Rod Porter

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Sent: 13 September 2012 12:01
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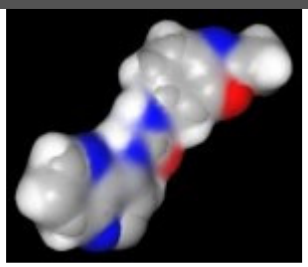
Subject: Medicinal Chemistry News September 2012



Medicinal Chemistry News from Rod Porter

September 2012 vol 3. no. 4

Dear Dr Porter,

1. Welcome

Welcome to the September edition of the Medicinal Chemistry newsletter from Rod Porter Consultancy. Again a week or so later than I had intended but other events intervened. If you would like to make sure you keep receiving this newsletter please add the new senders address to your safe senders list.

Unfortunately my plan to prepare a podcast of this edition has not materialised but it is still on the agenda for next time. In the meantime I have started a blog - my intention is to use the blog as a fast publish with the newsletter as an amalgam of blog articles with additional features.

I have dropped the synthetic chemistry this time round but hope to bring it back in the future

My intended schedule for newsletters for the rest of the year is early november and a brief letter in mid-December.

I am now getting to grips with Stardrop from Optibrium - a powerful bit of software and easy to get into to help with data analysis, compound design and decision making. Model building (based on your own data set), predictive ADME modules coupled with the option to add in Fieldalign from Cresset adds to the versatility of the package.

Please feel free to 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.

Half Marathon Charity Run

As in the past couple of years I have entered the Great North Run half marathon which will take place on the 16th September - dangerously close but at least I have the excuse of not running every morning during this last week before the event. I am running in aid of the Alzheimers Society to help fund them in their excellent support for patients and carers. If you would like to donate please go to my Just Giving page - thank you.

2. State of the industry - pipelines

Why we are here

As a research worker it can be easy to get a little detached from why you spending ludicrous hours working on a particular

In this issue:

problem - or lets face it a small part of a larger problem when it comes to drug discovery. I thought this article **1** was a timely reminder of the importance of reminding ourselves why we got into our chosen career. Very simply it is the story of a graduate student who organized a meeting of people affecting by Alzheimers disease, patients, carers, and research workers. Bottom line of this was that not only were the researchers re-enthused for their work but the patient/care group benefited enormously as well. As the author pointed out patient communities spend a lot of time raising money for research and the researchers spend most hours of the day trying to discover treatments but direct contact is rare. Its only a page long but worth a read.

. T. Nuriel Nature 2012, 487, 7

Learning lessons

A short article from Richard Elliott at the Gates Foundation suggesting some lessons that pharma can learn from those working on neglected diseases - disease areas working in a lean business environment. Briefly they are

- Go for compounds not targets that is advocating phenotypic screening – broadly hard to argue with except there are major areas of unmet medical need such as CNS where phenotypic screening can be tough.
- Consider compound libraries as pre-competitive, the IP tends to be found in what was done after the hit was identified.
- Be open minded – citing Lipinski as an example of guidelines that became unbreakable rules.
- Have a long term strategy and stick with it – now that would be nice!

I guess we could all add few more items to this list.

. R. L. Elliott ACS Med. Chem. Lett., Article ASAP DOI: 10.1021/ml3002105

So far so not so good - 2012

Just noted **1** that for the first two quarters of 2012 there have been 12 new FDA drug approvals (NCE and biologics) this compares with 30 at the same stage last year. Two of the approvals this year were the two anti-obesity drugs - not exactly new compounds bearing in mind how long it took them to get approval. So the article I rerviewed last time talking about 2015 as perhaps crunch tiime when the reduced PhI pipeline catches up with launches perhaps looked a little optimistic.

