Rod Porter

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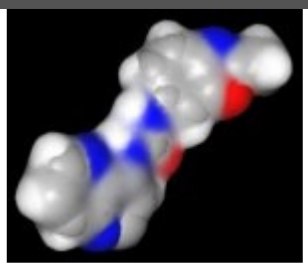
Subject: Medicinal Chemistry News October 2013



Medicinal Chemistry News from Rod Porter

October 2013 vol 4. no. 5

Dear Dr Porter,

1. Welcome

Welcome to the October edition of the Medicinal Chemistry newsletter from RodPorterConsultancy. Features this month include the reliability of drug sales forecasts, revisiting both pH and absorption and more hERG models, the proliferation of metrics and what do they mean, a discussion of H-bonding and permeability, kinases and neurodegeneration (no not GSK3) and an analysis of what makes oral macrocycles oral. For yet more discussion see the table of contents.

My thanks to ChemPharmaServe for sponsoring this issue of the newsletter - this allows me to keep issues rolling out.

It was nice to see the review I co-authored with Lee Dawson of Eisai "Progress in the development of neurokinin 3 modulators for the treatment of schizophrenia: molecule development and clinical progress" has now published. Now on with the GlyT-1 inhibitors for schizophrenia book chapter.

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 - I am happy to give attribution.

My next mailing is planned for December. I will be attending the SMR meeting December 12th "From Targets to Candidates: Emerging Strategies in Drug Discovery" not one I can miss seeing as I am chairing a session! For more details of this meeting see below.

Wishing you every success with your research.

In this issue:

ChemPharmaServe

ChemPharmaServe

ChemPharmaServe is an innovative chemistry solution provider, established in Cambridge UK in 2004, helping biopharmaceutical companies to fast-track their drug discovery and development projects. Their core expertise spans preclinical development and cGMP production of drug substances.

One of their most popular services is the provision of metabolites, custom-made compounds and labelled molecules, which has attracted the attention of Med Chem, DMPK and Toxicology groups.

They take the risk out of compound supply by investing in the chemistry, solving the technical issues and taking the responsibility for compound delivery to their clients allowing them to focus on drug discovery challenges. The costs are borne by them and they get paid only when products are delivered to the client's satisfaction. For more information and contact details please visit ChemPharmaServe.

SMR - next meeting

The next Society of Medicines Research meeting is on December 12th entitled "From Targets to Candidates: Emerging Strategies in Drug Discovery" will be held at the National Heart and Lung Institute South Kensington. Places are going fast so sign up soon to make sure of your place at this popular meeting.

This meeting brings together experts to highlight several of these developments describing work from hit identification through to candidate selection and beyond. Themes covered include the application of fragment based drug discovery to new target classes, antibodies in drug discovery, defining new chemical space with macrocycles and non-macrocycles, the renewed importance of phenotypic screening and approaches for the identification of allosteric modulators. The meeting will be of great interest to all involved in cutting edge drug discovery.

Optibrium

Optibrium of Stardrop reknown, is joining a major European project - the HeCaToS (Hepatic and Cardiac Toxicity Systems) project – co-ordinated by Maastricht UMC+ – for which the EU is providing €12 million. In the course of the project, Optibrium will extend and advance its unique quantum mechanical models that predict metabolism by Cytochrome P450 enzymes, while further developments will focus on predicting the formation of reactive or toxic metabolites. The resulting models will be integrated into the HeCaToS system, to determine if metabolites of new compounds may damage the liver and heart, and support the project's aim to enable the development of safer medications, cosmetics and industrial chemicals. See the full press release. Optibrium have also just announced an enhancement of their community web pages with more tutorials, free extension downloads and more

2. State of the industry

From little acorns big oak trees (might) grow

For those working in big pharma its easy to get isolated from the world of small biotech and for those in smaller organisations it can simply be too big a job to keep up with up and coming rivals/colleagues in your particular disease area. Fiercebiotechs Fierce 15 pick of 2013 is one way of looking at up and coming companies – not necessarily new – just regarded as (possibly) having a bright future. For the full list follow the link.

