CHAPTER – 1

General Introduction
1.1 GREEN CHEMISTRY: SCIENCE FOR “SUSTAINABILITY”

It is important to understand the word “Sustainability” before discussing the general concepts regarding “GREEN CHEMISTRY.” Sustainability is just one word and yet there exists over 300 definitions \(^1\).

The word sustainability is derived from the Latin sustinere (tenere, to hold; sus, up). Dictionaries provide more than ten meanings for sustain\(^2\)[3], the main ones being to “maintain”, "support", or "endure".\(^4\)[5] However, since the 1980s sustainability has been used more in the sense of human sustainability on planet Earth and this has resulted in the most widely quoted definition of sustainability and sustainable development, that of the Brundtland Commission of the United Nations: “sustainable development is development that meets the needs of the present without compromising the ability of future generations to meet their own needs.”\(^6\)

It is usually noted that this requires the reconciliation of environmental, social and economic demands - the "three pillars" of sustainability.\(^7\) This view has been expressed as an illustration using three overlapping ellipses indicating that the three pillars of sustainability are not mutually exclusive and can be mutually reinforcing.\(^8\)

Definitions of sustainability often refer to the "three pillars" of social, environmental and economic sustainability

Another representation of sustainability showing that how both economy and society are constrained by environmental limits.
The UN definition is not universally accepted and has undergone various interpretations.[9][10][11] What sustainability is, what its goals should be, and how these goals are to be achieved is all open to interpretation.[12] For many environmentalists the idea of sustainable development is an oxymoron as development seems to entail environmental degradation.[13][14]. A deeper understanding would make us appreciate that the economy is a subsystem of human society, which is itself a subsystem of the biosphere, and a gain in one sector is a loss from another[15], illustrated as three concentric circles above.

A universally-accepted definition of sustainability is elusive because it is expected to achieve many things. On the one hand it needs to be factual and scientific, a clear statement of a specific “destination”. The simple definition "sustainability is improving the quality of human life while living within the carrying capacity of supporting eco-systems",[16] though vague, conveys the idea of sustainability having quantifiable limits. But sustainability is also a call to action, a task in progress or “journey”[17] and therefore a political process, so some definitions set out common goals and values. The Earth Charter [18] speaks of “a sustainable global society founded on respect for nature, universal human rights, economic justice, and a culture of peace.”

Industries utilizing chemistry and chemical engineering have been major contributors to worldwide economic development over the past century, and yet the chemical industry is often taken to task for many serious environmental problems. The bad public image of modern chemistry has resulted in an alarming decrease in the number of talented high-school students who choose to pursue advanced studies and careers in the field. As evident from the statistics given below the use of chemicals is not going to be out of demand in the near future. Not only is environment in danger but as mentioned above the human species is also intricately intertwined with the environment and hence the pollution has had an adverse effect on the human beings as well. Hence, chemists, biochemists, and chemical engineers should therefore do all that we can to change the negative image of the chemical industry. Public awareness should be created regarding the chemical community’s positive and invaluable contributions to the continuous improvement of the quality of everyday life. Given below are 2 statistics revealing these bitter facts.
Growth in chemical production outpaces population growth. Global chemical production is expected to grow 3% per year, while global population will grow 0.77% per year. On this trajectory, chemical production will increase 330% by 2050, compared to a 47% increase in population, relative to year 2000. Source: Organization for Economic Cooperation and Development 2001; American Chemistry Council 2003; United Nations 2004

### Table 1. Selected examples of toxic substances found in umbilical cord blood, breast milk and adult tissues.

<table>
<thead>
<tr>
<th>Contaminants</th>
<th>Examples of sources</th>
<th>How people are exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volatile Organic Compounds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naphthalene</td>
<td>Vehicle exhaust, deodorizers, paints, glues</td>
<td>Outdoor and indoor air, drinking water, workplaces</td>
</tr>
<tr>
<td>Perchloroethylene</td>
<td>Dry cleaning solvent, degreasing products</td>
<td>Treated clothing, proximity to dry cleaners, workplaces</td>
</tr>
<tr>
<td>Benzene</td>
<td>Gasoline, glues, detergents, vehicle exhaust</td>
<td>Outdoor air, workplaces</td>
</tr>
<tr>
<td><strong>Agricultural Products</strong></td>
<td></td>
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<tr>
<td>Organophosphates</td>
<td>Pesticides, flea &amp; tick pet products</td>
<td>Food, proximity to agriculture, field work, indoor air</td>
</tr>
<tr>
<td>Atrazine</td>
<td>Herbicide</td>
<td>Food, water, proximity to agriculture, field work</td>
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<tr>
<td><strong>Persistent Organic Pollutants</strong></td>
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<tr>
<td>Polybrominated diphenyl ethers</td>
<td>Flame retardants in furniture and electronics</td>
<td>Food, indoor air and dust</td>
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<td>(PBDEs)</td>
<td>Byproduct of waste incineration, paper mills,</td>
<td>Food, outdoor air, drinking water</td>
</tr>
<tr>
<td>Dioxins &amp; Furans</td>
<td>Manufacturing</td>
<td></td>
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<tr>
<td>PFOA/PFOS</td>
<td>Non-stick and stain-resistant coatings</td>
<td>Consumer products, food, water, workplaces</td>
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<tr>
<td><strong>Plastics Components</strong></td>
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<tr>
<td>Phthalates</td>
<td>Cosmetics, detergents, household cleaners, vinyl</td>
<td>Cosmetics, detergents, household cleaners, vinyl materials,</td>
</tr>
<tr>
<td></td>
<td>materials, lacquers</td>
<td>lacquers</td>
</tr>
<tr>
<td>Bisphenol A</td>
<td>Hard plastic containers, canned food linings</td>
<td>Food, water</td>
</tr>
<tr>
<td><strong>Heavy Metals</strong></td>
<td></td>
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<tr>
<td>Cadmium</td>
<td>Batteries, fertilizer production, waste</td>
<td>Food, air, water, workplaces</td>
</tr>
<tr>
<td></td>
<td>incineration, plastics, metal coatings</td>
<td></td>
</tr>
<tr>
<td>Lead</td>
<td>Paint, electronics, batteries, fossil fuels</td>
<td>Toys, food, soil, drinking water, workplaces</td>
</tr>
</tbody>
</table>

**FIGURE 1. GROWTH IN CHEMICAL PRODUCTION**
As the natural resources are used up in the world, chemists and biotechnologists are being asked to come up with innovative ways in which renewable resources can be used to replace nonrenewable ones. But there will continue to be a demand for some non-renewable resources. If we wish to make materials that use fewer resources today, we should try to minimize the amount of raw material that is incorporated in the object.

The science of chemistry is central to addressing the problems facing the environment. Through the utilization of various sub disciplines of chemistry and molecular sciences, there is an increasing appreciation that the emerging area of green chemistry is need in the design and attainment of sustainable development. A central driving force in this increasing awareness is that Green Chemistry accomplishes both economic and environmental goals, simultaneously through the use of sound, fundamental scientific principles.

The term “Green Chemistry”, as adopted by the IUPAC Working Party on Synthetic Pathways and Processes in 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”.

The concept of “design” in the definition is an essential element in requiring the conscious and deliberative use of a set of criteria, principles, and methodologies in the practice of green chemistry. Because green chemistry is intentionally designed, it is definitionally impossible to do green chemistry by accident. The phrase the “use or generation” implies the requirement of life-cycle considerations. Green chemistry can be utilized anywhere in the life cycle, from feedstock origins to beyond end of useful life. The term “hazardous” is used in its broadest context including physical (e.g., explosion, flammability), toxicological (e.g., carcinogenic, mutagenic), and global (e.g., ozone depletion, climate change).

The term green chemistry[19][20] describes an area of research arising from scientific discoveries about pollution and from public perception, in much the same way as the identification and understanding of a deadly disease stimulating the call for a cure. This term, which was coined at the Environmental Protection Agency (EPA) by Paul Anastas, represents the assumption that chemical processes that carry
environmental negatives can be replaced with less polluting or non-polluting alternatives. Green chemistry is the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products, associated with a particular synthesis or process. Thus chemists can greatly reduce risk to human health and the environment.