. L. DeFrancesco Nature Biotechnology 2012, 30, 817

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3. In Brief

Liophilicity and protein degradation

An article that recently caught my eye set me thinking about the liabilities of hydrophobicity - that is, if a ligand binds to a protein, leaving a lipophilic motif exposed to cytosol. In this work **1, 2** the authors discuss the role of lipophilic motifs binding non-covalently to proteins, which directs the protein to the proteasome for degradation. Specifically, the authors investigated the binding of (Boc)3Arg conjugated Trimethoprim to DHFR and the resultant reduction of DHFR levels in mammalian cells. The effect was blocked by Trimethoprim or by proteasome inhibitors. Ethacrynic acid, a covalent inhibitor of GST, also induced degradation of GST when tagged with Boc3Arg.

The main thrust of the articles is in the context of a therapeutic strategy, but arguably, in the case of off-target proteins, could unanticipated degradation due to "tagging" by a drug result in toxic events possibly only manifested over the long term, if the lipophilicity enhanced degradation is modest?

While the authors discuss ligands with a Boc3Arg motif, it is not a huge leap to think of, for example, drugs with lipophilic biaryl groups that become exposed, on binding of a polar head group, to an off-target protein, with consequent demolition by the proteasome.

If this is truly physiologically relevant, can the (unwanted) degradation phenomenon be reduced with a more uniform distribution of polarity in a drug molecule? Or, put another way, is it better to have a molecule of lipophilicity X with a reasonably uniform surface distribution of polarity, or a compound with the same lipophilicity but a non-uniform surface distribution of polarity? Intuitively I would prefer the former, but if anyone has seen any analysis of the distribution of polarity and developability, I would love to see it. Given that lipophilicity seems to be discussed as a global phenomenon for a molecule, perhaps considering local lipophilicity may be useful as well.

A couple of additional relevant articles **3, 4** relate to covalent binding of a lipophilic tag.

. Long et al Chemistry and Biology 2012, 19, 629
. T. K. Neklesa and C. M. Crews, Nature 2012, 487, 308
. T. K. Neklesa et al Nature Chem. Biol., 2011, 7, 538

. H. S. Tae et al ChemBioChem 2012, 13, 538

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Alzheimers reviews

Perhaps appropriate to look at Alzheimer's again in the month I am running in aid of the Alzheimer's Society as this also coincides with a couple of extensive reviews from the biological chemistry perspective. It's also worth bearing in mind that while these discussions focus on Alzheimer's many of the principals may well apply to other disease states where peptide/protein aggregation is implicated. First is a review **1** of the recent increase in interest in the bioinorganic chemistry of Alzheimer's. The review starts with a useful summary of the current hypotheses on the pathogenesis for Alzheimer's namely the amyloid cascade, the metal ion, and the oxidative stress hypotheses. There is merging of these hypotheses as the author discusses, for example, the role of metalloenzymes in both the formation and removal of beta-amyloid and free metal ions in the formation of reactive oxygen species. Dyshomeostasis of iron, zinc and copper are particularly discussed paying attention to both free and bound ions. Aluminium, cadmium and mercury as exogenous metals are also discussed – with aluminium back in the frame, (all that acid fruit cooked in aluminium saucepans when I was a child!). Mechanisms for regulating metal ion concentrations are also discussed in particular metallothioneins in metal transport and storage. Finally there is a discussion of therapeutic interventions to regulate metal concentrations including, for example, natural products such as curcumin and melatonin.

The second review **2** focuses very much more on beta-amyloid considering for example neuronal mechanisms of amyloid plaque and oligomer toxicity. One topic that caught my eye was the proposition that oligomers can form membrane ion channels. Strategies for reducing amyloid oligomerisation by therapeutic intervention were also discussed.

I suppose what I took from looking at all this information is that simply targeting one mechanism for this destructive disease (or range of diseases when neurodegeneration is considered in a wider context) is unlikely to give a satisfactory response. Indeed we may need different longitudinal treatment strategies as subjects (not necessarily patients with overt disease) grow older.

