References:

Registry Number and Substance Counts

CAS is the leading provider of organic, inorganic, and biosequence substance information.

The Latest CAS Registry Number® and Substance Count

<table>
<thead>
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<th>Date</th>
<th>05/14/2007 01:37:19 EST</th>
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<td>58,914,183 sequences</td>
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<td>CAS RN</td>
<td>934672-05-6 is the most recent CAS Registry Number</td>
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CAS also provides specialized databases of chemical reactions, regulated chemicals, commercially available chemicals and Markush substance information.

Specialized Substance Collections Count

<p>| CASREACT® | 13,048,983 Single and multi-step reactions |
| CHEMLIST® | 245,415 Inventoried/regulated substances |
| CHEMCATS® | 14,061,477 Commercially available chemicals |
| MARPAT®   | 723,738 Searchable Markush structures |</p>
<table>
<thead>
<tr>
<th>Year</th>
<th>Nobel Laureate(s)</th>
<th>Work</th>
</tr>
</thead>
<tbody>
<tr>
<td>1902</td>
<td>Emil Fischer</td>
<td>sugars and purine syntheses</td>
</tr>
<tr>
<td>1905</td>
<td>Adolf von Baeyer</td>
<td>advancement of organic chemistry and the chemical industry, through his work on organic dyes and hydroaromatic compounds</td>
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<tr>
<td>1910</td>
<td>Otto Wallach</td>
<td>pioneering work in the field of alicyclic compounds</td>
</tr>
<tr>
<td>1912</td>
<td>Victor Grignard and Paul Sabatier</td>
<td>(V. G.) discovery of the Grignard reagent, (P. S.) hydrogenating organic compounds in the presence of finely disintegrated metals</td>
</tr>
<tr>
<td>1928</td>
<td>Adolf Windaus</td>
<td>research into the constitution of the sterols and the connection with the vitamins</td>
</tr>
<tr>
<td>1930</td>
<td>Hans Fischer</td>
<td>research into the constitution of haemin and chlorophyll and especially for his synthesis of haemin</td>
</tr>
<tr>
<td>1937</td>
<td>Walter Haworth and Paul Karrer</td>
<td>(W. H.) investigations on carbohydrates, vitamin C and (P. K.) investigation of carotenoids, flavins, and vitamins A and B2</td>
</tr>
<tr>
<td>1939</td>
<td>Leopold Ruzicka</td>
<td>work on polymethylenes and higher terpenes</td>
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<tr>
<td>1947</td>
<td>Robert Robinson</td>
<td>investigations on plant products of biological importance, especially the alkaloids</td>
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<tr>
<td>1950</td>
<td>Otto Diels and Kurt Alder</td>
<td>discovery and development of the diene synthesis</td>
</tr>
<tr>
<td>1955</td>
<td>Vincent du Vigneaud</td>
<td>work on biochemically important sulfur compounds, especially for the first synthesis of a polypeptide hormone</td>
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<tr>
<td>1963</td>
<td>Karl Ziegler and Giulio Natta</td>
<td>discoveries in the field of the chemistry and technology of high polymers</td>
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<tr>
<td>1965</td>
<td>Robert Burns Woodward</td>
<td>achievements in the art of organic synthesis</td>
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<tr>
<td>1968</td>
<td>H. Gobind Khorana (medicine)</td>
<td>interpretations of the genetic code and its function in protein synthesis</td>
</tr>
<tr>
<td>1969</td>
<td>Derek H. R. Barton and Odd Hassel</td>
<td>development of the concept of conformation and its application in chemistry</td>
</tr>
<tr>
<td>1975</td>
<td>Vladimir Prelog and John W. Cornforth</td>
<td>(V. P.) stereochemistry of organic molecules and reactions, (J. C.) stereochemistry of enzyme-catalyzed reactions</td>
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<tr>
<td>1979</td>
<td>Herbert C. Brown and Georg Wittig</td>
<td>development of boron (H. C. B.) and phosphorus (G. W.) compounds into important reagents in organic synthesis</td>
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<tr>
<td>1981</td>
<td>Roald Hoffmann and Kenichi Fukui</td>
<td>development of theories concerning the course of chemical reactions</td>
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<tr>
<td>1984</td>
<td>R. Bruce Merrifield</td>
<td>development of methodology for chemical synthesis on a solid matrix</td>
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<tr>
<td>1987</td>
<td>Donald J. Cram, Jean-Marie Lehn, and Charles J. Pedersen</td>
<td>development and use of molecules with structure-specific interactions of high selectivity</td>
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<tr>
<td>1990</td>
<td>Elias J. Corey</td>
