Rod Porter

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Sent: 24 July 2012 06:04
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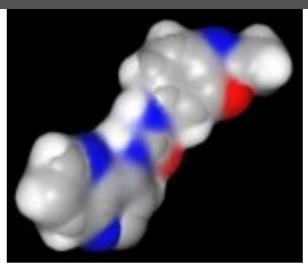
Subject: Medicinal chemistry news July 2012



Medicinal Chemistry News from Rod Porter

July 2012 vol 3. no. 3

Dear Dr Porter,

1. Welcome

Welcome to the July edition of the Medicinal Chemistry newsletter from Rod Porter Consultancy. My apologies for the delay - I have been busy setting up a new website - which is now linked to this newsletter. If you would like to make sure you keep receiving this newsletter please add the new senders address to your safe senders list.

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

Following a suggestion from a friend and former colleague I am planning a podcast version of the next newsletter. I would really appreciate any feedback if you think this woul;d be a good (or bad) idea.

I am looking forward to meeting up with the team at Optibrium, in the near future, to work with their software Stardrop for guiding decision making in drug discovery.

My intended schedule for newsletters for the ret of the year is early September, early november and a brief letter in mid-December.

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

Half Marathon Charity Run

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

2. State of the industry - pipelines

Make hay while the sun shines

An analysis from authors working at McKinsey's **1** on the outlook for drug innovation over the next 5 years does give some cause for optimism for that rather short time frame at least. The authors see a growth in revenues from "innovative" (NCE not novel target) products from 7% of global pharma sales for products introduced from 2007 - 2011 to 9% in for products introduced from 2012-2016. They predict an increase in market share for small molecules relative to biologics, a further increase in new drugs being brought forward as partnerships, oncology being a continued rich source of new products and an estimate that new launches will average 35 in 2012 – 2015 compared with 25 for the previous decade. This latter estimation is based on the increase in PhII

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8. Rod Porter Consultancy

and PhIII – PhIII compounds have been increasing at the rate of 9%/year since 2009. The devil however, as ever is in the detail or perhaps in this case in the timing as the problem that these authors gloss over is the crash in preclinical compounds 2009 – 2011 -9% (no surprise there) and a smaller drop in PhI compounds indicating that from 2016 life may be looking a little less up beat. The authors do highlight that the peak value of each new compound will decline substantially from around $900M now to around $600M in 2015.

. R. Berggren et al Nature Rev. Drug Disc., 2012, 11, 435

3. In Brief

Sorting out transporters

Efflux transporter interactions can be a significant liability when targeting the CNS or indeed oncology targets where resistance can emerge due to upregulation of, amongst others, P-gp (ABCB1 or MDR1) - MRP1 and BCRP are also implicated. No doubt efflux transporters also play an unrecognized role in local/cellular distribution in many other areas of pharmacology. From my own experience getting rid of P-gp activities can be a tough job. A review **1**, focuses on mitigation of P-gp liabilities with a comprehensive survey of examples where researchers have overcome P-gp as an issue in the distribution of their compounds. Affects can be subtle although the author does pull together trends such as reducing the number of H-bond donors and polar surface area. For example primary and secondary amides, urea's, sulphonamides, alcohols, phenols, carboxylic acids and NH heterocycles are highlighted as particular liabilities If these groups cannot be capped or replaced then an intramolecular (Goldilocks - not too strong and not too weak) H-bond may be a way to maintain target activity while limiting P-gp liabilities. Additional general guidelines identified include maximizing ligand efficiency, keeping the HBD count below 2 and polar surface area below 90 or even 70 angstroms – although we shouldn't forget the experience from Pfizer of the issues that can arise when PSA is reduced too far **2**.

Prof Hitchcock was rightly sceptical about the use, in isolation, of predictive models for this promiscuous transporter as it is disposition of physicochemical properties that is as important as the global properties themselves. He also observes that within his review there is a preponderance of cases where the biological target is an amino acid or a peptide which often requires polar substituent's for target activity.

