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GREEN CHEMISTRY IN DRUG DESIGN- A REVIEW

Athira A. S.*, Dr. Prashobh G. R., Dr. S. M. Sandhya, Reena S. R., Sheeja Rekha A. G.

Sreekrishna College of Pharmacy& Research Centre, Parassala, Thiruvananthapuram, Kerala.

***Corresponding Author: Athira A. S.**
Sreekrishna College of Pharmacy& Research Centre, Parassala, Thiruvananthapuram, Kerala.

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ABSTRACT
Green chemistry or environmentally benign chemistry is the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances. Green chemistry emerged from a variety of existing ideas and research efforts (such as atom economy and catalysis) in the period leading up to the 1990s, in the context of increasing attention to problems of chemical pollution and resource depletion. The development of green chemistry in Europe and the United States was linked to a shift in environmental problem-solving strategies: a movement from command and control regulation and mandated reduction of industrial emissions at the "end of the pipe," toward the active prevention of pollution through the innovative design of production technologies themselves. The set of concepts now recognized as green chemistry coalesced in the mid- to late-1990s, along with broader adoption of the term (which prevailed over competing terms such as "clean" and "sustainable" chemistry).

INTRODUCTION
‘Green Chemistry is the utilisation of a set of principle that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products. This concept was introduced in the early 1990s in a special programme launched by the US in an Environmental protection Agency [EPA] and soon adopted by mass media as the new approach of chemistry in opposition to the pollute-and-then-cleanup approach considered the common industrial practice. The concept of green chemistry has appeared in the United States and a common resulting from interdisciplinary operation of university teams, independent research groups, industry, scientific societies and governmental agencies, which each have their own programs devoted to decreasing.

Green chemistry incorporates a new approach to the synthesis, processing and application of chemical substances in such a manners to reduce treats to health and the environment. This new approach is aland processes that reduce or eliminate the use and generation of hazardous substances. Green chemistry works on risk and hazard factor.That means risk can be minimised by reducing hazard and then the coast and potential of exposure can be maintained. Attempts are being made not only to quantify the greenness of a chemical process but also to factor in other variables such as chemical yield, the price of reaction components, safety in handling chemicals, hardware demands, energy profile and ease of product workup and purification. Green chemistry is increasingly seen as a powerful tool that researchers must use to evaluate the environmental impact of nanotechnology. As nanomaterials are developed, the environmental and human health impacts of both the products themselves and the processes to make them must be considered to ensure their long-term economic viability.

Principle
The 12 principles focus on reducing the volume of chemicals used and pollution prevention.

Waste minimization and prevention
It is better to prevent waste than to treat or clean up waste after it has been created. Generally speaking, waste minimization involves the reduction of waste toxicity by reducing the volume or quantity of highly toxic chemical constituents through substitution, recycling, recovery and reuse efforts. The old adage; “An ounce 0f prevention is worth a pound of cure” applies here. It is better to prevent waste than clean it up after the fact.

Atom economy
Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.The concept of atom economy was developed by Barry Trost of Stanford University (us) for which he received the presidential green chemistry challenge award in 1998nwhich includes reducing the use of non-renewable resources, minimizing the amount of waste and reducing the number of steps used to synthesize chemicals.
The atom economy of a reaction can be calculated
Atom economy% = MW (desired products)/MW (all reactants)*100%

Percentage yield = (Actual quantity of products achieved)/(Theoretical quantity of products achievable)

Less hazardous chemical synthesis
Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment. Synthetic methodologies must be designed such that the chemicals used and by-product if generated, are not or less harmful to human health and environment. A better example is the formation of alkenes through more safe grub's catalyst produces very less waste in comparison with witting reaction.

Designing safer chemicals
Chemical products should be designed to be affect their desired function while minimizing toxicity. The design of chemicals with minimal toxicity reduce the potential to human health and the environment; decrease the cost of production and site remediation; and increasing team commitment to work place health and safety, For instance, prefer public transport instead of own vehicles, thereby minimizing the CO_2 emission, use recyclable paper in order to minimize the burden on natural resource and also to lessen the amount of toxic products coming out after bleach during paper production, Develop efficient methods of converting chemical energy into electrical energy to avoid necessity of generating power from nuclear plants which produces a lot of nuclear waste, gaseous emission and chemical pollutants.

