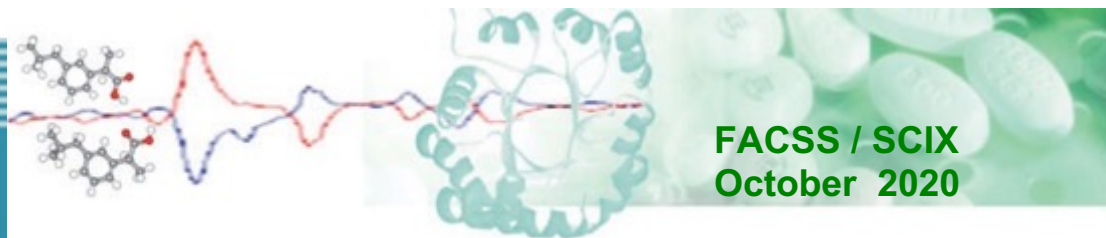


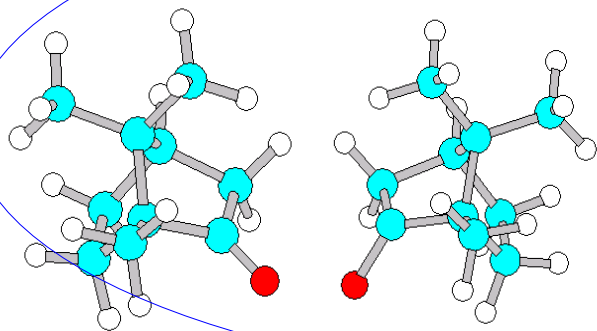
# COVID-19 & other Viral Treatments: The Role of VCD Spectroscopy in Expediting the Process

Rina K Dukor

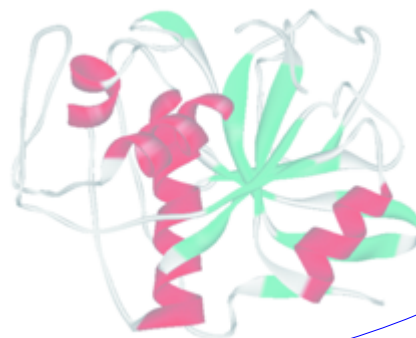


FACSS / SCIX  
October 2020

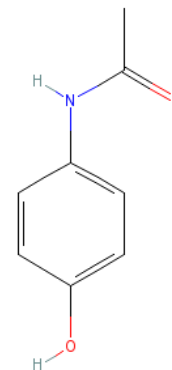
# 3 types of pharmaceuticals



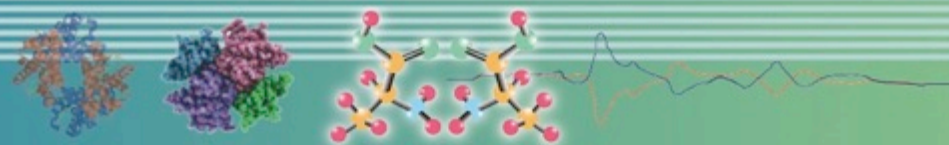
chiral



protein-based &  
other biopharmaceuticals



small organic,  
non-chiral



# 'Other' Types of Pharmaceuticals

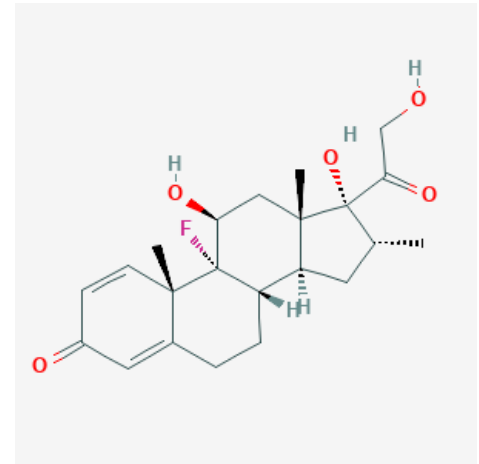
## 1. NBCD's – non-biological complex drugs

- a) Iron Sucrose
- b) Polypeptides
- c) Peptides with polymers or nano-materials
- d) Swelling polymers

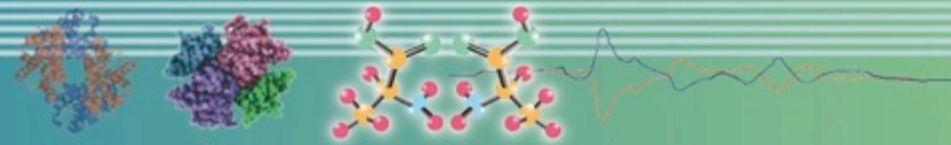
## 2. Nucleic Acid based

## 3. Carbohydrate based (heparin etc)

## 4. Steroids



Dexamethasone



Mirror

Mirror



(S)-asparagine  
flavourless



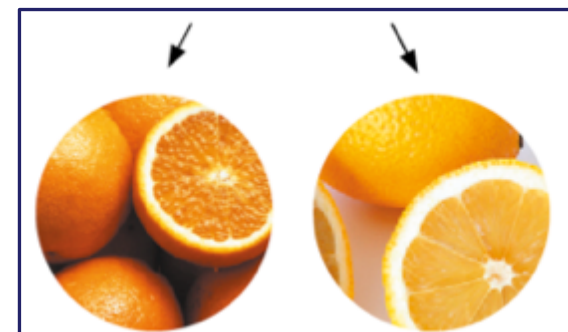
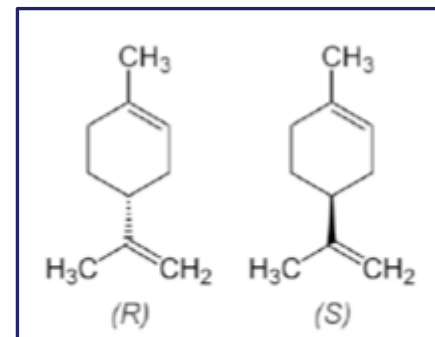
(R)-asparagine  
sweet



