Rod Porter1

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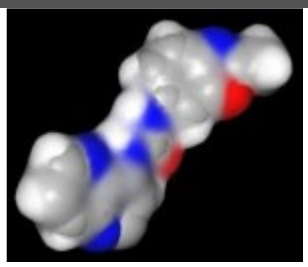
Sent: 16 October 2014 18:07
To: rod.porter@rodporterconsultancy.com
Subject: RPC October 2014 Newsletter



Medicinal Chemistry News from Rod Porter

October 2014 vol 5. no. 5

Dear Dr Porter,

1. Welcome

Finally here is the next edition of the Medicinal Chemistry newsletter from RodPorterConsultancy - my apologies again for delay September seemed to disappear all too quickly this year. As with last time round I have not been able to give as much consideration as I would like to some topics but I hope the referenes will none the less be useful. Topics featured this month include; .

It was good to see that the book chapter "GlyT-1 Inhibitors: From Hits to Clinical Candidates" co-authored with Lee Dawson of Eisai has now appeared in Topics in Medicinal Chemistry from Springer.

Don't forget to have a look at the CompChem Solutions services a range of complementary activities to those of RodPorterConsultancy.

Please forward this newsletter to your colleagues – just follow the link at the bottom of this mail. Any comments, criticisms or suggestions for future articles are very welcome please mail Rod Porter.

My next mailing is planned for early December.

Belatedly I hope you all had a good summer and are in fine fettle for the trudge to the end of the year. I must say travelling the Silk Road in Central Asia seems a long time ago now but happy memories. For those who manage to slog to the end of this mailing a few photographs for you - from left to right lake Song Kul (Kyrgyzstan) being a bit moody, the Registan Samarkand and the Kalyon Mar Bokhara (used to be used for throwing prisoners of!).

Wishing you every success with your research.

In this issue:

Society of Medicines Research- next meeting

The next meeting of the SMR, "SMR Award Meeting: Recent Disclosures of Clinical Candidates" will be on 4th December at the NHLI London. This is always a well attended meeting so please do book early for what promises to be an excellent day of science.

The SMR are pleased to announce that the 2014 SMR Award for Drug Discovery, is to be awarded to Pharmacyclics for the discovery and development of Ibrutinib (ImbruvicaTM), a first in human BTK covalent inhibitor for the treatment of a number of B-cell malignancies.The award will be presented during the the December 2014 SMR meeting "Recent Disclosures of Clinical Candidates".

Together with the SMR award lecture the "Recent Disclosures of Clinical Candidates" meeting features an excellent array of novel molecular therapeutics across several target classes and therapeutic areas, which include oncology (inhibitors of BTK and Mdm2), pain (Nav1.7 modulation), CNS (highly selective M1 agonists and BACE1 inhibitors), bacterial infection (inhibitors of Clostridium difficile) and allergic inflammation (intranasal TLR7 agonists).

For the full programme please visit here.

2. State of the industry

Q2 Regulatory approvals

Q2 FDA regulatory approvals for 2014 are on a par with Q2 2013 with five notable approvals interestingly none for oncology targets – diabetes and cardiovascular being the main areas of approval. There are sixteen significant regulatory decisions during 3Q 2014 (oncology, HIV/AIDS and hepatitis C dominate) which sounds good except for the fact there were eight regulatory setbacks drug 2Q 2014. Slightly surprising to me were the number of breakthrough drug designations – nine - mostly biologics as well.

3. In Brief

Patent cliff 2013

Some telephone numbers relating to savings on drug expenditure from patent expiries during 2013. The total is apparently a numbing (or spectacular) $213bn dollars a 14% increase over 2012 and $1.5 trillion in the past decade. Last year saw Lexapro, Actos and Singulair amongst others getting the full hit from losing p[patent coverage. The biggest savings have been on the introduction of generic cardiovascular drugs between 2004 and 2013 - Lipitor would always figure large in that tally. Biosimilars are also of course looming on the horizon.

Who holds what – NME's

An article **1** highlights increase in holdings of NMEs by companies with no research experience eg Valeant (40NMEs) and companies with no experience of progressing NMEs currently holding an estimated 200+ NMEs. This trend to increase NME holdings outside centres undertaking drug invention has particularly accelerated since 2000. Of the 1453 FDA NME's more than two thirds are controlled by ten companies largely as a result of consolidation of the market.