Perhaps one area that the author did not consider was the role of permeability in mitigating efflux although arguably the strategies identified for reducing P-gp efflux are likely to increase permeability as well. Overall, however, it is reasonable that if P-gp efflux can be avoided it is best to do so to reduce unnecessary systemic exposure

Continuing the theme of transporters an extensive article **3** on OATP's and the classification of inhibitors has recently appeared. The report includes the development of *in silico* predictive models of specific and general inhibitors of OATP1B1, OATP1B3 and OATP2B1. With nice timing is the report **4** of [11C] dehydropravastatin of potential use in studying OATP1B1 and MRP2 transporters in the liver. The key synthetic step is a [11C]methylation of an organoboron precursor with [11C]iodomethane.

. S. A. Hitchcock J. Med. Chem. 2012 55, 4877
. J. D. Hughes et al, Bioorg. Med. Chem. Lett., 2008, 18, 4872
. M. Karlgren et al J. Med. Chem., 2012, 55, 4740
. R. Ijuin et al Bioorg Med chem. 2012, 20, 3703

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Mitochondrial Pharmacology

A flurry of papers on the small but perfectly formed mitochondria – often neglected by drug discovery scientists both for new drug targets but also as a source of toxicity for compounds which may only be manifested after long term drug exposure – the sort of finding you really don't want.

A review **1** discussed the many roles of mitochondria – oxidation of course but also e.g. roles in apoptosis, mitochondrial dysfunction and strategies for targeting distribution of drugs to mitochondria and and conversely reducing mitochondrial exposure. There are summaries of compounds that directly target mitochondrial pharmacology and those that target indirectly. I found this a very useful read for starting to get to grips with mitochondria.

There are opportunities for drug discovery in a range of therapeutic areas including cancer, cardiovascular, metabolic and CNS disease states, the latter including autism and neurodegenerative diseases. These are described in some detail in **2** which also comments on the difficulties of developing agents to treat mitochondrial disorders. The authors are not entirely positive (to say the least) about clinical trial design in the area. A focus on neurodegenerative diseases **3** identifies that most neurodegenerative diseases have major evidence of mitochondrial dysfunction. The evidence for this is reviewed carefully. One issue with these slowly progressive diseases is, just that, slow progression perhaps indicative of quite subtle deficits – which might need quite subtle intervention.

Focusing in on more detailed biology of the mitochondria are two papers. The first **4** on the importance of impaired transport of nucleotides by a mitochondrial carrier which is the reason for some severe genetic disorders. The paper documents all the pathological mutations of the transporter and the effect on transport properties. Essentially two effects are seen, either the modulation of the electrostatics of the recognition surface for the nucleotide or by reducing conformational plasticity. In cancer there is a high rate of aerobic glycolysis and mitochondrial metabolism is suppressed – the Warburg phenomenon. One explanation for this is proposed in **5** which reports that mitochondrial voltage dependent ion channels in the mitochondrial outer

membrane are being closed down.

In a thought provoking paper Naviaux **6** argues that oxidative shielding through for example generation of reactive oxygen species and lipid/protein oxidation is actually protective and therefore represents an inappropriate target for intervention. More important is targeting what is causing the insult in the first place. Relevance here of courser is that the mitochondria are a major source of ROS's.

I do remember hearing a talk from James Dykens from Pfizer on "Drug induced mitochondrial dsysfunction..." at an SMR meeting in 2009 on "Approaches to Assessing Drug Safety in the Discovery Phase". Dr Dykens was a strong protagonist of investigating off-target effects of compounds on mitochondria at an early stage of their development.

Finally a free poster on mitochondria and cancer **7**.

1. R. A. J. Smith et al, Trends in Pharmacol. Sci., 2012, 33, 341
2. R E. Davis and M. Williams J Pharmacol Exp Ther published 13 June 2012, 10.1124/jpet.112.192104
3. A. Johri and M. F. Beal J Pharmacol Exp Ther published 13 June 2012, 10.1124/jpet.112.192138
4. S. Ravaud et al ACS Chemical Biology Article ASAP DOI: 10.1021/cb300012j Publication Date (Web): April 12, 2012
5. E. N. Maldonado and J. J Lemasters J Pharmacol Exp Ther published 13 June 2012, 10.1124/jpet.112.192153
6. R. K Naviaux J Pharmacol Exp Ther published 13 June 2012, 10.1124/jpet.112.192120
7. Free poster from Nature Group publishing

