Kratom:
Godsend or Menace?

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Outline

- Introduction
  - Pain and Analgesics
  - Kratom and Mitragynine
- Bioactivities of Mitragynine and Related MIA
  - Pharmacokinetics
  - Pharmacodynamics
- Total Synthesis of Mitragynine and Related MIA
  - Biosynthesis
  - Mitragynine
  - Mitragynine Pseudoindoxyl
  - Structurally-related Alkaloids (selected, recent examples)
- Summary and Prospective

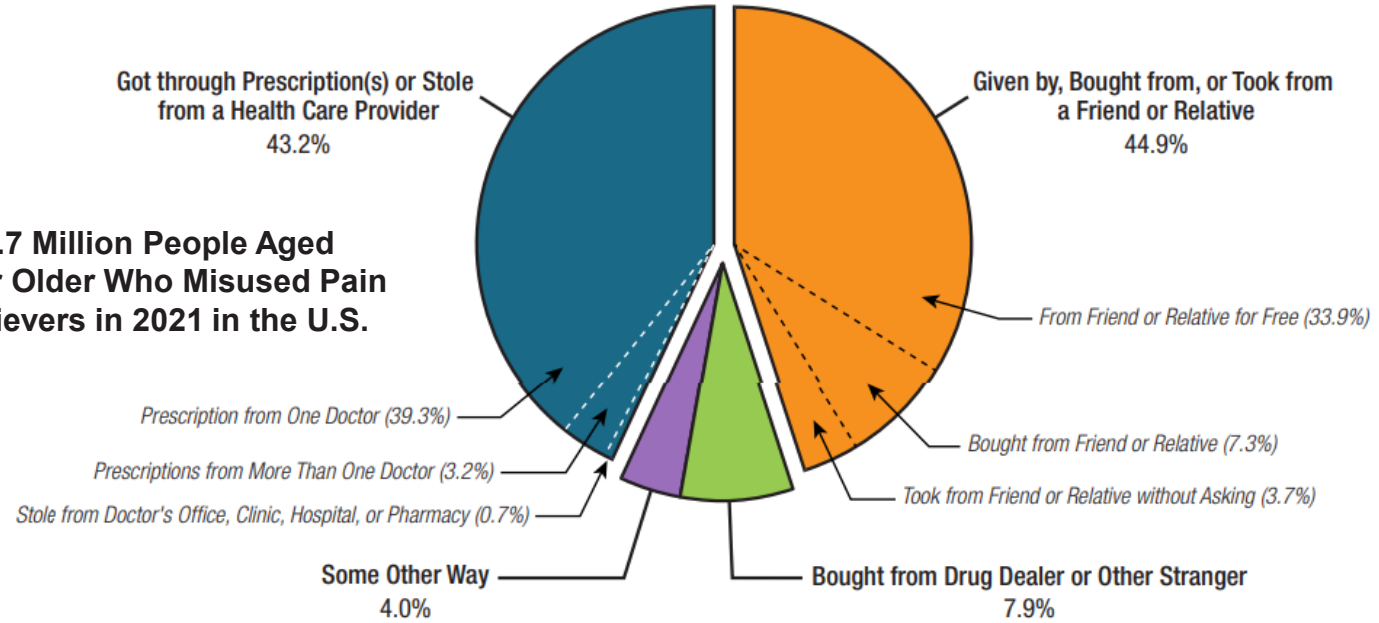
Pain and Analgesics

Paracetamol

NSAIDs

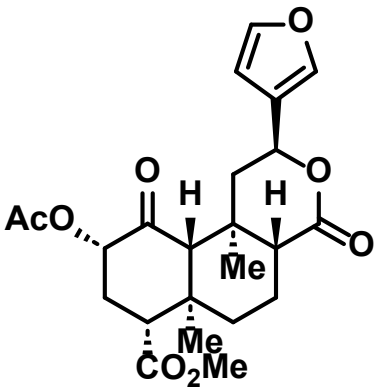
Opioids Derivatives

8.7 Million People Aged 12 or Older Who Misused Pain Relievers in 2021 in the U.S.

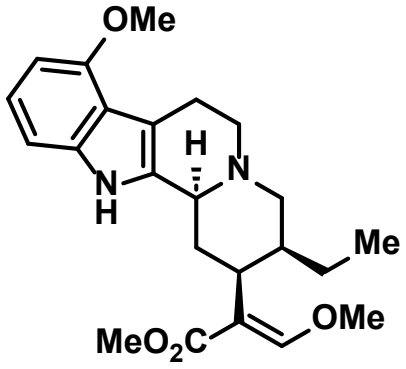


- https://www.thegoodbody.com/back-pain-statistics/
- https://www.samhsa.gov/data/report/2021-nsduh-annual-national-report

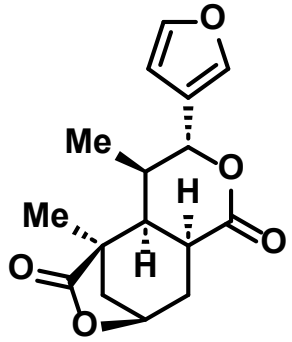
Gold Standard, OUD and Alternatives



Salvinorin A



Mitragynine



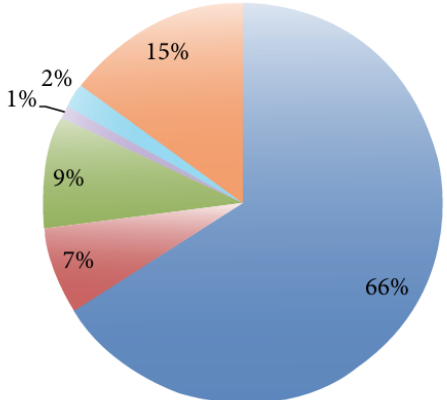
Collybolide

- Majumdar, S. *et al. Biochemistry* **2021**, *60*, 1381.

Kratom and Mitragynine

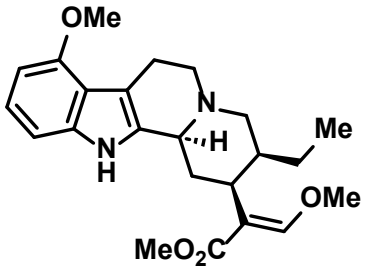
Kratom

Mitragyna speciosa

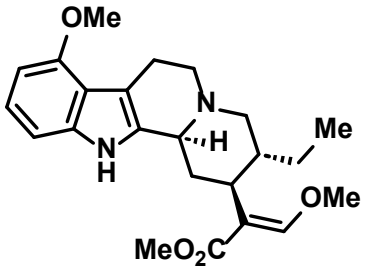


Leaf
Thailand

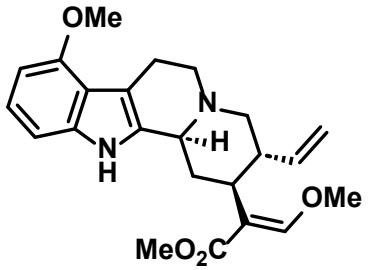
>50 corynanthe- and oxindole-type MIA



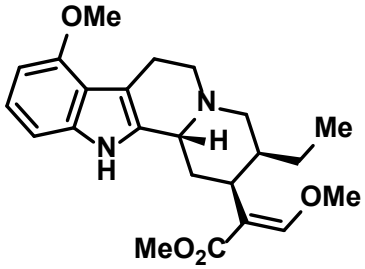
Mitragynine
0.8-1.9%, 66.2%



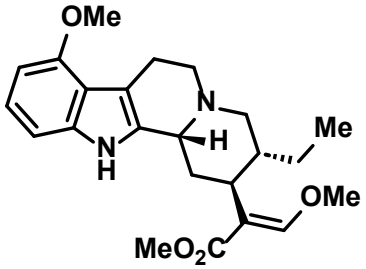
Speciogynine
0.1-0.2%, 6%



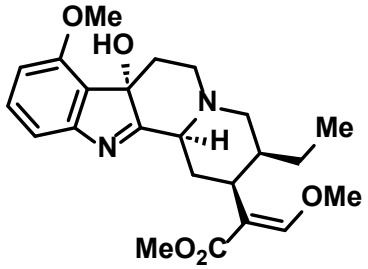
Paynantheine
0.09-0.2%, 8.6%



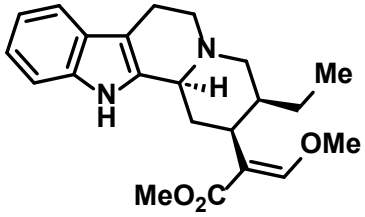
Speciociliatine
0.04-0.2%, 0.04%



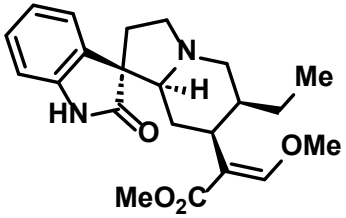
Mitraciliatine
0.01-0.2%



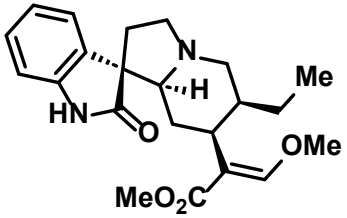
7-Hydroxymitragynine
BLLOQ-0.2%, 2%



Corynantheidine
0.003-0.04%



Corynoxine
BLLOQ-0.05%



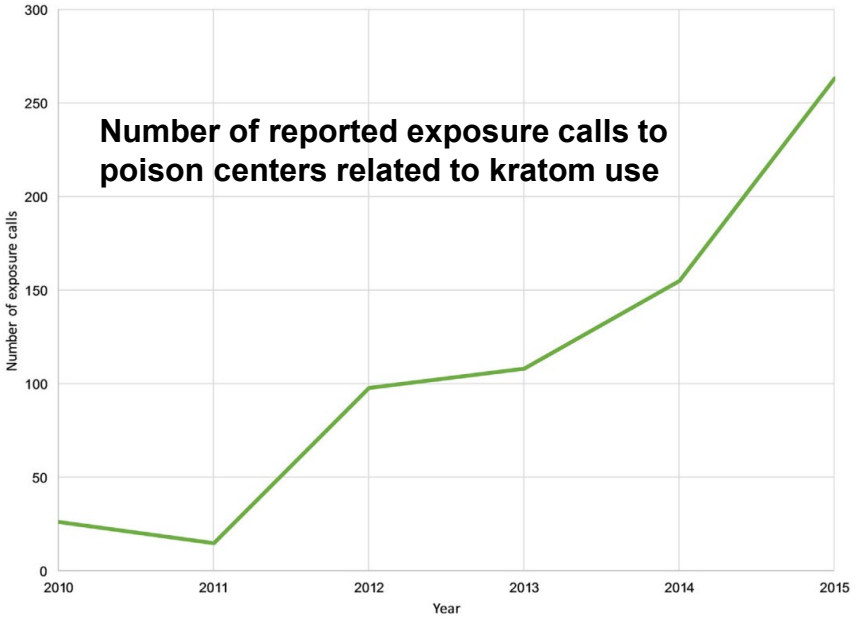
Corynoxine B
BLLOQ-0.01%

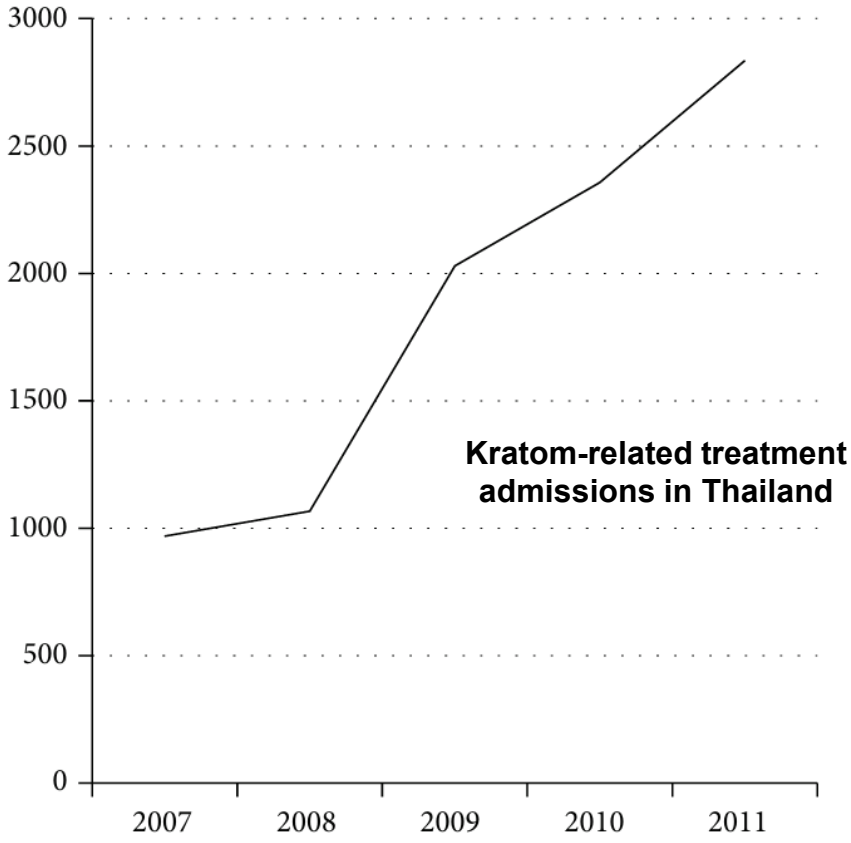
BLLOQ = below the lower limit of quantification

- https://www.npr.org/2023/07/08/1186514144/kratom-herbal-supplement-lawsuits-deaths-fda

- Gilliland, K. M. *et al. ACS Chem. Neurosci*. **2020**, *11*, 3870. Smith, K. E. *et al. ACS Chem. Neurosci*. **2023**, *14*, 195.

