Enrichment of Relevant Oxidative Degradation Products in Pharmaceuticals with Targeted Chemoselective Oxidation

October, 2019

Kausik Nanda

Merck Sharp & Dohme Corp.

API

excipients

DP

stress

Degradate

enrichment

ICH Q3B
ICH M7

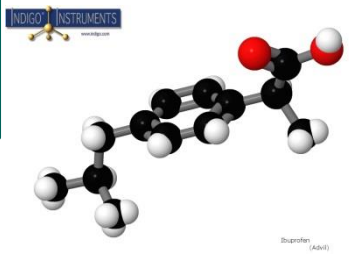
API+Deg

isolation

Deg

NMR/MS

Structure ID (Degradate)



MSD
INVENTING FOR LIFE

Reporting, ID and Qualification Triggers

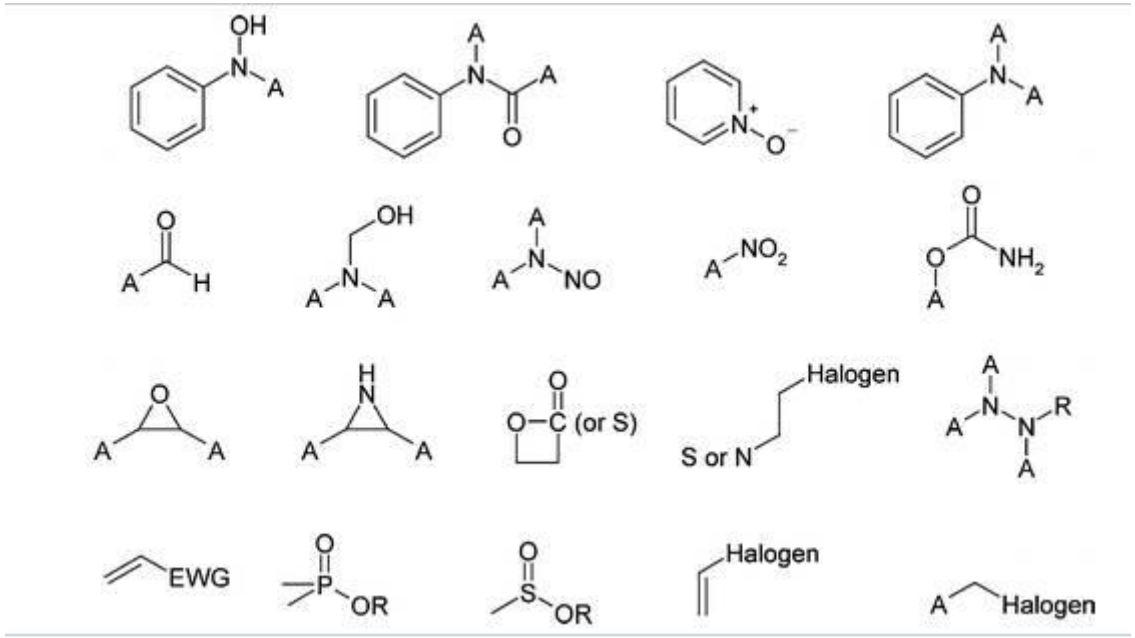
Maximum Daily Dose	Reporting Threshold	Identification Threshold	Qualification Threshold
Drug Substance Impurities (ICH Q3A)			
≤2 g/day	0.05%	0.10% or 1.0 mg per day*	0.15% or 1.0 mg/day*
>2 g/day	0.03%	0.05%	0.05%
Drug Product Degradation Products (ICH Q3b)			
≤1 g	0.10%		
>1 g	0.05%		
<1 mg		1.0% or 5 µg/day*	
1 mg–10 mg		0.5% or 20 µg/day*	
>10 mg–2 g		0.2% or 2 mg/day*	
>2 g		0.10%	
<10 mg			1.0% or 50 µg/day*
10 mg–100 mg			0.5% or 200 µg/day*
>100 mg–2 g			0.2% or 3 mg/day*
>2 g			0.15%

*Whichever is lower

MSD INVENTING FOR LIFE

ICH M7 and Mutagenic Impurity (MI) assessment

ICH M7 describes expectations for drug products on how degradation products should undergo mutagenicity assessment.



