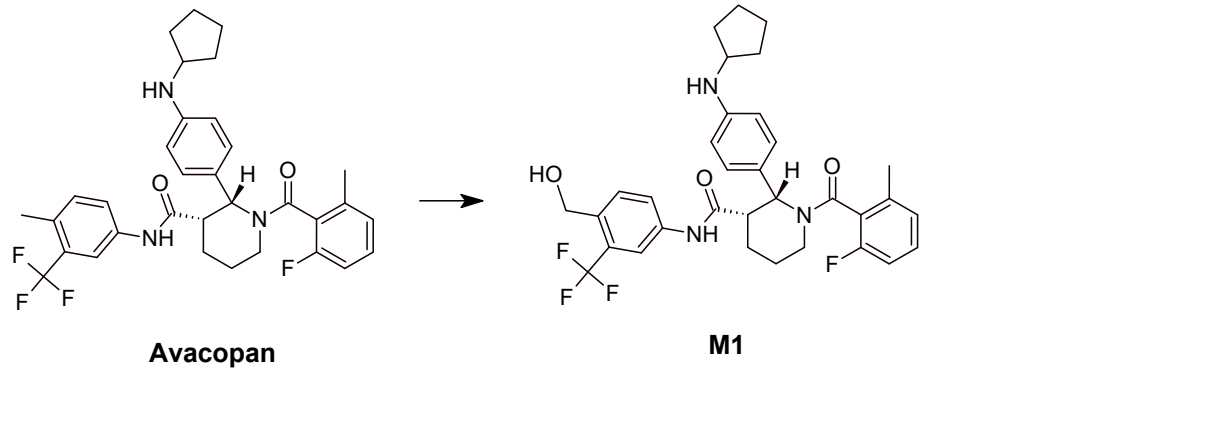
Comments on Drug Structures, June 2026

By ALF CLAESSON (E-mail: alfeaclaesson@gmail.com. Comments most welcome!)

Approved medications can sometimes cause unexpected or more severe side effects than those observed in clinical trials. If these safety risks are significant, regulatory bodies must intervene.

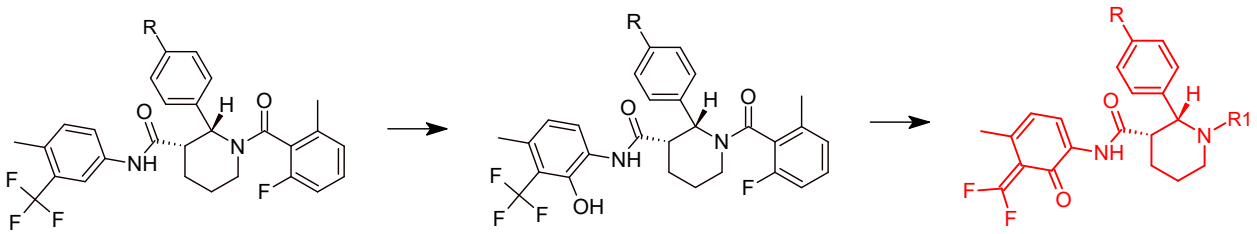
The case of adverse effects of **avacopan**, an orphan drug for treating rare, severe, and active forms of ANCA-associated vasculitis, is relevant for the current blog since the side-effects likely originate from reactive metabolites (RM). In addition, it is a high-dose drug with a daily dose of 1600mg that increases the risks. FDA's CDER proposed last April that the medicine TAVNEOS, containing avacopan, should be voluntarily withdrawn because of serious side-effects and untrue statements of material facts. So far (June 12), this withdrawal has not taken place.

It is often difficult to spot a clear-cut offending substructure (RM precursor) when looking at a drug structure. Not so in this case since the major metabolite **M1**, which is the methyl-hydroxylated parent, should be an unstable compound that can give rise to a reactive methide. This is a well-known RM that comes in many different forms, see e.g. a Perspective in JMC22. Obviously, this constitutes a close analogy with **M2** of **pazopanib,** dosed at 800 mg/day, which has been shown to generate a methide (Xen19).



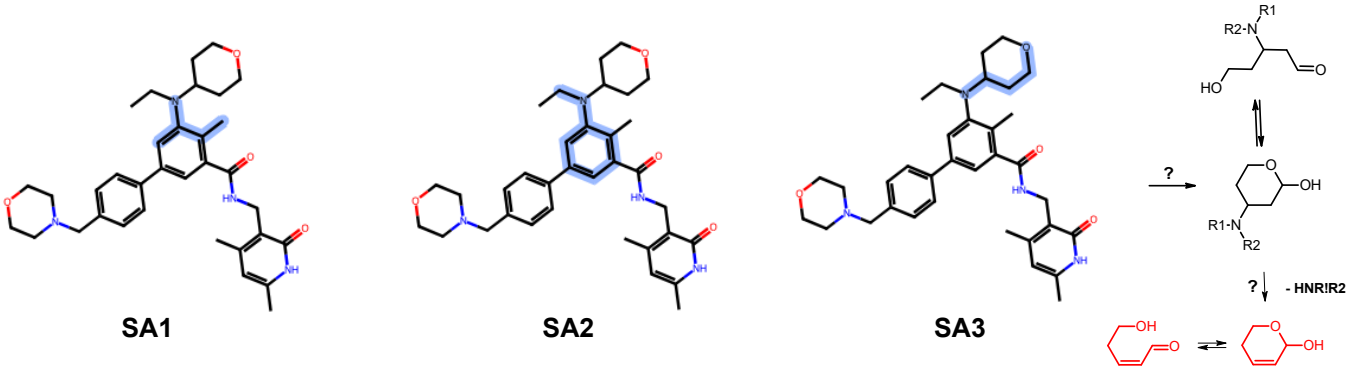
For both drugs there are more possibilities for forming other RMs and pazopanib gives rise to more than three cysteine-containing adducts. Both drug structures contain anilines, which are well-known to be activated towards epoxide→ phenol formation. In the case of avacopan, this might

