What is the matter?
How to make good decisions in chemistry.

Periodic Table of the Elements

1 IA 1A	2 IIA 2A	3 IIIB 3B	4 IVB 4B	5 VB 5B	6 VIB 6B	7 VIIB 7B	8	9 VIII 8	10	11 IB 1B	12 IIB 2B	13 IIIA 3A	14 IVA 4A	15 VA 5A	16 VIA 6A	17 VIIA 7A	18 VIIIA 8A
1 H Hydrogen 1.008																	2 He Helium 4.003
3 Li Lithium 6.941	4 Be Beryllium 9.012											5 B Boron 10.811	6 C Carbon 12.011	7 N Nitrogen 14.007	8 O Oxygen 15.999	9 F Fluorine 18.998	10 Ne Neon 20.180
11 Na Sodium 22.990	12 Mg Magnesium 24.305											13 Al Aluminum 26.982	14 Si Silicon 28.086	15 P Phosphorus 30.974	16 S Sulfur 32.066	17 Cl Chlorine 35.453	18 Ar Argon 39.948
19 K Potassium 39.098	20 Ca Calcium 40.078	21 Sc Scandium 44.956	22 Ti Titanium 47.867	23 V Vanadium 50.942	24 Cr Chromium 51.996	25 Mn Manganese 54.938	26 Fe Iron 55.845	27 Co Cobalt 58.933	28 Ni Nickel 58.693	29 Cu Copper 63.546	30 Zn Zinc 65.38	31 Ga Gallium 69.723	32 Ge Germanium 72.631	33 As Arsenic 74.922	34 Se Selenium 78.971	35 Br Bromine 79.904	36 Kr Krypton 83.798
37 Rb Rubidium 85.468	38 Sr Strontium 87.62	39 Y Yttrium 88.906	40 Zr Zirconium 91.224	41 Nb Niobium 92.906	42 Mo Molybdenum 95.95	43 Tc Technetium 98.907	44 Ru Ruthenium 101.07	45 Rh Rhodium 102.906	46 Pd Palladium 106.42	47 Ag Silver 107.868	48 Cd Cadmium 112.414	49 In Indium 114.818	50 Sn Tin 118.711	51 Sb Antimony 121.760	52 Te Tellurium 127.6	53 I Iodine 126.904	54 Xe Xenon 131.294
55 Cs Cesium 132.905	56 Ba Barium 137.328	57-71	72 Hf Hafnium 178.49	73 Ta Tantalum 180.948	74 W Tungsten 183.84	75 Re Rhenium 186.207	76 Os Osmium 190.23	77 Ir Iridium 192.217	78 Pt Platinum 195.085	79 Au Gold 196.967	80 Hg Mercury 200.592	81 Tl Thallium 204.383	82 Pb Lead 207.2	83 Bi Bismuth 208.980	84 Po Polonium [208.982]	85 At Astatine 209.987	86 Rn Radon 222.018
87 Fr Francium 223.020	88 Ra Radius 226.025	89-103	104 Rf Rutherfordium [261]	105 Db Dubnium [262]	106 Sg Seaborgium [266]	107 Bh Bohrium [264]	108 Hs Hassium [269]	109 Mt Meitnerium [278]	110 Ds Darmstadtium [281]	111 Rg Roentgenium [280]	112 Cn Copernicium [285]	113 Nh Nihonium [286]	114 Fl Flerovium [289]	115 Mc Moscovium [289]	116 Lv Livermorium [293]	117 Ts Tennessine [294]	118 Og Oganesson [294]

Lanthanide Series	57 La Lanthanum 138.905	58 Ce Cerium 140.116	59 Pr Praseodymium 140.908	60 Nd Neodymium 144.243	61 Pm Promethium 144.913	62 Sm Samarium 150.36	63 Eu Europium 151.964	64 Gd Gadolinium 157.25	65 Tb Terbium 158.925	66 Dy Dysprosium 162.500	67 Ho Holmium 164.930	68 Er Erbium 167.259	69 Tm Thulium 168.934	70 Yb Ytterbium 173.055	71 Lu Lutetium 174.967
Actinide Series	89 Ac Actinium 227.028	90 Th Thorium 232.038	91 Pa Protactinium 231.036	92 U Uranium 238.029	93 Np Neptunium 237.048	94 Pu Plutonium 244.064	95 Am Americium 243.061	96 Cm Curium 247.070	97 Bk Berkelium 247.070	98 Cf Californium 251.080	99 Es Einsteinium [254]	100 Fm Fermium 257.095	101 Md Mendelevium 258.1	102 No Nobelium 259.101	103 Lr Lawrencium [262]

Periodic Table of the Elements

"Oh!
Organic Chemistry
I hated that class!"

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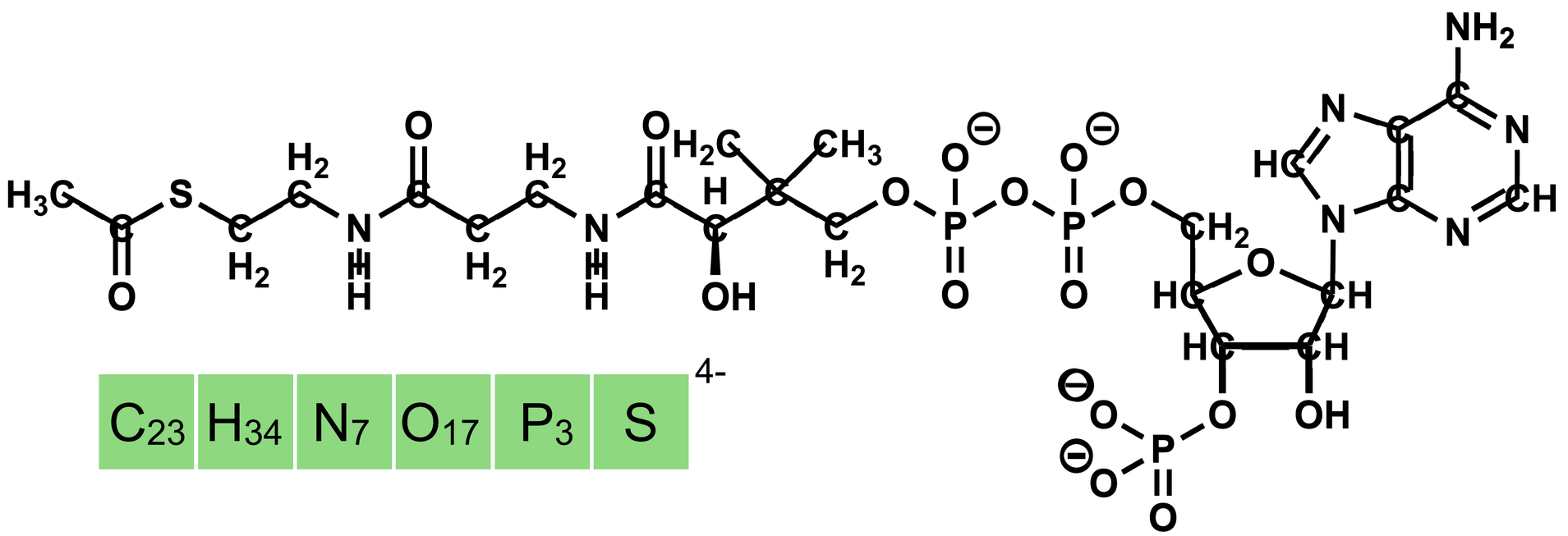
Organic Chemistry

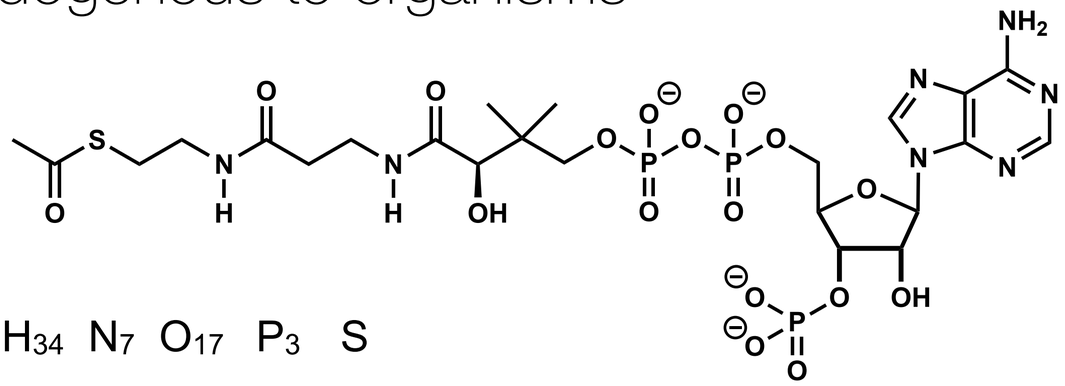


$C_{23}H_{34}N_7O_{17}P_3S^{4-}$

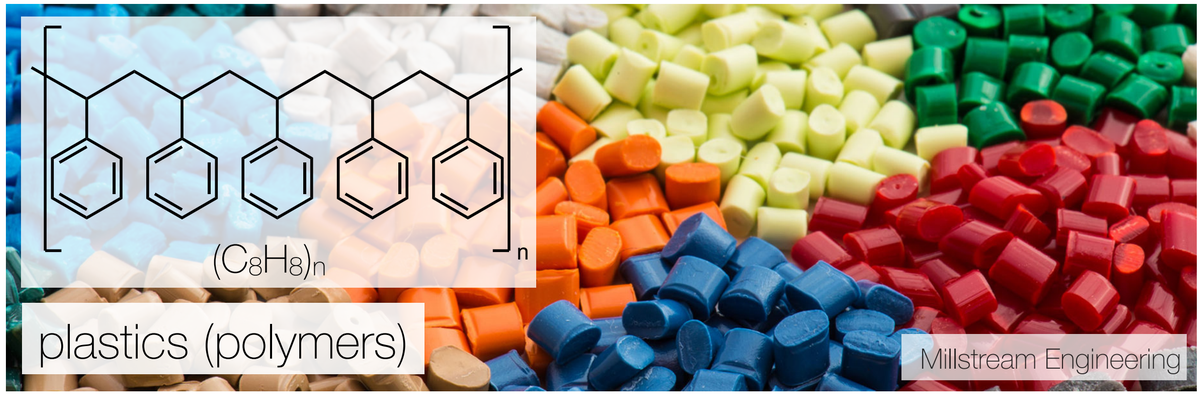
acetyl-CoA

an organic molecule (and a *compound*: 2+ kinds of elements)

endogenous to organisms



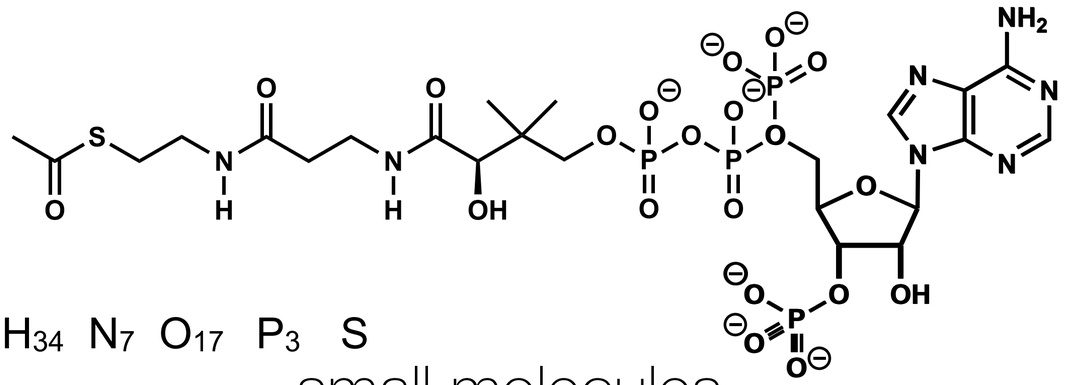
$C_{23}\ H_{34}\ N_7\ O_{17}\ P_3\ S$



F. Wöhler (1828): silver cyanate + ammonia *or*
lead cyanate + ammonia yields **urea**

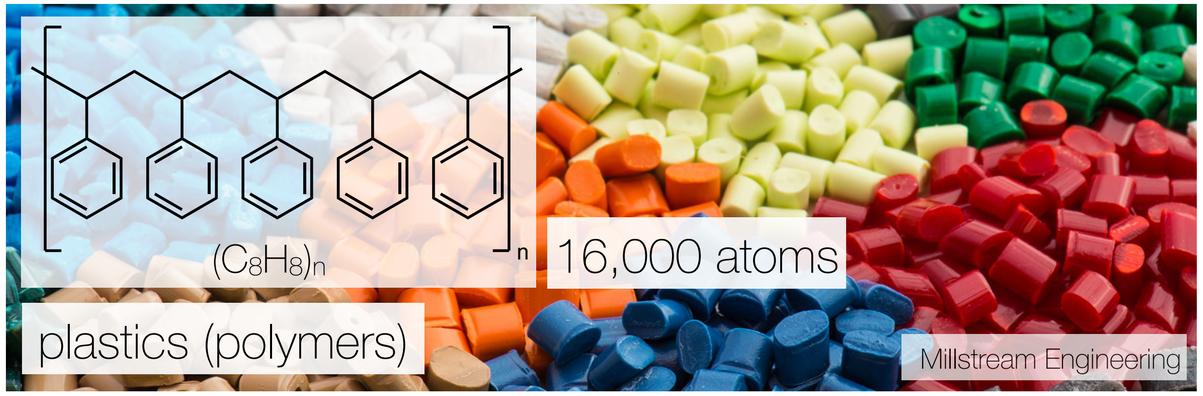
ores and minerals

JXSC Mineral

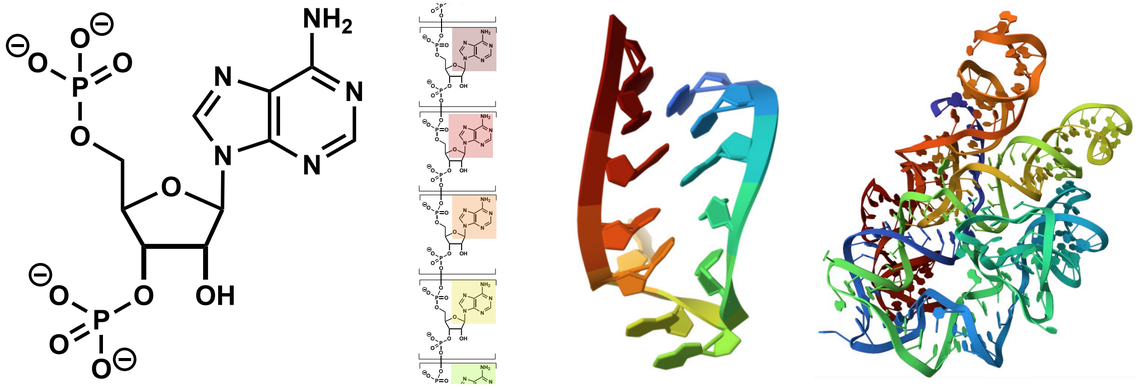


$C_{23}\ H_{34}\ N_7\ O_{17}\ P_3\ S$

small molecules



large molecules a.k.a. biologics, biopolymers



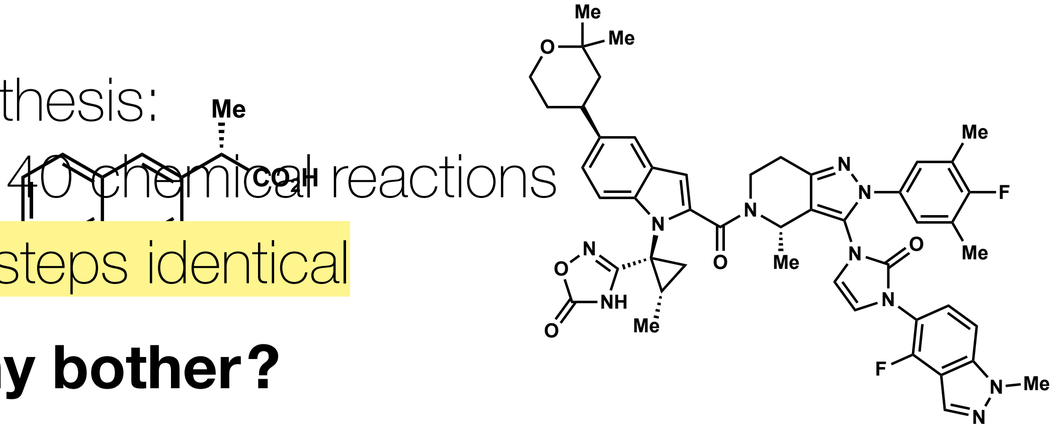
naproxin: 230 Da; orforglipron: 883 Da

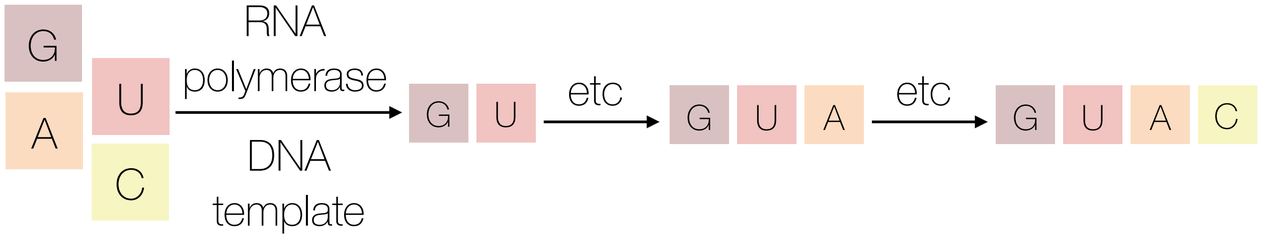
Moderna mRNA Covid vaccine: 1,329,683 Da

synthesis:

ca. 40 chemical reactions

no steps identical



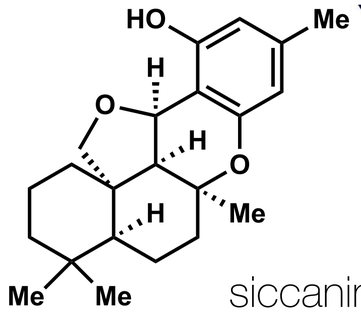


synthesis: 1 chemical reaction (4100 times)

