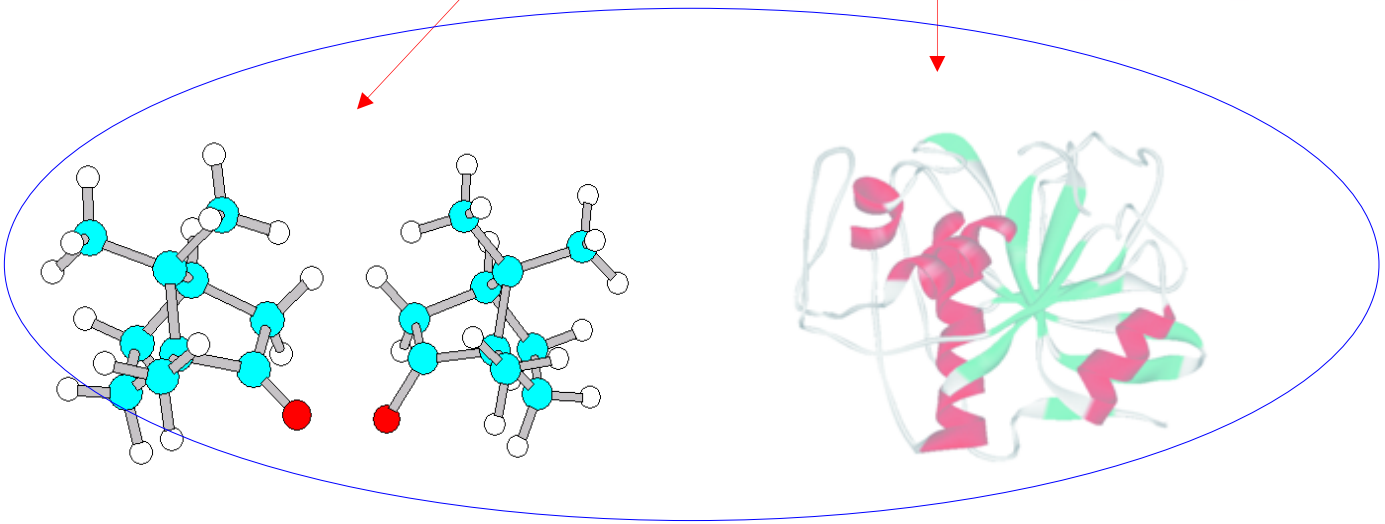
COVID-19 & other Viral Treatments: The Role of VCD Spectroscopy in Expediting the Process

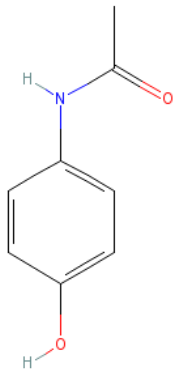
Rina K Dukor

BioTools
20 YEARS OF INNOVATION

FACSS / SCIX
October 2020

3 types of pharmaceuticals

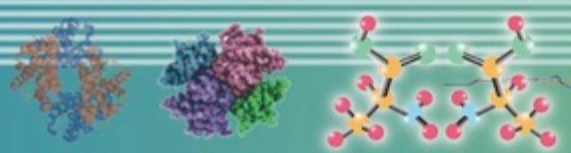




chiral

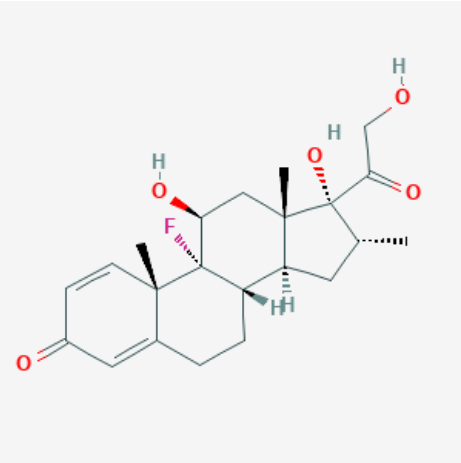
protein-based &
other biopharmaceuticals

small organic,
non-chiral



‘Other’ Types of Pharmaceuticals

1. **NBCD’s – non-biological complex drugs**
   a) Iron Sucrose
   b) Polypeptides
   c) Peptides with polymers or nano-materials
   d) Swelling polymers
2. **Nucleic Acid based**
3. **Carbohydrate based (heparin etc)**
4. **Steroids**



