state of play of hydrocarbon stapled peptides that made such a splash a few years ago now. These stapled peptides are reported to confer α-helical structure, metabolic stability and cell penetrating properties. The paper provides a useful summary table of proteins that have been targeted with stapled peptides and some of the work needed to design ligands, the work to characterize them and the care in how this work is done – highlighting examples where design had been inappropriate. I do still have an issue with how one can say a stapled peptide is cell penetrant by sticking a large FITC label on and using that analogue. To be fair examples of activity against intracellular targets e.g. the stapled BH3 domain of MCL-1 have been reported. Aileron has reported a successful PhI study with a stapled peptide long acting GHRH agonist – perhaps more examples will follow

1. M. D. Simon et al ChemBioChem 2014, 15, 713
2. S. K. Mong et al ChemBioChem 2014, 15, 721
3. L. D. Walensky and G. H. Bird J. Med. Chem., Article ASAP DOI: 10.1021/jm4011675
   Publication Date (Web): March 06, 2014 Copyright © 2014, American Chemical Society

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Unbound drug fraction

Life is moving on with methods to determine interaction of compounds with tissues and membranes. A recent report **1** suggests that homogenates of cultured HEK293 cells can provide a reasonable measure of unbound brain fraction. Furthermore the group used cassettes of 5 or 8 compounds further increasing throughput without degrading quality of the read out. The same group also reported this method **2** for looking at intracellular drug concentrations in the liver which I discussed in an earlier letter. This work also pointed out that binding to HEK293 cell homogenates correlated with binding in liver derived systems but binding in plasma did not.

In another report **3** of rapid generation of tissue binding data solid supported porcine brain vesicles gave a good correlation with whole brain tissue homogenate. The authors also reported using rat brain vesicles with resulting being essentially the same as with porcine vesicles. While this method

does require animal tissue it should be more economical than whole brain homogenate equilibrium dialysis. This is another report showing the consistency of brain tissue binding across species increasing confidence in translation to human.

Of course it is the free concentration we should be ultimately interested in which is going to be dictated by the free blood concentration and any effects of blood brain barrier transporters for better or worse. None the less fubrain is required to generate that free brain concentration and to act as an alarm for any discrepancies between fubrain and fublood and to understand high BB ratios versus *in vivo* efficacy.

1. A. Mateus et al J. Med. Chem., Article ASAP DOI: 10.1021/jm401963n Publication Date (Web): March 20, 2014
2. A. Mateus et al Mol. Pharmaceutics 2013, 10, 2467−2478.
3. R Longhi et al Drug Met Disp., 2011, 39, 312

Rapid detection of intramolecular H-bonds

Ready detection of intramolecular H-bonds (IMHB's) remains a bit of a challenge. IMHB's can be detected by using LogP's determined in both polar and non-polar solvents but this is laborious and has practical limitations on the range of compounds that can be investigated. NMR can also be used but again is slow. Mining of the CSD **1** or CSD and PDB **2** has identified patterns that are predicted to form IMHBs, however, this is not the same as demonstrating the existence of an IMHB in your molecule of interest. A piece of work **3** now demonstrates the use of supercritical chromatography with non-polar liquid carbon dioxide as mobile phase and a polar stationary phase. For conformationally constrained analogues not capable of forming an intramolecular bond retention correlated well with tPSA. The term EPSA for the chromatographic estimation of PSA was introduced. Using topologies identified as forming IHMB's by Kuhn **2**, the authors identified a substantial number of compounds from the Pfizer compound collection that could form IMHB's. Similarly the team identified a set of related structures that could not form H-bonds that could be used as matched-pair comparators. From this pairwise comparison and confirmation with NMR work intramolecular H-bonds could be identified with high confidence. However, it was found that not all IMHB's were equal "*While EPSA appears to be effective at discriminating IMHB forming compounds from their controls in topologies featuring six-or seven-membered ring IMHBs from N−H to C=O or from N−H to aromatic N, the differences between matched pairs in topologies featuring five-or six-membered ring IMHBs from C−O to N−H, from C=O to O−H, or from N−H to aromatic N were less obvious.*" Clearly there is still more work to be done to make this a broadly applicable method.

The authors also noted the carboxylic acids in the current system do need to be treated with care as the acid group has a dominating interaction with the stationary phase. This could be a useful addition to the tools a medicinal chemist has to understand how biological systems see's his/her molecules. Perhaps also this approach represents an opportunity to assess the relative strengths of different H-bond donors and acceptors in matched molecular pairs – ignoring IMHB's for a moment

1. C. Bilton et al. Acta Crystallogr. 2000, B56, 849−856
2. B. Kuhn, P. Mohr and M. Stahl J. Med. Chem. 2010, 53, 2601−2611.
3. G. H. Goetz et al J. Med. Chem., Article ASAP DOI: 10.1021/jm401859b Publication Date (Web): March 31, 2014 Copyright © 2014, American Chemical Society

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Chromones as drugs

Following on from last editions comment on chromones/chromenes as structures to support lead optimisation a nice piece form Heptares **1** describing early optimisation of an A2A receptor virtual screening hit identified from docking (initially) to a homology model of the receptor and subsequently to a crystal structure of the receptor. The initial hit (1) was recognised as potentially docking in two different modes, detailed analysis and early analogue synthesis resolved this dilemma. Removing the charged acid gave a marked increase in target activity. Further optimisation of side chains focused on displacing "unhappy" water from lipophilic hotspots and perturbing the water network in binding sites. An example of this is a regioisomeric thiazole substitiuent where apparent drug target interactions are identical but one regioisomer unfavourably affects the water network while the other (2) doesn't. No PK or developability data is presented but a good account of the exploitation of crystallographic data in optimising GPCR ligands.