Example of an intercalation complex with DNA 2

Out-of-scope: Oncology^, oligonucleotides*, peptides*, APIs derived from a fermentation process, biologics.

^materials dosed in healthy volunteers are in scope

*(e.g. linkers conjugating to PEG), or delivery system (e.g. lipid nanoparticle), **will be in scope for ICH M7**, if the specific chemical modifications have not previously been assessed

MSD INVENTING FOR LIFE

ICH M7 and Mutagenic Impurities

Impurities classification (ICH M7)

Class	Definition
1	Known Mutagenic carcinogens
2	Known mutagen with unknown carcinogenic potential
3	Alerting structure, unrelated to DS; no mutagenicity data
4	Alerting structure, same alert in DS which have been tested and are non-mutagenic
5	No structural alerts

Acceptable intakes for an individual impurity

Duration of treatment	≤ 1 month	>1 – 12 months	>1 – 10 years	>10 years
Daily intake (µg/day)	120	20	10	1.5

MSD INVENTING FOR LIFE

Common degradation pathways

1. **Hydrolytic**
2. **Oxidative**
3. **Thermal**
4. **Photolytic**

MSD
INVENTING FOR LIFE

Oxidative Degradation

One Electron (radical intermediate)

Reactive species: $\dot{O}R$ $\dot{O}OR$

Forced stress with AIBN

API

Two-electrons

Reactive species: ROOH