Dexamethasone

Mirror

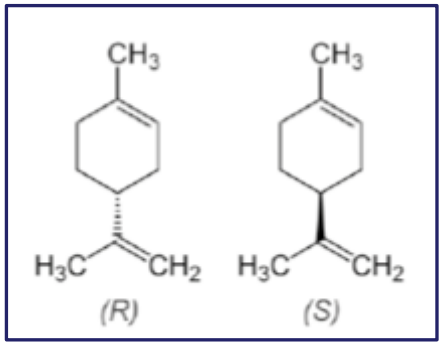
(*S*)-asparagine
flavourless

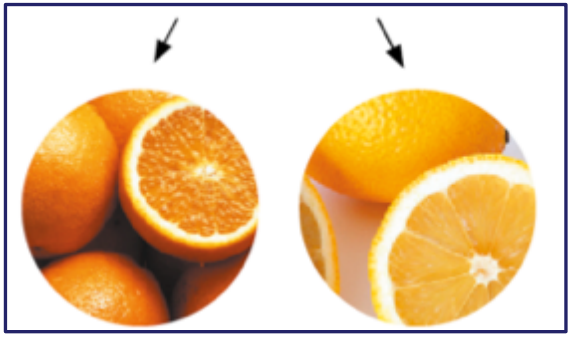
(*R*)-asparagine
sweet

Mirror

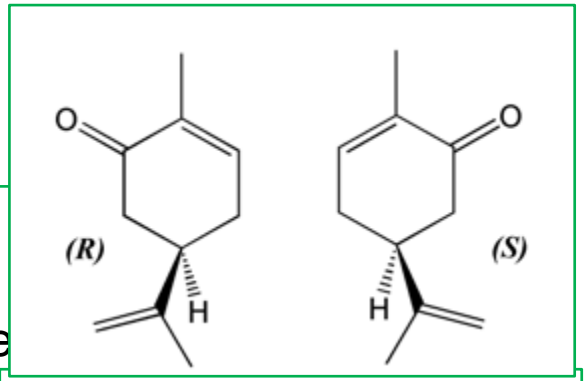
(*S*)-Thalidomide
teratogenic

(*R*)-Thalidomide
sedative





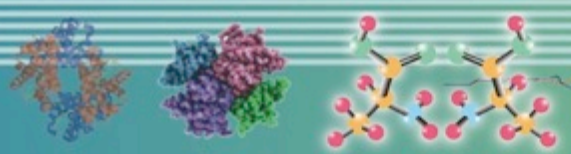
R-(-)-carvone smells like spearmint



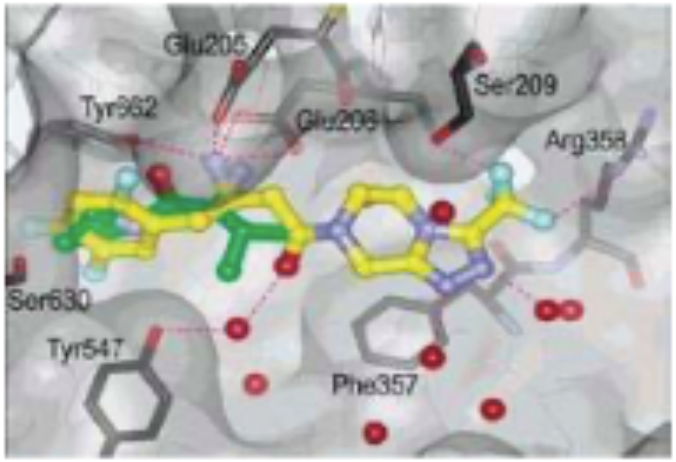
S-(+)-carvone smells like caraway seeds

(R)-(+)-limonene - fresh citrus; orange

(S)-(-)-limonene - harsh, turpentine-like, lemon note

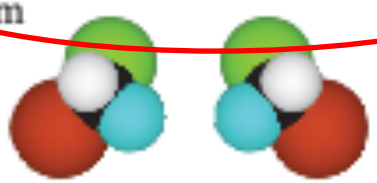


Why Chirality is Important in the Pharmaceutical Industry



- Chirality important for
  - Potency
  - Selectivity/off target profile
  - Pharmacokinetic properties
  - Metabolism
  - Toxicity
  - *etc.*

** Biological targets are chiral and so are the molecules which interact with them

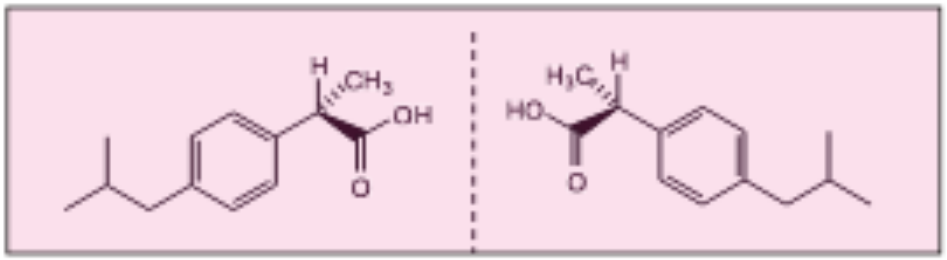


Because Shape Matters!

Slide courtesy of Dr. Chris Welch

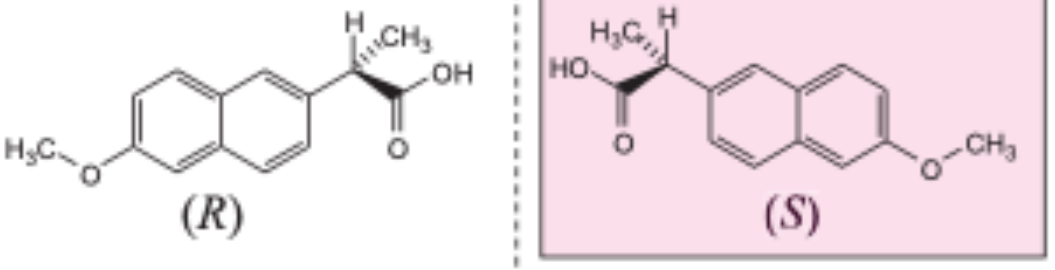
Chirality and Pharmaceuticals

ibuprofen



sold as racemate (1:1 mixture of enantiomers)

naproxen



Closely related naproxen sold as single enantiomer

Slide courtesy of Dr. Chris Welch

Examples of Chiral and Biologic Blockbuster Drugs

Chiral 

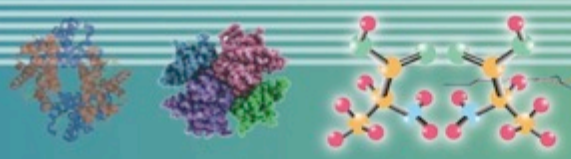
1. LIPITOR – Pfizer
2. ZOCOR – Merck
3. Nexium – AstraZeneca
4. PREVACID – Abbott & Takeda
5. ADVAIR DISKUS – GlaxoSmithKline
6. PLAVIX – BMS & Sanofi-Aventis
7. ZOLOFT – Pfizer

protein-based!
(in 2018, 20% of all approvals were antibodies);
over 200 approved; 1000's in development

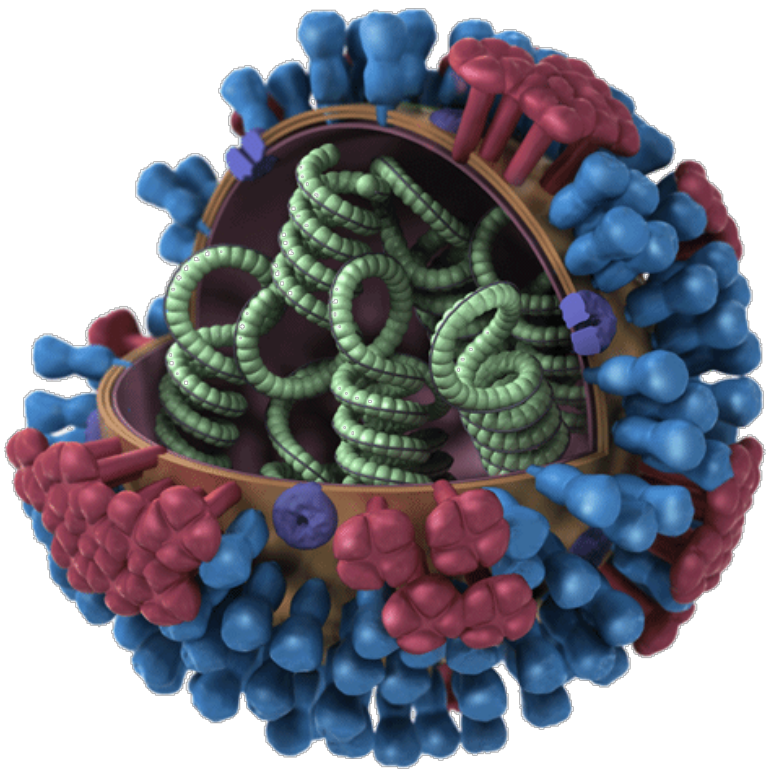
1. HUMIRA – Abbvie
2. Rituxan – Roche
3. ENBREL – Pfizer / Amgen
4. HERCEPTIN - Roche