Most companies have only developed one NME FDA approval with 152 of 275 companies in this bin 67 have 2-5. Merck leads the way with 63 NME's. At the moment 115 companies control at least one NME of which 54 have only one NME. Twelve companies control more than 20NME's. Lots of numbers here but some intriguing reading with a few surprises.

The report was generated from a comprehensive a comprehensive database of all NMEs approved for use in the USA. The data include historical information about the drug itself as well as the organizations involved in the development and marketing of each novel molecule and changes that have occurred over time.

M. S. Kinch et al, Drug Discovery Today 2014, 19, 1032

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Oncology reasons for approval failure

A short interview with Tatiana Prowell (Breast Cancer Scientific Lead in the US Food and Drug Administration (FDA)'s Office of Hematology & Oncology Products) discusses some of her experiences of pitfalls in bringing ocology products to approval. This really follows on from an item I featured in April on reasons for development failure of compounds. Particular to oncology seems to be decisions on dose with a tendency to go in at as high a dose as is (apparently) tolerated and then run into tox problems. This was suggested to reflect history of oncology where cytotoxics were the name of the game but with targeted therapies this is less likely to be an appropriate strategy. Second was the clinical trial design with an example of failure to isolate drug effect as drug was administered to both arms of a PhIII trial this does seem a tad basic as errors go(!). Biomarkers seem to cause a problem as well not only due to a slow start to identify them but also misinterpretation of their use. Manufacturing problems and failure to better use patient reported outcomes as a way of achieving approval were also highlighted. Dr Prowell did make the observation that problems were recurring partly because reasons for rejection could not be made public for legal reasons hence a failure to learn from failure – if you see what I mean. All together a bit frustrating as Dr Prowell clearly found and really unacceptable potentially denying patients medicines and continuing to (entirely avoidably) drive up failure rates and costs of drug development. Pretty upsetting for the research scientists as well I think.

- T. Prowell Nature Rev. Drug Disc. 2014, 13, 410

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4. Medicinal Chemistry

PAINful screening (items from Steve Smith (StortMedChem)

A number of articles are coming out reprising some of the discussion that happened earlier this decade e.g. **1** regarding frequent hitters or compounds interfering with assays. An article from early this year **2** systematically assayed four PPI targets with robust α-screen assay protocols against 25,000 compounds. 137 compounds were active in all four assays and seemed to fall into two about equal categories, those that interefered with the alpha screen chemistry and those that prevented binding of the protein His-tag moiety to nickel chelate (Ni2+-NTA) beads of the AlphaScreen detection system. In TR-FRET assays these particular compounds did not cause a problem indicative of the fact that different assay technologies will come up with different frequent hitters. It would be interesting to see if this particular set of frequent hitters demonstrate particular cytotoxicity issues based on the chemistries they have. Of the compounds affecting the alphascreen detection system the great majority (52 of 60) were detected by the PAINS filters of **1**. In contrast the frequent hitters interefering with the His-tag were not so well identified and new filters were developed outlined in the supplementary material **3**.

The importance of identifying promiscuous compounds or PAINS is highlighted in a recent Nature article **4** which nicely summarises some of the sources of the PAIN phenomenon – including membrane disruptors redox cyclers, metal chelators and covalent modifiers amongst others. The real problem the authors highlight is the growth of publications from academic labs reporting activity of compounds well known as PAINS and claiming them as selective leads for further development. If followed up this clearly wastes a lot of resource that could be better used elsewhere. Possibly worse the reports of activity get picked up and the compounds get used as tools for biological profiling and thus activities get ascribed to the alleged target that are incorrect contaminating the whole scientific literature and magnifying the wasted resource. These themes are reprised in a piece inIn the Pipeline **5** and in the Practical Fragments Blogspot **6**. A further point made is that referees should be much more critical of the nature of the actives being reported and asking for justification for the publication – and this needs editorial back-up. With scarce academic and industrial finances we cannot afford such basic wastage.