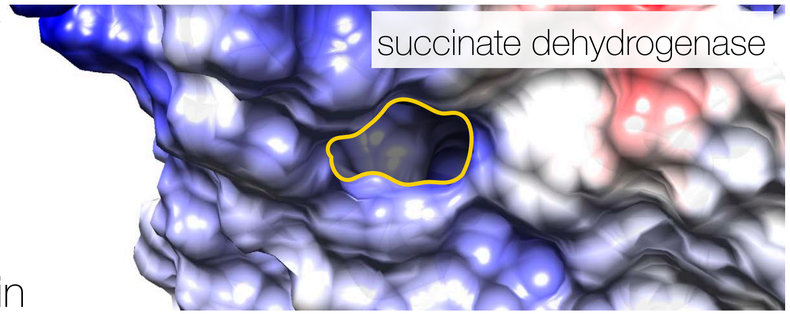
Why bother?

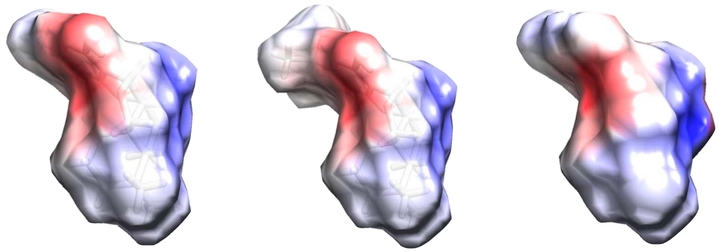
Why bother with small molecules? Atomic (subatomic?) resolution!

Exquisite control of properties and functions via *structure*: shape, electronics, movements



siccanin

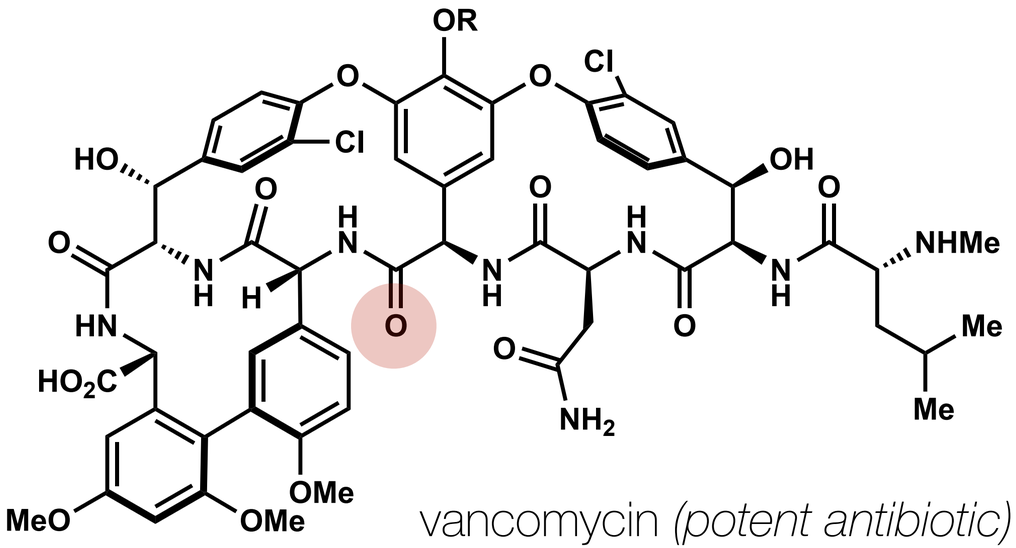




siccanin

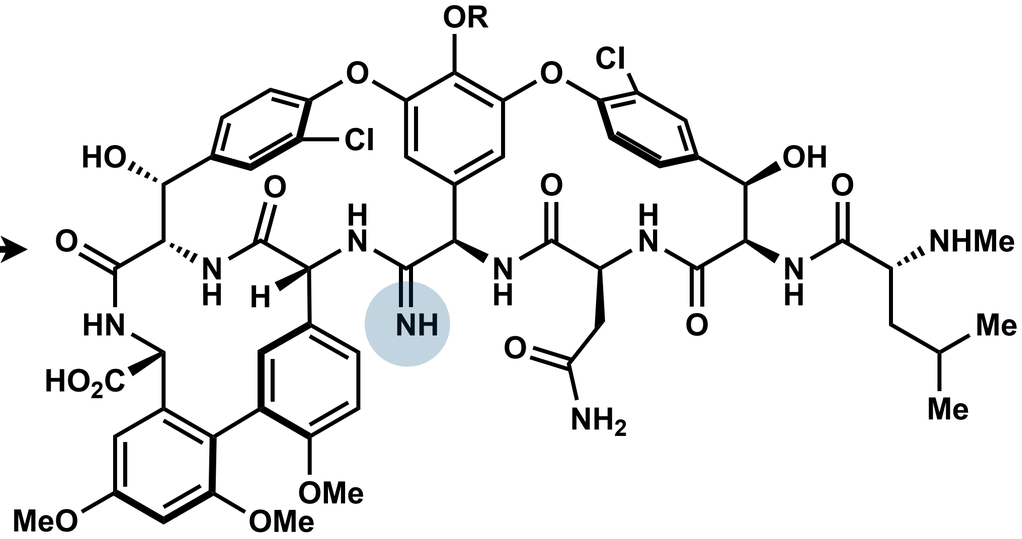
key in a lock?
no, cow in a tent!

Pharmacodynamics (PD): what a drug (molecule, compound) does to the body



vancomycin *(potent antibiotic)*

1000X potency increase



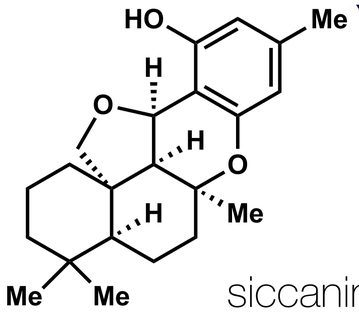
E. faecalis (VanA) MIC: 640 µg/mL *(low potency)*

E. faecalis (VanA) MIC: 0.5 µg/mL *(high potency)*

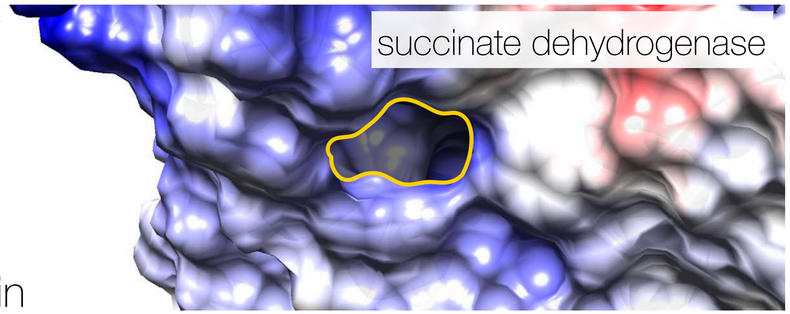
See: Boger *et al. J. Am. Chem. Soc.* 2011, *133*, 13946

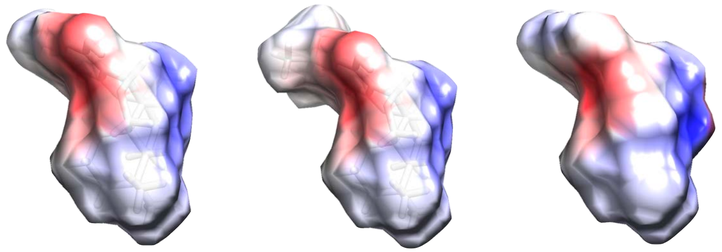
Why bother with small molecules? Atomic (subatomic?) resolution!

Exquisite control of properties and functions via *structure*: shape, electronics, movements



siccanin





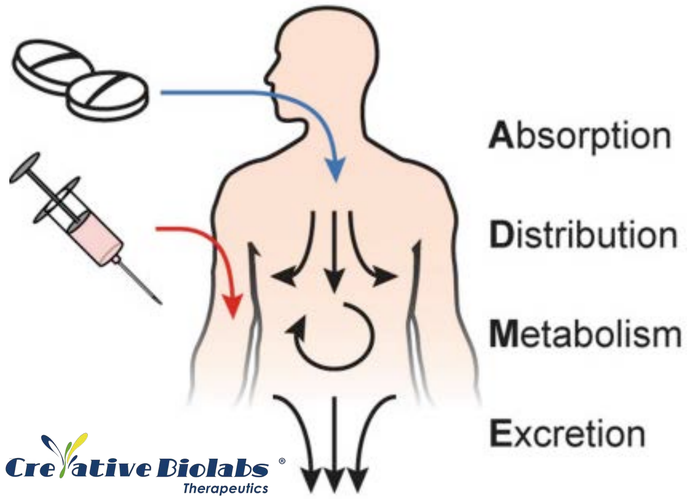
siccanin

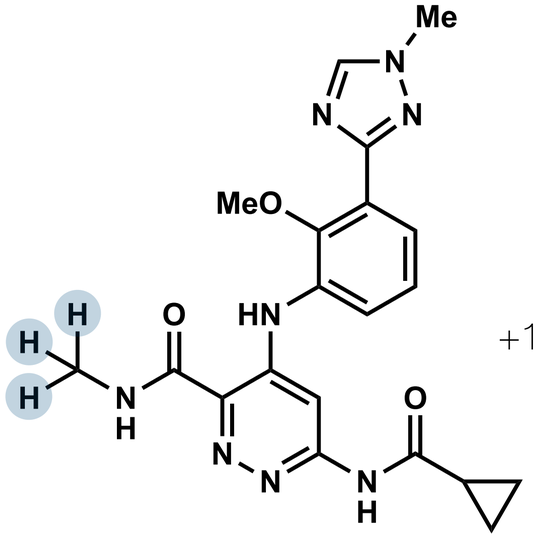
key in a lock?
no, cow in a tent!

Pharmacodynamics (PD): what a drug (molecule, compound) does to the body

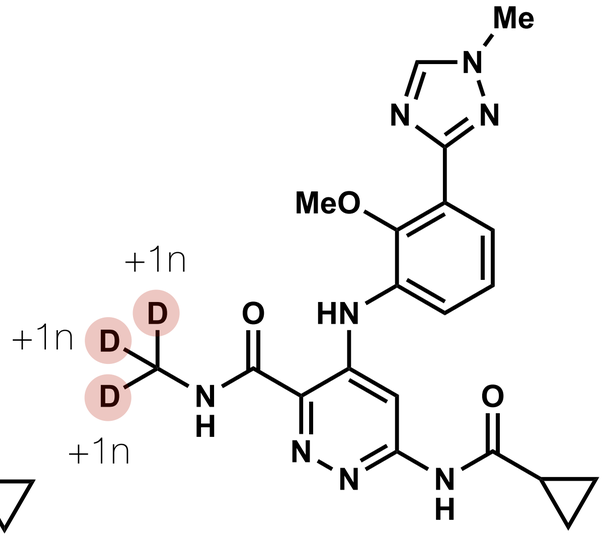
vs.

Pharmacokinetics (PK): what the body does to the drug



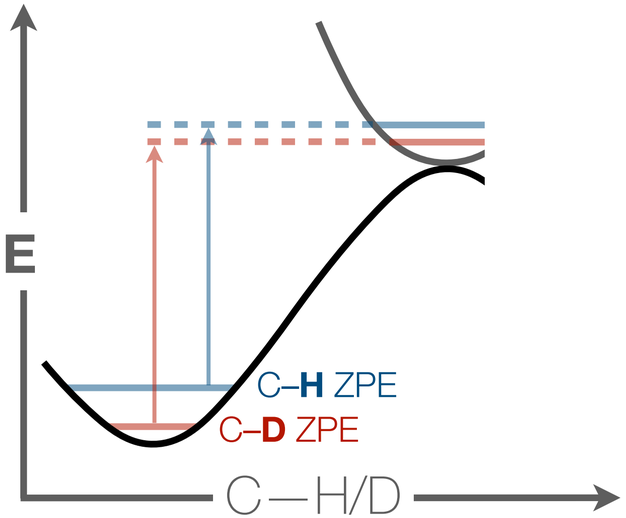


metabolism liability (BMS)

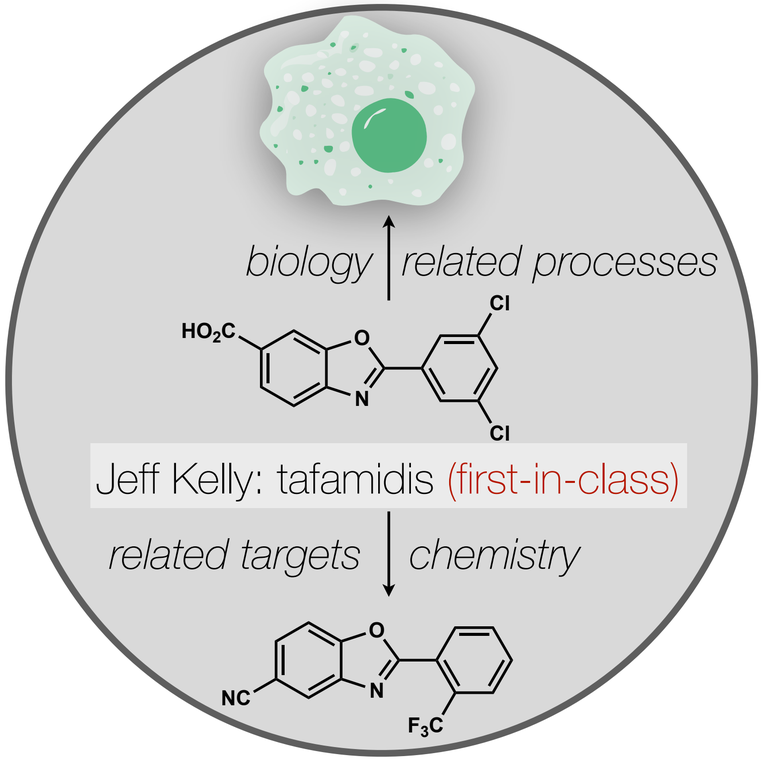


deucravacitinib (BMS)

reaction coordinate diagram



Where do small molecule drugs come from?