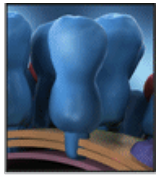
Source: Forbes. Com; 2/27/06

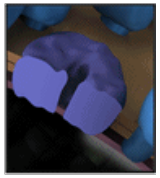
Viruses & Viral Treatments



Influenza A virus







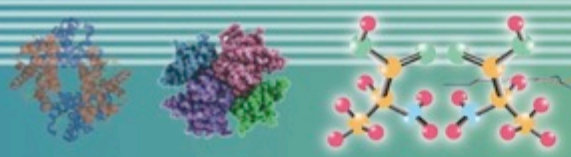
Influenza A viruses are classified by subtypes based on the properties of their hemagglutinin (H) and neuraminidase (N) *surface proteins*.

There are 18 different HA subtypes and 11 different NA subtypes. Subtypes are named by combining the H and N numbers – e.g., A(H1N1), A(H3N2).

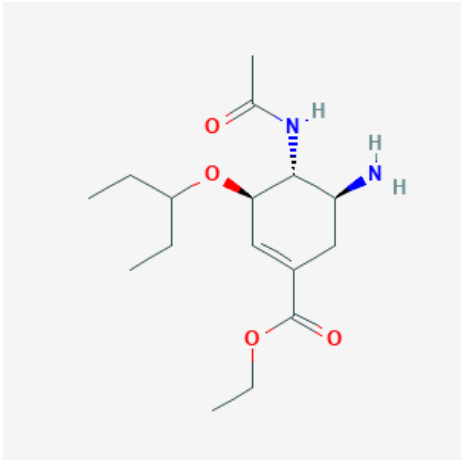
https://www.cdc.gov/flu/about/viruses/types.htm

Four FDA Approved Drugs for Influenza (Flu)

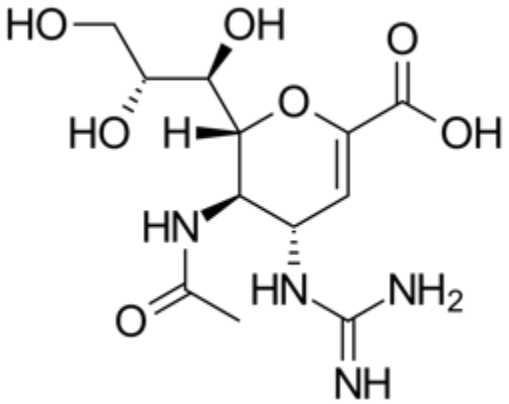
Antivirals interfere with an important enzyme of the influenza virus, called *neuraminidase*. The drugs keep the virus from escaping from one cell to infect a neighboring cell. – https://www.health.harvard.edu/drugs-and-medications/what-you-should-know-about-antiviral-drugs



Tamiflu
oseltamivir phosphate
Prescription for flu

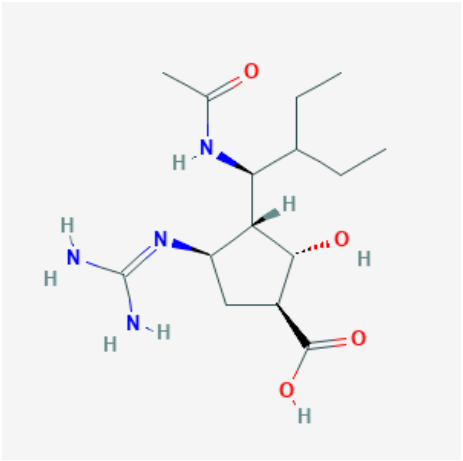


https://www.tamiflu.com
Genentech / Roche



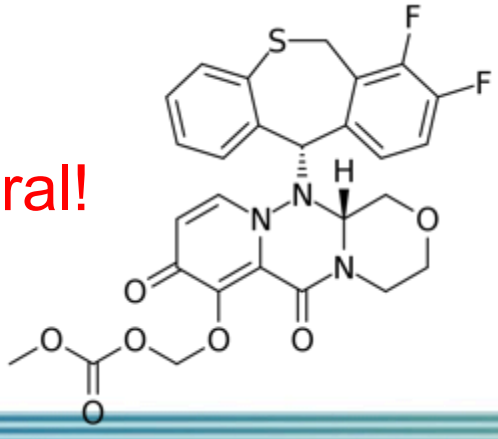
www.gsksource.com
GSK

Rapivab
peramivir injection



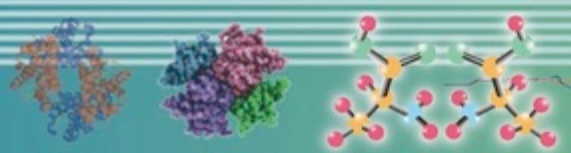
https://www.rapivab.com
BioCryst Pharmaceuticals

ALL four drugs are chiral!

