On Elimination Reactions and Reactive Metabolites. Part III (Addendum)

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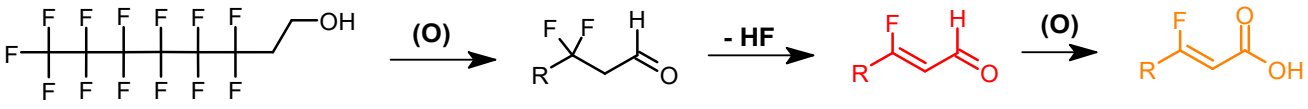
Having produced two parts on the theme in the title, there might yet be a need for a minor addendum caused by a recent literature report.

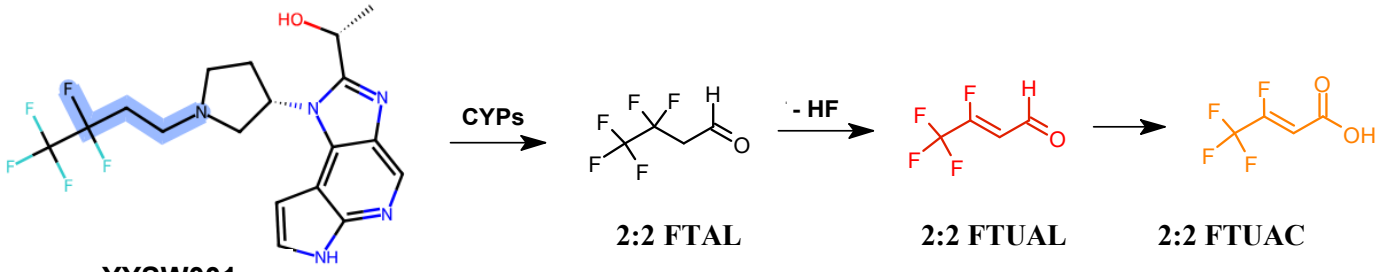
The infamous PFAS environmental pollutants are found everywhere while their structures are of no particular concern or interest to drug designers, who usually aren't keen to incorporate massive amounts of fluorine in their test compounds (trifluoromethyl groups could be an exception). Mechanisms of toxicity of PFAS compounds might therefore have been seen as unnecessary knowledge. But connect then the mechanism of bioactivation of the fluorotelomer alcohols (**FTOHs**), one example in Scheme 1, which are more toxic than most PFAS compounds, with the publication of compound **YYSW001** as a new JAK inhibitor (JMC26).

Scheme 1



8:2 fluorotelomer alcohol (FTOH) **FTAL** **FTUAL** **FTUAC**

The bioactivation mechanism of FTOHs has been known for 20+ years and the principle reaction was discussed in the Part II post on elimination reactions forming unsaturated keto compounds, a type of reactive metabolite (RM) formation for which one can construct a reasonably

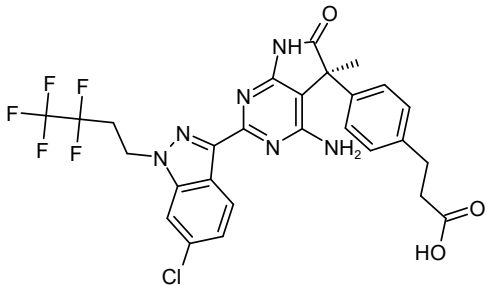


YYSW001 **2:2 FTAL** **2:2 FTUAL** **2:2 FTUAC**

accurate alert in SMARTS code, as found in the app SpotRM. However, the recent report on a fluorinated JAK inhibitor made it relevant to mention this structural alert again. The inhibitor reported last March contains an N-linked pentafluorobutyl chain, which can readily form an aldehyde by N-dealkylation and an RM is thus formed as described above. Compound **YYSW001** is the only one of this kind reported in the paper but on the other hand, the authors inform that this is the one chosen for clinical development.

Regarding FTOH toxicity. The literature on fluorotelomer alcohols toxicity and health effects is vast, as expected from their wide use in the industry and known potential for bioactivation. A couple of picks: reactivities of aldehydes and carboxylic acids from FTOHs have been looked into by investigating reactions with various nucleophiles (EST12). The FTUAL type of RM, formed by spontaneous elimination of HF, is very reactive and does not survive for long in a biological medium, as first reported by Martin et al. (CBI05). The unsaturated acids, FTUACs, are less reactive. Furthermore, fluorotelomer alcohols (FTOHs) are significantly more toxic in biological studies than their corresponding fluorotelomer acids (FTCAs), possibly pointing to a more efficient bioactivation.

Similar compounds. A substructure search on 3,3,4,4,4-pentafluorobutanamine with two explicit hydrogens, [FC(F)(C(C(N)([H])[H])[H])C(F)(F)F], results in 1095 hits in PubChem. A very large majority are patent compounds and only one, **frespaciguat**, is a development compound, a guanylate cyclase (sGC) stimulator aimed for inhaled administration, which means it will be given in a very low dose. It is currently in a Phase 2a clinical trial (INSIGNIA-PH-COPD, NCT05612035) to treat Pulmonary Hypertension associated with Chronic Obstructive Pulmonary Disease (JCP25).



Frespaciguat