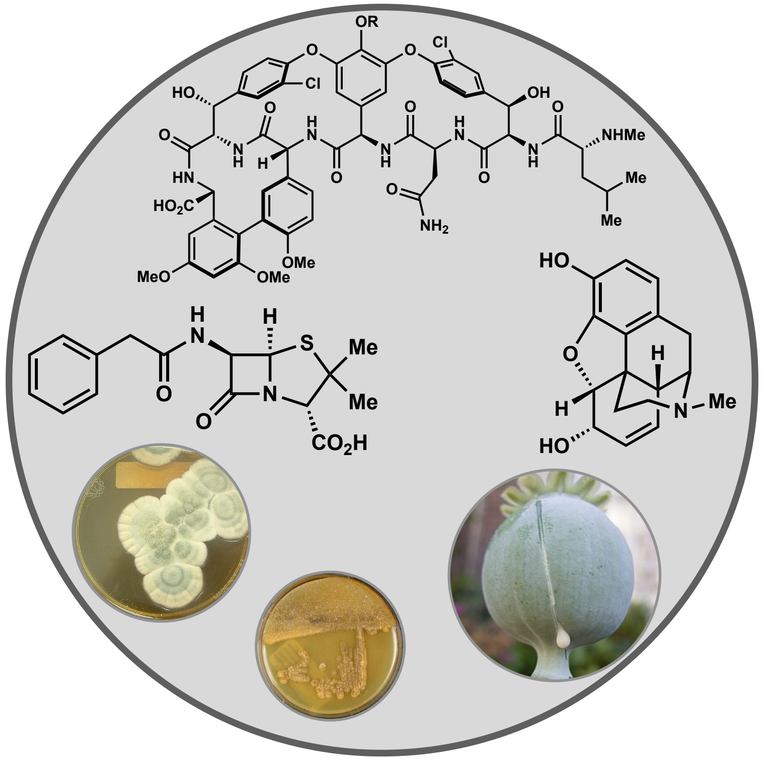


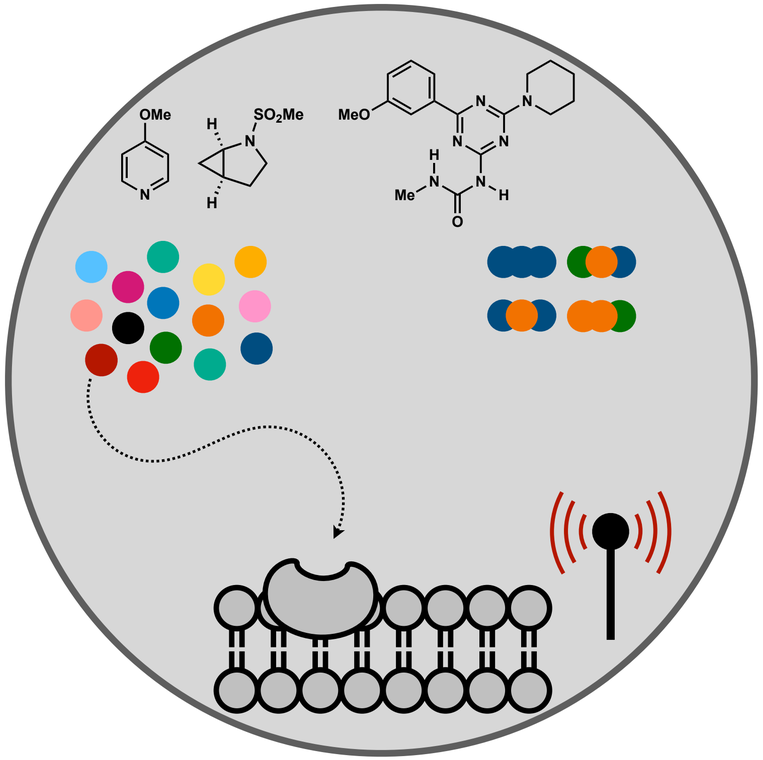
other drugs

James Black (1988 Nobel Prize)
"the most fruitful basis
for the discovery of a new drug
is to start with an old drug"

metabolites

aka natural products (NPs)





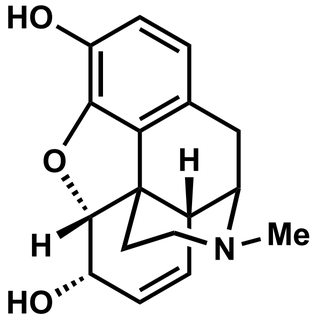
molecular libraries

fragments or
modular, combinatorial
chemical reactions:
AAA, **ABA**, **CBA**, **BBC**

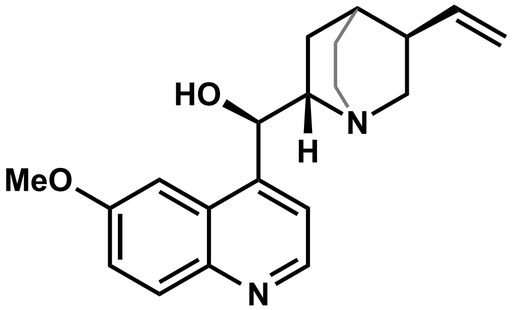
Front Row Lecture (May 2024): "Fixing Misfolded Proteins"

Traditional medicine: the **apothecary**, the original pharmacy

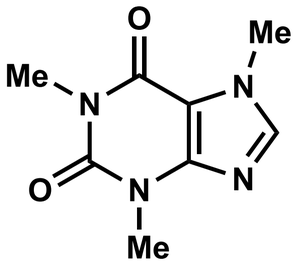
ἀποθήκη (store-house)



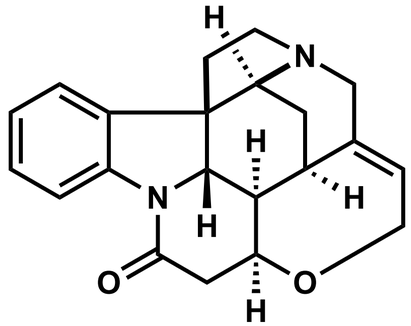
morphine
(opium poppy)



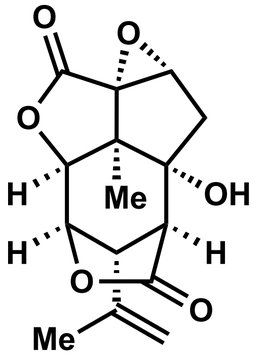
quinine
(*Cinchona calisaya*)



caffeine
(coffee, tea)



strychnine
(*Strychnos nux-vomica)*



picrotoxinin
(fishberry)

grass-associated fungi:

(source: Missouri Botanical Garden)

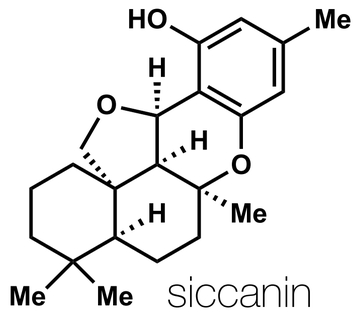
Erysiphe graminis
Puccinia graminis
Colletotrichum graminicola
Rhizoctonia solani
Moellerodiscus sp.
Sclerotinia homeocarpa
Laetisaria fuciformis

Helminthosporium sp.
(on grass blade)

competition for resources

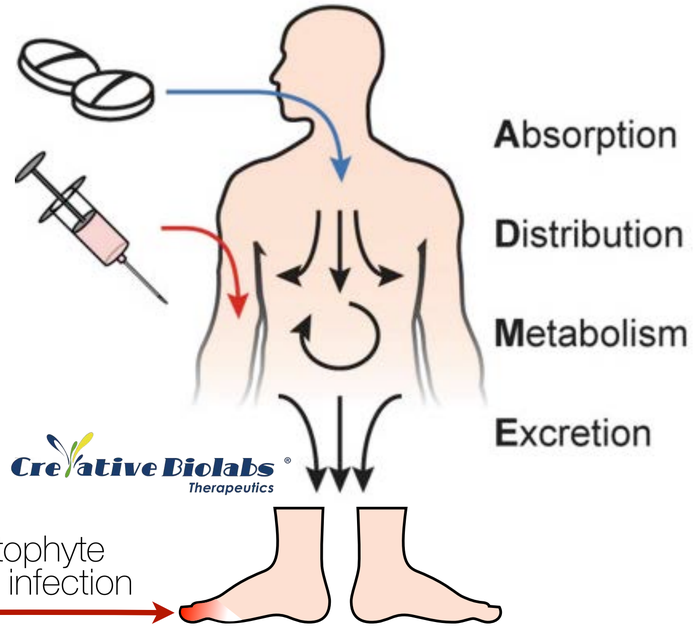
Tackle™
[athlete's foot]

Daiichi-Sankyo



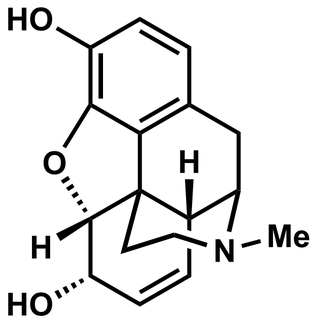
siccanin

dematophyte
fungal infection



Traditional medicine: the **apothecary**, the original pharmacy

ἀποθήκη (store-house)



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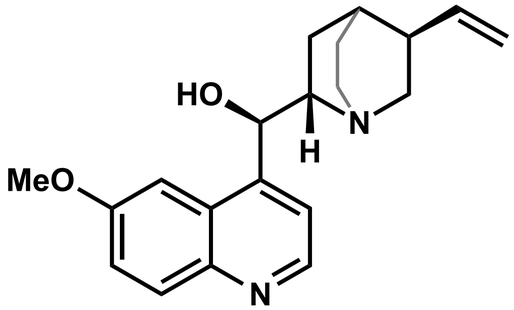
(opium poppy)



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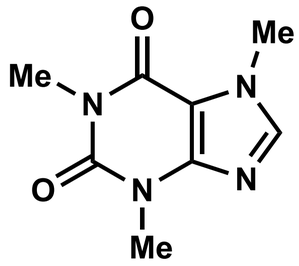
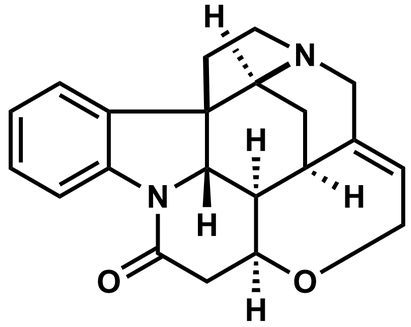
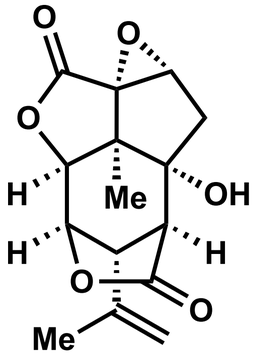


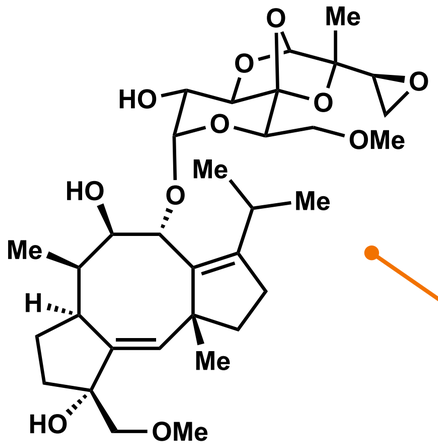
caffeine
(coffee, tea)



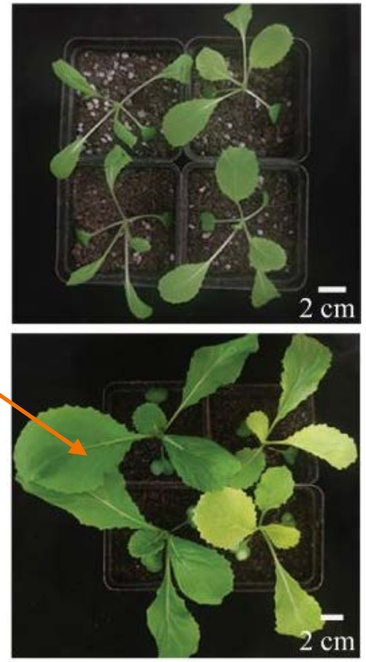
strychnine
(*Strychnos nux-vomica)*

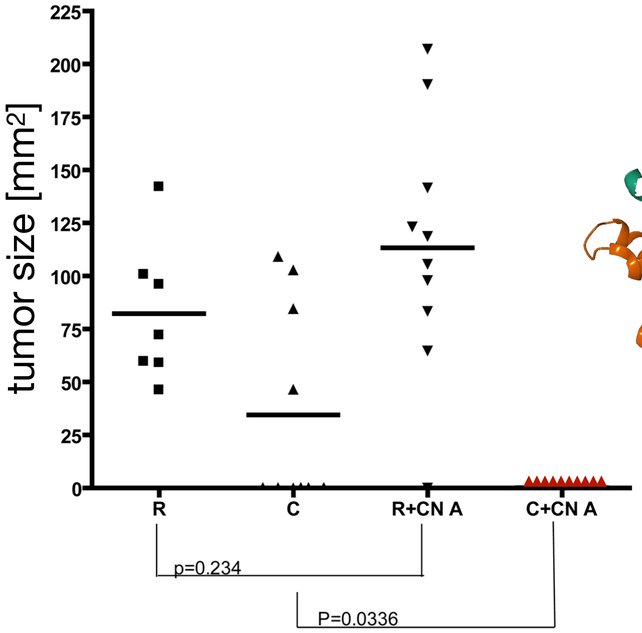


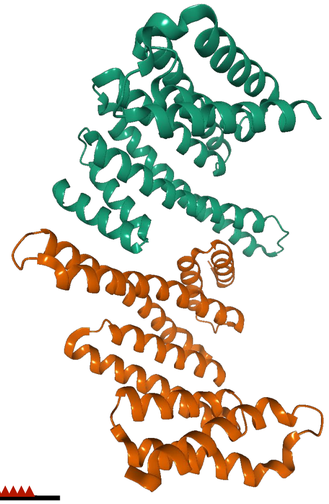
picrotoxinin
(fishberry)



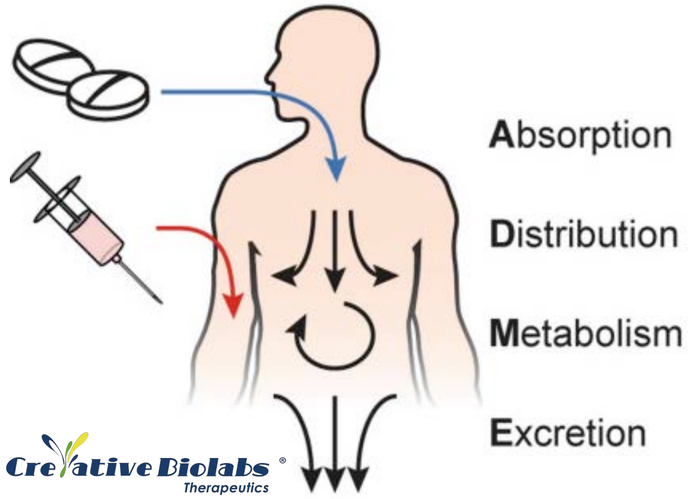
cotylenin A
(*Cladosporium* fungus)



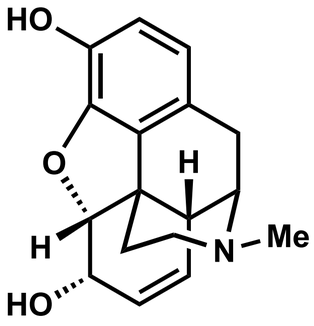




14-3-3 protein/
client stabilizer

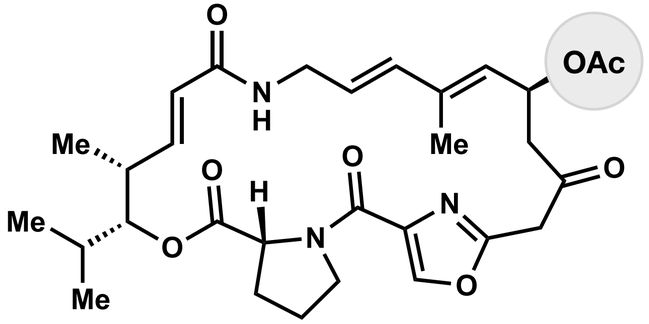


In the modern era, we can tailor natural products for human use



morphine

(μ-OR: pain, addiction, pulmonary function)



virginiamycin M2

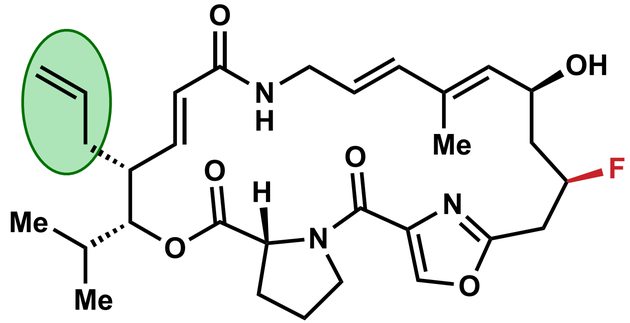
(low potency antibiotic)

Vat (enzyme)

acetyl-CoA

inactive!