Drug sales forecasts don't bother they will (almost certainly) be wrong

Perhaps something we all suspected - forecasts of sales for drugs are usually wrong and sometimes vey wrong both in over and underestimating their value but now confirmed in a report from McKinsey **1** that was highlighted in Fierce Pharma **2**. Some numbers - 60% of forecasts were more than 40% over or under estimated with some overestimates of greater than 160%! These forecasts were made a year pre launch. Estimates do improve post launch but not by as much as you would expect with a variance between estimated and actual peak sales of 45% 6 years post launch. Larger companies do seem to be a bit better at not over estimating value of assets relative to smaller companies. CNS and cardiovascular drugs also tended to suffer more over estimates of value with oncology often underestimated with the latter perhaps easy to understand.

This difficulty in estimating the commercial value of a product does have ramifications, as the article points out, for the company, but also for the stock market factoring in perceived value (or lack of it) to the value of shares and finally the impact on portfolio decision making way before a drug is going to get to the market. How many promising drugs were abandoned for "commercial" reasons because the estimated market was seen as too small – fair enough for the 7th drug in its class but what about a pioneer product with unrecognised potential.

For those who wish to take vicarious pleasure in someone else's embarrassment here is a 10 top of launch disasters **3** and for the more charitable amongst you the top 15 underestimates of peak sales **4**. While we may wonder about the divergence from reality of many of these predictions let's face it the job isn't easy with so many variables to consider as long as wishful thinking doesn't play a role!

1. M. Cha, B. Rifai and P. Sarraf Nat. Rev. Drug Disc. 2013, 12, 737 doi:10.1038/nrd4127
2. T Staton, FiercePharma Oct 7th 2013
3. J. Carroll, T. Statton FiercePharma Nov 27th 2012
4. T. Statton FiercePharma Oct 2nd 2013

3. In Brief

pH and drug absorption

The article last time on high stomach pH and the impact on absorption seemed to attract a bit of interest and as it happens there

seems to have been a bevy of papers considering similar matters published over the last few weeks.

First up is the report **1** of a rat model to assess impact of changes in gut pH on absorption of compounds with pH dependent solubility. Pentagastrin and famotidine are used to manipulate the rats GI tract pH. The weak bases dasatinib and ketoconazole showed reduced absorption, ~4.5 fold reduction in AUC, on treatment with famotidine while mefenamic acid showed no change in AUC relative to controls. Pentagastrin doubled AUC for ketoconazole relative to control while there was no effect of pentagastrin on AUC of dasatinib. Effects of dasatinib absorption under various GI conditions now in the dog are subject of another report **2** of particular note was the ability of betaine to, at least temporarily reduce the increase in stomach pH caused by famotidine and to restore to a little above control level AUC of dasatinib.

Now looking *in vitro*, a report **3** of a novel in vitro approach to assess risk of pH dependent effects absorption of drugs with a strategy proposed for early clinical risk assessment based on in silico, in vitro, in vivo and physicochemical analysis. Unfortunately physicochemical properties alone were not found to be a good predictor of clinical behaviour.

1. J. W. Lubach et al Mol. Pharmaceutics, Article ASAP DOI: 10.1021/mp400283j Publication Date (Web): August 20, 2013

2. J. Pang et al Mol. Pharmaceutics, Article ASAP DOI: 10.1021/mp400356m Publication Date (Web): September 11, 2013

3. N. R. Mathias et al, Mol. Pharmaceutics, Article ASAP DOI: 10.1021/mp400426f Publication Date (Web): September 26, 2013

More hERG analysis

Analysis of hERG data continues with two new reports. Firstly an analysis of hERG data from Chembl has been reported **1** looking at both binding and functional data with as a result some queries about existing guidelines for designing out hERG liabilities. Guidelines considered included reducing lipophilicity, and pKa, adding an acidic group introducing an oxygen based H-bond acceptor and increasing the rigidity of any linker. The author argues that for binding data the analysis supports the idea that reducing lipophilicity (and increasing PSA) is beneficial, basic compounds can give both active and inactive compounds (although changes in basicity were not calculated) and introduction of an acid – looking at matched molecular pairs was also beneficial. However rigidity and increased H-bond acceptor count were not good indicators of reducing hERG. In functional assays all basic compounds were active at at least 10uM and no matched molecular pairs +/- a carboxylic acid were identified. Active was defined by activity being seen at either 1 or 10uM.