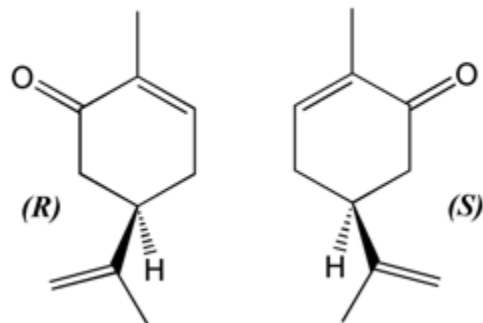
(S)-Thalidomide  
teratogenic



(R)-Thalidomide  
sedative



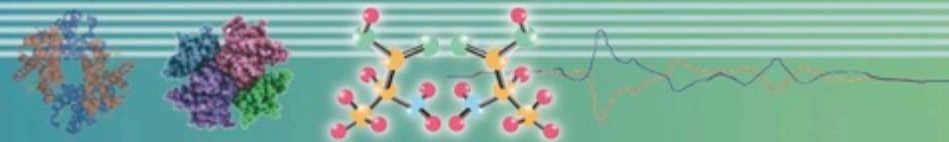
*R*-(-)-  
carvone  
smells like  
spearmint



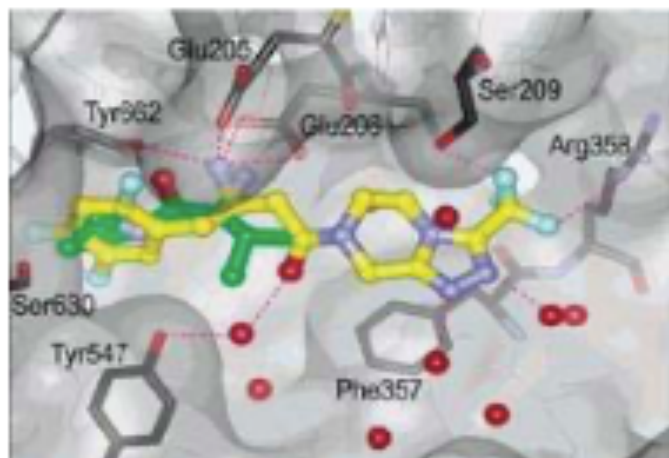
*S*-(+)-  
carvone  
smells like  
caraway  
seeds

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

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



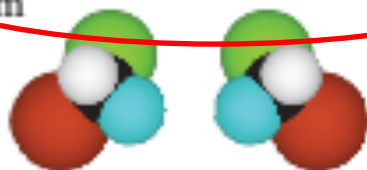
# Why Chirality is Important in the Pharmaceutical Industry



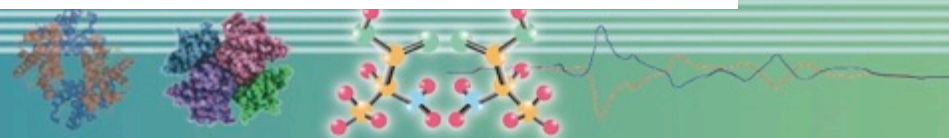
- Chirality important for
  - Potency
  - Selectivity/off target profile
  - Pharmacokinetic properties
  - Metabolism
  - Toxicity
  - *etc.*

\*\*

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



**Because Shape Matters!**

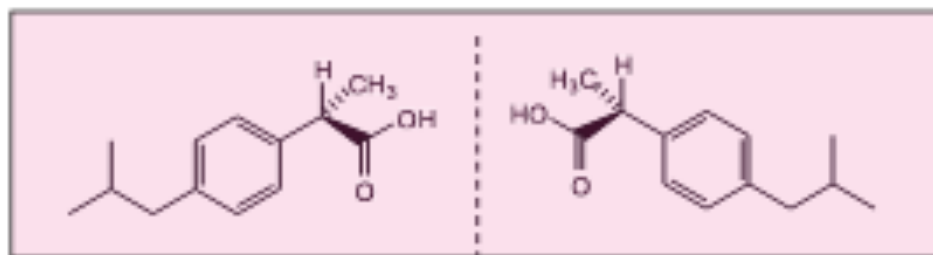




# Chirality and Pharmaceuticals



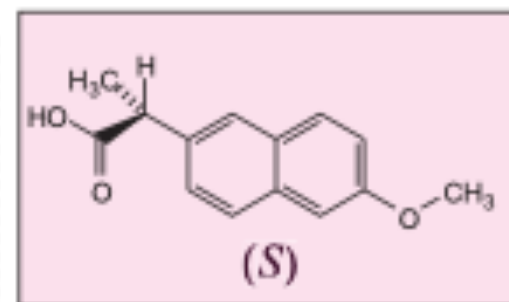
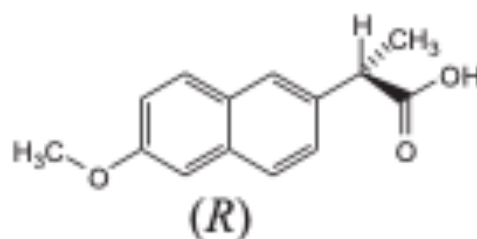
ibuprofen



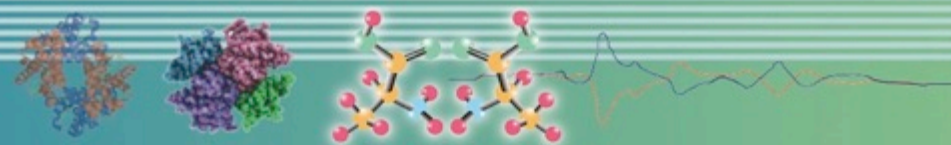
sold as racemate (1:1 mixture of enantiomers)