<td>development of the theory and methodology of organic synthesis</td>
</tr>
<tr>
<td>1994</td>
<td>George A. Olah</td>
<td>contributions to carbocation chemistry</td>
</tr>
<tr>
<td>Year</td>
<td>Laureate</td>
<td>Country</td>
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<td>------</td>
<td>-----------------------------------</td>
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<tr>
<td>1902</td>
<td>Emil Hermann Fischer</td>
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<td>1905</td>
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<td>Victor Grignard</td>
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<td></td>
<td>Paul Sabatier</td>
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<td>1937</td>
<td>Walter N. Haworth</td>
<td>Great Britain</td>
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<tr>
<td></td>
<td>Paul Karrer</td>
<td>Switzerland</td>
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<tr>
<td>1939</td>
<td>Adolf F. J. Butenandt</td>
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<td></td>
<td>Lavoslav Stjepan Ružička</td>
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<tr>
<td>1947</td>
<td>Sir Robert Robinson</td>
<td>Great Britain</td>
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<tr>
<td>1950</td>
<td>Kurt Alder</td>
<td>Germany</td>
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<td>1965</td>
<td>Robert B. Woodward</td>
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<tr>
<td>1968</td>
<td>Lars Onsager</td>
<td>United States, Norway</td>
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<td>1975</td>
<td>John Cornforth</td>
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<tr>
<td></td>
<td>Vladimir Prelog</td>
<td>Yugoslavia - Switzerland</td>
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<td>United States</td>
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<tr>
<td>1994</td>
<td>George A. Olah</td>
<td>United States</td>
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<tr>
<td>1997</td>
<td>Paul Delos Boyer John E. Walker Jens C. Skou</td>
<td>United States Great Britain Denmark</td>
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<td>2005</td>
<td>Yves Chauvin Robert H. Grubbs Richard R. Schrock</td>
<td>France United States United States</td>
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<tr>
<td>2010</td>
<td>Ei-ichi Negishi Akira Suzuki Richard Heck</td>
<td>Japan Japan United States</td>
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<tr>
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<td>------</td>
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<tr>
<td>2011</td>
<td>Dan Shechtman</td>
<td>Israel</td>
</tr>
<tr>
<td></td>
<td>Robert Lefkowitz</td>
<td>United States</td>
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<tr>
<td></td>
<td>Brian Kobilka</td>
<td>United States</td>
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<tr>
<td>2012</td>
<td>Martin Karplus</td>
<td>United States Austria</td>
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<tr>
<td></td>
<td>Michael Levitt</td>
<td>United States United Kingdom Israel</td>
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<td></td>
<td>Arieh Warshel</td>
<td>United States Israel</td>
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<tr>
<td>2013</td>
<td>Eric Betzig</td>
<td>United States</td>
</tr>
<tr>
<td></td>
<td>Stefan W. Hell</td>
<td>Romania</td>
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<tr>
<td></td>
<td>William E. Moerner</td>
<td>United States</td>
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<tr>
<td>2014</td>
<td>Tomas Lindahl</td>
<td>Sweden</td>
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<tr>
<td></td>
<td>Paul Modrich</td>
<td>United States</td>
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<tr>
<td></td>
<td>Aziz Sancar</td>
<td>Turkey</td>
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<tr>
<td>2015</td>
<td>Jean-Pierre Sauvage</td>
<td>France</td>
</tr>
<tr>
<td></td>
<td>Sir J. Fraser Stoddart</td>
<td>United States</td>
</tr>
<tr>
<td>2016</td>
<td>Bernard L. Feringa</td>
<td>Netherlands</td>
</tr>
</tbody>
</table>
The scientists will equally share the $1.11 million award.
Total Synthesis in the Nineteenth Century

Total Synthesis in the Twentieth Century

I. The Pre-World War II Era
II. The Woodward Era
III. The Corey Era
IV. The 1990s Era
Total Synthesis in the Nineteenth Century

Friedrich Wöhler
Germany
(1800-1882)
Hermann Kolbe
Germany
(1818-1884)
Fischer achieved the first synthesis of the first truly complicated organic molecules, the sugar molecule D-glucose in 1890.