Forced stress with H_2O_2

enrichment

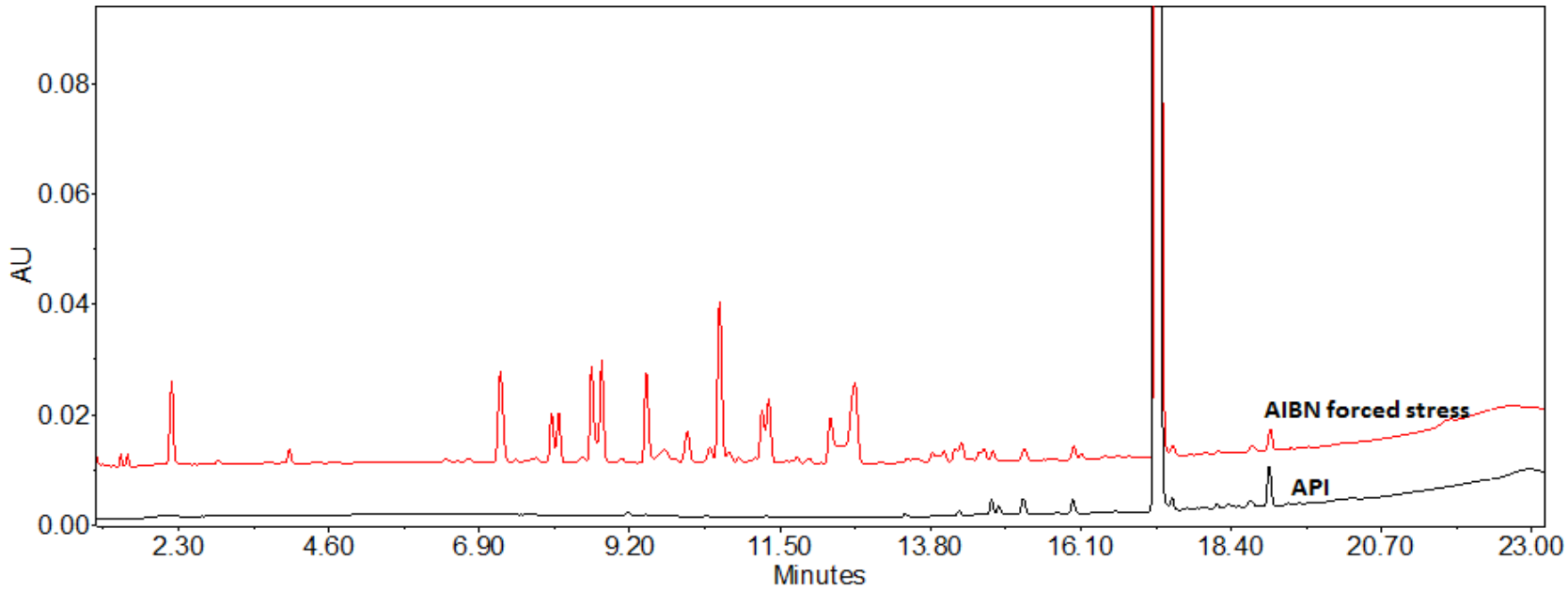
Transition Metal

Most abundant metal ion: Fe^{3+}

API+Deg → *isolation* → Deg → *NMR/MS* → **Structure ID (Degradate)**

MSD INVENTING FOR LIFE

Typical Oxidative Forced Stress

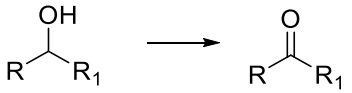
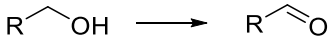
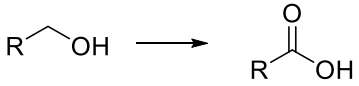
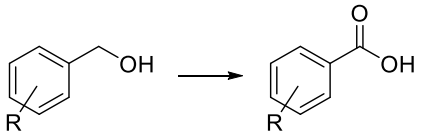


Oxidative forced stress experiment with AIBN for a MSD development candidate

Not ideal for isolation of an oxidative degradation product!!

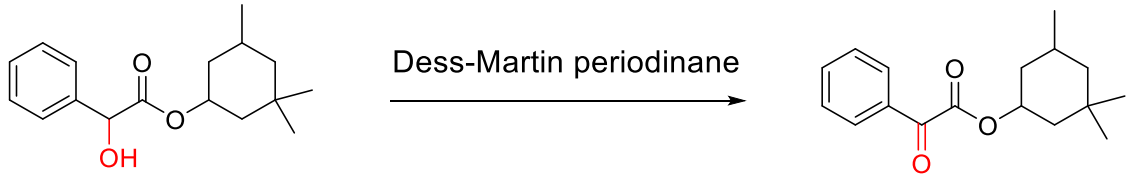
MSD
INVENTING FOR LIFE

Relevant Oxidative Transformations and Recommended Reagents to Enrich API

Transformation	Reagents
	i) Dess-Martin periodinane ii) Pyridinium chlorochromate iii) Pyridinium dichromate iv) RuO_2.xH2O/$NaIO_4$
	i) Dess-Martin periodinane ii) Pyridinium chlorochromate iii) Pyridinium dichromate
	i) TPAP/NMO
	i) $KMnO_4$

MSD
INVENTING FOR LIFE

Oxidation with Dess-Martin Periodinane



Cyclandelate

(86%)

Enrichment and isolation were done in 1 day

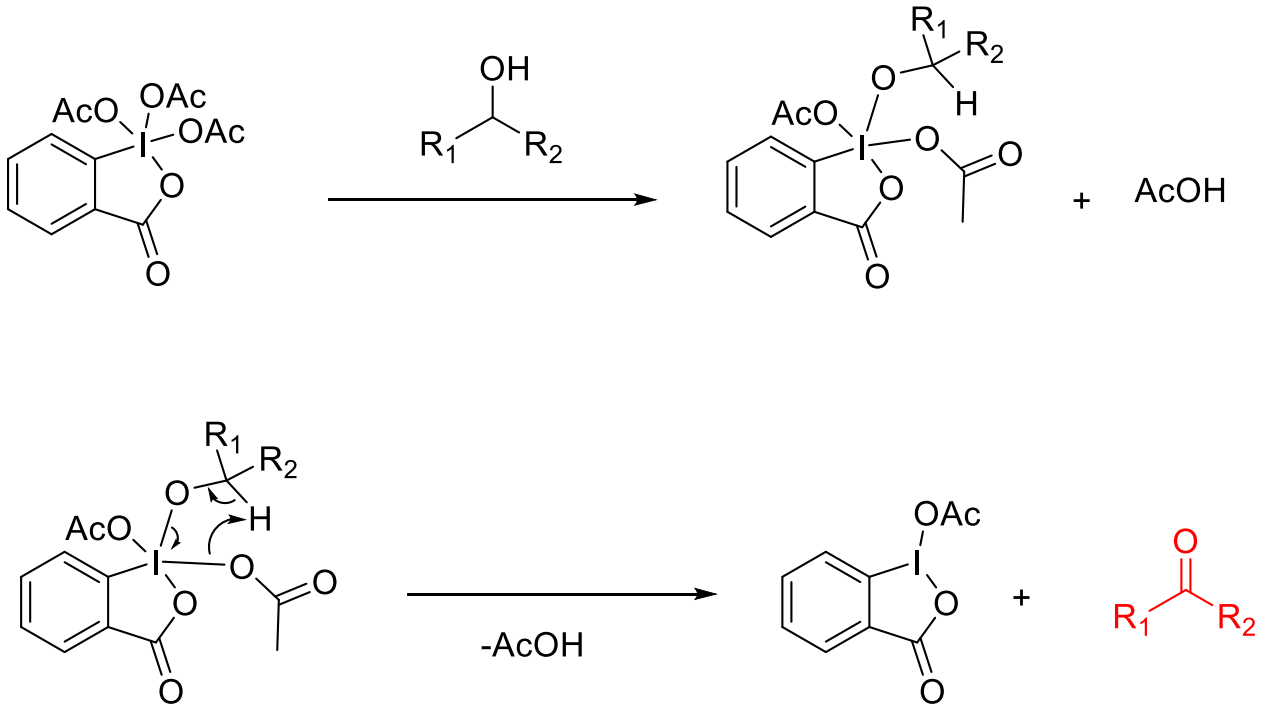
300 mg API in 6 mL CH_2Cl_2 → Add D-M periodinane (700 mg) → Stir for 2h → Filter and concentrate