naproxen



Closely related naproxen sold as single enantiomer

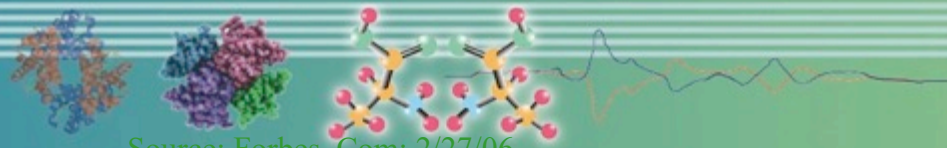


# Examples of Chiral and Biologic Blockbuster Drugs

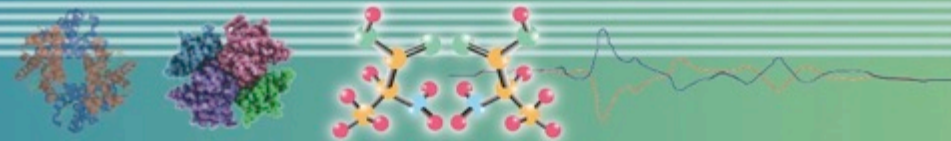
**Chiral** 

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

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

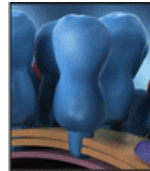
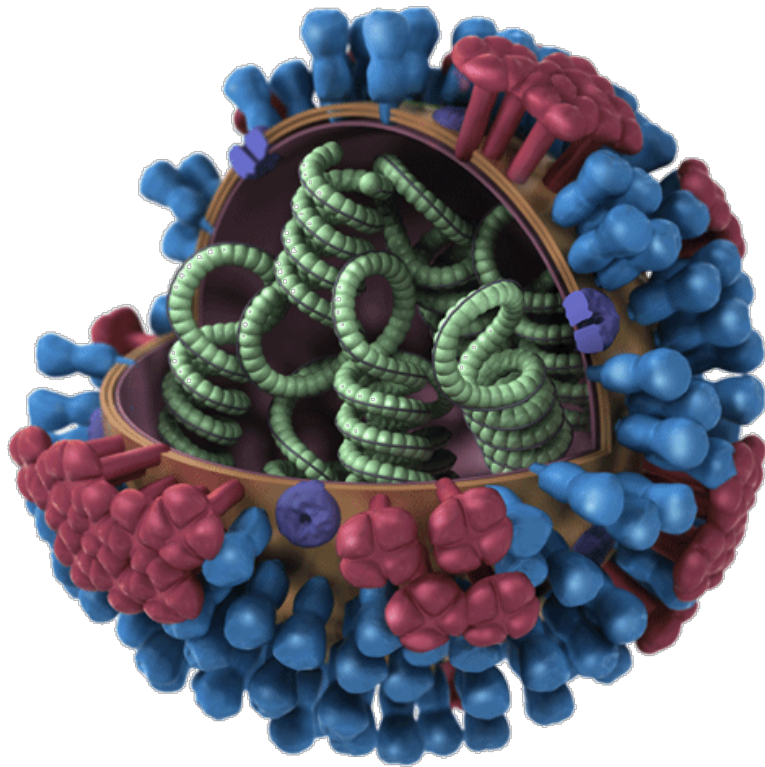


# Viruses & Viral Treatments





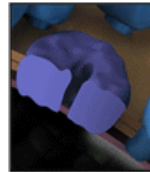
# Influenza A virus



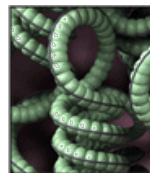
Hemagglutinin



Neuraminidase



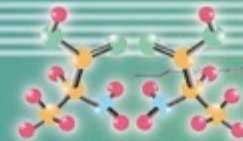
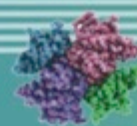
M2 Ion Channel



RNP

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

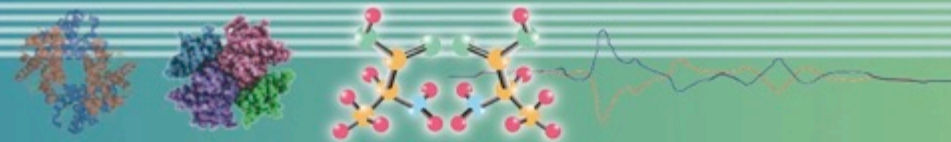
There are 18 different HA subtypes and 11 different NA subtypes. Subtypes are named by combining the H and N numbers – e.g., A(H1N1), A(H3N2).

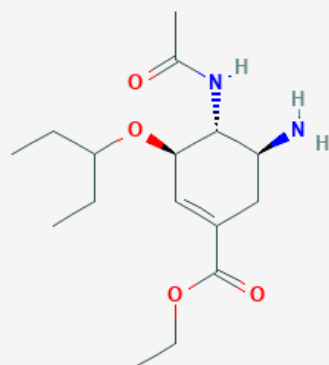


## Four FDA Approved Drugs for Influenza (Flu)

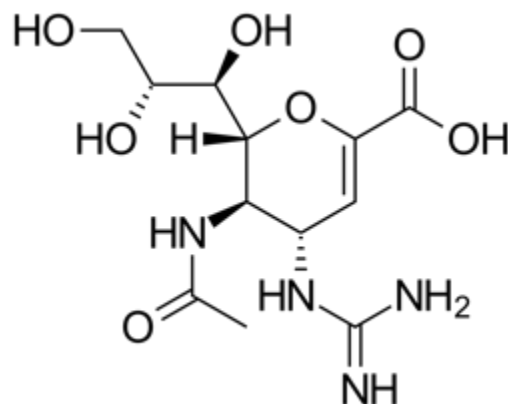
*Antivirals* interfere with an important enzyme of the influenza virus, called *neuraminidase*. The drugs keep the virus from escaping from one cell to infect a neighboring cell. –

<https://www.health.harvard.edu/drugs-and-medications/what-you-should-know-about-antiviral-drugs>