. K. P. Kepp Chem. Rev., Article ASAP, DOI: 10.1021/cr300009x, Publication Date (Web): July 13, 2012
. I. W. Hamley Chem. Rev., Article ASAP DOI: 10.1021/cr3000994 Publication Date (Web): July 19, 2012

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Mitochondria – a reprise

Slightly unfortunate timing – this free poster on Mitochondrial function and cancer from Nature Reviews Cancer appeared just after I mailed my July Newsletter. It reviews some of the recent discoveries around mitochondrial function which has renewed interest in the role of mitochondria in cancer. I have highlighted a number of these posters over time - personally I do find them useful summaries of an area.

Finally on this topic, at least for now, a paper **1** reporting the ability to measure levels of free zinc in mitochondria. Zinc levels are an important marker of cell health and in particular for mitochondria. With few method available for measuring zinc in mitochondria the authors developed three dynamic range, genetically encoded, fluorescent Zn2+ sensors which can be used in a variety of cell types. One of these sensors mito-ZAP-Cy1 indicated that free Zn2+ in mitochondria is at picomolar levels substantially lower than previously thought. Arguably these sensors could provide valuable tools in sensing mitochondrial health via changes in Zn2+.

. J. G. Park et al, ACS Chem. Biol., Article ASAP DOI: 10.1021/cb300171p Publication Date (Web): July 31, 2012

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4. Medicinal Chemistry

Molecular properties and *in vitro* and *in vivo* toxicology and disposition

An important contribution from the group at Lilly **1** outlining their analysis of physicochemical and ADMET properties with PK and toxicology data on some 3,773 compounds from 173 different chemical classes. Firstly the authors provide a critique of the numerous previous studies which have analysed physicochemical properties of compounds in relation to toxicology or surrogates of toxicology readouts pointing out the lack of consideration in many of covariants for example the relationship between solubility and molecular weight should also perhaps consider the impact of ionisation or lipophilicity as well.

The study highlighted the importance of rat *in vitro* hepatocyte toxicity combined with volume of distribution for in vivo toxicology (LOAEL based on histology or death) outcomes and microsomal clearance with cLogP for predicting unbound clearance. Higher clearance looked like bad news for toxicology as well all of which tends to make intuitive sense but now with a sense of quantitation. Indicators of oral bioavailability were weak - decreasing PSA or increasing solubility gave modesteffects on improving bioavailability with permeability also only having a minor impact

Further work was done to look at the effects of single point changes in structure, however within the constraints of the data set there were not too many surprises. Having said that I did find it a little surprising that replacing a CF3 with F gave an increase in LOAEL and replacing F with H gave a further increase although as the authors admit the sample sets were small. I also found the observation that Vdss is reduced going from a nitrile to a methyl group but I suspect here that context is all as this is looking at

the point substitutions in isolation and ignoring long range electronic effects. I think this is a valuable paper particularly with its focus on toxicology outcomes but taking a slightly different approach to the Pfizer groups analysis **2** of their tox data.

. J.J. Sutherland et al, J. med. Chem. 2012, 55, 6455
. J. D. Hughes et al, Bioorg. Med. Chem. Lett., 2008, 18, 4872

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Transporter expression changes – disease, diurnal effects(?) and drugs

There has been some work reported on changes of transporter expression following insult in the liver and kidney and a little on expression in brain endothelium. However transporter behaviour in microglia has not so far been studied. This has now changed **1** with the report of the effects of LPS on expression of ABC transporters in murine BV-2 microglia cells. Functional (retention of fluorescent calcein AM for example) and mRNA expression were consistent with the decreased expression of Mdr1, BCRP and Mrp's. However, based on mRNA expression levels, it appears that Mrp1 and Mrp5 expression levels were increased in microglia. The authors speculate that the broadly net reduction in transporter expression levels may lead to the retention of toxic substances and impair cell-cell communication during neuroinflammation.

Mrp's substrates include organic anions such as conjugates of sulphate, phosphate, glutathione etc. and over expression of Mrp's have been attributed to development of resistance to some drugs such as antifolates **2**.

All this does raise the question of the local impact of changed transporter expression on the pharmacological efficacy of a drug in disease. As medicinal chemists we tend to worry about transporters in the context of effects on gross drug distribution and increasingly with respect to toxicity. Perhaps we need to look more closely at the local or microscopic effects of changes in transporter expression in disease.