40 g silica gel
0 to 30% ethyl acetate in hexanes
20 minutes

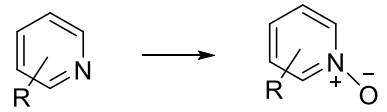
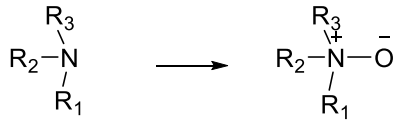
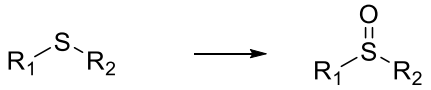
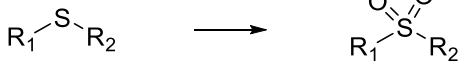
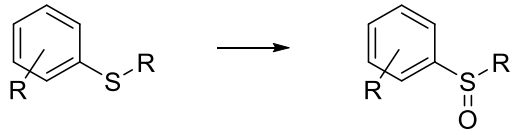
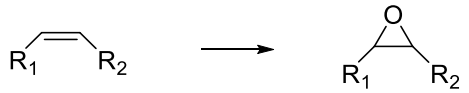
→ **Isolated yield: 86%**

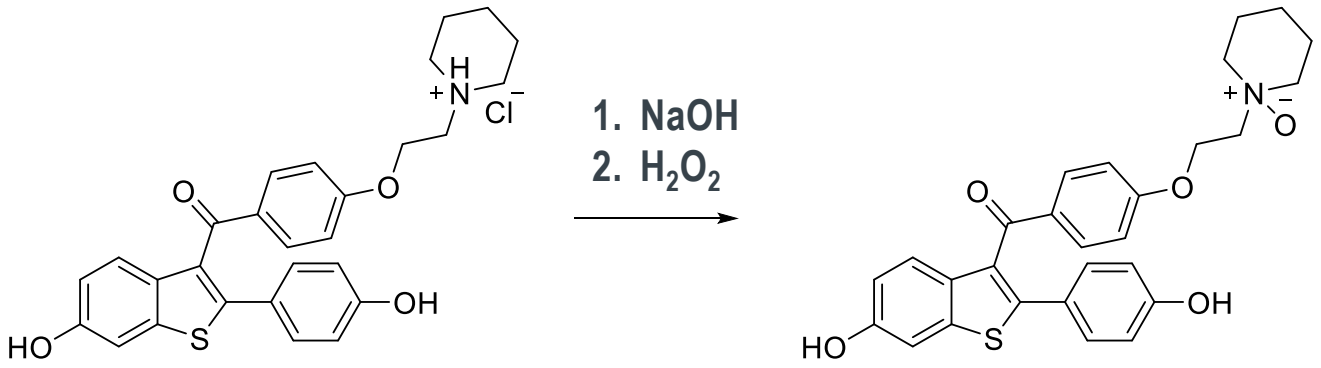
MSD INVENTING FOR LIFE

Mechanism: D-M Periodinane Oxidation



Relevant Oxidative Transformations and Recommended Reagents to Enrich API

Transformation	Reagents
	i) MTO/H_2O_2 ii) *m*-CPBA
	i) H_2O_2 ii) Peracetic acid iii) $O_2/RuCl_3$
	i) Oxone ii) $H_2O_2/[VO_2F(dmpz)_2]$
	i) Oxone
	i) $NaNO_2$/HCl
	i) *m*-CPBA