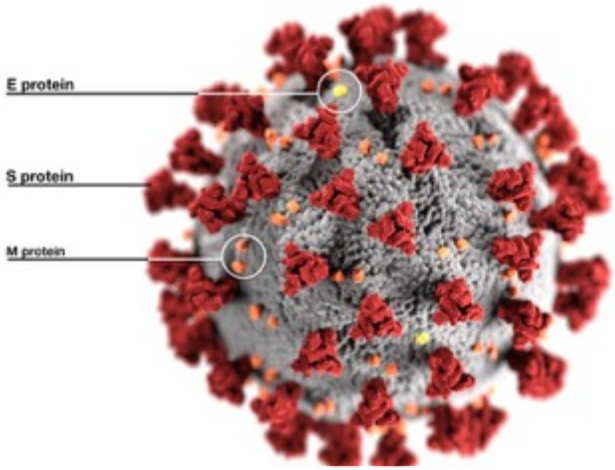


xofluza™
(baloxavir marboxil) tablets 20mg 40mg

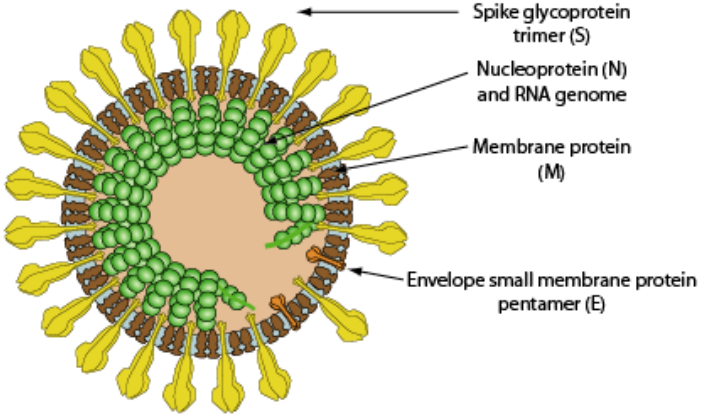
https://www.xofluza.com
Genentech / Roche

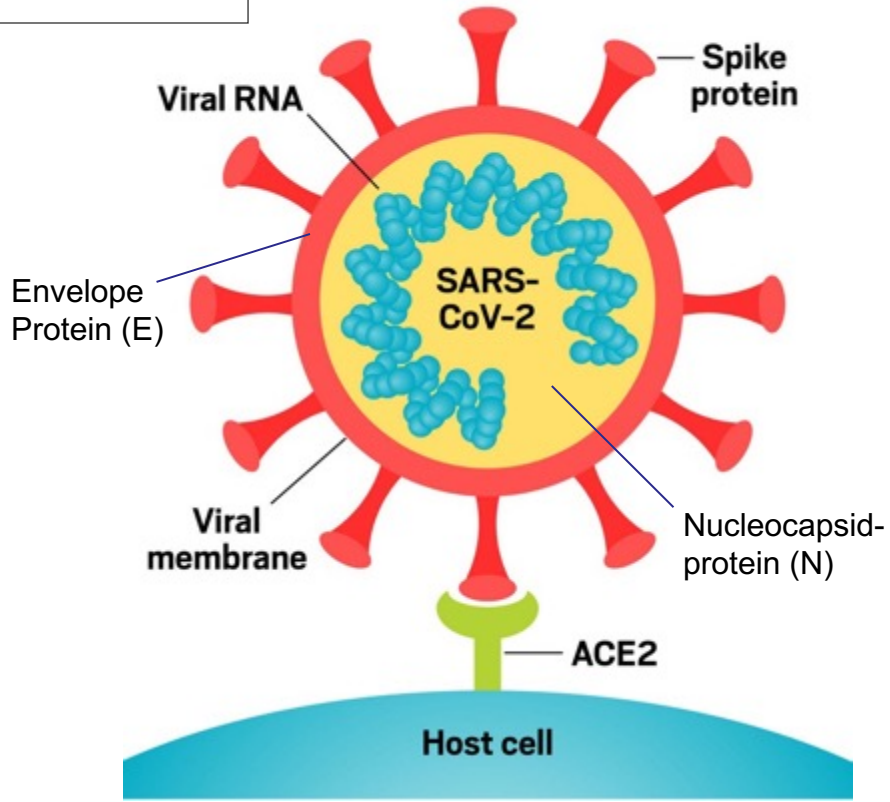


SARS- coV-2 virus



SARS-CoV / SARS-CoV-2





American Chemical Society Journal

Can old drugs take down a new coronavirus?

Several approved and well-studied small molecules could be repurposed as treatments for COVID-19

MORE than 50% are chiral!!

by ***Lisa M. Jarvis***

MARCH 12, 2020

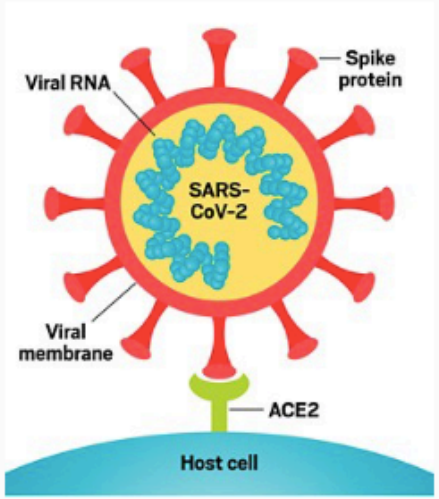
When any new virus emerges, drug and vaccine developers spring into action, searching for products to stop it in its tracks. Drug discovery campaigns launch, vaccine development efforts ramp up, and everyone mobilizes to get it all into the clinic as quickly as possible.

The current pandemic, driven by a coronavirus known as SARS-CoV-2, is no different. Already, a Phase I study of an mRNA-based vaccine **developed by Moderna** has begun, and major pharma companies and small biotechs are working on other types of vaccines. But even if they work, the most optimistic timelines put a vaccine a year to 18 months away.

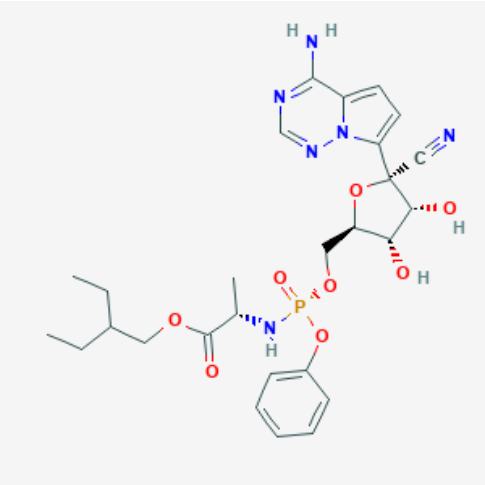
The more immediate approach to an outbreak is to scour the medicine cabinet for existing molecules that could be repurposed against a new virus. The most advanced potential treatment is Gilead Sciences' remdesivir, an antiviral discovered during the 2014 Ebola epidemic. The compound is already being tested in four, Phase III trials—two in China and two in the US—against the respiratory disease COVID-19. Gilead expects the first dataset from those studies to come out in April.

