A Look at Six New Drug Candidates 2026

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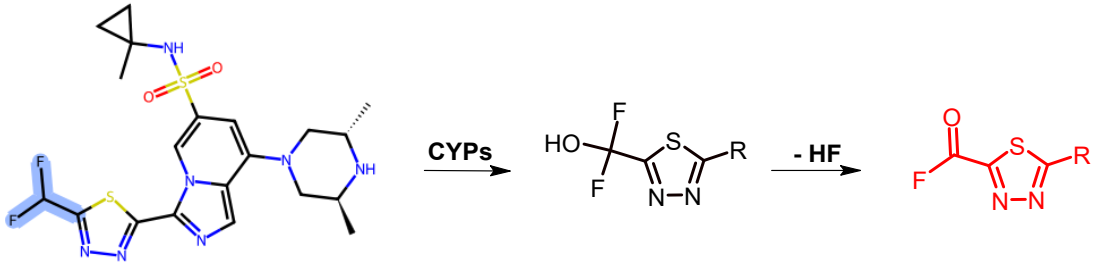
Six new candidate drugs from the recent Atlanta ACS spring meeting were highlighted in C&EN, March 2026. Being extremely interested in mechanisms of formation of reactive metabolites (RM) from xenobiotics, I naturally viewed these structures from that perspective and will comment on them, plus a little more, in this blog.

I started by running these structures through our screening machine SpotRM (see also CRT24), which will detect many substructures that constitute structural alerts for RMs (SARM). All the compounds have a hit somewhere in the molecule that has to be assessed in some way but most alerts found are rather trivial and likely don't affect safety (that is for the stated anticancer indication). Starting with the compound that has the most conspicuous feature: **FORX-428**, a poly(adenosine diphosphate ribose) glycohydrolase (PARG) inhibitor for cancer, has a difluoromethyl group on an aromatic. This group is unusual and is nonexistent among approved drugs but is found in 10 investigational drugs (DrugBank April 2026). Among these are the

Scheme 1

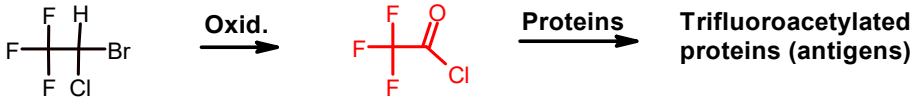


FORX-428

BACE-1 inhibitors **AZD3839**, which was made at AstraZeneca while I was still working there (but not involved in Alzheimer's research), and **elenbecestat**.

Why is it a remarkable group? Scheme 1 explains it all since an acyl fluoride that is likely to be formed to some degree is an acylating agent, which is popular in amide/peptide synthesis. Among the first examples of this type of bioactivation was the anesthetic **halothane** (Scheme2) with the

Scheme 2

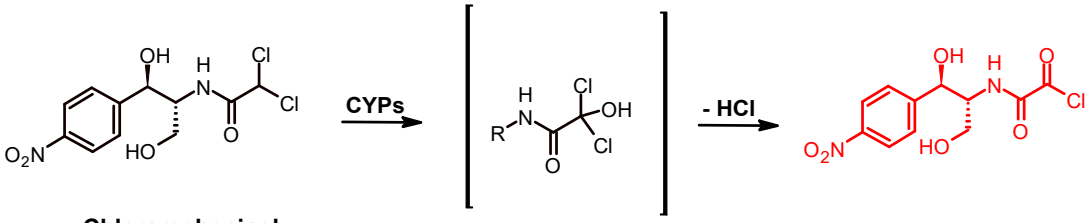


Halothane

problem identified around 1991 (see general review on RMs in CDM05). But even earlier, the antibiotic **chloramphenicol** (Scheme 3) was shown to undergo the same activation steps

(Miller, Halpert 1986). For more examples, see a large review on metabolism of organofluoro compounds by Johnson et al. JMC20.

