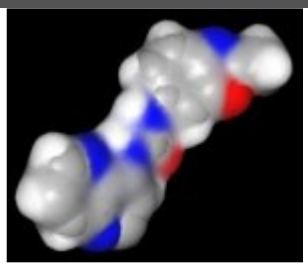
Rod Porter

From: Rod Porter <News@rodporterconsultancy.emailmsg.net> on behalf of rod.porter@rodporterconsultancy.com
Sent: 04 March 2014 15:37
To: rod.porter@rodporterconsultancy.com
Subject: Newsletter from Rod Porter March 2014

Medicinal Chemistry Newsletter | View Web Version



Medicinal Chemistry News from Rod Porter

March 2014 vol 5. no. 1

Dear Dr Porter,

1. Welcome

Welcome to the rather delayed February/March edition of the Medicinal Chemistry newsletter from RodPorterConsultancy. Features this month include; the surge in IPO's, predicted value of the prospective 2014 pipeline. a simple concussion detection (an interest from my past) ADMESARfari from Chembl, total synthesis of EPO a miscellany of developability topics include an intriguing approach to addressing concens over aldehye oxidase, looking at the use of rings in drugs, some aspcets of CNS drug dleivery including a promising revisit of the transferrin receptorP-gp and possible drug drug interactions, ligand efficiencies - another review but summarising some interesting data the authors have extracted from the literature and finally druggable protin-protein interactions. Nanoparticle delivery particularly for cancer has seen a whole host of publciations too many for me to look at even briefly.

I hope the New Year has got of to a good start for you. I finally managed to get my Glycine Transporter-1 inhibitor book chapter of to the editors (much to my and I would guess my editors relief) and have got a few other things finished of.

As ever 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 April.

Wishing you every success with your research.

In this issue:

Brighton Marathon running in aid of Mind

The Brighton marathon (6th April) is looming up on the horizon with only a few weeks to go - training is going OK but running 20 miles on a Sunday morning I admit isn't my idea of fun! Most of us will have been affected by mental health problems at some time in our lives either directly or indirectly I am therefore running in aid of the mental health charity Mind. Mind works hard to support those with mental health problems giving advice and support and raising awareness of the issues sufferers have. I hope you feel able to make a donation any contribution will be greatly appreciated both by myself and more importantly will benefit Mind. To donate please visit my virginmoneygiving page and many thanks.

SMR - next meeting

The next meeting of the Society of Medicines Research will be 13th March in London on "Reducing Attrition through Early Assessment of Drug Safety"

Drug toxicity remains one of the main causes of compound attrition in the drug development process. Compounds displaying organ, mechanism-based or off-target toxicity are just some of the safety issues that have contributed to drug development failures, and the need for robust early drug safety screening in an integrative manner is clear.

This meeting will bring together a range of international experts from both industry and academia to present the new technologies and their applications in early drug safety assessment. The meeting will be of great interest to anyone involved in drug discovery and development, or has an interest in the science behind drug safety screening. For the full programme please click here

Optibrium - Stardrop™

Optibrium, a developer of software for drug discovery, today announced the release of a new version of its StarDrop™ software platform. The latest release introduces MPO Explorer™, which provides innovative new methods to guide 'strategic' decisions in research programmes, by helping to identify the key properties and selection criteria with which to select compounds with a high chance of success. The new module, alongside data visualisation enhancements, further extends StarDrop's capabilities to reduce the time and cost to deliver high quality drug candidates

2. State of the industry

IPO's off to a good start in 2014

IPO's seem to have got off to a rip-roaring start this year with, in just one week during February, $500M raised by eight companies. That was an exceptional week but other weeks have seen $250M raised. By no means all companies are getting the price they want but there seems to be renewed appetite to invest in biotech - at least at the moment. With rumour that there are 25 or so more companies looking to go public and that companies that have recently gone public have often seen sharp falls in share price shortly after launch it would be a brave rhinoceros who would predict this level of interest will be sustained.