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Post translational modifications - epigenetics

Lysine acylation

While lysine acetylation and methylation is central to epigenetic mechanisms lysine is involved in a wide range of additional, recently discovered, post translational acylation reactions including formylation, propionylation, butyrylation, crotonylation, malonylation, succinylation and myristoylation. These acylations all involve intermediates important in metabolism and several of the acylated lysine products regulate metabolic activity **1**. Sirtuins are involved in the deacylation mechanisms of acyllysines. Broadly, at least so far, propionyl and butyryl lysines behave like acetyl lysine and are recognised and regulated by similar proteins. However, there are indications that bromodomains may bind the longer chain acyl compounds less tightly than the corresponding acetyl lysine. A couple of examples of differences in behaviour between acyl lysines: levels of succinylated CPS1 a metabolic enzyme are regulated by Sirt5 which does not deacetylate acetylCPS1. P. falciparium sirtuin protein PfSir2A is much more efficient at demyristoylating lysine than it is deacetylating. This is an under developed area of research lacking, as the authors highlight, good analytical tools and an understanding of physiological function and regulation in large part due to the lack of suitable tool antibodies/small molecule inhibitors but clearly represents an opportunity for future drug discovery.

Epigenetics reviews

An excellent review **2** of the proteins involved in epigenetic signalling, including the obvious HDACS/sirtuins and methyl transferases but also covering bromodomains and proteins that bind to methylated histones. Links of these protein classes to disease are discussed ranging widely across oncology but also covering neuropsychiatric disorders, inflammation, metabolic disorders and regenerative diseases. Progress in the pharmacological modulation of each of these protein classes is also discussed and includes a useful summary of compounds in clinical trial or late stage development. This is a very useful resume of the epigenetic area. The prospects for therapeutics emerging from the sirtuins is addressed in detail elsewhere **3** with a particular focus on Sirt1 and the role of sirtuins in health span and lifespan. Not wishing to sound flippant but red wine in moderation still seems good to me.

Finally and just caught my eye is the review from Dash Dhanak on "Cracking the code: The Promise of epigenetics" **4** nicely complements the other articles highlighted here - a minisymposium in four articles. I should also highlight the excellent graphics in this particular review which really bring it alive.

1. H. Lin et al ACS Chemical Biology 2012, 7, 947
2. C. H. Arrowsmith et al Nature Rev. Drug Disc., 2012, 11, 384
3. J. A. Baur et al Nature Rev. Drug Disc., 2012, 11, 443
4. D. Dhanak ACS Med. Chem. Lett 2012 Publication Date (Web): June 14, DOI: 10.1021/ml300141h

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4. Medicinal Chemistry

2,5-Diketopiperazines

From former colleague Alan Borthwick an extensive and valuable review **1** of 2,5-diketopiperazines covering conformational aspects, synthesis, chemistry, occurrence in natural products and most relevant to this group, applications of diketopiperazines in medicinal chemistry. Important features of these cyclic dipeptides for drug discovery are; the high density of functionality coupled with some, but limited, conformational freedom with a low energy barrier between planar and a slightly puckered boat conformation; the chirality allowing ready introduction of molecular complexity and the ability to manipulate physicochemical properties. Examples of application to generate high affinity ligands that are discussed include PDE V inhibitors, oxytocin

antagonists, cell cycle and BCRP inhibitors, metalloprotease inhibitors and CCR5 antagonists. 2,5-Diketopiperaziens also serve as valuable peptidomimetic templates for example as RGD mimetcs, β-turn templates and dopamine receptor modulating peptide mimetics amongst others. Many bioactive natural products are 2,5-diketopiperazines – in particular Cyclo(Trp-Pro) derivatives are well represented often with additional heterocyclization and isoprenylation. Perhaps its also significant here that Trp while relatively low occurrence often has an important role in interactions between proteins.

Coincidentally a second review on 2,5-diketopiperazines **2** focuses on nootropic and neuroprotective properties of this template and argues that it represents a valuable "shuttle" into the CNS – I must admit I haven't come across this phenomenon before.

