Greening of Medicinal Chemistry

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Definition of ***Green Chemistry***

The design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances .

Advantages of Green Chemistry

- Promotes innovation.
- Can be cost effective.
- Builds environmental health and safety considerations into the development process.

Challenges and Opportunities

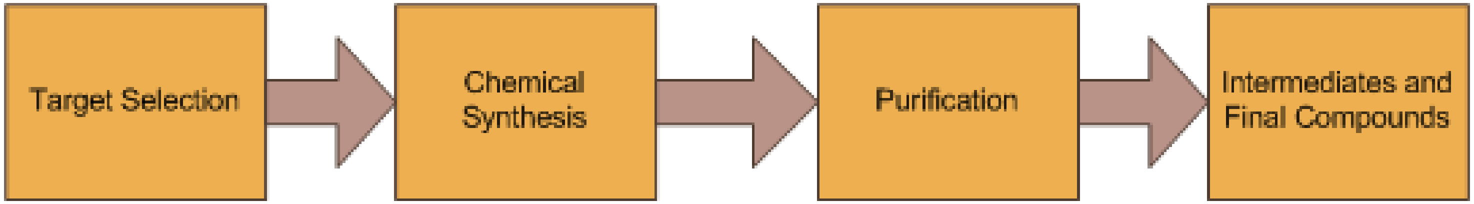
- Medicinal Chemistry relies on speed of generating new molecules, and use of reliable techniques and methodologies.

- Getting the compound is key; the route and process is a secondary concern for medicinal chemists.

- Reactions found in the literature are likely to be run exactly as published rather than risk having the reaction not work.

Acceptance of Green Chemistry practices depends on not impeding the medicinal chemist's ability to generate lead compounds quickly.

Green Chemistry and the Med Chem Process



- Green Chemistry can impact both the synthesis and purification steps.
- Choice of solvents, reagents and purification techniques
  - ➢Solvent selection could be the simplest way to green med-chem process
  - ➢Use a less toxic solvent with less environmental impact...and use less of it.

Solvent Selection

- What is a green solvent?
  - Safer for the scientist: less toxic, carcinogenic, mutagenic etc.
  - Safer for the process: less flammable, lower emissions, less chance of peroxide formation. etc.
  - Less harmful to the environment: lower potential to deplete ozone, less ecotoxic, derived from renewable resources.

Solvent Selection Guide

Preferred	Usable	Undesirable
Water	Cyclohexane	Pentane
Acetone	Heptane	Hexane(s)
Ethanol	Toluene	Di-isopropyl ether
2-Propanol	Methylcyclohexane	Diethyl ether
1-Propanol	Methyl *t*-butyl ether	Dichloromethane
Ethyl acetate	Isooctane	Dichloroethane
Isopropyl acetate	Acetonitrile	Chloroform
Methanol	2-MethylTHF	Dimethyl formamide
Methyl ethyl ketone	Tetrahydrofuran	*N*-Methylpyrrolidinone
1-Butanol	Xylenes	Pyridine
t-Butanol	Dimethyl sulfoxide	Dimethyl acetate
	Acetic acid	Dioxane
	Ethylene glycol	Dimethoxyethane
		Benzene
		Carbon tetrachloride

Fig. 1 Pfizer solvent selection guide for medicinal chemistry.

A ‘use this instead’, rather than ‘don’t use’ philosophy.
Reference: *www.dtsc.ca.gov/PollutionPrevention/.../mann_GC_II_reduced.pdf*

Use of Greener Solvents

- 2-methyl THF as a substitute for dichloromethane and THF,
- Cyclopentyl methyl ether-an alternative to THF, dioxane,
- Ionic Liquids
- Supercritical $CO_{2,}$
- Ethyl Lactate

Greener Solvents

- Use of 2-methyl THF as a substitute for dichloromethane and THF.
  - Manufactured from such by-products of agricultural waste as corncobs and bagasse (the biomass that remains after sugar cane stalks are crushed to extract their juice). CO_2 neutral to environment.
  - As opposed to THF (which is completely water miscible) 2-methyl THF doesn't mix with water. This makes it not only more environmentally safe, but it also makes it easier and faster to complete organometallic chemistry reactions with less waste.
  - Higher boiling point (78-80^{o}C) than THF or DCM. Higher reaction temperature may reduce overall reaction time and/or reduce the need to use sealed reaction flasks.
  - Lower peroxide formation than THF.
  - Improved safety-lower volatility and higher flash point.