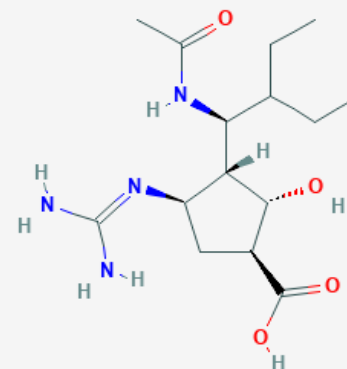




<https://www.tamiflu.com>  
Genentech / Roche

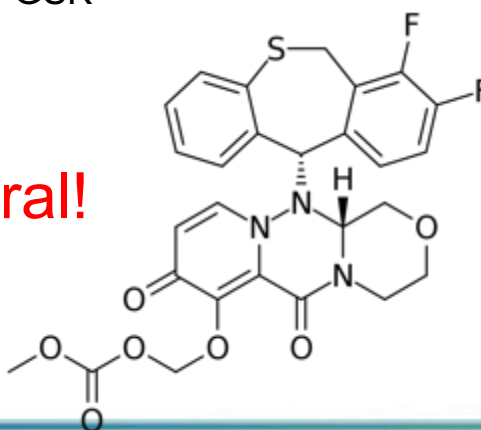


[www.gsksource.com](http://www.gsksource.com)  
GSK

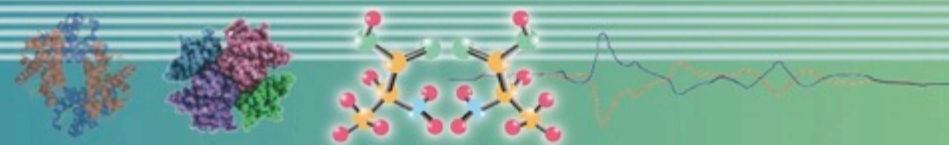


<https://www.rapivab.com>  
BioCryst Pharmaceuticals

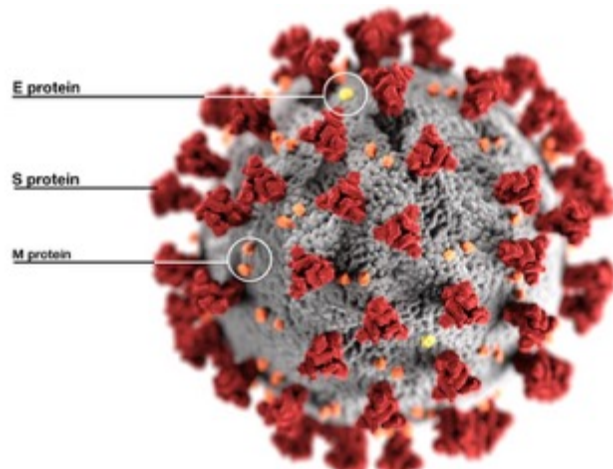
ALL four drugs are chiral!



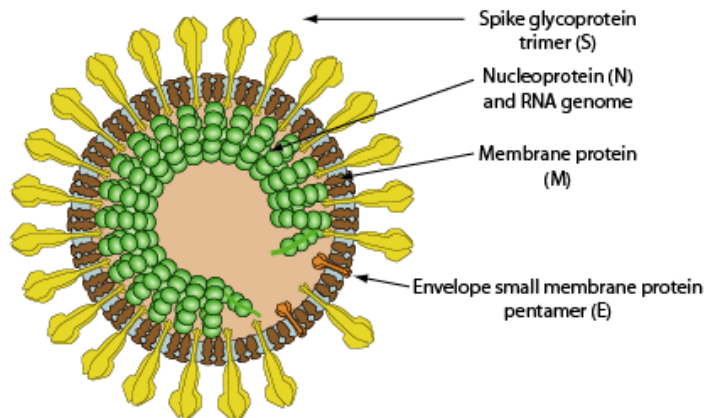
<https://www.xofluza.com>  
Genentech / Roche



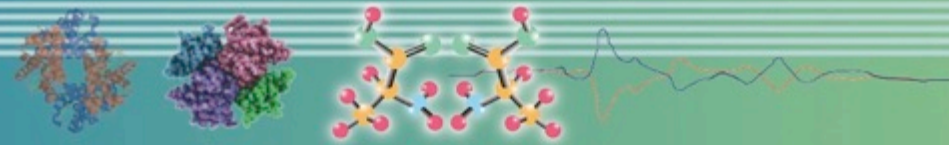
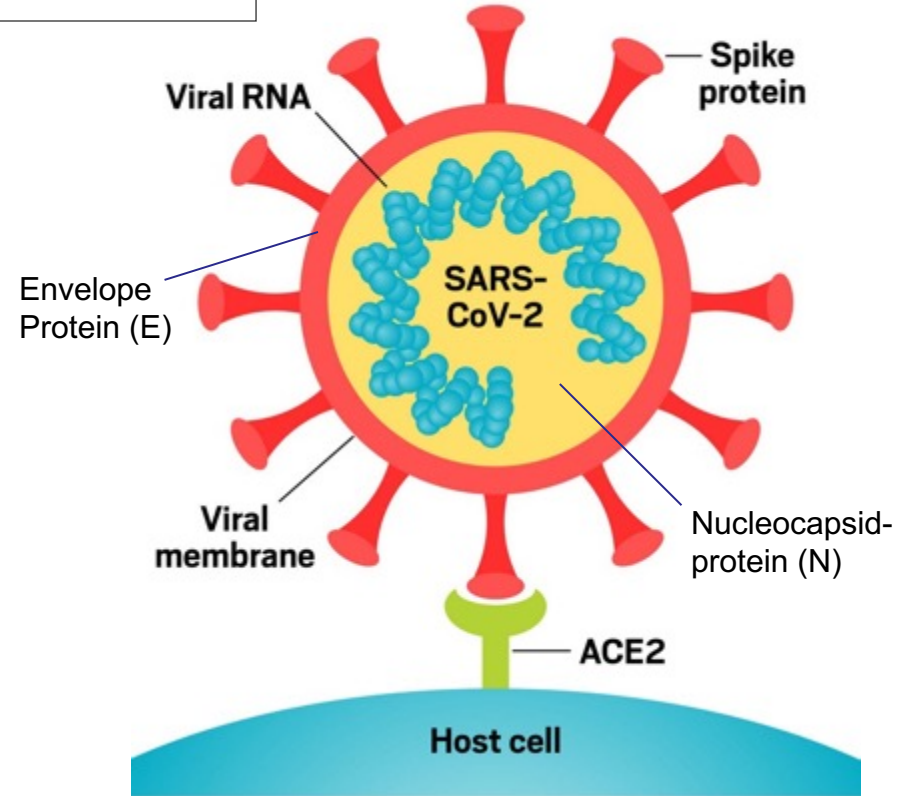
# SARS- coV-2 virus



SARS-CoV / SARS-CoV-2



© ViralZone 2020  
SIB Swiss Institute of Bioinformatics





## Can old drugs take down a new coronavirus?

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

by *Lisa M. Jarvis*

MARCH 12, 2020

**MORE than 50% are chiral!!**

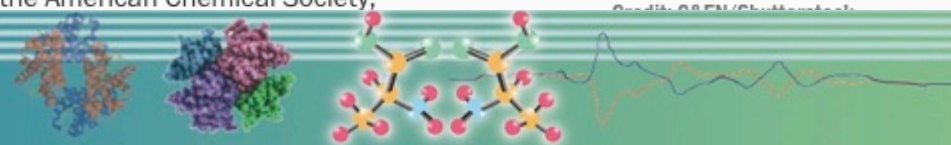
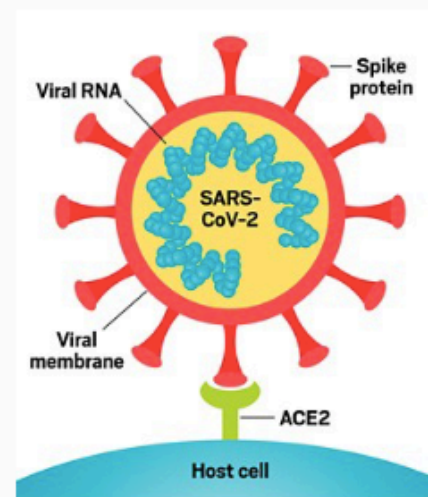
When any new virus emerges, drug and vaccine developers spring into action, searching for products to stop it in its tracks. Drug discovery campaigns launch, vaccine development efforts ramp up, and everyone mobilizes to get it all into the clinic as quickly as possible.

