

Navigating you through
drug development

ARDENA

PFAS webinar
DJ van Zoelen

12 December 2024

Agenda of the webinar

- PFAS and API's
- PFAS and API synthesis
- PFAS and API manufacturing

PFAS and API's

- API's containing a CF₂, CF₃ or multiple fluorine atoms are considered as PFAS
- Since the introduction of the first fluorocorticosteroid, fludrocortisone, in 1954
- with 20% of those on the market being fluorinated drugs and around 30% of fluorinated drugs being blockbuster pharmaceuticals, such as Lipitor, Fluoxetine, Linezolid or Fluticasone
- To date, more than 300 fluorinated pharmaceuticals have been approved for use as drugs

PFAS and API's

- The success of the introduction of fluorine atoms is linked to the peculiar physicochemical properties of the C-F bond, which are the high bond strength, polarity and minimal steric hindrance of fluorine, combined with a general metabolic stability
- The importance of fluorinated compounds is also linked to their use as diagnostic tools within imaging techniques such as ^{19}F -MRI and ^{18}F -PET

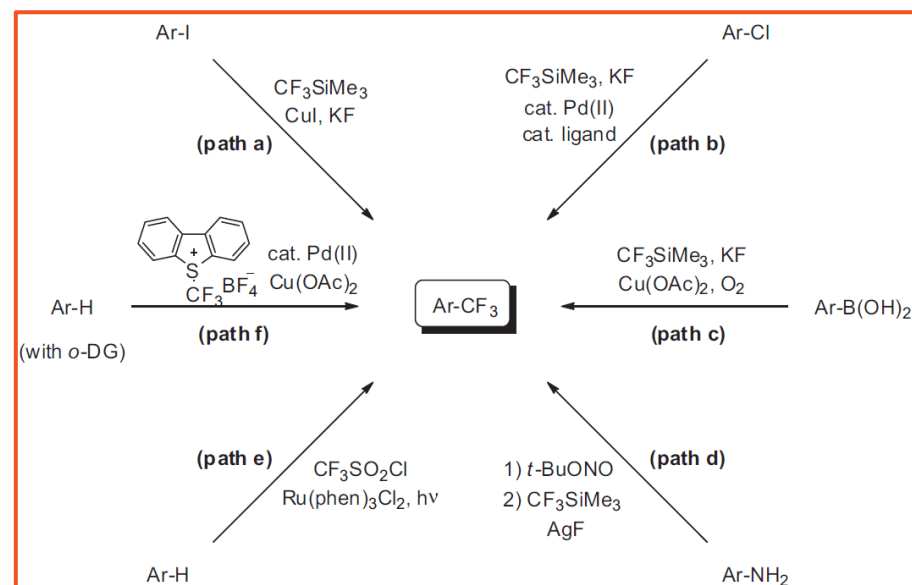
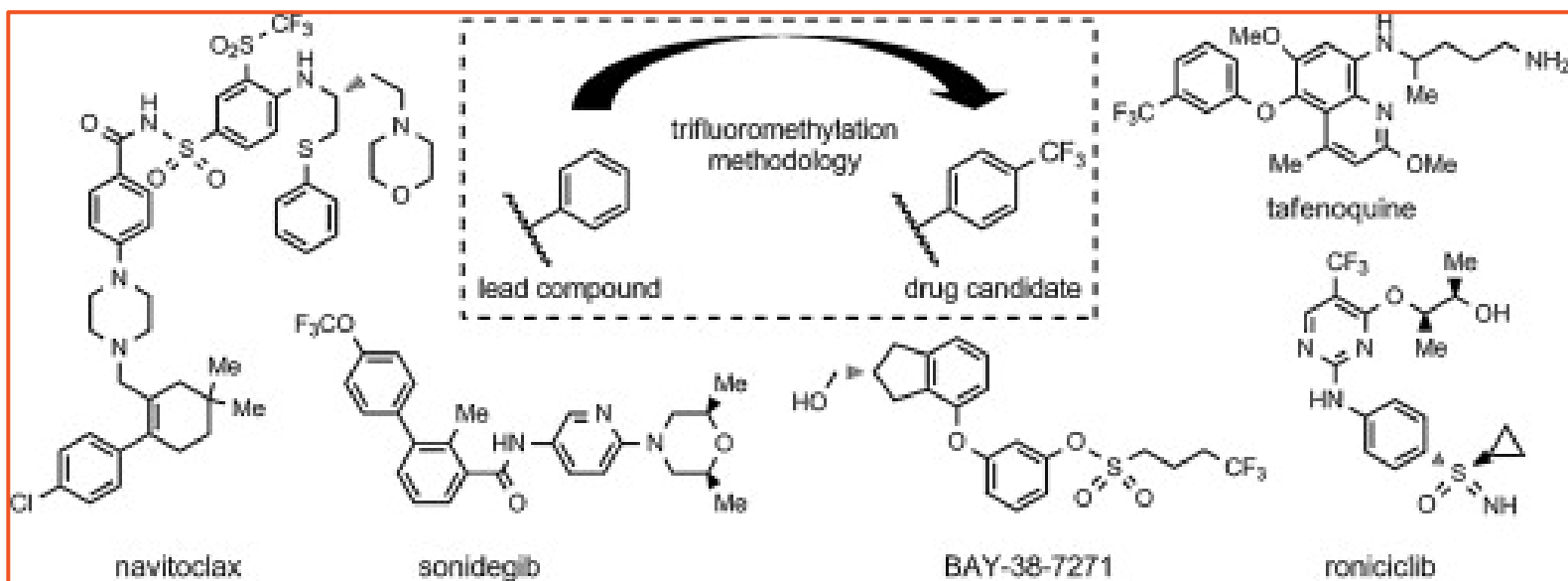
PFAS and API's → Challenge