A new paper from CAS explored remdesivir and other possible options the cabinet might contain (*ACS Cent. Sci.* 2020, DOI: **10.1021/acscentsci.0c00272**). CAS, a division of the American Chemical Society,

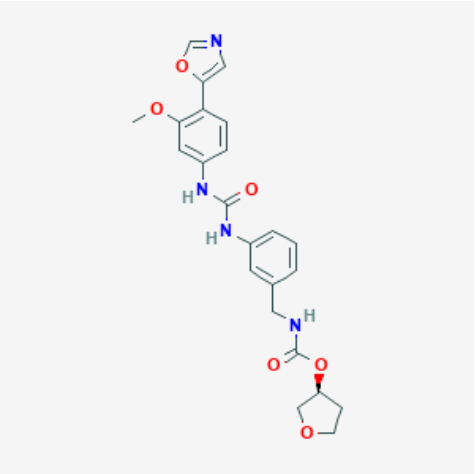
[+]Enlarge



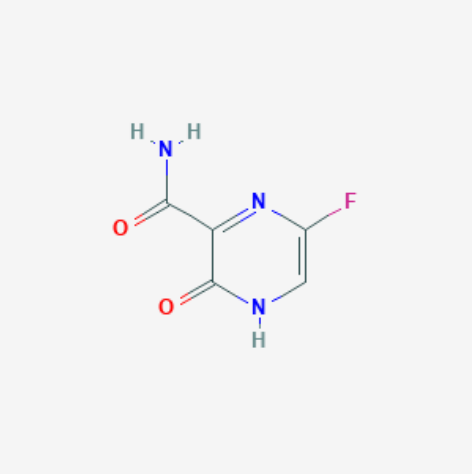
Anti-viral Drugs Tested for COVID-19:



Veklury (**Remdesivir**)
www.gilead.com



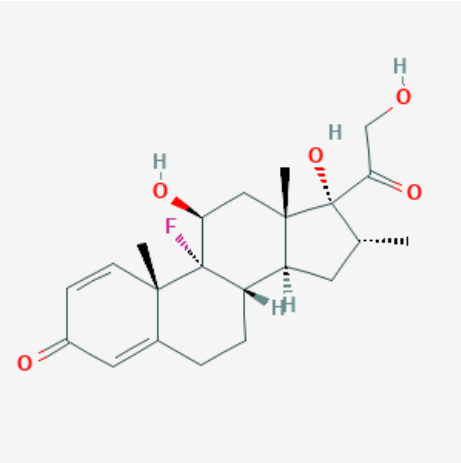
Merimepodib (VX-497)
www.biosig.com



Favipiravir (tradename Avigan) www.Fujifilm.com)

Other Drugs Tested for COVID-19:

Dexamethasone



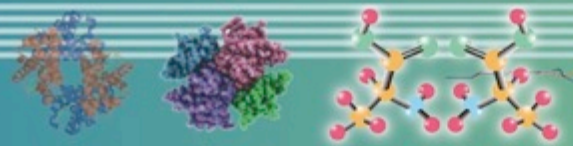
REGN-COV2 antibody cocktail:

REGN-COV2 is a combination of two monoclonal antibodies (REGN10933 and REGN10987) and was designed specifically to block infectivity of SARS-CoV-2, the virus that causes COVID-19.

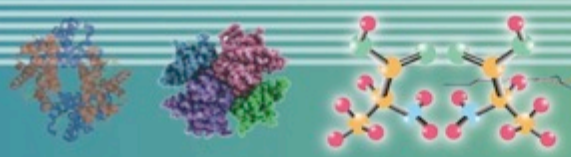
To develop REGN-COV2, Regeneron scientists evaluated thousands of fully-human antibodies produced by the company's *VelocImmune*® mice, which have been genetically modified to have a human immune system, as well as antibodies identified from humans who have recovered from COVID-19. The two potent, virus-neutralizing antibodies that form REGN-COV2 bind non-competitively to the critical receptor binding domain of the virus's spike protein, which diminishes the ability of mutant viruses to escape treatment and protects against spike variants that have arisen in the human population, as detailed in *Science*.

https://investor.regeneron.com/news-releases/news-release-details/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and

Note: Antibodies are chiral molecules but recommended techniques for structure are Raman/ROA & FTIR.



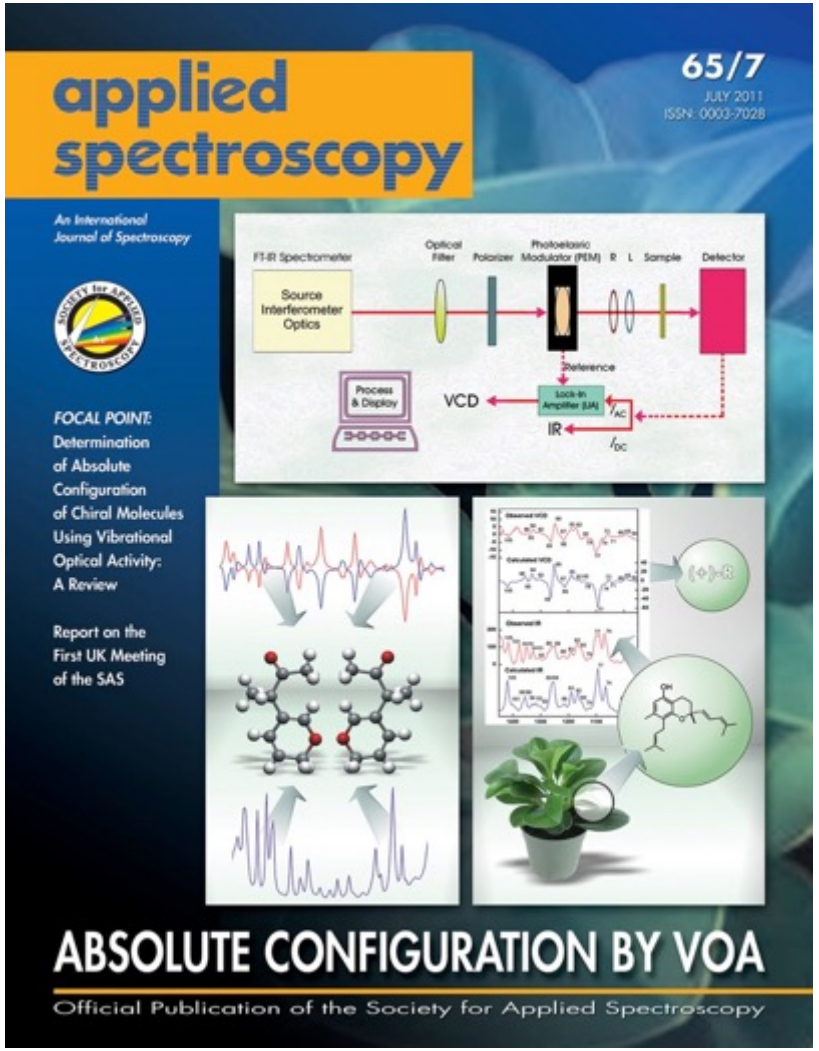
How can VCD
(Vibrational Circular Dichroism)
expedite the process of the new anti-viral drug development?