Kratom Use in the US and Asia

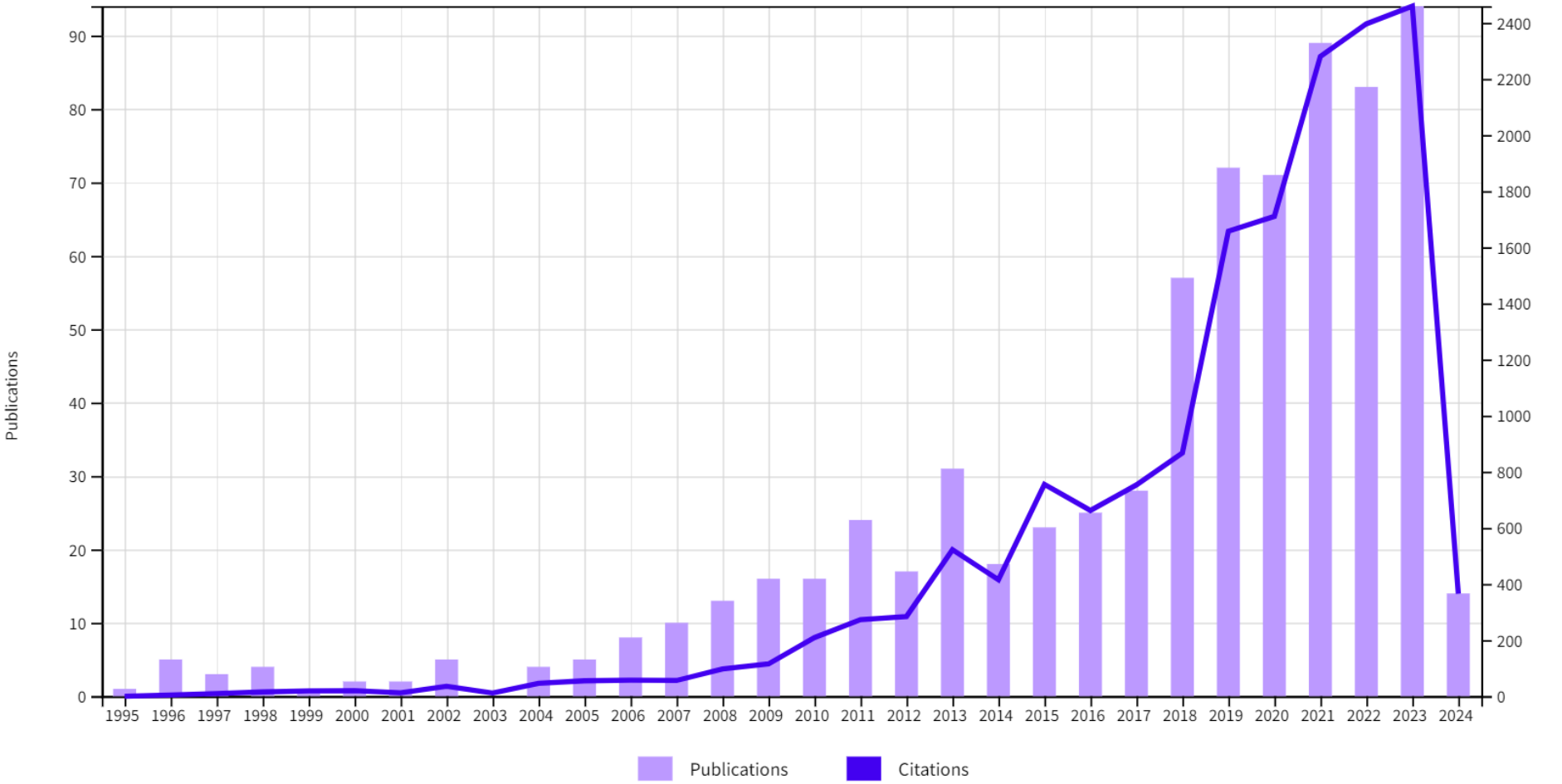




- *Biomed Res Int*. **2015**, 968786.
- https://www.samhsa.gov/data/report/2021-nsduh-annual-national-report

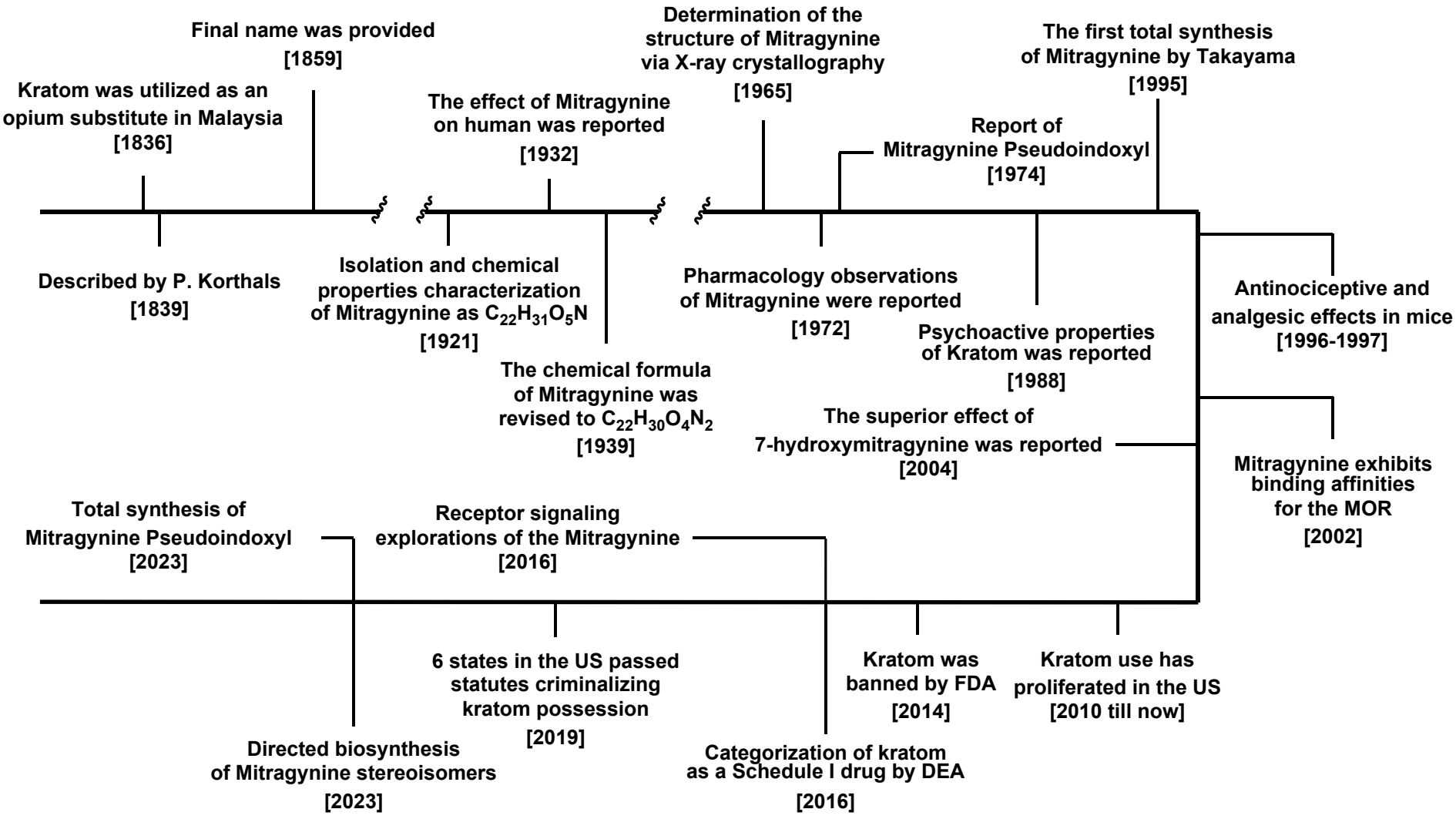
Proliferation

- Searching “Mitragynine” in *WOS*



- https://webofscience.clarivate.cn/wos/alldb/summary/dfca6f36-191c-4154-9e03-5423d7b784e4-d7c55f7f/relevance/1

Milestones


Kratom was utilized as an opium substitute in Malaysia [1836]
Final name was provided [1859]
Described by P. Korthals [1839]
The effect of Mitragynine on human was reported [1932]
Isolation and chemical properties characterization of Mitragynine as $C_{22}H_{31}O_5N$ [1921]
The chemical formula of Mitragynine was revised to $C_{22}H_{30}O_4N_2$ [1939]
Determination of the structure of Mitragynine via X-ray crystallography [1965]
Pharmacology observations of Mitragynine were reported [1972]
Report of Mitragynine Pseudoindoxyl [1974]
The first total synthesis of Mitragynine by Takayama [1995]
Psychoactive properties of Kratom was reported [1988]
Antinociceptive and analgesic effects in mice [1996-1997]
The superior effect of 7-hydroxymitragynine was reported [2004]
Mitragynine exhibits binding affinities for the MOR [2002]
Total synthesis of Mitragynine Pseudoindoxyl [2023]
Receptor signaling explorations of the Mitragynine [2016]
6 states in the US passed statutes criminalizing kratom possession [2019]
Directed biosynthesis of Mitragynine stereoisomers [2023]
Categorization of kratom as a Schedule I drug by DEA [2016]
Kratom was banned by FDA [2014]
Kratom use has proliferated in the US [2010 till now]

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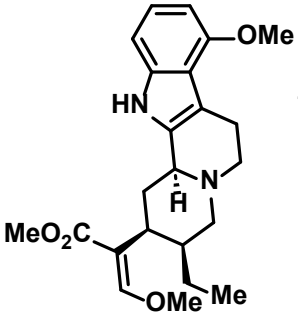
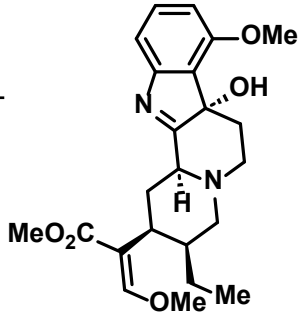
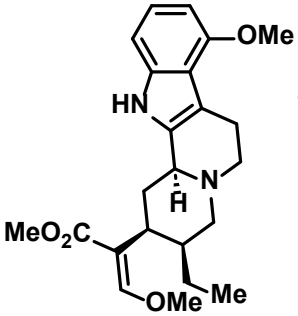
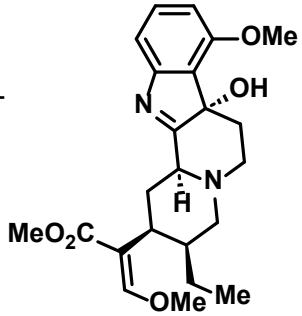
Stability

- Stability of Mitragynine and 7-hydroxymitragynine

	Time (min)		Degradation Ratio		Degradation Ratio
pH = 1.2	30		8.9%		7.6%
	60		20.0%		15.7%
	120		26.0%		27.0%

	Time (min)		Degradation Ratio		Degradation Ratio
pH = 6.8	30		0.96%		1.23%
	60		2.67%		3.88%
	120		3.56%		6.08%

Oral bioavailability in rat = 3.03±1.47%

- Hassan, Z. *et al. Brain Res. Bull*. **2016**. *126*, 29.
- Manda, V. K. *et al. Planta Med*. **2014**. *80*, 568.

