IN THE PIPELINE

Derek Lowe's commentary on drug discovery and the pharma industry. An editorially independent blog from the publishers of *Science Translational Medicine*. All content is Derek's own, and he does not in any way speak for his employer.

By Derek Lowe

DRUG DEVELOPMENT

The Open Source Malaria Project, So Far

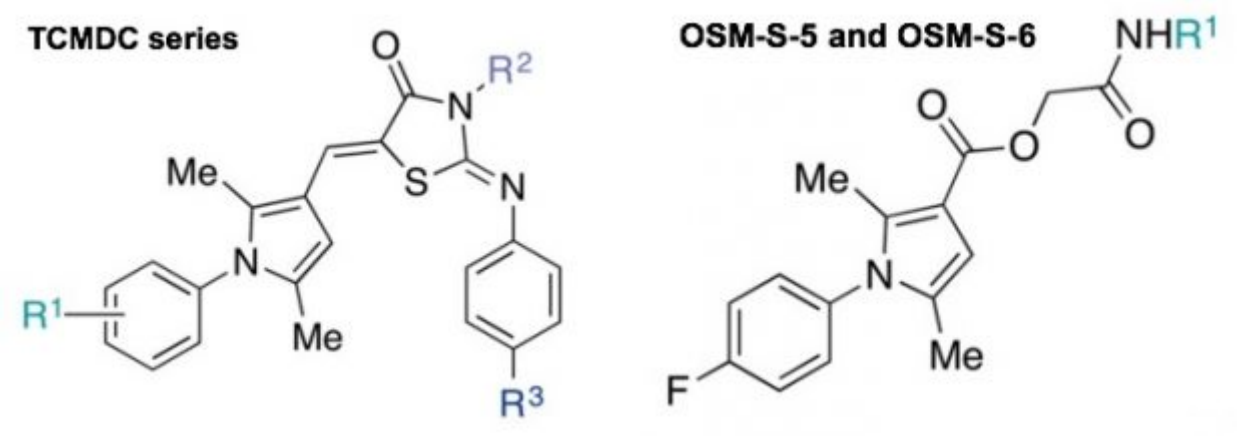
By Derek Lowe | 16 September, 2016

The Open Source Malaria (**OSM**) project has **a paper out** (open-access, fittingly) in *ACS Central Science*, and it's an interesting read. This is the effort from Mat Todd at Sydney and many, many others around the world to build on the malaria phenotypic screening results **released** in 2010 (and **prioritized** in 2011) by GSK. They've been following a true open-source model – every part of the project is out there for people to see, and for anyone to join in with suggestions. That's always going to be trickier to do than it is in the software world, where the amount of equipment needed is far lower and there are correspondingly few barriers to entry, but this work shows that (under favorable conditions) it can be done. There's a **lot** of **rot** talked about open-source drug discovery, but this is one of the closest examples to the open-source-coding world that I'm aware of.

The paper's actually a good read, and I think it's the open-source nature of the work that does it. More than almost any paper I've ever read, it goes into the ins and outs of the work on the various lead series. It's actually a very accurate look into how these things work – synthetic difficulties, re-routing, structure-activity surprises, arguments about which structures are worth moving on

with, tradeoffs at every turn. This is exactly how medicinal chemistry works, and in the future I'll be recommending this paper to show people a blow-by-blow account of it.

In the end, the arylpyrrole series being investigated here looks like it will be put to one side in favor of pursuing other leads. The OSM-S-5 and OSM-S-6 compounds shown (5 has an H at R1, 6 has a heterocycle) were hits from the GSK work. The problem with them is that ester functionality buried in the middle of the structure, which was expected to be labile (experiments to determine blood levels in mice and followup mouse plasma stability assays were consistent with this worry). Unfortunately, changing that to an amide, any sort of amide, completely killed the biological activity. While the team was working on these, they were also looking at the structurally related TCMDC hits, also from the GSK data set. These had more robust SAR (albeit with potency coming along with greater lipophilicity), but the team seems to have had quite a debate about whether these structures had a future or not. They are indeed getting into PAINs territory, and were also filtered out by the ALARM NMR assay, which is food for thought. In the end, since the compounds were heading into even more unfavorable property space along with these potential liabilities, they were deprioritized.



A range of other arylpyrrole structures were then investigated (see the paper for details). The team had a big meeting online, with a prioritized "hit list" of desired structures emerging from it, and in the end about half of these got made (or purchased, in a few cases, when something was available). As the paper shows, though, none of the modifications were tolerated. One series was unstable on storage, and both it and the other modifications were much less active (or completely dead) in the assays. There are, though, some promising ideas that haven't been investigated yet, such as replacement of that ester with a suitable oxadiazole. That's an isosteric substitution (along with some other heterocycles) that has worked in many previous med-chem efforts, and it's probably the outstanding thing on the list. And since this is an open-source effort, anyone who wants to try to make it (or any other analog in this area) is welcome to do so.