**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.

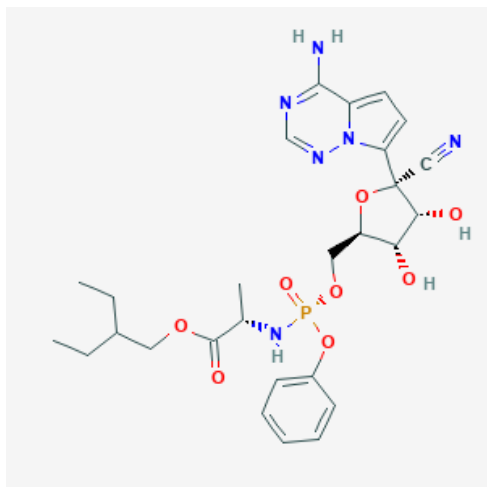
The more immediate approach to an outbreak is to scour the medicine cabinet for existing molecules that could be repurposed against a new virus. The most advanced potential treatment is Gilead Sciences' remdesivir, an antiviral discovered during the 2014 Ebola epidemic. The compound is already being 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](https://doi.org/10.1021/acscentsci.0c00272)). CAS, a division of the American Chemical Society,

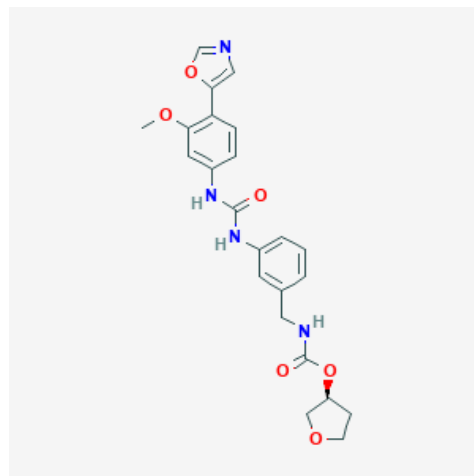
[+]Enlarge



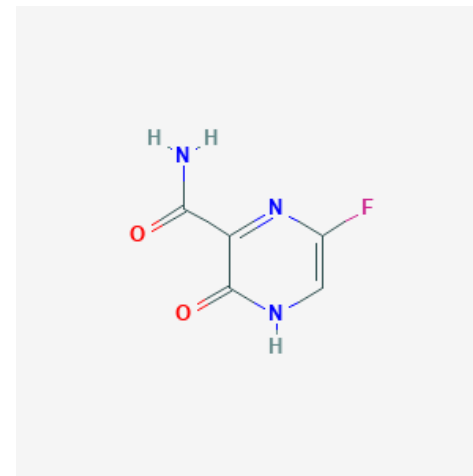
# Anti-viral Drugs Tested for COVID-19:



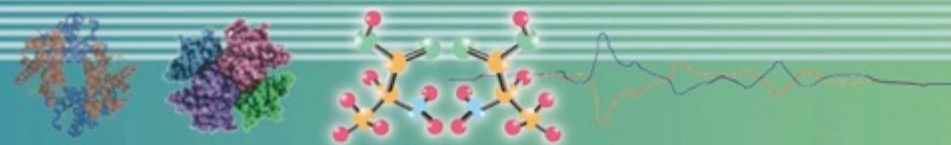
Veklury (**Remdesivir**)  
[www.gilead.com](http://www.gilead.com)



**Merimepodib** (VX-497)  
[www.biosig.com](http://www.biosig.com)



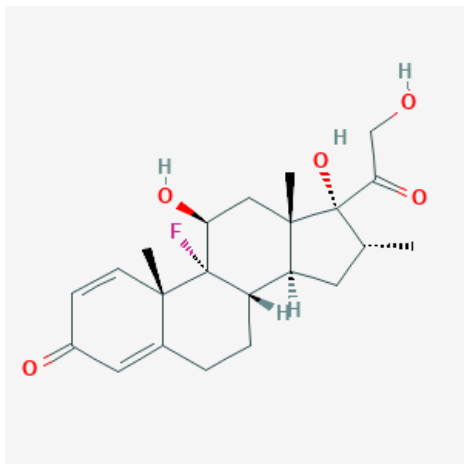
**Favipiravir** (tradename Avigan) [www.Fujifilm.com](http://www.Fujifilm.com)





# Other Drugs Tested for COVID-19:

## Dexamethasone



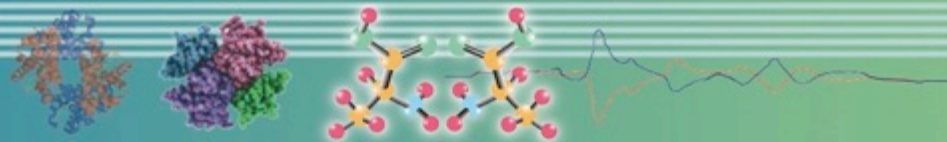
## REGN-COV2 antibody cocktail:

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.

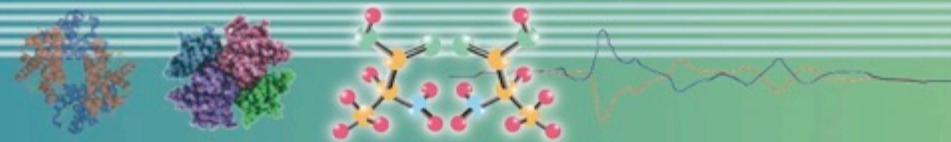
To develop REGN-COV2, Regeneron scientists evaluated thousands of fully-human antibodies produced by the company's *VelocImmune*<sup>®</sup> mice, which have been genetically modified to have a human immune system, as well as antibodies identified from humans who have recovered from COVID-19. The two 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.



