Synthetic Chemistry and Medicine

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"Has it ever occurred to you that medicinal chemists are just like compulsive gamblers: the next compound will be the real winner."

Goal of talk: to provide a little understand on medicinal chemistry and relate it to applied synthetic chemistry

- Medicinal chemistry—a definition—*the use of synthetic organic chemistry to create molecules that will alter in a useful way some disease process in a living system.* -D. Lednicer

- Not unlike catalyst optimization with many more variables?

- Where do drugs come from? Both from natural sources and new entities from a bench.

- Method of Drug Discovery:
  - Classical pharmacology (screening of chemicals to find biological)
  - Reverse pharmacology (find chemicals based on biological target)

- Why do drugs work? Receptors.
  - Substrate must find and binds to target – lipids / proteins / nucleic acids
  - Binding due to non-covalent interactions.
  - Leads to biological response
Topics discussed

• Analgesics – Traditional to Modern Drug Design
• Selected Medicines
  • Antihistamines
  • Antivirals
  • Antidepressant
  • Antifungal
Opioids – alkaloids derived from opium (poppy)

-One of the oldest fields in medicinal chemistry, yet one where true success is yet to be found

-Perhaps oldest known drug with recording use dating back 2000 years in china.

-Analgesic effects “detachment from pain” + euphoric properties lead to severe dependence of the drug.

-Total alkaloid content of opium is ~5–10%.

Major constituents:

- Pure morphine isolated 1803 - functional group determination 1881
- structure determination 1925 - first total synthesis 1952
First total synthesis of Morphine by Gates. JACS 1953, 4340

31 steps
0.06% overall yield

Other syntheses:

Fuchs 1988  Parsons 1996  Taber 2002  Stork 2009
Tius 1992  White 1997  Trost 2002  Fukuyama 2010
Parker 1992  Hudlicky 1998  Michels 2005  + More...

Morphine obtained by fractionation of opium.
Projected opium production in Afghanistan 6,400 metric tons or 6,400,000 kg (2014)
Goal: Eliminate side effects while retaining activity.

Traditional approach: Trial and error.

1. Identification of drug molecule with biological response (poppy plant)
2. Synthesis enables testing of Structure-activity relationships – see which parts responsible for function
3. Drug development – synthesize analogs to improve activity and reduce side effects
4. Propose theories on mechanism of action.

What happens when we modify functional groups? (many studies done prior to knowledge of full structure)
(Morphine functional groups determined by 1881)

 Leads to weakening or loss of analgesic effect
Free phenol essential for function

Due to superior pharmacodynamic properties rather than higher receptor affinity.
Easier to cross Blood-brain barrier - Greater drug bioavailability
Can we retain function with simpler structure?

**Simplification of Structure**

**Grewe and Mondon** Chem. Ber. 81, 279, 1948

**bare morphine skeleton**


**racemorphan**

**Levorphanol** 5x potency

**Dextrorphan** negligible analgesic hallucinogen
Further Simplification of Structure

- Morphine
- Levorphanol (5x potency)
- Phenazocine (4x potency)
- Pethidine (0.2x potency)
- Fentanyl (100x potency)

Identification of receptor site can allow for rational design

Use of H\(^3\)-Naxolone led to identification of opioid receptors in mammalian brain. Multiple receptors (\(\delta, \kappa, \mu\)) on peripheral sensory neurons. Each receptor responsible for multiple functions. (anagesia, sedation, dependence, etc.) \(\mu\) Opioid receptor particular important - trigger for analgesia and also side effects


Naxolone
*opioid antagonist*
used for cases of opioid overdose
Crystal structure incorporating the opioid allows for better understanding of structural basis for \( \mu \)-Opioid receptor function

Structure-based discovery

Crystal structure as basis, computationally dock libraries of molecules into \( \mu \)-OR pocket.

3 million available lead-like compounds, average of 1.3 million configurations evaluated for each.

Manually examined the top 2,500 (0.08%) - Ultimately settled on screening 23 high-scoring molecules

PZM21 is less potent (0.25x) than morphine yet has very low \( \beta \)-arrestin-2 recruitment (protein responsible for undesired effects)

doi:10.1038/nature19112
Manglik Nature Aug 17, 2016
**Histamines and Anti-histamines**

**Histamine** is released from mast cells (White blood cell) in event of:
Tissue injury or introduction of foreign substance.

