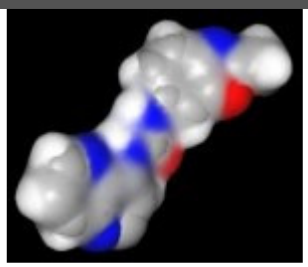
Rod Porter

From: Rod Porter [News@rodporterconsultancy.emailmsg.net] on behalf of rod.porter@rodporterconsultancy.com
Sent: 11 December 2012 06:02
To: roderick.porter@btinternet.com
Subject: Medicinal Chemistry News December 2012



Medicinal Chemistry News from Rod Porter

November 2013 vol 3. no. 6

Dear Dr Porter,

1. Welcome

Welcome to the December edition of the Medicinal Chemistry newsletter from Rod Porter Consultancy. A little bit shorter than previous issues but I hope you find something to interest you.

Do have a look at the CompChem Solutions website offering a range of complementary services to those of RodPorterConsultancy. The CompChem Solutions newsletter will be out very shortly

I spent a good day at the Optibrium consultant user group meeting near Cambrdge 27th Nov hearing about some of the new developments with Stardrop. Stardrop 5.3 coming soon will have virtual library design capabilities exploiting StarDrop's unique Probabilistic Scoring algorithm for multi-parameter optimisation.

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 February 2013. If you would like to make sure you keep receiving this newsletter please add the new senders address to your safe senders list.

Finally wishing you all a very happy and peaceful Christmas and a successful New Year.

In this issue:

2. State of the industry

The best of 2012 and the cliff for 2013

The turn of the year is always a favourite time of the year for lists. Fiercebiotech have compiled a list of the 15 estimated top selling drugs for 2012. The top 5 are Humira (est $8.37Bn), Enbrel, Advair/Seretide, Remicade and Rituxan ($6.94Bn). Of these two are co-promoted products which I thought interesting. I think I am corrrect that if the estimate is correct this will be the first year a biologic has had the number one sales spot. Four of the top 15 are oncology drugs, Herceptin, Avastin, Gleevec and Rituxan and is the largest therapeutic group. Lipitor and Plavix still make it into the group despite being off patent but only because of their sales in the early part of the year. Two more, Cymbalta and Rituxan come of patent next year although as a biological Rituxan doens not feature on the next list.

Patent expiries will continue to haunt the industry next year with an estimate that compounds with combined annual sales of $29Bn will come of patent led by Cymbalta. The report prepared by EvaluatePharma estimates that 70% of the market value will be lost - this is the sort of money that could make a difference to a country's national deficit!

Rumours have it that 31 new compounds were approved by the FDA this year maintaining the increased level of new approvals

that was seen last year. However, as the saying goes when you have just finished celebrating a candidate selection - "now do it again".

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3. In Brief

Chemists without Borders

Chemists without Borders is an organisation that "solves humanitarian problems by mobilizing the resources and expertise of the global chemistry community and its networks." A recent mailing from the ACS highlighted the action this group is taking to support chemistry education in secondary schools in Sierra Leone to help it recover from the destruction of its civil war.

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Archael lipids

Having a long standing belief that lipid membranes are really rather more important and subtle than medicinal chemists tend to give them credit for, this short piece on the properties of archael lipid membranes in the PSI/Nature Structural Biology Knowledge Base, caught my eye. Highlighted are some of the features of archaea that allow them to live in the extreme environments where they can be found. Accompanying the article are the links to relevant crystal structures. Tricks archae use include use of ether rather than ester linkage from lipid to glycerol, branched chain lipids and inverting glycerol stereochemistry.

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4. Medicinal Chemistry

Treating anemia HTS by MS *highlighted by Thorsten Nowak (Conformetrix)*

In an indirect approach to boost EPO and consequently red blood cell production a team from Merck **1** have focused on up regulating HIF (which in turn up regulates EPO) by protecting HIFalpha through inhibition of prolylhydroxylase 1-3 (PHD1-3). Exploiting the availability of isolated purified PHD2 the team applied high-throughput (HT) affinity selection mass spectrometry (AS-MS) **2** to identify initial small molecule hits. In brief, the method consists of incubating the enzyme with mixtures of many (hundreds) of compounds per well. The resulting incubates were subjected to size exclusion chromatography to separate unbound from potential protein−ligand complexes. Protein−ligand complexes were dissociated, yielding unbound compounds which were analyzed by mass spectrometry. 500,000 compounds were assayed using this technique – subsequent follow up resynthesis of actives and retested against the isolated enzyme quantitatively confirmed the qualitative data generated from the MS approach giving a series of potent spiroindoles e.g. (1) inhibitors of PHD1, 2 and 3.

As it turned out the optimisation of the spiroindolones was not straightforward – while excellent enzyme potency was achieved only marginal in vivo exposure was seen. Hopping to a spiro hydantoin (2), however, and exploiting both the SAR learned with the spiroindolones and maintaining N-aryl hydantoin substitution resulted in compounds with good PK and PD efficacy in raising EPO levels e.g. (3).