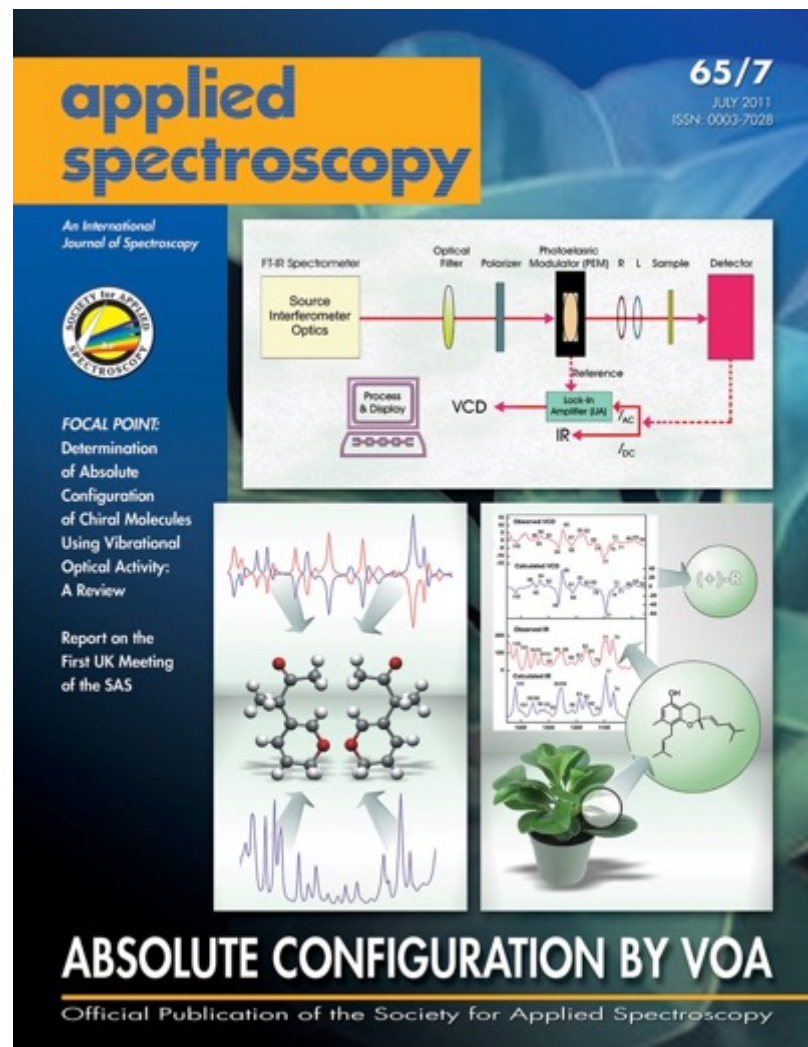
How can VCD  
(Vibrational Circular Dichroism)  
expedite the process of the new anti-viral  
drug development?



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

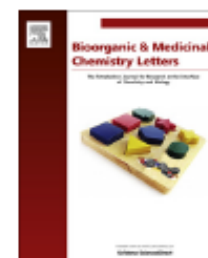
Bioorganic & Medicinal Chemistry Letters 23 (2013) 4019–4025



Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: [www.elsevier.com/locate/bmcl](http://www.elsevier.com/locate/bmcl)

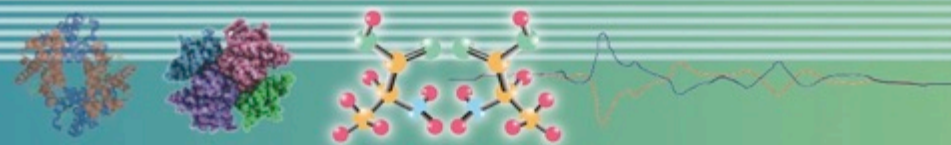


BMCL Digest

## **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 <sup>\*,†</sup>, Don E. Pivonka <sup>‡</sup>

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





## LETTERS

### Absolute configuration of chirally deuterated neopentane

J. Hämmerli<sup>1</sup>, J. Schindler-Petro<sup>1</sup>, E. Baur<sup>2</sup>, C. G. Bachler<sup>2</sup> & W. Haeberli<sup>1</sup>

in the relationship between macroscopic stability and kinetic rate in the molecular level was unequivocally established in 1910 through the work of the German chemist August Wilhelm von Baeyer, who defined the method for determining the strain of conformation of a molecule by measuring the rate of its reaction with an oxidizing reagent (now known as Baeyer's strain test). The direct measurement of the conformational strain of a series of cyclic molecules has recently been accomplished by the use of a laser Raman spectroscopy.<sup>1</sup> Thus we have three instrumental methods to determine the conformational strain of a molecule: (1) by the Baeyer strain test, (2) by the use of x-ray diffraction, and (3) by the use of laser Raman spectroscopy. The latter two methods are more accurate and can be performed without isolating molecules that would result in a possible conformational change of the molecule. However, the Baeyer strain test is the most convenient and can be performed without isolating molecules that would result in a possible conformational change of the molecule. The Baeyer strain test is the most convenient and can be performed without isolating molecules that would result in a possible conformational change of the molecule. The Baeyer strain test is the most convenient and can be performed without isolating molecules that would result in a possible conformational change of the molecule.

Figure 11 Synthesis routes of fully chlorinated compounds 1. Trifluoromethane is given in percentage. (a), chloromethane; (b),  $\text{CH}_2\text{Cl}_2$ ; (c),  $\text{CHCl}_3$ ; (d),  $\text{CCl}_4$ .

## ChemComm

Chemical Communications

Volume 48 | Number 15 | 10 March 2012 | Pages 1075–1096



RSC Publishing

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## Science &amp; Technology

Julv 18, 2005

## A DREAM REALIZED

Spectroscopic tool championed by two chemists makes it easier to determine absolute configuration

A. MAUREEN RDUHL, C&amp;EN WASHINGTON

HK has often been cited as solid proof of this magazine's impact on the outside world. Here one *Atlantic* on chiral drugs (CA&B, Oct. 9, 1995, page 46) helped bring vibrational circular dichroism (VCD) spectroscopy to the market, says Rina K. Zuker, cofounder and president of the company that first offered these instruments off the shelf in 1997.