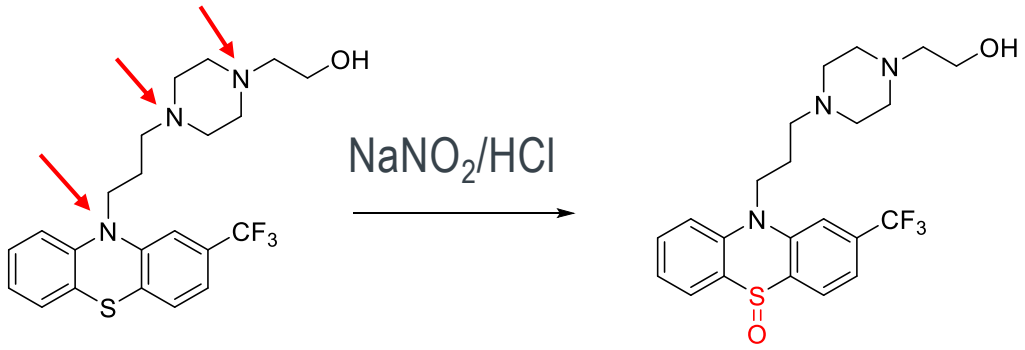


Raloxifene hydrochloride

Raloxifene-*N*-oxide

(isolated yield: 75%)

Oxidation of Fluphenazine to Fluphenazine-Sulfoxide



Fluphenazine

Fluphenazine-sulfoxide

Not a 2-electron oxidation. Oxidation via cation radical intermediate.

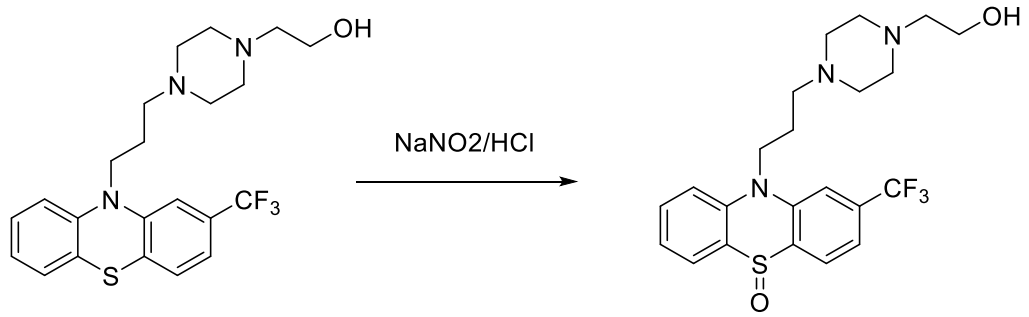
$$NaNO_2 + HCl \longrightarrow HNO_2 + NaCl$$

$$NO_2^- + 2H^+ \longrightarrow NO^+ + H_2O$$

Oxidant

MSD INVENTING FOR LIFE

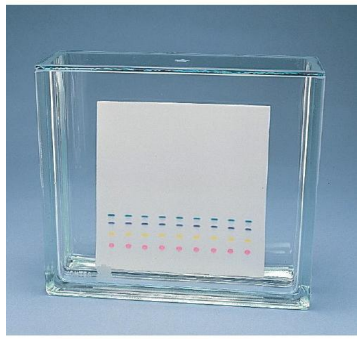
Oxidation of Fluphenazine to Fluphenazine-Sulfoxide