[MIC 16 vs. 64 μg/mL]

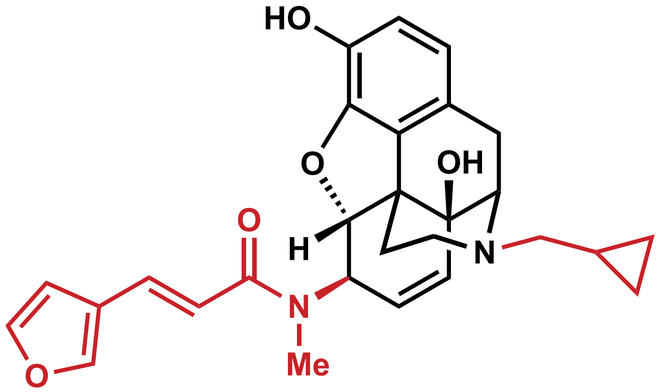


no Vat susceptibility!

[MIC 0.125 vs. 0.5 μg/mL]

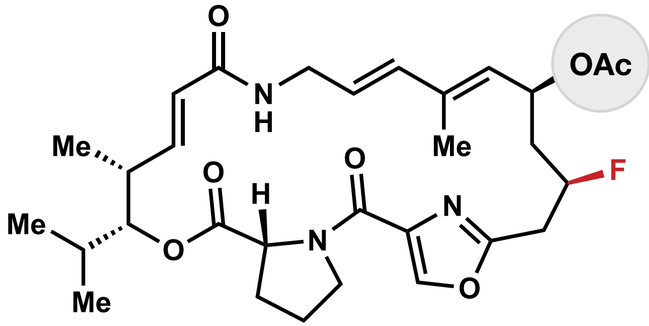
nalfurafine

(κ-OR: itch not pain, no addiction liabilities)



flopristin

(high potency antibiotic)



Vat (enzyme)

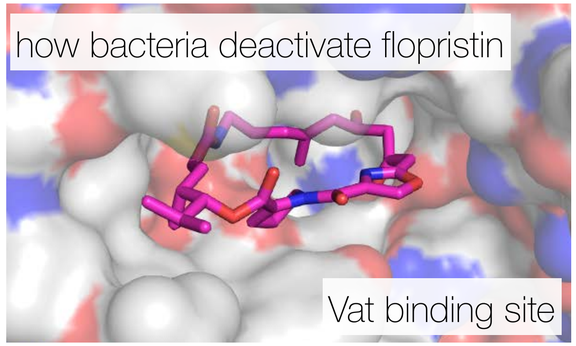
acetyl-CoA

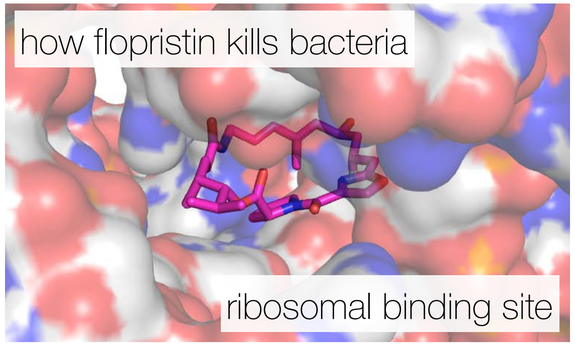
inactive!

[MIC 0.5 vs. 8 μg/mL]

Professor Ian Seiple *et al. Nature* **2020**, 145.

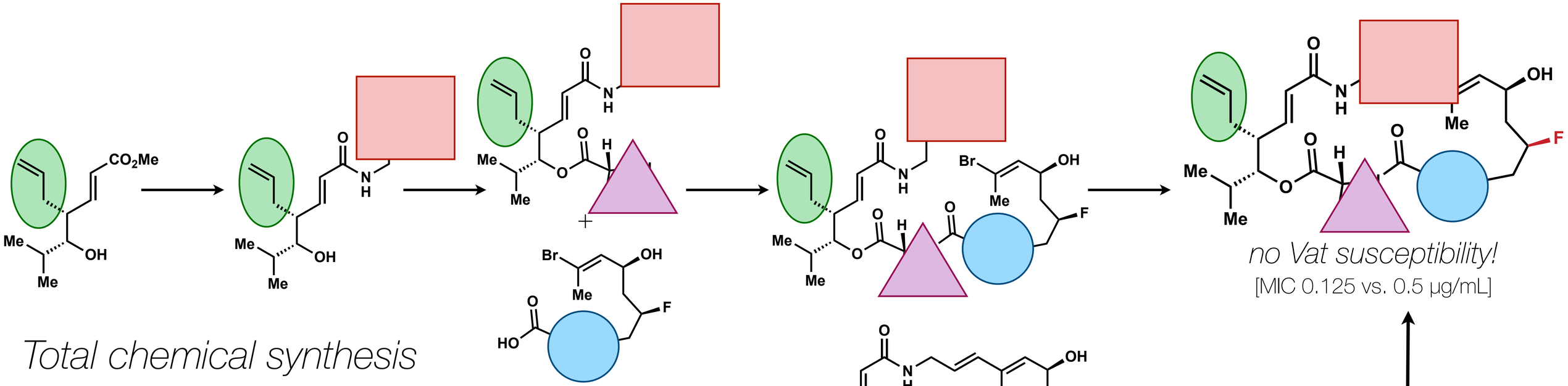
In the modern era, we can tailor natural products for human use





How do chemists like Ian design and execute chemical syntheses?

access to hundreds of diverse but related molecules



Total chemical synthesis

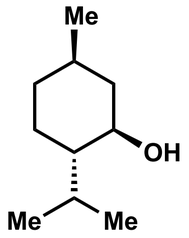
flopristin
(high potency antibiotic)

How did Ian's lab make this change??

Seiple *et al. Nature* **2020**, 145.

A plant metabolite at global supply & demand

How do chemists like Ian design and execute chemical syntheses?



menthol:
active principle in mint

reverse engineering
is not haphazard

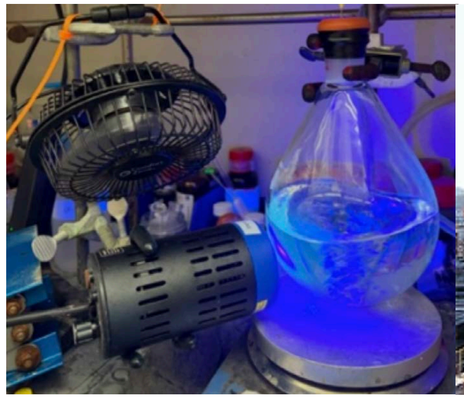
vs.

it corresponds to
established patterns

To design a synthesis, we work backwards by taking the molecule apart, breaking bonds:
retrosynthetic analysis, a type of reverse engineering.

Ardem Patapoutian Front Row Lecture (Sept 2024): “How do you feel?”

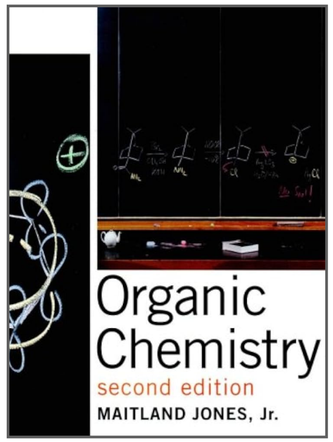
A plant metabolite at global supply & demand



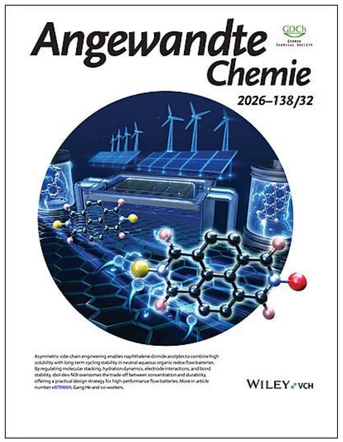
laboratory scale

plant scale

PhD trainee: ca. 200 chemical reactions



textbooks



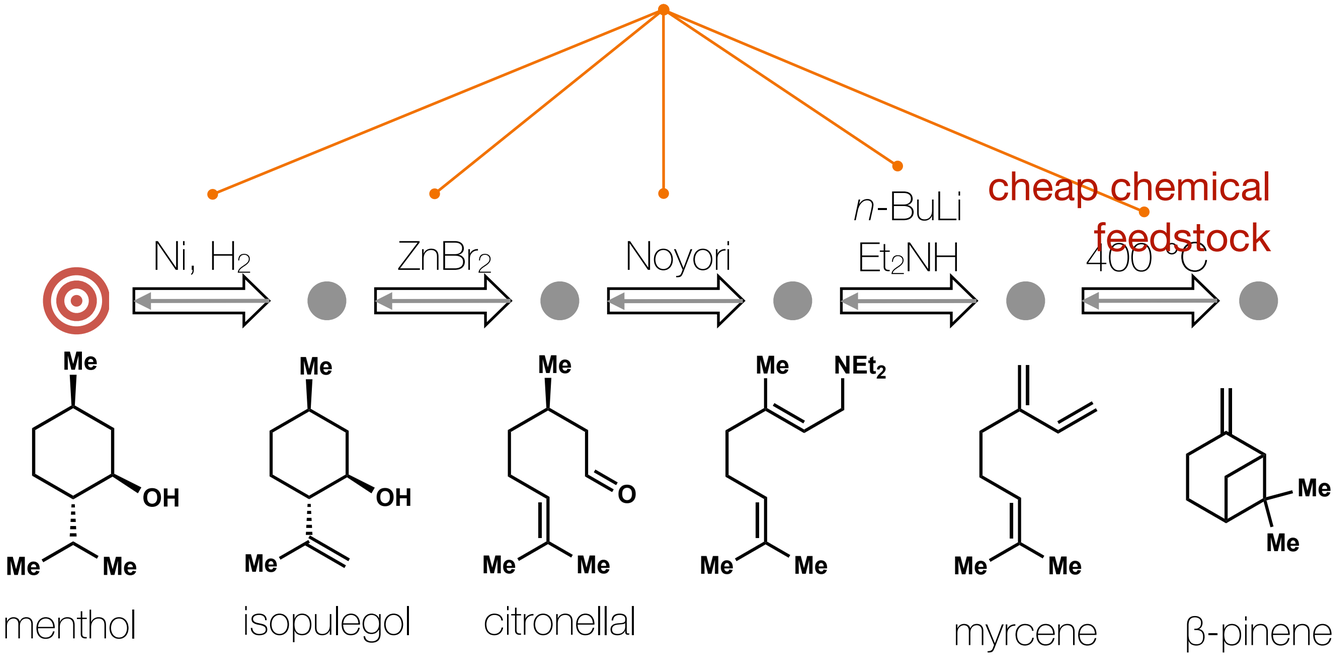
academic journals

computer databases
patterns & rules

CAS SciFinder^n

1 **2** **3** new tools & methods

known, analogous or at least physically reasonable chemical reactions



menthol

isopulegol

citronellal

myrcene

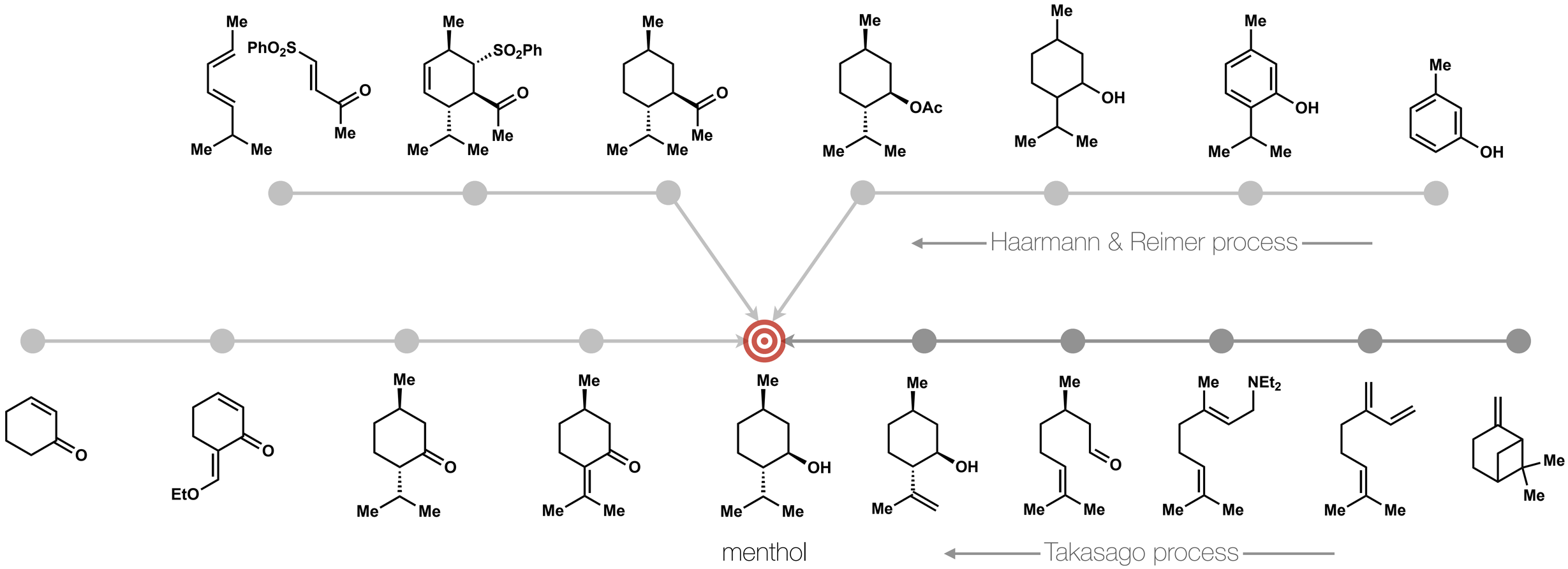
β-pinene

3000 metric tons per annum

← Takasago process

from turpentine!

A plant metabolite at global supply & demand



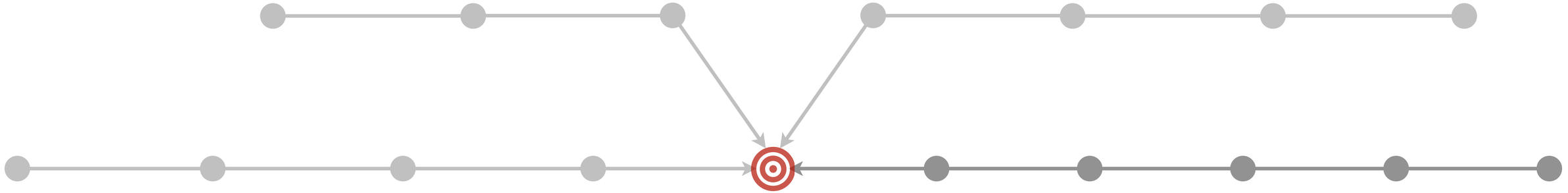
Which route do we take?

Hard to answer in advance…

Two simple questions:

1. Is it possible? …easy to answer after the fact.
2. Is it any good? (cost of labor, materials, environmental impact, supply chain)

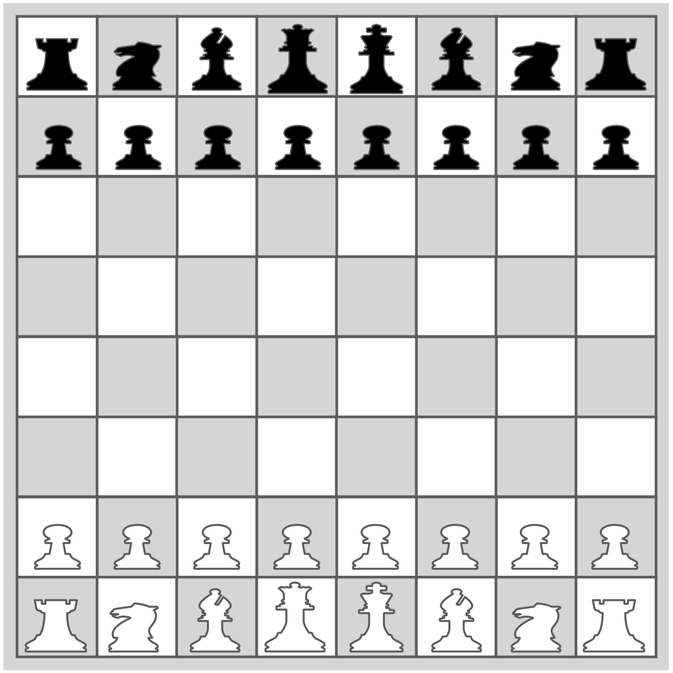
How to choose the best synthesis route?



