Rod Porter

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Sent: 10 November 2012 13:14
To: rod.porter@rodporterconsultancy.com
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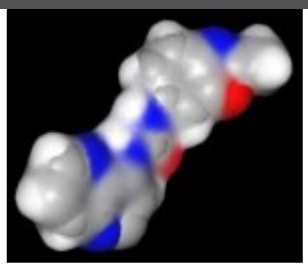

Medicinal Chemistry News from Rod Porter

November 2012 vol 3. no. 5

Dear Dr Porter,

1. Welcome

Welcome to the November edition of the Medicinal Chemistry newsletter from Rod Porter Consultancy. If you would like to make sure you keep receiving this newsletter please add the new senders address to your safe senders list.

Dont forget to visit my blog I was a bit slack this last month but I will be aiming to add items that catch my eye on a more regular basis between now and Christmas.

My next mailing is planned for mid(ish) December with the first of 2013 during February.

While I am able to offer a range of services in drug discovery from hit validation to candidate selection I have always been aware of areas where some teamwork would be good particularly in the hit id phase and for modelling support during hit validation and lead optimisation. I am therefore pleased to announce an informal association between Rod Porter Consultancy and CompChem Solutions. Rod Porter Consultancy will benefit from CompChem Solutions extensive molecular modelling expertise while conversely CompChem Solutions will be able to offer enhanced medicinal chemistry support for clients project.

Themes this month seem to revolve around networks and large datasets, volatiles as signalling agents, a new take (to me at least) on drug resistance ion channels and PDE inhibition in the CNS.

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.

In this issue:

Half Marathon Charity Run

A final opportunity before my Just Giving page closes in December to contribute to my half marathon run which I completed in September in aid of the ALzheimer's Society. Thank you.

2. State of the industry - pipelines

The Worst is over - apparently

Or at least so says a report from Moody's Investors Service courtesy of Fierce Biotech an observation which is based on the fact that the worst of a whirlwind of patent expiries are now behind the industry. While that may be true it does seem a little premature to say everything is now in great shape in the pharma industry. Personally I would have preferred to see a slightly

more balanced analysis - after all there are enormous pricing pressures in Europe at the moment, emerging markets are not a shoe-in for long term growth and new products are still not pouring out of research cf "So far so not so good" from the last edition of this newsletter. Lets face it the slash and burn that R&D has been put through over the last few years can have done nothing to boost company pipelines. Still perhaps we should celebrate the fact that by and large (and so far) the industry has shown resilience in withstanding patent losses on some major products.

You can see that this analysis is the sort of thing various CEO's have been leaning on over the past couple of weeks cf Viehbacher at Sanofi with the latest quarterly sales figures. Mind you AZ may have to postpone the just turning the corner bit with sales figures down 19% due to the Seroquel expiry and they still have the Nexium expiry to come.

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3. In Brief

Big data

Two big projects have recently released data, Encode - the Encyclopedia of DNA elements and an Anatomically comprehensive atlas of the mature human brain transcriptome.

Encode picked up where the Human Genome Project left of and has now identified function to roughly 80%of the genome including about 70,000 promoter and nigh on 400,000 enhancer regions in the non-coding regions of the genome. Thirty papers were published together on 6th September so no attempt by me to cover this landmark. Nature published six of these papers and is a good lead in to this project. NPG has also produced an iPad app for all the papers - search apps for Encode.

Brain Atlas a recent paper 1 part of the Allen Human Brain Atlas project describes the generation and analysis of a transcriptional atlas of the mature human brain with extensive histological analysis and comprehensive microarray profiling of about 900 neuroanatomicaly precise subdivisions of two individuals. Data is readily available.