Predicted value of the 2014 product pipeline

Some concerns are being raised about the market value of prospective launches in 2014. One report suggests that only three compounds anticipated to launch this year will achieve $1Bn sales, most years have seen at least six compounds with blockbuster potential. Compounds anticipated to meet this mark are GSK/Theravance combination COPD therapy, Anoro Ellipta, Lundbeck's Brintellix for major depressive disorder and Celgene's psoriatic arthritis drug, Apremilast. Furthermore these are predicted to achieve combined sales of only $4.3Bn by 2018. This total will be exceeded individually by two launches from 2013, Biogen Idec's Tecfidera, ($5.1Bn) and Gilead's Sovaldi ($7.4Bn). The report also highlights the diabetes sector as likely to have most new products with oncology and (interestingly) anti-infectives also well represented. 2014 may also be a big year for biologicals. The perceived lack of blockbuster potential may have a knock on effect on the currently healthy IPO activity – see above. The picture painted here looks like it may be a downside analysis and there are products waiting in the wings that might make it to market in 2014 – of course compounds may well fail as well. Let's see what I am writing, if anything, this time next year.

3. In Brief

A finger-prick blood test could uncover sports concussions on the field

Perhaps not directly relevant to med chem but this caught my eyein diagnostics. Repeated concussion is an increasing concern in professional rugby and of course has been so for some time in American football. Perhaps a bit late for people like myself but it's good to see serious effort being made to assess possible concussion rather more reliably than being asked what day of the week it is as you lie stunned on the turf after a kick (accidental)/clash of heads/hitting the ground head first (delete as applicable).

Development of Chembl - ADME and patent structures

Access to large data sets and informatics tools is a major need in modern drug discovery. Thus the announcement of two new features of Chembl are very welcome. First the introduction of ADME SARfari "a freely available online resource, focused on making it easier to search against ADME related data found in the ChEMBL database and other data sources. The additional data sources include PharmaADME, Ensembl and the Human Protein Atlas. ADME SARfari allows users to search with keywords, protein sequences and small molecule structures. In addition to standard search types listed above, it is also possible to ask the system which ADME target a small molecule is likely to interact with. To achieve this a naive Bayesian model has been built using binding data extracted from the ChEMBL database. GSK contributed funding and support.

In a second Chembl initiative access to compounds disclosed in patents has been enacted through " Digital Science, a Macmillan company, and EMBL-EBI are transferring SureChem data on patented chemical structures into the public domain. It is the first time a world patent chemistry structure collection of this size has been made publicly and freely available, making it a significant advance in Open Data for use in drug discovery. This donation from Digital Science will give researchers access to a new source of highly relevant compounds related to the curing of human disease." I don't think the Surechem data is yet available through Chembl I gather it may take some months to get access up and running

Back to top

Total synthesis of EPO

A synthetic tour de force is the total chemical synthesis of the glycoprotein EPO **1, 2**. Like other commercial glycoproteins EPO is sold as a mixture of glycosylated forms (with four glycosylation sites) which may affect the stability and biological activity. However, due to the inaccessibility of pure individual glycosylated forms it is impossible to define the individual therapeutic contributions of each. Synthesis comprised preparation of 5 peptides using native chemical ligation in conjunction with desulfurisation methods to convert the cysteines required for NCL, to alanines. Three consensus dodecasaccharide N-glycans were prepared alongside a glycophorin tetrasaccharide to prepare the single O-glycan. The glycans were coupled via convergent aspartylation. Overcoming some probems in coupling the peptides encountered due to the proposed problems of bulky proximal N-glycans by reengineering the peptide coupling point (easy to write but pity the poor student!) a pure fully synthetic EPO was generated. This product showed *in vivo* EPO activity comparable to the clinical drug Procrit. While hardly competing yet with biologic methods for scalability or speed this is a tremendous 10 year effort.