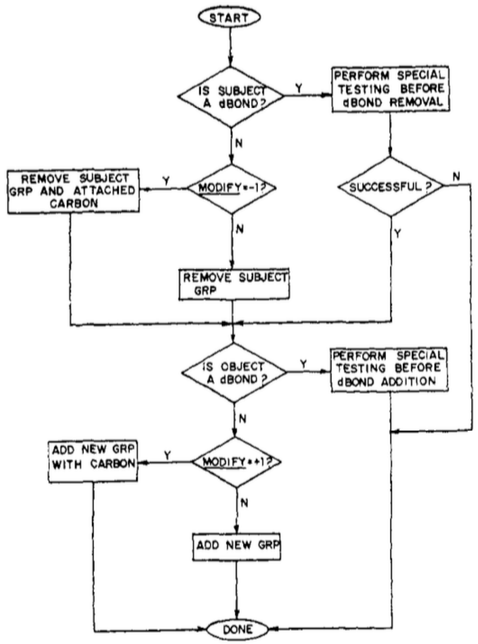
Hard to answer in advance…

1. Is it possible? The rules of chess.
2. Is it any good? The strategies.

THE LAWS OF PHYSICS



chemist



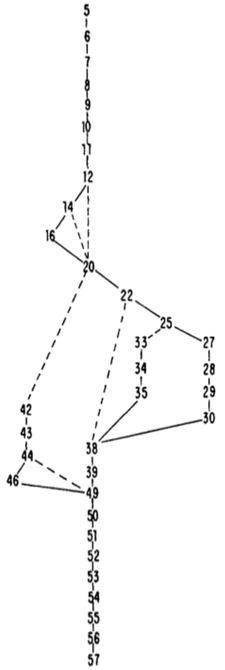
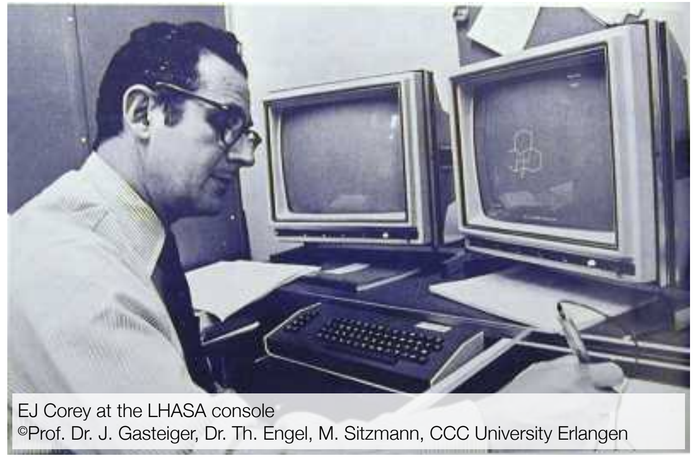


Figure 1. Computer decisions during the evaluation of qualifiers



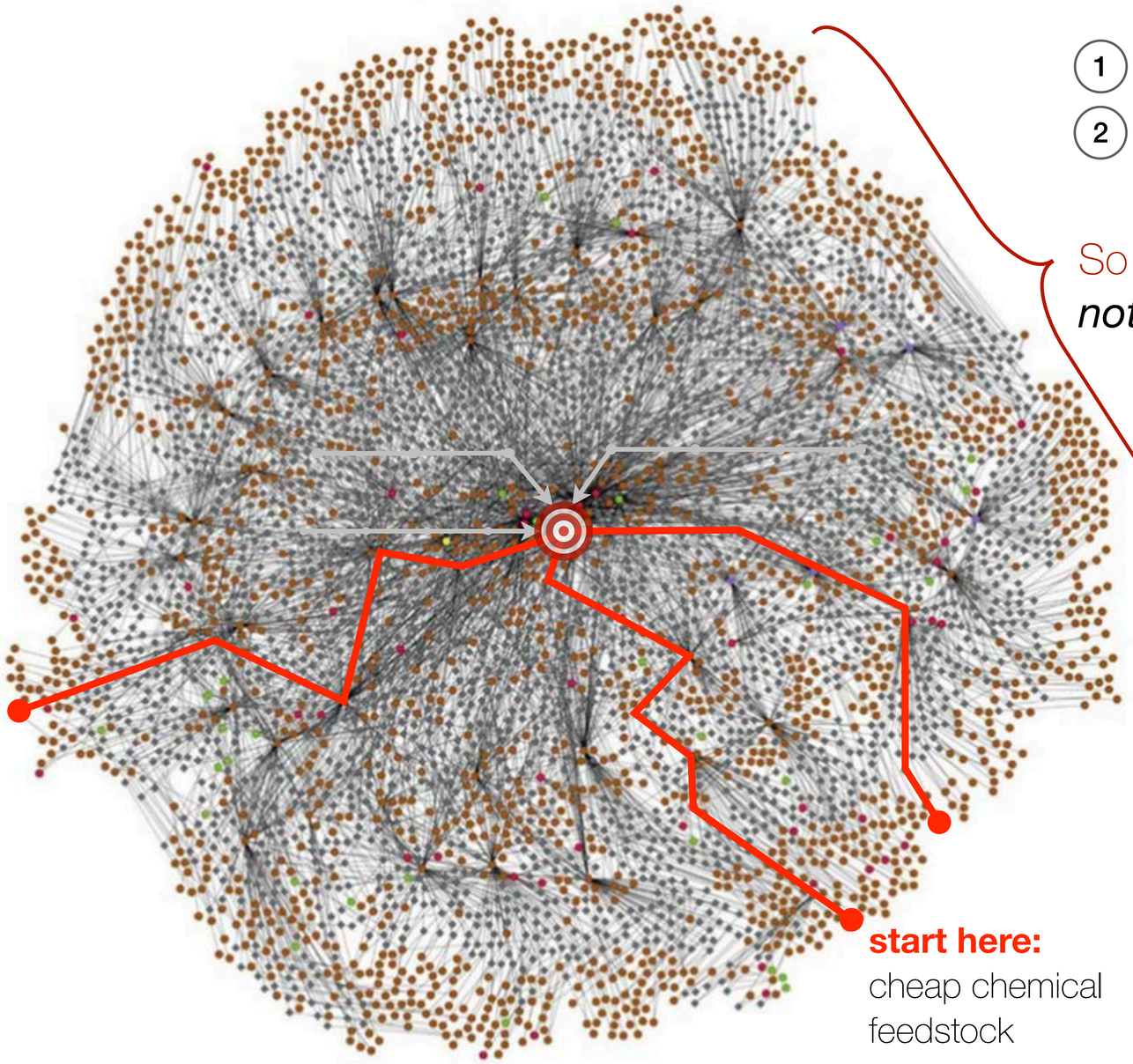
EJ Corey at the LHASA console
©Prof. Dr. J. Gasteiger, Dr. Th. Engel, M. Sitzmann, CCC University Erlangen

EJ Corey (1990 Nobel Prize)
"for his development of the theory and methodology of organic synthesis"

[Happy Belated 98th Birthday!]

Like chess, can we automate synthetic planning?

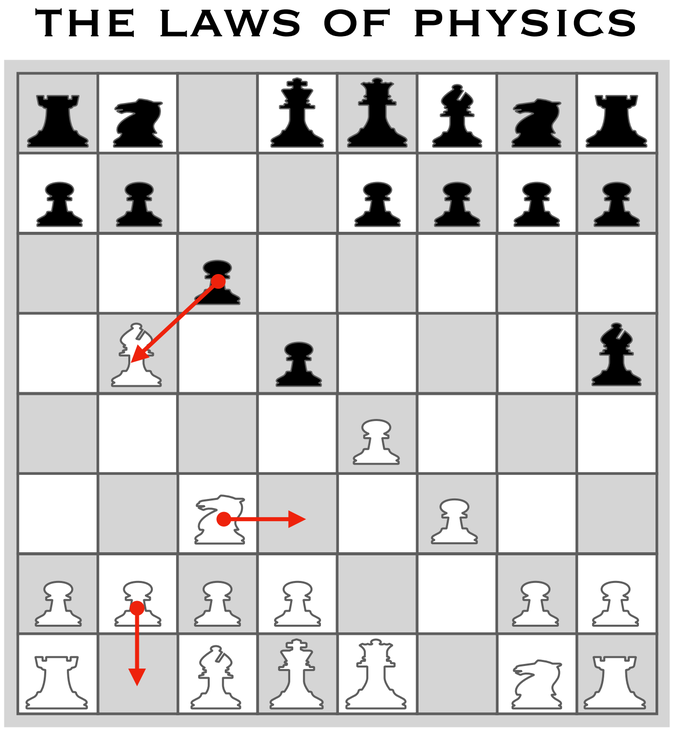
Can we automate synthetic planning? Yes and no.



start here:
cheap chemical feedstock

1. Is it possible? Not exactly like chess moves….
2. Is it any good? Routes can be refined by goals: *projected* length, cost, labor, waste.

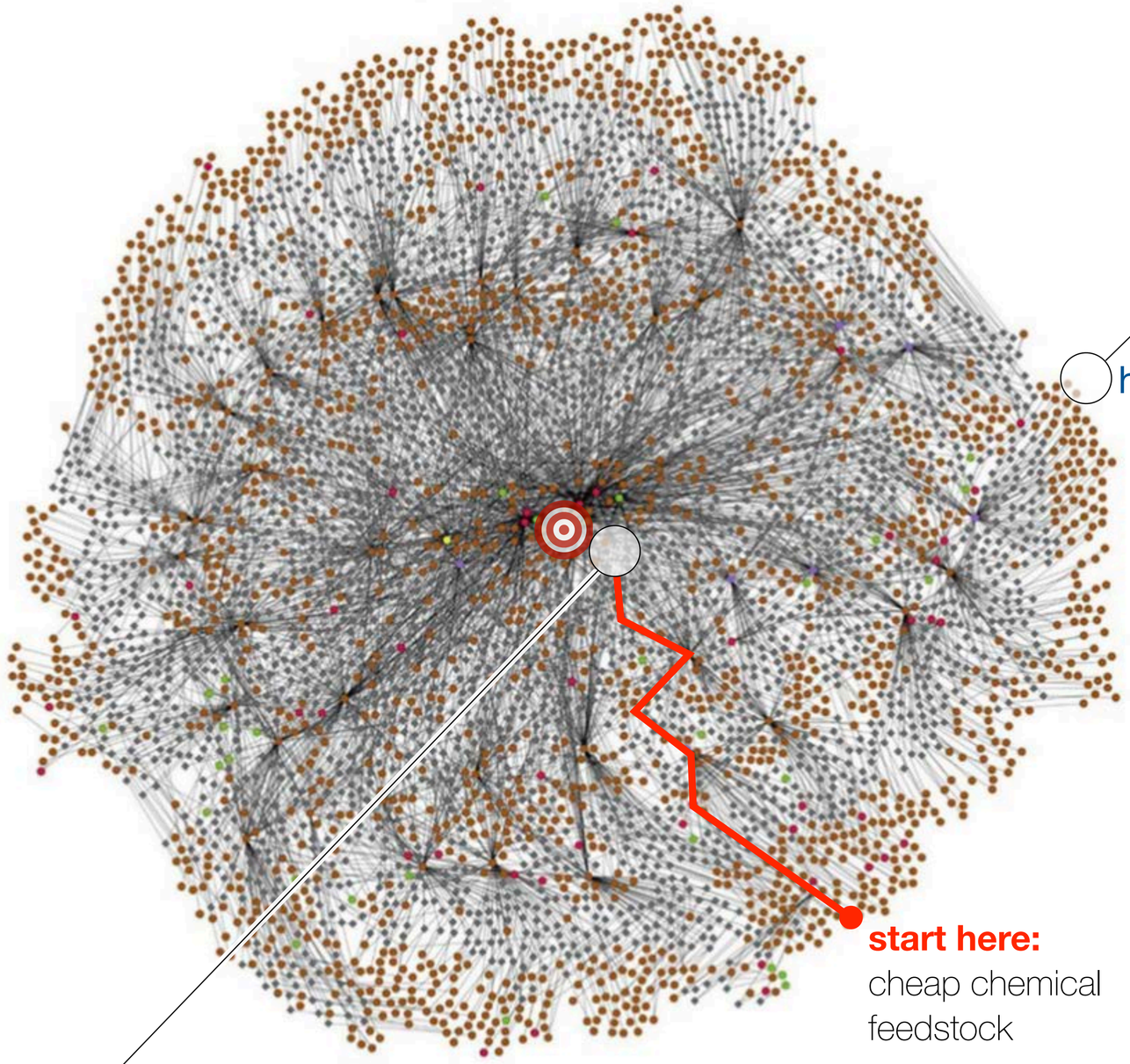
So far, automation is rules-based & patterns-based; analogies *not physics-based*



chemist

Grzybowski *et al. Chem* **2018**, 522.
Cernak *et al. Nat. Rev. Methods Primers* **2021** 23.

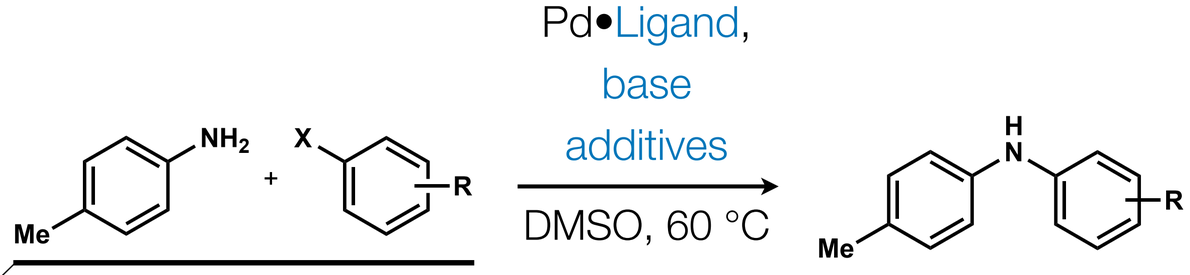
Lack of computation & automation does not stop chemists from making molecules!



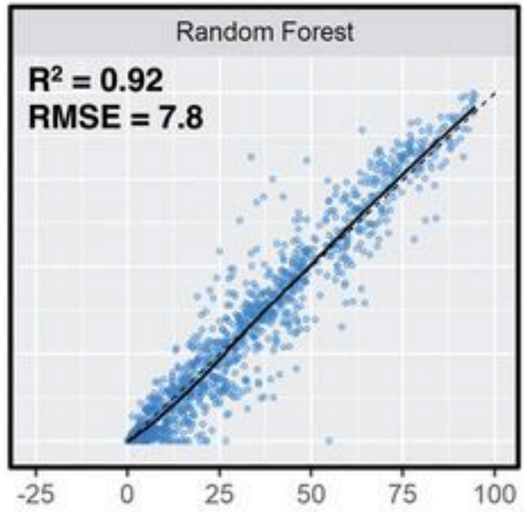
high data regime

start here:
cheap chemical feedstock

low to no data regime



"Three 1536-well plates consisting of a full matrix of 15 aryl and heteroaryl halides, 4 ligands, 3 bases, and 23 additives . . . **4608 reactions**"