Safer solvents and auxiliaries
The use of auxiliary substances (e.g. solvents, separation agents etc.) should be made unnecessary wherever possible and innocuous when used. The idea of "green" solvents express the goal to minimize the environmental impact resulting from the use of solvents in chemical production. Many organic solvents such as benzene, chloroform, toluene, carbon tetra chloride etc. are volatile organic compounds and it means that their high volatility very useful for industrial application, contributes both to increase the risk of fire and explosion and to facilitate the release in the atmosphere in which these solvents can act as air pollutants causing ozone depletion, photochemical smog and global warming. Commonly used solvents are water, ionic liquid, furious solvents and supercritical fluids.

Design for energy efficiency
Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible synthetic methods should be conducted at ambient temperature and pressure. Rising consumption and heavy future demand on energy that is primarily generated from petroleum and depleting resources has raised serious concerns in the international community.

Use of renewable feedstocks
A raw material material or feedstock should be renewable rather than depleting whenever technically and economically practicable. Renewable feedstock's are often made from agricultural products or from wastes of other processes; depleting feedstock are made from fossil fuels or are mined. Significant developments in using renewable feedstock's to make fuels and chemicals are blooming and effort are being put in to produce organic chemicals ; related products to be obtained from natural resources.

Reduce derivatives
Unnecessary derivatization should be minimized or avoided if possible. Because such steps require additional reagents and can generate waste. Many traditional chemical reaction based routes, elegant multistep syntheses were designed that employed increasingly clever protecting groups that would temporarily block the reactivity of a specific functional group until a deprotecting group was introduced into remove it.

Catalysis
Catalytic reagents are superior to stoichiometric reagents.Catalytic chemistry is one of the most important aspects of eco-friendly chemistry which promotes most of the green chemistry goals in terms of atom efficiency, lower energy use, attain high levels of selectivity at minimal waste through biocatalysts most of which is fast biodegradable and non-polluting, decreased use of separating and processing agents and the activation of inert material, thereby reducing reliance on toxic material. It is for this central role it plays that catalysis is referred to as a foundational pillar of green chemistry. Catalytic reagent also eliminate stoichiometric amounts of it in the reaction.

Design for degradation
Chemical product should be designed so that end of their function they breakdown into innocuous degradation products and do not persist in their environment. Not only do we want materials and products come from renewable resources but we would also like them to not persist in their environment. There is no question that products we use in our daily life are far too persistent. Plastic do not degrade in our landfill and pharmaceutical drug such as antibiotics build up in our water stream. The principles seeks to design products in such a way that they perform their intended function. Simple green products are designed to provide cleaning function with chemicals that are nontoxic and biodegradable.

Real time analysis for pollution prevention
Analytical methodologies need to be further develop to allow real time, in process monitoring and control prior to the formation of hazardous substance. There are two aspect of this principle time and material. Real time analysis for a chemist is the process of 'checking the progress of chemical reaction as it happens. If better,

more responsive monitors can be decide, then the use of just in time reagents and techniques can be employed to improve process yields, products consistency, use of raw materials that will minimize the environmental toll.

Inheritantly safer chemistry for accident prevention

Substances and form of a substance used in a chemical process should be chosen to minimize the potential for chemical accident, including reactions explosions. The Bhopal gas tragedy 1984 in India is the worst remainder of an industrial tragedy, 40 tons of methyl isocyanate was accidently released when a holding tank over heated at a union carbide pesticide plant. Some diseases which become famous by the discharge of poisonous pollutants from the industries where Minamata disease (mercury poisoning) **itai**-itai disease (cadmium poisoning), methamoglobenemia.

Examples

Green solvents

Solvents are consumed in large quantities in many chemical syntheses as well as for cleaning and degreasing. Traditional solvents are often toxic or are chlorinated. Green solvents, on the other hand, are generally derived from renewable resources and biodegrade to innocuous, often naturally occurring product.

Synthetic techniques

Novel or enhanced synthetic techniques can often provide improved environmental performance or enable better adherence to the principles of green chemistry. For example, the 2005 Nobel Prize for Chemistry was awarded, to Yves Chauvin, Robert H. Grubbs and Richard R. Schrock, for the development of the metathesis method in organic synthesis, with explicit reference to its contribution to green chemistry and "smarter production." A 2005 review identified three key developments in green chemistry in the field of organic synthesis: use of supercritical carbon dioxide as green solvent, aqueous hydrogen peroxide for clean oxidations and the use of hydrogen in asymmetric synthesis. Some further examples of applied green chemistry are supercritical water oxidation, on water reactions, and dry media reactions.