Pharmacokinetics

kratom tea (6.25–23 mg) P.O.	
parameters	mean ± SD
C_{max} (μM)	0.26[a]
T_{max} (h)	0.83 ± 0.35
V_d/F (L/kg)	38.04 ± 24.32
CL/F (L/h kg)	98.1 ± 51.34
$AUC_{0\rightarrow\infty}$ (μM/h)	1.68[a]
$t_{1/2}$ (h)	3.85 ± 1
terminal $t_{1/2}$ (h)	23.24 ± 16.07

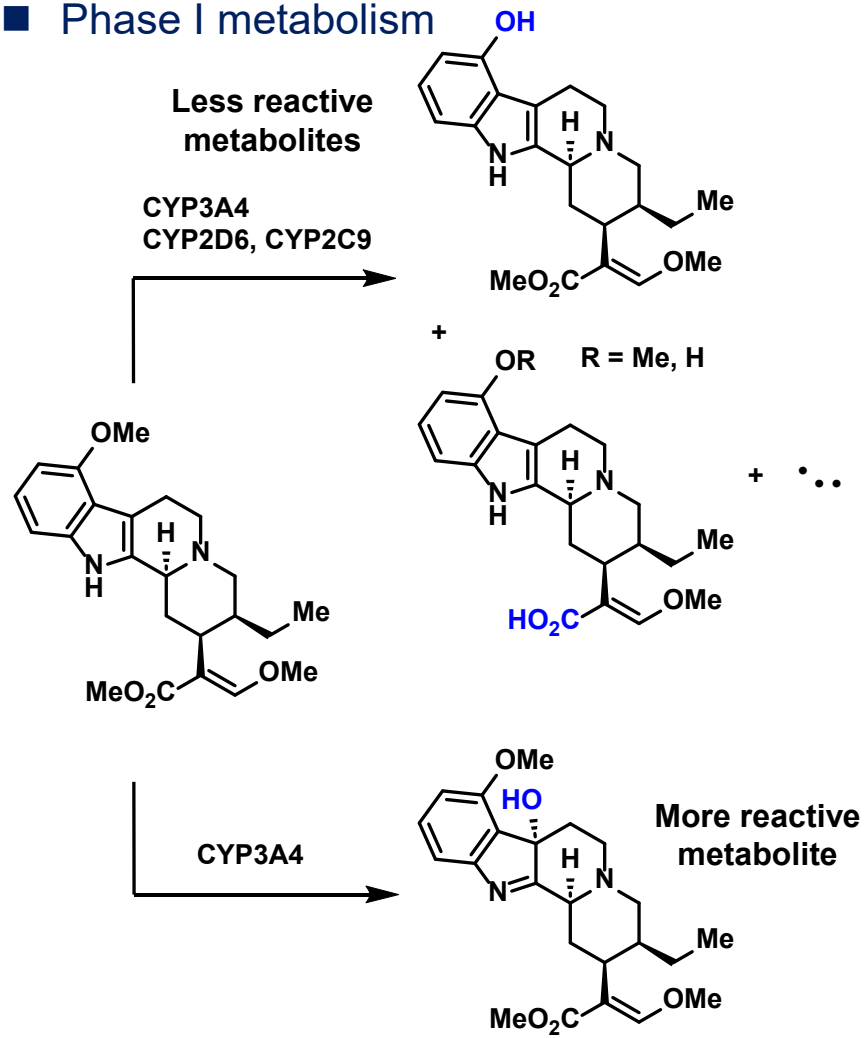
[a]Detected at 23 mg loading dose.

P_{app} = (**25.3**±2.2)×10^{-6} cm/s
(10 μM, absorptive direction)
between atenolol and propranolol

Caco 2 efflux ratio = 1.1
(10 μM)
As a P-gp inhibitor

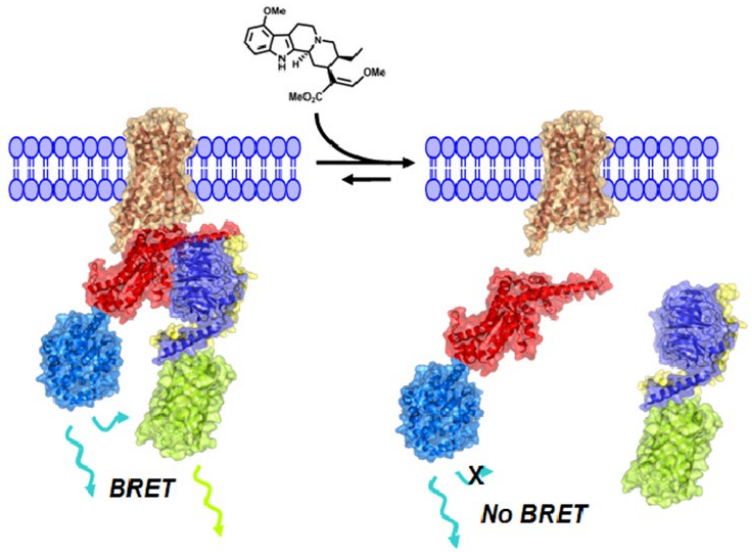
0.14% of the administered mitragynine in urine

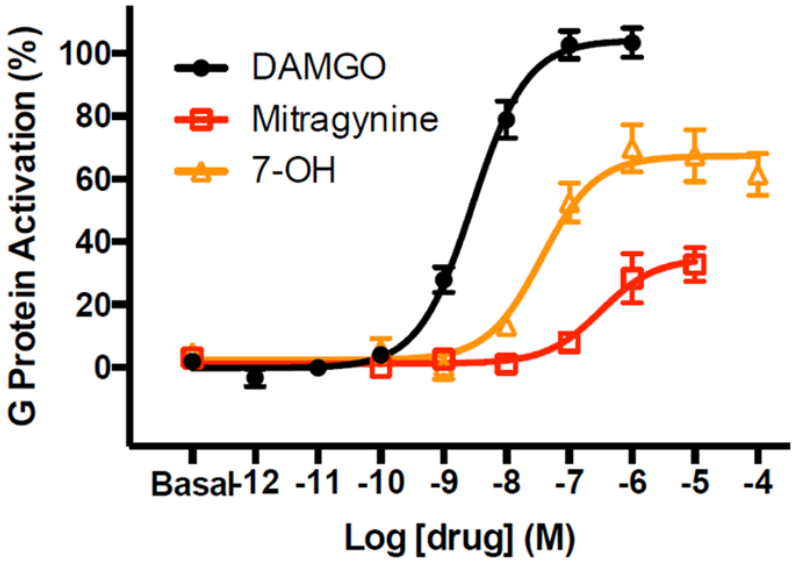
- Phase I metabolism



- Wananukul, W. *et al. Drug Des., Dev. Ther*. **2015**, *9*, 2421.
- Maurer, H. H. *et al. J. Mass Spectrom*. **2009**, *44*, 1249

Partial Agonist of Human MOR





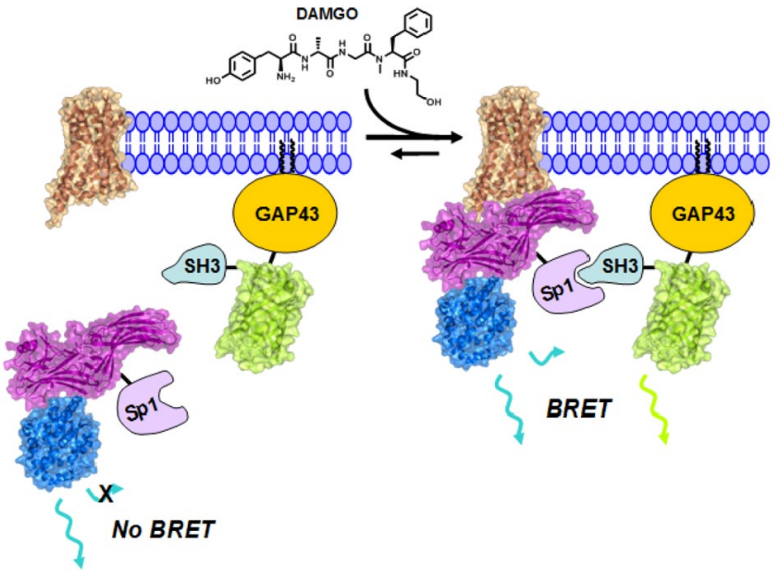
	hMOR		hKOR	hDOR
	EC_{50} (nM)	E_{max} (%)	IC_{50} (μM)	IC_{50} (μM)
Mitragynine	339±178	34	8.5±7.6	>10
7-hydroxymitragynine	34.5±4.5	47	7.9±3.7	>10

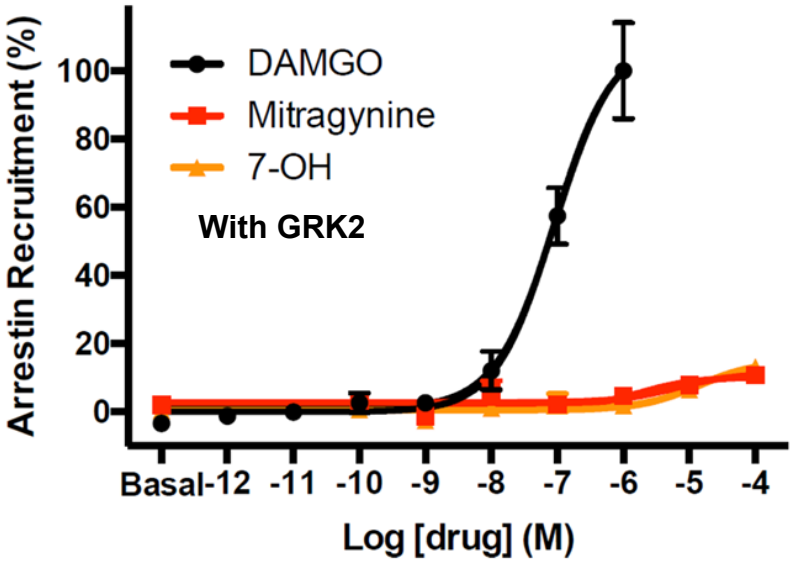
- ✓ Agonist at hMOR
- ✓ Antagonist at hKOR
- ✓ Antagonist at hDOR with low potency

- Gilliland, K. M. *et al. ACS Chem. Neurosci*. **2020**, *11*, 3870.
- Sames, D. *et al. J. Am. Chem. Soc*. **2016**, *138*, 6754.

Mitragynine is G-Protein Biased

- Mitragynine Does Not Recruit β-arrestin





- Mitragynine exhibits less respiratory depression than codeine

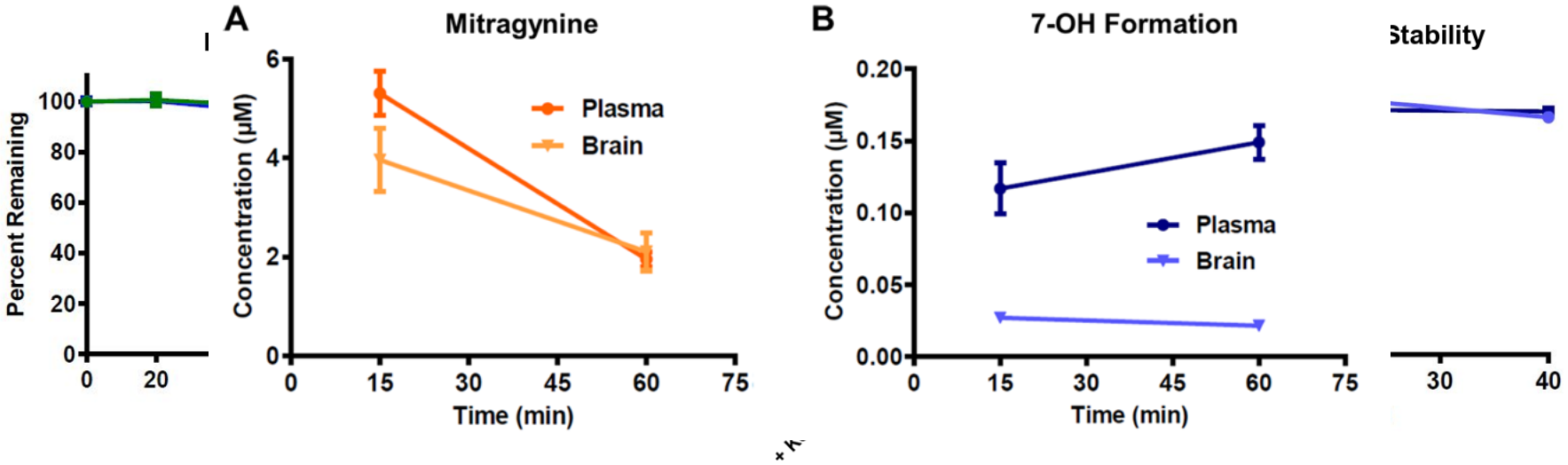
Mitragynine and 7-OH exhibit significant efficacy for activation in the G protein dissociation assay, there is a strong qualitative bias in favor of G protein signaling.