1.2 A BRIEF HISTORY

In the United States, the Pollution Prevention Act of 1990\cite{21} established source reduction as the highest priority in solving environmental problems. Passage of this act signaled a move away from the “command and control” response to environmental issues and toward pollution prevention as a more effective strategy that focused on preventing waste from being formed in the first place. Shortly after the passage of the Pollution Prevention Act, it was recognized that a variety of disciplines needed to be involved in source reduction. This recognition extended to chemists, the designers of molecular structures and transformations. In 1991, the Office of Pollution Prevention and Toxics in the U.S. Environmental Protection Agency launched the first research initiative of the Green Chemistry Program, the Alternative Synthetic Pathways research solicitation.\cite{22} Foundational work in chemistry and engineering at the National Science Foundation’s program on Environmentally Benign Syntheses and Processes was launched in 1992, and formed a partnership with EPA through a Memorandum of Understanding that same year. In 1993, the EPA program officially adopted the name “U.S. Green Chemistry Program”. Since its inception, the U.S. Green Chemistry Program has served as a focal point for major activities within the United States, such as the Presidential Green Chemistry Challenge Awards and the annual Green Chemistry and Engineering Conference.

In the first half of the 1990s, both Italy \cite{23} and the United Kingdom \cite{24} launched major initiatives in green chemistry. Several researchers in the U.K. established research and education programs in green chemistry. In Italy, a multi university consortium (INCA) featured research on green chemistry as one of its central themes. During the last half of the decade, Japan organized the Green and Sustainable Chemistry Network (GSCN),\cite{25} with an emphasis on promoting research and development on green and sustainable chemistry. The first books, papers, and
symposia on the subject of green chemistry were introduced in the 1990s. The inaugural edition of the journal *Green Chemistry*, sponsored by the Royal Society of Chemistry, appeared in 1999. [26] Research groups in many countries quickly coalesced, and adoption by industry was evident but difficult to quantify. In 1995, the U.S. Presidential Green Chemistry Challenge Award was announced as a way of recognizing accomplishments by industry, academia, and government in green chemistry. The five awards first given in 1996, along with the numerous nominations for the award, provided a first, if understated, measure of adoption of green chemistry. Japan, Italy, the U.K., Australia, and other nations have adopted green chemistry awards for the purpose of highlighting the environmental and economic accomplishments of green chemistry.

Green chemistry, an approach to the synthesis, processing and use of chemicals that reduce risks to humans and the environment, covers the following areas:

- Application of innovative technology to established industrial processes.
- Development of environmentally improved routes to important products.
- Design of new green chemicals and materials.
- Use of sustainable resources.
- Use of biotechnology alternatives.
- Methodologies and tools for evaluating environmental impact.

Green chemistry involves the design and redesign of chemical syntheses and chemical products to prevent pollution and thereby solve environmental problems. The 12 principles postulated for Green Chemistry are as follows:

1. **Prevention**
   It is better to prevent waste than to treat or clean up waste after it has been created.

2. **Atom Economy**
   Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. **Less Hazardous Chemical Syntheses**
   Wherever practicable, synthetic methods should be designed to use and
generate substances that possess little or no toxicity to human health and the environment.

4. **Designing Safer Chemicals**
   Chemical products should be designed to effect their desired function while minimizing their toxicity.

5. **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.

6. **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.

7. **Use of Renewable Feedstocks**
   A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. **Reduce Derivatives**
   Unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

9. **Catalysis**
   Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. **Design for Degradation**
    Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. **Real-time analysis for Pollution Prevention**
    Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. **Inherently Safer Chemistry for Accident Prevention**
    Substances and the form of a substance used in a chemical process should be
chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

Over the course of the past decade, green chemistry has demonstrated how fundamental scientific methodologies can protect human health and the environment in an economically beneficial manner. Significant progress is being made in several key research areas, such as catalysis, the design of safer chemicals and environmentally benign solvents, and the development of renewable feedstocks. Current and future chemists are being trained to design products and processes with an increased awareness for environmental impact. Outreach activities within the green chemistry community highlight the potential for chemistry to solve many of the global environmental challenges we now face. The origins and basis of green chemistry chart a course for achieving environmental and economic prosperity inherent in a sustainable world.

1.3 SOME ASPECTS OF ORGANIC SYNTHESIS - A GREEN CHEMISTRY PERSPECTIVE

Since its commencement in the last decade there were quite a few new technologies, new routes and new approaches that were developed in synthetic organic chemistry viz. Microwave Assisted Organic Synthesis, Aqua Mediated Organic Synthesis, Synthesis using different solvents like Ionic Liquids as well as some super critical solvents etc. which brought about a kind of revolution and also a shift in the mind set of common people as well as a shift of focus among the scientific fraternity.

As expected, green chemistry has grown into a significant internationally engaged focus area within chemistry. The importance of green chemistry was highlighted aptly in a cover story in *Chemical and Engineering News.* Major research, education, and outreach initiatives have been established around the globe. Major research programmes in all the major continents started focusing efforts around Principles of Green chemistry. The breadth of this research was very wide and incorporated areas such as polymers, solvents, catalysis, biobased / renewables, analytical method development, synthetic methodology development, and the design
of safer chemicals. Excellent research started being conducted within each of these areas that strived to incorporate one or more of the 12 Principles of Green Chemistry.

1.3.1 Polymers

The nature of the hazards that can be posed by polymers in their manufacture, use, and disposal has been widely recognized in recent years, as have the green chemistry methodologies that can be used to address these hazards.\[28\] Research on renewable feedstocks and biobased transformations, structural design, and design for degradability are all promising areas.\[29\] Carbon dioxide, for example, is a renewable feedstock that has been recovered from flue gas and, in its supercritical state, combined with pastes from fly ash to yield products such as roofing tiles and wallboard.\[30\]-\[33\] Polymers derived from carbohydrate feedstocks such as soy\[34\] and corn\[35\] are found in consumer products like automobiles and food packaging. Microbial fermentation has been used to convert glucose to a biodegradable polymer.\[36\]

1.3.2 Solvents

The design of environmentally benign solvents and solventless systems has been one of the most active areas of green chemistry over the past 10 years. Solvents are highly regulated and used in large quantities. Organic solvents pose a particular concern to the chemical industry because of the sheer volume used in synthesis, processing, and separations. Many are classified as volatile organic compounds (VOCs) or hazardous air pollutants (HAPs) and are flammable, toxic, or carcinogenic.

Breakthroughs in the use of supercritical fluids such as carbon dioxide have met with success in the research laboratory as well as commercially. Supercritical fluids offer a number of benefits, such as the potential to combine reaction and separation processes and the ability to tune the solvent through variations in temperature and pressure. In the supercritical fluids area, CO\(_2\) has received the most attention\[37\]-\[43\] because its critical temperature and pressure (\(T_c\) 31.1 °C, \(P_c\) 74 bar) are more accessible than those of other solvents (water, for example, has \(T_c\) 374 °C and \(P_c\) 221 bar). CO\(_2\) offers numerous advantages as a benign solvent: it is nontoxic, nonflammable, and inexpensive, and can be separated from the product by simple
Part 1 “Investigations of some Aqua mediated as well as microwave assisted…”,

depressurization. Applications of supercritical CO₂ are found in the dry cleaning industry, where CO₂ replaces perchloroethylene as a solvent,[44-45] in semiconductor manufacturing, where the low surface tension of supercritical CO₂ avoids the damage caused by water in conventional processing,[46] and in chemical processing.[47]

The use of supercritical CO₂ as a reaction medium in organic synthesis provides an excellent example of the evolution from fundamental academic research into a commercial process. In collaboration with Thomas Swan & Co. Ltd,[48] researchers at the University of Nottingham[49] developed synthetic methodologies in supercritical CO₂ that are being employed in a new supercritical fluid plant in the U.K., with a capacity up to 1000 tons per year. Conventional solvents are replaced with supercritical fluids in such key technologies as hydrogenation, Friedel-Crafts alkylations and acylations, hydroformylations, and etherification.

The use of water as a solvent in ways previously not realized has been an active area of research in green chemistry (Scheme 1).[50,51] A number of classic organic reactions, traditionally run in organic solvents, can be carried out in water with the proper design of catalysts and reaction conditions. Even variants of the Grignard reaction, notoriously sensitive to water, can be run in an aqueous solvent using a variety of metals, such as indium[52] and zinc.[53] The use of an obviously benign and inexpensive solvent like water could yield significant green chemistry benefits if challenges of energy and separations can be met.