1. J. B. Baell, G. A. Holloway, J. Med. Chem. 2010, 53, 2719–2740.
2. K. Schorpp et al. J Biomol Screen. 2014, Vol. 19(5) 715–726
3. Supplementary material for J Biomol Screen. 2014, Vol. 19(5) 715–726
4. J. Baell and M. A. Walters Nature 2014, 513, 481
5. In the Pipeline Sept 4 2014

6. Practical Fragments 2014 26th June

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Target intrinsic clearance to maximise free drug exposure

A useful perspective **1** on plasma protein binding and drug discovery drums in the message that optimising on plasma potein binding is not an appropriate strategy pointing out that 45% of drugs launched since 2003 have PPB >95% and 24% with PPB greater than 99%. Crunching the numbers comes back to the point that reducing intrinsic clearance is the key approach to increasing free drug AUC. Assuming the well stirred model and the major metabolic clearance is hepatic (quite a lot of assumptions!) then AUCu = dose/Clin although AUCtotal (=dose/(Fu x Clin)) does have a dependency on PPB. A number of examples are discussed to illustrate the merits of minimising intrinsic clearance independent of PPB although within a series practically there is often an interelationship between logP, PPB and intrinsic clearance. Arguably therefore under those particular circumstances PPB may act as a surrogate for intrinsic clearance. The authors recommended determining PPB to establish if it has a role in plasma dependent potency shifts, for supporting PK/PD studies, in conjunction with brain tissue binding for assessment of brain distribution and for supporting predictions to human. Their real message was that reducing intrinsic clearance is the way to maximising free drug concentration at least under the set of assumptions that are used earlier in this discussion.

1. X. Liu, M.Wright and C.E. C. A. Hop J. Med. Chem., Article ASAP, DOI: 10.1021/jm5007935, Publication Date (Web): August 06, 2014, Copyright © 2014, American Chemical Society,

Ionisation state and drug discovery

A useful review from a team at Vertex **1** assess the impact of ionisation state on the properties of compounds from drug discovery projects. The group used various sets of data extracted from Drugbank, Chembl and Pubchem to examine impact of basic, acid, neutral and zwitterionic state of compounds on a number of behaviours. definition of acids and bases were as follows acids - compounds that are able to donate a proton and are at least 50% ionised at pH 7.4, bases as compounds that are able to accept a proton and are at least 50% ionised at pH 7.4.

Some behaviours explored included

- Therapeutic targets and classes acids reasonably are most frequent in anti-infective and musculoskeletal categories while basic compounds dominate in transporter and Membrane targets
- Pharmacokinetics - impact on permeability and efflux, volume of distribution, oral bioavailability and metabolism amongst others. I hadn't fully appreciated that basic compounds are often extensively metabolised by FMO's rather than P450's although CypP450 2D6 is also a frequent issue.
- Cell activity surprisingly zwitterionic came out of this looking at least as good if not rather better than other classes
- Safety issues including selectivity transporter interactions and accumulation in intracellular compartments. Reactive metabolite sand the risks posed by acylglucuronides but also oxidation of some amines such as piperidines to reactive metabolites was also highlighted.

Having highlighted the issues the authors went on to discuss some of the routes taken to manipulate pKa to overcome issues with examples of increasing CNS (total) brain exposure and addressing cell targeting among these. There was a particular emphasis on bringing pKa closer to neutrality the view being that moderating pKa was generally a "good thing".

One issue just touched on is that changes in pKa are inevitably linked in to changes in LogP as well as LogD and this does seem to be a gap in the discussion. While to my mind pKa is clearly playing a role in some behaviours thus LogD may be relevant are others more related to the LogP i.e. the unionised state of the molecule after all the LogD is effectively a composite trying to take account of an equilibrium between ionised and unionised species. It would have been good to have seen this analysis using LogP as well as LogD to try to disentangle this possible confusion.

1. P. S. Charison and W. P. Walters, J. Med. Chem., 2014, Article ASAP, DOI: 10.1021/jm501000a Publication Date (Web): September 18, 2014 Copyright © 2014, American Chemical Society

HDAC Imaging and applications

HDAC inhibition has been the subject of intense interest in the recent past primarily in oncology. However there is increasing interest in the role of HDAC inhibition in other therapeutic areas particularly the CNS so two complementary papers describing a brain penetrant PET ligand and its use in evaluating new compounds is of interest. First is the report of the PET ligand an adamantane substituted hydroxamic acid Martinostat (1), **1** which is described as having excellent activity against HDAC's 1, 2, 3 and 6. In rodents and non-human primates it shows robust uptake and high specific binding in brain, heart, spleen, kidney and pancreas. In rat brain sections specific binding of (1) was observed to be reduced on preincubation with SAHA or CI-994.

