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Green chemistry in search of novel drug molecules

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Abstract
With the discovery of hybrid seeds, insecticides, fertilizers, herbicides, drugs and antibiotics, revolution of medicinal chemistry began which leads to better quality life. Chemistry plays a vital role in improvement of our modern life standards. Further, adverse effects of chemistry began with the release of industrial chemical byproducts and chemical toxic materials in air, rivers / oceans and lands that results in pollution of land, water and atmosphere. This marked the beginning of Green Chemistry in 19th century. As on today maximum environment pollution is caused by numerous chemicals and Pharma-ceutical industries. Therefore, chemical and pharmaceutical industries influenced the use of Green Chemistry and Green Chemistry principles. This change introduced chemical and pharmaceutical in- dustries towards greener raw materials, alternative organic synthetic solvents, higher yields, less waste, increased economy and minimized environmental pollution. Thus, Green chemistry is also called envi-ronmentally benign chemistry or sustainable chemistry. Therefore Green Chemistry is defined as "the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances". Green Chemistry is an simple or direct method to synthesis drug molecules, drug intermediates and synthetic chemistry research by utilizing lowest amount of re- sources and energy with slight or no waste material generation in proper, ecofriendly, non-hazardous, reproducible, efficient, nonpolluting and protected manner. This article summarized implementation of green chemistry principles in day-to-day life, in chemical reactions, in pharmacy and in analytical chemistry and generation of novel drug molecules with suitable examples.

Keywords: Green chemistry, principles, advancement, novel drug molecules

Introduction
The term green chemistry was coined by Anastas in 1990s at US Environmental Agency (EPA) pro- gram [1, 2]. EPA stimulates substantial development and technologies in chemistry [3]. To be called green each reaction should have three components i.e. solvent, reagent and energy consumptions. Green chemistry found uses of pharmaceutical product which include in the development of new methods of synthesis, synthesizing new pharmaceutical products with less consumption of sources as well as less production of wastes [4]. It includes new synthesis, process and application of chemical substances to reduce human health hazards as well as environmental pollution [5]. Green chemistry use renewable cat-alyst and non stochiometric reagents to control environmental hazards and increase economy [1]. Green Chemistry is also known as [6]:

- Environmentally Benign Chemistry
- Clean Chemistry
- Atom Economy
- Benign-by- design chemistry

The traditional aprroaches used in hazard control are [7]
1. Green chemistry describes the quandery usage of starting materials synthesis and reduction of waste produced by them.
2. Green Chemistry correlates with the manufacturing, usage of chemicals and their disposals.
3. Green Chemistry deals with the safety, environmental issues and health concerns.

Green Chemistry is an advance section of chemistry that reduces the dangerous effect of chemicals and minimize environmental pollution. The goals of green chemistry is environmental protection and eco- nomic profit which are achieved through catalysis, biocatalysis, the use of alternative renewable raw materials (biomass), alternative reaction media (water, ionic liquids, supercritical fluids), alternative reaction conditions (microwave activation, mechanochemistry and ultrasound) as well as new photo- catalytic reactions [8, 9].

Ryoji Noyori described the three key developments in green chemistry i.e. use of supercritical carbon dioxide as green solvent, aqueous hydrogen peroxide for clean oxidations and the use of hydrogen in asymmetric synthesis [10]. It also increase the efficiency of synthetic methods to use less toxic solvents/ reduce the stages of synthetic routes and minimize waste as for as practically pos-sible [11]. Green Chemistry principles and practice control, regulation results in environmental benefit that expressed in economic impact terms [12].

Development of green chemistry

In the early 1990s, new values and techniques introduced. During the twentieth century, chemistry de- velopment in pharmaceutical industries (development of organic medicinal molecules) increased the economic growth and benefits that changed the way of people lived [13]. With industrial growth environ- mental problems began. Due to environmental problems and concerns, companies changed their prod- uct development habits to use conventional solvents i.e. glycerol, ethyl lactate and water by adopting ecological engineering methods [14].