Use of Greener Solvents-CPME

- Cyclopentyl methyl ether-an alternative to THF, dioxane, and other ether solvents.
  - Resistant to formation of peroxides
  - Limited miscibility in water-reduces the waste stream by easy separation and recovery from water
  - Higher boiling point than other ether solvents allows higher reaction temperature-shorter reaction time.
  - Low heat of vaporization saves energy during distillation and recovery.

Use of Greener Solvents-Supercritical CO_2

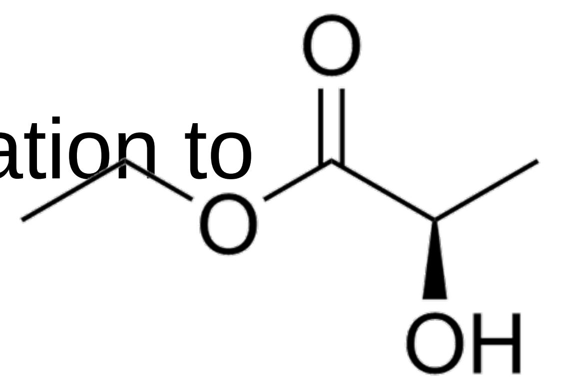
- Natural, cheap and plentiful.
- Carbon neutral.
- Easy to remove by evaporation-no solvent effluent.
- Non-toxic (asphyxiant at high concentrations)
- Useful for separations and extractions. May also be useful as a reaction medium.

Use of Greener Solvents-Ionic Liquids

- Typically consist of organic cation and inorganic anion andcan be fine tuned to give a wide array of solvent properties.
- Very low vapor pressure
- However, workup usually involves other solvents. Toxicity may be an issue, and these still require disposal at end of life (even though they may be recycled).

Use of Greener Solvents-Ethyl Lactate

- Derived from processing corn-a renewable source.
- Biodegradable
- Non-corrosive, non-carcinogenic and does not deplete ozone.
- Limited examples of application to synthetic chemistry so far.



Solvent Recycling

- Depending on the application, some solvents may be recycled by distillation (HPLC, wash acetone)
- Initial hardware purchase needed
- Less solvent waste generated
- May not be the required purity or dryness for all applications

Reagent Selection Guide?

- What is a green reagent?
  - The assessment should include worker safety, environmental effects, and atom economy (how efficiently is the starting material converted to product?)
  - Encourage use of catalytic rather than stoichiometric reagents
- A reagent guide is not as simple to design as a solvent selection guide.

Less Hazardous Chemical Syntheses

- One strategy for encouraging use of less hazardous chemicals is to control them at the source, i.e. an approval system for highly hazardous, toxic chemicals. Offer suggestions for substitute chemicals.

- Require formal risk assessments for highly hazardous or toxic chemicals. This will encourage scientists to think of alternative reagents.

  - Not only will the chemistry be greener, it may be safer as well.

Reaction Conditions

- Choice of reaction conditions should favor ambient temperature and pressure as a way to save energy and be safer
  - Use of timers with hot plates to limit heating time (e.g. maybe the reaction only needs 4 hours heating rather than overnight).

Other Avenues of Exploration

– Solid supported reagents as alternatives to traditional reaction workups or purifications. Potential to decrease solvent usage and waste generation.

– Alternatives to traditional silica gel columns for chromatography. Chromatography is currently a high volume usage of halogenated solvents (DCM). Technologies exist that allow purifications using non-halogenated solvents.

– Use of biocatalysis (use of natural catalysts, such as enzymes to promote chemical transformations of organic compounds).

Strategies

- Education and information about what green chemistry is, and emerging green technologies.
- Green techniques must be as good as or better than traditional techniques.
- Greener solvents and reagents must be made readily available so scientists can easily access them

➢ A cross functional team with representation from HSE, the scientific community and sourcing/suppliers can make this a sustainable process