- Sames, D. *et al. J. Am. Chem. Soc.* **2016**, *138*, 6754.

7-Hydroxymitragynine Is an Active Metabolite

- Some "strange" phenomena

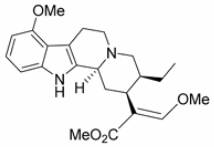
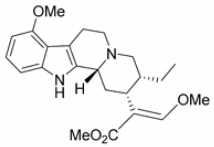
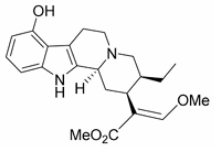
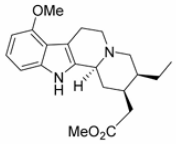
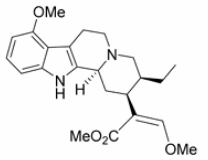
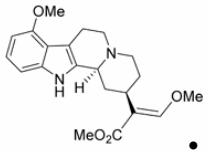
	Route	Test	ED_{50} (mg/kg)	hMOR		mMOR
	s.c.	Tail flick	>31	EC_{50} (nM)	E_{max} (%)	IC_{50} (μM)
Mitragynine	i.p.	Tail flick	14.4	339±178	34	1.1
	p.o.	Tail flick	17.8			

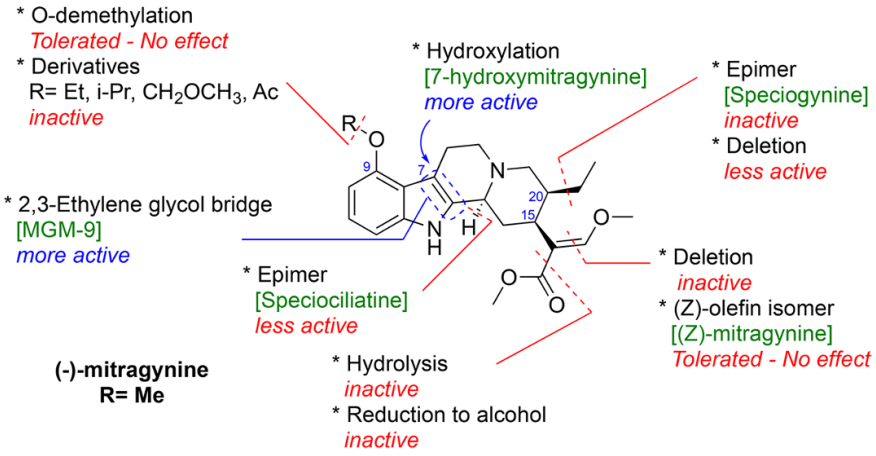


Further, the analgesia induced by mitragynine appears to depend largely on formation of 7-OH as a metabolite and not on the parent compound.

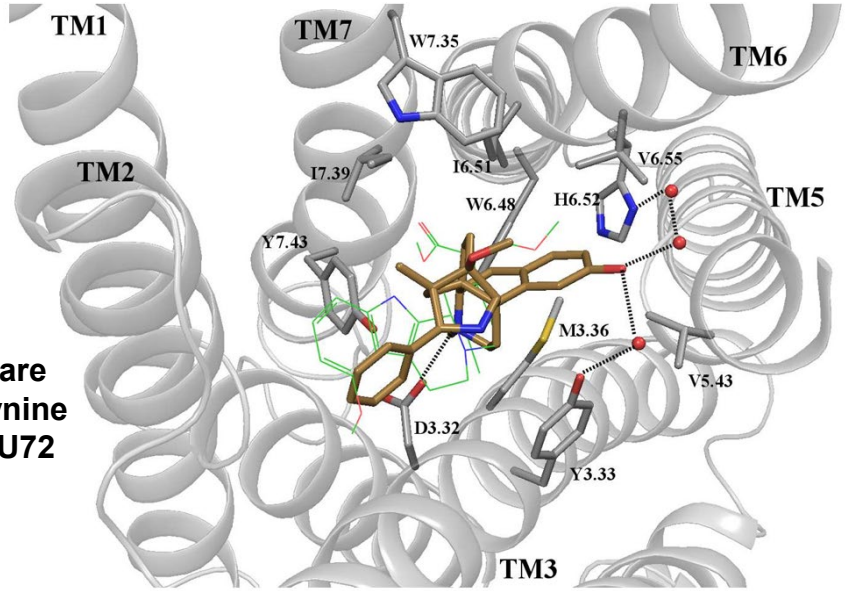
- Douglas, B. *et al. Arch. Int. Pharmacodyn. therapie* **1972**, *198*, 145.
- Sames, D. *et al. ACS Cent. Sci.* **2019**, *5*, 992.

Structure–Activity Relationships

Compound	Structure	$EC_{50} \pm SEM$ (% efficacy) (μM) [a]
(-)-mitragynine		0.339 ± 0.178 (34%)
(+)-mitragynine		3.34 ± 1.1 (18%)
1		0.681 ± 0.379 (29%)
2		>50
11		0.219 ± 0.071 (38%)
3		12 ± 7.6 (59%)



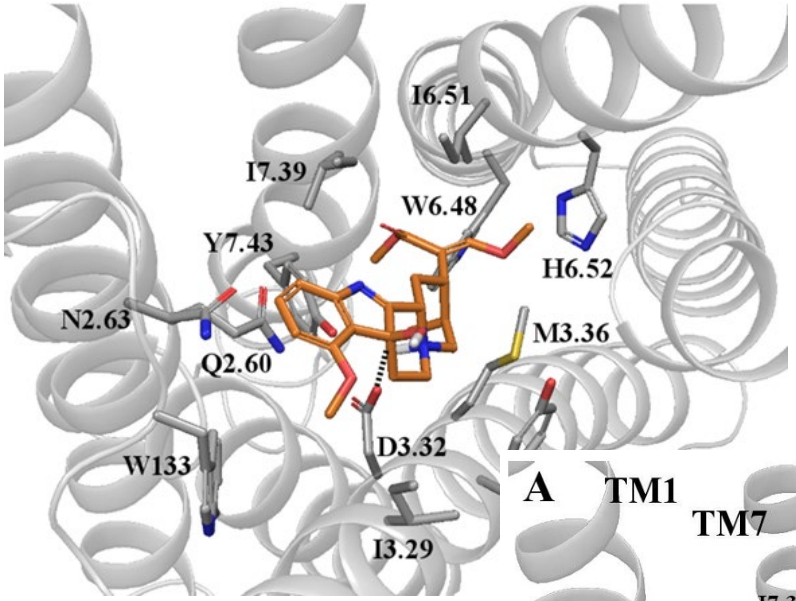
Compare mitragynine with BU72



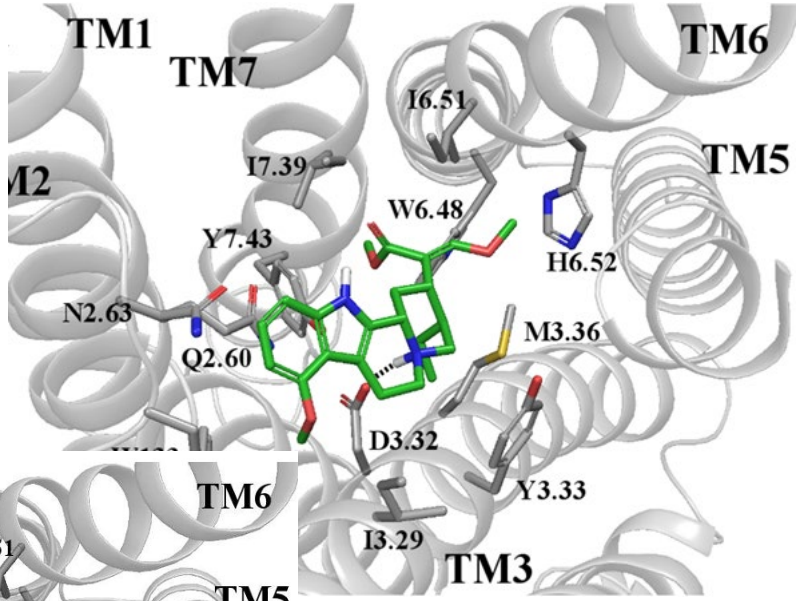
- Sames, D. *et al. J. Am. Chem. Soc*. **2016**, *138*, 6754.
- Gilliland, K. M. *et al. ACS Chem. Neurosci*. **2020**, *11*, 3870.

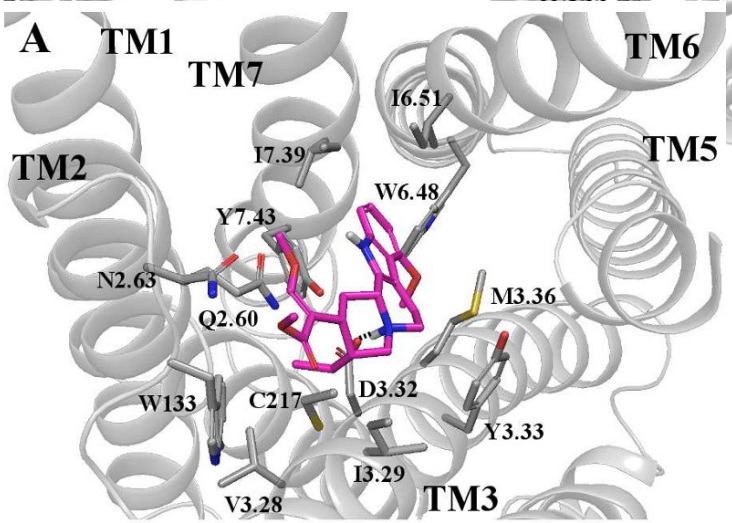
Structure−Activity Relationships

Mitragynine



7-Hydroxymitragynine



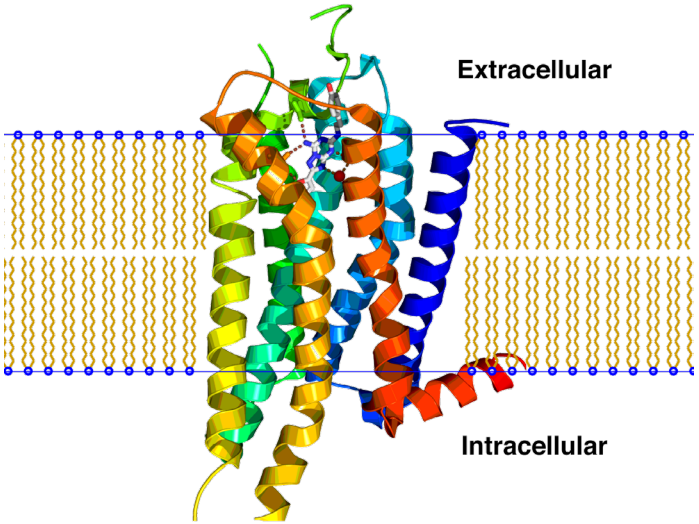


***ent*-Mitragynine**

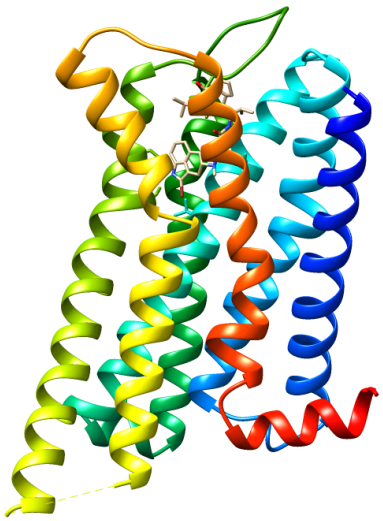
- Sames, D. *et al. J. Am. Chem. Soc*. **2016**, *138*, 6754.

Non-opioid Pharmacology

- Mitragynine binds to non-opioid CNS targets



- ✓ **Alpha-2 adrenergic receptors (a2R)**
- ✓ **Adenosine A_{2a} receptors**
- ✓ **Dopamine D_2 receptors**
- ✓ **Serotonin receptors 5-HT_{2C} and 5-HT_7**



	Binding site				
Mitragynine	5-HT_{1A}	5-HT_{1B}	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}
100 nm	9.7	-0.2	-0.9	23.0	-8.2
10 µm	76.7	8.2	49.9	90.7	14.7

Percent Displacement of Radioligands

- McCurdy, C. R. *et al. J. Med. Chem.* **2021**, *64*, 13510.
- Grundmanm, O. *et al. Neuropharmacology* **2018**, *134*, 108.