![Scheme 1: Metal Mediated reaction of an aldehyde and an Allyl Halide in water as a solvent](image)

Ionic liquids, a relatively new area of solvent investigation, are attractive because of their negligible vapor pressure and their use in polar systems to generate new chemistries[54-57]. A plethora of ionic liquids can be produced by varying the cations and anions, permitting the synthesis of ionic liquids tailored for specific applications. While questions of intrinsic hazard must still be answered for this class
of solvents, the potential for the design of next generation ionic liquids holds significant promise for improved environmental benefits.

Fluorous solvent systems have demonstrated particular advantages in synthetic systems.\cite{58-60} Fluorous systems are particularly appealing in fluorous biphasic catalysis in which the homogeneous catalyst and the product reside in separate phases, thereby eliminating the need for energy-intensive separations. In addition to efficiency, fluorous biphasic systems may reduce accident potential by eliminating the possibility of runaway exothermic reactions.

### 1.3.3 Catalysis

The area of catalysis is sometimes referred to as a “foundational pillar” of green chemistry.\cite{61} Catalytic reactions\cite{62-68} often reduce energy requirements and decrease separations due to increased selectivity; they may permit the use of renewable feedstocks or minimize the quantities of reagents needed. There is little doubt that the 2001 Nobel Prize-winning work of Sharpless, Noyori, and Knowles met many green chemistry goals.\cite{69} Their research on catalytic asymmetric synthesis has been crucial in producing single enantiomer compounds, particularly for the pharmaceutical industry.

Catalysis often permits the use of less toxic reagents, as in the case of oxidations using hydrogen peroxide in place of traditional heavy metal catalysts.\cite{70} Renewable resources, such as soya sterols\cite{71} (Scheme 2) and glucose,\cite{72} serve as feedstocks when catalytic methods are employed. Recently, water has been split into oxygen and hydrogen using a photocatalyst that absorbs light in the visible range.\cite{73} While still at the research stage, this technology has the potential to provide an efficient source of hydrogen for use in fuel cells. Hydrogen fuel cells in cars would greatly reduce air pollution, as the oxidation product (water) is environmentally benign.\cite{74} The application of catalysis to dematerialization, reduced toxicity systems, benign and renewable energy systems, and efficiency makes it a central focus area for green chemistry research.
1.3.4 Biobased / Renewables

The utilization of benign, renewable feedstocks is a needed component of addressing the global depletion of resources. More than 98% of all organic chemicals are derived from petroleum. \[^{75}\] Achieving a sustainable chemical industry dictates switching from depleting finite sources to renewable feedstocks. Research in this area has focused on both the macro and molecular levels. The carbohydrate economy provides a rich source of feedstocks for synthesizing commodity \[^{76}\] and specialty chemicals. For example, agricultural wastes have been converted into useful chemical intermediates such as levulinic acid,\[^{77}\] alcohols, ketones, and carboxylic acids.\[^{78}\] Shells from crabs and other sea life serve as a valuable and plentiful source of chitin, which can be processed into chitosan, a biopolymer with a wide range of potential applications that are being currently explored for use in the oil-drilling industry.\[^{79}\] At the molecular level, genetic engineering produces valuable chemical products via nontraditional pathways. Glucose yields catechol and adipic acid \[^{80}\] (Scheme 3) using genetically engineered \textit{Escherichia coli}. Recombinant \textit{Saccharomyces} yeasts convert both glucose and xylose, present in cellulosic biomass, into ethanol.\[^{81}\] Carbon dioxide is also a renewable feedstock that has been incorporated into polymers.\[^{82}\]
1.3.5 Synthetic Methodologies

Synthetic methodologies are being designed in both academia and industry that are more environmentally benign and more atom efficient. New synthetic protocols have eliminated waste streams, improved worker safety, and increased yield in pharmaceutical processes (Scheme 4). Polymer synthesis has been redesigned to eliminate the use of highly toxic reagents and organic solvents. The utilization of biomimetic approaches, cascading reactions, and molecular self-assembly represents some of the new chemistries being developed with green chemistry goals incorporated at the design stage.

1.3.6 Analytical Methods

Analytical chemistry played a central role in the environmental movement by detecting, measuring, and monitoring environmental contaminants. As we move toward prevention and avoidance technology, analytical methods are being incorporated directly into processes in real time in an effort to minimize or eliminate...
the generation of waste before it is formed.\textsuperscript{[96,97]} Continuous process monitoring assists in optimizing the use of feedstocks and reagents while minimizing the formation of hazardous substances and unwanted byproducts. In addition, analytical methodologies have, themselves, historically used and generated hazardous substances and are being redesigned with green chemistry goals in mind by using benign mobile and stationary phases and placing greater emphasis on in situ analysis.

### 1.3.7 Design for safer chemicals

Design for reduced hazard is a green chemistry principle that is being achieved in classes of chemicals ranging from pesticides to surfactants, from polymers to dyes\textsuperscript{[98-100]}. The principles of mechanistic toxicology allow for molecular design for reduced toxicity. Pesticides have been designed that are more selective and less persistent \textsuperscript{[101]} than many traditional organic pesticides. Surfactants \textsuperscript{[102]} and polymers, \textsuperscript{[103]} have been developed to degrade in the environment at the end of their useful lifetime. Dyes without heavy metals \textsuperscript{[104]} are finding applications in the textile industry. Understanding the physicochemical properties that underlie even global hazards allows for manipulation to reduce those hazards. The systematic development and application of design rules for reduced hazard is one of the most important challenges facing green chemistry.

In the upcoming chapters we will throw some light on Microwave Assisted Organic Synthesis (MAOS) as well as Aqua Mediated Organic Synthesis (AMOS) which are now an integral part of green chemistry cause they have numerous advantages over classical organic synthesis. The following headings would also serve as the introductions for the upcoming chapters regarding the synthesis of some new chemical entities in this thesis, so as to build up a solid foundation. More over the biological significance of some of the class of chemicals which have been synthesized would also be discussed ahead.
1.4 MICROWAVE ASSISTED ORGANIC SYNTHESIS (MAOS): A BRIEF REVIEW

From the kitchen to the laboratory, ‘microwave chemistry’ has come up as a boon in disguise for the eco friendly conscious chemists. As an integral part of Green Chemistry, the field of Microwave assisted organic synthesis (MAOS) has seen tremendous development in the recent years. The microwave mediated organic reactions \[^{105,106}\] take place more rapidly, safely, and in an environmentally friendly manner, with high yields. Very little solvent and even the use of water as a solvent is a big advantage of microwave chemistry. In many cases, microwave-mediated reactions are carried out in dry media on solid support, i.e. without the use of solvent. Therefore the use of toxic and expensive organic solvents can be avoided. Such reactions not only reduce the amount of waste solvent generated, but also the products often need very little or no purification. These processes will hopefully be adapted by big industries as well, thereby contributing to the betterment of the environment.

Within two decades is should be possible to:

- Eliminate nearly 100% of emissions in polymer manufacturing and processing.
- Replace all solvents and acid-based catalysts that have adverse environmental effects with solids, or ‘greener alternatives’.
- Achieve 30–40% reduction in waste.
- Reduce more than 50% quantity of plastics in landfills.

Heterogeneous organic reactions have proven useful to chemists in the laboratory as well as in the industrial context. These reactions are effected by the reagents immobilized on the porous solid supports and have advantages over the conventional solution phase reactions because of the good dispersion of active reagent sites, associated selectivity and easier work-up. The recyclability of some of these solid supports renders these processes into truly eco-friendly green protocols. Although the first description of surface-mediated chemistry dates back to 1924, \[^{107}\] it was not until the late 1970s that the technique received genuine attention with the appearance of two reviews, \[^{108}\] followed by a series of books and account articles \[^{109}\].
A related development that had a profound impact on these heterogeneous reactions was the use of microwave (MW) irradiation techniques for the acceleration of organic reactions. Since the appearance of the first article on the application of microwaves for chemical synthesis in polar solvents, the approach has blossomed into a useful technique for a variety of applications in organic synthesis and functional group transformations. The focus has lately shifted to less cumbersome solvent-free methods wherein the neat reactants, often in the presence of mineral oxides or supported catalysts, undergo facile reactions to provide high yields of pure products thus eliminating or minimizing the use of organic solvents.