Bioengineering is also seen as a promising technique for achieving green chemistry goals. A number of important process chemicals can be synthesized in engineered organisms, such as shikimate, a Tamiflu precursor which is fermented by Roche in bacteria. Click chemistry is often citedas a style of chemical synthesis that is consistent with the goals of green chemistry. The concept of 'green pharmacy' has recently been articulated based on similar principles.

Carbon dioxide as blowing agent

In 1996, Dow Chemical won the 1996 Greener Reaction Conditions award for their 100% carbon dioxide blowing agent for polystyrene foam production. Polystyrene foam is a common material used in packing and food transportation. Seven hundred million pounds are produced each year in the United States alone. Traditionally, CFC and other ozone-depleting chemicals were used in the production process of the foam sheets, presenting a serious environmental hazard. Flammable, explosive, and, in some cases toxic hydrocarbons have also been used as CFC replacements, but they present their own problems. Dow Chemical discovered that supercritical carbon dioxide works equally as well as a blowing agent, without the need for hazardous substances, allowing the polystyrene to be more easily recycled. The CO_2 used in the process is reused from other industries, so the net carbon released from the process is zero.

Hydrazine

Hydrazine is traditionally produced by the Olin Raschig process from sodium hypochlorite (the active ingredient in many bleaches) and ammonia. The net reaction produces one equivalent of sodium chloride for every equivalent of the targeted product hydrazine

$NaOCl + 2\ NH_3 \rightarrow H_2N\text{-}NH_2 + NaCl + H_2O$

hypochlorite hydrazine

In the greener Peroxide process hydrogen peroxide is employed as the oxidant, the side product being water. The net conversion follows:

$2\ NH_3 + H_2O_2 \rightarrow H_2N\text{-}NH_2 + 2\ H_2O$

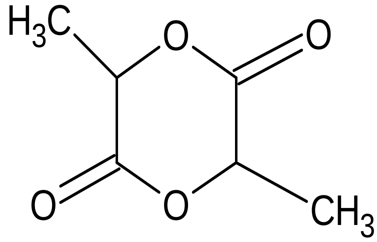
Ammonia hydrazine

Addressing principle #4, this process does not require auxiliary extracting solvents. Methyl ethyl ketone is used as a carrier for the hydrazine, the intermediate ketazide phase separates from the reaction mixture, facilitating workup without the need of an extracting solvent.

1,3-Propanediol

1,3-propanediol, which is traditionally generated from petrochemical precursors. It can be produced from renewable precursors via the bioseparation of 1,3-propanediol using a genetically modified strain of *E. coli*. This diol is used to make new polyesters for the manufacture of carpets.

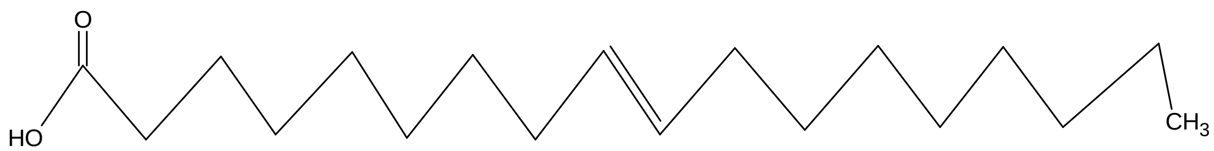
Lactide



Lactic acid is produced by fermenting corn and converted to lactide, the cyclic dimer ester of lactic acid using an efficient, tin-catalyzed cyclization. The L,L-lactide enantiomer is isolated by distillation and polymerized in the melt to make a crystallizable polymer, which has some applications including textiles and apparel, cutlery, and food packaging. Wal-Mart has announced that it is using/will use PLA for its produce packaging. The NatureWorks PLA process substitutes renewable materials for petroleum feedstocks, doesn't require the use of hazardous organic solvents typical in other PLA processes, and results in a high-quality polymer that is recyclable and compostable.