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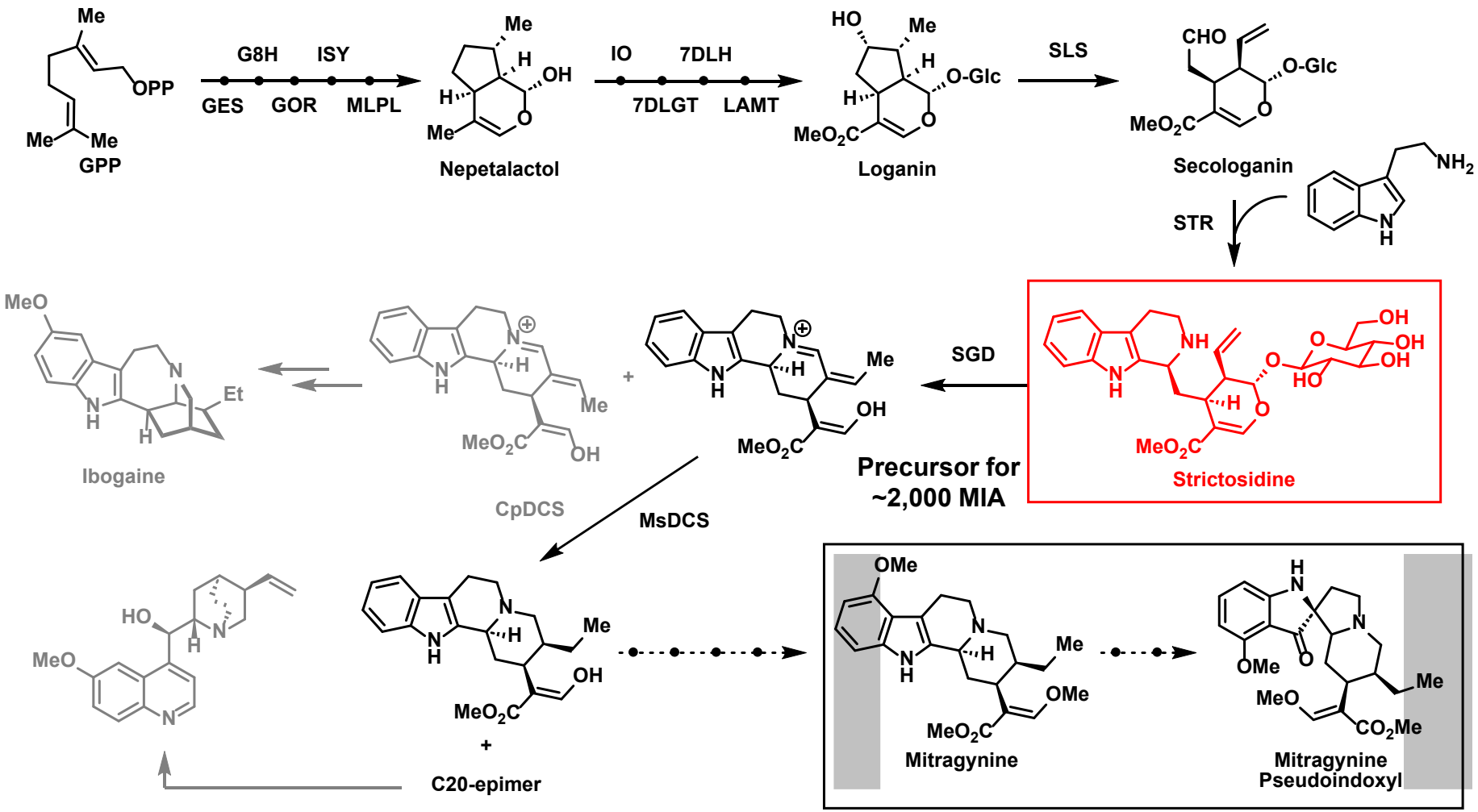
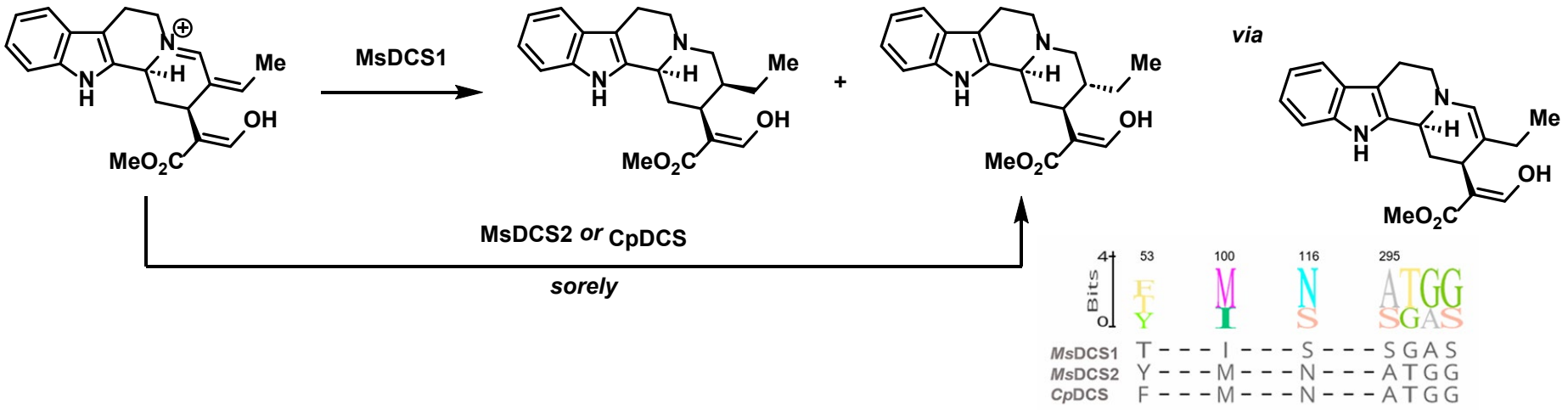
- Introduction
  - Pain and Analgesics
  - Kratom and Mitragynine
- Bioactivities of Mitragynine and Related MIA
  - Pharmacokinetics
  - Pharmacodynamics
- Total Synthesis of Mitragynine and Related MIA
  - Biosynthesis
  - Mitragynine
  - Mitragynine Pseudoindoxyl
  - Structurally-related Alkaloids (selected, recent examples)
- Summary and Prospective

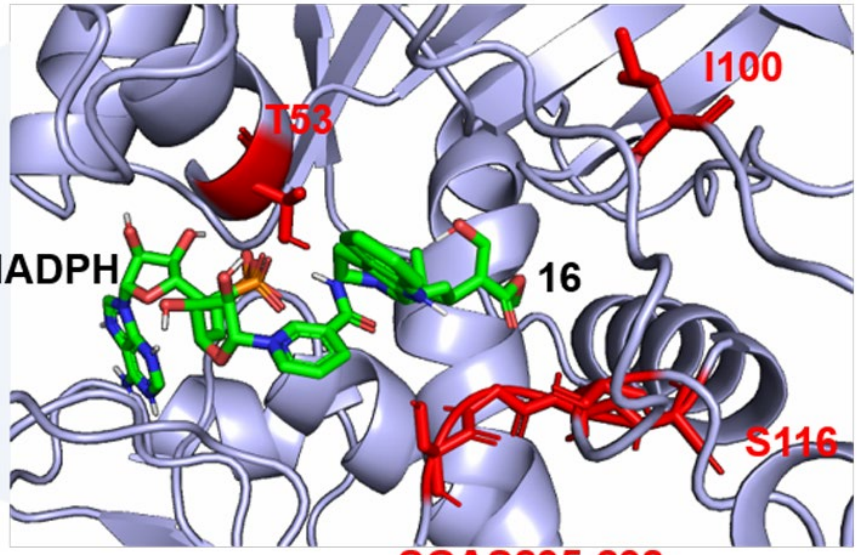
Biosynthesis of Mitragynine



- For a review, see: Tang, Y.; Billingsley, J. M. *et al. Chem. Soc. Rev.* **2021**, *50*, 6950.

Selectivity of *Ms*DCS





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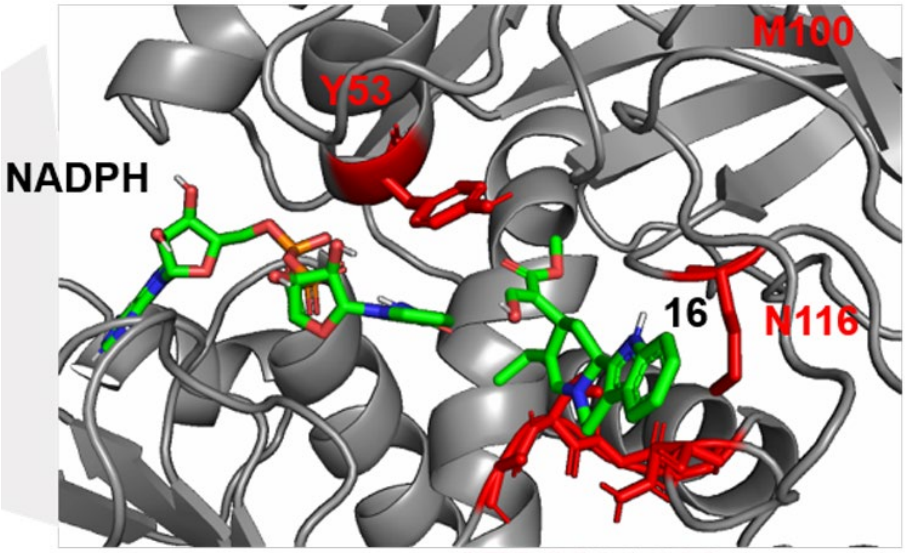
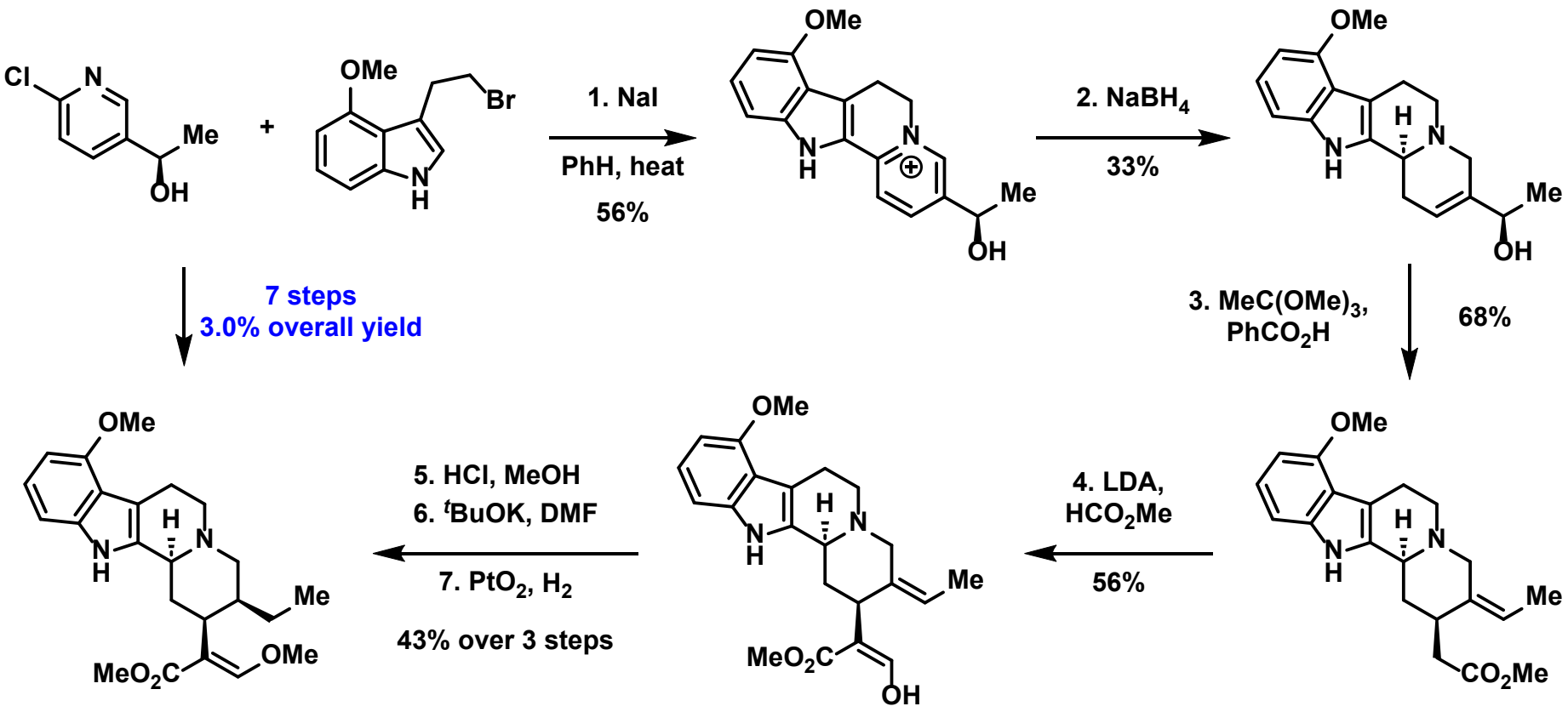


ATGG304-308

- O'Conner, S. E. *et al. J. Am. Chem. Soc.* **2023**, *145*, 4957.