Microwave reactions involve selective absorption of MW energy by polar molecules, non-polar molecules being inert to MW dielectric loss. The initial experiments with microwave techniques centered on the use of high dielectric solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF). The rate enhancements in such reactions are now believed to be due to rapid superheating of the polar solvents. However, in these solution-phase reactions, the development of high pressures and the use of specialized Teflon vessels and sealed containers are some of the limitations. During recent years, a practical dimension to the microwave heating protocols has been added by accomplishing reactions on solid supports under solvent-free conditions. In these reactions, the organic compounds adsorbed on the surface of inorganic oxides, such as alumina, silica and clay, or ‘doped’ supports absorb microwaves whereas the solid support does not absorb or restrict their transmission. The bulk temperature is relatively low in such solvent-free reactions although higher localized temperatures may be reached during microwave irradiation. These solvent-free MW assisted reactions provide an opportunity to work with open vessels thus avoiding the risk of high pressure development and increasing the potential of such reactions to upscale.

1.4.1 A brief history of Microwave assisted organic synthesis

While fire is now rarely used in synthetic chemistry, it was not until Robert Bunsen invented the burner in 1855 that the energy from this heat source could be applied to a reaction vessel in a focused manner. The Bunsen burner was later superseded by the isomantle, the oil bath or the hot plate as a means of applying heat to a chemical reaction. In the past few years, heating and driving chemical reactions
by microwave energy has been an increasingly popular theme in the scientific community. [111]

![Scheme 5](image)

**Scheme 5** Hydrolysis of benzanilide: The first published example (1986) of microwave-assisted organic synthesis.

In those early days, experiments were typically carried out in sealed Teflon or glass vessels in a domestic household microwave oven without any temperature or pressure measurements. The results were often violent explosions due to the rapid uncontrolled heating of organic solvents under closed-vessel conditions. In the 1990s, several groups started to experiment with solvent-free microwave chemistry (so-called dry-media reactions), which eliminated the danger of explosions [118]. Here, the reagents were pre-adsorbed onto either an essentially microwave-transparent (i.e., silica, alumina or clay) or strongly absorbing (i.e., graphite) inorganic support, that additionally may have been doped with a catalyst or reagent. Particularly in the early days of MAOS, the solvent-free approach was very popular since it allowed the safe use of domestic microwave ovens and standard open-vessel technology. While a large number of interesting transformations using “dry-media” reactions have been published in the literature [119], technical difficulties relating to non-uniform heating, mixing and the precise determination of the reaction temperature remained unresolved, in particular when scale-up issues needed to be addressed.

Alternatively, microwave-assisted synthesis has been carried out using standard organic solvents under open-vessel conditions. If solvents are heated by microwave irradiation at atmospheric pressure in an open vessel, the boiling point of the solvent typically limits the reaction temperature that can be achieved. In order to nonetheless achieve high reaction rates, high-boiling microwave-absorbing solvents have been frequently used in open-vessel microwave synthesis. However, the use of these solvents presented serious challenges in relation to product isolation and recycling of the solvent. Because of the recent availability of modern microwave
reactors with on-line monitoring of both temperature and pressure, MAOS in
dedicated sealed vessels using standard solvents – a technique pioneered by
Christopher R. Strauss in the mid-1990s [120] – has been celebrating a comeback in
recent years. This is clearly evident surveying the recently published (since 2001)
literature in the area of controlled microwave-assisted organic synthesis (MAOS). It
appears that the combination of rapid heating by microwaves with sealed-vessel
(autoclave) technology will most likely be the method of choice for performing
MAOS on a laboratory scale in the future. Importantly, recent innovations in
microwave reactor technology now allow controlled parallel and automated
sequential processing under sealed-vessel conditions, and the use of continuous- or
stop-flow reactors for scale-up purposes.

Since the early days of microwave synthesis, the observed rate accelerations
and sometimes altered product distributions compared to oil-bath experiments have
led to speculation on the existence of so-called “specific” or “non-thermal”
microwave effects [121]. Historically, such effects were claimed when the outcome of a
synthesis performed under microwave conditions was different from that of the
conventionally heated counterpart at the same apparent temperature. Reviewing the
present literature [122], it appears that today most scientists agree that in the majority
of cases the reason for the observed rate enhancements is a purely thermal/kinetic
effect, i.e., a consequence of the high reaction temperatures that can rapidly be
attained when irradiating polar materials in a microwave field, although effects that
are caused by the unique nature of the microwave dielectric heating mechanism
(“specific microwave effects”) clearly also need to be considered. While for the
medicinal chemist in industry this discussion may seem largely irrelevant, the debate
on “microwave effects” is undoubtedly going to continue for many years in the
academic world. Regardless of the nature of the observed rate enhancements,
microwave synthesis has now truly matured and has moved from a laboratory
curiosity in the late 1980s to an established technique in organic synthesis, heavily
used in both academia and industry.

The initially slow uptake of the technology in the late 1980s and 1990s has
been attributed to its lack of controllability and reproducibility, coupled with a
general lack of understanding of the basics of microwave dielectric heating. The risks
associated with the flammability of organic solvents in a microwave field and the lack of available dedicated microwave reactors allowing for adequate temperature and pressure control were major concerns. Important instrument innovations now allow for careful control of time, temperature and pressure profiles, paving the way for reproducible protocol development, scale-up and transfer from laboratory to laboratory and from scientist to scientist. Today, microwave chemistry is as reliable as the vast arsenal of synthetic methods that preceded it. Since 2001, therefore, the number of publications related to MAOS has increased dramatically, to such a level that it might be assumed that, in a few years, most chemists will probably use microwave energy to heat chemical reactions on a laboratory scale. Not only is direct microwave heating able to reduce chemical reaction times significantly, but it is also known to reduce side reactions, increase yields and improve reproducibility. Therefore, many academic and industrial research groups are already using MAOS as a technology for rapid reaction optimization, for the efficient synthesis of new chemical entities or for discovering and probing new chemical reactivity.

1.4.2 Applications of microwaves in heterocyclic ring formation

1.4.2.1 Five-membered heterocyclic rings

A. Pyrroles

The classical Paal-Knorr cyclization of 1,4-diketones to give pyrroles is dramatically speeded-up under microwave irradiation and high yields are obtained as shown in scheme 6 [123].

![Scheme 6](image)
B. Pyrazoles

Another recent application of microwaves in cyclization is the preparation of pyrazoles from hydrazones using the Vilsmeier cyclization method by treatment with POCl$_3$ and DMF$^{[124]}$. As shown in Scheme 7, once again the reaction is speeded-up by factors of several 100-fold.

C. Imidazoles

An important classical preparation of imidazoles is from an $\alpha$-diketone, an aldehyde and ammonia. Here again, excellent yields can be obtained in reaction times of a few minutes as shown in Scheme 8$^{[125]}$. 

![Scheme 7](image1.png)

![Scheme 8](image2.png)
D. Oxazolines

The example of Scheme 9, the preparation of oxazolines shows that partially saturated five-membered rings can also be prepared advantageously using microwaves\textsuperscript{[126]}.

\begin{center}
\includegraphics[width=\textwidth]{scheme9.png}
\end{center}

\textbf{Scheme-9}

\begin{itemize}
\item R = 2-furyl, phenyl, heptadecenyl
\item 80-95\%
\end{itemize}

\textbf{E. Triazoles and Tetrazoles}

Schemes 10 and 11 continue the overview of five-membered rings with illustrations of the advantageous preparation of 1,2,4-triazoles (Scheme 10)\textsuperscript{[127]} and tetrazoles (Scheme 11)\textsuperscript{[128]} using microwaves. Notice that in Scheme 6 the starting aryl cyanides are also made by a Pd-catalyzed but microwave-enhanced replacement of aryl bromides using zinc cyanide.

\begin{center}
\includegraphics[width=\textwidth]{scheme10.png}
\end{center}

\textbf{Scheme 10}

\begin{itemize}
\item Ar = C_{6}H_{5}, 4-CH_{3}C_{6}H_{4}, 4-NH_{2}C_{6}H_{4}, 4-OH_{2}C_{6}H_{4}, 4-CH_{3}OC_{6}H_{4} etc.
\end{itemize}
Part 1 “Investigations of some Aqua mediated as well as microwave assisted…”

F. Oxadiazoles

The dehydration of unsymmetrical diacylhydrazines (themselves prepared by a conventional Mitsunobu reaction) using Burgess’s reagent is shown in Scheme 12 to give 1,3,4-oxadiazoles rapidly under microwave irradiation.\(^{129}\)

G. Isoxazolines and pyrazolines

The acceleration of 1,3-dipolar cycloaddition reactions to give isoxazolines and pyrazolines by the addition of activated olefins to nitrile oxides or nitrile imides, respectively, is illustrated in Scheme 13; the resulting compounds are obtained in far higher yield than under conventional conditions.\(^{130}\)
1.4.2.2 Benzo-derivatives of five-membered rings

A. Benz-imidazoles, -oxazoles, and -thiazoles

Ring closure reactions of appropriate o-substituted anilines to give benzimidazoles, benzoxazoles, and benzthiazoles takes place much faster and in significantly high yield under microwave conditions than conventionally [131] as shown in Scheme 14.