Looking at transporter regulation of physiological function a recent report **3** highlights the role of the prostaglandin transporter (PGT) and OAT3, both in the choroid plexus, for the regulation of PGD2 levels in cerebrospinal fluid. PGD2 is a sleep promoting substance that regulates physiological sleep. This raises the question of how diurnal changes in PGD2 are managed – one option of course is changes in production or degradation of PGD2, the other – raised by the authors, is that there is a diurnal regulation of transporters as well. While the authors present no data to address this possibility, they do highlight that LPS does reduce the expression of PGT at the choroid plexus. Furthermore they report that indomethacin and diclofenac inhibit OAT3 mediated PGD-2 transport. The authors have previously **4** discussed the effect of a range of drugs on the inhibition of PGE2 efflux from the brain probably due to inhibition of MRP4.

. C. J. Gibson et al, J. Pharm. Expt. Ther., 2012, Published online before print August 31, 2012, doi: 10.1124/jpet.112.196543
. P. Wielings et al, Cancer Res, 2005, 65, 4425
. M. Tachikawa et al, J. Pharmacol. Expt. Ther., 2012 Published online before print August 29, 2012, doi: 10.1124/jpet.112.197012
. S. Akanuma et al, J. Pharmacol. Expt. Ther., 2010, 333, 912

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Biased dopamine agonists

Biased GPCR ligands have a relatively limited history of medicinal chemistry exploration – a recent discussion **1** of biased dopamine receptor agonists can now be added to the inventory. The SAR of Aripiprazole the D2 partial agonist marketed for the treatment of schizophrenia, for both cAMP production and beta-arrestin activation was investigated with the ultimate result that selective beta-arrestin ligands were identified showing good "antipsychotic" behaviour in mouse models which was ablated in beta-arrestin KO animals. Key changes in developing beta-arrestin agonist activity at the expense of the cAMP pathway in this systematic study of the different regions of Aripiprazole were:-

- Replacement of the quinolone with a benzthiazole or introduction of additional ring nitrogen amongst other heterocycles
- Replacement of the piperazine with a homopiperazine or a piperidine
- Aryl ring substitution had little effect on the signalling pathway bias of the partial agonist

Several compounds were identified such as (35 and (44) which show good selectivtyfor the beta-arrestinover the cAMP pathway. One concern I do have is that for example compound (35) does have broad aminergic receptor affinity **2** thus the loss of in vivo activity in beta-arrestin KO animals is an important observation. In view of some of the comments in the following article its perhaps unfortunate that sulphur heterocycles and 7-membered rings look like they benefit beta-arrestin selectivity, at least in this case!

. X. Chen et al J. Med. Chem., Article ASAP, DOI: 10.1021/jm300603y, Publication Date (Web): August 13, 2012
. Supplementary Information to 1.

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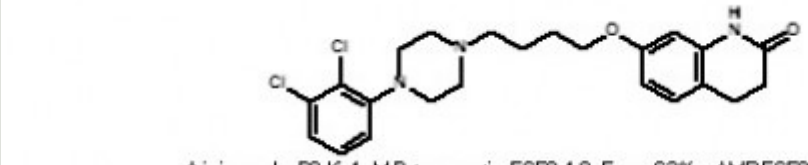
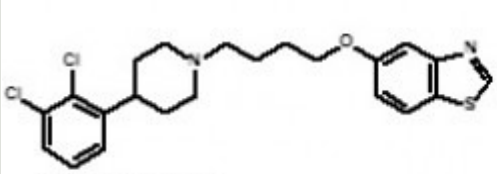
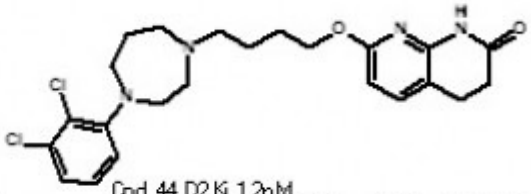