1. P Vachal et al J. Med. Chem., 2012, 55, 2945
2. D. A. Annis et al Int. J. Mass Spec., 2004, 238, 77

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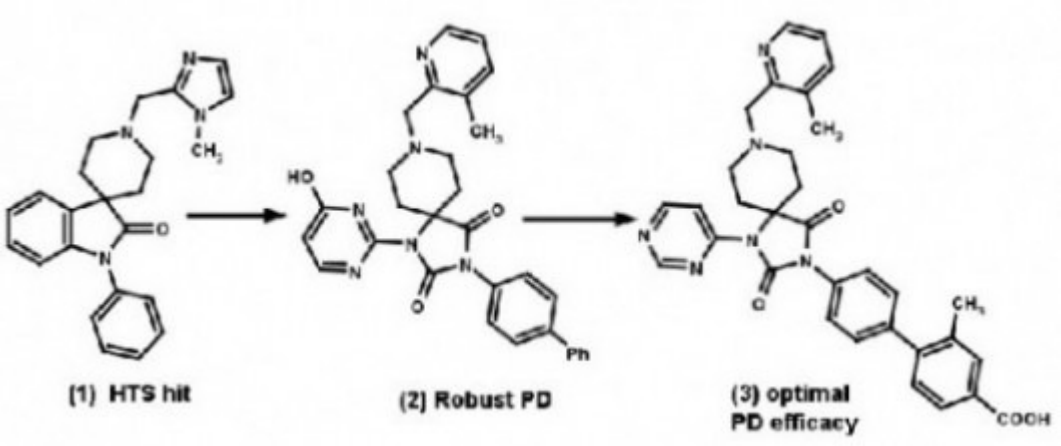

When you want efflux transporter substrates

While I have written numerous times on matters relating to the CNS, minimising drug exposure in the CNS can also be desirable with classic examples being H1 antagonists. The Pfizer group discuss some DMPK considerations in avoiding CNS side effects while maintaining good oral bioavailability **1** with a useful summary **2**. Broadly identifying efflux transporter substrates is seen as the best chance of success in minimising CNS exposure. In particular achieving efflux via both P-gp and BCRP is seen as beneficial. Downsides to the approach might be the risk of clinical drug-drug interactions and transporter polymorphisms known to be present in humans. The Pfizer approach to ensuring efflux substrate activity was to increase polar surface area. This has also been discussed recently in the context of CB1 antagonists **3**. Alternative strategies to achieving (or avoiding) efflux have also been discussed recently **4** particularly focusing on considering not just the number but the strength of H-bonds which goes back to the Abrahams work on alpha and beta as measures of strength of H-bond donors and acceptors see for example **5**. This work also emphasises thinking about intramolecular H-bonds to increase permeability and reduce P-gp efflux – or avoiding as desired.

Of course an alternative is to, if your target will accept the motif, go back to zwitterions such as the H1 antagonists already mentioned which certainly give good oral bioavailability and are broadly free of CNS side effects although perhaps not ideal for intracellular targets!

Finally its worth noting the recent publication **6** of a *C. Elegans* P-gp crystal structure albeit at a modest 3.4A resolution. One observation the authors make is the much higher affinity of P-gp for Actinomycin D and paclitaxel, 4,000 and 100 fold respectively for the membrane bound compared with detergent. This may reflect the importance of membrane partitioning when a drug accesses the transporter in the membrane although it may reflect disturbances in the transporter conformation in a non-native environment.

See the article below on virtual predictive modelling of P-gp substrates.

1. S. Cole et al, Xenobiotica 2012, 42, 11.
2. S. K. Bagal and P. J. Bungay ACS Med. Chem. Lett., Article ASAP DOI: 10.1021/ml300378n Publication Date (Web): November 15, 2012
3. A. Fulp et al, J. Med. Chem., 2012, 55, 2820
4. P. V. Desai et al Bioorg. Med. Chem. Lett., 2012, 22, 6540
5. Y. H. Zao et al, J. Chem. Inf. Model., 2007, 47, 170
6. M. S. Jin et al, Nature 2012, 490, 566

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Virtual ADMET modelling

Another new database with predictive ADMET models **1, 2** has recently been disclosed using over 200,000 literature data points on 96,000 compounds. Models include BBB permeability, CaCo2 permeability, human intestinal absorption, transporter substrate/inhibition, P450 inhibition and hERG inhibition amongst others. A specific report **2** is devoted to the groups model for predicting Ames mutagenicity. Fortunately it does ping 2-naphthylamine as Ames positive. The database is free to use – one compound at a time entered as a smiles string.