Research remains active in the field, for example, there is a recent report **3** on the isolation of diketopiperazine Aspergillus fumigatus metabolites poissessing anti-feedant and antifungal activities. Synthesis is active with the report of the total synthesis of Mycocyclosin a tyrosine cyclic dimer **4**.

1. A. D. Borthwick Chem Rev., 2012, 112, 3641
2. I. Cacciatore et al Mini Reviews in Medicinal Chemistry 2012, 12, 2
3. X-J Li et al., J. Agric. Food Chem., 2012, 60, 3423
4. J. R. Cochrane et al Org. Lett., 2012, 14, 2402

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Imaging agents - PET ligands

PET ligands have been regarded for a long time as being challenging which, while there has been little dispute of their value particularly for CNS drug discovery, has tended to dampen enthusiasm to discover them. However this seems to have changed with multiple recent reports on PET ligand. For example a team **1** reporting distribution studies have apparently gone direct to an 18F labelled fluoroethyl tropane derived PET ligand in this case for the dopamine transporter. Unfortunately the compounds obtained while having reasonable target affinity, < 10nM, had poor biodistribution to the CNS based on experiments with the [18F] compounds. The label was introduced via a nucleophilic displacement of an alkyl chloride with [18F]. Predictably PET ligands for the dopamine transporter is an area of significant activity.

A little more successful is the report **2** of diazabicycloheptane based [11C] ligand (1) for imaging cerebral α7-nAChR's in mice which was shown to distribute well to the CNS and label acetylcholine receptors. The key synthetic step was an N-methylation with [11C]iodomethane.

Various PET ligands have been reported for labelling of cerebral β-amyloid plaques in Alzheimer's Disease and the latest additions to the bill of fare are **3** an [18F] labelled pegylated benzoxazole (2). This compound showed differences in rate of clearance from the CNS of Tg2576 mice relative to WT and showed excellent binding to Aβ plaques in ex vivo experiments. A second paper **4** also describes closely related structures such as the benzofuran (3) also PET ligands for β-amyloid plaques. This paper focused strongly on the importance of physicochemical properties for a PET ligand coupled with a short half-life to maximise the signal to noise ratio and good brain exposure after 2 minutes coupled with good target activity. The preferred molecule from this investigation (3) had eLogD 2.8, t1/2 8 min and 1% of dose in brain 2 minutes post dose. eLogD **5** is an estimated log D based on comparison of reverse phase chromatographic retention times of standards compared with test substance.

1. H. Qiao et al Bioorg. Med. Chem. Lett., 2012, 22, 4303
2. Y. Gao et al, Bioorg. Med. Chem Lett., 2012, 22, 3698
3. M. Cui et al J. Med. Chem., 2012 Article ASAP DOI: 10.1021/jm300251n Publication Date (Web): June 12, 2012
4. B-M Swahn et al., Bioorg. Med. Chem. Lett, 2012, 22, 4332
5. F. Lombardo et al, J. Med. Chem., 2001, 44, 2490

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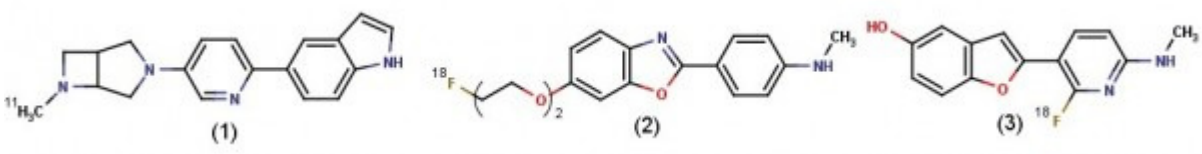

