Rod Porter

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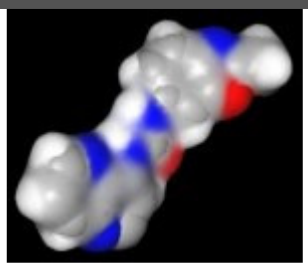
Subject: Medicinal Chemistry News April 2013



Medicinal Chemistry News from Rod Porter

April 2013 vol 4. no. 2

Dear Dr Porter,

1. Welcome

Welcome to the April edition of the Medicinal Chemistry newsletter from RodPorterConsultancy.

My thanks to Cyclofluidic for sponsoring this issue of the newsletter - this allows me to keep issues rolling out. I should also highlight a paper just out from Cyclofluidic which has been featured below which would have been included sponsorship or not.

Optibrium recently announced a collaboration with LHASA using their DEREK platform for knowledge based predictive toxicity as an optional plug-in to Optibriums multiparameter optimisation software Stardrop.

Do have a look at the CompChem Solutions website offering a range of complementary services 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 June 2013.

Wishing you every success with your research.

In this issue:

Cyclofluidics - shortening your medicinal chemistry cycle times

Cyclofluidic is working with collaborators in the pharmaceutical industry to optimise hits to quality leads using its proprietary CyclOps™ platform. CyclOps™ allows biological data to be collected on each compound minutes rather than weeks after it has been designed allowing true integrated data driven medicinal chemistry - saving time and money. A case study optimising inhibitors of abl-1 kinase using this technology platform has been published recently **1** and is reviewed in section 4 of this newsletter. For more information or to discuss evaluation and collaboration opportunities please contact Elizabeth Farrant.

. B. Desai et al J. Med. Chem 2013, 56, 3033

Running for Muscular Dystrophy Campaign

I will be running in a team with current and former GSK'ers in the Oxford Town and Gown 10K run (May 12th) in memory of

James Kew a friend and former colleague from GSK who died tragically last year. We will be running in aid of Action Duchenne, a charity James actively supported - please give generously (GSK will double the total of all contributions made)

SMR - next meeting

The next Society of Medicines Research meeting 'Partnerships:Future models for Drug Discovery' will take place on 20th June 2013 at Lilly Windlesham. 'This timely meeting explores the new paradigms emerging in drug discovery and development, bringing together senior figures from the worlds of big Pharma, academia, public and charitable institutions. These speakers will highlight opportunities for future models to lead to successful research and development programmes and explore the changing dynamic of interactions between the traditional models of academia, funders and industry.' The 3rd October meeting will be held at the National Heart and Lung Institute South Kensington and is entitled 'Kinases: New Horizons'

UK QSAR meeting

The UKQSAR and Chemoinformatics Group Spring 2013 meeting is being hosted by Unilever at the science park near their Colworth site in Bedfordshire on April 23rd. The meeting will emphasise approaches to compound safety - the full programme as well as the registration page is available here. Registration officially closed 9th April but do get in touch with the committee via the website if you wish to attend.

2. State of the industry

A 'Freshness' index

A new metric for the pharma industry outlined by Bernard Munos writing for Forbes is the 'Freshness Index' or how much of a companies sales are generated by new products. On aggregate for the top 13 companies only 10% of sales cames from products launched post 2007 and perhaps even more scary only 48% of sales came from products launched since 2001. A surprise that emerged out of the analysis was that so many sales came from compounds that were about to become generic or that had already become generic surviving for a range of reasons including brand recognition and life cycle management. The 'Freshest' pipeline is that from Novartis (19% of sales from post 2007 launched products) followed by GSK (12%) and JnJ (11%) and Pfizer (10%) following. See also the commentary in FierceBiotech.

Public Private Partnerships

A survey of public private partnerships shows that the concept is continuing to catch on in Europe and particularly in the UK, through IMI and Framework 7 programmes, with European PPP numbers only 4% down on US numbers in 2012 compared with 13% down in 2011. While oncology programmes were the largest in number the highest value PPP's were in the infectious diseases area.

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3. In Brief

pH-Sensitive Fluorescent Dyes: Are They Really pH-Sensitive in Cells?