Secondly a matched molecular pair analysis by a group from Novartis **2** looking at internal dofetilide binding data. Conclusions were introduction of oxygen or sp2 nitrogen to increase polarity, removing carbon/reducing lipophilicity and reducing basicity were all beneficial with 3-10 fold improvements. The biggest benefit seen was with an N-methylimidazole - N-methyltetrazole transformation with a 15 fold reduction. The authors also observed introduction a cyclopropyl adjacent to basic nitrogen could also help perhaps rather reflecting a change in basicity. Ominously they also observed that hERG SAR did tend to be moderately flat.

While there have now been many analyses of hERG SAR all coming up with braodly similar conclusions little analysis has yet emerged of structural features relevant for activity for other cardiac ion channels - presumably reflecting a lack of data - as yet. Perhaps a gap that now needs to be addressed.

1. P. Czodrowski J. Chem. Inf. Model., Article ASAP DOI: 10.1021/ci400308z Publication Date (Web): August 21, 2013
2. C.Springer and K.L. Sokolnicki Chemistry Central Journal 2013, 7, 167

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4. Medicinal Chemistry

Too many optimisation metrics

I don't think anyone can disagree with the idea that some way of estimating compound quality as a drug discovery programme progresses is a good idea. Like any metric it needs to be chosen with great care to avoid the often found law of unintended consequences. It is therefore good that questions are asked about metrics which is what Schultz from Novartis has done with two papers. In the first **1** he takes apart metrics which include heavy atom counts and log potency - targeting in particular but not only ligand efficiency - which he reckons falls over by trying to combine linear HAC and logarithmic activity plus assuming all heavy atoms are equal. He is much more positive about LipE (pIC50 – LogP) which of course is working with two log scales and has a track record of showing improvement with the progression of a drug discovery programme **2**. Furthermore it keeps the focus on controlling lipophilicity, control of which seems to be more important than controlling molecular weight in ADME models and in maintaining a chance of success in development. The work centres on comparisons of matched molecular pairs (MMPs) and the often contradictory consequences for optimisation metrics. This paper is also an excellent collation of different optimisation metrics with 40 references with a convenient graphic summarising some of the most commonly used. This paper has been reviewed by Derek Lowe on his blog – worth reading in its own right of course, but I would particularly draw your attention to some of the comments including stories of the consequences of following "rules" too blindly. Also worth noting that some commenters are unhappy with LipE as well because it suggests a direct linear relationship when most likely there should be a correction factor included. So what is the answer? It seems to me apply something like LipE with caution, use ADME predictive models with caution and certainly validate these models against your particular chemical series, don't let (c)LogP(D?) drift upward, don't invent proscriptive (arbitrary) parameter cut-offs and application of common sense.

Schultz argues for another reason **3** that LipE has more going for it than other metrics in that he argues it is a better predictor of compound "quality" defined by enthalpic binding e.g. **4** again compared with LE or LELP. In his analysis Schultz again compares

enthalpic binding energies using MMP's and this does feel like a reasonable conclusion.

With all the above discussion I am slightly hesitant to introduce another optimisation metric but just published from Pfizer **5** is a proposed LipMetE = log D7.4 − log10(CLint,u). The group propose using this in conjunction with LiPE after all the two metrics are not collinear. The parameter emerged from analysing changes in microsomal clearance with lipophilicity for a series of gamma secretase inhibitors but was then supplemented by a MMP analysis across the Pfizer data set. I must admit this does all seem to make sense as it does keep ones mind on designing a stable enough molecule which doesn't necessarily follow from maximising LipE which goes back to my comments about unintended consequences.