Fluphenazine

Fluphenazine-sulfoxide

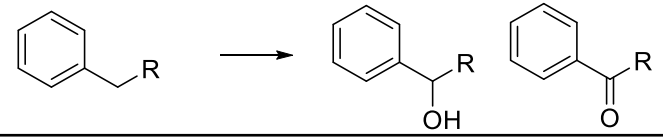
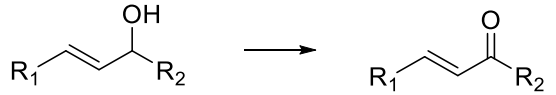
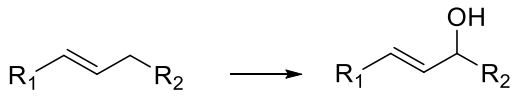
22 mg API in 1 mL H_2O + 2 drops conc. HCl → Add 2 drops aq $NaNO_2$ 100 mg/mL → *2 minutes* → Add NH_4OH → Extract w CH_2Cl_2 → Concentrate CH_2Cl_2 extracts



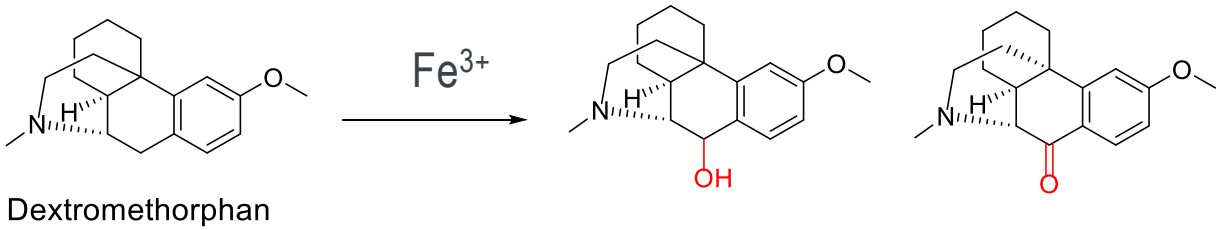
Prep-TLC → **Isolated yield: 70%**

MSD INVENTING FOR LIFE

Relevant Oxidative Transformations and Recommended Reagents to Enrich API

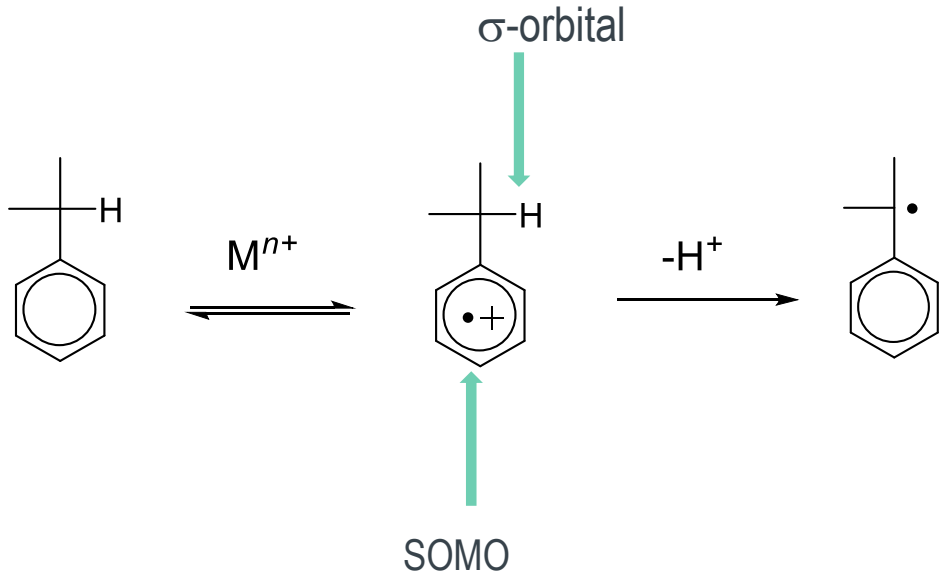
Transformation	Reagents
	i) $FeCl_3$ ii) AAPH
	i) H_2O_2 (g) ii) Dess-Martin periodinane
	i) SeO_2