The authors discuss the merits of quantitatively determining central and peripheral target engagement for disease understanding and for prioritising compounds to minimise systemic burden. (1) has undergone safety and toxicology studies and is progressing to the clinic.

Martinostat (1) was used to assess central target engagement of a number of HDAC inhibitors **2**. Not too surprisingly there were significant differences in results but with often modest target engagement e.g SAHA but they reported one o-aminoanilide CN147 (2) showing good target engagement and excellent BB ratios >10 compared with ~0.1 for a related les lipophilic aminoanilide CI-994 (3). CN147 was also reported to have an anti-depressant like profile following chronic dosing in the rat forced swim test model.

Finaly a review **3** of HDAC's and their inhibitors in cancer, neurological disease and immune disorders.

1. C. Wang, et al J. Med. Chem., Article ASAP, DOI: 10.1021/jm500872p, Publication Date (Web): September 18, 2014 Copyright © 2014, American Chemical Society
2. F. A. Schroeder, Cet al ACS Chem. Neurosci., Article ASAP DOI: 10.1021/cn500162j Publication Date (Web): September 19, 2014 Copyright © 2014, American Chemical Society
3. K. J. Falkenberg, and R. W. Johnstone Nature Reviews Drug Discovery 2014, 13, 673

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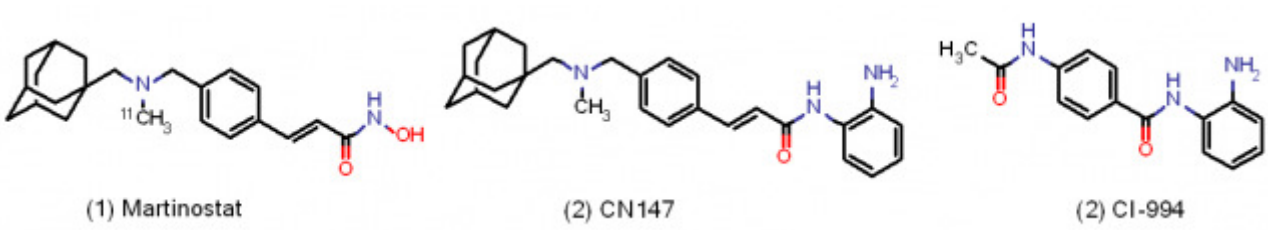

Screening strategies

In the well known paper from 2008 from Swinney and Anthony **1** it was suggested that phenotypic screening was a more productive approach to drug discovery – particularly for first in class compounds. In a new analysis **2** researchers (from target based screening/discovery groups be it noted) advocate the success of target based approaches for identification of 113 FDA approved first in class compounds based on their analysis of 1999 – 2013 data. They actually suggest three categories of approach, targeted based, "chemocentric" (often pertinent to natural products with an identified activity if not target) and phenotypic screening. Seventy-eight (45 small molecule and 33 biologics) of the 113 compounds were arguedas being identified through target based screening 25 were from the authors definition of chemocentric screening with only eight compounds identified from phenotypic screening. In the previous study **1** the chemocentric and phenotypic screens were lumped together – one could spend for ever arguing over the merits of that decision none the less it does suggest phenotypic screening has a less dominant role, at least currently, than was previously proposed. Furthermore it is also suggested that the route to market is quicker by about 20% using a targeted approach although this is not an easy sort of calculation to make. This paper will generate some controversy no doubt I would take issue with their definition of first in class which is

for the first compound that engages a target so for example different ways of modulating the same target would be ignored despite the fact quite different outcomes could be obtained.