Thanks to Ashley Jarvis (Domainex) and Steve SMith (StortMedChem) for both picking up this theme

1. M. D. Schultz Bioorg. Med. Chem. Lett., 2013, 23, 5980
2. A. Tarcsay et al J. Med. Chem., 2012, 55, 1252
3. M. D. Schultz Bioorg. Med. Chem. Lett., 2013, 23, 5992
4. G. G. Ferenczy and G. M Keseru Drug Discovery Today 2010, 15, 919
5. A. P. Stepan et al J. Med. Chem. 2013, 56, 6985 dx.doi.org/10.1021/jm4008642

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Manipulating H-bond strength and permeability

A nice discussion **1** on increasing permeability of compounds by manipulating hydrogen bond donor strengths while avoiding increases in lipophilicity. Potent monoacylglycerolacetyltransferase-2 (MGAT2) inhibitors had been identified containing 3 H-bond donors e.g.1 with consequent modest permeability. N-methylation of each of these acidic protons individually resulted in unacceptable loss of target activity although N-4 methylation caused the least drop-off in activity. In each case methylation increased permeability from two fold (N1) to 18 fold for the sulphonamide NH/NMe pair. Further SAR studies highlighted C-9 was amenable to modification e.g. (2) while retaining target activity. Furthermore permeability also varied according to the nature of the C-9 substitution which seemed to best correlate (P = 0.0018) with the H-bond donor strength of NH-4 as calculated by Gaussian 09 using B3LYP functional and 6-31G* basis set giving through-bond and through-space effects. Correlation with LogD (P=0.024) was weaker although still not bad. The H-bond donor effect of NH-4 was lowest with a C-9 chloro substituent although this substituent increased H-bond donor strength of NH-1. The permeability effects were relatively modest at 4 fold between C-9 H and C-9 chloro. Substitution of the benzenesulphonamide also enhanced permeability perhaps more due to steric influence than changes in H-bond donor strength at this particularly problematic acidic proton although this was not discussed in detail.

Overall a nice example of manipulation of molecular donor acceptor properties by simple substitution and also highlighting the merit of both measuring LogD rather than relying on calculation and formally calculating H-bond donor properties which raised some slightly unexpected results – at least to me. A prospective exercise looking at calculated properties first would be interesting. Additional recent references include, in the context of P-gp transporters and permeability **2**, and an article focusing on the importance of 3D analysis in identifying intramolecular H-bonds to improve permeability **3** particularly focused on peptides. A further recent reference **4** identifies use of ΔLogP to support identification of intramolecular H-bonds using the difference between measured LogP oct/water and LogPtol/water. ΔLogP in some shape or another emerges every so often but never seems to catch on perhaps because it requries two measurements and using a hydrocarbon must also be tricky experimentally as solubilities cannot be great

It would be interesting also to see how the Abrahams α- and β- parameters would have worked in this example see e.g. **5**.

1. J. S. Scott et al Med. Chem. Commun., 2013,4, 1305-1311 DOI: 10.1039/C3MD00156C
2. P. V. Desai, T. J. Raub and M.-J. Blanco, Bioorg. Med. Chem. Lett., 2012, 22, 6540.
3. S. B. Rafi et al, J. Med. Chem., 2012, 55, 3163
4. M. Shalaeva et al J. Med. Chem., 2013, 56, 4870
5. J. A. H. Schwobel et al J. Phys. Org. Chem., 2011, 24, 1072

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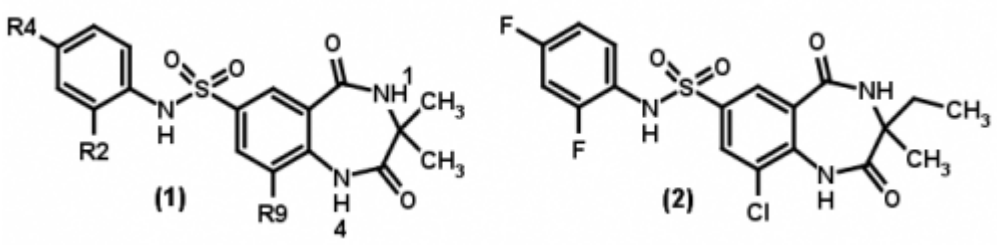