1. P. Wang et al Science 2013, 342, 1357
2. L. C. Hsieh-Wilson and M. E. Griffin Science 2013, 342, 1332

Back to top

4. Medicinal Chemistry

Miscellaneous developability - Toxcast, hepatoxicity, aldehyde oxidase

A report from Pfizer **1** describes initial results of an analysis of 52 compounds with preclinical and clinical data they submitted to the EPA Toxcast programme. The analysis identified particular in vitro assays (486 in total) run under the Toxcast programme of relevance to the Pfizer compound set. One important point was that the team identified differences in both chemical and biological space of pharmaceuticals compared to environmental chemicals which may make it difficult to interpret results for pharmaceuticals using in silico models developed with environmental chemicals. The analysis did identify novel interactions of the Pfizer compounds with multiple nuclear receptors in particular which had not previously been recognised.

Hepatoxicity is a significant problem in development of drugs. While there are some ways to check e.g. for reactive metabolites with glutathione trapping etc a more sophisticated alternative is now described **2**. The approach uses microarray based toxicogenomics in an attempt to classify hepatoxic and non-hepatoxic using gene expression profiles determined in vitro from HepG2 cells. Use of 36 genes gave a 92% (training set) or 91% (validation set) accuracy. For cholestasis only 12 genes were required to detect 8 of 9 cholestatic compounds. Tentatively the group suggested that endoplasmic reticulum stress and the unfolded protein response re particularly relevant in predicting hepatoxicity although they do recommend that more compounds need to be evaluated

Finally in this developability miscellany an elegant strategy to identify aldehyde oxidase substrates **3** – see following discussion on rings in drug discovery. Aldehyde oxidase substrates are difficult to predict *in silico* and furthermore compounds show significant cross species differences in susceptibility. The approach exploits the proposed nucleophilic mechanism of AO and the likelihood that susceptibility to AO metabolism may be related to the susceptibility of a heterocycle to nucleophilic attack – particularly adjacent to ring nitrogen atoms. The team therefore used the observation of the predictable nature of alkylsulphinate derived radicals attacked heteroarenes to develop a chemical method for testing for introduction of a CF2H group to a molecule. Those molecules that generated an M+50 mass spec peak under a 2h incubation with Zn(SO2CF2H)2 were found to be aldehyde oxidase substrates while those that did not, were not substrates. False positives were also found as the introduction of the CF2H group was not as regioselective as AO nor was the chemical reagent as susceptible to steric interference as AO can be. None the less these data were a useful early warning. Furthermore the CF2H adducts formed were resistant to the effects of AO thus in one experiment you can identify your compounds liability towards AO and potentially fix it – ignoring any effects on biological activity just for now.

1. F Shah and N Greene Chem. Res. Toxicol., 2014, 27, 86–98
2. W. F. P. M. Van den Hof, et al Chem. Res. Toxicol., Article ASAP DOI: 10.1021/tx4004165 Publication Date (Web): January 28, 2014 Copyright © 2014, American Chemical Society
3. F O'Hara, et al J. Med. Chem., 2014, 57, 1616–1620 DOI: 10.1021/jm4017976

Back to top

Rings in drugs review diversity

In an analysis of rings, ring systems (complete ring or rings formed by removing all terminal and acyclic linking groups without breaking any ring bonds) and frameworks (all the ring systems but also includes ring systems that are linked by nonterminal acyclic groups) present in the FDA Orange Book for NMEs upto the end of 2012 a group from UCB drew several conclusions including;

- only 351 ring systems and 1197 frameworks have been used in current drugs.
- There are over 204 ring systems and 901 frameworks that have only been used once in a drug.
- On average six new ring systems enter drug space per year which has remained fairly constant over time.
- Each year, on average 72% of new drugs will comprise only those ring systems found in previously marketed drugs which sounds like a lot of cut and pasting!
- The overall count of 3, 4, and 5 respectively for O, N, and heteroatoms in a ring system has not particularly changed over time though I might have expected to see a trend to a slight increase in recent years with the focus on keeping lipophilicity down.
- Perhaps reflecting the privileged template idea ring systems cross therapeutic areas and target classes - If a ring system is reused, 62% of reuses will be for a different therapeutic area and 71% for a different target class.