An alert that use of apparently pH sensitive dyes to examine events within cells need to be used with caution. Aza-BODIPY dyes showed not only flurescence changes with pH but also fluorescence changes in hydrophobic microenvironments. BSA also turned on fluorescence with these compounds. After separation of cell components highest fluorescence was seen in membranes and endoplasmic reticulum. Thus checking fluorescence pH sensitivity in the presence of a range of cell constituents is important to understanding cellular fluorescence read-outs.

The mastermind approach to CNS drug therapy

Outlined **1** is an approach (Mastermind) for the prediction of drug distribution in the human brain, target kinetics and efficacy translational prediction of human brain distribution, target site kinetics, and therapeutic efficacy **1**. The approach is reliant on acquiring a range of data from preclinical experiments – as I understand it one aspect that may be a limitation is the need for microdialysis data for the drug, not always easy to obtain. Nonetheless a couple of examples are given of prediction of drug distribution, target site kinetics and drug efficacy.

. E. C. M. de-Lange Fluids and Barriers of the CNS 2013, 10:12

Nature Reviews Key Advances in Medicine 2012

A collection of reviews presented as an e-book pulled from articles commissioned by the eight clinical Nature Review journals highlighting 43 key papers in various disease areas that had appeared during 2011. What's more it's free to download!

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4. Medicinal Chemistry

Predictive DMPK/ADMET

An issue of Molecular Pharmaceutics **1** largely dedicated to "Predictive DMPK: in silico ADME predictions in drug discovery" is worth a visit. Papers that caught my eye included a review **2** from a group at Genentech that discusses calculable physicochemical properties, the quality of these calculations and, interestingly strategies to increase use of models by chemists. The authors are particular advocates of coupling of property calculations with 3D drug design. There are a couple of papers predicting (human) PK from in silico parameters one of which was highlighted last month **3** while the second **4** used GastroPlus modeling and simulation with in silico or in vitro data to predict plasma drug concentration/time profiles of compounds in early research.

1. Molecular Pharmaceutics 2013 10(4) 1151
2. D. F. Ortwine and I. Aliagas Mol. Pharmaceutics, 2013, 10, 1153
3. K. H. Grime, P. Barton , and D. F. McGinnity Mol. Pharmaceutics, 2013, 10, 1191
4. N. A. Hosea and H. M. Jones Mol. Pharmaceutics, 2013, 10, 1207

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Automating medicinal chemistry - hammering cycle times

In a recent paper **1**, Cyclofluidic using their integrated flow chemistry/purification/biology/ADME screening platform have exemplified their approach to shortening cycle times. In this case a cycle time of 90 mins rather than weeks (or months!) was achieved permitting very efficient iterative exploration of large areas of chemistry space and avoiding at risk synthesis without compromising speed. The paper presents a case study where SAR data from compounds related to the Ariad BCR-Abl kinase inhibitor ponatinib were used as a starting point for optimisation. In this example, abl-1 and abl-2 activity were measured on-line in parallel along with a range of calculated physical properties were used to optimise the compounds. After 90 design cycles, a set of 4 compounds showing excellent target activity and novelty were profiled off-line and were found to be active against the key abl mutants required to avoid resistance as well as showing lead-like profiles in PAMPA and HLM assays. This is the first example of the use of integrated design, synthesis and assay to optimise a chemical series"

The team are now working with pharma collaborators, aiming to reduce hit to lead optimisation times by 50% while improving the quality and number of differentiated leads.

Also read Derek Lowe's comments on this paper.

1. B. Desai et al J. Med. Chem 2013, 56, 3033

GPCR's

A useful compilation of GPCR structure papers **1** has been put together by Nature Publishing Group Access some of which are free for two months. While this is an important collection of individual papers – a valuable summary identifying key residues for ligand interaction and to define a conserved network of non-covalent contacts defining the GPCR fold has now been published **2**. This proved a useful reference for me while preparing a review on neurokinin receptors recently.

An alternative approach to organizing GPCR's has recently been published by Schoichet's group **3** using pharmacology that "organizes proteins by ligand similarity". The authors found, using data from Chembl and a cheminformatic similarity ensemble approach that GPCR's with apparently unrelated sequences could be closely related based on ligand similarities – for example a compound was shown to have affinity at both 5-HT2B and κ-opioid receptor a novel finding. Relationships based on pharmacology across GPCR's and non GPCR's could also be seen. However, there was a fairly high false positive rate so, as ever, wet experiments need to complement the predictions.