B. Indoles

The classical Fischer-indole synthesis from an aryl hydrazine and a ketone is speeded-up by several 100-fold as documented in Scheme 15 [132].
C. \(\gamma\)-Carbolines

The Graebe-Ullmann synthesis which converts 1-arylbenzotriazoles into carbazoles or their heterocyclic analogs is also accelerated under microwave conditions as shown in Scheme 16 where the 1-(4-pyridyl)benzotriazole is converted into a \(\gamma\)-carboline \(^{[133]}\).

1.4.2.3 Six-membered rings

A. Dihydropyridines

The Hantzsch dihydropyridine synthesis remains one of the most important routes to pyridine ring systems. Under conventional conditions long periods of heating are required and yields are poor to moderate. Microwaves dramatically reduce
the heating times and also significantly increase the yields as shown in Scheme 17 [134].

\[
\begin{align*}
\text{Me} & \quad \text{EtO} \quad \text{C} \\
\text{O} & \quad \text{CO}_2 \text{Et} \\
\text{CO}_2 \text{Et} & \quad \text{NH}_2 \\
\text{H} & \quad \text{Ar} \\
\text{H} & \quad \text{Me}
\end{align*}
\]

\[\text{MW, 140 °C, 10-15 min., solvent-free}\]

\[\text{Ar} = \text{C}_6\text{H}_5, \text{2-NO}_2\text{C}_6\text{H}_5, \text{2-CH}_3\text{OC}_6\text{H}_5, \text{2-ClC}_6\text{H}_5 \text{ etc.}\]

**Scheme-17**

Microwave: 10-15 min., 51-92%
Conventional: 12 h, 15-61%

---

**B. Dihydropyridopyrimidinones**

Dihydropyridopyrimidinones have been produced by ring annulations of aminopyrimidinones. Once again the reaction time is dramatically reduced and yields are much better with the solvent-free microwave conditions. (Scheme-18) [135].

\[
\begin{align*}
\text{Me} & \quad \text{X} \\
\text{N} & \quad \text{OH} \\
\text{R} & \quad \text{CN} \\
\text{Ph} & \quad \text{Ar}
\end{align*}
\]

\[\text{MW, 600 W, 20 min., solvent-free}\]

\[\text{Microwave: 15-20 min., 70-75%}\]
\[\text{Conventional: EtOH reflux, 40-48 h, 21-25%}\]

**Scheme-18**

\[\text{X} = \text{O, S; R = H, CH}_3; \]
\[\text{Ar} = \text{C}_6\text{H}_5, \text{4-CH}_3\text{OC}_6\text{H}_4, \text{4-ClC}_6\text{H}_4\]

---

**C. Dihydropyrimidines**

The Biginelli reaction is important for the preparation of dihydropyrimidine derivatives and excellent results are found for reactions carried out with microwave enhancement (Scheme 19) [136].
D. Tetrazines

The Diels-Alder reaction between aza-olefins and aza-dicarboxylic ester to give tetrazines is speeded-up by a factor of 1000 by microwave enhancement as shown in Scheme 20\textsuperscript{[137]}.

\textbf{1.4.2.4 Polycyclic six-membered rings}

A. Quinolines

The Skraup synthesis has a bad reputation as it involves very messy conditions and gives only low yields of quinolines when carried out conventionally. Recently, it has been reported that microwave enhancement reduces the reaction time to a few minutes and allows high yields to be isolated (Scheme 21)\textsuperscript{[138]}.
B. **Pyrimido [1,2-a]pyrimidines**

Pyrimido [1,2-a]pyrimidines are prepared from dihydroaminopyrimidines and chromone-3- aldehydes as is shown in Scheme 22 \[139\]. Although the conventional reaction must proceed in refluxing ethanol, reactions are much faster and better yields have been obtained with microwaves.
1.4.2.5. Nucleophilic Substitution Reactions

A. Heterocyclic C-alkylations

Nucleophilic substitution reactions can be speeded-up very considerably as is illustrated in Scheme 23 for a chloro-naphthyridine derivative.\textsuperscript{[140]}

\textbf{Scheme 23}

B. Heterocyclic N-alkylations

Another class of nucleophilic substitution is involved in heterocyclic N-alkylation which we have illustrated in Scheme 24. This shows that nucleophilic substitution on the nitrogen atom of saccharin is significantly speeded-up by microwave irradiation.
C. Selective-alkylation

In Scheme 25, the results presented indicate that selectivity is achieved in the \( N \) alkylation of 1,2,4-triazole under microwave conditions where only the \( N^1 \)-alkyl derivative was formed in contradistinction to the conventional conditions which give a considerable amount of the di-1,4-substituted compound \[^{[141]}\].

D. Transition metal cross-coupling

An important type of nucleophilic substitution reactions which are recently much exploited are comprised of transition metal cross-coupling. A Suzuki coupling is shown at the top of Scheme 26 to give significantly better yield in the presence of microwave irradiation. At the bottom of Scheme 26 another Suzuki coupling is speeded-up by a factor of 100 \[^{[142]}\].
1.4.2.6 Hetero-Diels–Alder reactions

A. Intramolecular reactions

Hetero-Diels-Alder reactions involving cyclic components which lead to polycyclic ring systems are of great importance. An intramolecular example shown in Scheme 27 indicates that the reaction was accelerated by a factor of around 1000 by microwave irradiation \(^{[143]}\).
B. Intermolecular reactions

Scheme 28 shows two impressive examples of rate enhancement for intermolecular hetero-Diels–Alder reactions \[^{[144]}\]. In the first example on the top of Scheme 28 the initial reaction is followed by elimination thus involving the conversion of a pyrazine derivative into a pyridine. Perhaps more impressive is the lower example in Scheme 28 where an autoclave is required under conventional conditions but which can be dispensed with when microwave acceleration is utilized.

![Scheme 28](image)
1.4.2.7 1, 3-Dipolar cycloaddition reactions

A. Synthesis of C-carbamoyl-1, 2, 3-triazoles

Recently, this laboratory group has been involved in microwave induced 1,3-dipolar cycloaddition of organic azides to acetylenic amides. As shown in Scheme 29 we were able to achieve these reactions under microwave conditions in a reasonable time at temperatures of around 70±15 °C. Under conventional conditions the times were roughly 100 times as long and the temperature had to be taken up to 120 °C [145].