- For current launched API's derogation conditions are being discussed
- API's under development (clinical trials) are excluded from the derogation conditions
- Rethink your strategy when you are developing a PFAS API
- Other mechanisms should be developed metabolic stability

PFAS and API Synthesis

PFAS and API Synthesis

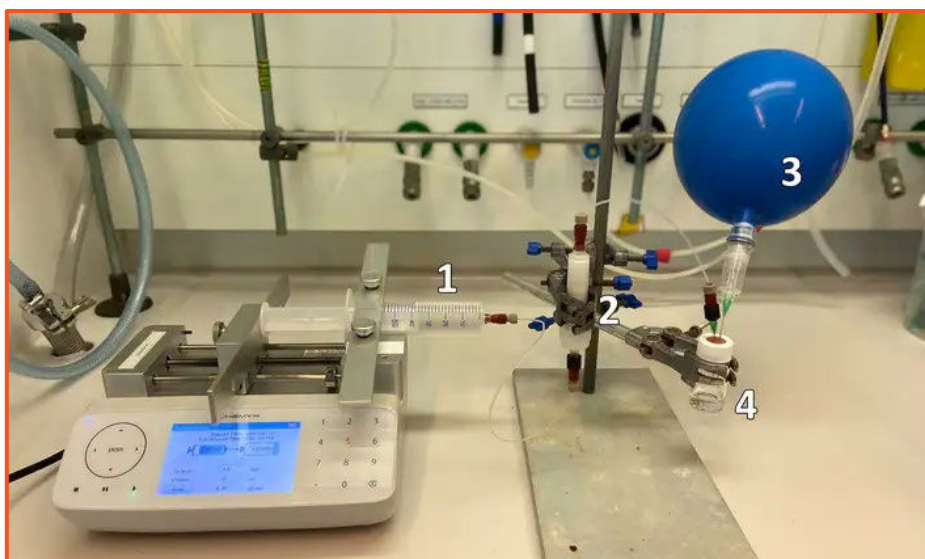
- While launched PFAS API's are not "restricted" yet, PFAS chemicals will be restricted in the near future. But how to make the PFAS API's when PFAS chemicals are restricted?