Historical growth of green chemistry [15]

- In the United States, in 1990s beginning EPA focused on green chemistry, with higher activity in research, symposia, and education. In 1995, the United States launched "Presidential Green Chemistry Challenge Awards", that provide visibility and recognition to companies and academic researchers hav- ing outstanding achievements in green chemistry.
- In Italy, in 1993, the Interuniversity Consortium Chemistry for the Environment (INCA) established with the aim of joining academic groups dealing with chemistry and the environment together, having focus in pollution prevention through research for cleaner reactions, products and processes. In Febru- ary 1993, INCA organized first meeting in Venice "Processi Chimici Innovativie Tutela dell'Ambente".
- In August 1996, IUPAC approved the Working Party formation on Green Chemistry under Commis- sion III.2.ber 1997. In September the First International Green Chemistry Conference in Venice was held under the IUPAC sponsorship. In the same year, the Green Chemistry Institute was founded. Various organizations and Commissions were currently involved in green chemistry programs at the national or international level, for example [16]:
- U.S. Environmental Protection Agency (EPA), launched "Green Chemistry Program" which involve the other National Science Foundation, the American Chemical Society, and the Green Chemistry In- stitute.
- European Directorate for R&D (DG Research), included the goals of sustainable chemistry in the research of the European Fifth Framework Program.
- UK Royal Society of Chemistry, promotes the concept of green chemistry through "UK Green Chem- istry Network" and the scientific journal Green Chemistry;
- Monash University, is the first organization in Australia which undertake a green chemistry program.

Application and objective of green chemistry

The main objectives of Green Chemistry are listed below:

1. Green chemistry enables creativity and the advancement of innovative research1.
2. The use of "exotic" reagents, reduces the required energy, and replace the organic solvents with water are significant savings [17].

Various applications of Green Chemistry are given below

1. In day – to- day life

a. Turbid Water Clearance: Tamarind seed kernel powder and aluminium salt, is used for municipal and industrial waste water clearance [18].

b. Solar Water Heater: Solar water heater installation reduce energy costs at lower initial expense.

c. Rainwater Harvesting System: Rain collector systems stores rain water in a barrel or cistern for later nonpotable use (like watering plants, flushing toilets, and irrigation). These systems are extremely inexpensive.

d. Building with Green Technology: Green buildings techniques reduced the environmental prolems. Reclaimed materials, passive solar design, natural ventilation and green roofing technology are used in formation. These techniques not only benefit the environment, but they can produce economically at- tractive buildings. The benefit of building green is reducing building's impact on the environment. Us-ing green building techniques can also reduce the associated costs with construction and operation of a building [19].

e. Green Dry Cleaning of Clothes: Perchloroethylene (PERC) and micelle technology (CO_2 and sur- factants) are commonly used for dry cleaning. Dry cleaning machines have now been developed using this technique [18].

f. Production of adipic acid: Benzene and glucose is used for the production of adipic acid. Glucose is converted into adipic acid by the action of bacterial enzymes [20].

g. Production of biodiesel: Biodiesel oil is echo friendly. It is produced from cultivated plants oil (soya beans). It is synthesized from plant oils embedded fat by removing the glycerin molecules. This fuel is obtained from renewable resources and contrary to normal diesel oil [20]. Reaction of production of bio- diesel is as:

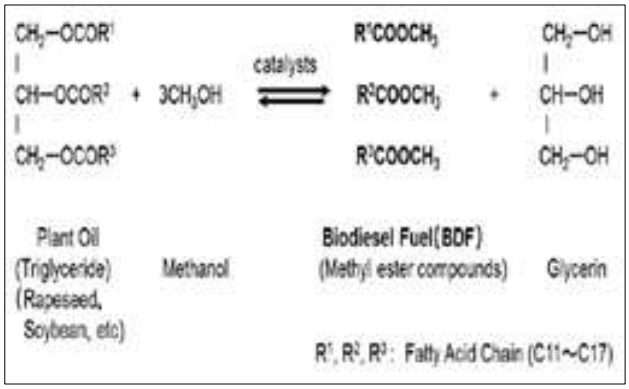

Fig 3.1: biodiesel formation

In chemical reactions

a. Green chemical reactions

1. Production of aromatic amines: Production of halide free aromatic amines is done by treating chlorine with nitrogen. In this process nitrobenzene is heated with aniline in the presence of tetrame- thylammoniumhydroxides to form tetramethylammonium salt.