I guess one problem with this analysis is it doesn't necessarily reflect the number of new rings exemplified in, for example, patents. Are there, for example, developability liabilities of novel rings exemplified in patents that prevent progression of such compounds? Is there anything particularly significant about the rings and ring systems that do make it to market perhaps intrinsic metabolic stability or lack of P450 interactions? While developability issues might be a factor the concern does remain that chemists feel unable to commit to the time to develop novel rings under normal circumstances – a situation which, in my view, is unlikely to improve with so much outsourcing of chemistry.

This is an interesting read and reflects again the lack of new chemistries and perhaps the "unfashionable" nature of hetero(ali)cyclic chemistry and mirrors previous reports on the under exploitation of heterocycles. As a bit of a counterpoint is a review **2** on acylhydrazides as reagents for synthesis of O-, N- and S- containing heterocycles.

1. R. D. Taylor, M. MacCoss and A. D. G. Lawson J. Med. Chem., Article ASAP DOI: 10.1021/jm4017625 Publication Date (Web): February 17, 2014 Copyright © 2014, American Chemical Society
2. P. Majumdar et al Chem. Rev., Article ASAP DOI: 10.1021/cr300122t Publication Date (Web): February 07, 2014 Copyright © 2014, American Chemical Society

Back to top

CNS delivery a break through?

CNS targeted biologicals should have enormous therapeutic potential but for the problem of delivery of adequate reagent. The idea of using the transferrin receptor to carry ligands into the CNS has been around for decades but never really caused much of a stir. Now, however, Roche/Genentech report **1** a monovalent fragment of a transferrin receptor antibody as a Brain Shuttle module to deliver a standard therapeutic antibody to the CNS which has caught the eye of various groups e.g **2, 3**. A divalent antibody ends up being sorted into the lysosome with presumably subsequent destruction. Use of the Brain Shuttle modified Aβ antibody gave a 55 fold increase in target engagement relative to the non-modified antibody which translated into an increased reduction in amyloid. This all sounds very encouraging for CNS biotherapeutics but of course this is early days.

Intranasal delivery of a lactose analogue of endomorphin 1 via the olfactory epithelial pathway has been reported **4** with drug appearing in the olfactory bulb within 10 minutes of dosing with negligible drug appearing in either the blood or in other regions of the brain. The compound has previously been reported to show activity comparable to morphine when dosed either iv or orally – perhaps surprising in view of the tetrapeptide/linker/lactose structure a total of ~72 heavy atoms and 14 H-bond donors.

Disrupting the blood brain barrier has been seen as a way of getting drugs into the CNS for a while with approaches like osmotic shock and treatment with bradykinin antagonists. Another approach now reported **5** is the use of synthetic E-cadherin peptide HAV. HAV has been demonstrated to rapidly increase the permeability of the BBB following iv dosing to give 2-5 fold increase in permeability to a low molecular weight gadolinium marker a high molecular weight marker and a P-gp efflux transport substrate. Effects on the barrier were fully reversed after 60 min and were not attributable to changes in cerebral blood flow. Unfortunately there were no reports of improved therapeutic efficacy of any pharmacologically active agent. I must admit opening the BBB even temporarily does make me uneasy after all it is there for a purpose but I guess for intermittent dosing with for, an example, an oncology product needs must.

Finally a nice review of dendrimers for facilitating drug delivery to the CNS **6**. Emphasis of the discussion is particularly on targeting brain tumours. Also discussed are toxicity of dendrimers, biodistribution and transport mechanisms. There have been an enormous number of articles on nanoparticle delivery especially in the oncology area but space, time and life are all too short to review all the recent reports.