Aripiprazole D2 Ki 4nM Beta-arrestin EC50 4.0, Emax 62%, cAMP EC50 1.0nM, Emax 51%



Cpd. 35 D2 Ki 42nM
Beta-arrestin EC50 79, Emax 78%, cAMP EC50 N/A, Emax <20%



Cpd. 44 D2 Ki 1.2nM
Beta-arrestin EC50 1.6, Emax 47%, cAMP EC50 N/A, Emax <20%

Heterocycles and carbocycles - developability (highlighted by Ashley Jarvis, Domainex)

A blog entry **1** from the inestimable Derek Lowe looks at a papers from GSK and AZ **2, 3** analysing the frequency of switching from a phenyl group to a heteroaromatic and the impact on, solubility, human serum albumin binding and P450 interactions. To précis, winners generally seem to be heterocycles with two adjacent nitrogens, imidazoles (particularly effective in reducing HSA binding), pyrazines and pyridazines. Not so good were any heterocycle containing sulphur – brick dust that stuck to plasma proteins and usually have P450 interactions. Derek does prevaricate a bit about thiophen as a heterocycle, no doubt to my mind it is but equally it would not be the first or second (or third) choice to replace a phenyl ring with. Interestingly, extending the analysis to heteroalicyclic compounds, while limited due to the size of the data set, did highlight piperidines, morpholines and imidazolines as being favourable switches. Sulphonamides perhaps no surprise were bad news. Continuing the theme of analysing heterocycles and developability, an additional paper from the AZ group **4** looks at matched pair consideration of metabolic stability.

Following on from this blog is an extensive review **5** of heterocycle metabolism and strategies to reduce metabolic liabilities. Both heteroalicyclic and heteroaromatic systems are discussed. For heteroalicyclic compounds broadly reducing lipophilicity works well, along with steric crowding. Interestingly the preferred approach, if starting with a 7-membered ring, is to reduce the ring size – a pity when one thinks of all the valuable conformational information that can be found in a 7-membered ring. However, it is worth pointing out that the 7-membered rings were generally undecorated so perhaps polar substitution represents an under explored opportunity for someone. Four membered rings are also discussed in a little detail, while generally seen as a "good thing" their positive effects are not guaranteed. Heteroaromatic 5-membered rings were broadly stabilised by increasing the nitrogen content although the authors note that, for example, 1, 2, 4-triazoles were generally more metabolically stable than 1, 2, 3-triazoles. While reducing electron density in 6-membered rings – fluorination, additional nitrogen was again generally beneficial, things could be overdone turning the ring system into an electrophile susceptible to attack by aldehyde oxidase for example. This is a useful review of an important area of medicinal chemistry

One thing that struck me with the analyses was the lack of 7-membered or larger rings – either polyunsaturated or fully aromatic – clearly 6,7 fused systems have had a lot of attention over time perhaps we are missing a trick underexploiting larger, information rich, ring systems.

. Derek Lowe Blog The Best Rings for your Molecule
. T. J. Ritchie et al, Med. Chem. Commun., 2012,3, 1062-1069
. A. Leach and N. J. Kidley, J. Chem. Inf. Model., 2011, 51, 1048–1063
. A. G. Dossetter , A. Douglas and C. O'Donnell Med. Chem. Commun., 2012,3, 1164-1169
. D. J. St Jean and C. Fotsch J Med Chem 2012, 55, 6002

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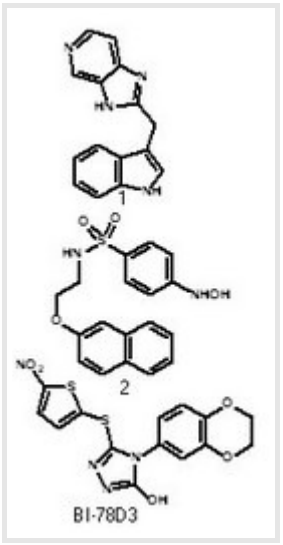
Managing PPI's