2. **Homogeneous catalysis and atom economic system:** This system reduced the useless by products of atoms formed during process [21].

b. Reaction conditions for green solvents

Making solvents immobile: Solvents having high quantity and vast applicability, produce poor impact on human health and produce greater impact on environment [22].

c. Manufacturing drugs

Formation of oligonucleotide: Artificial oligonucleotide production is done by the use of HL-30™, (a polystyrene bead) at a dose of 90 mmol/g.

In pharmacy

Pharmaceutical companies improved environmental safety by using green chemistry [23]. Green chemis-try engaged development of innovative drug deliverance methods such as:

a. Phosphoramidite: phosphoramidite forms antisense oligonucleotides to alter entrain concepts of green chemistry by discarding the usage and formation of toxic or hazardous materials and recycling the important materials like protecting groups, amidites and solid support, therefore increase cost-efficiency and atom economy [22].

b. Anastas described the formation of Naproxen with chiral metal catalyst containing 2,2'-bis[diphe-nylphosphino]-1,1'-binaphthyl ligand results in fine quantity of product [24].

c. Manufacturing of atorvastatin intermediates

1. In first step, Ethyl-4-chloro-3- oxobutanoate undergo biocatalytic reduction with keto-reductase and glucose combination for the formation of the useful substance which is essential for activity of enzyme forming a product ([S]ethyl-4-chloro-3- hydroxybutyrate) with high yield.
2. In last step, to accelerate the substitution of chloro with cyano group halohydrinde halogenase is added. Neutral pH and atmospheric temperature is maintained during the reaction [25].

d. Amines production: Industries produce amines in a two-step process at high cost which results in formation of large amount of by-products as a waste material [12]. But by using green chemistry concepts amine formation occurs in single step with little or no production of by-products [13].

e. By microwave irradiation method Aspirin synthesis follows the use of catalysts (H_2SO_4, $MgBr_3$, OEt_2, $AlCl_3$, $CaCO_3$, NaOAc, Et_3N) and solvent free approach [26].

f. Production of polymers: Polymers are large molecules or macromolecules that contains many small molecular fragments known as repeating units. They are used as plastics, rubbers, fibers, coatings, ad- hesives, foams [27].

Analytical chemistry

a. Ashing: Ashing of petroleum and fuels, plastics, pharmaceuticals and food industries is done by microwave heating. Microwave powdered muffle furnace is used for ashing in industries laboratories [28].

b. Digestion: Digestion is a process where samples are broken down into their basic constituents for chemical analysis. Microwave digestion systems are used for sample decomposition and preparation. In microwave digestion the heating of microwave-absorbing reagents occurs inside a pressurized, microwave transparent container. Thus, it increases the speed of digestion and Rapid heating results in rapid increase the rate of digestion.

c. Moisture analysis: Microwave assisted moisture analysis is highly effective in reducing testing time in food and beverages, chemicals, environmental, organic and pharmaceutical industries.

d. Computer aided drug designing: The computational method of drug designing will be able to predict affinity before a compound is synthesized and hence in theory only one compound needs to be synthesized, saving enormous time and cost. It reduces other compounds and intermediates during synthesing of the drug molecules. Computational methods have accelerated discovery by reducing the number of iterations required and have often provided novel structures [29, 30]. Some examples are:

Drug	Approved in Year	Biological Action
Captopril	1981	Antihypertensive
Dorzolamide	1995	Carbonic anhydrase inhibitor
Saquinavir	1995	Human immunodeficiency virus (HIV)
Indinavir	1996	Human immunodeficiency virus (HIV)
Ritonavir	1996	Human immunodeficiency virus (HIV)
Triofiban	1998	Fiborogen antagonist
Aliskiren	2007	Human renin inhibitor
Raltegravir	2007	Human immunodeficiency virus (HIV)
Boceprevir	Phase-lll clinical trials	Hepatitis C Virus (HCV) Inhibitor
Nolatrexed	Phase-lll clinical trials	Liver cancer
TMI-005	Phase-lll clinical trials	Rheumatoid arthritis
Zanamivir	1999	Neuramides inhibitors
NVP-AUY922	Phase-lll clinical trials	Inhibitors of HSP90
LY-517717	Phase-lll clinical trials	Serine protease inhibitor
Oseltamivir	1999	Active against influenza A and B virus

Figure 3.2: CADD drug products

Green chemistry advancement

Green chemistry has major contributions in the formation of quality of life, human welfare, and sus- tainable development. For example

1. **Quinapril:** Quinapril is an ACE inhibitor and used in hypertension and CHF. Methylene chloride used is a

potentially violent hydroxy-benzotriazole, dicyclohexylcarbodiimide [DCC] used as sensi- tizer, and sufficient amount of toluene volumes is used for separating acetic acid from the mixture by the process called solvent exchange method. The production of toxic material has been reduced significantly and less chemicals and greener solvents have been used [31].

2. **Celecoxib:** It is used as a cyclooxyginase -2 antiinflammatory agents. There has been increase in the yield from 63 to 84% when waste product formed is 35% and hydrazine is less used. By changing the reaction condition there is a need of cooling the product upto 208ºC in place of 58 ºC. The process is completely abolishes the use of undesirable and unwanted solvents like methylene chloride and hexane, and eliminates the need for 5200 metric tons of solvent annually when combined with other changes [31].
3. **Sildenafil citrate:** It is first drug used for oral treatment for erectile dysfunction. The route was first developed at Pfizer's UK laboratories which includes a straight eleven steps for synthesis, and gave a 4.2% total production from 2-pentanone. The redesigned chemistry process increases yield of Sildeafil citrate. This process improved production, decreased the wastage of green solvents like ethyl acetate, water and t-butanol. According to the development process ethyl acetate used over three regular steps i.e. a] Addition of hydrogen, b] Activation by acid, c] Acylation, which made the process easy, simple and eliminated the requirement of totally exchange solvents among entire steps, and also made it a most important energy saving and waste elimination solvent method [31, 32-34].
4. **Amino acid derivatives for hepatoprotection:** Synthesis of different amino acids having thieno [2, 3-d] pyrimidine group was done through green chemistry by incorporating water (as a solvent) to produce 2a-f, which further acidified to get the targeted compound 3-9. Synthesis of a tricyclic imid- azothienopyrimidine is done by microanalysis, FT-IR, Mass and 13C1HNMR spectroscopy. Oxidative stress was induced using γ-Irradiation. By enhancing the activity of different biochemical parameters in blood and altering the hematopoietic system, newly synthesized derivatives showed protective effects against against injuries produced by γ-irradiation. Thus, an anti-inflammatory and antioxidant mecha- nism of these compounds is due to the down-regulation of NF-κB protein expression in hepatic tissues. Therefore, NF-κB regulate IL-6 levels and TNF-α, CYP2E1 gene expression and COX-2 ef fects. The most active moiety was found to be Methionine derivative [35].
5. **Metal organic:** cause the adsorptive elimination and partition of chemicals. Today, adsorption and removal of various nitrogen containing compounds, olefins, Sulphur compounds and π-electron-rich gases via π-complex formation between an adsorbent and adsorbate molecules is very competitive. Porous metal-organic frameworks are much efficient in the adsorption or separation of different liq- uids and gases without harming their distinct characteristics [36].
6. **Human bone replacement with Coral skeletons:** Coral skeletons regenerate replacement human bone in nonloadbearing excavated skeletal locations. Multiscale combination, interconnected pores and channels. Highly bioactive surface chemistry established corals for healthy host bone replacement. Coral skeletal systems are remolded into new calcified structures and synthetic corals are remolded by biomimetic processes. Coral modification and synthetic coral formation is done by aquaculture and self-oganization inorganic chemistry. This method is used when there is an intrinsic skeletal deformities and metabolic conditions [37] occur.
7. **Synthesis of carotenoids from natural sources:** The synthesis of Atisane-type diterpenoids are widely isolated from the plant kingdom. It is the principle constituent of tetracycline C_{20} and had numerous degrees of structural complexity and pharmacological activity. Divergent total synthesis is an tactic method for synthesize effectively a large number of atisane-type diterpenoids by common inter- mediate structural interconversion. They are also very helpful in synthesis of carotenoids [38].
8. **Extraction of Carotenoids from Microalgae and Seaweeds:** In industries from an algal source production of carotenoids occurs in a large scale. Marine microlage and seaweeds are the sustainable source of several biologically active substances. They are source for various natural carotenoids including β-carotene, zeaxanthin, violaxanthin, lutein, astaxanthin and fucoxanthin. Conventional processing techniques serve simple procedure to isolate carotenoids [39].
9. Replacement of phosgene and methylchloride by diphenylcarbonate in the synthesis of polycarbonate.
10. Green synthesis of acetaldehyde is done by Wackeroxidation of ethylene with O_2 in the presence of catalyst.
11. Replacement of conventional methylation reaction for remove hazard is done by dimethylcarbonate.
12. Metal catalysis used in medicinal chemistry and in drug manufacturing chemistry [40].
13. Pladinium catalysis enable the coupling of important and challenging substrates i.e. heterocycles and sterically encoumbered substrates.
14. The reaction between napthyl sulfamate and phenylboronic acidin the presence of potassium phos- phate with 5% mol catalyst provide a quanitative yield [41].
15. Use of green solvents for green synthesis: water, liquid polymers, ionic liquids, bioethanol, supercritical fluids and ethylacetate are green solvents and used in green synthesis processes.