Carpet tile backings
In 2003 Shaw Industries selected a combination of polyolefin resins as the base polymer of choice for EcoWorx due to the low toxicity of its feedstocks, superior adhesion properties, dimensional stability, and its ability to be recycled. The EcoWorx compound also had to be designed to be compatible with nylon carpet fiber. Although EcoWorx may be recovered from any fiber type, nylon-6 provides a significant advantage. Polyolefins are compatible with known nylon-6 depolymerization methods. PVC interferes with those processes. Nylon-6 chemistry is well-known and not addressed in first-generation production. From its inception, EcoWorx met all of the design criteria necessary to satisfy the needs of the marketplace from a performance, health, and environmental standpoint. Research indicated that separation of the fiber and backing through elutriation, grinding, and air separation proved to be the best way to recover the face and backing components, but an infrastructure for returning postconsumer EcoWorx to the elutriation process was necessary. Research also indicated that the postconsumer carpet tile had a positive economic value at the end of its useful life. EcoWorx is recognized by MBDC as a certified cradle-to-cradle design.

Transesterification of fats
In 2005, Archer Daniels Midland (ADM) and Novozymes won the Greener Synthetic Pathways Award for their enzyme interesterification process. In response to the U.S. Food and Drug Administration (FDA) mandated labeling of *trans*-fats on nutritional information by January 1, 2006, Novozymes and ADM worked together to develop a clean, enzymatic process for the interesterification of oils and fats by interchanging saturated and unsaturated fatty acids. The result is commercially viable products without *trans*-fats. In addition to the human health benefits of eliminating *trans*-fats, the process has reduced the use of toxic chemicals and water, prevents vast amounts of byproducts, and reduces the amount of fats and oils wasted.



trans-oleic acid

Bio-succinic acid
Succinic acid is a platform chemical that is an important starting material in the formulations of everyday products. Traditionally, succinic acid is produced from petroleum-based feedstocks. BioAmber has developed process and technology that produces succinic acid from the fermentation of renewable feedstocks at a lower cost and lower energy expenditure than the petroleum equivalent while sequestering CO_2 rather than emitting it.

Laboratory chemicals
Several laboratory chemicals are controversial from the perspective of Green chemistry. The Massachusetts Institute of Technology has created the to help identify alternatives. Ethidium bromide, xylene, mercury, and formaldehyde have been identified as "worst offenders" which have alternatives. Solvents in particular make a large contribution to the environmental impact of chemical manufacturing and there is a growing focus on introducing Greener solvents into the earliest stage of development of these processes: laboratory-scale reaction and purification methods. In the Pharmaceutical Industry, both GSK and Pfizer have published Solvent Selection Guides for their Drug Discovery chemists.

Applications of green chemistry
Oxidation of alcohol to corresponding carbonyl compounds using oxygen or even better air as stereomeric oxidants. Using this method only water is been produced as a bi-product. This reaction involves utilization of transition metals as catalyst in the form of either homogenous catalyst, Heterogeneous catalyst or even better Nano catalyst.For transamidation of picolinamide with n-octylamine, cerium oxide (CeO2) has been used which shows highest catalytic activity. This reaction has been done under solvent free conditions.

1,2,3-Triazoles were synthesized in water using magnetically recoverable heterogeneous Cu catalyst via one-pot multi component reaction using Micro Wave irradiation. Catalyst so used can be easily recovered using an external magnet which can be efficiently recycled. 1,2,3-Triazoles were synthesized in water using magnetically recoverable heterogeneous Cu catalyst via one-pot multi component reaction using Micro Wave irradiation. Catalyst so used can be easily recovered using an external magnet which can be efficiently recycled. A greener way of utilizing air, sun light, water and spirulina to transform readily available furan derivatives into a wide range of synthetically useful polyoxygenated compounds which are commonly found in natural products is now possible with green chemistry.

For synthesizing useful heterocyclic in medicinal chemistry such as pyridazinones, dihydropyrimidinones, and dihydropyrimidinthiones, a “green”, mild and highly efficient one-pot triple cascade has been developed involving Claisen– decarboxylation, electrophilic reaction, and subsequent heterocyclization. In addition, indazoles and benzofurans could also be synthesized via a double cascade. To develop the cascade process, a direct Claisen–decarboxylation reaction was firstly optimized. This reaction was then coupled with electrophilic reactions including alkylation, Michael addition or aldol reaction to enable the preparation of various aryl ketones in a one-pot fashion.A study of Hydrogenation of 4-isopropylphenol cyclohexanol over activated carbon-supported rhodium catalysts in supercritical carbon dioxide (scCO2) at 313 K in a batch reactor has been done and the results were compared with those in 2propanol. An increase in the yields of cis-4-isopropylcyclohexanol were obtained in scCO2 than in 2-propanol, and the formation of a by-product, isopropyl cyclohexane, was suppressed in scCO2.