D-Glucose

Fischer’s work on the total synthesis of D-glucose is regarded as the catalyst for the development of synthetic organic chemistry in the 20th century.

[Mittheilung aus dem chemischen Laboratorium der Universität Würzburg.]

(Eingegangen am 11. März.)

Die d-Mannose, deren Synthese vor Kurzem beschrieben wurde\(^1\), ist mit dem Traubenzucker stereo-isomer\(^2\). Da beide Zucker bei der Einwirkung von Phenylhydrazin das gleiche Oxyzol liefern, so beruht ihre Verschiedenheit, bei Zugrundelegung der Le Bel-van 't Hoff'schen Betrachtungsweise, auf der Asymmetrie des in der nachfolgenden Formel

\[
\text{CHO} \cdot \text{CHO} \cdot \text{CHO} \cdot \text{CHO} \cdot \text{CHO} \cdot \text{CH}_2\text{OH}
\]

mit dem Zeichen \(\alpha\), markirten Kohlenstoffatoms \(^3\). Leider sind die Methoden, welche wir für die Verwandlung stereo-isomerer Verbindungen ineinander kennen, bei den so leicht veränderlichen Zuckerarten selbst nicht anwendbar.

Viel bequemer ist die experimentelle Behandlung der zugehörigen Säuren. Ich habe deshalb die letzteren für den Versuch gewählt und mich dabei von folgender Betrachtung leiten lassen:

In der Mannose und der Mannonsäure ist höchst wahrscheinlich das zuvor als \(\alpha\) bezeichnete Kohlenstoffatom nicht optisch wirksam, sondern spielt eine ähnliche Rolle wie die beiden asymmetrischen Kohlenstoffatome in der Traubensäure. Dafür sprechen folgende gewichtige Gründe:

1. In der Lävulose, welche die Ketongruppe enthält, hat gerade dieses Kohlenstoffatom seine Asymmetrie eingebüsst. Durch Reductionlässt sich nun die Lävulose sehr leicht in Mannit verwandeln. Das Kohlenstoffatom der Ketongruppe wird dadurch wieder asymmetrisch. Da nun aber bei einer derartigen Entstehung von asymmetrischen Kohlenstoffatomen durch Synthese nach der bisherigen Erfahrung immer die beiden optischen Modifikationen zu gleicher Zeit gebildet werden (ich erinnere nur an die Reduction der Brenzcaraubensäure zu inaktiver Milchsäure \(^4\)), so folgt daraus, dass auch in dem Mannit und der Mannonsäure das Kohlenstoffatom \(\alpha\) optisch unwirksam ist.

2. Die der Mannonsäure optisch entgegengesetzte Arabinosesäure entsteht aus Arabinose durch Auflagerung von Blausäure. Dabei wird das Kohlenstoffatom der im Zucker enthaltenen Aldehydgruppe asymmetrisch. Da dieses aber wiederum durch die Synthese

---

\(^1\) Diese Berichte XXIII, 370.
\(^2\) Diese Berichte XXII, 374.
\(^3\) Diese Berichte XXII, 375.
Total Synthesis in the Twentieth Century

I. The Pre-World War II Era

\[ \text{\textalpha-terpineol} \]
[Perkin, 1904][14]

\[ \text{camphor} \]
[Komppa, 1903][15]
[Perkin, 1904][15]

\[ \text{tropinone} \]
[Willstätter, 1901][17]
[Robinson, 1917][16]

\[ \text{haemin} \]
[Fischer, 1929][18]

\[ \text{pyridoxine hydrochloride} \]
[Folkers, 1939][19, 20]

\[ \text{equilenin} \]
[Bachmann, 1939][21]
Sir Robert Robinson  
United Kingdom  
(1886-1975)  

The Nobel Prize in Chemistry 1947

Willstatter’s synthesis of tropine in 1901

Robinson’s synthesis of tropinone in 1917

The Robinson’s synthesis of tropinone was hailed as revolutionary. This was to look at the target molecule and try to imagine how the molecule could be constructed from simpler chemical units.
tropinone (1)

2

CH2CHO

3

H2N-Me

4

CO2-

Ca2+

5

N+Me

6

CO2-

Ca2+

7

8

Me-N

H

CO2-

Me-N

H

CO2-

Me-N

H

CO2-
II. The Woodward Era

Selected syntheses by the Woodward Group (1944-1981)
In 1965, he was awarded the Nobel Prize in Chemistry.
Some of the Complex Molecules Made by Woodward

“There is excitement, adventure, and challenge, and there can be great art in organic synthesis.”