For development and approval of chiral drugs two / three critical parameters must be determined:

1. **Absolute configuration**
2. Enantiomeric (chiral) purity
3. Diastereomer identification & determination of diastereomeric ratio (if the molecule has more than one chiral center).

VCD has become a technique of choice for *rapid*, unambiguous determination of absolute configuration in solution replacing X-ray crystallography.



Paper describing application of VCD to the Determination of Absolute Configuration of Chiral Pharmaceutical Molecules

Bioorganic & Medicinal Chemistry Letters 23 (2013) 4019–4025

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

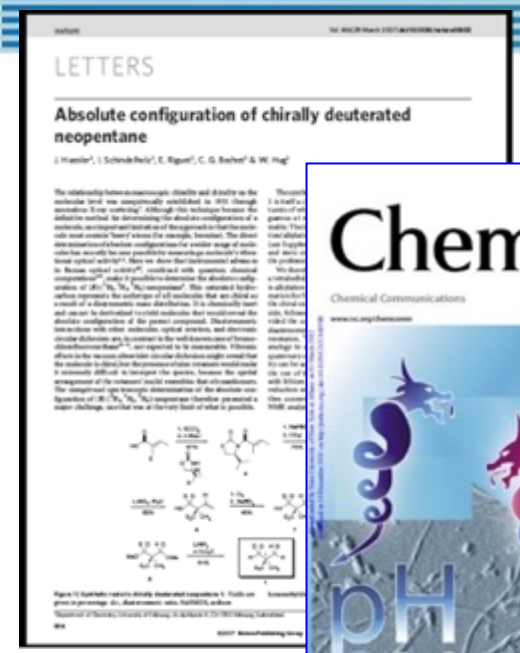
journal homepage: www.elsevier.com/locate/bmcl

BMCL Digest

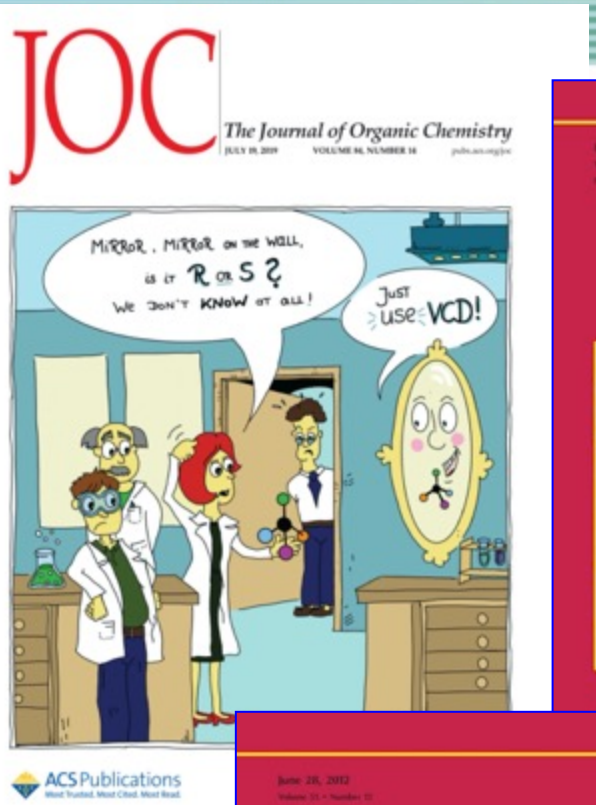
A rapid alternative to X-ray crystallography for chiral determination: Case studies of vibrational circular dichroism (VCD) to advance drug discovery projects

Steven S. Wesolowski *,†, Don E. Pivonka ‡

AstraZeneca Pharmaceuticals, 1800 Concord Pike, Wilmington, DE 19850, USA

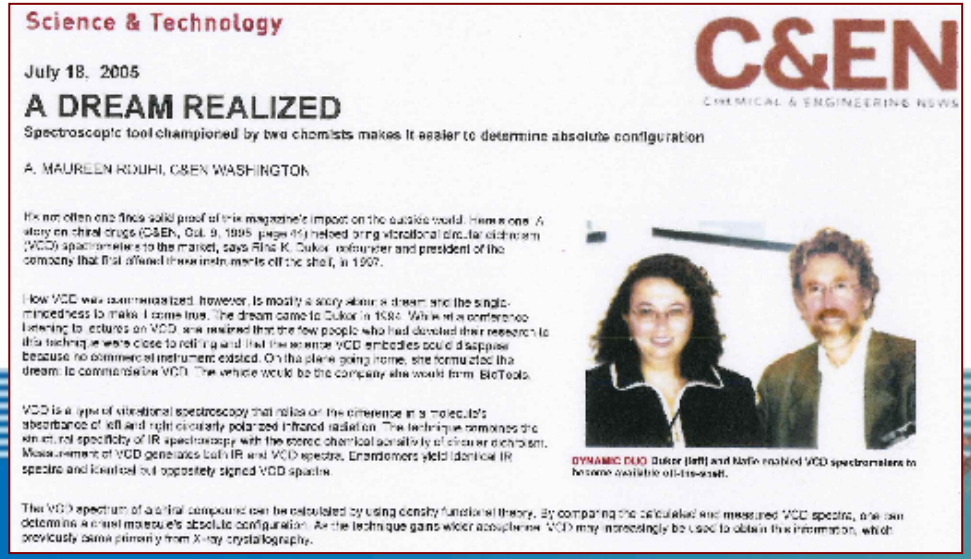

LETTERS
Absolute configuration of chirally deuterated neopentane


ChemComm
Chemical Communications
pH
RSC Publishing


JOC
The Journal of Organic Chemistry
MIRROR, MIRROR ON THE WALL, IS IT R OR S ?
WE DON'T KNOW AT ALL!
JUST USE VCD!
ACS Publications