When the catalyst was modified with hydrochloric or phosphoric acid, better yield of cis-4-isopropylcyclohexanol in both scCO2 and 2-propanol solvents were observed. Kinetic analyses of these reaction profiles revealed higher reaction rates in scCO2 than those in 2-propanol for the 4-isopropylcyclohexanol formation both by the direct hydrogenation of 4 isopropyl phenol and by the consecutive hydrogenation rate of 4-isopropylcyclohexanone to 4-isopropylcyclohexanol.

A new environmentally friendly, efficient and easy process for the synthesis of 2-imidazolines has been developed which aims to give a better results which can be performed by reacting aldehydes with ethylenediamine using hydrogen peroxide as an oxidant in the presence of sodium iodide and anhydrous magnesium sulfate as catalyst. Using this synthesis no production of bi-products were observed. Now, friedel craft acylation of aryl and alkyl carboxylic acid can be done using methane sulfonic anhydride (MSAA) which allows the preparation of aryl ketones in a good yield with minimal waste containing no metallic or halogenated components, clearly differentiating it from other available methodologies.

A new method of Hiyama Cross-Coupling was recently modified using Magnetically Recoverable Pd/Fe3O4-Catalyst. Cross coupling of Aryl Bromides with Aryl Siloxanes was done to yield desired product which requires comparatively less time and energy.A new method of Hiyama Cross-Coupling was recently modified using Magnetically Recoverable Pd/Fe3O4-Catalyst. Cross coupling of Aryl Bromides with Aryl Siloxanes was done to yield desired product which requires comparatively less time and energy.

A new recyclable catalysts for Suzuki-Miyaura Cross-Coupling Reactions has been developed which can work at moderate Temperature. This catalyst is based on a Simple Merrifield Resin Supported Phenanthroline-Palladium (II) Complex. A new recyclable catalysts for Suzuki-Miyaura Cross-Coupling Reactions has been developed which can work at moderate Temperature. This catalyst is based on a Simple Merrifield Resin Supported Phenanthroline-Palladium (II) Complex.

A new method of preparing Carbonyl compounds in very good yields has been developed. This can be done by treating oximes with 2 molar equivalent of CuCl2• 2 H2O in the presence of acetonitrile and water in ratio 4:1 and reflexing the resulting solution for about three hours. An added advantage of recovering cupric salts can also be done in this method.Nano sized sulphated titanium dioxide which was prepared by a sol-gel hydrothermal process showed high catalytic activity in a direct amidation of fatty acids as well as benzoic acids with various amines under solvent-free conditions.

A new catalytic method for preparing pure triazoles has been developed which is based on commercially available [CuBr(PPh3)3]. This method do not require any special conditions, and can work ven in the absence of additive. This method does not require any purification step also.

An efficient and simple method for “phosphine-free” Heck reactions in water in the presence of a Pd(L-proline)2 complex as the catalyst under controlled microwave irradiation conditions is an excellent method and provides very good yields of products in short reaction times. This modified reaction system minimizes production cost, reduces operational hazards and environmental pollution.

An Efficient Aqueous-Phase Heck Reaction which is Catalysed by a Robust Hydrophilic Pyridine-Bridged Bisbenzimidazolylidene-Palladium Pincer Complex. Replacing conventional thermal reating methods with Microwave heating enables a Borrowing Hydrogen strategy to form C-N bonds from alcohols and amines. It also eliminates the need for solvent and reduces the reaction times, while the results are comparable with those using conventional thermal heating methods.A simple, cost efficient and effective method of synthesis of 3(2H)-furanones by cycloisomerization of allenic hydroxyketones has been carried out in water. This method eliminates the use of any expensive metal catalyst.

A simple method for the production of 3-unsubstituted 2-aroylindoles using N-(2-formylphenyl) trifluoroacetamides and αbromoacetophenones as starting materials in the presence of K2CO3 and PEG-

400 as an efficient and reusable solvent enables a one pot and environmentally fiscible method for the production.