1. J. Niewoehner et al Neuron 2014, 81, 49-60
2. R. D. Bell and M. D. Ehlers Neuron 2014, 81, 1-3
3. Drug Discovery Today 9th Jan 2014
4. C. D. Cros et al Bioorg. Med. Chem. Lett., 2014, 24, 1373-1375, 2014
5. N. H. On et al. Mol. Pharmaceutics, Article ASAP DOI: 10.1021/mp400624v Publication Date (Web): February 19, 2014 Copyright © 2014, American Chemical Society

6. L. Xu, et al ACS Chem. Neurosci., 2014, 5 , 2–13

Back to top

P-gp - not just for the CNS

Removal of efflux liabilities from a series isn't always easy and is relevant to CNS and non-CNS intracellular targets **1**. A new predictive model may therefore be of some assistance built from 423 substrates, 399 non-substrates and 735 P-gp inhibitors. Non-substrates seemed to have lower molecular weights and higher solubility than substrates – frankly not very useful on its own but interesting was the discrimination of substrates and inhibitors. This suggested that the latter were more hydrophobic than substrates and further more substrates had an increased proportion of H-bond donors with particular spatial patterns. This is somewhat reminiscent of the work from Anna Seelig some years ago e.g. **2**.

The potential for drug-drug interactions with P-gp substrates/inhibitors has been a source of some debate. New work **3** using PET indicates that this effect can be small as in the case of verapamil (substrate) and cyclosporine (inhibitor) However this work also suggests that these interactions are more likely to be a concern where fractional contribution of P-gp to CNS distribution is high - ft > 0.97 e.g. with nelfinavir. The authors predicted that cyclosporin (at clinically relevant blood concentration of 1.5 μM) would increase nelfinavir human brain concentrations by 236%. Presumably a similar argument might apply for intracellular targets.

Finally a nice development of serial sampling of CSF from rat cisterna magna to determine free brain concentrations **4.** The technique avoids the problems of inter animal variance and saves on animal useage and was corroborated by comparing results with discrete CSF sampling and from whole brain. Of relevance to the previous discussion P-gp substrates that were assessed showed little increase in CSF concentrations in the presence or absence of the P-gp inhibitor elacradir.

1. D. Li et al Mol. Pharmaceutics, Article ASAP DOI: 10.1021/mp400450m Publication Date (Web): February 18, 2014 Copyright © 2014, American Chemical Society
2. A. Seelig and E. Landwojtowicz E. J. Pharm Sci 2000, 12, 31
3. P. Hsiao and J.D. Unadkat Mol. Pharmaceutics, 2014, 11, 436–444
4. T. Thanga Mariappan et al Mol. Pharmaceutics, 2014, 11, 477–485

Back to Top

More ligand efficiencies

Another review **1** on ligand efficiency metrics in drug discovery albeit with an impressive list of authors. Focus is particularly on various definitions of ligand and lipophilic ligand efficiencies alongside discussion of group efficiency and size independent ligand efficiency. There are some useful tabulations of changes in affinity required to maintain constant LE and LLE for different substituents. The authors analysed 59 optimisation programmes where LLE was used as a guide and highlighted that in the large majority of cases LLE was increased alongside increased target activity with most optimised compounds showing a reduction in cLogP – median increase in LLE of +1.96 with a p(activity) of +1.22. Interestingly the mean LE did not change during these optimisation programmes. Using a slightly different approach looking at the drug target level similar it was also concluded that increase in afifinity does not mean an increase in bulk physical properties. In a further analysis this time comparing ligand efficiencies of marketed drugs with other compounds binding to the target it is evident that for the majority of targets the marketed agent is amongst the most highly optimised with respect to LE and LLE. The notable exception is kinases where there tend to be large numbers of compounds in the literature with higher LE and LLE than the marketed exemplar. This may reflect the challenges of identifying compounds with appropriate selectivity profile for example. Finally looking at sets of compounds progressed to the clinic for the same target the authors point out that the compounds that have failed have been sitting in less optimal LLE/LE space than competitors that are still progressing. This really needs revisiting when clinical studies have completed.