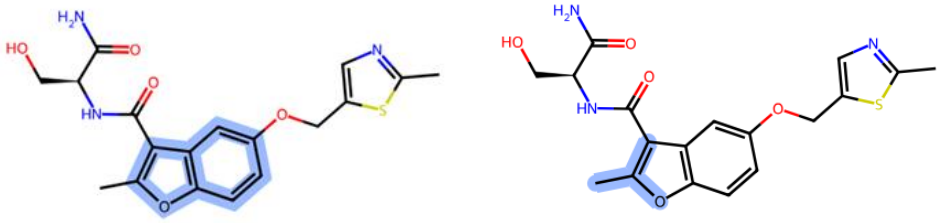
Scheme 3



Chloramphenicol

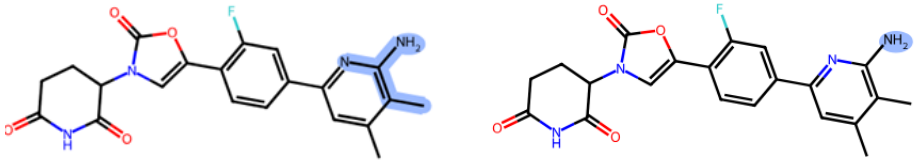
These days, most drugs entering the clinic seem to be anticancer agents and 5 of 6 drug candidates follow this trend. Therefore, it's nice to highlight the outlier, benzofuran **BHV-2100**, a TRPM3 antagonist that is intended for treatment of neuropathic pain. Here, one can note two alerts located on the benzofuran part where a methyl on the electron rich furan is a general one for five-membered heterocycles and the benzofuran readily forms quinones (or a methide including the methyl group) by initial hydroxylation.

BHV-2100

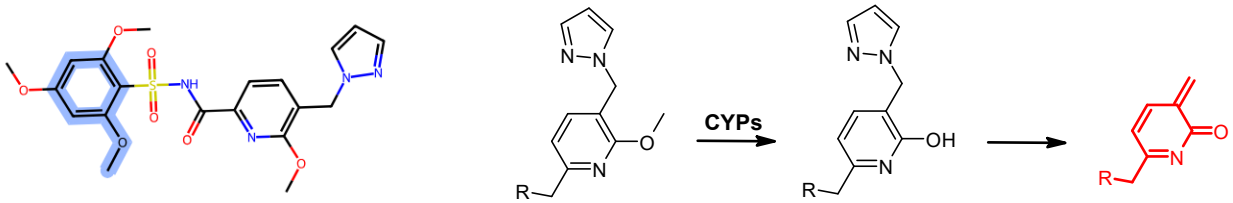


Returning to the anticancer agents, **BMS-986482** is a an Ikaros family zinc finger 1–4 (IKZF1–4) antagonist that is not weighed down by too many SARMS. An *ortho* methyl to an amino group on an aromatic ring might be oxidized to a very labile benzylic alcohol (alkyls on aromatics were discussed in JMC22). An aromatic primary amine might give rise to RM problems even on a pyridine although the field is extremely difficult to discuss toxicologically since relevant cases are mostly lacking.