Also mining Class A GPCR structural information is an analysis **4** looking at mechanisms involved in receptor activation and possible allosteric sites in the extracellular loops. The authors identify an extracellular salt bridge which might be a target for allosteric regulation. Finally moving away from structural information is a review **5** of GPCR regulatory processes such as endocytosis, internalization and down regulation and the impact of allosteric regulation on these processes.

1. GPCR focus collection
2. A. J. Venkatakrishnan et al Nature 2013, 494, 185
3. H. Lin et al Nature Methods 2013, 10, 140–146
4. C-I. Anderson Wang, R. J. Lewis 2013, 85, 153
5. J. R. Lane, A. Abdul-Ridha and M. Canals ACS Chem. Neurosci., Article ASAP DOI: 10.1021/cn400005t Publication Date (Web): February 21, 2013

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Fragment based drug design - not always an easy path

Fragment based drug design has been around for some years now and already has a number of successes to its credit **1**. However, it's perhaps timely to critically consider the strategy and look at some of the problems that have emerged for teams attempting to implement a FBDD approach. Two articles just out are particularly pertinent to this discussion - follow the link to read more.

1. M. Baker, Nature Reviews Drug Discovery 2013, 12, 5

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Allosterism

There has been a flurry of publications examining allosteric protein regulation including a whole section in Drug Discovery Technologies Articles in Press covering a range of GPCR targets but also technologies. For example a team from Addex **1** outline methods for detection of allosteric modulators such as Phoenyx™ and ProxyLite™ while also touching on exploiting structural information from GPCR's.

A couple of papers referring to GPCR allosteric modulation are given elsewhere in this newsletter a third **2** reviews allosteric modulation and functional selectivity i.e. downstream events triggered by a modulators activity. Non GPCR allosteric inhibitor examples discussed include a review on LEDGIN inhibition **3** for the treatment of HIV. From other sources is a review **4** of allosteric kinase inhibitors particularly looking at those that disrupt helix αC which seems to be a common mode of allosteric kinase regulation. Indeed the authors suggest allosteric kinase inhibition may be more highly conserved than has been previously thought.

Finally an allosteric database web site collating allosteric targets (904), sites (259) and modulators (15,743). I was also pleased to see the compilers have a separate list of 298 endogenous allosteric modulators - I suspect this represents the tip of the iceberg and will be intrigued to see how this the endogenous field progresses not least as a source of starting points for drug discovery exercises.

1. R. Lütjens et al Drug Disc. Today Technologies, 2013 http://dx.doi.org/10.1016/j.ddtec.2013.01.001
2. Z. G. Gao and K. A. Jacobson Drug Disc. Today Technologies, 2013 http://dx.doi.org/10.1016/j.ddtec.2012.08.004
3. B. A Desimmie et al Drug Disc. Today Technologies, 2013 http://dx.doi.org/10.1016/j.ddtec.2012.10.002
4. L. Palmieri and G. Rastelli Drug Disc. Today, 2013, 18, 407.

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α-Helix Mimetics

A useful review of α-helix mimetics **1** discusses both approaches to constraining peptides into α-helices (Type I mimetics) and Type III mimetics that mimic the spatial orientation of key recognition residues – non-peptides. Referring to the latter specifically a common problem has been the high number of heavy atoms required to build a template often via a terphenyl or tris benzamide e.g. (1) mimicking residues i, i+4, i+7. However there have been some interesting recent developments leading to lower molecular weight templates such as pyrrolopyrimidines **2** (2) putative i, (i+3/ i+4), i+7 examples of which were sub micromolar inhibitors of P53/MDM2 and P53/MDMX with evidence of cellular apoptosis at 5-20uM. While the focus of much research has been on i, i+4, i+7 helix mimetics, approaches to i, (i+4), i+5 (and i+7) e.g. oxopiperazines **3** (3) and i, (i+3) i+4 mimetics such as pyridylpyridones **4** (4) to compete as mimics of the LXXLL box of coactivator peptides for the estrogen receptor blocking ER–coactivator interaction, have been reported. Its worth noting, however, that no reports of biological data for oxopiperazines are provided, only spectroscopic data which is consistent with helix mimicry.

One issue that all these mimetics will have trouble addressing is the generally hydrophobic nature of the α-helix residues that are being mimicked cf the LXXLL sequence above, intrinsically leading to high lipophilicities.