All in all a useful read but the last word has to go to Hansch **2** and a quote from one of his (nigh on 30 year old) papers "*Without convincing evidence to the contrary, drugs should be made as hydrophilic as possible without loss of efficacy*"

1. A. L. Hopkins et al Nature Reviews Drug Discovery 2014, 13, 105–121 doi:10.1038/nrd4163

2. Hansch C., Bjorkroth J., Leo A., J. Pharm. Sci., 76, 663 (1987)

Back to top

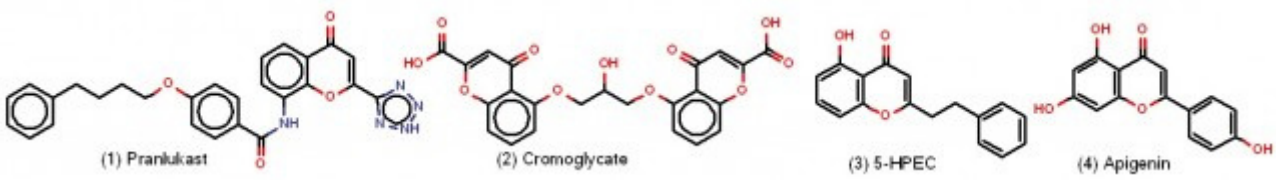
Chromones - are they all bad?

Chromones – including flavones and isoflavones have a bad reputation in screening as being frequented hitters and certainly some of the simpler natural products with a plethora of phenolic substituents and multiple activities do not look appealing. However looking at crystal structures of these low molecular weight compounds docked to various proteins it's not always clear that these phenols are critical for direct binding to the target protein nor is there any evidence of covalent binding. Several marketed drugs – pranlukast (1) and cromoglycate (2) as examples contain a decorated flavone so should we ignore all flavones simply because they are flavones accepting polyphenolics are a bit of a non-starter. The synthetic and medicinal chemistry of the chromone field has now been nicely reviewed **1** highlighting this motif as a privileged fragment we just need to work out how to optimise them by appropriate decoration. One thing that would be good would be to look at the protein structural motifs that are recognised by flavones to look for commonalities. One aspect of flavones that does need to be treated with some respect/caution is their ability to chelate metals **2** such as copper and ferric iron particularly those compounds such as apigenin with a 5-hydroxy substituent but as already mentioned you would probably be discarding such compouds for other reasons anyway

Interestingly a contemporaneous report **3** describes a chromone HPEC (3) as a non-basic, non-nitrogenous ligand for the 5HT2B receptor admittedly with the 5-hydroxy discussed above. Perhaps also timely is an article reviewing flavonoids targeting proteins involved in Alzheimer's disease **4**. Some of the mechanisms of flavonoid action discussed included their interaction with the phosphatidylinositol 3-kinase/Akt and MAP kinase pathways that regulate prosurvival transcription factors and gene expression. Other processes include the disruption of amyloid-β aggregation and changes in APP processing through modularion of secretases, and inhibiting CDK-5 and GSK-3β activation, preventing abnormal tau phosphorylation

1. A Gaspar et al, Chem. Rev., Article ASAP DOI: 10.1021/cr400265z, Publication Date (Web): February 21, 2014 Copyright © 2014, American Chemical Society
2. L. Mira et al Free Radic Res. 2002 Nov;36(11):1199-208.
3. D. A. Williams et al Bioorg. Med. Chem. Lett., 2014 Available online 19 February 2014 In Press, Accepted Manuscript
4. D. F. I. Baptista et al ACS Chem. Neurosci., 2014, 5, 83–92

Back to top



Druggable protein-protein interactions

From hot spots to hot segments PPI's continue to attract increasing interest – specific examples later. A timely review **1** takes a look at what makes a PPI druggable and concludes that PPI's with a dominant epitope (segment) is more likely to be druggable. Furthermore the authors argue that many PPI's fall into this category and that peptides based on the interacting segments can form an accessible starting point for inhibitors. I certainly agree with that latter point to the extent of provision of tool compounds, however, how easy it is to then convert such peptides into (preferably oral) drugs is another matter either by peptide modification or by conversion to a peptidomimetic. Certainly one of the areas of medicinal chemistry we are not so good at addressing is rapidly generating good peptidomimetics.