![Scheme 29]

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Ph</td>
<td>H</td>
<td>CONHCH₂Ph</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>H</td>
<td>COPip.</td>
<td>63</td>
</tr>
<tr>
<td>9</td>
<td>Ph(CH₂)₂</td>
<td>H</td>
<td>CONHCH₂Ph</td>
<td>62</td>
</tr>
<tr>
<td>10</td>
<td>Ph(CH₂)₂</td>
<td>H</td>
<td>COPip.</td>
<td>65</td>
</tr>
<tr>
<td>11</td>
<td>C(CH₃)(CH₂OCH₂)</td>
<td>H</td>
<td>CONHCH₂Ph</td>
<td>84</td>
</tr>
<tr>
<td>12</td>
<td>C(CH₃)(CH₂OCH₂)</td>
<td>H</td>
<td>COPip.</td>
<td>80</td>
</tr>
</tbody>
</table>

*Isolated yield of major regioisomer. Scheme-29

1.4.2.8 Oxidation

The osmium-catalyzed dihydroxylation reaction, the addition of osmium tetroxide to olefins to produce a vicinal diol, is one of the most selective and reliable organic transformations. Recent work by Sharpless, Fokin, and coworkers [146] has uncovered that electron-deficient olefins can be converted into the corresponding diols much more efficiently when the reaction medium is kept acidic (Scheme 30).
1.5 AQUA MEDIATED ORGANIC SYNTHESIS (AMOS): A BRIEF REVIEW

The medicinal chemistry community has been under increased pressure to produce, in an environmentally benign fashion, the myriad of drugs required by society in short periods of time. Because of high molecular complexity in drug discovery processes accompanied by time constraints, the primary driver of pharmaceutical green chemistry has become the development of efficient and environmentally benign synthetic protocols. This can be achieved through the proper choice of starting materials, atom economic methodologies with a minimum number of chemical steps, the appropriate use of greener solvents and reagents, and efficient strategies for product isolation and purification. Thus, green chemistry has emerged as a discipline that permeates all aspects of synthetic chemistry. A major goal of this endeavor must then be to simultaneously maximize the efficient use of safer raw materials and to reduce the waste produced in the process.\[147]\)

There is a variety of approaches for the development of sustainable methods, which reflects the enormity and complexity of this field. Alternative reaction media is one of the ways to make a protocol greener. However, solvent replacement in itself may not be enough. The whole process must be well thought-out, and the solvent is only one part of this puzzle. The atom efficiency, energy uses and deployment of renewable resources must also be taken into account. Solvents define a major part of the environmental performance of processes in chemical industry and also impact cost, safety, and health issues. Being volatile and highly inflammable, they are the main root of environmental pollution and are high on the green-chemistry agenda.
Use of solvents in reactions cannot be avoided as they are necessary for various processes like the mixing of reactants, constant and uniform supply of energy by transfer of heat, and in some cases, control of the regio- and chemo-selectivity of reactions. However, the use of organic solvents for isolation and purification of products (which involves the use of large amounts per mass of final products) can be prevented or minimized by developing atom-economic synthetic methods, which selectively generate the desired product without producing any by-products.

Environmental improvements, in terms of solvents, can be achieved by implementing several alternative methodologies as described below:

(1) Replacement of hazardous solvents with those that show superior ecological, health, and safety properties.

(2) Bio-solvents: solvents produced with renewable resources such as ethanol produced by fermentation of sugar containing feeds and starchy feed materials.

(3) Substitution of organic solvents with supercritical fluids such as CO$_2$ that are environmentally benign, and with benign ionic liquids that have low vapor pressure, and thus, curb release into the environment.

(4) Biphasic technologies: using fluorous and regenerable ionic liquids along with aqueous systems and supercritical carbon dioxide.

### 1.5.1 Is Water the Green Solvent?

The idea of “green” solvents expresses the goal to minimize the environmental impact resulting from the use of solvents in chemical production, thus identifying green solvents is a top priority for the organic chemist. Use of no-solvent, i.e. solvent free reactions is another solution, however, this may work for only a few reactions; a lack of reaction medium may lead to overheating of the reaction mixture, in view of the poorly understood heat- and mass-transfer issues. Biphasic technologies, using fluorous and ionic liquids along with aqueous systems and supercritical carbon dioxide, have formed the main thrust of this movement. However, the cost and toxicity of ionic liquids are big concerns in using them as a solvent. Thus, naturally abundant water appears to be a better option because of its non-toxic, non-corrosive and non-flammable nature. Also, water can be contained...
because of its relatively high vapor pressure as compared to organic solvents, which are favorable traits to render water as a sustainable alternative.

**1.5.2 What are the limitations of water as a solvent?**

The main difficulty with water as a solvent is that most organic substrates are insoluble in it, which makes the reaction mixture heterogeneous. This can be overcome by using phase transfer catalysts, but this will cause the process to be more expensive. Also, the isolation of products from aqueous medium is another concern. For this, evaporation of water from the reaction mixture may be an option, but this is not an energy-efficient process. However, some of these issues can be overcome by using microwave (MW) heating for reactions in aqueous medium.

**1.5.3 How do microwaves promote the reaction in aqueous medium?**

Water is rapidly heated to high temperatures under microwave irradiation, enabling it to act like a pseudo-organic solvent. Also, precise control of the reaction temperature can be achieved efficiently because of the very high heat capacity of water. MW-enhanced chemistry is based on the efficiency of the interaction of molecules in a reaction mixture (substrates, catalyst and solvents) with electromagnetic waves generated by a “microwave dielectric effect”. This process mainly depends on the specific polarity of molecules. Since water is polar in nature, it has good potential to absorb microwaves and convert them to heat energy, thus accelerating the reactions in an aqueous medium as compared to results obtained using conventional heating [153].

This can be explained by two key mechanisms: dipolar polarization and ionic conduction of water molecules (Fig. 2). Irradiation of a reaction mixture in an aqueous medium by MW results in the dipole orientation of water molecules and reactants in the electric field.

This causes two distinguishing effects:

**(i) Specific microwave effect:** The electrostatic polar effects which produce the dipole–dipole type interaction of the dipolar water molecules and reactants with the electric field component of MW, resulting in energy stabilizations of an electrostatic nature (Fig. 2b). This concept of a specific MW (non-thermal) effect is controversial.
and the subject of debate among various chemists. Recent studies by Kappe et al. have shown that this effect is essentially due to thermal phenomena and is thus, not non-thermal; however, more in-depth study is required to obtain a definite answer. 

(ii) Thermal effect: the dielectric heating that ensues from the tendency of dipoles (mostly water molecules in addition to reactants) to follow the inversion of alternating electric fields and induce energy dissipation in the form of heat through molecular friction and dielectric loss, which allows more regular repartition in reaction temperatures compared to conventional heating (Fig. 2c).

![Mechanism of Aqueous Microwave Chemistry](image)

Fig. 2 Effect of microwaves on the reaction mixture in aqueous medium.

1.5.4 How does aqueous chemistry expedite Organic synthesis?

MW-assisted chemistry has blossomed into a useful technique for a variety of applications in drug discovery and organic synthesis. Although MW-assisted reactions in organic solvents have developed rapidly, the focus has now shifted to the
more environmentally benign methods, which use greener solvents and supported renewable catalysts. There are many examples of the successful application of MW-assisted chemistry to organic synthesis; these include the use of benign reaction media, solvent-free conditions, and the use of solid supported and reusable catalysts. As with most organic solvents, the loss tangent (\(\tan \theta\)) for water is strongly influenced by temperature. Since the dielectric constant \(\epsilon\) for water drastically decreases with temperature (Table 2), the dielectric loss \(\epsilon\cdot\epsilon\) and therefore the loss tangent are also reduced. For that reason it is not a trivial affair to heat pure water to high temperatures under microwave conditions. While water can be heated rather effectively from room temperature to 100 °C, it is more difficult to superheat water in sealed vessels from 100 to 200 °C and very difficult to reach 300 °C by microwave dielectric heating. In fact, SCW is transparent to microwave radiation. Thus in this manner the organic reaction gets accelerated.

### Table 2: Properties of Water Under Different Conditions

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Ordinary Water ((T &lt; 150 °C, p &lt; 4 \text{ bar}))</th>
<th>Near-Critical Water ((T = 150−350 °C, p = 4−200 \text{ bar}))</th>
<th>Supercritical Water ((T &gt; 374 °C, p &gt; 221 \text{ bar}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temp ((°C))</td>
<td>25</td>
<td>250</td>
<td>400</td>
</tr>
<tr>
<td>Pressure (bar)</td>
<td>1</td>
<td>50</td>
<td>250</td>
</tr>
<tr>
<td>Density ((\text{g cm}^{-3}))</td>
<td>1</td>
<td>0.8</td>
<td>0.17</td>
</tr>
<tr>
<td>Dielectric constant (\epsilon)</td>
<td>78.5</td>
<td>27.1</td>
<td>5.9</td>
</tr>
<tr>
<td>pKw</td>
<td>14</td>
<td>11.2</td>
<td>19.4</td>
</tr>
</tbody>
</table>

* Data from ref 26.