1. V. Azzarito et al Nature Chem., 2013, 5, 161
2. J. H. Lee et al., J. Am. Chem.Soc., 2011, 133, 676
3. P. Tosovska and P. S. Arora Org. Lett., 2010, 12, 1588
4. J. Becceril and A. D. Hamilton Angew. Chemie. Int. Ed., 2007, 46, 4471

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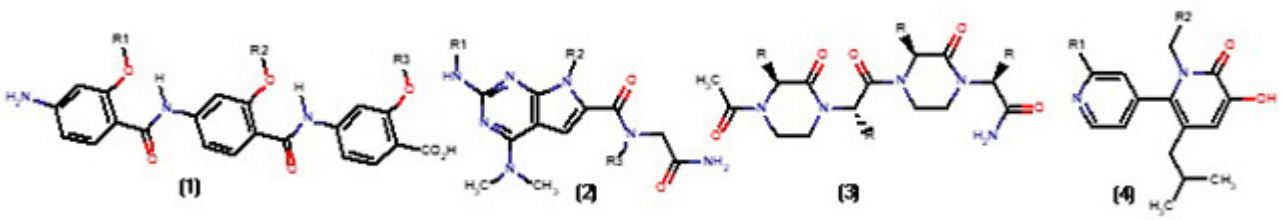

sp3 Atom count, cLogP– promiscuity and developability

Further analysis of complexity of molecules as determined by Fsp3 (number of sp3 hybrid carbon/toal carbon) and number of chiral centres and the role of lipophilicity in promiscuity of compounds **1**. Briefly promiscuity increases with increased lipophilicity, consistent with previous observations, and decreases with increased Fsp3 and increased number of chiral centres. Aminergic compounds also tended to be markedly more promiscuous than non-aminergic although because there was no analysis of the relative lipophilicity of aminergic versus non-aminergics this may simply reflect a higher lipophilicity. Aminergic compounds also tended to have higher Fsp3 which may be due to the need for at least three sp3 carbons to define a tertiary amine - piperidines and piperazines will boost sp3 count as well The author goes on to consider promiscuity for Cyp P450 interactions where, interestingly, basicity appeared to play no particular role. Again as expected increasing logP gave increased Cyp inhibition while Cyp inhibition decreased markedly as Fsp3 increased – numbers of chiral centres played no role in P450 inhibition.

A second publication **2** specifically addresses important physicochemical properties that need particular attention when working outside "non-ideal" space, in this case when cLogP >4 and mol wt >400. Developability parameters addressed were solubility, artificial membrane permeability, HSA binding and Cyp3A4 inhibition – data being combined to create a "developability score". As expected not large, not greasy (clogP <4.0, Mol wt <400) and large not greasy had a high proportion of compounds with good and medium scores. "Greasy" compounds either small or large showed a marked increase in low scorers although each still had 15-20% of high scorers suggesting some opportunities remained even in these unfavourable physchem spaces. Analysis of what these opportunities might be via regression models of properties most closely correlated with developability suggested, as above, that increasing Fsp3 or composite descriptors such as [cLogD+ (Ar ring count – sp3 C count)] was beneficial as was lowering logD particularly with more greasy compounds. Reducing numbers of H-bond donors can also be beneficial with larger/more greasy molecules.

Both studies highlight the importance of particularly controlling LogP not molecular weight for a molecule though managing lipophilicity with larger molecules is not easy of course. I am a bit wary of the idea of reducing polarity by use of basicity as emphasised by Loverings analysis while basicity can introduce benefits there are so many down-sides it seems a risky strategy unless desired target SAR dictates a basic centre is essential. Lovering **1** points out that several publications demonstrate how few chemical reactions medicinal chemists actually use and that these reactions broadly do not encourage increase in Fsp3 or in numbers of chiral centres i.e. there is a real need to introduce new synthetic chemistries to drug discovery.

1. F. Lovering Med. Chem. Commun., 2013, 4, 515-519
2. T. J. Ritchie et al MedChemComm 2013, 4, 673

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5. Chemistry

Distorting rings

Following on from the previous item particularly with reference to maximising Fsp3, complexity and use of more synthetic transformations a report **1, 2** of a ring distortion strategy – cleavage, fusion, rearrangement, ring expansion directed to natural product starting points. The synthesis allows for analogue generation at potentially more than one stage. The concept is illustrated with some examples from work with adrenosterone - Scheme 1. Other examples explored were gibberellic acid and quinine. Comparison of the 100+ compounds generated from this exercise with a screening collection from Chembridge showed much higher Fsp3 average 0.59 v. 0.23 and perhaps most extreme stereocentres Chembridge average 0.24 and this work 5.17. cLogP's were also lower by one log unit. Another reminder of the value of natural products as starting points at least for building diverse libraries.