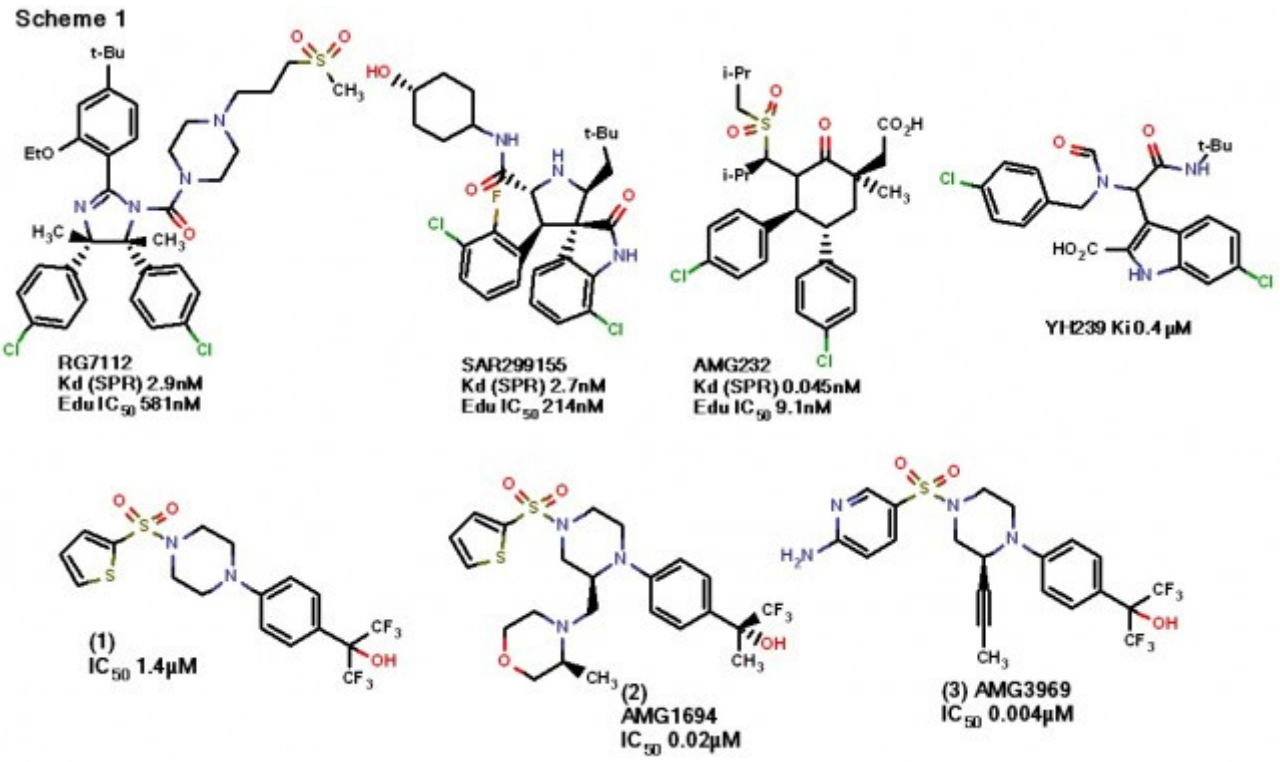
Yet more convenient timing therefore a review by Hamilton et al **2** looks at α-helix mimetics shown to be present in about two thirds of protein-protein interactions. Early helix mimetics focused on presenting suitable side chains on one face i.e. i, i=4, i+7 only but many helix mediated PPI's interact through two or three surfaces ie i, i+1, i+2, i+3, i+4 on the often amphoteric helix. Examples of helix mimetics are given but there are a number of downsides not least the atom

efficiency is low with many heavy atoms to generate template rather than direct interaction. Not considered perhaps as much as I would have thought were the helix mimetics which have evolved from the work on P53/MDM2 inhibitors with four clinical candidates on the go examples of which are in Scheme 1. The latest of these is reported by Amgen **3** which evolved from targeted optimisation of the N-substituent giving a substantial increase in target activity, cellular potency and in PK profile. The sulphone side chain accesses a new so called glycine shelf pocket that other inhibitors do not seem to reach (PDB 4OAS). Using a rather different template derive from virtual screening and an ester prodrug strategy the simple indole acid template (prepared using an Ugi synthesis) YH239 has been characterised (PDB 3TJ2) as showing activity comparable to the Nutlins in patient derived AML samples **4**. Just aking the cut for this newsletter a review **5** discussing different strategies to "drugging the P53 pathway" including MDM2 inhibitors that are attempting to activate or restore P53 action.