The loss tangent of a solvent such as water in other words the ability of the medium to convert electromagnetic energy into heat can be significantly increased, for example, by addition of small amounts of inorganic salts. The electric component of an electromagnetic field causes heating by two main mechanisms: dipolar polarization and ionic conduction. When irradiated at microwave frequencies, the dipoles or ions of the sample align in the applied electric field. As the applied field oscillates, the dipole or ion field attempts to realign itself with the alternating electric field, and in the process, energy is lost in the form of heat through molecular friction...
and dielectric loss. The amount of heat generated by this process is directly related to the ability of the matrix to align itself with the frequency of the applied field. From a chemical point of view, introduction of ions into a solution leads to a marked increase in dielectric heating rates due to the ionic conduction mechanism. Thus the organic reactions are accelerated.

1.5.5 Some Examples of Microwave Assisted Organic Synthesis Using Water as Solvent

1.5.5.1 Transition Metal Catalyzed Reactions

Homogeneous and heterogeneous transition-metal-catalyzed carbon-carbon and carbon-heteroatom bond-forming reactions represent one of the most important reaction types performed in MAOS. These reactions, which are known to need hours or days for completion, often in an inert atmosphere, can be conducted very efficiently in a rapid manner under microwave heating.

A. Suzuki Reaction

The Suzuki reaction (palladium-catalyzed cross-coupling of aryl halides with boronic acids) is one of the most often used C-C cross-coupling reactions and displays a convenient method for the synthesis of biaryls. Leadbeater and Marko reported in 2002 on the ligand free palladium-catalyzed Suzuki couplings of aryl halides with boronic acids using water as solvent \[157\]. Palladium acetate loadings as low as 0.4 mol % proved to be sufficient, and with addition of 1 equiv of the phase-transfer catalyst tetrabutylammonium bromide (TBAB), aryl bromides and iodides could be coupled successfully in high yields and short reaction times (Scheme-31).
Scheme 31 (a) & (b) are other 2 examples of Suzuki coupling wherein the scientists have synthesized the Pyridazinones successfully which by themselves proved to be a potent $\alpha_4$-integrin receptor antagonists.

B. Heck Reaction

Palladium-catalyzed vinylic substitution, also known as the Heck reaction, is generally performed with aryl halides and alkenes. In recent years, development of “ligand-free” palladium-catalyzed protocols has gained much interest. Arvela and Leadbeater reported on Heck couplings of aryl halides with styrene and acrylic acid, respectively, applying their aqueous ultra low palladium protocol developed for Suzuki couplings (Scheme 14) $^{[158]}$. Palladium concentrations down to 0.5-1 ppm are sufficient for the coupling at 170 °C for 10-20 min, although a limited substrate scope was observed. Interestingly better yields were obtained by stirring of the reaction since it is believed that the reaction takes place at the aqueous/organic interface, and with stirring the aryl halide would be exposed to the basic aqueous medium, resulting in faster decomposition $^{[160]}$. A 10-fold scale up performing the reaction in a stop-flow microwave approach was possible with only a slight change in time (20 vs 10 min) and solvent. Here, a mixture of water/DMF 7:1 proved to be better with respect to pumping the reaction mixture through the lines $^{[159]}$. 

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C. Sonogashira Reaction

The Sonogashira reaction (palladium and copper co-catalyzed coupling of terminal alkynes with aryl and vinyl halides) is a general method for the preparation of unsymmetrical alkynes. In recent years, investigations toward the design of new catalyst systems or protocols for copper-free reactions have been made. The group of Na’jera has performed aqueous copper-free Sonogashira couplings of aryl bromides and iodides with phenylacetylene, applying both polymeric complex 35 and the monomeric 36 as catalyst (see Chart 2), pyrrolidine as base, and TBAB as additive [161]. Under conventional heating better yields in shorter reaction times could be achieved for the polymeric complex; additionally dimerization of the alkyne was decreased. Applying microwave heating for the reaction of 4-chloro-bromobenzene with phenylacetylene, lower yields were obtained for 0.1 mol % of catalyst 35 than for the monomeric 36 (47 vs 66%) (Scheme 33).
D. Stille Reactions

Very few examples are known of microwave-assisted Stille reactions involving organo-tin reagents as coupling partners. In the course of scaffold decorations of the 2(1H)-pyrazinone core 39, the Stille reaction at the C-3 position was performed by Van der Eycken and co-workers (Scheme 34) [162]. For tetraphenyltin a higher temperature (200 °C) had to be applied in order to achieve full conversions. A great acceleration compared to conventional heating in refluxing toluene could be reached (3 days vs. 15 min), albeit the yields being somewhat lower for the aqueous microwave synthesis.

E. Hiyama Reaction

The Hiyama reaction (palladium-catalyzed cross-coupling of organo-silicon compounds with organic halides) has become a good alternative to other coupling reactions which employ different organo-metallic reagents from an environmental point of view since the organo-silicon compounds are attractive because of their stability, ease of handling, and/or low toxicity [163]. Several types of organo-silicon reagents have been applied for this carbon-carbon bond-forming reaction such as alkyl-, fluoro-, chloro-, hydroxy-, and alkoxysilanes. In general, Hiyama couplings are promoted by the fluoride anion, usually obtained from tetrabutylammonium fluoride (TBAF), but recently it was found that inorganic bases like KOH, NaOH, and K₂CO₃ are also able to promote the reaction in water as solvent under fluoride-free conditions [164].
F. **Carbonylation Reaction**

For the palladium (0)-catalyzed carbonylations of aryl halides to give aromatic acid derivatives (e.g., acids, amides, esters) the group of Larhed developed a rapid microwave assisted procedure where solid Mo(CO)$_6$ is used as carbon monoxide source \[165\]. Very recently the authors additionally showed that amino carbonylations can also be conducted in water as solvent, the amine being a better nucleophile than water \[166\]. Aryl iodides, bromides, and even the otherwise unreactive chlorides could be reacted with diverse primary and secondary amines to the aryl amide products in moderate to excellent yields (Scheme 36 a). The competing hydroxy carbonylation could be inhibited by fine tuning of the reaction parameters; in particular, the stoichiometry of aryl halide to amine was crucial for the successful reaction as well as the proper catalyst. With this general protocol, aryl iodides could be reacted at 110 °C whereas the bromides and chlorides needed the higher temperature of 170 °C and sometimes longer reaction times.

Aqueous hydroxycarbonylations of aryl and vinyl triflates were reported by Silvani and co-workers \[167\]. A concentration of 0.1 equiv of the catalyst/ligand system Pd(OAc)$_2$/dppf (1,1'-bis(diphenylphosphino)ferrocene), pyridine as base, and Mo(CO)$_6$ as CO source proved to be the best conditions (Scheme-36 b). By heating to 150 °C for 20 min, moderate to excellent yields for aryl carboxylic acids were achieved. Complete chemoselectivity was obtained for halogenated aryl triflates, affording only the halogenated aryl carboxylic acids.
G. Cyanation Reaction

Preparation of aryl nitriles from aryl iodides using CuCN was disclosed by Leadbeater and co-workers (Scheme 37)\textsuperscript{[168]} Key to the success of this reaction is the addition of TBAB as phase-transfer agent and a high concentration of cyanide, resulting from a 1:2 ratio of aryl halide/CuCN. Conventional heating under identical conditions resulted in no product; also, activated aryl bromides did not show any conversion. The reaction can also be performed when less expensive NaCN in combination with Cul is employed, forming CuCN in situ.
1.5.5.2 N-, O-, S- Functionalization Reactions

A. N-Acylations

In the transformation of fused succinic anhydrides 51 with hydrazines to the fused N-aminosuccinimide derivatives of bicyclo[2.2.2]oct-7-enes 52, microwave heating in aqueous media proved to be very efficient (Scheme 38) \(^{[169]}\). Compared to conventional heating the reaction times could be reduced from several hours to 13-90 min, less hydrazine was necessary (2.2-2.4 vs 10 equiv), and most importantly, cleaner conversions were achieved, giving the products in high yields (80-94%).

```
<table>
<thead>
<tr>
<th>R^1</th>
<th>R^2</th>
<th>R^3</th>
<th>R^4, R^5</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>H, Me, Ph, pyridyl</td>
</tr>
</tbody>
</table>

**Scheme-38**
```

B. N-Alkylations

Varma and Ju reported on the synthesis of tertiary amines via N-alkylation of primary and secondary amines (aromatic, cyclic, and noncyclic) with alkyl halides (Scheme 39) \(^{[170]}\). By applying microwave heating (open vessel, 45-100 °C), not only could the reaction time be reduced from 12 h to 20-30 min but also formation of side products, mainly secondary amines, could be suppressed. Water as solvent, compared to solventless conditions, MeCN and PEG300, proved to be the best choice in regard to product yield and environmental friendliness.

```
| Scheme-39 |
```

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C. N-Arylation

Yadav and co-workers disclosed base-free inter- and intramolecular N-arylations promoted by active copper \[^{171}\] . Reactions of aryl halides with amines, amides, imides (Scheme 40 a), and α-lactams (Scheme 40 b) proceeded under very mild conditions. Key to the successful intramolecular N-arylations of α-lactams is the absence of a base since decomposition of the starting material is otherwise observed. Interestingly, a protocol with irradiation for 2 min at 85-90 °C and subsequent mixing for 2 min outside the microwave instrument was applied (this irradiation-mixing cycle was repeated until completion of the reaction was detected; times given in Scheme 40 correspond to total irradiation times). Similar or lower yields, especially in the case of α-lactam derivatives, were achieved by performing the reaction under solvent-free microwave conditions.

