# On Elimination Reactions and Reactive Metabolites. Part I

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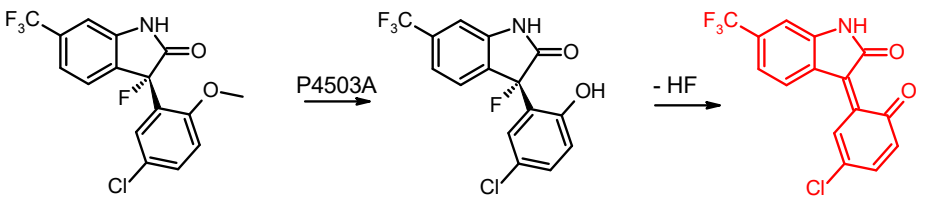
The most common initiating reaction on a path to a reactive metabolite (RM) is an oxidation where the P450 enzymes play a prominent role while other enzymes, for example various flavin-containing oxidases are less important.

After the first insertion of an oxygen usually something more has to happen to generate an RM (direct formation of an epoxide on a double bond is an exception). The next step can be elimination of water over one or several bonds, e.g. to form a conjugated keto compound, or it can be elimination of something else, which then acts as the *leaving group* (LG). This is what this and the next post will be about: a closer look at different ions and groups as LGs in two situations where initial oxidation has occurred; this post is on formation of *quinone methides* and the next one is on formation of *conjugated keto compounds*.

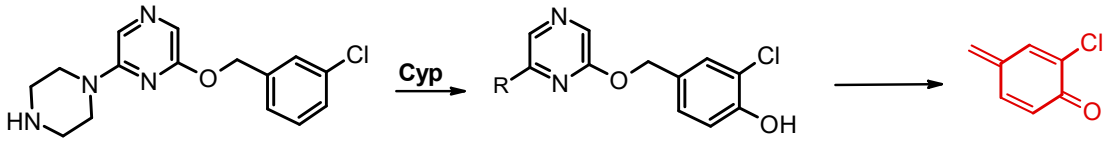
**Influence of LG on methide formation**. In a previous blog post (7 Dec25), I gave a few examples of drugs in which quinone methides can form from drugs and where a fluoride anion serves as a surprisingly effective enabling LG (despite the high binding energy of fluorine to carbon). A now almost classical example is that of **flindokalner** (**BMS-204352**) in which, after an initiating O-dealkylation, decomposition gives rise to an *ortho* quinone methide (Scheme 1).[1] Somewhat surprisingly, further verified examples of precisely this two-step mechanism featuring fluoride have not been published. But LGs usually considered less efficient have been shown to be effective: a pyrazine-oxy group was first reported in 2006 for a Pfizer 5-HT agonist, **CP-809101**, (Scheme 2) and later, in fact as recently as 2025, a phenoxy group was confirmed as the LG in **lapatinib** (Scheme 3).[2,3] An amine (or more correctly ammonium group) has also been shown to serve as an effective LG in hydroxylated **phencyclidine** (Scheme 4).[4] The amino group does not necessarily have to be an alkylamine: starting with another aim, destabilized benzylic 2-pyridylamines were designed to release a quinone methide as a covalent enzyme inhibitor active as an anticancer agent (Scheme 5).[5]