Finally while P53/MDM2 interaction have received intense scrutiny potent ligands to inhibit other PPI's are also continuing to emerge. Not least inhibitors of the interaction between glucokinase and glucokinase regulatory protein that bind to the GKRP via a previously unrecognised but well-defined binding pocket distinct from the sugar binding region - see PDB 4MSU and 4LY9. From an HTS hit (1) target initial optimisation led to an increase in Alpha screen target activity of >100 fold and cell activity by about 50 fold with AMG1694 (2) although rat PK was poor **6**. However, addressing metabolism by removing the morphline, stabilising the thiophene and methyl to trifluoromethyl conversion gave AMG3969 (3) with comparable *in vitro* profile but a dramatically improved rodent PK profile and a reduced heavy atom count **7**. AMG3969 showed activity in a mouse model of diabetes with no evidence of hypoglycaemia.

1. N. London et al. Curr. Opin. Cell Biology 2013, 17, 952
2. M. K. Jayatunga et al Bioorg. Med. Chem. Lett., 2014, 24, 717
3. D. Sun et al J. Med. Chem., Article ASAP, DOI: 10.1021/jm401753e Publication Date (Web): February 05, 2014 Copyright © 2014, American Chemical Society
4. Y. Huang, et al ACS Chem. Biol., Article ASAP DOI: 10.1021/cb400728e Publication Date (Web): January 17, 2014 Copyright © 2014, American Chemical Society
5. K. K. Hoe et al Nat. Rev. Drug. Disc. 2014, 13, 217
6. K.S. Ashton, et al J. Med. Chem., 2014, 57, 309
7. D. J. St. Jean, et al J. Med. Chem., 2014, 57, 325

Back to top



5. Chemistry

Non Friedel-Crafts aryl methyl ketones

A convenient green(ish) approach to aryl methyl ketones **1** using CsF activation of acylsilanes with Pd mediated coupling to (hetero)aryl halides has been reported Scheme 1. Yields are reported to be good - often >90% - and allows synthessi of non-Friedel Crafts regioisomers.

Also reported **2** was synthesis of unsymmetrical diaryl ketones from an appropriate benzoyl chloride via a palladium mediated acylindium coupling to an aryl halide Scheme 2.

1. S. D. Ramgren and N. K. Garg Org. Lett., 2014, 16, 824–827
2. D. Lee et al Org. Lett. 2014, 16, 1144

Back to Top

6. Conferences

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

- SME Bioinformatics Forum 6th, 7th March, EBI, Hinxton
- ELRIG Telford Research and Innovation into Cancer
- Reducing Attrition through Early Assessment of Drug Safety SMR NHLI South Kensington London, 13th March 2014
- 25th Symposium on Medicinal Chemistry in Eastern England 24th April 2014

Meetings Attended

No meetings attended over the past few weeks. The report on the SMR December meeting "From Targets to candidates: Emerging Strategies in Drug Discovery" submitted to Drugs of the Future has been accepted.

Back to top

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.

ACS Editors choice

Hats of to the ACS again for another initiative to increase access to literature. Perhaps a small step but exposing the interested reaser to an eclectic range of topics from the ACS journal stable with free public access to new research of importance to the global community—one article every day.

STITCH

STITCH is a resource to explore known and predicted interactions of chemicals and proteins. Chemicals are linked to other chemicals and proteins by evidence derived from experiments, databases and the literature. STITCH contains interactions for between 300,000 small molecules and 2.6 million proteins from 1133 organisms.

STITCH is currently live as version 3.1 with version 4 in beta test

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

Back to top

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 services.

Back to top