BMS-986482



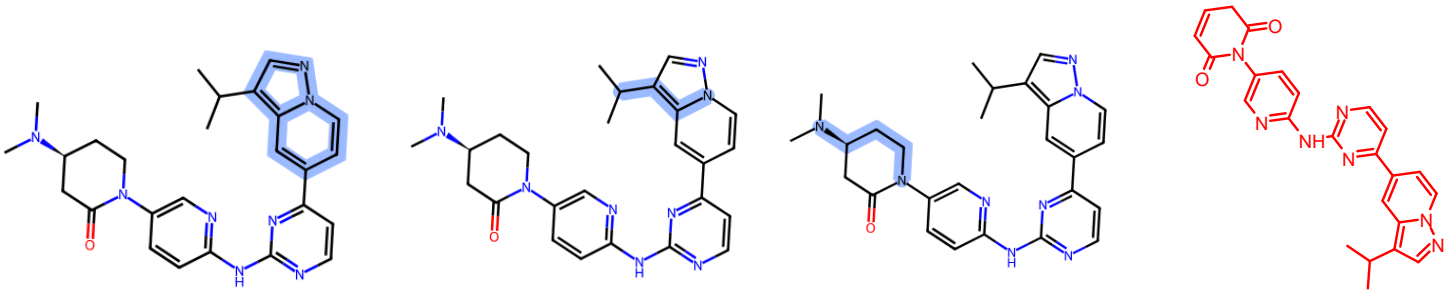
OP-3136 is a histone lysine acetyl transferase 6 (KAT6) inhibitor that has only one alert in SpotRM. This just advises watching out for the electron rich benzene, which will easily form quinoid species by initial phenol formation (via O-dealkylations and hydroxylations).



OP-3136

Regarding the pyridine part, had 1-pyrazolyl been a better leaving group such as a phenol or alkylamino group, the above right-hand scheme might have been applicable. Now, the pyrazole with a pK_a of 14.2 is probably staying on to the rest of the molecule after phenol/pyridone formation.

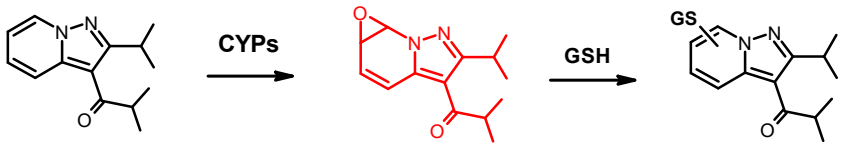
The CDK 4/2 inhibitor **GDC-4198** has a few alerts worth commenting on: its *pyrazolo[1,5-a]pyridine* is also present in the drug **ibudilast** (Scheme 4) that has been shown to form a reactive



GDC-4198 with three alerts **RM from the piperidine**

epoxide leading to glutathione adducts on this ring (ArchTox25). The other mark on this ring in GDC-4198 includes the alkyl group and is an alert for formation of a reactive benzylic alcohol, often observed in 3-alkylindoles (see JMC22 for a perspective on this). The third alert warns for alpha-N oxidation and elimination of the dimethylamino group, a path for RM formation that was discussed at length in a previous blog post. An important question here: how reactive is the unsaturated imide?

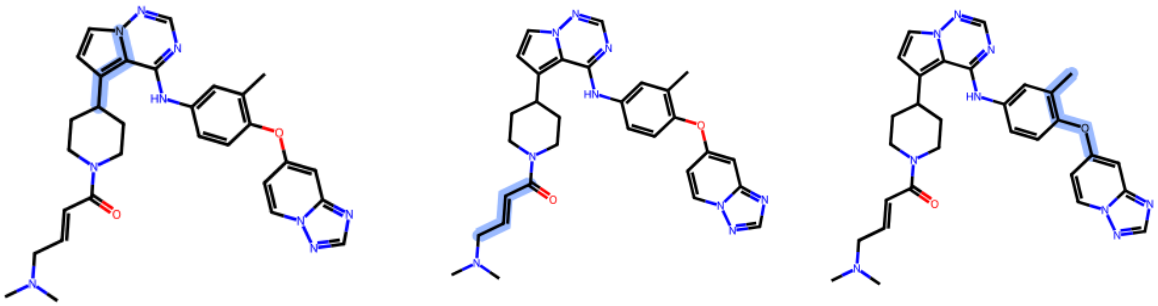
Scheme 4



Ibudilast

The HER2 receptor antagonist **IAM1363** has three alerts identified by SpotRM. The one involving the methyl group on benzene should be understood as risk of formation of a labile benzylic alcohol or a P450 mechanism based irreversible inhibition.