Green chemistry role in search of novel drug molecules

1. Hantzsch 1,4-dihydropyridine and polyhydroquinoline derivatives were synthesized in aqueous micelles in the presence of catalyst i.e. PTSA and strong ultrasonic irradiation [42].

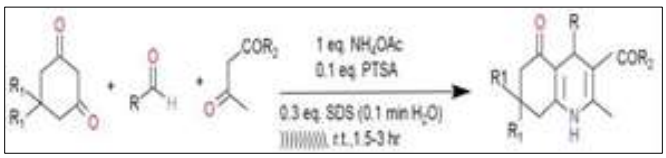

Fig 5.1: Ultrasonic irradiation in Hantcsch reaction

2. Aldol reaction in water by applying high intestiy ultrasound waves: large number of aldols were eliminated or side product is formed under conventional condtitons [43].

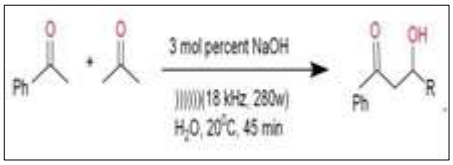

Fig 5.2: Aldol reaction

3. **Diazoketones formed from Fmoc- protected amino acid:** This reaction occurs in the pres- ence of silver benzoate and water by applying sonication a clean corresponding β- amino acid derivatives formation. By using capillary zone electrophoresis degree of racemization was ex- amined. Except phenylglycine no substantial epimerization would occur [44].

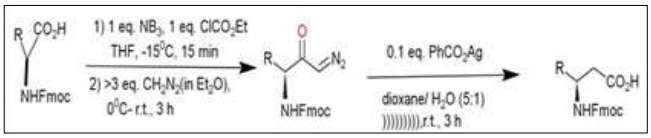

Fig 5.3: Diazoketone green synthesis

4. **Formation of arylesters by using sonication process:** When in THF magnesium powder, 1,2- dibromoethane, aryl bromide and diethyl dicarbonate powders are mixed and treated with BF3OEt2 at room temperature [43].