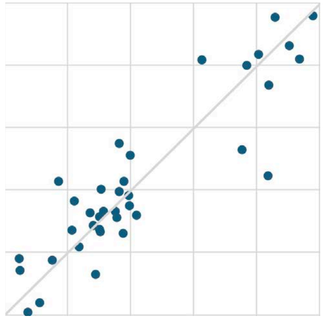


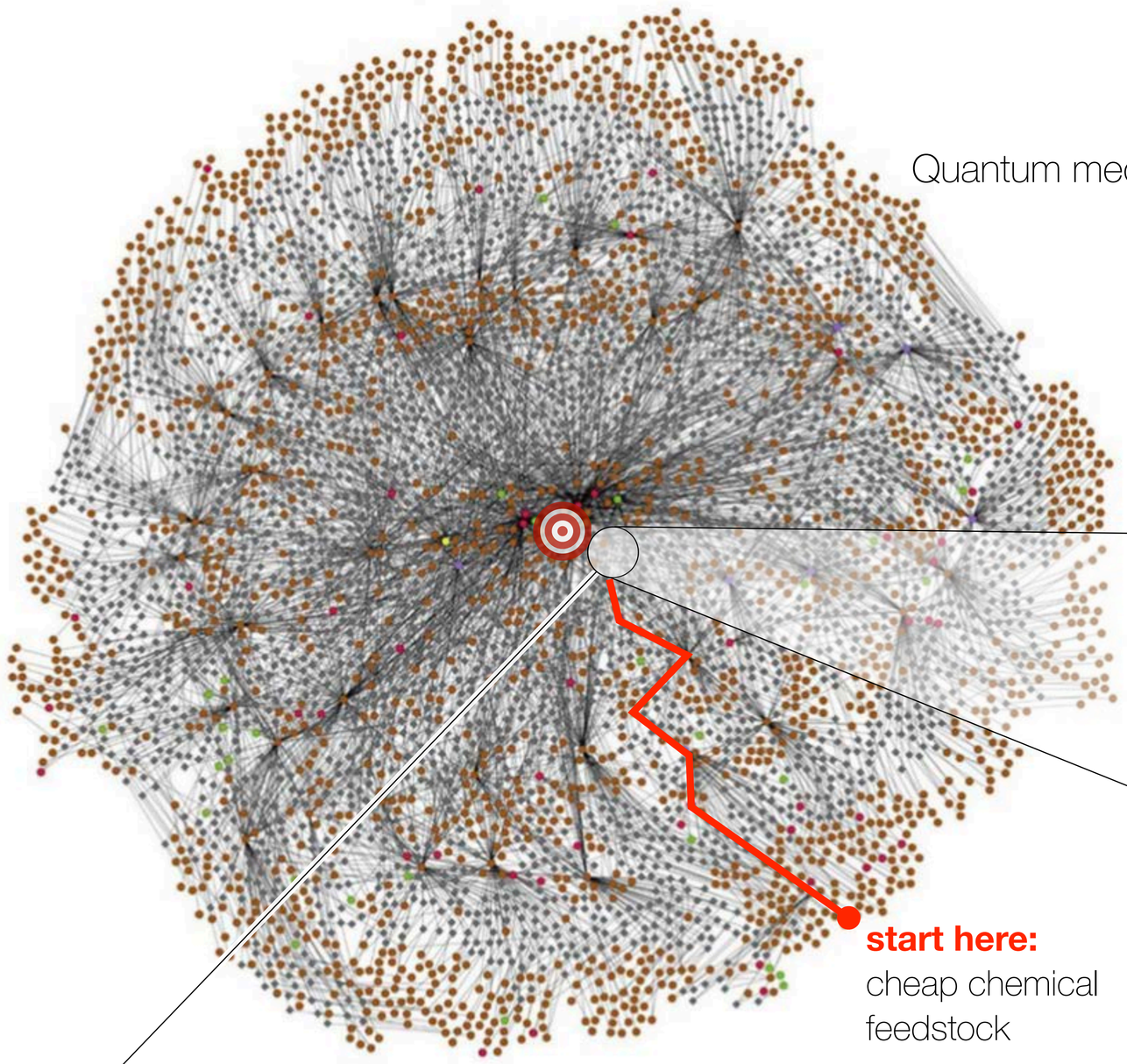
Dreher & Doyle et al. *Science* **2018** 186.

BUT we require extensive trial-and-error ***or*** large data sets (no material ⟶ no data!)

Unless you can simulate physics

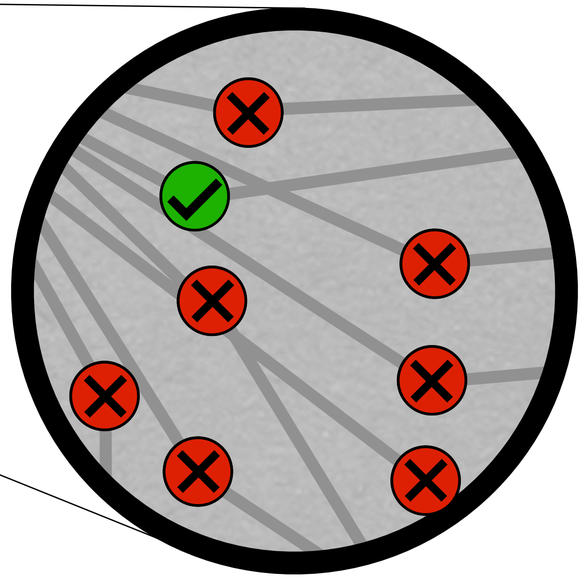
Quantum mechanical models (approximations to reality): virtual experimental data





start here:
cheap chemical
feedstock

good decisions



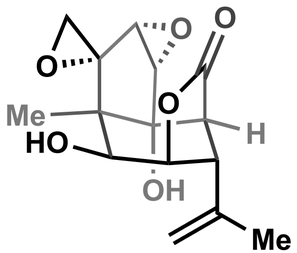
low to no data
regime

we require extensive trial-and-error ***or*** large data sets (no material ⟶ no data!)

Related ion channel inhibitors: major differences in reactivity

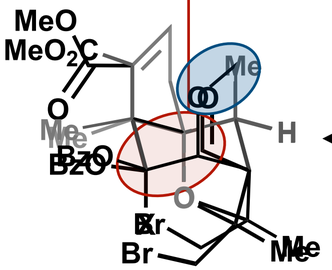
metabolized slowly?

tutin

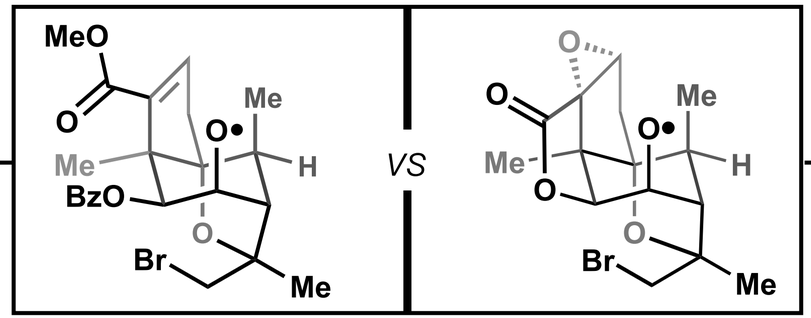


β-scission

a bond is broken!

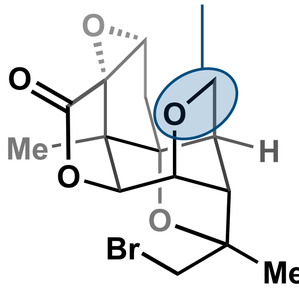


Pattern recognition fails: not enough data!



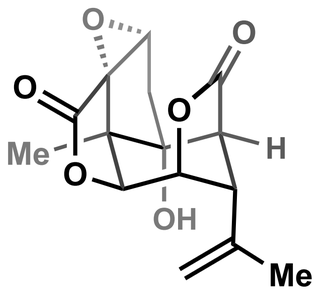
1,5-HAT (H-atom transfer)

new bond formed



metabolized too quickly

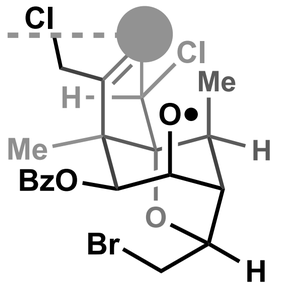
picrotoxinin



dead-end!

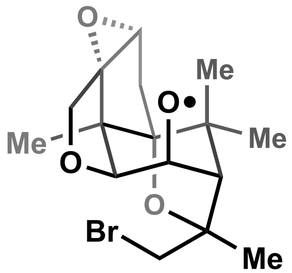
β-scission

dead-end!



β-scission

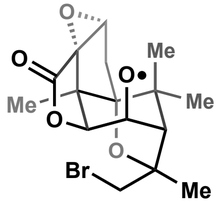
dead-end!

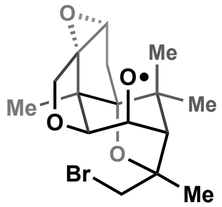


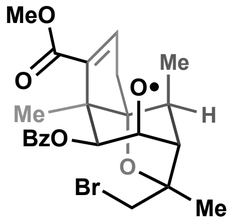
Chunyu Li

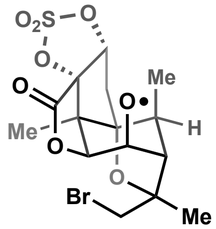
Crossley *et al. JACS* **2020**, 11376

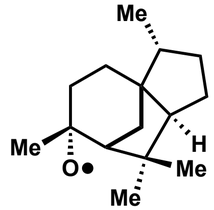
Can we model reality?





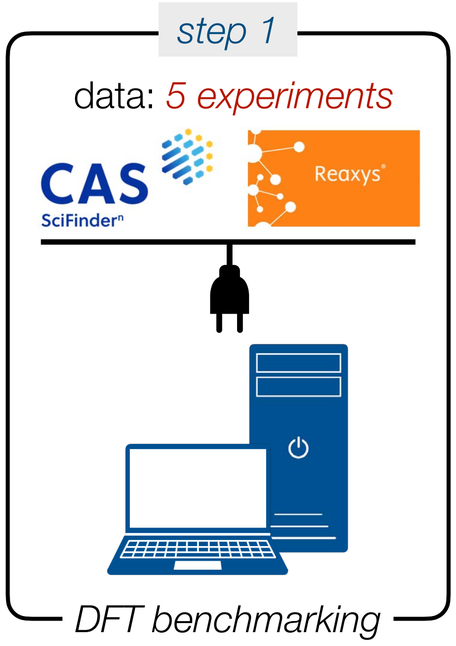


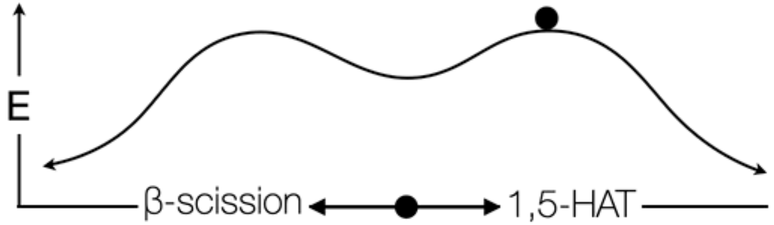




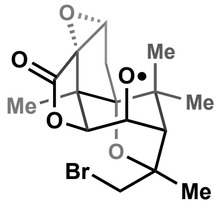
experimental ratio	9.5:1.0	1.0:20	1.0:20	20:1.0	2.3:1.0
calc. k_{HAT}/k_{β} ratio	0.95:1.0	1.0:50	1.0:16	20:1.0	1.0:1.0

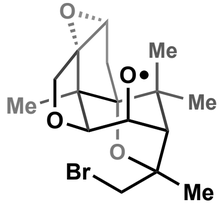
uM062x/ 6-311+G(d,p)/SMD(benzene)/em=GD3/ Eckart tunneling correction

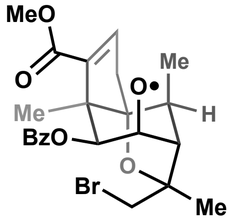


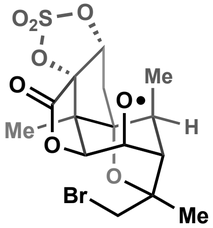


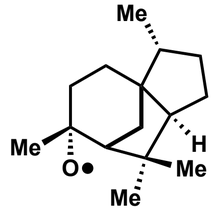
Can we model reality?





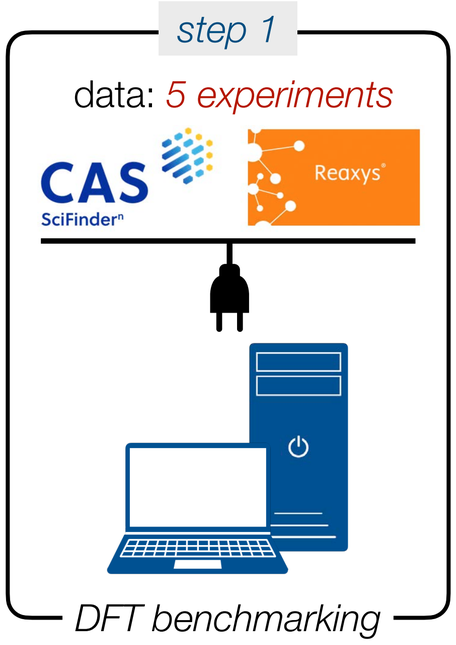


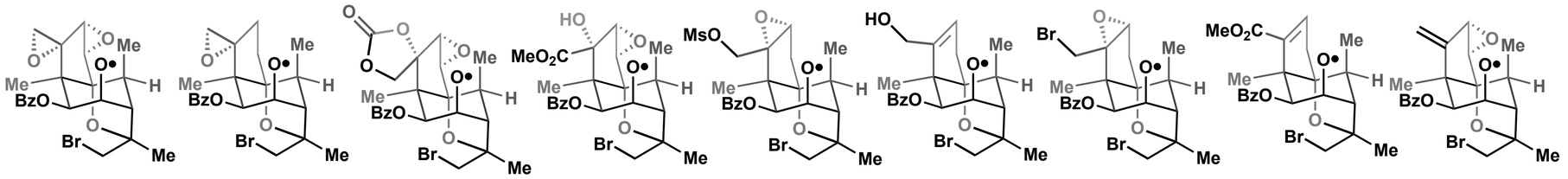




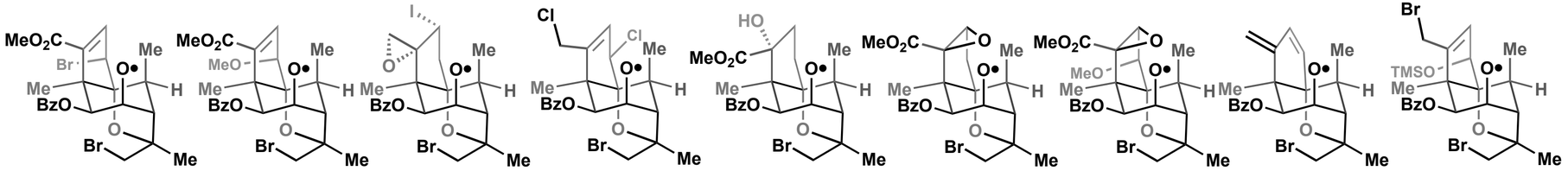
experimental ratio	9.5 : 1	< 0.05* : 1	< 0.05* : 1	> 20 : 1*	2.3 : 1
calc. k_{HAT}/k_{β} ratio	13 : 1	0.02 : 1	0.06 : 1	131 : 1	1 : 1

*not detected (^{1}H NMR); uM062x/ 6-311+G(d,p)/SMD(benzene)/em=GD3/ Eckart tunneling correction

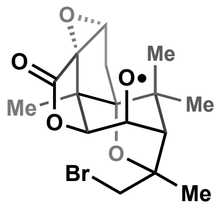
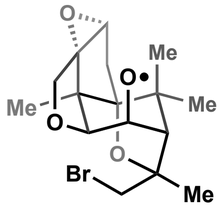
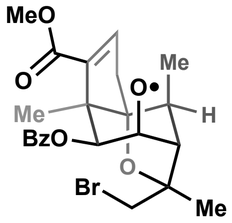
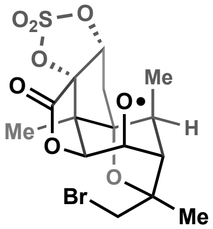
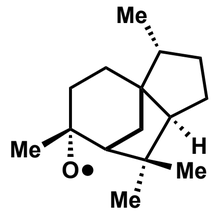




these are not "real" molecules (yet), just figments of our imagination



Can we model reality?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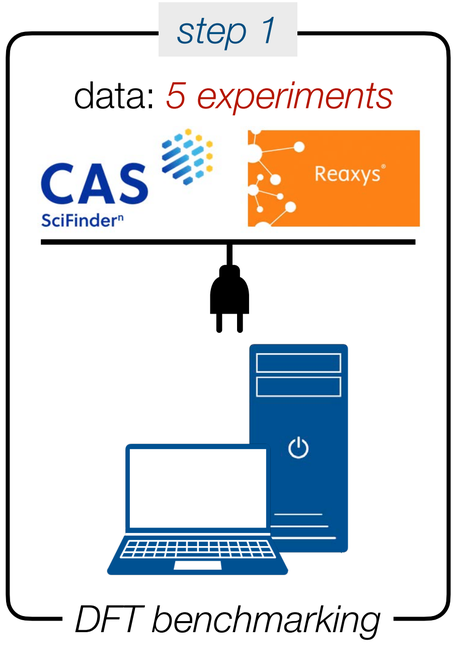
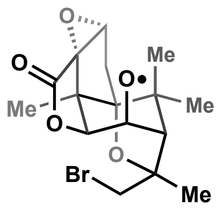
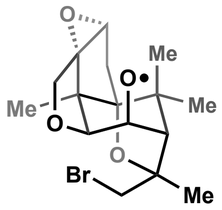
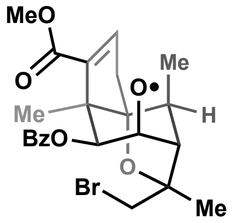
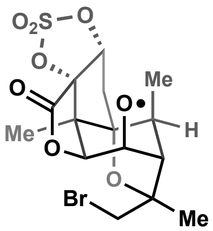
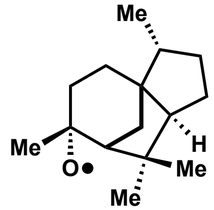


Can we model reality?