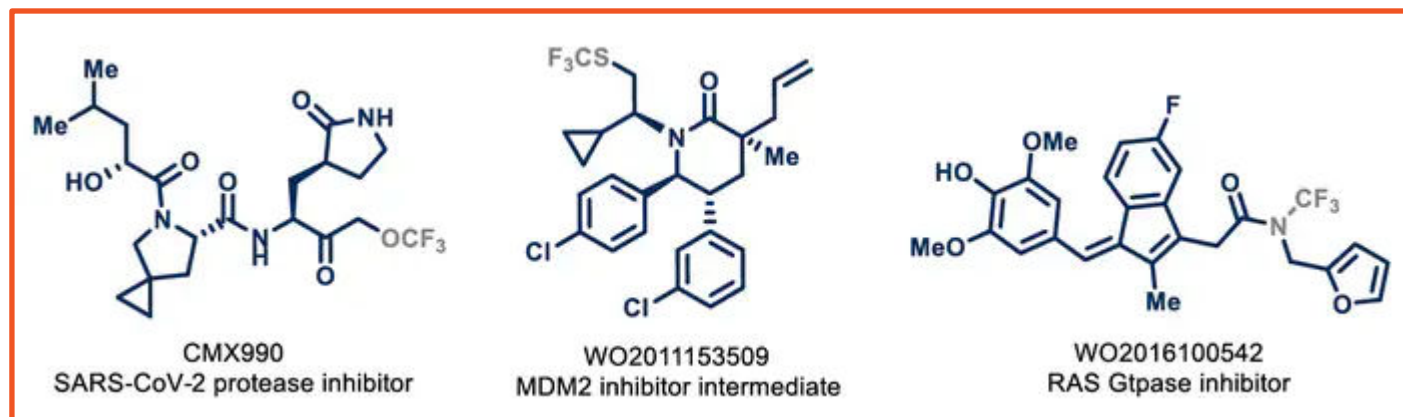
PFAS and API's Synthesis, There is hope!

Integrated flow system

The Science paper presents a versatile microfluidic flow module for generating reactive N-, S- and O-CF₃ anions. These are prepared in a packed bed flow reactor containing the caesium fluoride salt. Appropriate (S, O or N containing) precursors are then led through this reactor.



Laboratory set-up of the microfluidic flow module for generating reactive N-, S- and O-CF₃ anions. 1: Solution containing precursor molecules. 2: Packed bed reactor containing the caesium fluoride salt. 3: Nitrogen filled balloon that prevents pressure build-up. 4: Reception vial equipped with stirring bar. Image: HIMS / Science.



Mauro Spennacchio, Miguel Bernús, Jelena Stanić, Daniele Mazzarella, Marco Colella, James J. Douglas, Omar Boutureira, Timothy Noël. *Science*, 385, 6712, p991-996

PFAS and API Synthesis. There is hope!

OXYTOCIN

Oxy - quick Tokos- childbirth



- Appears Essential role in Child birth but Essential role is in **Milk Ejection**

Oxytocin - Peptide Hormone

Primary Role is milk ejection

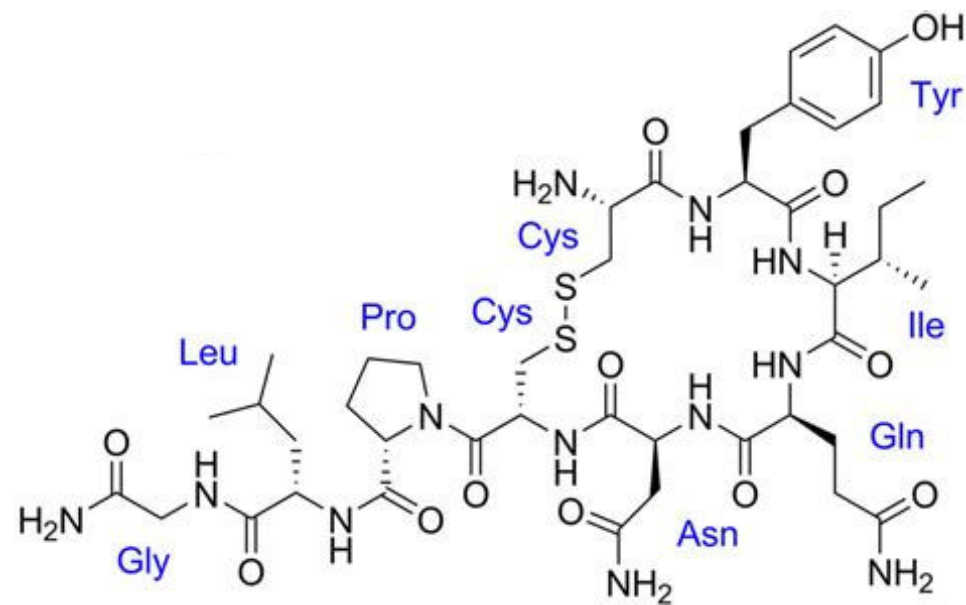
Faciliatory role in initiation of labor and parturition.