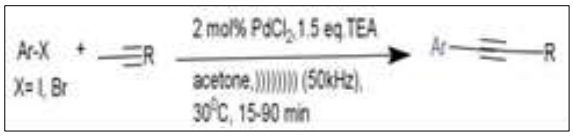

Fig 5.4: arylesters green synthesis

5. **Synthesis of Adipic Acid**

Adipic acid is synthesized by two methods i.e traditionl method and green method

a. Traditional method for adipic acid synthesis: In this method cyclohexanone/cyclohexanol mixed with nitric oxide adipic acid formed with nitrous orixde as a byproduct.
b. Green route: cyclohexene or cyclohexanone oxidized directly to adipic acid in the presence of catalyst $Na_2WO_4/KHSO_4$/aliquat336 [45].

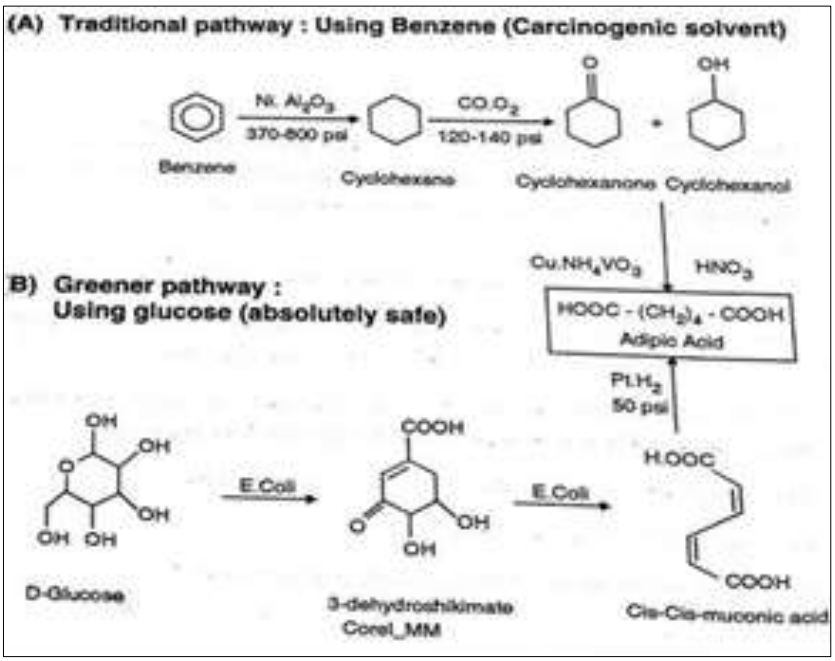

Fig 5.5: Traditional and greener pathways of adipic formation.

New greener route from cyclohexene with hydrogen peroxide and the catalyst Na2WO4.2H2O (1%) and $[CH_3(n\text{-}C_8H_{17})3N]HSO_4$ (1%) $C_6H_{10} + 4\ H_2O_2 \rightarrow$catalysts$\rightarrow C_6H_{10}O_4 + 4H_2O$.

This route does not produce any hazardous chemicals yield of adipic acid is 90%. Product mass = (6C)(12) (10H)(1) (4 O)(16) (2N)(14) = 146 g, Reactant mass = (6C)(12) (18H)(1) (8 O)(16) = 218 g,

Mass efficiency = 146/218 X 100 = 67%70.

Maleic Anhydrite synthesis

Maleic anhydride is prepared by45:

1. Passing air to either benzene/ butane/ butane over a vanadium pentoxide catalyst at 3-5 bar pressure and 350-4500C temperature. Malenic anhydride is used in manufacturing of polyester resins and paints.
2. Oxidation of naphthalene to phthalic acid and phthalic anhydride.

   $C_4H_{10} + 3.5\ O_2$ (air) $\rightarrow$catalyst $\rightarrow C_4H_2O + 4H_2O$

Chlorinated waste treatment: By sonolysis of chlorobenzene in a Fenton (Fe^{+}_2/H_2O_2) aque- ous system type. Also it is used for various chlorinated organic compounds sonochemical deg- radation [45].