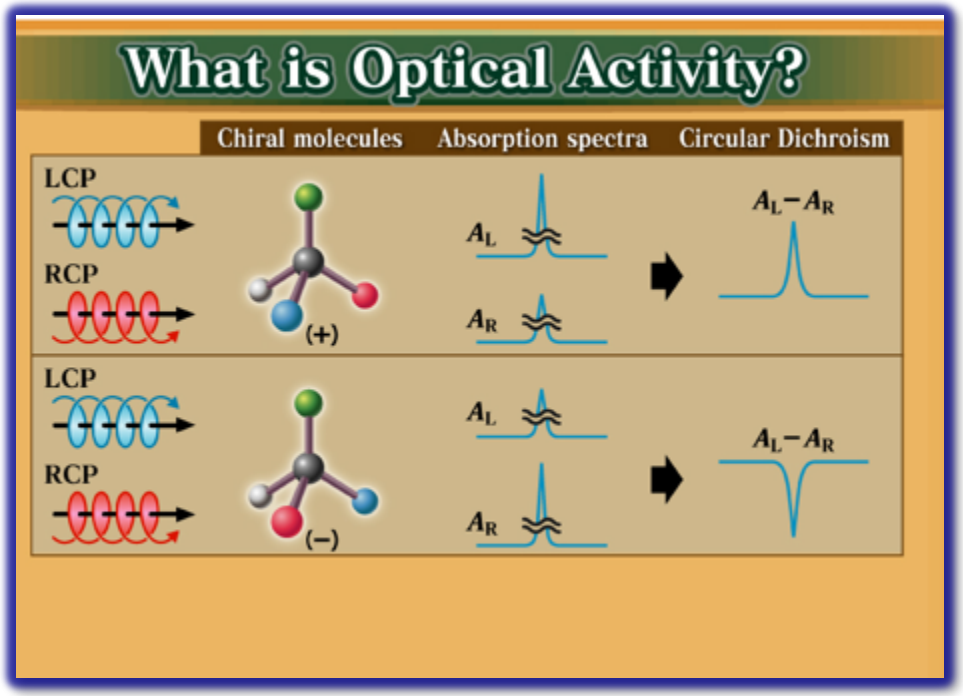

Journal of
Medicinal
Chemistry
V93
Q72
Y67
H96
M82
Leu26
Phe19
Trp23

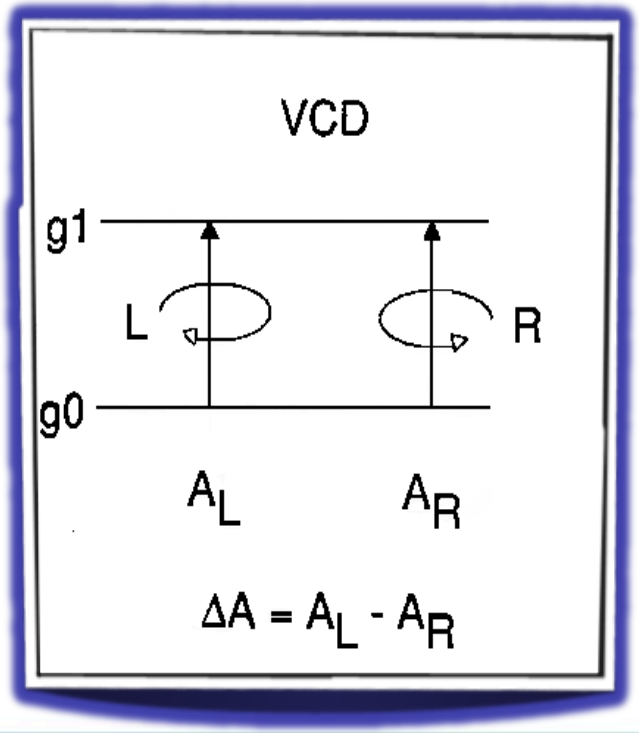

Journal of
Medicinal
Chemistry
ACS Publications


Science & Technology
C&EN
CHEMICAL & ENGINEERING NEWS
July 18, 2005
A DREAM REALIZED
Spectroscopic tool championed by two chemists makes it easier to determine absolute configuration
A. MAUREEN ROUHI, C&EN WASHINGTON
DYNAMIC DUO Duker (left) and Nafie modified VCD spectrometers to become available off-the-shelf.

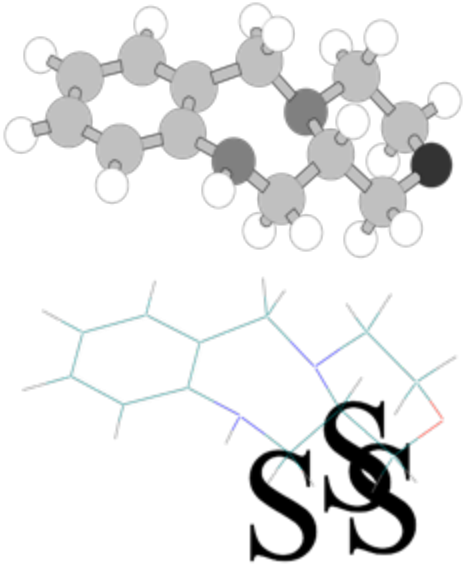
What is VCD?