In a discussion of phenotypic screening and oncology drug discovery **3** there is a clear bias towards the use of target based rather than phenotypic screening. Forty-eight oncology drugs have been launched since 1999 of these 31 were from target based approaches, ten from de novo phenotypic screening and the balance from some sort of combination. Three of the compounds identified from phenotypic screening were first in class and eleven were first in class from target based of which all but three were kinase inhibitor – probably no surprise there. Four of the compounds at candidate selection identified form phenotypic screening had no recognised target. Certainly this does not suggest a dominance of phenotypic screening in this particular field indeed it seems to emphasise that first in class is more likely to come from judicial choice of a target based approach. One thought discussed is that in this field cell based in vitro and in vivo models do not translate well to the clinic so perhaps being able to develop PK/PD relationships and on occasion exploit biomarkers may help the successful translation to the clinic. The authors speculate on the reasons for the preponderance of target based approaches issues identified have been the heterogeneous nature of the cells comprising a tumour, the move away from purely cytotoxic agents and the growth of the kinase field. Notwithstanding this there are still cytotoxic agents progressing through the clinic with no identified mechanism. It is argued that there may well be a rebound toward increased reliance on phenotypic or at least mechanism driven cell screening exploiting nigh content screening, 3D cell culture and cell models more consistent with the clinical situation. Of course in all of this there is no estimation of the amount of resource dedicated to target based approaches that have failed relative to the resource dedicated to phenotypic screening – the target based approaches are critically dependent on the correct choice of target at the very beginning.

1. D. C. Swinney, and J. Anthony, Nature Rev. Drug Discov. 2011, 10, 507–519
2. J. Eder et al, Nature Rev.Drug Discov.2014, 13, 577–587 DOI:doi:10.1038/nrd4336
3. J. G. Moffat, J. Rudolph and D.Bailey Nature Rev. Drug Disc. 2014, 13, 588 | doi:10.1038/nrd4366

Designing out P450 interactions

A considerable amount of structural work has been disclosed in recent years relating to P450's and their interactions with small molecules. A review **1** outlines some of the work frm AZ describing their work with cases histories describing the use of P450 structural information to reduce substantial P450 liabilities to something more manageable. The first example of a 2C19 liability helped to determine means to reduce the problem – unfortunately the strategy required, a conformational constraint of an aromatic amide, also lost target activity meaning the series was dropped. The positive aspect being this decision could be made during the hit validation phase due to the availability of the structural information rather than later in a more costly lead optimisation phase. The concern was that modelling of the series into the P450 prior to the availability of the bound crystal structures proved unreliable with major differences in predicted compared with found mode of binding. A second project looking at a P450 3A4 liability it was possible to demonstrate that the binding orientation (predicted from modelling and observed from crystallography for the P4503A4) were different between target and P450 and various medicinal chemistry strategies were proposed to exploit this observation. Unfortunatley these were not implemented before the project was closed. In this case crystallography information was a little late. Bottom line on this was the importance of not entirely relying on predictive modelling and getting structural data early – sounds like a business opportunity for someone! Of course it is a concern that the predictive modelling is not fully robust as yet perhaps a case where, in the absence of crystallographic data modelling interrogated with caution is probably better than nothing but the team shouldn't place too much reliance on prediction alone – no change there really!

1. G. Branden et al Drug Discovery Today 2014, 19, 905

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Thiophenes and toxicity

Thiophenes are commonly seen in lead optimisation programmes and in some drugs. However, they do have a track record of problems due to bioactivation to the S-oxide or to a 2,3-epoxide witness the prompt withdrawal of tienilic acid, as one example, due to severe cases of immune hepatitis. Clearly however they are not an automatic death knell for a compound reflecting either the drug is given at low enough dose or that other metabolic pathways kick-in avoiding the reactive thiophene

ring derived reactive metabolites. These aspects are discussed in a review **1** of the bioactivation of thiophene containing drugs. It does seem to me wise to avoid thiophenes however even if bioactivation is avoided that may only be becuase of rapid metabolism elsewhere in the molecule.

1. D. Gramec et al Chem. Res. Toxicol., Article ASAP DOI: 10.1021/tx500134g Publication Date (Web): July 21, 2014 Copyright © 2014, American Chemical Society

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5. Chemistry

Enzyme mediated chlorination

Just showing how smart nature is the report of regio- and stereospecific incorporation of a halogen atom to an unactivated sp3 carbon in a freestanding molecule This is thought to be the first example of a nonheme iron enzyme (WelO5) in the welwitindolinone biosynthetic pathway that can monochlorinate an aliphatic carbon usually beta to an alkene, substrates that are free from peptidyl or acyl carrier protein. Perhaps not very generic although it would be interesting to see how many other beta substituted alkenes could be substrates.