Macrocycles as oral drugs

Macrocycles (defined here as containing 12 or more atoms) are of continuing interest particularly as antibiotics and in oncology. They are also of expanding interest in other therapeutic areas as they can access chemical space and molecular targets not seen with more conventional small molecules. Furthermore, and relevant to another discussion in this newsletter, they tend to transgress many of the "guidelines/rules" that have been identified for drug discovery. Despite this, however, 43% currently in clinical trials are being administered orally. The question therefore arises why is it that such large and often high PSA compounds

are able to at least achieve oral exposure and furthermore in some cases access intracellular targets.In an attempt to understand what makes an oral macrocycle an AZ group has reviewed marketed and development phase macrocycles for their properties **1**. Oral macrocycles do tend to have LogP <10, PSA's < 250, mol wt <1,000 and =<5 hydrogen bond donors cyclosporin and two close analogues being the exceptions that exceed these figures. So arguably there is a space to work in which is however substantially larger than appears for conventional small molecules. Perhaps this reflects intermolecular interactions, shape or perhaps the exposure of sufficient lipophilic or polar surface area to allow a rolling through a membrane - or at least the gut wall.

. F. Giordanetto and J. Kihlberg J. Med. Chem., Article ASAP DOI: 10.1021/jm400887j Publication Date (Web): September 17, 2013

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Kinase inhibition and neurodegeneration

A paper out (rightly or wrongly) hitting the popular news broadcasts earlier this month **1** was the report that a GSK protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK) inhibitor, shuts down the unfolded protein response (UPR) which is over activated in the presence of prion proteins. UPR is an adaptive cellular response used to maintain homeostasis of the endoplasmic reticulum under conditions of stress. A PERK inhibitor dosed orally "prevented UPR-mediated translational repression and abrogated development of clinical prion disease in mice, with neuroprotection observed throughout the mouse brain" . This effect was seen in animals treated both prior to and following the emergence of clinical signs. Perhaps no coincidence that a paper reporting the invention of GSK2656157 a preclinical candidate PERK inhibitor also appeared in the last few weeks **2** including one of the authors of the neurodegeneration paper. This report is a continuation of earlier work and describes the optimisation of an advanced lead GSK2606414 (1) with P450 issues to give the candidate development compound (2) by reducing overall lipophilicity which had the additional benefit of improving PK parameters. Fluorination improved cell activity of the compound. Work to identify (1) is disclosed in **3** with the lead coming from the GSK kinase library with optimisation increasing target affinity 30 fold and providing good selectivity over 300 kinases. The work in **2, 3** was targeting oncology and more detailed biology of GSK2656157 has also been reported **4**. One note of caution is the authors of this work do comment "given the on-target pharmacologic effects of PERK inhibition on pancreatic function, development of any PERK inhibitor in human subjects would need to be cautiously pursued in cancer patients". Indeed in in vivo neurodegeneration models studies could not be continued too long due to substantial weight loss seen with the compound used - PERK pharmacology is also implicated in insulin regulation so it may not just be the compound. So it may be a while yet before we can think about success in hitting neurodengeneration clincially but none the less an encouraging development and if PERK falls over perhaps other parts of the UPR cascade can be targeted safely. The biology of UPR has also been recently reviewed **5.** A further report on reducing the phosphorylation of eIF2α, a key regulator of mRNA translation, by genetic deletion of either PERK or GCN2 two of the four kinases that regulate eIF2α helped protect mice from neurodegeneration **6.**

For those who missed the national television coverage here in the UK here is FierceBiotechs take on the work**.**

For more kinase involvement in neurodegeneration - 3-phosphoinositide dependent kinae (PDK1) activity is increased in Alzheimers patients with consequent reduction inTACE activity **7**. Using a commercial PDK1 inhibitor BX912 the authors showed an improved cognitive and memory effects in mice.

Finally in a fascinating talk from Prof. Chris Miller IoP Kings College London at the recent Society of Medicines Research meeting on kinases he described his work looking at alternative approaches to regulate GSK3 particularly looking at Lemur Tyrosine Kinase (LMTK2) and the role of kinases in axonal transport a possibly neglected field of neurodegenerative research. Keep an eye out for the meeting report that should be out in the next few weeks.