Histamine binds to protein known as Histamine H₁ Receptor - leads immune response and undesirable symptoms

**Anti-histamines** are drugs that reduce or eliminate the effects by histamine

Mechanism of action:
- Bind H₁ receptor thus inhibit histamine binding
- Displaces histamine from receptor H₁ receptor
- Generally most beneficial when given early

**Histamine**

**Anti-histamine common structure**

**anti-histamine**
diphenhydramine discovered 1943
**Early Route to Loratadine** Schering Corporation Patent: US 4282233 (1981)

1. Pd/C, EtOAc
2. H₂O₂, AcOH
1. SO₂(OMe)₂
2. NaCN, H₂O then, NaOH, Δ

**Multi-kilo scale synthesis (Schering-Plough)** JOC 1989 2242

1. SOCl₂, PhH, Δ
2. AlCl₃, CS₂

**Loratadine**

**Clarithin**

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**Chemical Structures:**
- Loratadine
- Clarithin

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**Reagents and Conditions:**
- NaOMe, DMF
- Na₂CO₃, THF
- Pd/C, EtOAc
- H₂O₂, AcOH
- SO₂(OMe)₂
- NaCN, H₂O
- NaOH, Δ
- SOCl₂, PhH, Δ
- AlCl₃, CS₂
- CO₂EtCOCl, Δ
- HF, BF₃

Scalable route to (S)-Cetirizine: Sepracor TL, 2002, 923 (C. Senanayake)
Crystal Structure of the histamine $H_1$ receptor complex with doxepin

R. Stevens and S. Iwata *Nature* 2011 65-70
Anti-virals

Nucleoside analog reverse-transcriptase inhibitors (NRTIs) mimic nucleosides.

Zidovudine (AZT) is a HIV reverse transcriptase inhibitor and is a analog of thymidine. Upon phosphorylation, competes for incorporation into viral DNA, terminating DNA synthesis.

Lamivudine is an analog of cytidine. A reverse transcriptase inhibitor in for HIV and hepatitis B virus.

The lack of a 3'-OH group in the nucleoside mimic prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation.
Early route to AZT: Horwitz JOC 1964 2076

\[
\begin{align*}
\text{epi-thymidine} & \\
\text{1. } & \text{Ph}_3\text{CCl, pyr.} & \rightarrow & \text{TrO}_\text{OMs} & \rightarrow & \text{1. LiN}_3, \text{DMF, 100 °C} & \rightarrow & \text{Zidovudine (AZT)} \\
\end{align*}
\]

Updated route from thymidine: Glinksli JOC 1973 4299

\[
\begin{align*}
\text{thymidine} & \\
\text{1. } & \text{Ph}_3\text{CCl, pyr.} & \rightarrow & \text{TrO}_\text{OMs} & \rightarrow & \text{K-Phthalimide} & \rightarrow & \text{1. NaN}_3, \text{H}_2\text{O, DMF, }\Delta \\
\text{70 °C} & \rightarrow & \text{Mechanism?} & \rightarrow & \text{NaN}_3 & \rightarrow & \text{Zidovudine (AZT)} \\
\end{align*}
\]

\[
\begin{align*}
\text{Br} & \quad \text{OEt} & \quad + & \quad \text{Ph} & \quad \text{SH} & \quad \text{KOT-Bu, DMF, Then, NaOH, H}_2\text{O} & \quad \text{HS} & \quad \text{OEt} & \quad \text{PhO} & \quad \text{CHO} & \quad \text{TsOH, PhH, } \Delta \\
\text{TMSHNN} & \quad \text{N} & \quad \text{O} & \quad \text{OTMS} & \quad \text{H}_2\text{N} & \quad \text{N} & \quad \text{O} & \quad \text{S} & \quad \text{O} & \quad \text{Ph} & \quad \text{Ac}_2\text{O, separation} & \quad \text{H}_2\text{N} & \quad \text{N} & \quad \text{O} & \quad \text{S} & \quad \text{O} & \quad \text{OH} & \quad + & \quad \text{H}_2\text{N} & \quad \text{N} & \quad \text{O} & \quad \text{S} & \quad \text{O} & \quad \text{OH} \\
\text{TMSOTf, MeCN, } \Delta & \quad \text{r} & \quad \text{ac-trans Lamivudine} & \quad \text{r} & \quad \text{ac-cis Lamivudine} & \quad \text{active anti-viral}
\end{align*}
\]

Enantioselective synthesis of Lamivudine (GSK) TL 2005 46 8535

\[
\begin{align*}
\text{HO} & \quad \text{C} & \quad \text{O} & \quad \text{OH} & \quad \text{1. } \text{SOCl}_2 & \quad \text{\begin{align*}
\text{HO} & \quad \text{C} & \quad \text{O} & \quad \text{OH} & \quad \text{\(-\)menthol} \\
\text{HO} & \quad \text{C} & \quad \text{O} & \quad \text{OH} & \quad \text{\(-\)menthol}
\end{align*}} \quad \text{\text{KMnO}_4, acetone} \\
\text{H}_3\text{O}_6 & \quad \text{THF} & \quad \text{\text{SOCl}_2, toluene, } \Delta & \quad \text{then, n-hexane, Et}_3\text{N, crystallization} & \quad \text{Dyamic KR} \\
\text{TMSHNN} & \quad \text{N} & \quad \text{O} & \quad \text{OTMS} & \quad \text{NaBH}_4, \text{EtOH} & \quad \text{\text{HO}_2\text{S} & \quad \text{O} & \quad \text{N} & \quad \text{Cl}} \quad \text{Reason for inversion/retention?}
\end{align*}
\]
Mechanism of Anti-depressants

• **monoamine hypothesis of depression** hypothesizes the basis of depression due to a depletion of serotonin and/or other neurotransmitter at synaptic cleft.