result in the following sequence of reactions; a *para* hydroxylation would give the same overall result. Regarding substructures giving rise to methides from phenols, I discussed several cases in this blog post.



Last May FDA posted this message: "FDA Alerts Health Care Providers and Patients about Increased Risk of New Blood Cancers with TAZVERIK (tazemetostat) Use; Sponsor to Voluntarily Withdraw Product from Market."

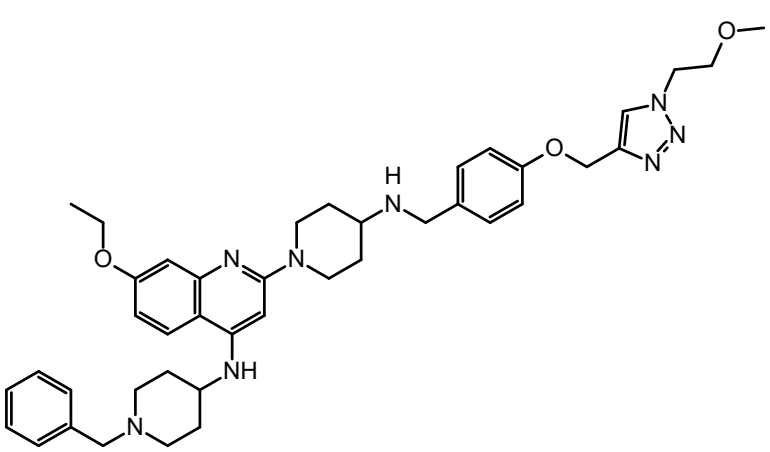
The structure of **tazemetostat** is of a kind that presents multiple possibilities for RM formation but three draw extra attention. Below are shown these sites (**SA1**-**SA3**), identified by SpotRM, that by oxidation could generate RMs; they are all centered around the (aryl)amine part.



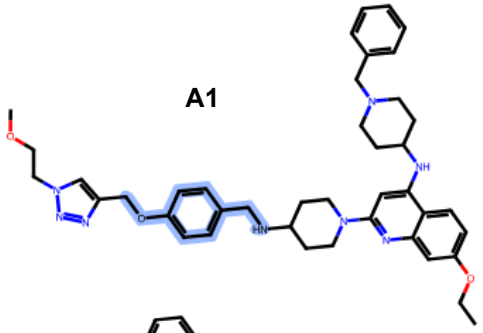
SA1 could give rise to a reactive benzylic alcohol and if the amine is dealkylated, a step shown to occur (CPDD25), the alcohol can give rise to a quinone imine methide just as avacopan can. The alert **SA2** warns for a normally facile hydroxylation of a substituted aniline, which would be bound to form a quinone imine (or iminium ion). This does not seem to have been shown to occur, which is not unexpected considering the many sites of metabolism in this drug, making identification of all metabolites a nearly impossible task. Instead, what was shown on the aniline was double N-dealkylation thus setting the aniline nitrogen free, this certainly warranting an RM problem. The alert **SA3** appeared rather surprisingly since it is not often seen when running SpotRM. The question of probability of this occurring and causing adduct formation will not be easily resolved.

Any new issue of Jornal of Medicinal Chemistry regularly holds at least 100 pages full of new biologically active structures. Here, it's easy to spot compounds that based on previous experience of a certain substructure should form RMs. Sometimes the published structures have ameliorating features, e.g. low lipophilicity or soft spots for metabolism that make prediction of RM formation less certain but in many cases, one can feel confident about one's expert view. Unfortunately, answers to a very large number of such cases remain in the world of hypotheses. I will highlight one recent example of a structure, **FRC-303**, which has a few features slightly overlapping those

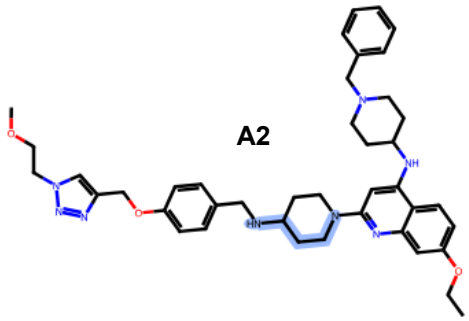
of the mentioned tazemetostat. FRC-303 is a CHD1 chromodomain inhibitor, a potential target in prostate cancer. The authors clearly state that this is a lead compound aimed for optimization.