Total Synthesis of Mitragynine

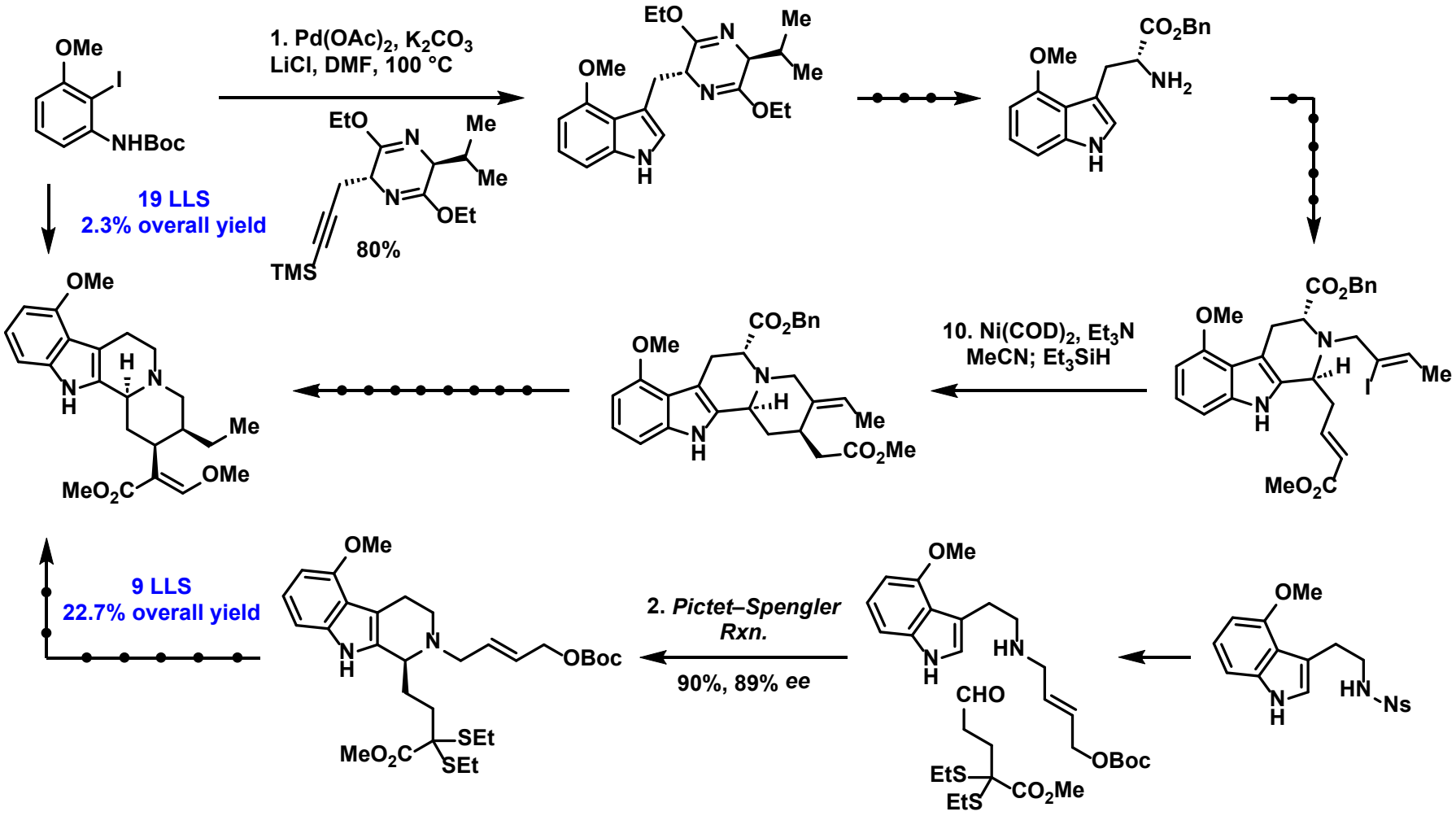
- Takayama's first total synthesis of Mitragynine



- Takayama, H. *et al. Tetrahedron Lett*. **1995**, *36*, 9337.

Total Synthesis of Mitragynine

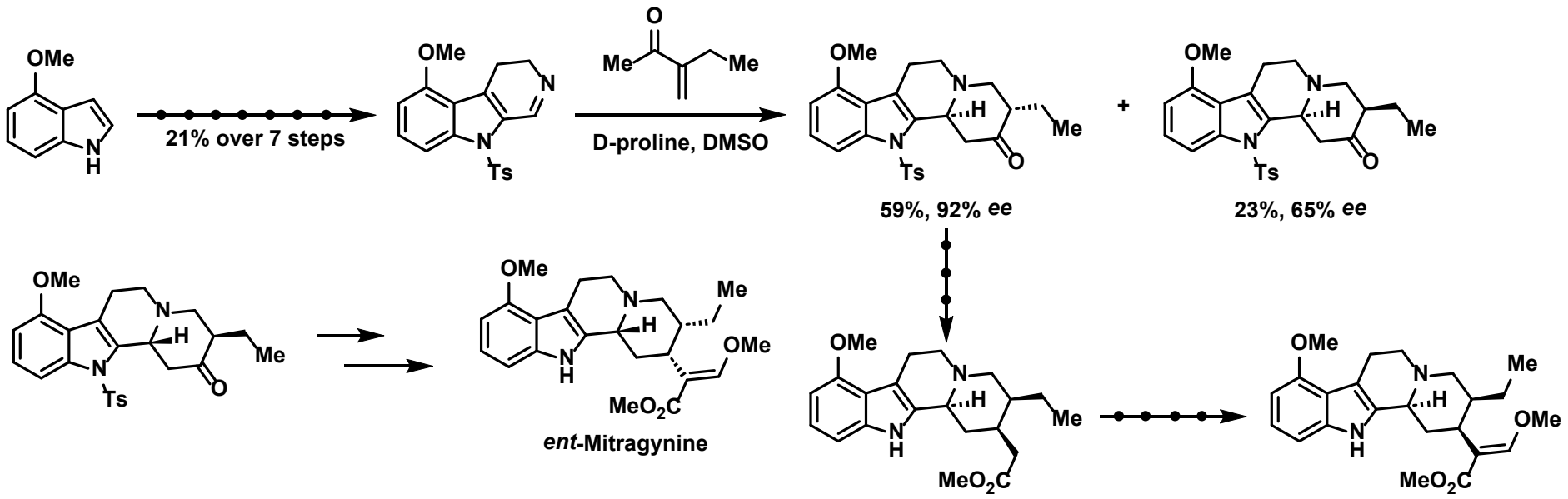
- Cook's and Hiemstra's synthesis of Mitragynine



- Cook, J. M *et al. J. Org. Chem.* **2009**, *74*, 264.; *Org. Lett.* **2007**. *9*. 3491.
- van Maarseveen, J. H.; Hiemstra, H. *et al. Chem. Commun*. **2012**, *48*, 12243.

Total Synthesis of Mitragynine

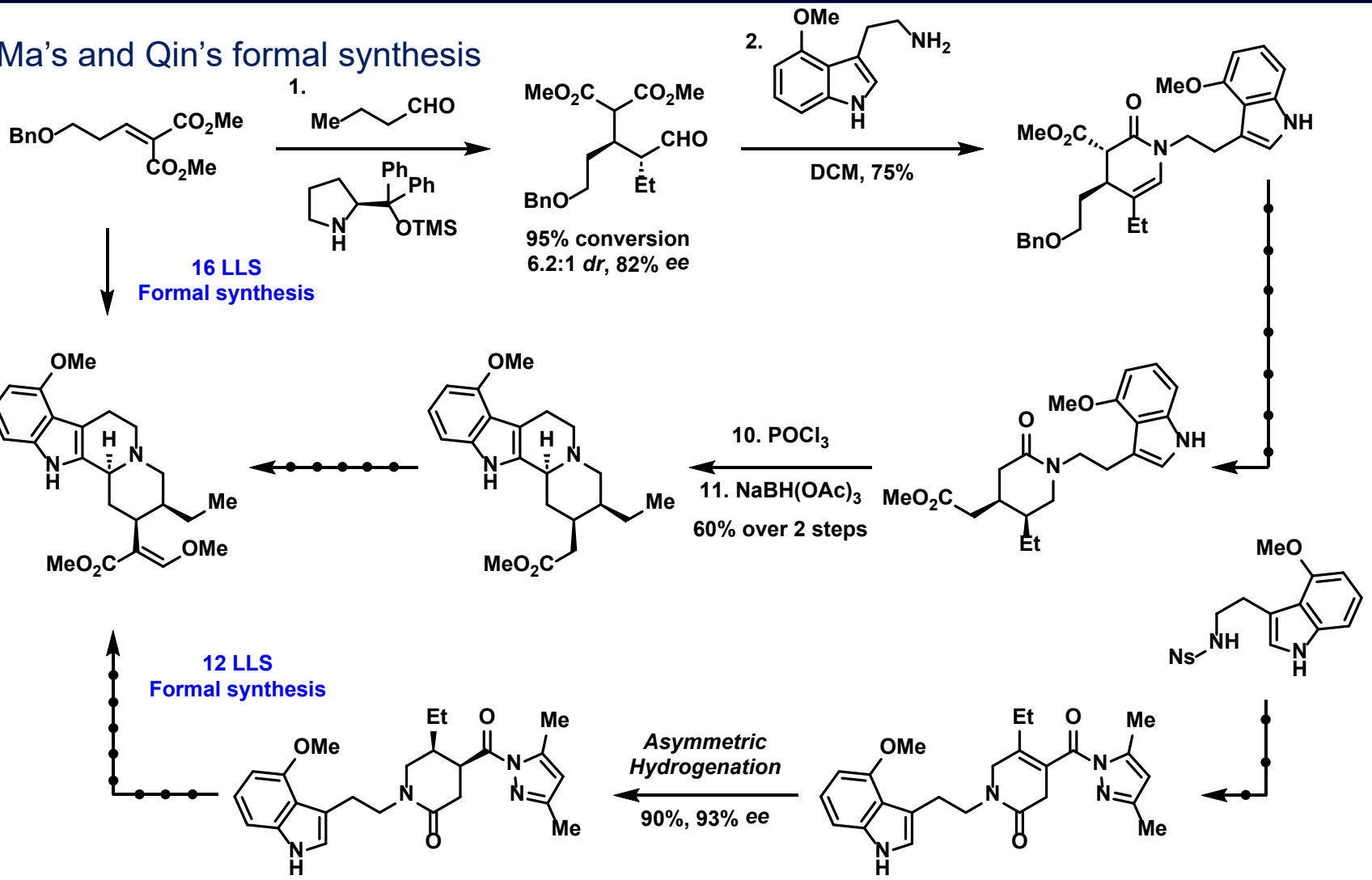
- Sames' study on Mitragynine



- Sames, D. *et al. J. Am. Chem. Soc*. **2016**, *138*, 6754.