Low VCD was commercialized, however, is mostly a story about a dream and the single-mindedness to make it a reality. The dream came to Zukor in 1934. While at a conference listening to lectures on VCD, he realized that the few people who had devoted their research to this technique were close to retiring and that the science VCD embodies could disappear because no commercial instrument existed. On the plane going home, he formulated the dream: to commercialize VCD. The vehicle would be the company she would form, BioTools.

VCD is a type of vibrational spectroscopy that relies on the difference in a molecule's absorbance of left and right circularly polarized infrared radiation. The technique combines the chemical specificity of IR spectroscopy with the stereochemical sensitivity of circular dichroism. Measurement of VCD generates both IR and VCD spectra. Enantiomers yield identical IR spectra and identical but oppositely signed VCD spectra.

The VCD spectrum of a chiral compound can be calculated by using density functional theory. By comparing the calculated and measured VCD spectra, one can determine a chiral molecule's absolute configuration. As the technique gains wider acceptance, VCD may increasingly be used to obtain this information, which previously came primarily from X-ray crystallography.

## JOC

The Journal of Organic Chemistry

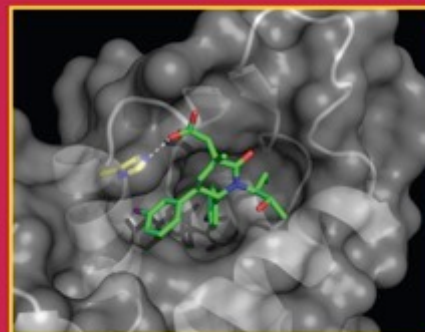
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**DYNAMIC DUO** Dukez (left) and Nafie enabled VCD spectrometers to become available off-the-shelf.

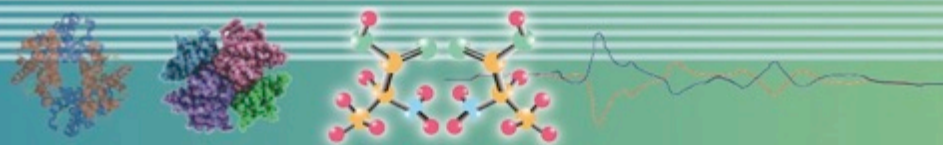
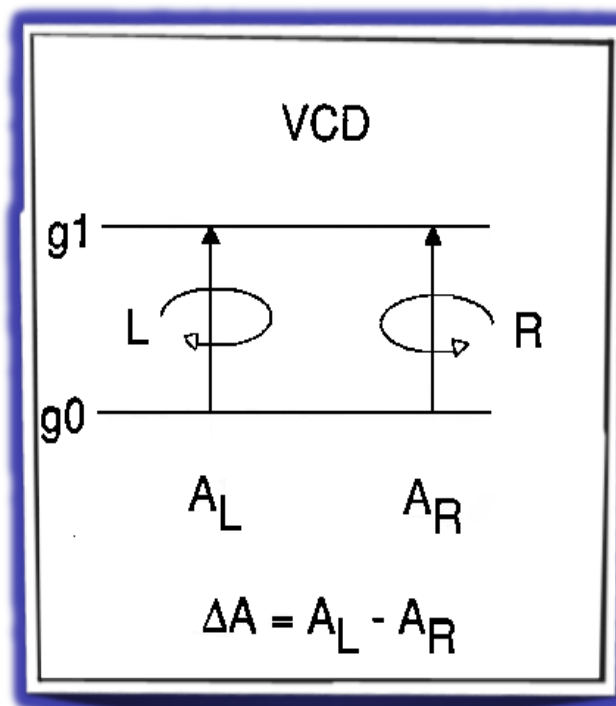
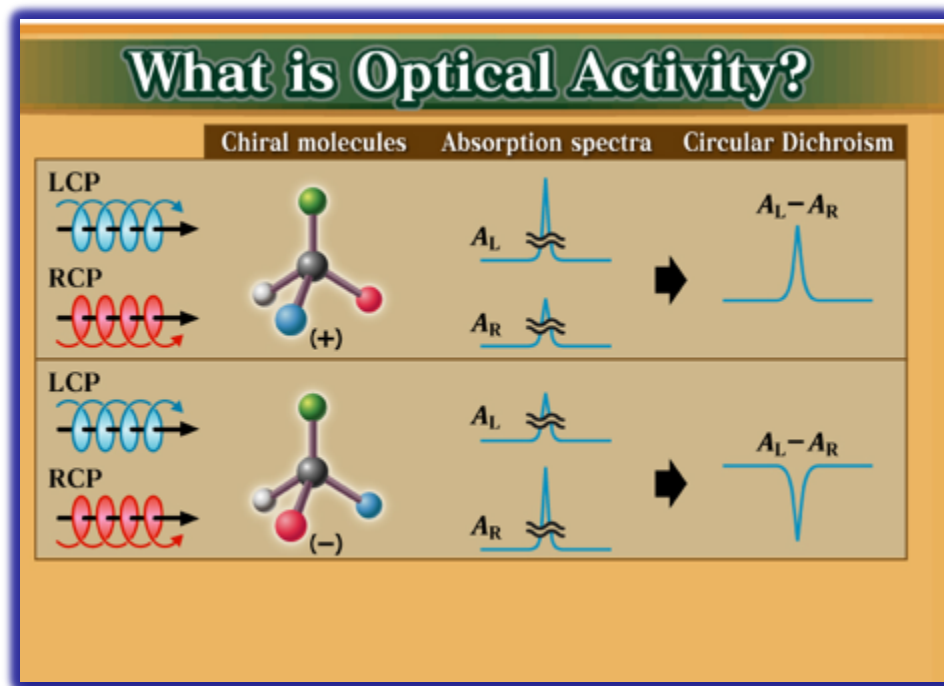
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**Abstract**

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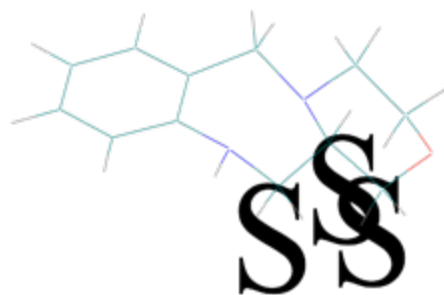
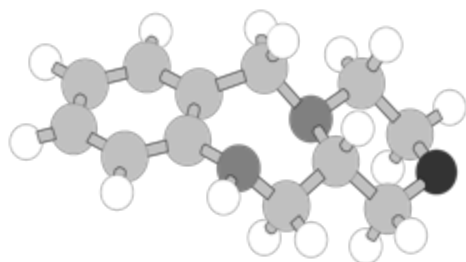
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VIBRATIONAL CIRCULAR DICHROISM is the difference in absorbance between Left and Right Circularly Polarized IR radiation