- Woodward
III. The Corey Era

Selected syntheses by the Corey Group (1961-1999)
Elias James Corey
United States
(1928-)

In 1990, he was awarded the Nobel Prize in Chemistry.


Some prostaglandins affect human blood pressure at concentrations as low as 0.1 microgram per kilogram of body weight. Substances that inhibit prostaglandin synthesis may be useful in controlling pain, asthma attacks, and anaphylactic shock and in reducing the clotting ability of blood.
Retrosynthetic Analysis by Corey

**Retrosynthetic analysis** (or retromolecule) : the process of mentally breaking down a molecule into starting materials

**Retrosynthetic arrow**: an open-ended arrow, \( \rightarrow \), used to indicate the reverse of a synthetic reaction

**Synthon**: idealized fragments resulting from a disconnection. *Synthons* need to be replaced by *reagents* in a suggested synthesis

Retrosynthetic analysis for violet oil component

![Diagram of target molecule (TM)]

Synthesis of violet oil component

![Diagram of target molecule (TM)]
Efficiency and selectivity are important characteristics that have to be taken into account.

[Efficiency: yields, number of steps]
[Selectivity: chemoselectivity, regioselectivity, stereoselectivity]
Organic Synthesis:

1. Carbon-Carbon Bond Formation
2. Functional Group Interconversion

Stereoselectivity

\[ \text{CH}_3\text{CH}_2\text{MgBr} \rightarrow \text{H}_3\text{O}^+ \]

\[ \begin{align*}
\text{H}_3\text{C} & \quad \text{Br} \\
\text{C} & \quad \text{CH}_3 \\
\text{Br} & \quad \text{H}
\end{align*} \rightarrow \begin{align*}
\text{H}_3\text{C} & \quad \text{C} \equiv \text{C} \quad \text{CH}_3 \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H}
\end{align*} \]

\( \text{trans} \)

\[ \begin{align*}
\text{H}_3\text{C} & \quad \text{Br} \\
\text{C} & \quad \text{CH}_3 \\
\text{Br} & \quad \text{H}
\end{align*} \rightarrow \begin{align*}
\text{H}_3\text{C} & \quad \text{C} \equiv \text{C} \quad \text{CH}_3 \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H}
\end{align*} \]

\( \text{cis} \)
Organic Synthesis:

1. Carbon-Carbon Bond Formation
2. Functional Group Interconversion

Enantioselectivity

\[
\text{HO}_2\text{C}-\text{C} \xrightarrow{\text{H}_2\text{O}} \text{H}^+ \text{CO}_2\text{H} \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{HO}_2\text{C}-\text{C} \xrightarrow{\text{fumarase}} \text{H}^+ \text{CO}_2\text{H}
\]

1 : 1 (racemic mixture)

(enantiopure)
M.F. (Stereoisomers)

**C₂H₂Cl₂**
- *cis*-1,2-dichloroethylene (bp: 60 °C)
- *trans*-1,2-dichloroethylene (bp: 48 °C)

**C₇H₁₄**
- cis
- trans

**C₄H₉I**
- (+)-2-iodobutane (bp: 119 °C)
- (-)-2-iodobutane (bp: 119 °C)

Chiral compounds
- "Enantiomer"
Enantiomers and the Tetrahedral Carbon

Chiral Molecules and Achiral Molecules

- **CH₃X**: achiral (superimposable)
- **CH₂XY**: achiral (superimposable)
- **CHXYZ**: chiral (nonsuperimposable)

Mirror Images
Louis Pasteur was born on December 27, 1822 in Dole, in the region of Jura, France.

Twenty years later, J. H. van’t Hoff and J.-A. Le Bel independently explained the origins of enantiomers based on the tetrahedral nature of carbon bonding.

“Chance favors only prepared mind.”

-Louis Pasteur

"بخت به یاری اندیشه‌های پیشرو وارد می‌شد.

- لویی پاستور

Resolution of enantiomers in 1848

Sodium ammonium tartrate
Optical Activity

- Light restricted to pass through a plane is *plane-polarized*.