Oxone as an oxidant

Bearing in mind the use of oxidants for several manipulations descibed in the above paper a timely review **3** on the use of oxone including coverage of oxidation of CH bonds, olefin and functional group oxidation, halogenation lactone formation amongst other topics.

1. R. W. Huigens III et al Nature Chemistry 2013, 5, 195
2. I. Sharma and D. S. Tan Nature Chemistry 2013, 5, 157
3. Hussain et al Chem. Rev., Article ASAP DOI: 10.1021/cr3004373 Publication Date (Web): March 01, 2013

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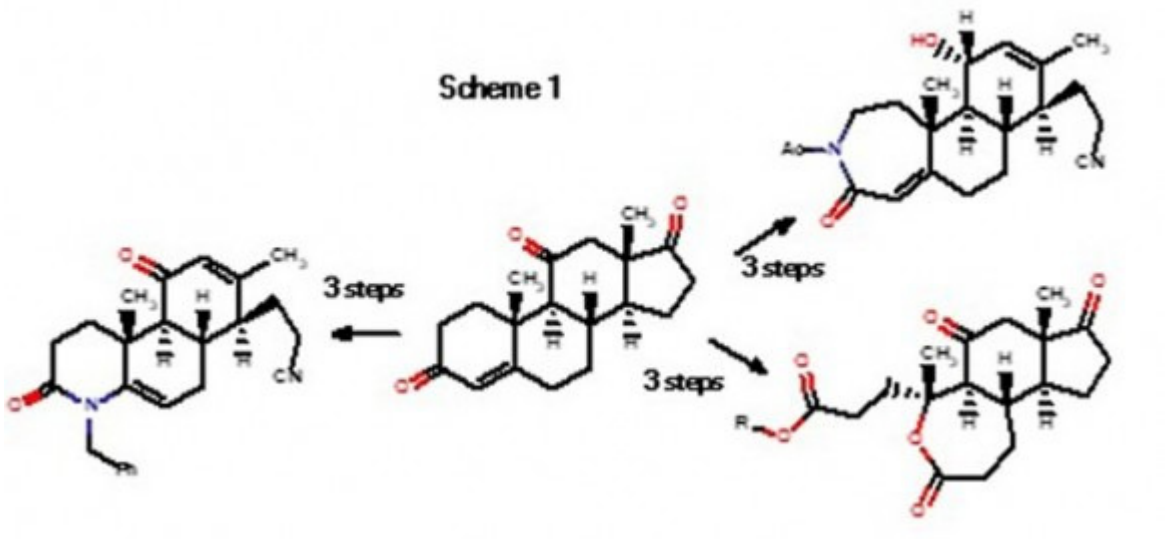

6. Conferences

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

- SciNovo Unlocking the value of drug candidates, Stevenage Biocatalyst, 23rd April
- 24th Symposium on Medicinal Chemistry in Eastern England, Hatfield 25th April 2013
- Blood brain barrier club Kings College London (invitation only)
- Target Validation Workshop RSC Burlington House 30th April
- Choosing the Right Target in Drug DIscovery, SCI London 15th May
- Partnerships: future models for drug discovery SMR Lily Horsham, 20th June
- ELRIG Manchester 3rd, 4th September
- RSC Medicinal Chemistry Symposium Cambridge 8th-11th Sept

Meetings Attended

Meetings attended during February and March SMR Therapeutic Opportunities in Infectious Diseases 14th March London; PPI-Net meeting measuring intracellular drug concentrations 11th, 12th March. 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. Of course nothing compares with actually attending the meetings and speaking with old and new friends.

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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.

Kegg pathway Wiring diagrams of molecular interactions, reactions, and relations

A set of manually drawn pathway maps on the molecular interaction and reaction networks for metabolism cellular processes and human diseases amongst others. There are also links to drug databases and Kegg Ligand that contains "our knowledge on the universe of chemical substances and reactions that are relevant to life"

These sites are featured because has found them of interest - featuring these sites does not reflect any endorsement or accountability for their use from 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.

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.

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