Why we get (molecularly) obese and how to avoid it

This report 1 discusses some of the reasons why medicinal chemists end up with obese molecules and also - importantly - suggests some solutions. Considered first is the nature of the target for example peptide hormone GPCR's are more likely to get you into trouble than an ion channel. Ligandability is the term the authors use to define the chemical tractability of the target. However, all targets tend to suffer property inflation. Starting points are of course important and is is where FBDD is starting to have an impact although as the authors note it's very easy to allow a fragment to grow rapidly if the focus is not continuously on maintaining ligand/lipophilic efficiency. The thermodynamic merits of starting with polar soluble fragments with a substantial enthalpic binding component is considered in some detail with the important comment that striving to achieve low nanomolar affinities will require increased entropic contribution with a likely deterioration in properties. Bottom line is that a passion for potency is misguided in many cases -after all most drugs are not low nanomolar affinity at their target. The importance of focusing on efficiency parameters is discussed and happily a "dictionary" of the various efficiency parameters is provided. The conflict between desirable as opposed to doable chemistry and programme timelines (and budgets) is discussed as is the problem of the

limited number of truly robust chemical reactions and even they tend to work better with more lipophilic substrates.

Medicinal chemistry guidelines are provided in the text and as a useful poster available for download **2**. This review is well worth reading as it pulls together new work from these authors coupled to a valuable resume of others work in the field on which the authors build their conclusions.

1. M. M. Hann and G. M. Keseru Nature Rev. Drug Disc., 2012, 11, 355
2. Poster summary

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Predicting unbound brain and unbound plasma Cmax

Bold in scope this report **1** describes an approach to estimate maximum unbound concentrations of drug in plasma and in brain following sub-cut. dosing based on a combination of calculated compound properties. These properties include fraction unbound (plasma microsomes and brain), microsomal clearance and Vdss and various calculated physicochemical properties

A few comments: the compounds discussed are all for casein kinase inhibitors and likely to have strong structural similarity (although no structures are shown), calculated fraction unbound in plasma and brain is apparently based solely on cELogD with modest r2, it is assumed that there are no efflux transporter issues. Perhaps my biggest concern is the calculation of t1/2 and Tmax from a calculation of microsomal clearance and an estimate of the first order rate constant of absorption. While literature methods are cited for calculating the various PK parameters there are inevitably significant errors with each calculated property. This is reflected by the fact that while a number of predictions are quite impressively comparable to measured data there is a wide spread in quality of prediction of 10 - 100 fold with other examples between calculated and measured drug.

It seems to me there is real power to this approach using limited measured data to support calculated data for virtual compounds and prioritisation of compounds for *in vivo* evaluation. This could be a powerful approach within a lead op. programme which is supported with some experimental *in vitro* and ideally *in vivo* data but seems high risk to me for deployment at an earlier stage of drug discovery if relying entirely on calculated results. My experience of, for example, calculating tissue binding is that within chemical series there is a reasonable relationship with lipophilicity but the same relationships across series does not hold. The supplementary information is useful to look at **2**.

1. S. Mente et al ACS Med. Chem. Lett., 2012, 3 515
2. S. Mente et al ACS Med. Chem. Lett., 2012, 3 515 Supplementary material

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Cheminformatics

Hit identification Different approaches to identify new hits for targets, old or new, and to promote scaffold hopping and new thinking for a target have been proliferating over the last few years driven by the availability of large amounts of screening and genomic data as well as structural information. A further driver has to be the economic advantages of running more *in silico* screening prior to wet work rather than going straight to HTS. A collection of recent publications serves to highlight some of the trends in screening strategies and in repurposing of existing drugs. One problem to me is that few of these strategies are appropriate to novel targets where there is little information available to steer compound selection.

A summary of the most common target oriented computational drug discovery approaches has recently been published **1**.

The group of Tropsha **2** highlight running a virtual screen against a QSAR model for 5-HT6 antagonists and subsequent querying of chemogenomic data from the Connectivity Map (see also of interest section for more on this resource) with the gene expression profiles of Alzheimers patients. Compounds identified from both approaches were screened to give a hit rate of 10 of 13 compounds tested with affinities in the range mid nanomolar to low micromolar. Interestingly four of these are selective estrogen receptor modulators although all actives are relatively hydrophobic tertiary amines.

Reymonds group **3** discusses their work on the concept of "chemical space" which focuses on the exhaustive enumeration of small molecule chemical space creating the freely accessible database GDB. Examples of application of this approach are drawn from NMDA glycine site ligands, glutamate transport inhibitors and α7 nAChR inhibitors.