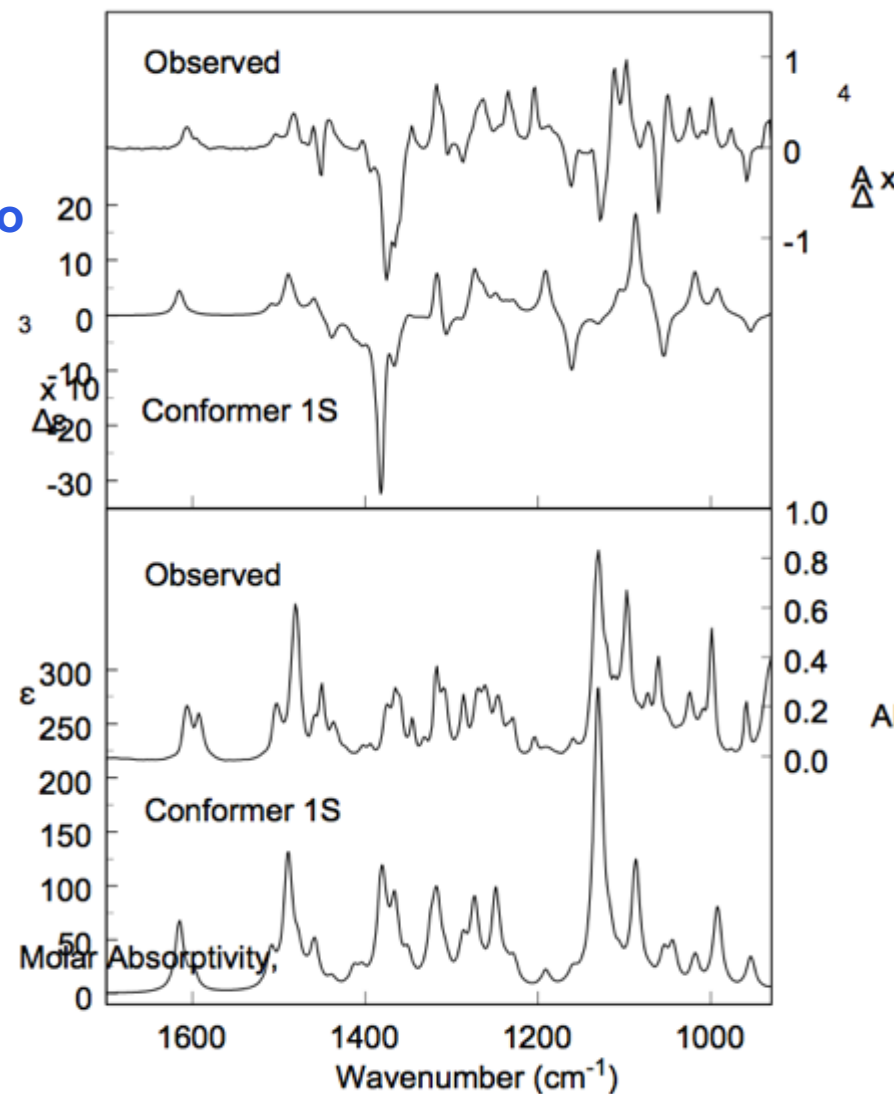




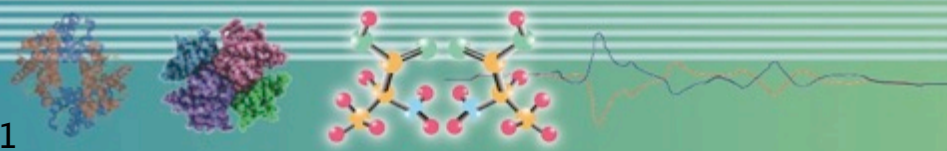
VCD provides a very rapid determination by comparing experimental spectrum to that of *ab initio* theoretical calculation so the results can be obtained in days instead of weeks and months. No need to grow a crystal.



Benzodiazepine  
Vasopressin  
Receptor  
15 heavy atoms, 3  
chiral centers.

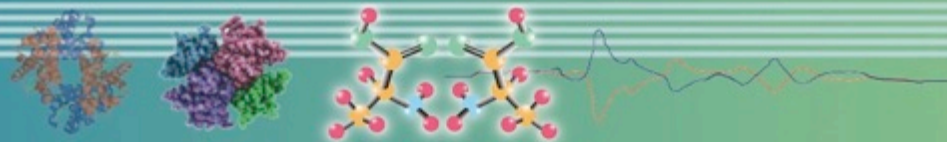


Drs. Dyatkin and Shah  
Johnson Pharmaceutical Research Institute



# 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



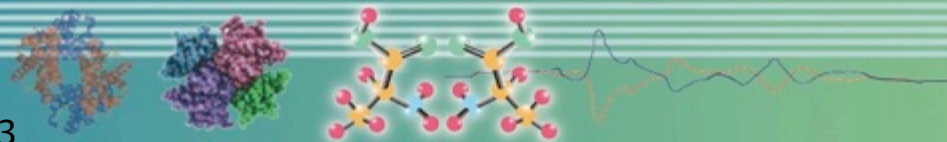


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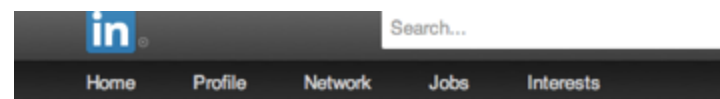
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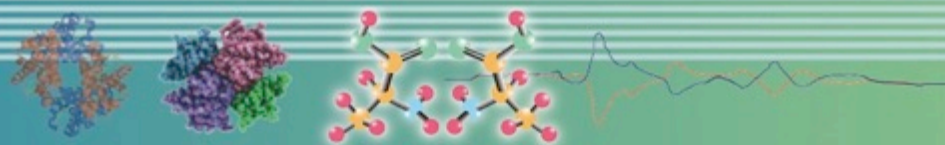
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