> *One of the unique features of this project, the open source research method, ensures that the unexplored lines of inquiry remain open alongside the attendant data posted online that makes it straightforward for others to resume any portion of the research project as fully fledged participants, with access to both positive and negative data, details of all procedures as they were carried out (to aid reproducibility), and anecdotal insight into project loose ends that are easy to explore. The machine-*

> *readability of the present project (for example the use of cheminformatic strings in the online electronic lab notebook) permits an unusually straightforward link between a high throughput screening result in a public database and a "live" research project that has investigated that compound.*

The original GSK assay was phenotypic, so it's still an open question how any of these compounds might work. The team has done a number of assays against different stages of the malaria parasite to try to narrow things down, but the target (or targets) of these compounds remains unknown. That brings up the traditional phenotypic assay project decision – press on with what you have, in the knowledge that an *in vivo* assay will probably wipe out most of your compounds (but what's left may be gold), and you may well stumble around a lot, or take the time to identify the target and run screens against it. In that case, you may find yourself working on things that will be harder to develop *in vivo* (although not necessarily), but you're also working with a lot more tools to try to get a compound series going. Neither of these is a slam dunk, and if you have the resources, there's no reason not to try going on with both, if possible, since they don't rule each other out. The team has done some work into mechanisms of action, but there's a lot more to do if something more interesting comes up.

This, then, ends up being a pretty typical medicinal chemistry project – if you didn't know that it was being done by an assortment of different people all over the world, you wouldn't be able to guess it. I look forward to seeing where things go from here, and what tools the project puts together to keep things moving.

27 comments on "The Open Source Malaria Project, So Far"

PotStirrer says:
16 September, 2016 at 9:20 am

I wonder if they checked to see whether those esters were acylating anything. I suppose that would be potentially hard to do when working with a phenotypic assay. Those OSM compounds remind me of some hits we got in an enzymatic HTS that turned out to be acylating the active site nucleophile in the enzyme.

Nick K says:
19 September, 2016 at 9:25 am

My first thought was also that the esters were acylating an active site. That would certainly explain the SAR intolerance for changes as minor as a methyl substitution.

Imaging guy says:
16 September, 2016 at 9:22 am

About a deuterated drug from Teva getting FDA approval in Bloomberg

http://www.bloomberg.com/news/articles/2016-09-16/a-decades-old-drug-technology-finally-nears-its-big-breakthrough

Annon says:
16 September, 2016 at 9:33 am

What did you think about the malaria paper in Nature last week?

Phil says:
16 September, 2016 at 1:34 pm

You mean the Schreiber/Eisai one? Definitely not a flat structure….

http://www.nature.com/nature/journal/vaap/ncurrent/full/nature19804.html

Anon says:
16 September, 2016 at 9:38 am

Welcome to the world of flat sticky-stacky aromatics with little capacity to make specific hydrogen bonding interactions. Do things like this really make any good drugs?

A Nonny Mouse says:
16 September, 2016 at 10:09 am

http://www.mmv.org/research-development/interactive-rd-portfolio

See DSM625. We didn't work on this one, but did development work on several of the others.

A Nonny Mouse says:
16 September, 2016 at 10:12 am

Oops. DSM 265

mad chemist says:
16 September, 2016 at 2:23 pm

Wow!!! As someone who did part of his PhD work on -SF5 chemistry, I'm really really excited to see that this is taking off in medicinal chemistry!

A Nonny Mouse says:
18 September, 2016 at 4:48 am

A friend was involved in a cancer start-up where they were substituting Me for CF3 and SF5. They have now run out of money (would not give the VCs 90% of the company for

minimal funding- this is the UK), but I am told that a SF5 analogue of a known drug is about 50 x more potent.

Anon says:
19 September, 2016 at 8:33 am

Silly question, but one has to ask: Would they have been better off having 10% of something than 100% of nothing?

Anon says:
16 September, 2016 at 10:18 am

Looks like DSM 265 isn't quite as flat, but still, that's an ugly-looking drug. 😉

A Nonny Mouse says:
16 September, 2016 at 11:03 am

Certainly sticky with that SF5!