Polypharmacology/drug repurposing/toxicology An induced fit protocol has been used to screen, *in silico*, FDA approved drugs against 5-HT2A models **4**. Of six compounds selected for screening the kinase inhibitor Sorafenib showed affinity at 5-HT2A 1959nM, 5-HT2B 56nM and 5-HT2C 417nM. Key to this is proposed to be the urea motif of Sorafenib which the authors don't seem to have picked up is present in the widely published SB biaryl urea 5-HT2C/2B antagonists such as SB-200646 **5**. Nonetheless this is just one of several examples exploring ways of investigating off-target activity of compounds.

In a molecular docking experiment **6** against the LEDGF/p75-binding pocket of HIV-1 IN, a protein-protein interaction, 26 drugs were selected from the DrugBank and purchased for bioassays. Eight of these including Atorvastatin were identified as potential inhibitors with IC50 values ranged from 7 μM to 37 μM. Atorvastatin was previously reported to block HIV-1 replication.

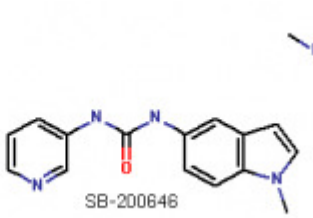
An approach to effectively virtual cross screen GPCR's combined a consensus scoring procedure that combined a ligand based frequent substructure ranking procedure with structure based tools **7**. An interesting result of this was that Sildenafil was found to be a high nanomolar inhibitor of the adenosine A2A receptor. The authors found that the more diverse training set of ligands

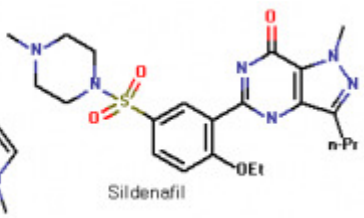
available for the adenosine A2A receptor gave more robust ligand based models relative to the β2 or S1P1 receptor models which needed both ligand based and structure based models to identify novel ligands.

Leading on from this is work describing the "Large scale prediction and testing of drug activity on side-effect targets" **8** in which the activity of 656 marketed compounds is assessed against 73 unintended side-effect targets – the Novartis *in vitro* safety panel targets. About half the predictions were confirmed either from available literature data or from new experimental data. The team also developed a measure to prioritize these off-targets as explanations for side-effects of the drugs seen clinically. While this is always going to be a work in progress type project and it did give about a 50% false positive effect this approach could play a useful role in prioritising compounds in the early stages of research and perhaps an indicator of where to focus off-target screening at later stages.

A lot of the work discussed above does rely on pooling biological data from a variety of assays from different labs and perhaps a timely reminder of the differences in results in the same assay for the same compound comes from a group at Novartis **9** (who seem to have had a flurry of papers on screening generally over the last couple of months). Experimental uncertainty is estimated (mean error) at 0.55 pKi units with sd 0.51 pKi. The main point of the work was to show that prediction of affinities could not be better than the data it was based on for relevant to both looking for new leads and for estimating off-target activities.

1. S. Kortagere et al J. Pharmacol. Toxicol. Methods, 2010, 61, 67
2. R. Hajjo et al J. Med. Chem., 2012, 55, 5704
3. J-L Reymond and M. Awale ACS Chemical Neuroscience, 2012
4. X. Lin et al J. Med. Chem., 2012, 55, 5749
5. I. Forbes et al J. Med. Chem., 1993, 36, 1104
6. G. Hu et al, J. Mol. Model, 2012, epub ahead of print
7. M. P. A. Sanders et al, J. Med. Chem., 2012, 55, 5311
8. E. Lounkine et al, Nature 2012, 486, 361 see also commentary Nature 2012, 486, 326
9. C. Kramer et al, J. Med. Chem., 2012, 55, 5165