Scheme 1



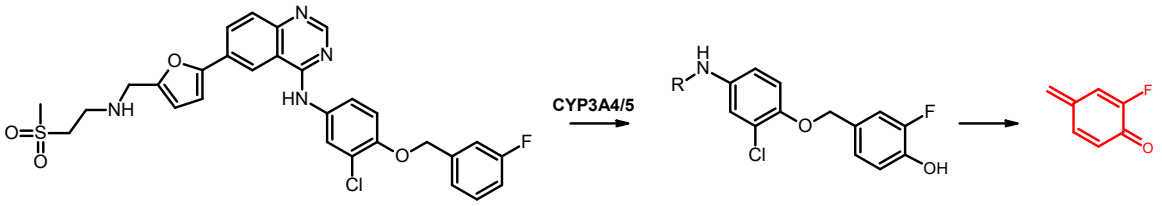

**Flindokalner**

Scheme 2



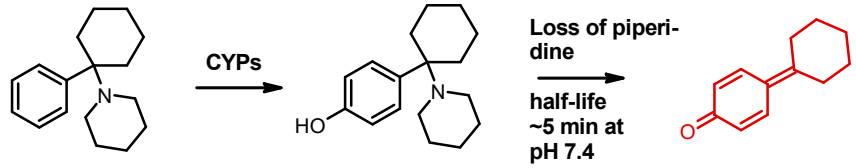

**CP-809101**

Scheme 3



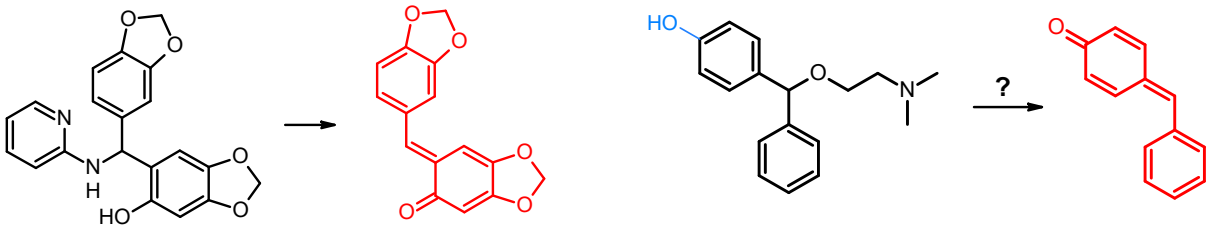

**Lapatinib**

Scheme 4




**Phencyclidine**

Schemes 5/6




**2-Pyridylamine as LG**

**Unstable metabolite from diphenhydramine?**

The interesting question now arises: which other LGs can be equally efficient, i.e. creating danger in a similar potentially methide-creating situation? These LGs would then have to get attention and be largely avoided by drug designers. This question has not been explicitly raised but should deserve some thought. Most chemists trained in organic chemistry would not think of an alkyl benzyl ether to be destabilized by a 2- or 4-hydroxyphenyl group (causing methide formation). But this has to be put in context: addition of other electron-releasing substituents, e.g. amino groups, will make the compound more prone to form a delocalized carbenium ion (see examples in JMC22).[7]

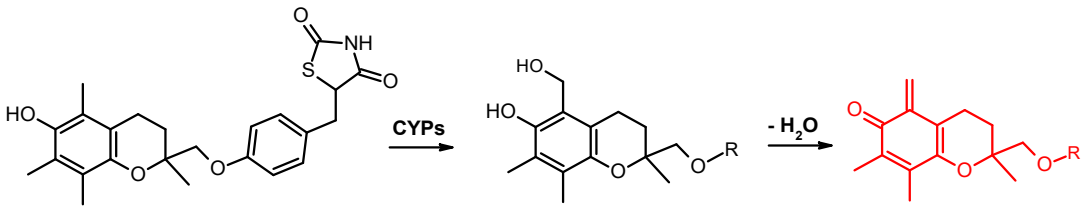
Another factor that might influence rate of methide formation (decrease of activation energy) should be formation of a more stabilized methide. For example, this could happen when a more conjugated system containing double bonds/aromatics is created. Examples from the literature are

hard to find but one might speculate that a phenol metabolite from a drug such as **diphenhydramine** (Scheme 6) might be somewhat labile.

When discussing LGs with properties resembling those of an alkoxy group, one might think of amido groups. Here too, the literature gives little guidance but since the $pK_a$ of a typical amide NH is in the same range as some alcohols, the thinking might go in the same direction; the case of **sorbinil** is discussed in the next section as a potential candidate for this mechanism.

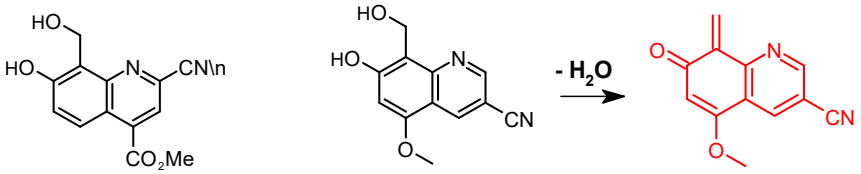
In contrast, the situation with a benzylic alcohol having an *ortho*- or *para*-phenolic OH, with $H_2O$ as the LG, has been fully clarified. The case of **troglitazone** forming a methide (Scheme 7) has been invoked many times in the literature on RMs with the basic reaction sequence tracing back to the simple ***ortho*-** and ***para*-cresols**, which are readily bioactivated to methides. Therefore, it is clear that $H_2O$ is a generally good LG in this context but one should note that rate of elimination/ dehydration is highly dependent on the aromatic substituents; for example have these effects been studied by DFT calculations (Zhang et al. 2015).[6] An illustrative example is found in Scheme 8. When not limiting the discussion to methide formation, it is obvious that benzylic alcohols can also form highly reactive carbenium ions when further substituted with electron-donating groups, see examples in JMC22.[7]

Scheme 7




**Troglitazone**

Scheme 8




**The right-hand quinoline loses water 27x faster than the other one**[6]

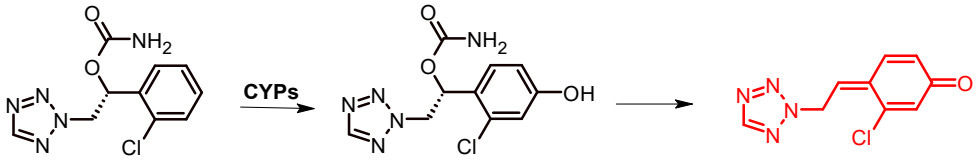
**Hypotheses**. Approved drugs have very rarely been investigated in detail regarding all metabolites formed, for obvious reasons. As a consequence, minor formation of RMs will not be noticed. However, most drug structures give rise to RM formation to some degree,[8] fortunately not reaching a level that negatively affects the benefit-risk balance for clinical use. Based on the methide-forming mechanism, I will discuss a few drug structures that were marked as hits in SpotRM app but which have not received general attention for specific RM issues.