Formal Synthesis of Mitragynine

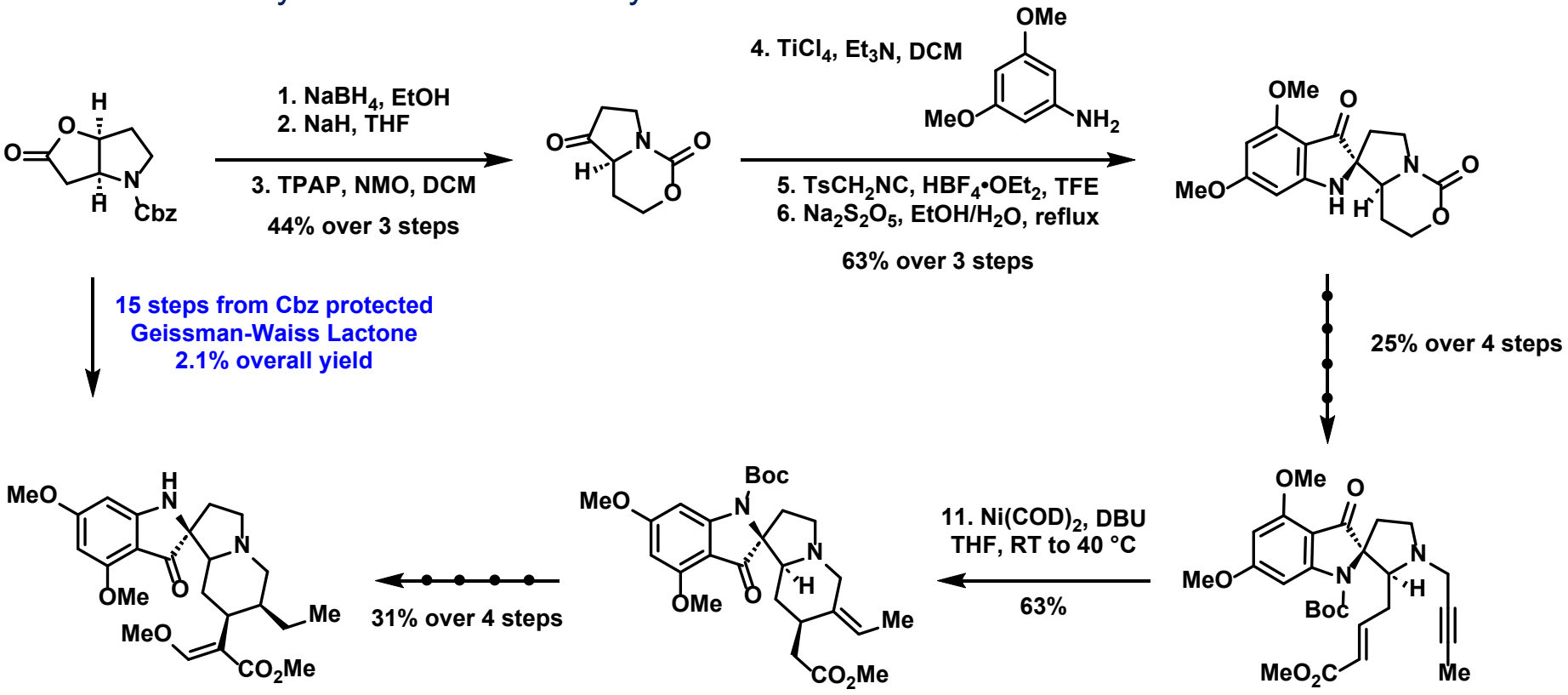
- Ma's and Qin's formal synthesis



- Ma, D. *et al. Chem. Asian J.* **2011**, *6*, 2158.
- Qin, Y. *et al. Org. Chem. Front.* **2024**, *11*, 1456.

Mitragynine Pseudoindoxyl

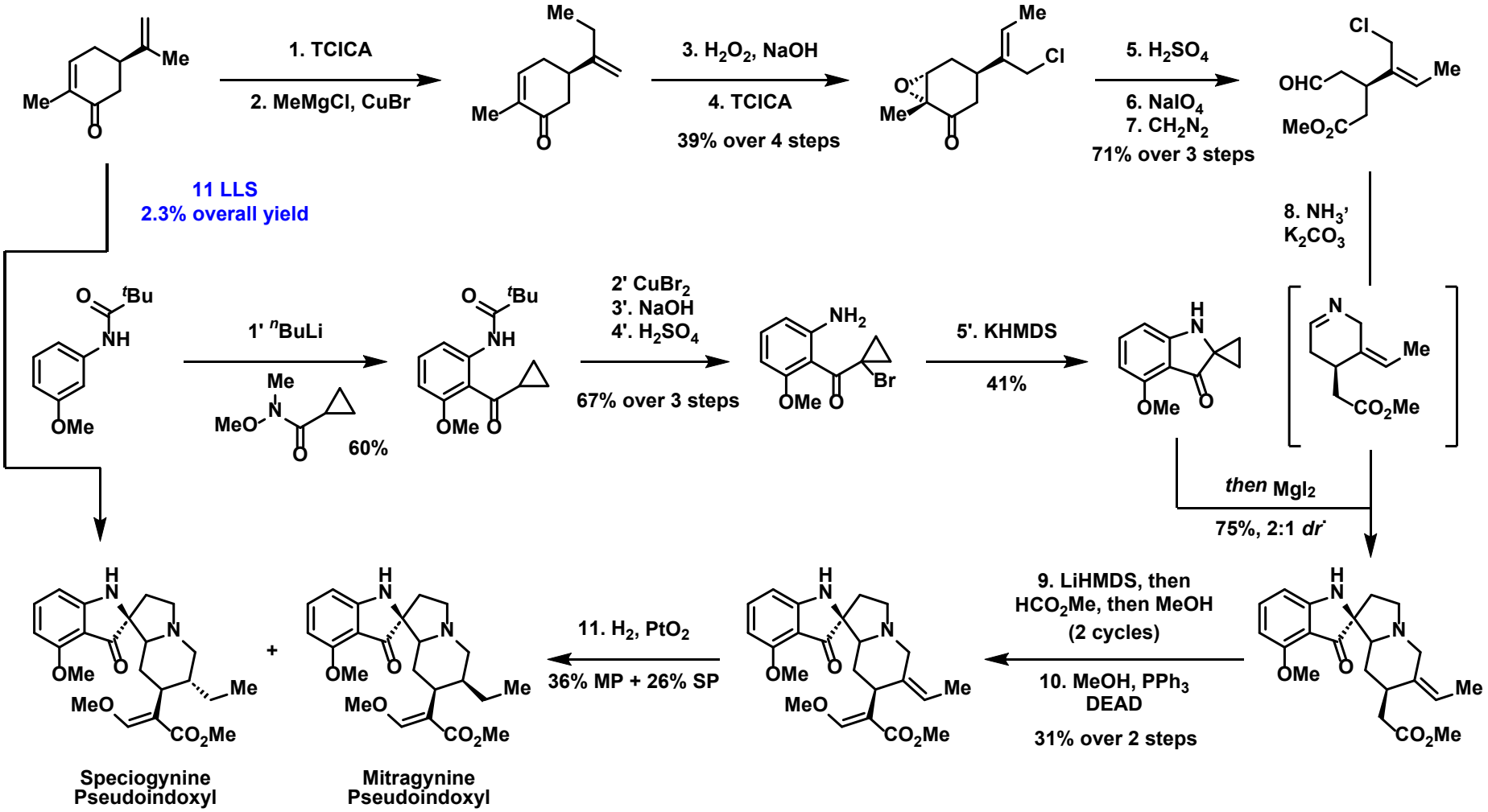
- Sorensen's synthesis of 11-methoxy MP



- Sorensen, E. J. *et al. Chem. Sci*. **2012**, *3*, 2849.

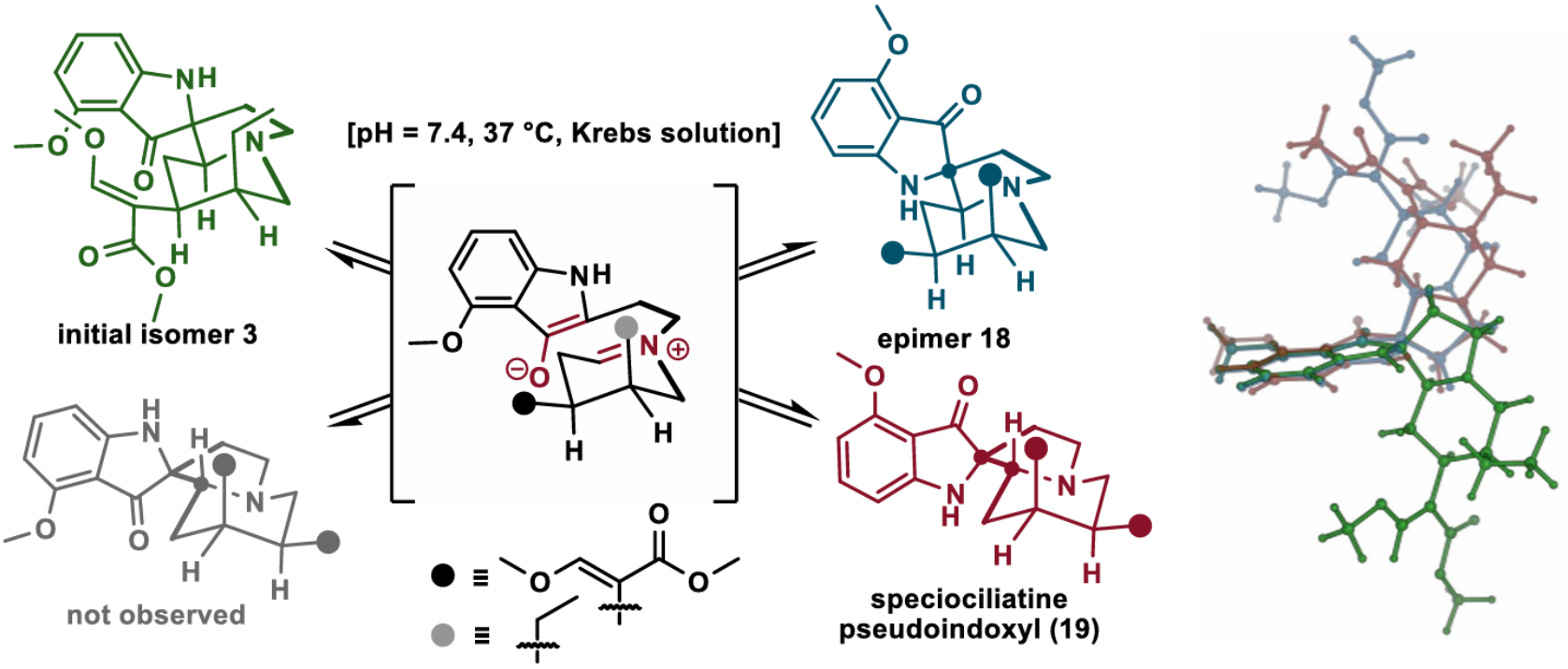
Mitragynine Pseudoindoxyl

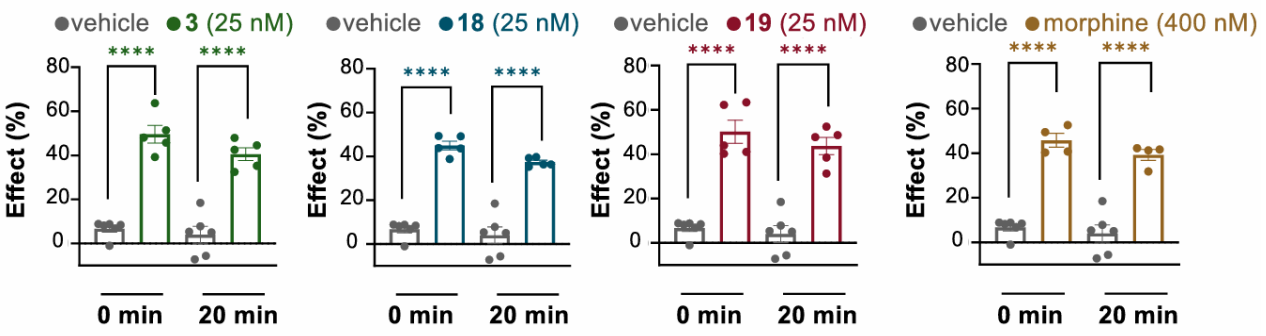
- Tibor Soós' synthetic research of MP



- Al-Khrasani, M.; Varga, S.; Soós, T. *et al. Angew. Chem. Int. Ed*. **2023**, e202303700.