. M. J. Hawrylycz et al, Nature 2012, 489, 391

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And the nose have it

Composition of breath is being investigated in various areas as possible disease biomarkers - this subject has recently been reviewed with reference to cancer **1** see also **2** for a very recent article identifying malignant mesothelioma with an electronic nose. Volatiles discussed include an interesting range of compounds - hydrocarbons, alcohols, aldehydes, ketones and esters perhaps not so surprising but nitriles and aromatics perhaps a little more so. Biochemical pathways to these compounds are discussed. Following this theme of volatiles and signalling was an article **3** on head space analysis of bacterial cultures which identified 254 compounds from 50 different bacteria. Some of these compounds are known insect pheromones and a few are novel. There are some real surprises – or at least they are to me - I wouldn't have expected a nitroalkane (1), a dichloromethylene sulphide (2) or aromatic thioether (3) for example. Others are perhaps less surprising from a structural perspective for example pentadienones (4). Admittedly the role of these volatiles is unclear at this stage Then we move to plants and a quick google search picked up many hits but one that caught my eye was a volume **4** on insect plant interactions and induced plant defence – for example "Attraction of Parasitic Wasps by Caterpillar-Damaged Plants" clever stuff from a cabbage. Finally going down the genera mosses apparentyl emit volatiles to attract microarthropods to help disseminate their motile sperm between mail and female reproductive structures **5**.

We have all read/heard about human pheromones but perhaps we are underestimating the role of volatiles in human behaviour – perhaps aroma therapy really has something going for it after all.

. M. Hakim et al Chem. Rev., Article ASAP, DOI: 10.1021/cr300174a, Publication Date (Web): September 19, 2012
. E.A. Chapman et al Eur. Resp. J., 2012, 40, 448
. C. A. Citron et al, J. Nat. Prod., 2012, 75, 1765
. T. C. J. Turlings, Maria Elena Fritzsche Novartis Foundation Symposium 223 - Insect-Plant Interactions and Induced Plant Defence Published Online: 28 SEP 2007 DOI: 10.1002/9780470515679.ch3
. T. N. Rosenstiel et al, Nature, 2012, 489, 431

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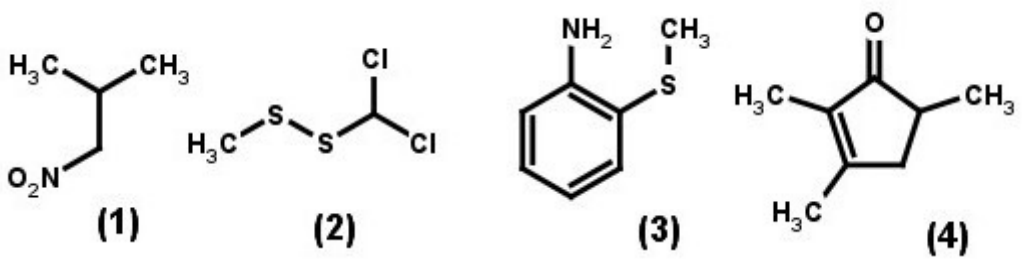

Drug resistance - or stuck in a membrane with you*

A new (at least to me) perspective on the development of drug resistance comes from a recent report **1** suggesting that changes in cell permeability/efflux transport activity may, in part, be regulated by changes in lipid composition due to epigenetic changes - specifically DNA hypermethylation. Drug resistant breast cancer cell line MCF-7/ADR when treated with the DNA methyltransferase inhibitor decitabine showed increased sphingomyelinase activity, reduced sphingomyelin, increased membrane fluidity and increased sensitivity to doxorubicin. Expression of P-gp was reduced - 45% at 24h but back to previous levels at 72h - unfortunately direct comparison with P-gp expression in sensitive cells is missing. Endocytic function enabling drug delivery of e.g. liposomes was improved with decitabine treated resistant cells. This is a follow-up to an earlier paper **2** from the same group which described differences in largely lipophilic interactions' of doxorubicin with membranes from MCF-7/ADR cells to largely ionic for sensitive MCF-7 cells. These changes reflected changes in lipid composition with resistant cell membranes being more condensed and less fluid. In MCF-7/ADR's drug appeared to get trapped in membranes. The authors noted that similar intracellular doxorubicin concentrations were required for threshold anti-proliferative activity in both sensitive and resistant cell lines, which suggests that access to the cytosol is the barrier not changes in biochemistry which leads to Doxorubicin resistance.

It would be interesting to see these studies replicated with other DNA methyltransferase inhibitors and also to establish if this is a reasonably general mechanism for drug resistance and if it is therapeutically relevant. Perhaps it is also a pointer to the difficulties encountered in converting isolated target activity into a cell – with different membrane compositions of different cell lines impacting sensitivity to a test molecule.