• The **Serotonin transporter is responsible** for re-uptake of serotonin. If blocked by a foreign chemical (*Selective serotonin reuptake inhibitor (SSRI)*) leads to greater serotonin concentration.

• **5-HT$_{1A}$** receptor that inhibits firing of serotonergic neurons. After a few weeks, of **chronic overstimulation**, **5-HT$_{1A}$ receptor becomes subsensitive** due to and is **downregulated** – leading to therapeutic effects.
Early route to Sertraline (Zoloft) - Pfizer Patent: US 4536518 (1985)

1 SOCl₂, PhH, Δ
2. AlCl₃, CS₂

resolution
D-(-) Mandelic acid

rac-cis-Sertraline 70%
rac-trans-Sertraline 30%

active form
cis-(R,R)Sertraline
Enantioselective Route to Sertraline: Corey, TL, 1994, 5373

\[
\text{MeO}_2C\text{N}_2 + \text{PhCH}_2CH_2\text{Ph} \rightarrow \text{Ph}_{\text{DOC}_{\text{Me}}} + \text{CO}_2\text{Me}
\]

94% ee
Recryst. >99% ee

\[
(3,4\text{-diClC}_5\text{H}_4)\text{CuLi}_2\text{CN} \rightarrow \text{Cl}_2\text{CO}_2\text{Me}
\]

\[
6\text{N HCl, } \Delta \rightarrow \text{Cl}_2\text{Cl}_2\text{CO}_2\text{H}
\]

\[
\text{CISO}_3\text{H, DCM} \rightarrow \text{H}_5\text{Cl}_4\text{Cl}_2
\]
Merck Process: OL, 1999, 293

\[ \text{BrCH} \text{CHO} \overset{(\text{MeO})_3\text{CH}, \text{TsOH, MeOH}}{\rightarrow} \text{OMe} \overset{\text{then, Mg, THF}}{\rightarrow} \text{MgBr} \]

\[ \text{Cl_3C} \text{H} \overset{\text{PivCl, Et_3N, LiCl}}{\rightarrow} \text{Cl} \]

\[ \overset{\text{CuBrSMe}_2}{\rightarrow} \text{THF} \]

\[ \text{complete diastereoselection} \]

\[ \overset{\text{NaBH}_4}{\rightarrow} \text{THF/H}_2\text{O} \]

\[ \overset{\text{NHMe}}{\rightarrow} \text{t-BuLi} \]

\[ \text{sertraline} \]

\[ \overset{\text{THF-tol, -78 °C}}{\rightarrow} \]

\[ \overset{\text{MeNH}_2}{\rightarrow} \text{THF} \]

\[ \overset{\text{PPh}_3, \text{I}_2, \text{imid. then, 2N HCl}}{\rightarrow} \]
Amphotericin B - an anti-fungal agent

Concept of action

phospholipid bilayer

Bone Marrow Transplantation. AmBisome targeting to fungal infections. 1994;14:S3-S7

fumigatus incubated for 14 hours with gold-labeled liposomes:
(a) without AmBisome, showing lipid from the liposomes in association with the surface of the fungal cell wall.
(b) with AmBisome penetrating through the cell wall, and lipid accumulating in the cytoplasm.
“A compelling example of the relationship between pharmacological activity and molecular chirality was provided by the tragic administration of thalidomide to pregnant women in the 1960s. (R)-Thalidomide has desirable sedative properties, while its S enantiomer is teratogenic and induces fetal malformations. Such problems arising from inappropriate molecular recognition should be avoided at all costs.”

Ryoji Noyori – Nobel Lecture 2001

Thalidomide route

**Glutamic acid**

\[
\begin{align*}
\text{HOOC-C_2H_4COOH} & \quad \text{pyr.} \\
\text{NH}_2 & \quad \text{NH}_2 \\
\text{HOOC-C_2H_4COOH} & \quad \text{NH}_2 \\
\end{align*}
\]

(R)-Thalidomide

(S)-Thalidomide

Thalidomide also found to be effective for treatment of certain cancers


**CBz-glutamine**

\[
\begin{align*}
\text{H}_2\text{N-C_2H_4COOH} & \quad \text{CDI} \\
\text{NHCbz} & \quad \text{then, H}_2, \text{Pd/C} \\
\text{Et}_3\text{N, DMF, 80 °C} & \quad \text{then, H}_2, \text{Pd/C} \\
\end{align*}
\]

Lenalidomide

Myleoma treatment

$447.62$ per $10$-mg tablet (2012)

or $163,381$ / year for the average patient
Main Sources:

The Organic Chemistry of Drug Synthesis Vol I-V (Daniel Lednicer)
Strategies for Organic Drug Synthesis and Design (Daniel Lednicer)
An Introduction to Medicinal Chemistry (Graham Patrick)
Top Drugs, Top Synthetic Routes (John Saunders)
Molecules and Medicine (Corey, Czako, Kurti)
Contemporary Drug Synthesis (Jie Jack Li)

Thank you for your attention!