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*not detected (^{1}H NMR); uM062x/ 6-311+G(d,p)/SMD(benzene)/em=GD3/ Eckart tunneling correction

synthesized
25 natural products…

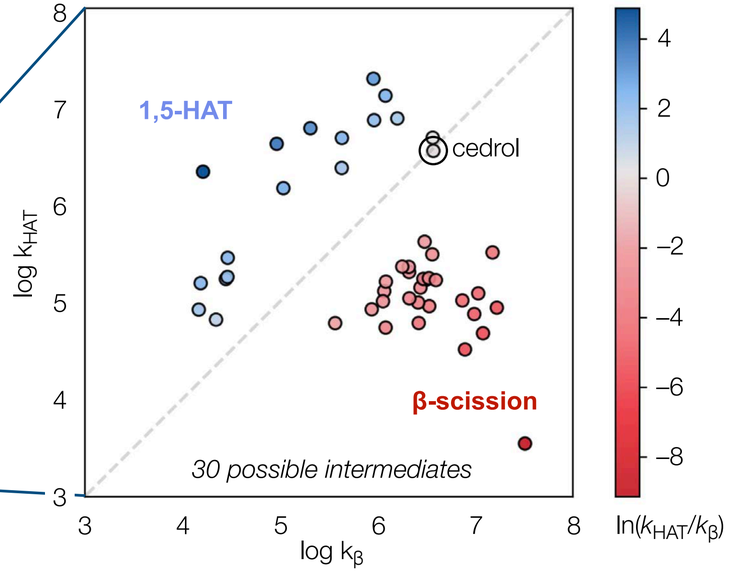
step 1

data: *5 experiments*

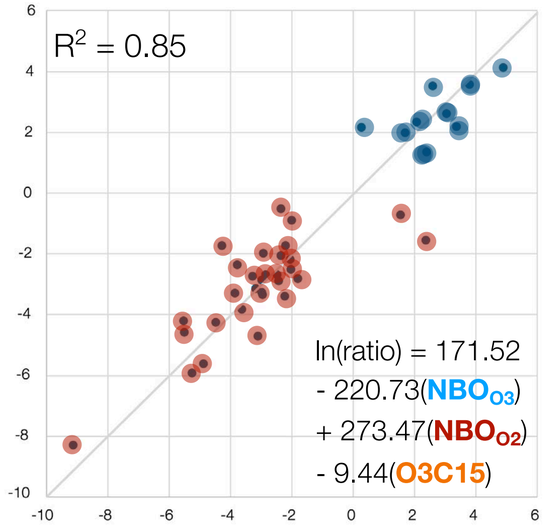
CAS SciFinder^n Reaxys®

DFT benchmarking

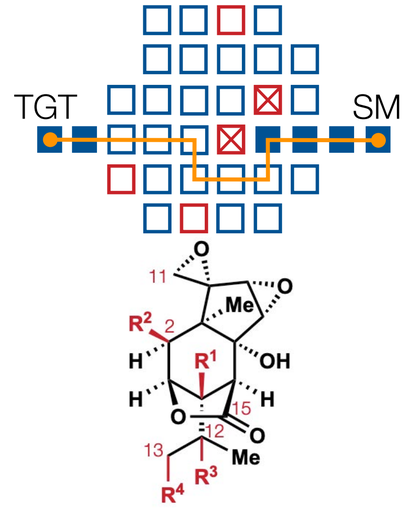
step 2



step 3



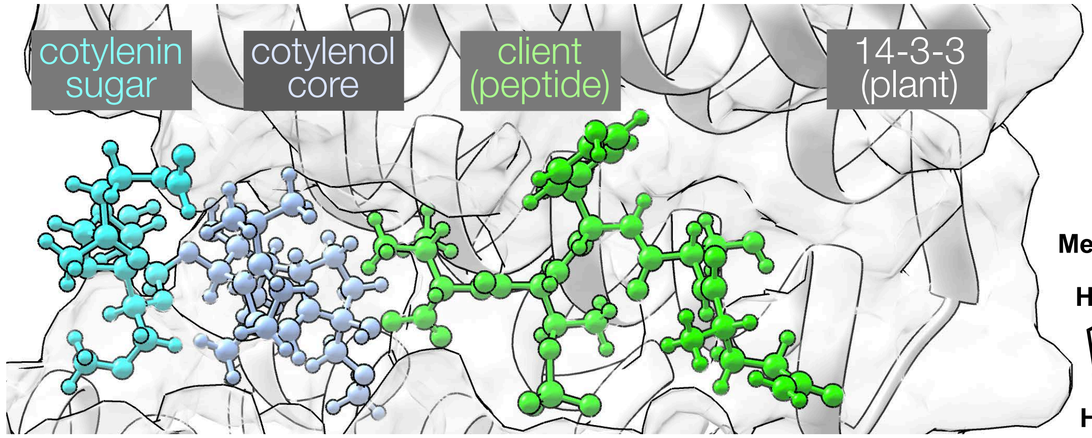
step 4

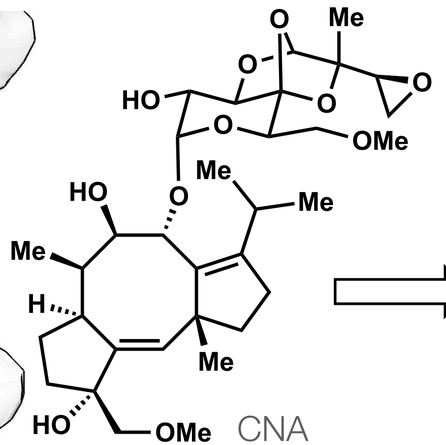


validation

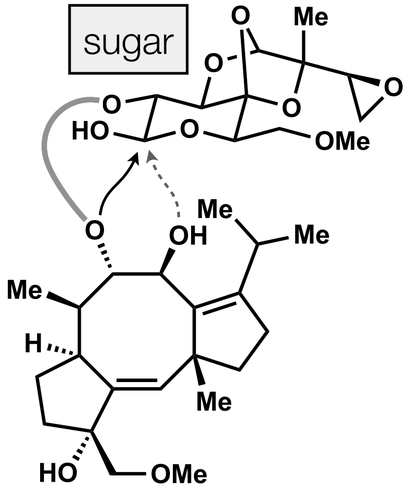
…which is crazy

Modeling glycosylation to reduce trial-and-error



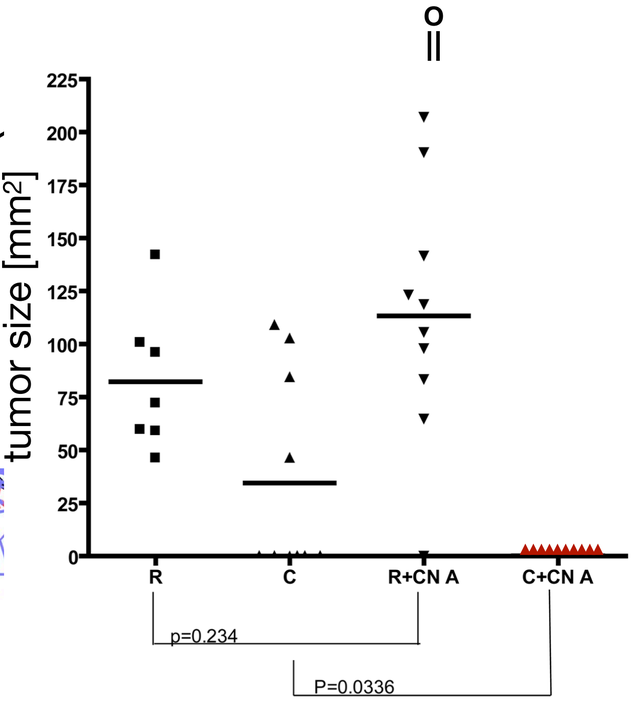


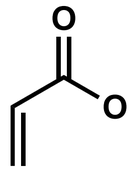
CNA

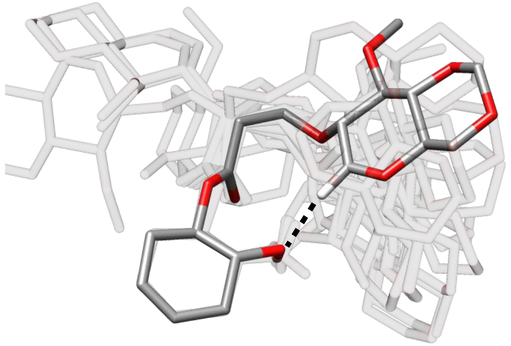


Kusumoto molecular clamp

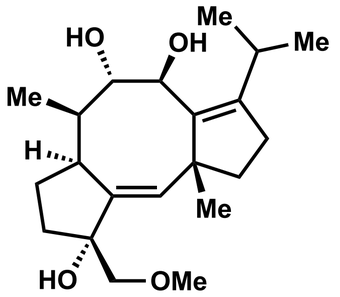
succinate



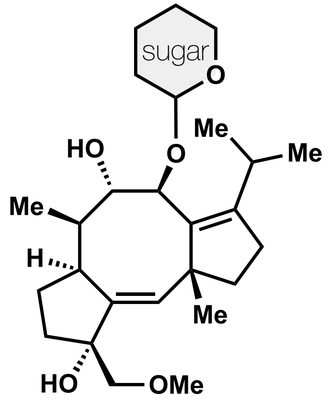




G_{rel} = 2.1 kcal/mol
C–H···O = 2.02 Å



one shot
one goal

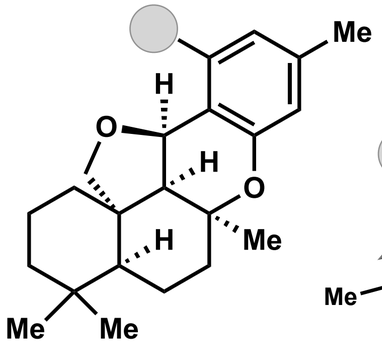


J. Am. Chem. Soc. **2025**, *147*, 1327.

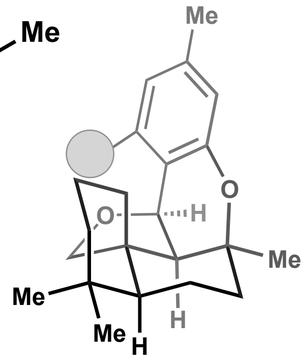
Modeling multiple reactions to access siccanin

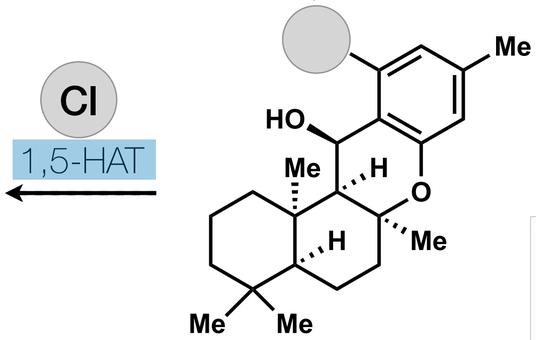
small change: *dramatic* effect on chemical reactivity!

Larisa Pop

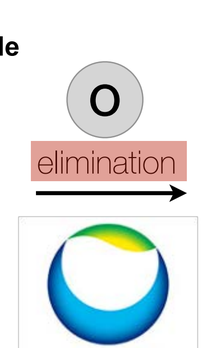


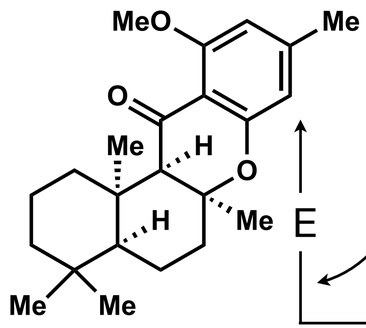
siccanin *aka* Tackle™ [for athlete's foot]



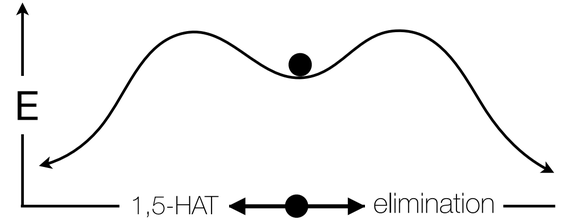


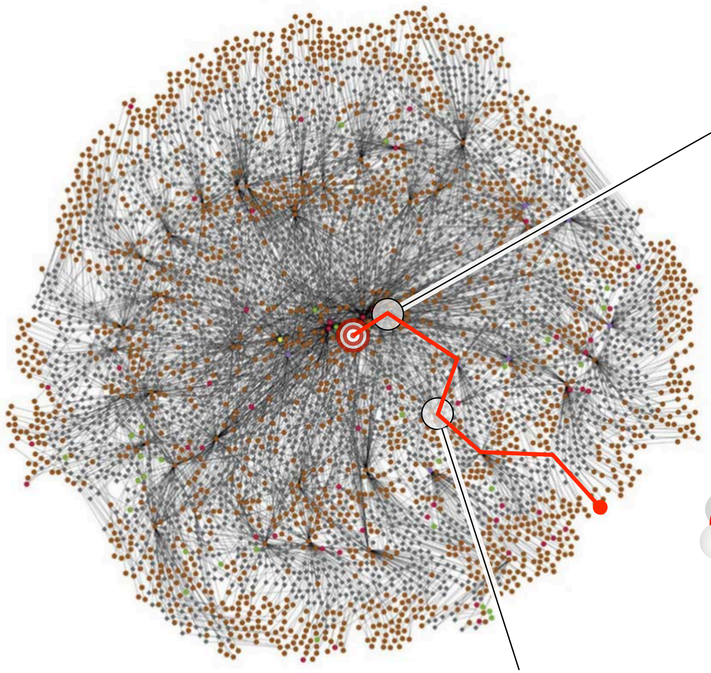
low data regime
(1 datum?)



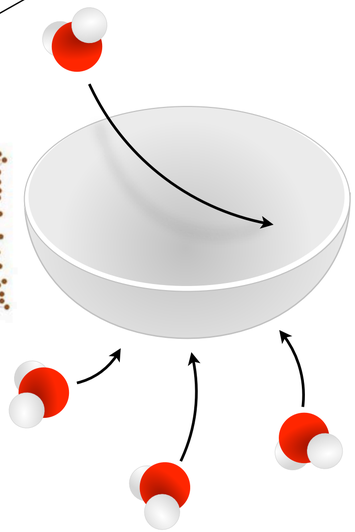


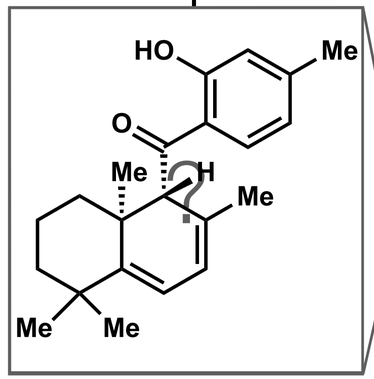
dead-end!

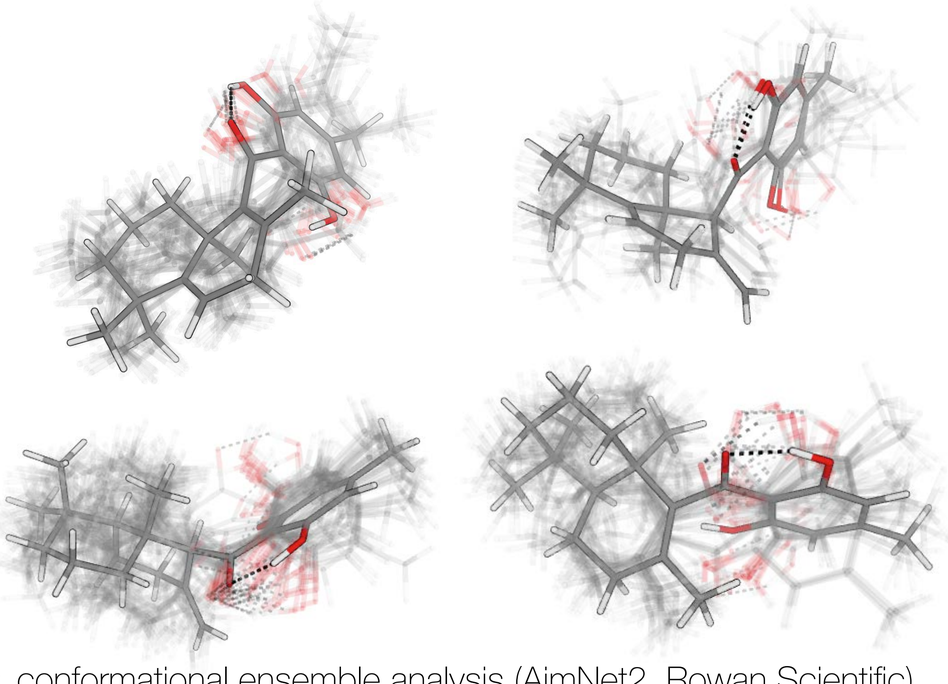




still low data….