Regarding other drugs that can potentially form methides according to the current mechanism, but which have not yet been reported as such, one can mention the new (2019) antiepileptic **cenobamate**. The LG in this case would be carbamic acid (Scheme 9). The case is analogous to

lapatinib and phencyclidine above (Schemes 3 and 4), in which methide formation is initiated by *para*-hydroxylation of a benzylic derivative. Cenobamate has been reported to have DILI issues (DailyMed). To offset these, the recommended dosing starts with a low 12.5 mg/day dose and during several weeks goes up to 200 mg/day.

Whether this mechanism is valid is open to question but one might consider the fact that cenobamate is heavily oxidized on the benzene ring[9] and chances that the *para*-phenol would *not* be formed should be slim. The odds for methide formation are also lowered when one knows that a plausibly formed *ortho*-phenol would lead to the same negative outcome.

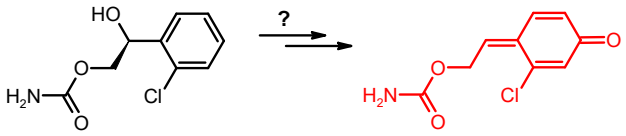
Scheme 9




**Cenobamate**

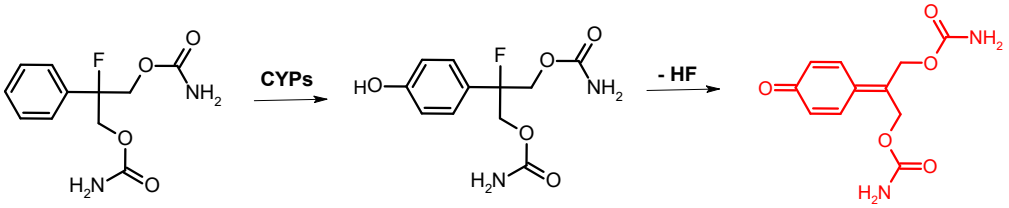
**Carisbamate** is an older analog of cenobamate that yet might be in development, specifically by SK Life Science, Inc. for the treatment of Lennox-Gastaut syndrome with phase 3 clinical studies initiated in 2022. This carbamate might likewise form a methide in two steps. A commentary from 2019 says "..alkylcarbamates enjoyed varying levels of success as antiseizure drugs; however, they have all been plagued by the emergence of serious and sometimes life-threatening adverse events".[10] I will write more on this kind of alert in a later blog post.

**Carisbamate**




In 2002 a fluoro-modified analog, **fluorofelbamate,** of the old antiepileptic felbamate was announced (in Scheme 10 felbamate has H instead of F). The modification was aimed at mitigating the severe RM issues of felbamate, which has a black box warning, by obviating the third activation step to a reactive 2-phenylacrylaldehyde (to be detailed in Part II).[11] Phase 1 studies were completed in 2006 but the results were negative: "Unfortunately, unanticipated idiosyncratic toxicity was observed after approval and the drug is now relegated to second- or third-line therapy, depending on patient history and seizure type".[12] So, it seems that one serious RM problem was exchanged for another in that it is likely that the problem with fluorofelbamate goes via methide formation and is the same as assumed to plague cenobamate.

Scheme 10

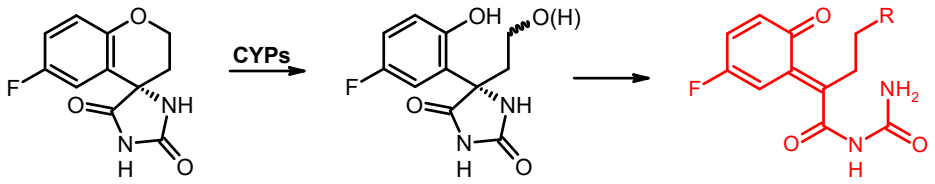



**Fluorofelbamate**

Metabolism studies of fluorofelbamate did not find any adducts with glutathione but one should also consider that the reactions of the methide are not readily predicted.