. J. A. Moreno et al,. Sci. Transl. Med. 2013, 5, 206ra138.
. J. M. Axten et al, ACS Med. Chem. Lett., Article ASAP DOI: 10.1021/ml400228e Publication Date (Web): August 23, 2013
. J. M. Axten et al J. Med. Chem., 2012, 55, 7193 dx.doi.org/10.1021/jm300713s
. C. Atkins et al Cancer Res., 2013, 73, 1993
. C. Hetz, E. Chevet, and H. P. Harding Nature Reviews Drug Discovery 2013, 12, 703
. T. Ma et al Nature Nat. Med. 2013, 19, 1124–1131. doi:10.1038/nn.3486
. M. Pietri et al Nature Med., 2013, 19, 1124 doi:10.1038/nm.3302

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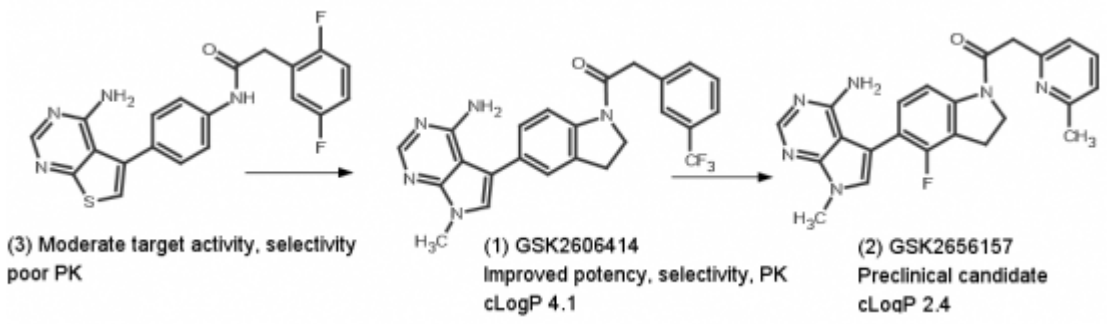

CH bond activation – real world application

I have written several times about CH bond activation as I feel it is such an important achievement with application to many aspects of drug discovery not least synthesis of putative metabolites of drugs or more highly functionalised/polar analogues. Another example of directed CH activation has now been reported focusing on the selectivity achieved by previously reported bulky, bis(trifluoromethyl)phenyl ligands **1**. This paper reports improved regioselective oxidation of artemisinin with either C-9 or C10 (1) targeted based on catalyst or target control respectively. Another example of regioselective introduction of functionality, albeit mechanistically rather different, is the Markovnikov radical functionalization of alkenes with an Fe(III)/NaBH4 mediated reaction **2**. The authors demonstrate the synthesis of previously inaccessible C20' functionalised vincristine analogues in particular some ureas. The authors then go on to show **3** that these compounds have excellent cell inhibition activity – sub-nanomolar much more potent than vinblastine. Compounds also show upto 200 fold greater activity than vinblastine in vinblastine resistant P-gp overexpressing HCT116/VM46 cells. – and also have activity against.

A good review of approaches to prepare metabolites of drugs **4** includes biotransformations, biomimetic and CH functionalization and electrochemistry.

1. P. E. Gormisky and M. C. White J. Am. Chem. Soc., 2013, 135, doi: 10.1021/ja407388y
2. E. K. Leggans et al Org. Lett., 2012, 14, 1428 DOI: 10.1021/ol300173v
3. T. J Barker et al ACS Med Chem Lett 2013 DOI: 10.1021/ml400281w
4. K. P. Cusack et al Bioorg. Med. Chem. Lett., 2013, 23, 5471

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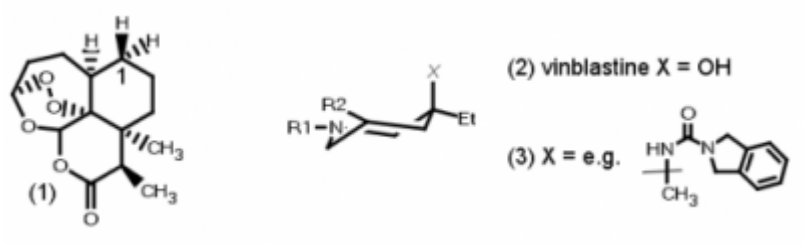