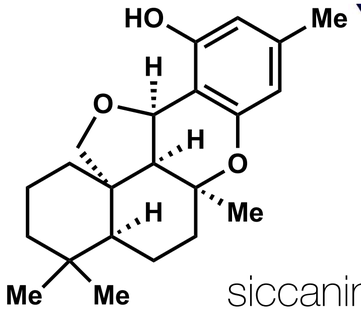




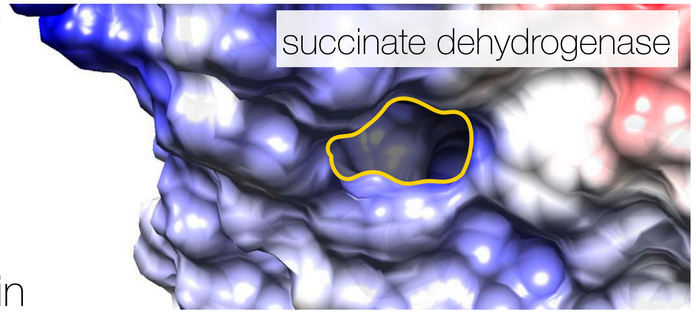
conformational ensemble analysis (AimNet2, Rowan Scientific)

Why bother with small molecules? Atomic (subatomic?) resolution!

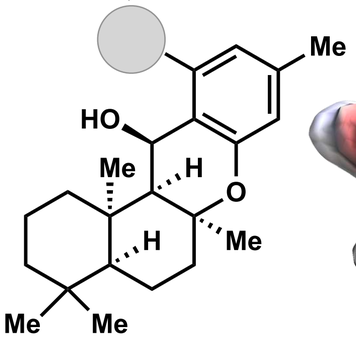
Exquisite control of properties and functions
via *structure*: shape, electronics, movements

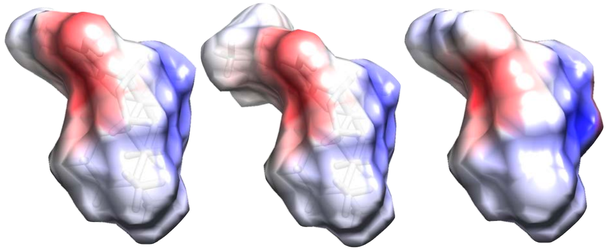


siccanin



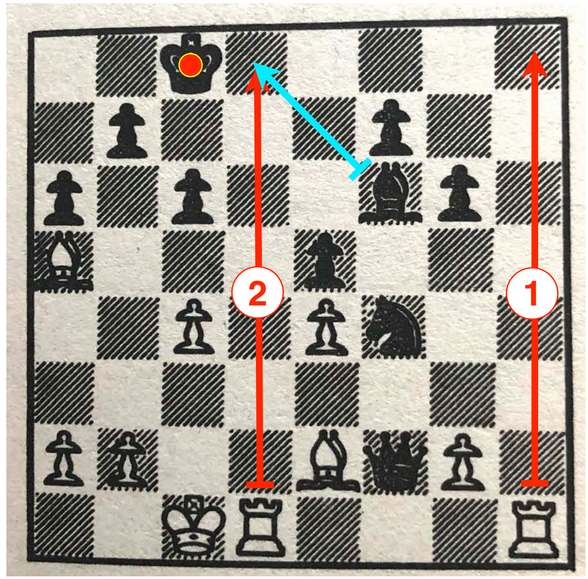
small change: *dramatic* effect on chemical reactivity!

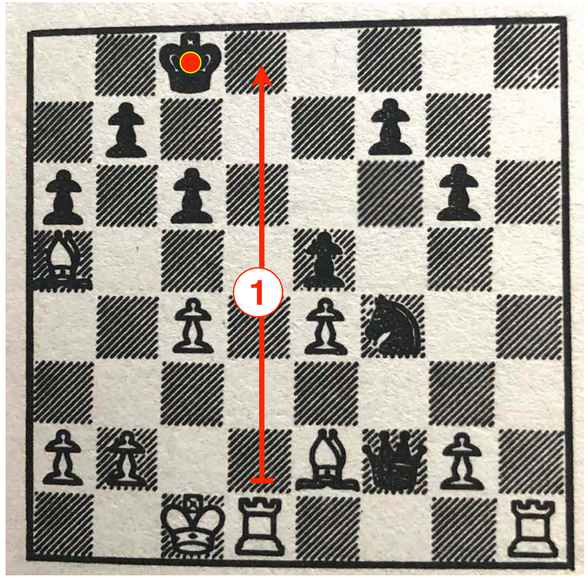


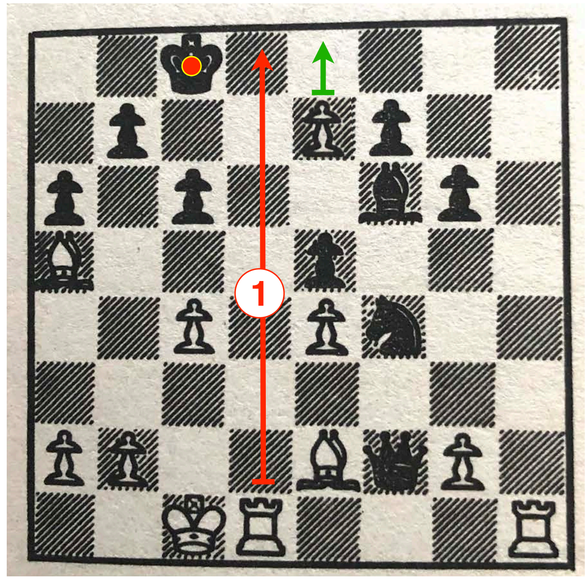


changes to structure affect binding to biological target

Small (atomic) changes can dramatically impact <u>function</u>, <u>reactivity</u> and <u>strategy</u>: dynamic retrosynthetic analysis







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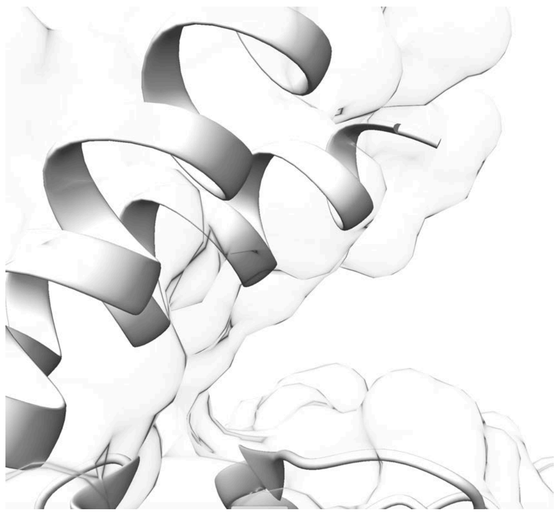
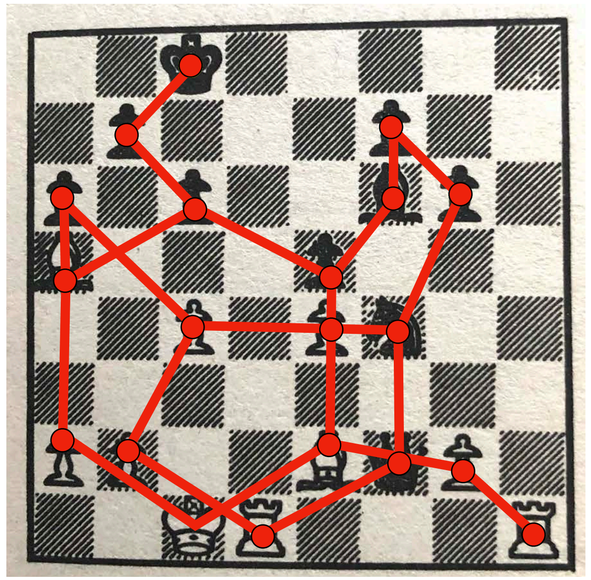
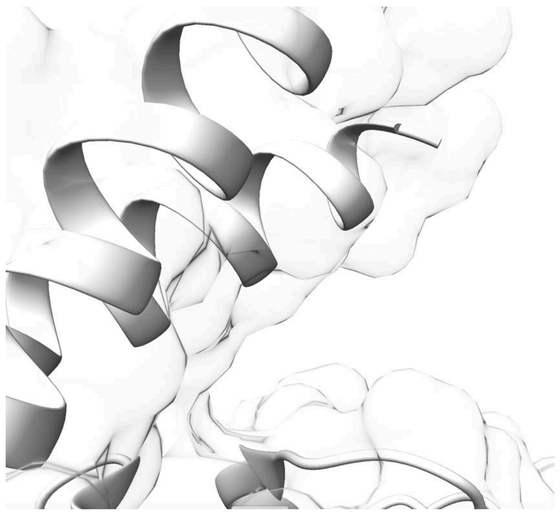
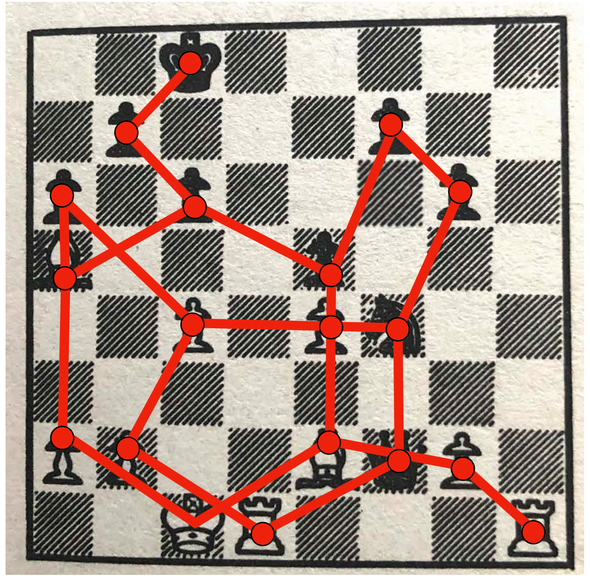
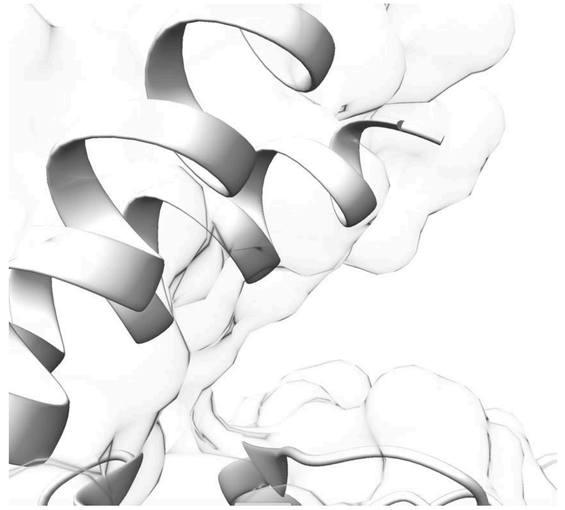
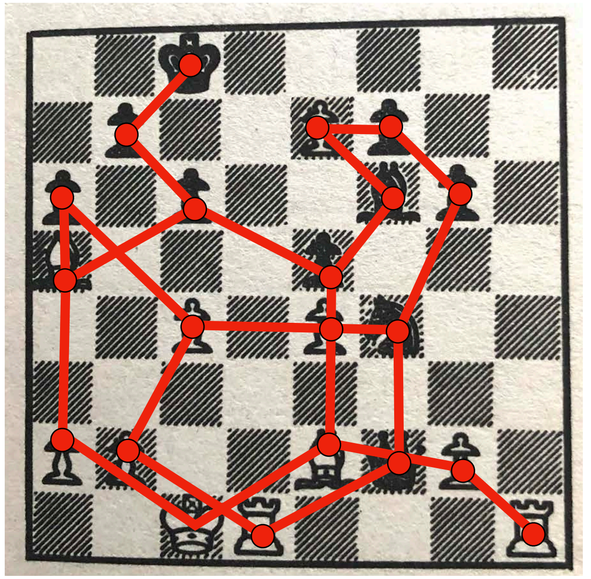








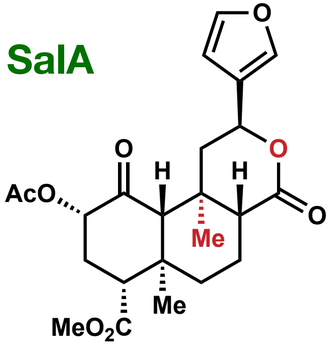




Dynamic retrosynthetic analysis

Mazatec
traditional medicine & ritual

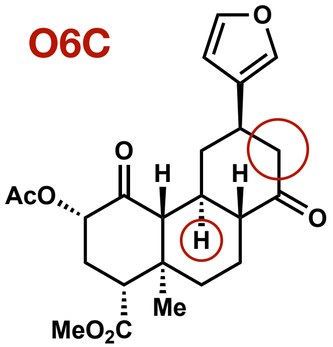
SalA



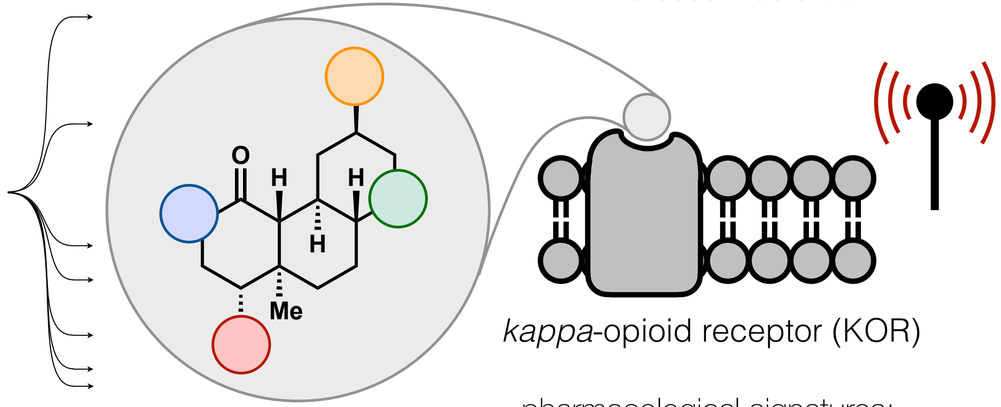
unstable to
textbook chemical reactions

–Me
O to C

O6C



stable
and diversifiable



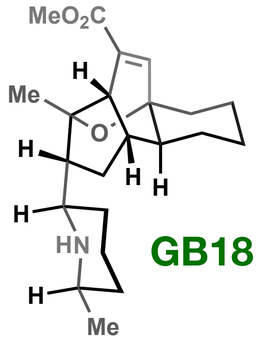
with Professor Laura Bohn

kappa-opioid receptor (KOR)

pharmacological signatures:
treatment of itch/pain without drowsiness

Gimi (Papua New Guinea)
traditional medicine & ritual

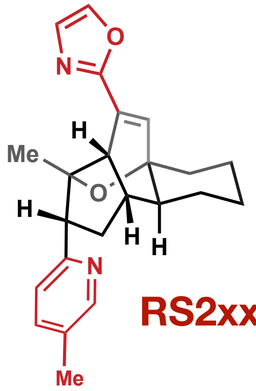
with Professor Laura Bohn



GB18

turns KOR off
lengthy route

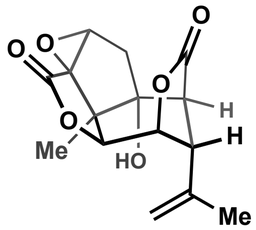
vs.



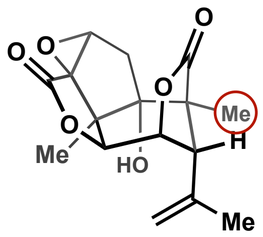
RS2xxx

turns KOR on
short, divergent route

with Corteva Agriscience

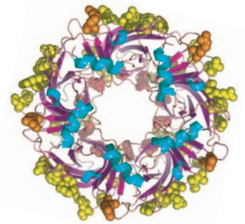


picrotoxinin (PXN)
toxic, unstable



5MePXN
remarkably stable

$GABA_A$ (mammals)



RDL (invertebrates)

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