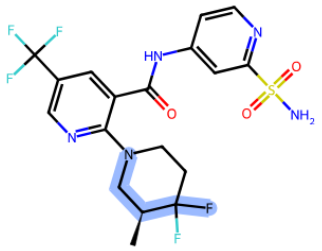
IAM1363



IAM363 is already chemically reactive since it is an irreversible kinase inhibitor through its 4-aminocrotonamide warhead but what SpotRM catches here is not this intrinsic reactivity but a

group with allylic hydrogens, which can easily form an allylic alcohol that in turn can form a reactive sulfate or an unsaturated ketone. Another interesting feature of this drug is the presence of two fused nitrogen rings, *[1,2,4]triazolo[1,5-a]pyridine* and *pyrrolo[2,1-f][1,2,4]triazin*. The first mentioned ring has the theoretical potential to form an epoxide in analogy with what was discussed regarding GDC-4198, which contains a very similar *pyrazolo[1,5-a]pyridine* that has demonstrated sensitivity to epoxidation (ArchTox25). This is not something that has been reported in the literature and so far, we have not made a SARM in SpotRM for *[1,2,4]triazolo[1,5-a]pyridine*.

Finally, a recently published drug will be added to the six reported candidate drugs. The potential development candidate **MK-5661** represents a particularly relevant example of the alerts for elimination reactions that were discussed in a previous blog post; it was published in MCL26. The alert as marked warns of potential alpha-N oxidation and elimination of HF generating a very reactive unsaturated aldehyde (the automatically generated mark had been better placed along the other stretch of the piperidine).



MK-5661, a new NaV1.8 inhibitor

Whether this potential liability will have any relevance for metabolism in humans remains to be seen but one can note that the compound should have good prospects to evade bioactivation: XLogP3-AA is 2.5 indicating intermediate lipophilicity and clearance data in three species seem promising. For a comparison, one can note that the DPP-4 inhibitor **gosogliptin**, also having the current SARM, was not metabolically activated due to its physicochemical properties, see last page for a clarifying excerpt from a SpotRM monograph.

Discussion, summary. The new compounds presented at the Atlanta meeting should all have undergone the cumbersome process of weighing RM risks against the many other design parameters impacting the final selection. However, since most compounds are aimed at the cancer indication, one might guess that these risks have played no large role. The outcome is still acceptable considering the many uncertainties characterizing substructures that have been designated as RM alerts. These involve, e.g. the question of potential activation when considering the other metabolic sites in the molecules and, if activated, will the RM likely involve covalently with proteins at a problematic rate?

Possibly excepting the difluoromethyl group on aryl, most of the SARMs identified by SpotRM are difficult to kick out as showstoppers. The added Merck compound **MK-5661** represents a special case where a potential RM problem is likely to already have been internally identified.

Structure class: **3-fluoropyrrolidines (and related)**

Daily dose: **not relevant**

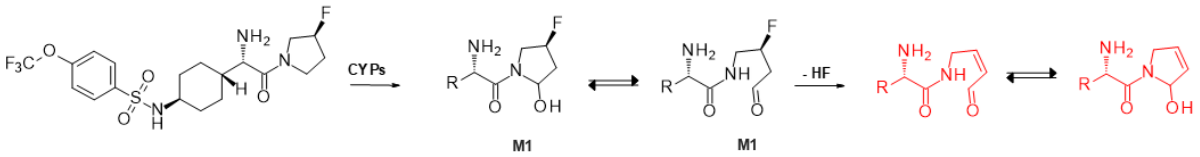
Type of ADR: **not relevant; preclinical compounds**

Also mentioned below: **difluorinated azepanes, MK-8768, UK-290795, TAK-994, amcenestrant,** and **haloperidol.**