- Solutions of chiral compounds rotate plane-polarized light and the molecules are said to be *optically active*.
Some Physical Properties of the Stereoisomers of Tartaric Acid

<table>
<thead>
<tr>
<th></th>
<th>(R,R)-Tartaric acid</th>
<th>(S,S)-Tartaric acid</th>
<th>Meso Tartaric acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific rotation, [a]</td>
<td>+12.7</td>
<td>-12.7</td>
<td>0</td>
</tr>
<tr>
<td>Melting point (°C)</td>
<td>171-174</td>
<td>171-174</td>
<td>146-148</td>
</tr>
<tr>
<td>Density at 20 °C (g/cm³)</td>
<td>1.7598</td>
<td>1.7598</td>
<td>1.660</td>
</tr>
<tr>
<td>Solubility in water at 20 °C (g/100mL)</td>
<td>139</td>
<td>139</td>
<td>125</td>
</tr>
<tr>
<td>pK₁ (25 °C)</td>
<td>2.98</td>
<td>2.98</td>
<td>3.23</td>
</tr>
<tr>
<td>pK₂ (25 °C)</td>
<td>4.34</td>
<td>4.34</td>
<td>4.82</td>
</tr>
</tbody>
</table>
To obtain one pure enantiomer, resolution is required.

Only one enantiomer is obtained by **asymmetric synthesis**.

\[
\begin{align*}
\text{HO}_2\text{C} &= \text{CO}_2\text{H} \\
\text{H}_2\text{O} &\xrightarrow{\text{H}^+} \text{HO}_2\text{C} \text{CO}_2\text{H} + \text{HO}_2\text{C} \text{CO}_2\text{H} \\
&= 1 : 1
\end{align*}
\]
Asymmetric Synthesis

Synthesis of One Enantiomer using a Chiral Auxiliary

Both handed forms of product (racemic mixture; 1:1 mixture of enantiomers)

Put auxiliary on

take auxiliary off

chemical steps

Chiral Auxiliary :
Asymmetric Synthesis

Synthesis of an Enantiomer using a Chiral Reagent

\[
\text{Diisopinocampheylchloroborane}
\]

Hebert Charles Brown
United States
(1912-2004)

The Nobel Prize in Chemistry
1979
Asymmetric Synthesis

Synthesis of an Enantiomer using a Chiral Catalyst

[Ru-(S)-BINAP], 135 atm H₂
(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)

92% yield, 97%ee

The Nobel Prize in Chemistry 2001

Ryōji Noyori
Japan
(1938- )
He has also worked on other asymmetric processes. Each year 3000 tonnes (after new expansion) of menthol are produced (in 94% ee) by Takasago International Co., using Noyori's method for isomerisation of allylic amines.
Asymmetric Synthesis

Synthesis of an Enantiomer using a Chiral Catalyst

Karl Barry Sharpless
United States
(1941-)

The Nobel Prize in Chemistry 2001
The anticancer drug, Taxol

Synthesis: K. C. Nicolaou at The Scripps Research Institute
Robert Holton at Florida State University
Kyriacoc Costa Nicolaou
Cyprus
(1946 - )

The Nobel Prize
in Chemistry

MOLECULES
THAT CHANGED THE
WORLD

K. C. NICOLAOU • T. MONTAGNON
Selected Medications of 20th Century

- **Viagra** (treatment of impotence)
- **Claritin** (antihistamine, i.e. antiallergic)
- **Viracept** (treatment of AIDS)
- **Zoloft** (psychotherapeutic)
- **Zantac** (treatment of ulcer)
- **Captopril** (treatment of hypertension)
- **Prozac** (antidepressant)
- **Carboplatin** (treatment of ovarian cancer)
- **Acyclovir** (antiviral)
- **Novocain** (local anesthetic)
- **Prilosec** (antispasmodic)
- **Tagamet** (treatment of ulcer)
- **Valium** (tranquilizer)
Selected Medications of 20th Century

17-ethynylstradiol

norethindrone

(the "Pill"; contraceptive)

R= H Mevacor
R= Me Zocor
(treatment of high cholesterol)

R= H Morphine
R= Me Cocaine
(pain killer)

Clarithromycin
(antibacterial)

Mevacor
Zocor
(treatment of high cholesterol)

Augmentin
(antibiotic)

Ampicillin
(antibiotic)

Clavulanic acid
(β-lactamase inhibitor)
http://www.synarchive.com/

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Completed Highlight Series: Multicomponent Reactions, Microwave Chemistry