Copper(I) isonitrile complex has been found to be an efficient heterogeneous catalyst for azide-alkyne 1,3-dipolar cycloadditions and three-component reactions of halides, sodium azide and alkynes to form 1,4-disubstituted 1,2,3-triazoles in high yields under mild conditions in water.Temperature Controlled microwave heating of aminopyridines and α-bromo-β-keto esters has been used for the synthesis of highly substituted imidazo[1,2-a]pyridines under solvent-free conditions. This method gives the highest yields of products in reaction times of less than two minutes compared to the traditional way of heating i.e. thermal heating.

A new, easily fiscible and practical method for Ullmann amination of aryl halides with aqueous methylamine and other aliphatic primary amines under organic solvent- and ligand-free condition at 100°C using powdered copper as catalyst in air gives a very good yield of N-arylamines as main products. The presence of a small amount of air is essential. This method is not suitable with Secondary amines and aniline as they do not react under these conditions.

An abnormal NHC complex of copper with 1, 4-diphenyl-1,2,3-triazol-5-ylidene [CuCl(TPh)] efficiently catalyzed click reactions of azides with alkynes to give 1,4-substituted 1,2,3-triazoles in excellent yields at room temperature with short reaction times. CuCl(TPh) was particularly effective for the reaction between sterically hindered azides and alkynes.

A straightforward, efficient, and sustainable method for intramolecular N-arylation yeilds a variety of substituted benzimidazoles in high yields using Cu_2O as the catalyst, DMEDA as the ligand, and K_2CO_3 as the base. Remarkably, the reaction was exclusively carried out in water, rendering the methodology highly valuable from both environmental and economical points of view.

An eco-compatible method for the formation of tert-butyl ethers of alcohols and phenols is performed in solvent-free conditions at room temperature using catalytic amount of $Er(OTf)_3$. The catalyst is easily recovered and reused several times without loss of activity. In addition, the tert-butyl group is removed very quickly from alcohols and phenols in methanol in the presence of $Er(OTf)_3$ using MW irradiation.

Used and exhausted vegetable oil has been used currently by researchers as a fuel for vehicles by making very less modifications in the cars of present use and a shocking result was found that by using vegetable oil CO_2 emission has been reduced to almost 67% without compromising with the efficiency of the vehicle.

Future trends

Oxidation reagent and catalysis

Historically, many of the oxidation reagents and catalysts have been comprised of toxic substances such as heavy metals. Since these substances were often used in extremely large volumes required to convert millions of pounds of petrochemicals, there was a significant legacy of these metals being released to the environment and having substantial negative effect on human health and environment. It can be changed by the use of benign substances.

Non covalent derivatization

Use of chemicals is dependent upon formation and breaking of covalent bond. chemistry happening without bond making physical, chemical properties are modified and performance measures are enhanced by utilization of dynamic complexation which allows for the temporary formations of modified chemical structures, the properties of molecules can be changed for the period of the necessary to carry out a particular function without all of the waste that would be generated if full derivatization is implemented.

Supramolecular Chemistry

Research is currently ongoing in the area of supra molecular chemistry to develop reactions which can proceed in the solid state without the use of solvents. The cycloaddition of trans-1,2-bis(4-pyridyl)ethylene is directed by resorcinol in the solid state. This solid-state reaction proceeds in the presence of UV light in 100% yield.

Biometric multifunctional reagents

While synthetic catalysis and reagents for the most part have centered on carrying out one discrete transformation. The manipulations may include activation, conformational adjustments, and one or several actual transformations and derivitizations.

Combinatorial green chemistry

It is the chemistry of being able to make large numbers of chemical compounds rapidly on a small scale using reaction matrices. The example is lead that has a large no of derivatives. This chemistry has enabled large no of substances to be made and their properties assessed without the magnitude of the effects of waste disposal.

Energy focus

The environmental effect of energy usage are profound but have not been as visible and as direct as some of the hazards that have not been posed by materials used in manufacture, use and disposal of chemicals. The benefit of catalysis is dramatic in photochemistry. There is a need to design substances and materials that are effective, efficient and inexpensive at the capture, storage and transportation.

Proliferation of solvent less reactions

One of the 'solvent alternatives' that is being: it is one of the solvent alternatives that is being developed in green chemistry is that of solvent less reaction system. The carrying of manufacturing process in solvent-less condition utilizes some non-traditional conditions. This helps in development of product isolation, separation and purification that will be solvent-less as well in order to maximize the benefits.

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