* With apologies to Stealers Whee

1. S. Vijayaraghavalu et al, Mol Pharmaceutics 2012, 9, 2730.
2. C. Peetla et al Mol. Pharmaceutics, 2012, 7, 2334

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Specific versus selective or am I just being grumpy

Am I the only one who worries about what might be a trivial point except for the ability to mislead when the word specific is used to describe how selective a compound is. Specific to me implies that said compound interacts with one target and one target only – this we all know is nonsense. At best a compound shows good selectivity (greater than 100 fold, greater than 1000 fold – whatever you might choose to define selective) against the targets it has been tested against and that of course assumes the assays can really be compared in such a simple way – is radioligand binding a good measure of selectivity – what about the kinetics at target, functional efficacy etc. Anyway back to selective v. specific the danger as I see it is when a compound gets described as "specific" any pharmacology seen with that compound is then ascribed to interaction with that target – which may be true but there again may not thus we can end up with a lot of fairly misleading literature. Of course the worst case is when a compound is shown to have weak interaction against one target, tested against no other target and promptly described as specific – you will have all seen examples.

Perhaps journal editors and referee's should ban the word "specific" from any article discussing the pharmacological profile of any compound – or am I being just being an unfair nit-picker.

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4. Medicinal Chemistry

PDE inhibitors and the CNS

Phosphodiesterases have certainly become more complex over the years with 11 classes now identified and multiple splice variants – upto 40 in total. This plethora of subtypes perhaps, in part, accounts for the relatively slow invention of isoform selective marketed compounds - with some obvious exceptions. An additional complication of the ubiquitous nature of cGMP and cAMP mediated signalling is teasing out therapeutic indications for isoform selective compounds. However, there are increasing reports of compounds entering the clinic – often for central indications with a recent review on PDE inhibitors and Alzheimer's disease **1** and a couple of papers on PDE9A inhibitors **2, 3** from Pfizer complementing previous papers reporting a clinical PDE10A inhibitor for schizophrenia **4.** A detailed review of the PDE10A area has recently published from the Pfizer team **5**.

First-off the review **1** nicely covers some of the issues in targeting PDE's in the CNS – firstly addressing which isoforms are present in the CNS – of both preclinical test species and man. Broadly PDE's 1B, 2A, 4, 5, 9 and 10 have relevance for cognition based on validation with pharmacological tools. This is a useful introductory guide to PDE's in CNS although I do take issue with the authors use of the word specific please let's stick with selective - so much nearer reality.

An account **2** of the identification of the PDE9A selective inhibitor PF-04447943 is a good example of the use of structure based drug design, coupled with exploiting array chemistry and physicochemical property based design to invent new CNS drugs. The compound has been into Phase II clinical trials for cognitive disorders although no results from the study have been disclosed. Starting with a potent, metabolically unstable and poorly selective compound (1) the team, exploiting the sequence difference between PDE1c and PDE9A (Phe/Tyr respectively), replaced the cyclopentyl with a 4-tetrahydropyranyl function which increased selectivity and metabolic stability in one go to give (2). However, moderate intrinsic clearance in human coupled with a low plasma protein binding suggested human PK would not be good enough. Consequently modification of the benzyl substituent was undertaken. While fluorination was tolerated well it did little to address the metabolic instability. In contrast heterocycles gave improved stability but depending on the regioisomer could give substantial efflux liability – a real problem for CNS indications.

Thus the 2,6-pyrimidine (3 = PF04447943) does not show evidence for efflux while the 3,5-pyrimidine had an efflux ratio of 15.8 and negligible brain/plasma ratio. Interestingly also (3) showed some evidence for efflux in the rat based on CSF/plasma unbound = 0.19 but in dog AUCcsf/AUCp,u = 0.93. Furthermore human Pgp transporter activity showed no major efflux liability. This is a nice example of cross species difference in transporters - the authors report that these observations will be discussed in more detail in the future - a paper to look out for. Its worth noting that this CNS penetrant compound which is effective in a range of cognition models has cLogP -1.5.

The second paper from the Pfizer group **3** addresses concerns over the suggested efflux seen at least in lower species with (3). To approach this the template leading to (3) was modified to reduce pKa as a possible approach to reduce P-gp liabilities and with some increase3 in lipophilicity while controlling molecular weight. This led to the ether (4) which however had some dopamine transporter activity. Introducing polar substituent's reduced the DAT activity but increased efflux activity. A combination of heteroaryls and going back to a more lipophilic cyclopentyl substituent gave selectivity over DAT and no increase in efflux liability (5). Unfortunately (5) showed a tendency to undergo azetidine ring opening under acid conditions via neighbouring group participation to give (6) – perhaps a caution on use of potentially labile azetidines. Fortunately removing the ether link was, as predicted from docking into crystal structures, well tolerated giving the new preclinical candidate (7).