1. S. P. Andrews et al Med. Chem. Commun., 2014, Advance Article DOI: 10.1039/C3MD00338H

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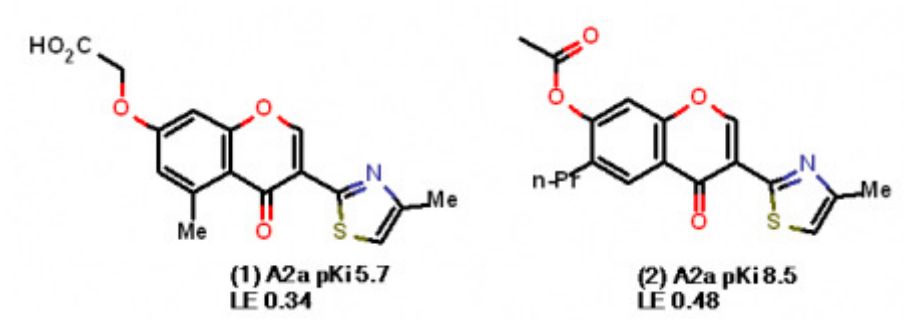

5. Chemistry

Directed *meta*-substitution, C-H bond activation

While ortho-directed substitution of aromatics is well documented using a variety of methods, *meta*-substitution is less straightforward. Using their end-on co-ordinating nitrile based template Yu's group now report meta substitution of anilines and benzylamines **1** – scheme 1. A key further component of the reagent combination was use of N-acetylglycine as a Pd(II) ligand. Olefination and acetoxylation (using PhI(OAc)2 as oxidant) have been accomplished in moderate to good yield and generally with >9:1 ratio of meta:ortho substitution. Some of the substrates functionalised are also shown in Scheme 1 with the option of a range of electron donating or withdrawing substituent's. The substituents are directing only to the extent of steric not electronic contribution.

From the same group is a report **2** of selective mono or diarylation of the methyl group of alanine Scheme 2. The approach exploits Pd chemistry again for C-H bond activation alongside ligands that activate the catalyst less (pyridine ligand) or more (quinoline ligand) strongly. Yields are generally good to excellent along with high diasteroselectivity with both enantiomers of the new sterocentre available. The reaction is not restricted to alanines – higher amino acids can also be arylated.

1. R-Y Tang et al Nature 2014, 507, 215
2. J. He et al Science 2014, 343, 1216

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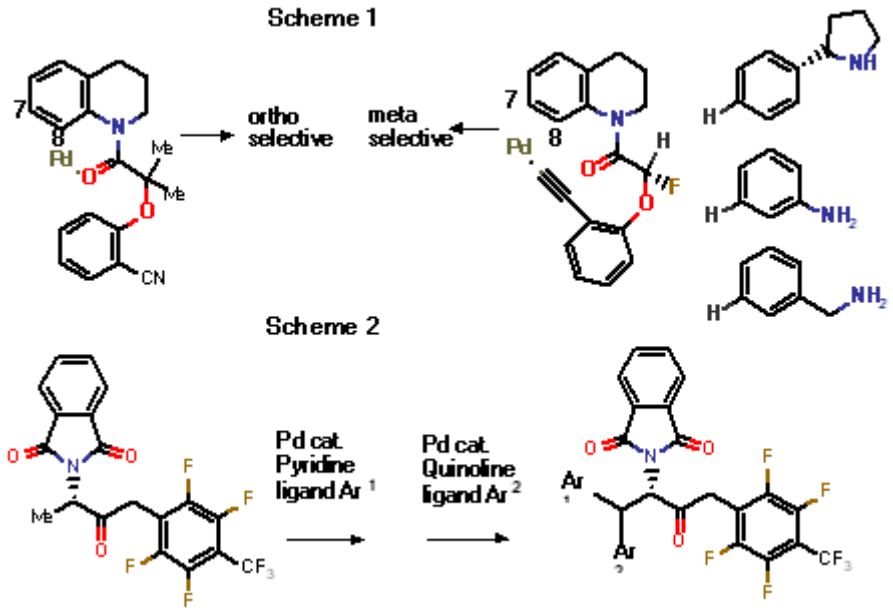

6. Conferences

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

- 25th Symposium on Medicinal Chemistry in Eastern England 24th April 2014
- Inflammation Research: New Horizons and Translational Challenges 5th June GSK Stevenage
- Blood Brain Barrier Club Kings College London, 2nd May (invitation only)
- 15th Tetrahedron Satellite meeting 24th June 2014

Meetings Attended

The report on the SMR December meeting "From Targets to candidates: Emerging Strategies in Drug Discovery" submitted to Drugs of the Future has now been published. The latest SMR meeting "Reducing Attrition through Early Assessment of Drug Safety" had a number of excellent talks discussing organs on chips, bioinformatics - a nice overview of ADMESARfari that I featured last time, miRNA's as markers of toxicity, use of metabolomics and of iPSC's amongst other topics

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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.

ToxTree

Highlighted by Tim Ritchie is Toxtree described as a flexible and user-friendly open-source application that places chemicals into categories and predicts various kinds of toxic effect by applying a range of decision tree approaches. The software is available through the sourceforge website. Also available for download is an add-on to allow identification of 260 functional groups.

Nature reviews key advances in medicine

A compilation of 45 papers each reviewing upto 8 key papers in the various areas of clinical interest such as cardiology and neurology that appeared in the Nature Clinical Reviews journals during 2013. This is a useful resume of clinical activity in these areas and it is free to download after registering

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.

CompChem Solutions is now CIR accredited.

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