Dimeric/polyvalent ligands

There seems to have been a quite a sequence of papers emerging over the last few months describing one form or another of di/poly valent ligands. Compounds seem to fall primarily into three categories. Firstly those where fortuitously required activity for (at least) two targets is present in a single core; secondly where two molecules are "glued " directly together and thirdly, similar to the second, where two independent motifs are attached via an extended linker particularly apposite for GPCR (hetero)dimers. Several of these are encapsulated in a useful introductory review on GPCR dimers **1** which includes a discussion of pharmacological consequences of oligomerisation. Examples of small molecules are shown to interact preferentially with GPCR (hetero)dimers although stoichiometry is not always clear – for example opioid ligands such as (1) and SKF83959 a dopamine agonist (2). SKF83959 has been shown to bind with high affinity to D2 receptors only in the presence of D1 receptors, to act as a full D1 agonist and a partial D2 receptor agonist. Rather larger dimeric ligands are also discussed in which two discrete GPCR ligands are linked by a long 20 atom chain (give or take) in length. This area seems to have been dominated by opioid ligands again. I haven't illustrated the long chain linked dimers for obvious reasons. The idea of small molecules such as (1) and (2) acting at (hetero)dimeric GPCR's intrigues me enormously. It does seem to me we really are missing some tricks in GPCR research underplaying the relevance of polymeric species – perhaps not something all the structural work will change either

Following the opioid and analgesic theme a polyfunctional mu/delta-opioid agonist/NK1 antagonist compound (TY027) is disclosed that has a preclinical profile of excellent antinociceptive efficacy, low abuse liability, and no opioid-related emesis or constipation **2**. An additional combination new to me is the mu opioid/mGluR5 modulator **3** gluing compounds with the respective pharmacologies together again with a long linker but none the less achieving *in vivo* efficacy in models of pain at least when dosed intrathecally. The authors did make the reasonable point that in cases of severe pain perhaps intraspinal administration might be tolerated

Other combinations of targets that I hadn't come across previously included topoisomerase I with sirtuin activity **4** and topoisomerse II/HDAC **5**. The former example is a simple substitution of the evodiamine core (3) in the latter a more dramatic addition of a SAHA HDAC tail onto a topo II inhibitory podophyllotoxin (4). Remarkably the latter was reported to have modest low micromolar cell activity. Continuing the HDAC theme is the report of an anti-androgen linked to an HDAC inhibitor **6** designed to target prostate cancer cells e.g. (5). Despite their size compounds showed comparable cell activity to SAHA in two prostate cancer cell lines.

Finally a review **7** examining some of the pros and cons of polypharmacology from both the safety and efficacy perspectives. In particular for safety the discussion is of off-target activity perhaps something we have got rather better about over the last few years although as pointed out relatively few drugs have been withdrawn due to off-target activity with hERG predictably the porimary offender here. With respect to efficacy I must confess I am a bit of a fan of targeted rich pharmacology perhaps reflecting my days of CNS research.

1. C. Hiller, J. Kühhorn and P. Gmeiner J. Med. Chem., 2013, 56, 6542. DOI: 10.1021/jm4004335
2. T. M. Largent-Milnes et al J. Pharmacol. Expt. Ther., 2013, 347, 7 doi: 10.1124/jpet.113.205245
3. E. Akgün et al, Proc. Natl Acad. Sci. USA 2013, 110, 11595
4. M. S. Christodoulou et al Bioorg. Med. Chem., 2013, 21, 6920
5. X. Zhang et al Bioorg. Med. Chem., 2013, 22, 6981
6. B. E. Gryder et al ACS Chem. Biol., Article ASAP DOI: 10.1021/cb400542w Publication Date (Web): September 20, 2013