Protein-protein interactions are being seen increasingly as attractive albeit tough targets. PPI's vary from clefts much like a ligand-protein binding site through to large fairly flat systems perhaps with a few binding hotspots. Generally success has been achieved in targeting the former and not the latter. In a recent review **1** the authors summarise the approaches that might be taken to address the latter targets in particular. Strategies discussed include allosterism and intervening in post translational modifications. Nature can also provide inspiration, cited for example, is the role of vinblastin in microtubule destabilisation. This is a short review but for those of you interested in PPI's a useful summary. I guess in a similar vein a paper **2** from a group at Genentech discusses RAS inhibition via direct RAS binding by compounds - a number of agents are known that show activity although affinities are generally low e, g (1), (2). The authors highlight the challenge is now to increase the activity of these compounds and selectivity particularly with respect to other GTPases.

A recent paper **3** discusses the use of virtual screening to identify inhibitors of the JNK-JIP1 interaction. This has been an active area of research with a number of inhibitors identified. The authors used one of these inhibitors BI-78D3 to identify *in silico* where it may bind to JNK and a putative bound conformation using the crystallographic data for the JNK-JIP1 interaction. A virtual screen of the NCI Diversity Set generated a number of hits which gave IC50's for displacement of JIP from JNK of between 0.7 and 22uM. Not a perfect story perhaps but a demonstration that "conventional" techniques have value for PPI's when appropriately used.

1. A. Thompson, et al, ACS Chem. Biol., Article ASAP, DOI: 10.1021/cb300255p Publication Date (Web): July 23, 2012
2. W. Wang et al, Bioorg. Med. Chem. Lett., 2012, 22, 5766
3. T. S. Kaoud et al, Med. Chem. Lett., Article ASAP DOI: 10.1021/ml300129b Publication Date (Web): August 13, 2012

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5. Conferences

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

1. BSP/RSC 17th/18th Sept, London Emerging Paradigms in Anti-infective Drug Design
2. SMR - London 4th Oct. The importance of (Bio)pharmaceutical properties in successful drug design
3. SCI - London 6th Nov. Enhancing drug discovery: The benefits of of kinetic and thermodynamic binding data in discovery.
4. UKQSAR Autumn meeting Takeda Cambridge (UK) see below
5. RCS BMCS Symposium 14th Dec. Chemistry Dept Cambridge.

Keep an eye out for the next UKQSAR meeting which is being held on the 8th Nov at Takeda Cambridge. Check the provisional agenda there are talks that will appeal to many medicinal chemists.

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

ELRIG - Manchester 5th, 6th September 2012 is designed as a showcase for suppliers but has an excellent scientific programme as well and is free for delegates. This year within the four parallel streams there were sessions on fragment based drug design, epigenetic drug discovery, compound collection enhancement and the Ubiquitin cascade. Other sessions focused on screening technologies and automation - the foundations of ELRIG

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6. 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.

I dont normally feature papers in this section but as I often feature databases I thought this paper **1** reviewing available public med chem databases fitted in quite nicely. This article is very much a walkthrough of the content of different databases. In a similar but more critical vein is a second paper **2** critiquing the quality of available databases emphasising the point that good quality curation is essential to allow the construction, for example, of robust predictive models. Curation is never going to be easy when trying to compare data for the same target (and same assay) between labs (remember the paper from the Novartis group I highlighted last month **3**) while human error is currently a major risk when data has to be transcribed. Hopefully the latter should

become less of an issue if standardising of electronic reading occurs. Perhaps slightly worrying is that Wikipedia came out in an on-line survey as being the most trusted source although its data content and use is somewhat different to sources such as ChEMBL. Useful to remember a paper I highlighted last time on the variability of data bet

. G. Nicola, T. Liu and M. K. Gilson J. Med. Chem., 2012, 55, 6987
. A. J. Williams et al, Drug Discovery Today, 2012, 17, 685
. C. Kramer et al, J. Med. Chem., 2012, 55, 5165

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.

7. About Rod Porter Consultancy

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Wishing you every success with your research.

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