Taking a different, *de novo*, approach to building a predictive P-gp model is the *ab initio* approach of **3**. Briefly the model correlates computed solvation free energy differences in water and chloroform with P-gp mediated efflux expressed as a logarithmic scale. Stats were an R2 and root-mean square error of 0.65 and 0.29, respectively

1. F. Cheng et al J. Chem. Inf. Model., Article ASAP DOI: 10.1021/ci300367a Publication Date (Web): November 01, 2012
2. C. Xu et al J. Chem. Inf. Model., Article ASAP DOI: 10.1021/ci300400a Publication Date (Web): October 17, 2012
3. H. Gunaydin et al ACS Med. Chem. Lett., Article ASAP DOI: 10.1021/ml300314h Publication Date (Web): November 12, 2012

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5. Chemistry

Practical and innate carbon–hydrogen functionalization of heterocycles and a novel solvent *(Ashley Jarvis, Domainex)*

A report **1** on the substitution of a range of nitrogen heterocycles with a tool kit of eleven different zinc sulfinate salts representing a significant advance in synthesis of substituted heterocycles. These reagents transfer alkyl radicals to nitrogen heterocycles under mild to moderate temperature (RT – 50°C). Yields are variable but reactions are rapid making these powerful reagents that offer complementary reactions to other CH functionalization methods such as Minisci, borono-Minisci, electrophilic aromatic substitution, transition-metal-mediated C–H insertion and C–H deprotonation. Sodium trifluoromethyl **2** and zinc difluoromethylsulfinates **3** have been previously reported to perform these reactions but the approach has now been substantially extended and the importance of the zinc counter ion highlighted. The paper reports activity across a wide range of heterocycles (natural products, drugs and building blocks) without use of protecting-group chemistry. Examples of transformations show the flexibility to prepare otherwise inaccessible targets, compatibility with functional or sensitive groups e.g. (1) as well as the ability to perform sequential reactions (2) that further increases the power of the method. Six reagents are discussed in detail but the author's report they have prepared reagents for the introduction of CH_2Cl, CH_2CO_2Me, cyclohexyl and perfluoroalkyl discussed in more detail in the supplementary material. Yields can be modest and mixtures of regioisomers can be formed – the authors suggest this may be an advantage in being able to identify reactive/metabolically vulnerable centres in these systems. Four reagents are already available

from Aldrich and chemistry has been "road-tested" by Pfizer.

A feature of this chemistry is its robustness for example it is reported to work in Oolong tea(!) although it does seem a waste of such a delicate, refreshing drink.

1. Y. Fujiwara et al, Nature 2012, Published online 28 November 2012 see also W. J. Pitts Nature News and Views
2. B. R. Langlois, B. R Tetrahedr. Lett., 1991, 32, 7525
3. Y. Fujiwara, Y. et al, J. Am. Chem. Soc., 2012, 134, 1494

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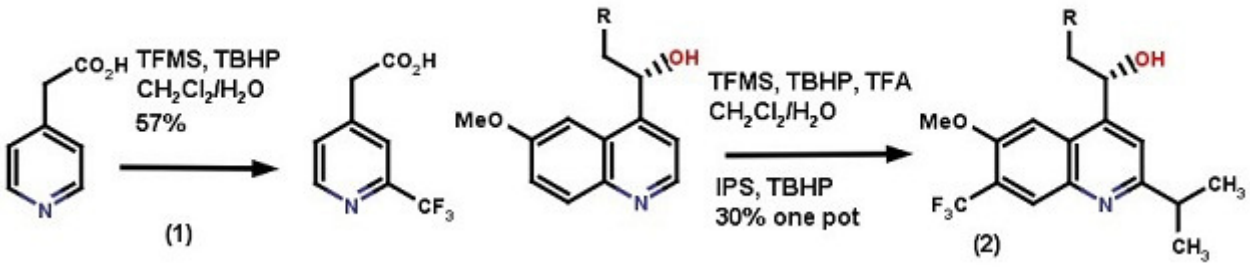

6. Conferences

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

1. RSC BMCS Symposium 14th Dec. Chemistry Dept Cambridge.
2. RSC BMS, PPINET MGMS and SCI International Protein-Protein interaction meeting 16th/17th Jan 2013 Royal Society London

Meetings Attended

I have not been preparing extended meeting reports as I have done on occaision in the past however it is now getting more common for speakers slides to be placed on the web - part of opening research - so I have put links below. Of course nothing compares with actually attending the meetings and speaking with old and new friends. Click on the links for slide packs presented: SCI - London 6th Nov. Enhancing drug discovery: The benefits of of kinetic and thermodynamic binding data in discovery. UKQSAR Autumn meeting Takeda Cambridge 8th Nov. Stevenage Biocatalyst 15th Nov. Open Innovation in Action, Stevenage, SMR 5th Dec Recent Disclosures of Clinical Candidates, London.

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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.

An App for collaboration

Just downloaded the The Open Drug Discovery Teams (ODDT) mobile app. This is intended as a research topic aggregator of predominantly open science data collected from various sources on the internet. "Research topics include areas of chemistry and adjacent molecule-oriented biomedical sciences, with an emphasis on those which are most amenable to open research at present. These include rare and neglected diseases, and precompetitive and public-good initiatives such as green chemistry."

CWM Global Search

Searching with structure across multiple databases on the web isnt always easy but CWM Global Search offers the option of searching based on structure, synonym, CAS Registry Number and free text. Data sources can be controlled using the advanced search option to give a more or less comprehensive search with the resulting links organized by topics. CWM Global Search presently searches more than 60 free chemical and pharma relevant databases - containing more than 100 million pages which associate chemical structures with data.

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 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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