'. J. U. Peters J. Med. Chem., Article ASAP DOI: 10.1021/jm400856t Publication Date (Web): August 22, 2013

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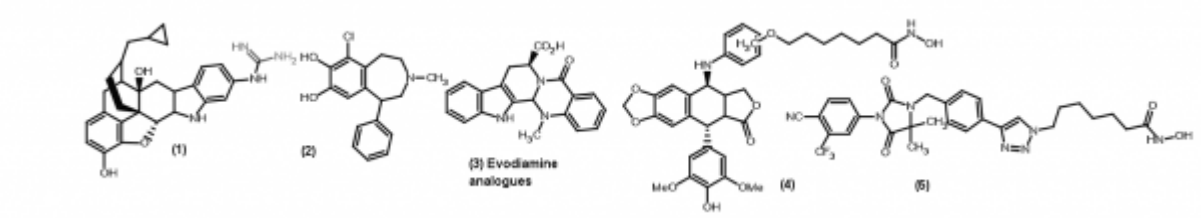

PAINS an interview with Prof Baell on PAINS HTS hits

A recording and transcript of an interview by Barry Bunin of Collaborative Drug Discovery with Prof Jonathan Baell of Monash discussing his paper **1** on Oan Assay Interference Compounds or HTS hitters that he published in 2010. Certainly I have found this to be a valuable paper and the compounds he highlights do seem to be around in a lot of collections and do seem to come up as frequent actives.

. J. B. Baell and G. A. Holloway J. Med. Chem., 2010, 53, 2719

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5. Chemistry

Flowing Trifluoromethylation

Flow chemistry, in many situations offers a powerfull approach to synthesis a recent example from Buchwald **1** being the successful trifluormethylation of aromatic and heteroaromatic iodides using potassium trifluoroacetate and copper(I) iodide in pyridine. Reaction times are short and the CF3 source is readily available and stable.

.. M. Chen and S. L. Buchwald Angew. Chemie. Int. Ed., published on line 5th Sept 2013, DOI: 10.1002/anie.201306094

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6. Conferences

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

- 3rd UK and Ireland Early Career Blood-Brain Barrier Symposium Medimmune 22nd Nov
- From Targets to candidates: Emerging Strategies in Drug Discovery, SMR NHLI, London 12th Dec

Meetings Attended

Meetings attended during September and early October included Drug Discovery, ELRIG, Manchester 3rd, 4th September, RSC/SCI Medicinal Chemistry Symposium Cambridge 8th-11th Sept and Kinases: New Horizons, SMR NHLI London, 3rd Oct. If you spot any items from these meetings that you would like to know more about I should be able to supply some notes to you. Some slide packs are available from the RSC/SCI meeting - just click on the link. Of course nothing compares with actually attending the meetings and speaking with old and new friends.Slide packs are now available for talks from the SCI meeting "Choosing the Right Target"

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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.

IgNobel on camera

Slightly different is this link to video of the IgNobel awards - almost 2hrs of it. I cant say I have watched all of it and some of it is a bit strange but entertaining none the less.

cMAP

Rumour has it that the cMAP (connectivity map) initiative is about to undergo a massive expansion I just hope that some chemical intelligence has been built into this upgrade - I have had no response to my query about this. When the upgrade takes place is not clear but on site training is supposed to take place in November which may be a clue. As a reminder 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".

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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

8. About RodPorterConsultancy

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

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About CompChemSolutions

CompChem Solutions offers computational chemistry & computational biology services to academic and industrial researchers involved in drug discovery and development. Established in 2004 and based in Cambridge, UK, CompChem Solutions has a wealth of experience across the range of chemoinformatic and computational chemistry disciplines, having worked extensively in many therapeutic areas, particularly oncology, inflammation and pain. Recent publications from CompChem Solutions have exemplified the use of in silico methodology for target validation and identification, particularly within the context of phenotypic screening. Services can be provided in virtual screening, rational ligand design, protein homology modelling, library design, ADMET property prediction, and many other areas.

We are currently offering fixed-price virtual fragment screening services for a limited period. Please contact Susan Boyd at CompChem Solutions for more details on any aspect of CompChem Solutions services.

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