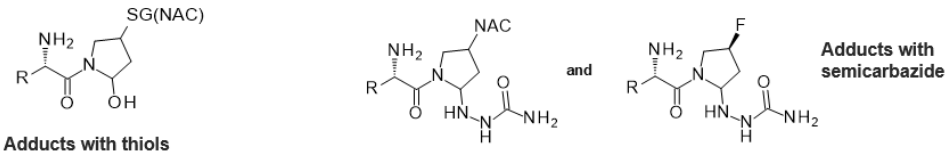
Mechanistic experiments

Two dipeptidyl peptidase IV (DPP-4) inhibitors studied by Merck researchers were found to bind irreversibly to rat liver microsomes in a time- and NADPH-dependent manner (Xu *et al*. DMD05). The binding was attenuated by the addition of glutathione (GSH) or N-acetylcysteine to the incubation indicating that RMs were formed. Since the amounts of bound tritiated drug (100 to 200 pmol equiv/mg protein at 1 h) were deemed to be above an acceptable risk level for the intended diabetes indication, development was stopped.

A mechanism of activation involving the 3-fluoropyrrolidine part was suggested: oxidation at the 5-carbon of the pyrrolidine gives a hydroxy compound, **M1** (a substituted methylol that in itself is alkylating via iminium ion formation), which is in equilibrium with the ring-opened aldehyde (see scheme below, for one of the compounds studied). A reactive, unsaturated aldehyde is formed by elimination of HF.



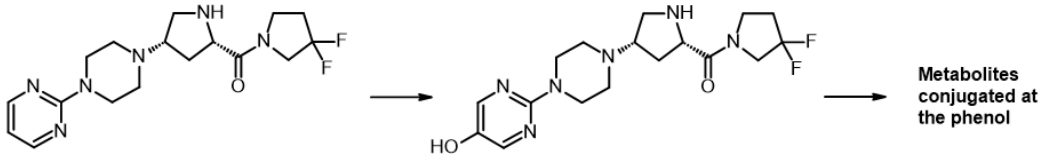
The scheme was backed up by trapping experiments using GSH and N-acetylcysteine (NAC) leading to the adducts shown below (left). Other trapping experiments employed semicarbazide in the incubations leading to the proposed adducts below, again supporting the proposed scheme of bioactivation. In further support, the amount of **M1** formed was greatly decreased in the presence of semicarbazide.



Adducts with thiols

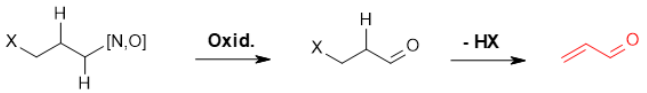
Adducts with semicarbazide

Another DPP-4 inhibitor, **gosogliptin** (PF-00734200), progressed to clinical phase 3 for diabetes several years ago but is only approved in Russia. Its metabolism in rats, beagle dogs, and humans was reported by Sharma et al. (DMD12). This drug, which obviously is much less lipophilic than the Merck compounds, is less affected by metabolism with only about 50% conversion, and thus has improved chances of obviating the 5-C pyrrolidine hydroxylation described in the above scheme. In fact, the studies confirmed that merely a trickle of the overall metabolism goes via hydroxylation in the fluorinated pyrrolidine ring.

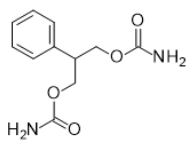


Gosogliptin **Major metabolite**

The current activation can be described in a generalized way by the scheme below. It belongs to a mechanistic class that involves formation of a labile keto compound, which can reach unsaturation by elimination of a leaving group, HX, in the 3-position. So far there are few reported examples among drug compounds (an early example is felbamate, structure shown).



More comments on this generalized mechanism at the end of this synopsis.



Felbamate

A direct analogy to the above dipeptidyl peptidase IV (DPP-4) inhibitors is the Takeda orexin receptor antagonist **TAK-994** (**firazorexton**) the stopped phase 2 clinical trials of which were recently reported (NEJM23). It is discussed in a separate monograph.