. A. García-Osta et al, ACS Chem. Neurosci., Article ASAP DOI: 10.1021/cn3000907, Publication Date (Web): October 10, 2012
. P. R. Verhoest et al, Liras J. Med. Chem., Article ASAP, DOI: 10.1021/jm3007799, Publication Date (Web): July 25, 2012
. M. M. Claffey et al., J. Med. Chem., Article ASAP DOI: 10.1021/jm3009635 Publication Date (Web): October 12, 2012
. P. R. Verhoest et al J. Med. Chem., 2009, 52, 5188
. T. A. Chappie et al J. Med. Chem., 2012, 55, 7299

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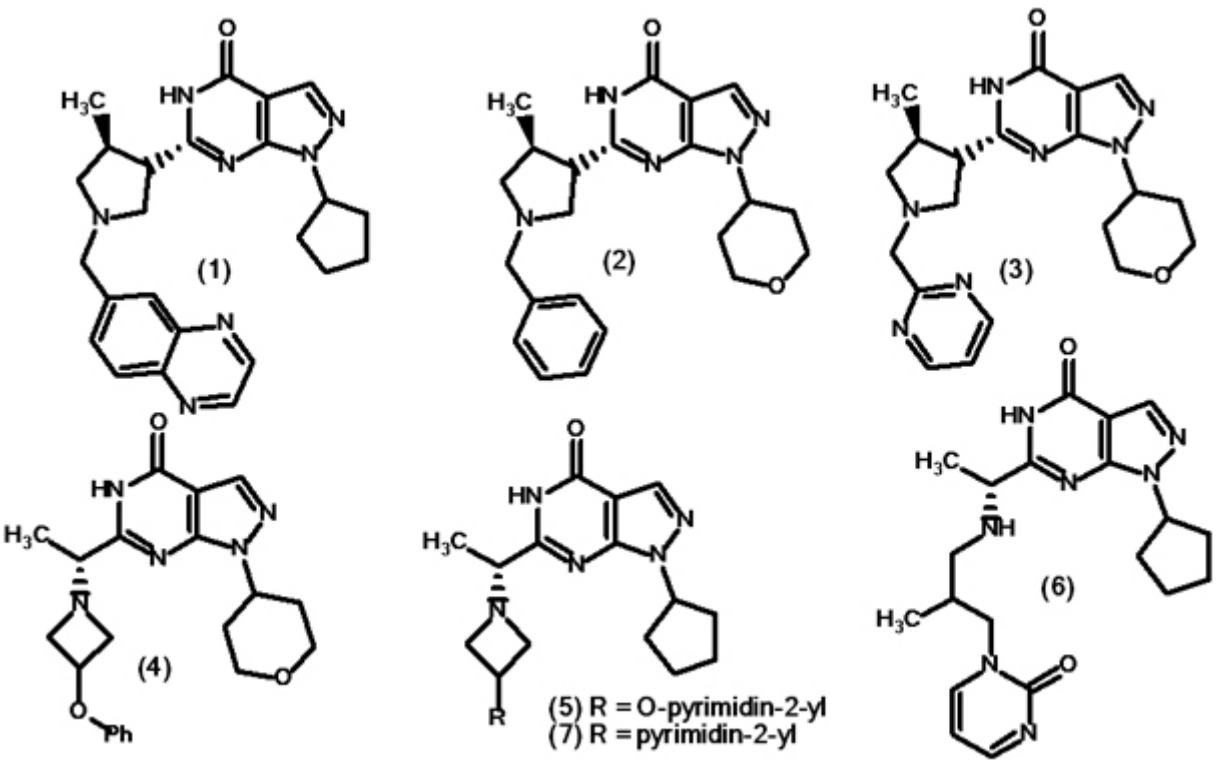

DMSO oxidising your precious compounds

We all know that using DMSO as a solvent for testing compounds and particularly for storing compound solutions has risks associated with it. A nice example **1** highlights a specific problem with 5-aminopyrimidines (1) detailing the formation of highly coloured pyrimidopteridines (3) in situ - not the most soluble entities - apart from anything else. The good thing with this transformation is that at least you can see something has gone wrong based on colour changes.