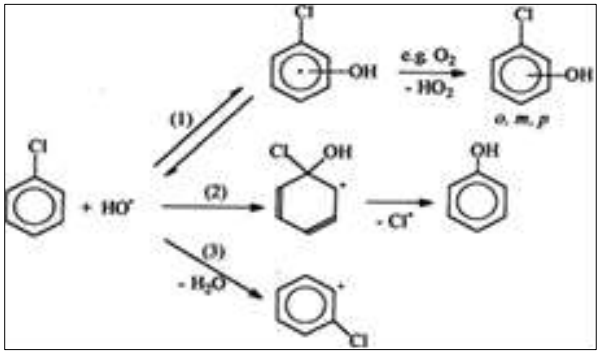

Fig 5.7: Waste water treatment reaction

Nanoparticle synthesis46

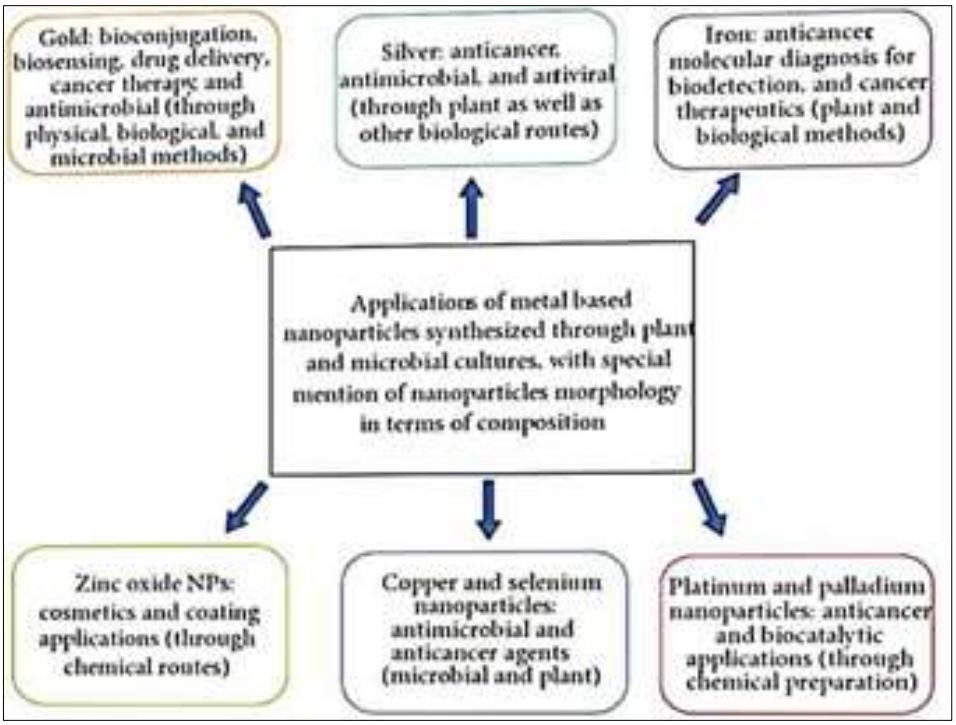

Fig 5.8: Polymer formation greener reaction

Synthesis of ketene 22: it can be formed by β-elimination of precursors with potassium t- butooxide or tetrabutyl ammonium [47].

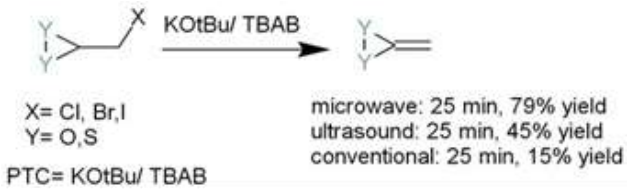

Fig 5.9: Ketene green synthesis

Conclusion

The potential of Pharmaceutical green chemistry is to reduce the cost of manufacturing and generation of hazardous substances. It encourages green chemistry to transform the pharmaceutical industry and drug manufacturing. Green Chemistry can deliver both environmental and economic benefit by adopt-ing its principles. Green chemistry becomes the frontier domains in the international chemical industries and research institutions. Green chemistry involved with biology, physics, medicines, material science and information science. In this new era by using green technology sustainable development will occur with formation of novel drug molecules. Novel drug or novel drug entity is an active compound, com-plex, molecule that previously has been not approved by FDA/EMA.

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