Oxidation of Dextromethorphan

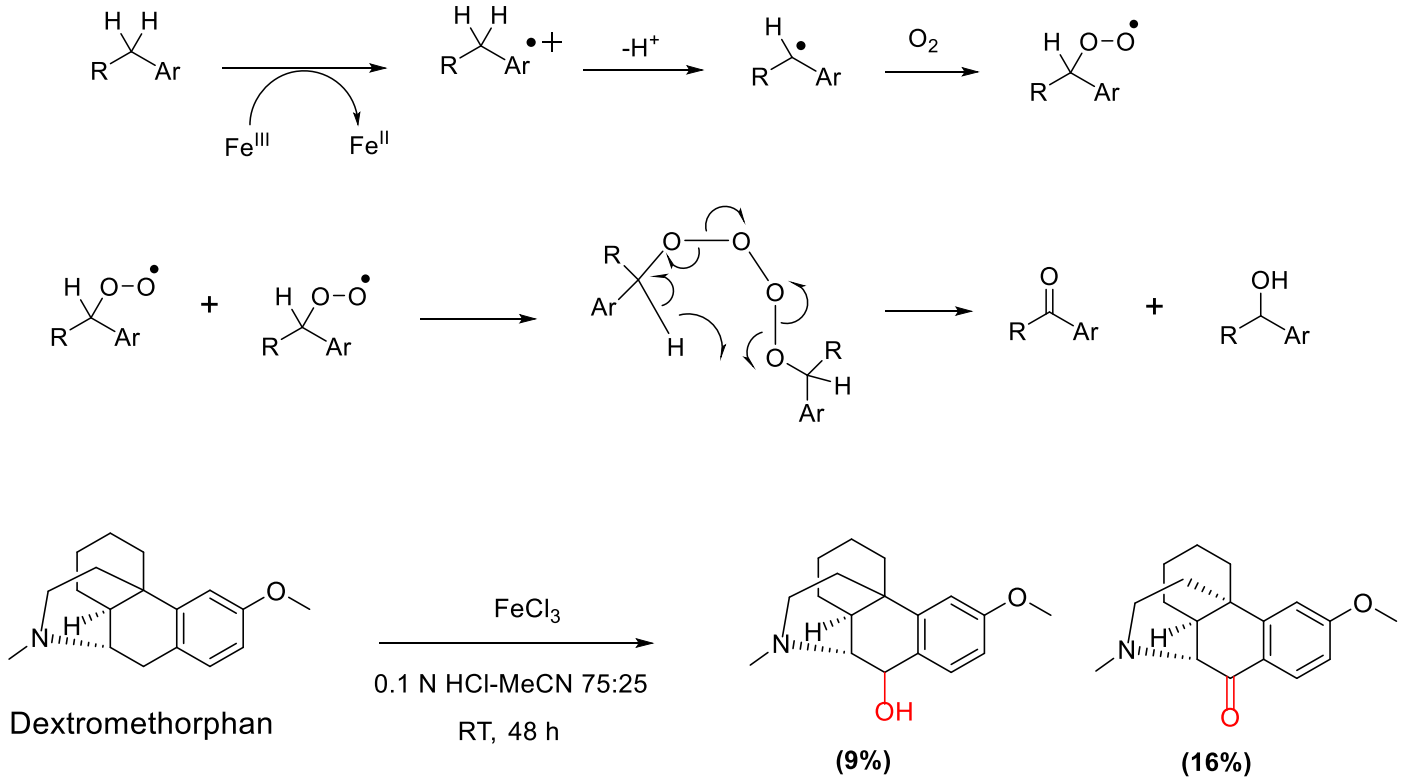


Dextromethorphan

Formation of benzylic radical *via* aromatic cation radical



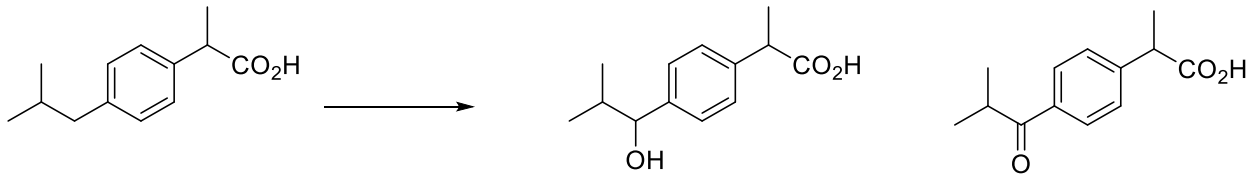
Oxidation of Dextromethorphan



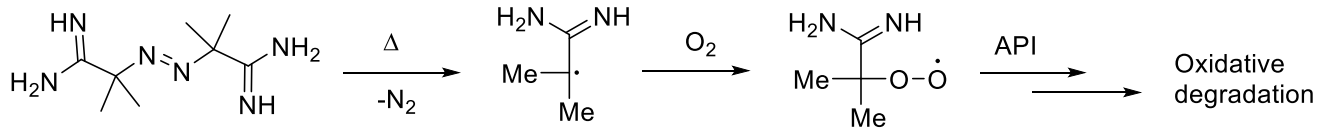
Iron(III)-mediated oxidative degradation on the benzylic carbon of drug molecules in the absence of initiating peroxides
Nanda, K. K.; Blincoe, W. D.; Allain, L. R.; Wuelfing, W. P.; Harmon, P. A. *J. Pharm. Sci.* 2017, *106*, 1347-1354.

MSD INVENTING FOR LIFE

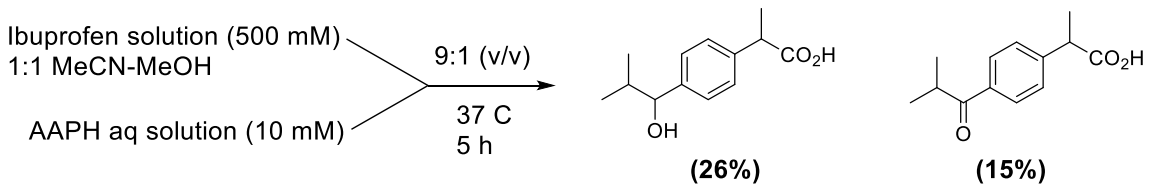
Oxidation of Ibuprofen



Ibuprofen



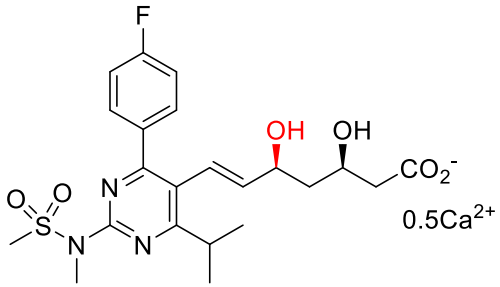
AAPH
(2,2'-Azobis(2-amidinopropane)dihydrochloride



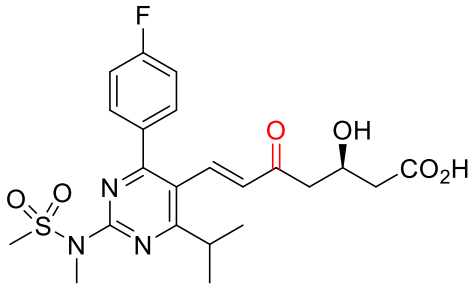
(26%) **(15%)**

MSD INVENTING FOR LIFE

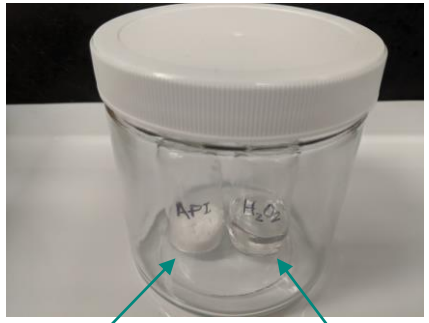
Oxidation of Rosuvastatin



Rosuvastatin calcium



5-Keto-rosuvastatin



50 °C, 1 week

24% conversion to 5-keto-rosuvastatin

$$2H_2O_2 \longrightarrow 2H_2O + {}^1O_2$$

MSD INVENTING FOR LIFE

Journal of Pharmaceutical Sciences 108 (2019) 1466-1475

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Enrichment of Relevant Oxidative Degradation Products in Pharmaceuticals With Targeted Chemoselective Oxidation

Kausik K. Nanda [1,*], Olivier Mozziconacci [2], James Small [3], Leonardo R. Allain [1], Roy Helmy [2], W. Peter Wuelfing [1]

[1] *Analytical Sciences, MRL, Merck & Company, Inc., West Point, Pennsylvania 19486*
[2] *Analytical Sciences, MRL, Merck & Company, Inc., Rahway, New Jersey 07065*
[3] *Structure Elucidation, MRL, Merck & Company, Inc., West Point, Pennsylvania 19486*