. E. Prochazkova et al., Bioorg. Med. Chem. Lett., 2012, 22, 6405

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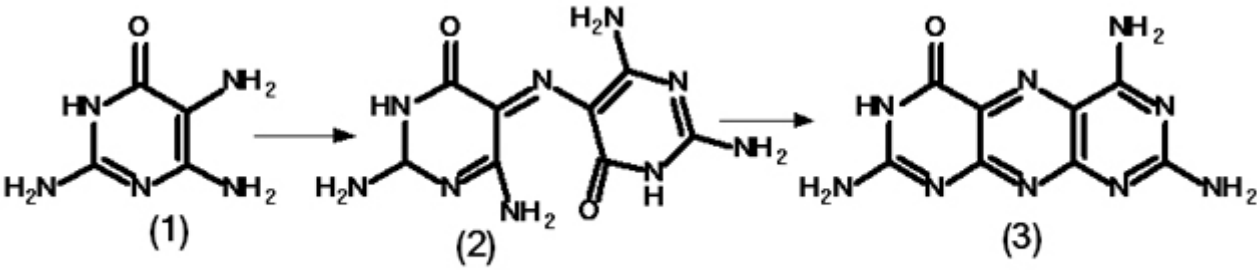

Ion channels

Not a target area I have really covered in this newsletter but there has been a bit of a flurry of reviews and articles on ion channels over the last couple of months. The Society of Chemical Industry and RSC are jointly organising a conference in the early part of 2013 on "Ion Channels as Therapeutic Targets".

Topics covered in recent reviews include

- Ion channel mutations in neuronal disease **1** covering both ligand and voltage gated ion channels
- Ligand gated ion channels: New Insights into Neurological Disorders and Ligand Recognition **2** a useful survey of ion channel involvement in, particularly, Alzheimer's, Parkinson's, epilepsy and neuropathic pain along with discussion of ligand gated ion channels as therapeutic targets.
- Modelling and simulation of ion channels **3** a rapidly developing field in view of the availability of structural information

A special issue of MedChemComm **4** also covers a number of reviews and hypotheses including Advances in Targeting Voltage-Gated Sodium Channels with Small Molecules (pages 1712–1740) and Ion Channel Phosphorylopathy: a Link between Genomic Variation and Human Disease – discussing changes in phosphorylation states based on ion channel point mutations.

Other articles that caught my eye in this edition include a virtual screening approach to identify Potassium Channel Kv1.1–1.2(3) inhibitors by high-throughput virtual screening and automated patch clamp nicely summarising some of the enabling advances in assay technology and structural information in this field **5**.

1. O. K. Steinlein Chem. Rev., Article ASAP DOI: 10.1021/cr300044d, Publication Date (Web): May 18, 2012
2. D. Lemoine et al, Chem. Rev., Article ASAP DOI: 10.1021/cr3000829 Publication Date (Web): September 18, 2012
3. C. Maffeo et al, Chem. Rev., Article ASAP, DOI: 10.1021/cr3002609, Publication Date (Web): October 4, 2012
4. ChemMedChem 2012, 7 issue 10
5. S. J. Wacker, et al ChemMed Chem Article first published online: 30 MAR 2012 DOI: 10.1002/cmdc.201100600

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5. Chemistry

Chemactica - networking synthesis

Continuing the networks theme - three papers from the Gryzbowski group describe three examples of the use of Chemactica 1, an assembly of chemical transformations codified and organised the known pathways through chemical space. The network is extensive with around 7 million compound notes and similar numbers of reaction nodes.

The first example **2** given demonstrates the power of this network was in identifying one pot reactions that could successfully substitute for multiple reaction steps with the obvious advantages of speed and reduction in the number of manipulations. The second example **3** is in the optimization of synthetic pathways rapidly either for a single target or for parallel optimization of syntheses of multiple targets. Finally and at first glance slightly more sinister **4** is the demonstration of the ability to find new short routes to compounds used (or at least prepared as) as chemical weapons from unlicensed precursors – Sarin is cited as an example. The authors argue that the benefit outweighs the risk as it identifies previously unrecognised precursors as risks for nefarious deeds.