5. Synthetic chemistry

meta-Directed aromatic substitution

It's good to see that Nature is reasonably regularly featuring synthetic chemistry these days – giving the discipline at least some of the recognition it deserves. In a very recent edition is a report **1,2** of catalytic palladium mediated meta-directed aromatic substitution which, not least, gives a valuable short approach to electron rich 1,3-disubstituted aromatic rings conceptually illustrated in Scheme 1 exploiting a removable linker e.g. ether (1) or amide (2). A copper mediated approach **3** had been reported previously for meta-arylation Scheme 2. While this new method currently has limitations with substrates limited to benzyl alcohols and arylpropionic acids this will no doubt soon change as, hopefully also, the need for stoichiometric silver salt. Chemical yields are moderate with >90% meta-regioselectivity, however, in view of the short synthetic sequence the moderate chemical yields look very acceptable to me. Key to success is the use of the nitrile as a chelating agent for palladium generating, in the case of the benzyl ether, a 12 membered ring. The ether can be cleaved back to the alcohol while the amide can be cleaved to recover the directing group precursor.

1. D. Leow et al, Nature, 2012, 486, 518
2. M. O. Kitching and V. Snieckus Nature 2012, 486, 478 News and Views comment
3. R. J. Phipps and M. J. Gaunt, Science 2009, 323, 1593

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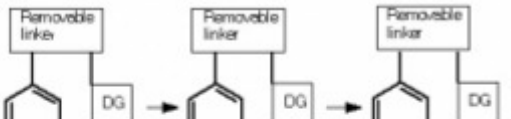

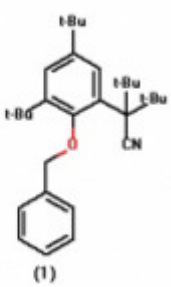

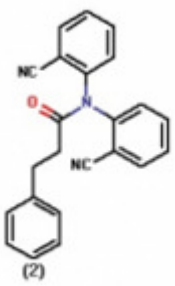

6. Conferences

Some links to slide packs from the kinase meeting I attended a couple of months ago are now on the SCI website.

Conferences attended by Rod Porter Consultancy in the last two months were:

1. Protein Kinase 2012, RSC/SCI, 21st, 22nd May Cambridge - slide packs for some of the talks are available here. Drug Discovery Today has also featured a series of papers on kinases as the editors choice.
2. Society of Medicines Research Respiratory Drug Discovery, current developments and future challenges 14th June hosted by Novartis UK
3. Cresset User group meeting 20th, 21st June Cambridge - a diverse range of talks which are nicely summarised on the Cressset website.

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

1. ELRIG - Manchester 5th, 6th September 2012 is designed as a showcase for suppliers but has an excellent scientific programme as well - almost forgot - its free for delegates
2. SMR - London 4th Oct. The importance of (Bio)pharmaceutical properties in successful drug design
3. SCI - London 6th Nov. Enhancing drug discovery: The benefits of of kinetic and thermodynamic binding data in discovery.

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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.

A lively discussion on Linked-In on phenotypic screening started by Jonathan Lee from Lilly I think you will need to be a member of the Medicinal Chemistry and Drug discovery group to read it. Its worth reading this in conjunction with Jonathan s recent paper on phenotypic screening where he advocates: "A hybrid of classic phenotypic and target-directed strategies, which blends the use of physiologically relevant biological systems with the high throughput and statistical robustness of modern assay technologies, may have a higher probability of technical success for launching first in class drugs than either classic phenotypic drug discovery or target based drug discovery" This seems pre-eminently sensible to me - perhaps we can get to tissue assays as a more common event again as well!

This database "The Connectivity Map (also known as cmap) is a collection of genome-wide transcriptional expression data from cultured human cells treated with bioactive small molecules and simple pattern-matching algorithms that together enable the discovery of functional connections between drugs, genes and diseases through the transitory feature of common gene-expression changes." It has about 7,000 expression maps from 1,300 compounds. As ever I need to spend some time looking at it but the principal looks good.

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

Wishing you every success with your research.

8. About Rod Porter Consultancy

Established in 2009 Rod Porter consultancy offers medicinal chemistry consultancy services to a widening client base of small biotechs, academic and charitable bodies. Services offered include assistance with or proposal of medicinal chemistry strategies, with a particular interest in CNS targets, independent, expert review of ongoing programmes and projects, review, critique and refereeing of research proposals, third party due diligence and more. If I can't help you perhaps my informal network of contacts can.

Visit my 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

Wishing you every success with your research.

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