Half Life - 5 mins.

Not bound to plasma proteins.

metabolized by liver & excreted through Kidneys.

2 mg + 1 IU of Oxytocin.



Brønsted Acid–Lewis Acid (BA–LA) Induced Final Deprotection/Peptide Resin Cleavage in Fmoc/*t*-Bu Solid-Phase Peptide Synthesis: HCl/FeCl₃ and AcOH/FeCl₃ as Viable PFAS-Free Alternatives for TFA



Jan Pawlas, Christophe André, Jon H. Rasmussen, Olivier Ludemann-Hombourger

Org. Lett. 2024, 26, 31, 6787–6791

Essential Medicines List includes Oxytocin for use during pregnancy, childbirth and postpartum care (who.int)

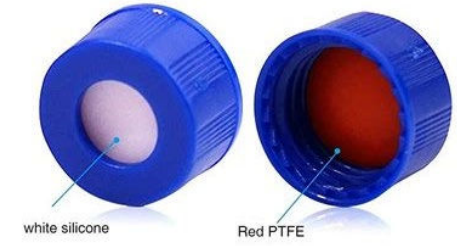
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PFAS and API's Synthesis → Challenge

- First alternatives for PFAS chemicals have been developed
- Continue this journey → Keep developing
- Start switching to alternatives, already in early development!
- Support each other, share results to the broader public. This challenge is not for a single company; it is for the broader community!

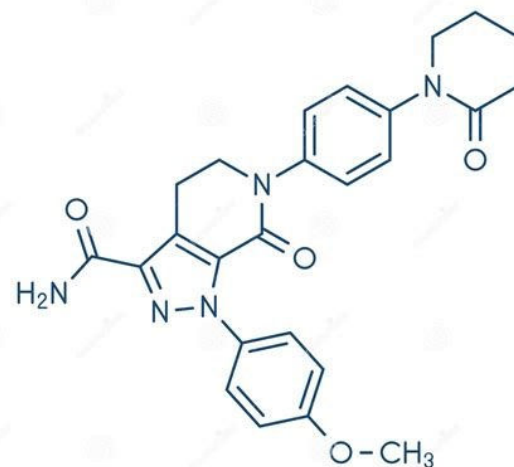
PFAS and API Manufacturing

PFAS and API Manufacturing



PFAS and API's Manufacturing → Challenge

- These PFAS materials are used in many types of equipment
- Equipment is protected to corrosive conditions
- Used a lot to manufacture non-PFAS API's without using PFAS chemicals
- Eliquis (Anticoagulant)

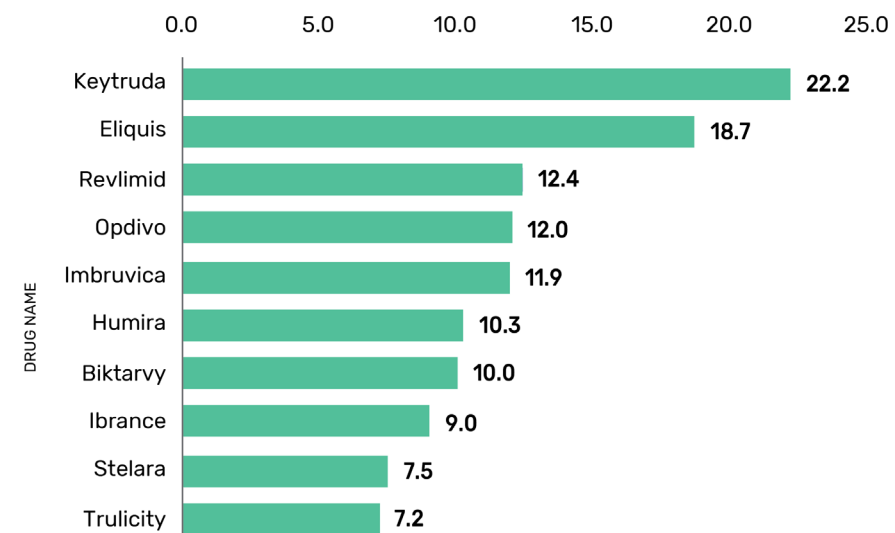


apixaban

- New materials should be developed
- We have done it before.....!

Forecast of Top 10 best-selling drugs, 2025, Global (\$bn)

GlobalData.



Source: GlobalData, Pharma Intelligence Center



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