This network which has been many years in development, seems to offer immense potential to chemists to allow them to concentrate on the objective of the chemistry and having to spend less time worrying about how to reduce ideas to practice although I do appreciate some purists might disagree.

1. Chemactica
2. C. M. Gotthard et al, Angew. Chemie Int. Ed. 2012, 51, 7922
3. M. Kowalik et al, Angew. Chemie Int. Ed. 2012, 51, 7928

. P. E. Fuller et al, Angew. Chemie Int. Ed. 2012, 51, 7933

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Chemistry of Graphene

Perhaps because the Nobel Prize season has just come and gone but a massive recent review **1** on the chemistry of grapheme, a subject about which I knew nothing, caught my eye. Graphene can be functionalized via, for example, ylid's, 1,3-dipolar cycloadditions and addition of radicals, fluorinated and chlorinated. It can be oxidised to graphene oxide (GO) giving a hydrophilic surface. Further functionalization can introduce, for example polylysine or PEG and a camptothecin analogue has been reported to interact with pegylated GO through Van der Waals interactions solubilising it. Non-covalent interactions of cations and perhaps more surprisingly anions have also been reported. I can't pretend I have studied this review carefully but perhaps some food for thought for medicinal and pharmaceutical development chemists

Fluorescently labelled pegylated nanoparticles have been dosed in vivo **2** and unlike pegylated carbon nanotubes show high uptake in cancer cells. Furthermore exploiting the strong optical absorbance of graphene in the near-infrared (NIR) region efficient tumour ablation was achieved following low-power NIR laser irradiation without overt toxic consequences. It would be interesting to understand why graphene accumulated in cancer cells (true for all cancer cells?) – could this be a vehicle for delivery to specific cell types.

. V. Georgakilas et al Chem. Rev., DOI: 10.1021/cr3000412 Publication Date (Web): September 25, 2012
. K. Yang, et al . Nano Lett. 2010, 10, 3318

6. Conferences

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

. 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..
. RCS BMCS Symposium 14th Dec. Chemistry Dept Cambridge.
. Stevenage Biocatalyst 15th Nov. Open Innovation in Action, Stevenage
. SMR 5th Dec Recent Disclosures of Clinical Candidates, London

Finally also do look out for the RSC Biological & Medicinal Chemistry Sector (BMCS) Postgraduate Symposium to be held in Cambridge 14th December. The majority of the speakers are students (who do a great job presenting their work) along side three industry key note speakers. While the primary audience is students working in drug discovery there is space for some industry people I must say its a great way to see what is happening in academia. For a registration form visit here and send the completed form to Dave Alker putting "REGISTRATION BMCS SYMPOSIUM" in the subject line.

Meetings Attended

BSP/RSC 17th/18th Sept, London Emerging Paradigms in Anti-infective Drug Design a valuable oversight of research on neglected diseases and some of the particular difficulties encountered - not simply the lack of big pharma money. SMR - London 4th Oct. The importance of (Bio)pharmaceutical properties in successful drug design a strong theme around the ability to develop amorphous drug substance. PPI-NET Round table discussion on Peptide based Cell Pentrant Inhibitors of Intracellular PPI's 29th-30th October, GSK Stevenage - an interesting debate round this topic.

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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.

Problems with searching for data

Following on from my comment last time about data bases this blog from former colleague Chris Southan nicely highlights some of the quirks in tracking information on the web and the care needed in both data entry and in searching the web relating to searching for information on a DPPIV inhibitor

Marblar

The RSC have just announced they are sponsoring 6 projects in conjunction with Marblar - a company recently set-up to try to crowdsoure ideas for real-world applications from the global science and technology community. Or put another way to identify uses for discoveries made particularly in academic labs that may not have an obvious application at the moment - the objective

being to create new products, companies and jobs.

Mole Day

Apparently it was Mole Day on the 23rd of October starting at 6.02 deriving from the American way of writing the date 6:02 10/23 – to cunningly reveal Avogadro's number. It was started in 1991 as a day to focus on for school students interested in chemistry particularly in the US, Canada, South Africa and Australia. With annual themes this year it was "Molar Eclipse"

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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Wishing you every success with your research.

8. About Rod Porter Consultancy

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

Visit my website, see my linked-in page or contact Rod Porter directly for more information.

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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.

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