VIBRATIONAL CIRCULAR DICHROISM is the difference in absorbance between Left and Right Circularly Polarized IR radiation

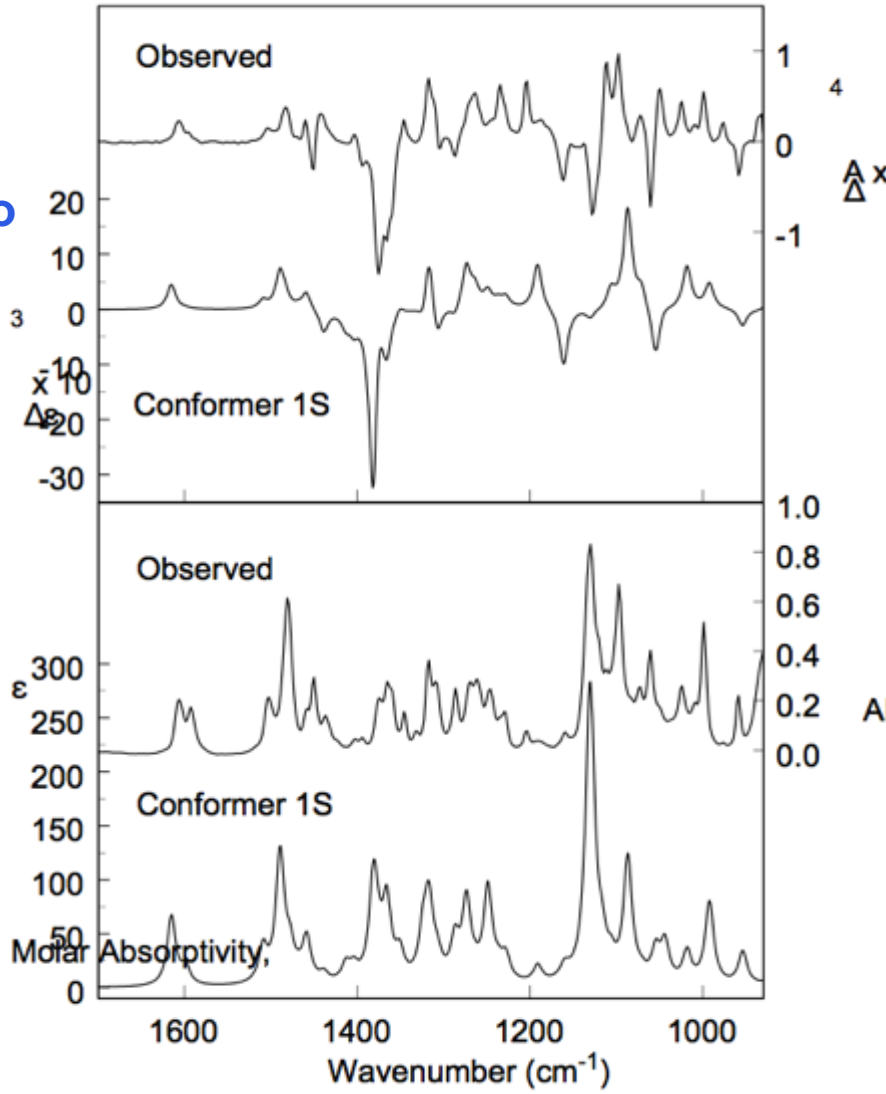




VCD provides a very rapid determination by comparing experimental spectrum to that of *ab initio* theoretical calculation so the results can be obtained in days instead of weeks and months. No need to grow a crystal.



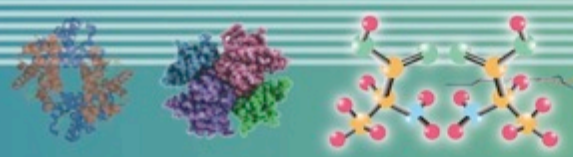
Benzodiazepine
Vasopressin
Receptor
15 heavy atoms, 3
chiral centers.



Drs. Dyatkin and Shah
Johnson Pharmaceutical Research Institute

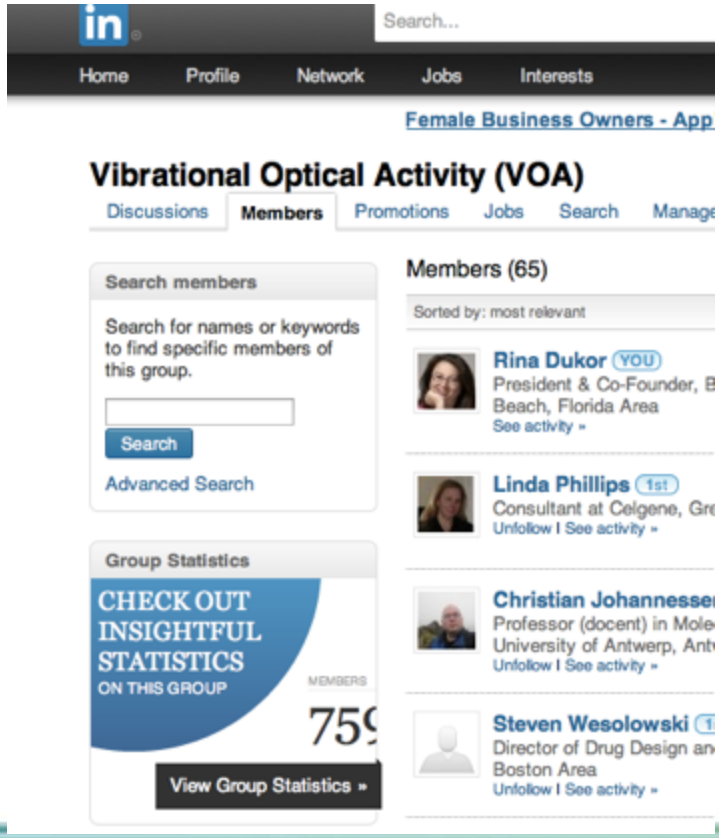
Use of VCD in Pharmaceutical Industry

- Amgen, Astra-Zeneca, BMS, Genentech, GSK, Eli Lilly, Merck,Wyeth (now Pfizer), J&J, Roche, BASF, Bayer, BioGen, Boehringer-Ingelheim, Celgene, Organon (now Schering-Plough / Merck), Sanofi-Aventis, Pfizer, Abbott/AbbVie, Vertex, Cell Therapeutics, Solvay Pharma, Neurocrine, Novartis, Sepracor, Astellas, Sunovion, Gilead,, Takeda, United Therapeutics, Cayman, Firminech, Syngenta, NIH, US Naval Research labs and US FDA among many others
- VCD is 'accepted' by regulatory agencies as proof of Absolute Configuration.
- We estimate that close to **8000** AC's have been done in the past few years
- Now, ~ **700-1000** AC's ever year!!!!!! 2020 has seen a dramatic increase in use of VCD



www.biotools.us

SOCIAL MEDIA



Thank you!