FRC-303

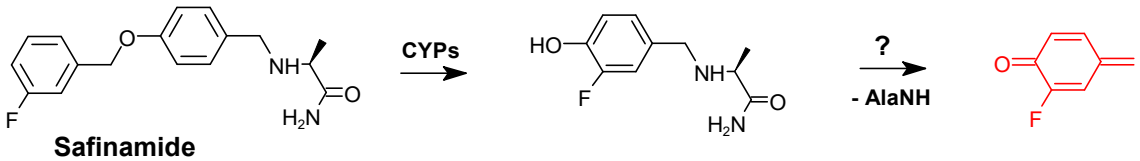


A1



A2

Two of the problematic substructures/alerts are marked on the structure. The alert **A1** has been discussed in full here in my blog. It goes back to the question: how stable are phenols with a *para* benzylic amine, such as e.g. released by debenzylation of **safinamide**? As mentioned in the earlier post, the discovery of this issue goes back to 2006 when a phenol derived from **phencyclidine** was found to decompose in this way. In this case, the ease of elimination of amine from the intermediate phenol ($t_{1/2}$ 6 min) can be explained by low activation energy caused by the crowded amine.



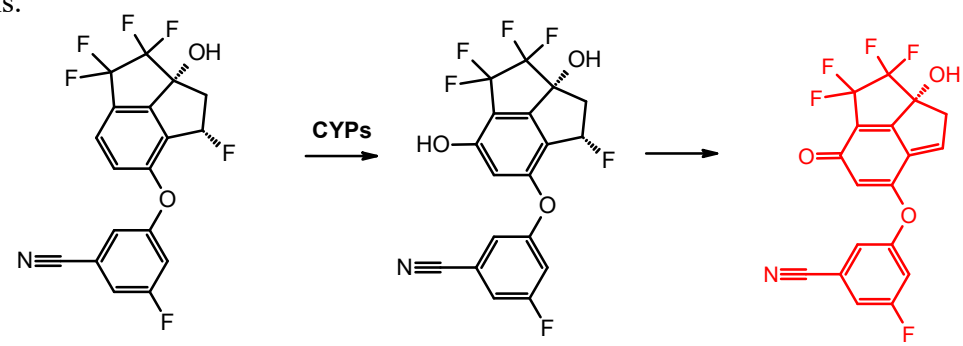
Safinamide

Phencyclidine

The other alert, **A2**, has been discussed too, in a related blog post on formation of conjugated keto compounds (*cf*. tazemostat **SA3** above). The number of verified examples in the literature is vanishingly small, making it difficult to assess potential RM hazard from this type of substructure.

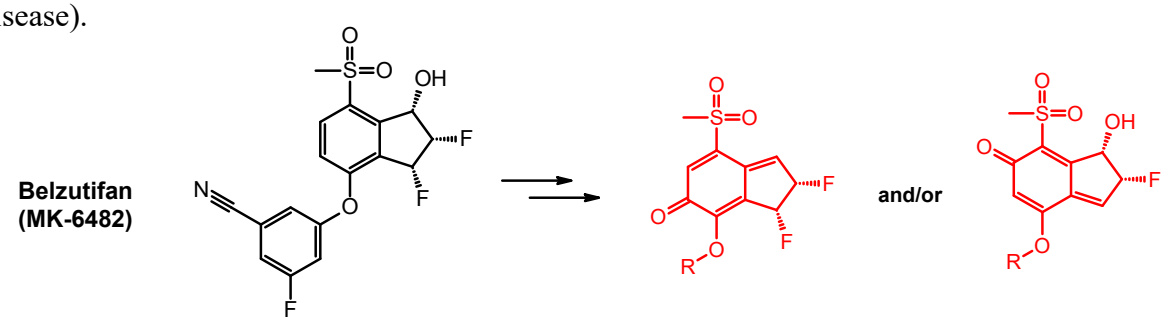
A fourth compound from the recent literature presents a very different structure where potential RM formation hinges on initiating aromatic hydroxylation(s). **NKT2152** (**imdatifan**) is a HIF-2α inhibitor with potential against brain metastases (MCL26). It has an unusual structure by containing six fluorine atoms.

Imdatifan (NKT-2152)



If this structure is hydroxylated in the position shown in the scheme, it will certainly generate a quinone methide by elimination of HF and if hydroxylation occurs in the *para* position to the benzylic alcohol, it will give rise to another methide by elimination of water (not shown but see next scheme).

The aim of the project according to the authors was to make an analog of the drug **belzutifan** (**MK-6482**), which was approved by FDA in 2021 (dosed at 120 mg/day for von Hippel-Lindau disease).



This drug has the same potential liability as imdatifan but in neither case has this hypothesis been substantiated through reports. However, belzutifan has a boxed warning that it can cause embryo-fetal harm, which might possibly be linked to RM formation; drug induced hepatotoxicity has not been reported.