As mentioned in the introduction (on flindokalner), O-dealkylation of a phenol followed by methide formation is a rarely reported mode of RM formation. However, there are certainly cases where one could imagine such a mechanism. This makes the withdrawn drug **sorbinil** a potential target, actually via two possible routes. One speculative route where a methide is formed is shown in Scheme 11. Sorbinil was in failed clinical trials around 1985, with the patients suffering from serious hypersensitivity reactions, from SpotRM: "Riley *et al*. (BJCP1988) and Spielberg *et al*. (Ann1991) did experiments with microsomal metabolism and concluded that sorbinil is oxidatively metabolized to one or more potentially toxic intermediates, the nature of which have not been elucidated." In Part II of the current post, another potential mechanism for RM formation from sorbinil will be discussed.

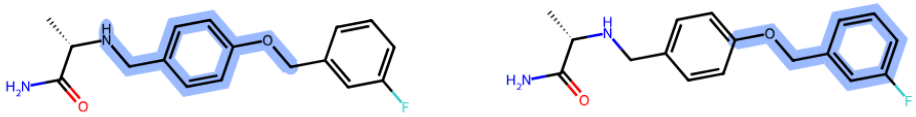
Scheme 11




**Sorbinil**

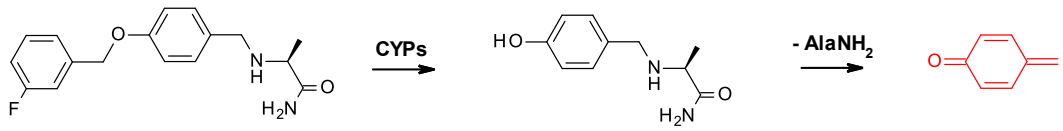
An analogous pattern of substructures to lapatinib is found in **safinamide** (Scheme 12), a MAO-B inhibitor for Parkinson's disease (daily dose 50-100 mg). This is an example of a drug that actually forms an identified metabolite, 4-hydroxybenzylamine, that is an immediate RM precursor.[13] In analogy with the mentioned phencyclidine (Scheme 4) this benzylic amine should

**Alerts in safinamide as shown in SpotRM**



be able to form a methide and the isolation of the phenol is therefore somewhat surprising; the benzylic amine-phenol from phencyclidine has t½ ~5 min at neutral pH. However, theoretically, the safinamide phenol should be more stable than the one from phencyclidine based on a simple chemical reasoning involving primary vs. tertiary carbocations (and more). Safinamide has not been reported with liver toxicity issues. This might be a representative example of the general difficulty of any attempt to use structural alerts in a too rigid ("predictive") way.

Scheme 12

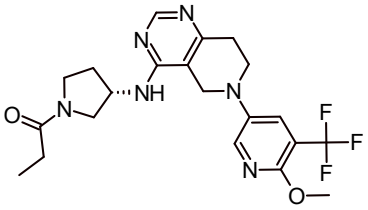



**Safinamide**

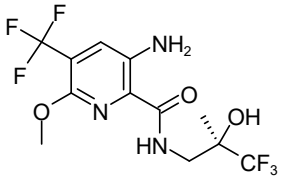
However, the hypothetical RM issues of safinamide do not stop there: its 3-fluoro-benzyloxybenzene group is also found in the mentioned kinase inhibitor lapatinib (Scheme 3) where it was reported to form a methide after initial hydroxylation of the fluorobenzyl group; most O insertion occurred in the ortho position next to fluorine (JMC25).[3]

To complete this odyssey on hypothetical methide formations, an RM hypothesis can be raised regarding the PI3Kδ inhibitor **leniolisib,** which, like flindokalner (Scheme 1) can eliminate HF and form a methide after initial O-dealkylation. The approved drug has warnings of "Risk of Hypersensitivity Reactions, Including Anaphylaxis" and "Embryo-Fetal Toxicity**"** (DailyMed)**.** The same theoretical RM mechanism is valid for the development candidate **icenticaftor** (for COPD; Novartis).

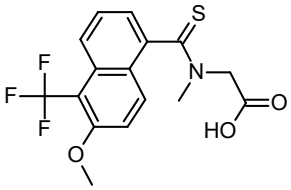
Here, one must also mention the old withdrawn antidiabetic drug **tolrestat**, which has the additional liability of being a thioamide (and a naphthalene).



**Leniolisib**



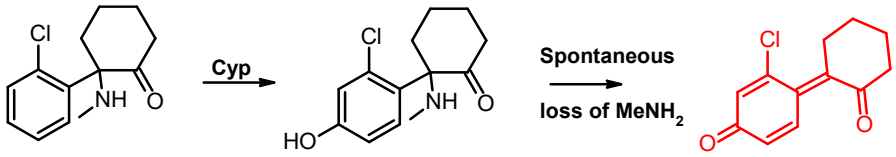
**Icenticaftor**



**Tolrestat**

Finally, the following potential bioactivation of **ketamine** has still not been reported (*cf.* Scheme 4).

Scheme 13

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