Anon says:
16 September, 2016 at 11:08 am

I was just thinking that's the "non-stick teflon pan" end! 🙂

A Nonny Mouse says:
18 September, 2016 at 4:45 am

The problem with things like that is plasma protein binding; once, in my med chem days, I switched a "F" to "CF3". Activity was great but all in vivo activity was lost as the molecule stuck like the provebial with plasma protein binding and was not released.

Canman says:
16 September, 2016 at 12:56 pm

Haven't looked at the paper, but I sure hope they have some other structural classes. Never liked the arylpyrroles (can someone say protecting group), and combined with that other awful heterocycle hanging off from it… just step away.

Barry says:
16 September, 2016 at 1:09 pm

there's a recent claim that malaria can be cured with one dose of a Phe(t)RNA synthase blocker. Why that should be -cidal rather than -static is obscure to me

Kriggy says:
16 September, 2016 at 1:28 pm

I wonder if anyone knows their facebook page they were talking about in the paper?

Anon says:
16 September, 2016 at 3:11 pm

Great efforts and leadership by Matt Todd @sydney.

Just curious as to what would be aftermath, if this project were to lead to a drug whose mechanism of action/target is new that can replace the existing drugs. Could a drug company take it from there and start producing without patenting it for the needy countries at low cost. Now that this data and structures or in public domain and have not been patented, could any one interested in developing them further patent the series so that not only they get the IP. Would some non-profit take it up instead? probably it's out on MVV website…just counting on the wisdom of this blog leaders

HTSguy says:
16 September, 2016 at 6:52 pm

The multimillion dollar question is how you pay for preclinical toxicology testing (and the associated GMP compound production, etc) and, assuming it passes that, clinical trials in the absence of a patent. That isn't going to be done with someone's spare change (unless their last name is Gates).

Chris says:
18 September, 2016 at 7:28 am

A good question. It may be funded by a combination of charities, WHO, DNDI, MMV etc. Or countries were malaria is a significant problem might see it as a reasonable investment for their health budget.

sgcox says:
16 September, 2016 at 3:46 pm

Oh yes, arylpyrrols…
One need go no farther then this blog to see what might actually go on..
http://blogs.sciencemag.org/pipeline/archives/2015/04/08/colorful_compounds_strike_again
Not sure why the paper gets an attention here ?

kriggy says:
17 September, 2016 at 11:37 am

Probably because it is open source effort where lots of ppl from different places are collaborating

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Josh Kangas says:
16 September, 2016 at 4:51 pm

I have often wondered how truly unique the challenges faced in developing these lead series were actually relative to other lead series. Because very few studies are open source we will probably never have a good estimate of overlap, but I suspect it is probably higher than most people would want to believe (i.e. most projects aren't as truly novel as researchers would think even when working on "novel" targets). I don't necessarily blame anyone for viewing their research as more novel than it actually is though as there are so many journals, conferences, databases, etc. available that fully digesting those is impossible.

That being said, I am very excited to see open source efforts like this involving making data publicly available very quickly.

Looking forward, for these types of efforts to be truly successful and transformative, there need to be many collaborators with an interest in the collaborative projects, which may be a very tall order for some projects. However, if researchers were to add their data to some kind of central repository, automated systems could be designed to search for patterns between projects where humans have no interest or time to look when the probability of finding a link is very small. These newly discovered relationships between projects could then be leveraged for the greater good.

At my company, we have been working on an approach that uses this idea and we have shown it to be quite useful in reducing experimental effort required for various tasks.

Christopher Southan says:
17 September, 2016 at 1:19 pm

Matt Todd's backstory blogpost https://intermolecular.wordpress.com/2016/09/14/open-source-malarias-first-paper/

and an addendum on the PubChem mappings
https://cdsouthan.blogspot.se/2016/09/series-1-antimalarials-publication.html

Pingback: For $20, high school kids develop life-saving drug | NewsCut | Minnesota Public Radio News

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JG4 says:
16 December, 2016 at 5:10 pm

stumbled into this and thought it relevant enough to post. there is a lot more open-source that could be applied to problems around the world

http://seedmagazine.com/content/article/mosquito_noses_and_baby_brains/

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In order to engineer these souped-up flies, researchers in John Carlson's lab first inserted mosquito genes into mutant 'empty neuron' fruit flies. Next they tested some 5,500 odorant-receptor combinations. Most mosquito receptors, they found, are "generalists," reacting to a number of different odors—chemical components of human sweat, animal urine, and fruit, among others. A few receptors, however, are "specialists," responding to a single or very small number of odors. Among these, they found 27 receptors that spiked when exposed to indole, a key ingredient of human sweat. Screening for compounds that interact with these receptors is now underway: Odors that excite the receptors could help lure mosquitoes into traps, while compounds that block their activity could mask the presence of humans.

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