A Dynamic Ensemble of Stereoisomers

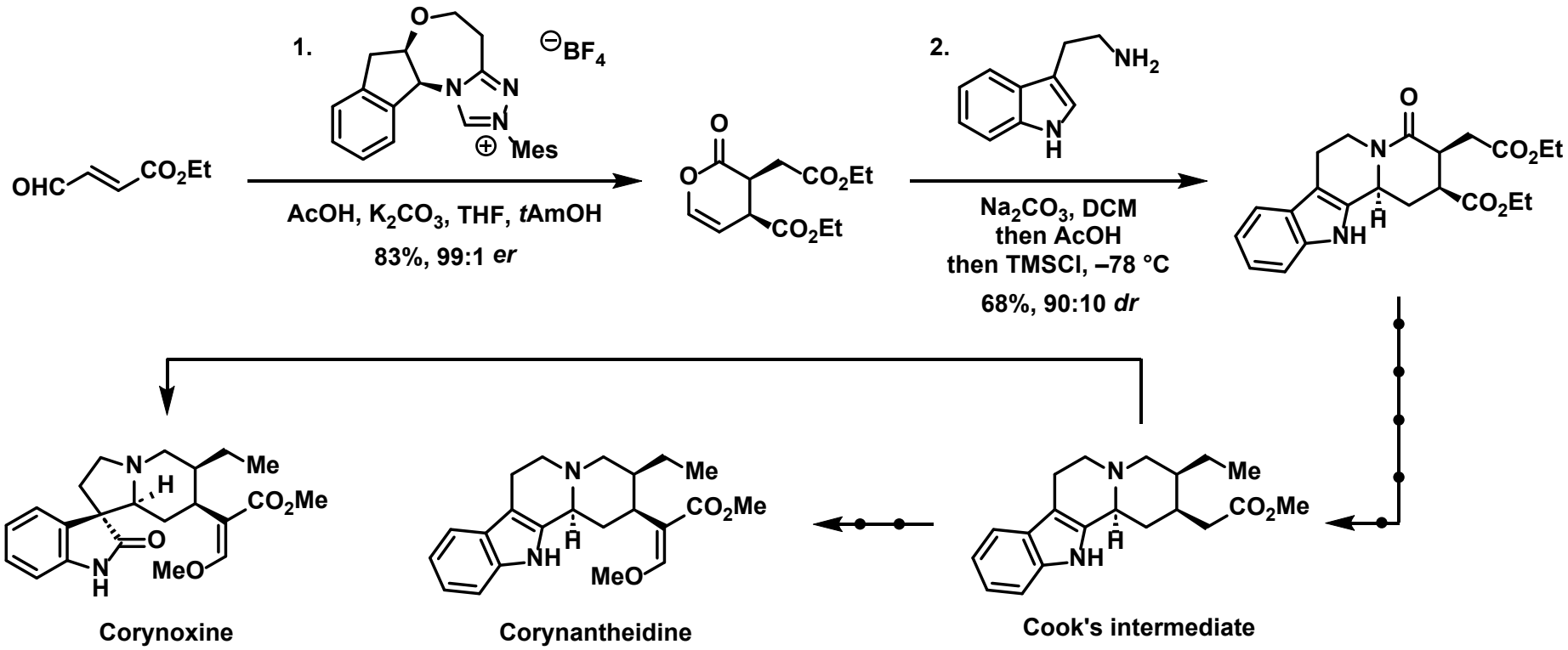




- Al-Khrasani, M.; Varga, S.; Soós, T. *et al. Angew. Chem. Int. Ed*. **2023**, e202303700.

Structurally-related Alkaloids

- Scheidt's synthesis of Corynantheine-Type Corynanthe alkaloids

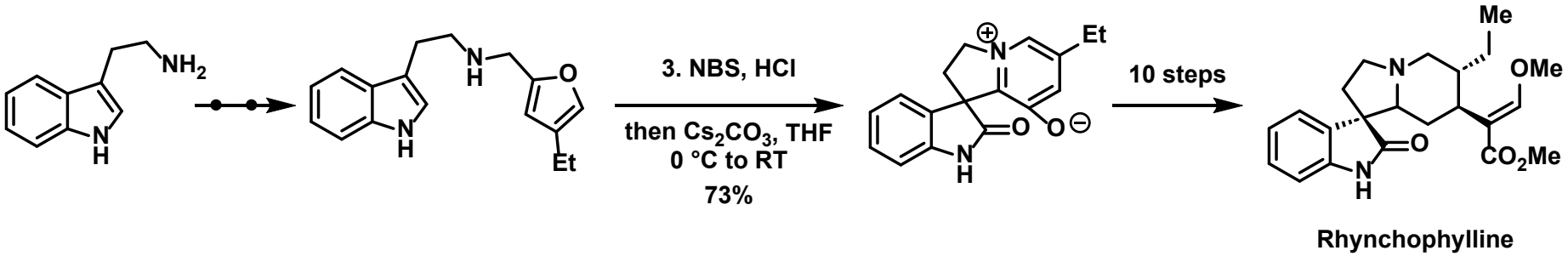


13 articles of the total synthesis of Corynanthe alkaloids have been reported.

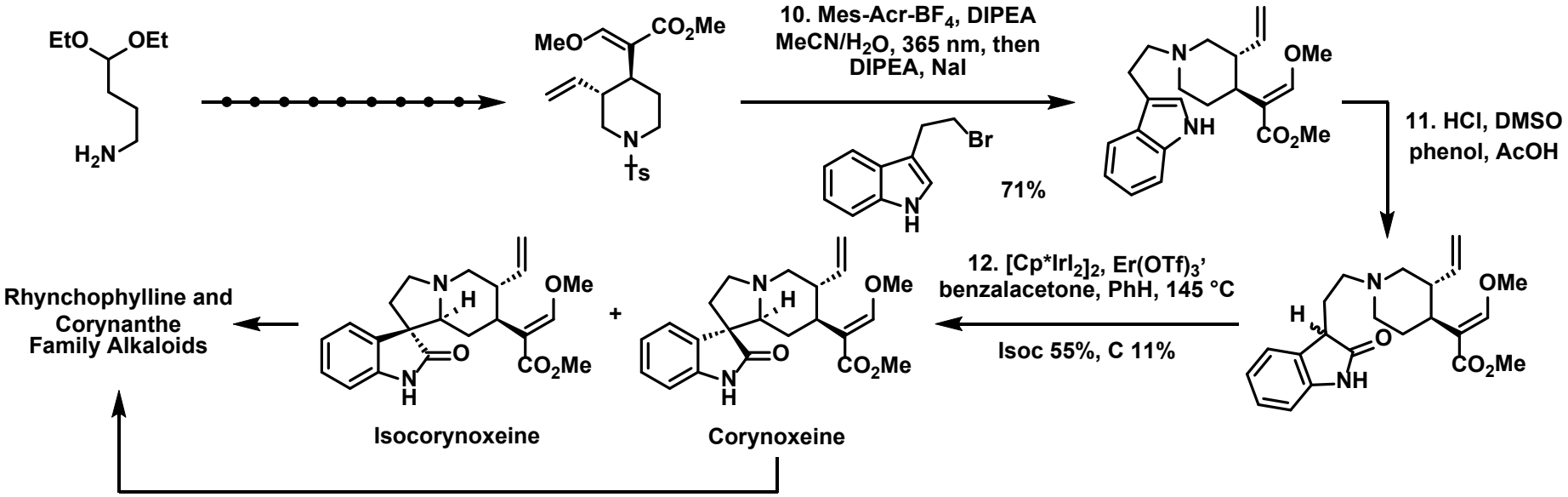
- Scheidt, K. A. *et al. J. Am. Chem. Soc.* **2024**, *146*, 118.

Structurally-related Alkaloids

- Qi's synthesis of Rhynchophylline (from *Uncaria* spp.)

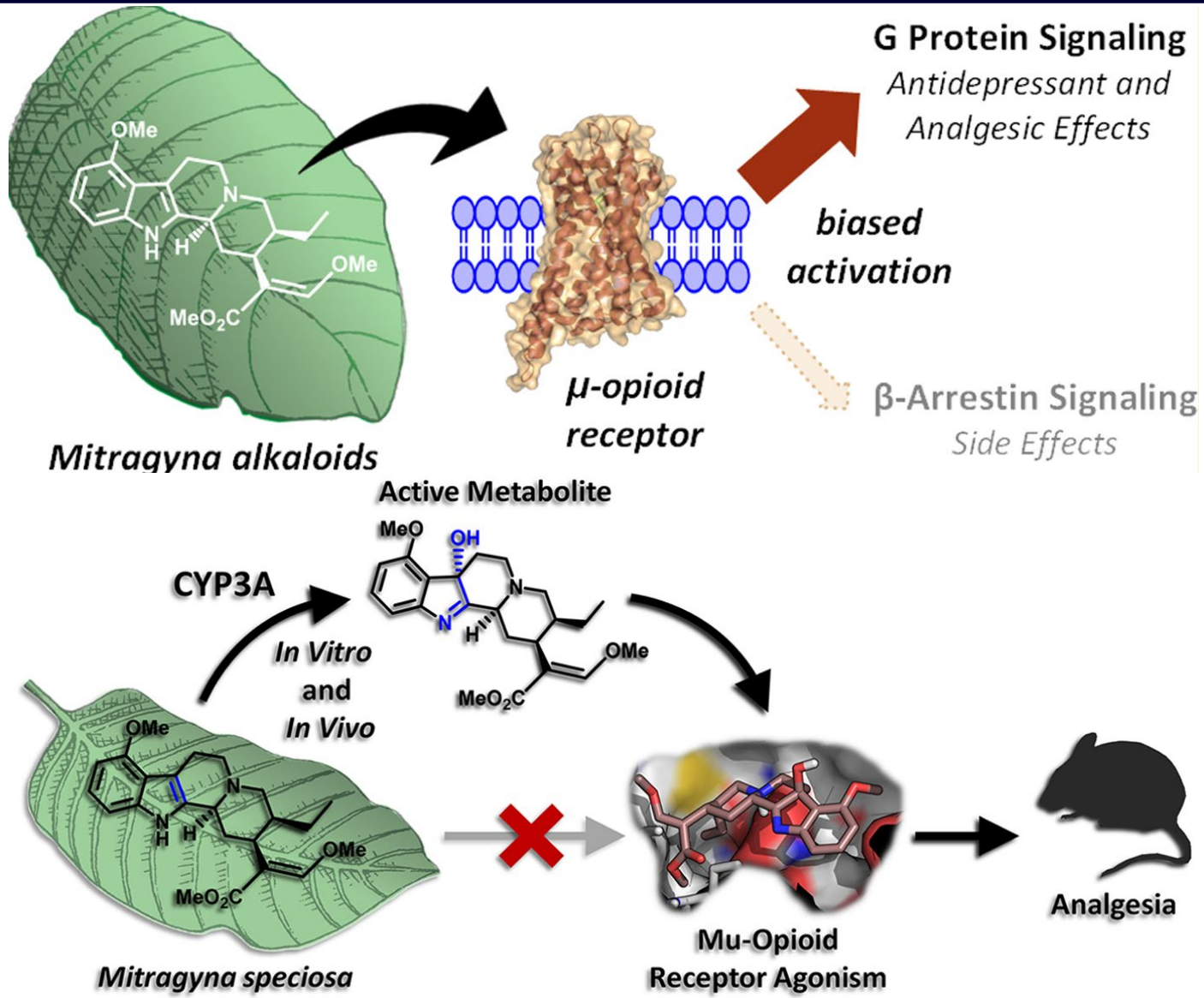


- Zhao's collective syntheses spirocyclic oxindole alkaloids



- Qi, X. *et al. Org. Lett*. **2024**, *26*, 824.
- Zhao, Q.-S. *et al. J. Am. Chem. Soc*. **2024**, *146*, 7616.

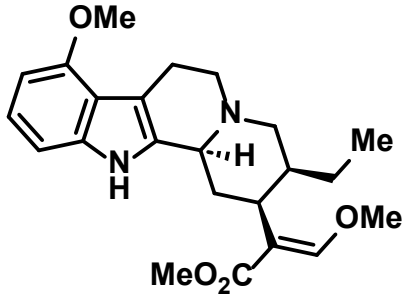
Summary

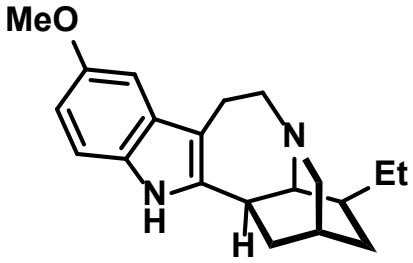

G Protein Signaling
Antidepressant and
Analgesic Effects
biased
activation
β-Arrestin Signaling
Side Effects
μ-opioid
receptor
Mitragyna alkaloids
Active Metabolite
CYP3A
In Vitro
and
In Vivo
Mitragyna speciosa
Mu-Opioid
Receptor Agonism
Analgesia

Prospective

The New York Times

Opioid Users Call Kratom a Godsend. The F.D.A. Says It's a Menace.





Powerful Psychedelic Gains Renewed Attention as a Treatment for Opioid Addiction

…st in ibogaine, which appears to

Gilgamesh Pharmaceuticals Awarded $14 Million National Institute on Drug Abuse Grant to Advance Novel, Cardiac-Safe Ibogaine Analog for the Treatment of Opioid Use Disorder

GILGAMESH

- https://www.nytimes.com/2019/04/17/us/kratom-overdose-deaths.html?searchResultPosition=1
- https://www.nytimes.com/2024/03/05/health/ibogaine-psychedelic-opioid-addiction.html
- https://www.prnewswire.com/news-releases/gilgamesh-pharmaceuticals-awarded-14-million-national-institute-on-drug-abuse-grant-to-advance-novel-cardiac-safe-ibogaine-analog-for-the-treatment-of-opioid-use-disorder-302089598.html?tc=eml_cleartime