1. M. L. Hillwig and X. Liu Nat Chem Biol 2014 DOI:10.1038/nchembio.1625

Photoredox with nickel catalysis

Something a little more generally applicable is the combination of photoredox chemistry with nickel catalysis. Focus in this article **1** is the coupling alpha-amino carboxyl sp3 carbons with aryl halides see scheme. Yields are generally excellent with examples of heterocyclic halides and of alpha O and aryl amino acids acting as substrates. With mild conditions this looks a versatile route to benzylic amines.

1. Z. Zuo et al Science 2014, 345, 437

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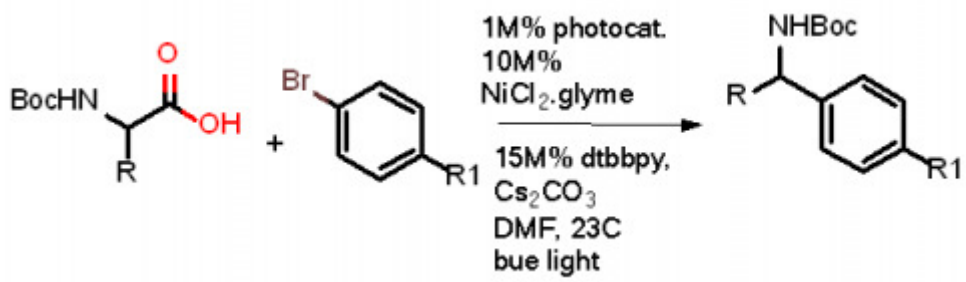

6. Conferences

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

- SMR Award Meeting: Recent Disclosures of Clinical Candidates SMR London, 4th December

Meetings Attended

Two meetings attended during this period although my planned attendacne at ELRIG in Manchester failed to materialise due to other commitments

- The Secrets of Success: CRO views of successful outsourcing SCI, London 30th September
- Personalised Medicine- are we there yet? SMR, London, 2nd October

Both these meetings gave some real insights into their respective topics please email if you would like more infomation on any of the talks. A review of the SMR talks will appear in Drugs of the Future in the next two - three months.

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 bit tongue in cheek perhaps to highlight this article on ten simple rules for better figures appearing in PLoS Comput. Biol> 10. E1003833 (2014). The authors used original illustrations to show where things can go well and go wrong. A key message was know your target audience – and use the appropriate level of complexity for that audience. Apparently this has been of particular interest to those involved in social media activity but it was highlighted in Nature during September – perhaps the editors feel submitters to their journals might benefit from reading it.

Also discussing getting your information over I have just spotted a webinar from the American Chemical Society entitled "Speaking Simply: Communicating Your Science" discussing how to speak clearly to get your message over. Normally these events are posted up on the ACS website after the event although I don't currently have a link.

Quoting from the LINCS project website "LINCS aims to create a network-based understanding of biology by cataloging changes in gene expression and other cellular processes that occur when cells are exposed to a variety of perturbing agents, and by using computational tools to integrate this diverse information into a comprehensive view of normal and disease states that can be applied for the development of new biomarkers and therapeutics". This is for fairly serious number crunchers but looks a good collaborative project based understanding of biology

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

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8. About RodPorterConsultancy

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

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

About CompChemSolutions

CompChem Solutions offers computational chemistry & computational biology services to academic and industrial researchers involved in drug discovery and development. Established in 2004 and based in Cambridge, UK, CompChem Solutions has a wealth of experience across the range of chemoinformatic and computational chemistry disciplines, having worked extensively in many therapeutic areas, particularly oncology, inflammation and pain. Recent publications from

CompChem Solutions have exemplified the use of in silico methodology for target validation and identification, particularly within the context of phenotypic screening. Services can be provided in virtual screening, rational ligand design, protein homology modelling, library design, ADMET property prediction, and many other areas.

CompChem Solutions is now CIR accredited.

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