![Scheme 40](attachment:image.png)

D. O- & S- Functionalization

A combined microwave and ultrasound (US) protocol for the Williamson ether synthesis from phenols and aryl or alkyl chlorides, respectively, was disclosed by Song and Peng (Scheme 41 a) \[^{172}\] . This rather uncommon combination, which is performed in a custom-built instrument, proved to give higher yields in much shorter reaction times compared to only microwave heating or sonication \[^{173}\] . With an ultrasound power of 50 W and a microwave power of 200 W, diphenyl and benzyl phenylethers were obtained in moderate to good yields very rapidly in 60-150 s. A
second “green” aspect in this heterogeneous synthesis is the absence of an otherwise required phase-transfer catalyst.

The group of Vanelle reported formation of new sulfonylmethylbenzothiazole derivatives which show significant cytotoxic activity [174]. The synthesis proceeds via aqueous \( S \)-alkylation of sodium salts of diverse substituted sulfinic acids with 2-chloromethyl-6-nitrobenzothiazole (Scheme 41b). All experiments were also conducted under conventional heating at the same temperature (100 °C), affording products in similar or lower yields in 24 h. Hence, the authors assumed that specific microwave effects due to a more polar transition state are responsible for the higher yields achieved by microwave heating.

![Scheme-41](image)

1.5.5.3 Heterocyclic Synthesis

A. Five membered N-Heterocycles

Molteni and co-workers described the three-component, aqueous one-pot synthesis of fused pyrazoles by reacting cyclic 1,3-diketones with \( N,N \)-dimethylformamide dimethyl acetal (DMFDMA) and a suitable bidentate nucleophile like a hydrazine derivative (Scheme 42) [175]. The reaction proceeds via initial formation of an enamino ketone in situ followed by a tandem addition-elimination/cyclodehydration step. An amount of 2.6 equiv of acetic acid is necessary to ensure a clean conversion at 200 °C within 2 min. For 1,3-cyclopentanediione (\( n \) 0), \( p \)-toluenesulfonic acid has to be used instead of AcOH at lower temperatures but...
with longer irradiation time (120 °C, 10 min) to afford the corresponding pyrazole in 27% yield. Pyrimidines and isoxazoles could be synthesized as well applying the same protocol employing amidines and hydroxylamine as nucleophiles.

**B. Six Membered O-Heterocycles**

Aromatic substitution by activated methylene compounds (1,3-diketones) with base and stoichiometric amounts of a copper(I) catalyst leads to different isochromenone derivates depending on the temperature, pressure, and nature of the activating methylene groups which was shown by the Bryson group (Scheme 43). Under standard reflux conditions (NaH, Cu+) in THF, isochromene is obtained as the main product after acidification, whereas under microwave irradiation (KOH, Cu+) in water at 100-150 °C (3-14 bar) it is the minor product and deacylated isochromene the main product (55-70%) due to cleavage of the acyl group in the high-temperature water media.

**C. Six Membered N-Heterocycles**

A well-known method for the preparation of Heterocycles is the Hantzsch dihydropyridine (DHP) synthesis. Ohberg and Westman presented a fast procedure for this multicomponent, one-pot condensation of an aldehyde, α-ketoester, and aqueous ammonium hydroxide, which was used as both reagent and solvent (Scheme
44) [176]. Best yields were obtained by exposing the reaction mixture to microwave heating at 140-150 °C for 10-15 min. Additionally, a small library of 24 compounds as prepared by applying a fully automated microwave instrument within hours.

![Scheme-44](image1)

D. **Six membered N, S- Heterocycles**

In order to evaluate the structure-activity relationship for the binding of phenothiazine derivatives to HIV-1 TAR RNA the group of James synthesized a small focused library of 10H-phenothiazines with novel substitution patterns around the ring system (Scheme 48) [177]. The synthesis proceeded by an iodine-catalyzed reaction of diarylamines with sulfur in doubly distilled water at 190 °C within 20 min in acceptable to moderate yields. Due to the hydrophobicity of the 10H-phenothiazine products, they directly precipitated upon cooling and could be isolated by filtration.

![Scheme-45](image2)

**1.5.5.4 Mannich Type Multi component Reaction**

The Mannich reaction is one of the most important transformations leading to \( \alpha \)-aminoketones. Although the reaction is powerful, it suffers from some disadvantages, such as the need for drastic conditions, long reaction times, and sometimes low yields of products. The group of Song reported on the Mannich
reaction of acetophenones, secondary amines in the form of their hydrochloride salt, and trioxymethylene as formaldehyde source (Scheme 46) \[^{178}\].

**1.5.5.5 Nucleophilic Aromatic Substitution**

The group of Van der Eycken explored the synthesis of pyrido-fused heterocycles which was performed in \(n\)-BuOH as solvent under microwave irradiation and usually consists of three steps: nucleophilic substitution, Knoevenagel condensation, and ring closure applying the \(\text{tert-amine effect}\) \[^{179}\]. In a case study, the authors were successful in performing all three reactions in water as solvent. Nucleophilic substitution of \(o\)-fluoro-benzaldehyde with pyrrolidine at 130 °C for 3 min gave intermediate, which was found to be converted to the pyrrolobenzoxazine by further heating at 210 °C for 50 min in 28% yield (Scheme 47).

**1.5.5.6 Epoxide ring opening reaction**

Recently, Pironti and Colonna described the synthesis of \(\alpha\)-hydroxy sulfides via the aqueous thiolysis of epoxides with thiophenol in the presence of a catalytic amount of NaOH (Scheme 48) \[^{180}\]. The ring opening proved to be completely anti stereoselective, and the trans products were obtained in excellent yields (six
examples, 85-98%). Additionally, a one-pot procedure was developed for the synthesis of $\delta$-hydroxy sulfoxide.

![Scheme 48](image)

### 1.5.5.7 Diels Alder Cycloaddition Reaction

Enhanced rate accelerations in Diels-Alder cycloadditions due to the combined effects of a water-soluble organotungsten Lewis acid catalyst (105), water as solvent, and microwave heating were observed by Yu and co-workers[181]. All reactions were completed in less than 1 min at 50 °C employing 3 mol % of the Lewis acid catalyst 105 (Scheme 49). When the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate (bmimPF$_6$) is employed as solvent, even higher accelerations were possible, the reactions being completed within 30 s. Another advantage of the ionic liquid medium is the higher degree of catalyst recovery. Lewis acid 105 can be reused up to 10 times without significant activity loss, whereas a 20% decrease in conversion after the sixth cycle was obtained for the water recovery.

![Scheme 49](image)
1.6 Biological and Medicinal significance of Pyrimidines and other related heterocyclic scaffolds

Many heterocyclic structures have been identified in various ways and they have shown potent biological activity starting from classical vitamins to modern drugs/receptor based drug molecules. A fair review of these heterocyclic scaffolds is mentioned here in a concise manner especially related to the subsequent chapters on synthetic aspects.

1.6.1 Biological significance

Pyrimidines have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in the chemotherapy of AIDS.

Alloxan (1) is known for its diabetogenic action in a number of animals \(^{182}\). Uracil (2), thymine (3) and cytosine (4) are the three important constituents of nucleic acids.

The pyrimidine ring is found in vitamins like thiamine (5), riboflavin (6) and folic acid (7) \(^{183}\). Barbitone (8), the first barbiturate hypnotic, sedative and anticonvulsant are pyrimidine derivatives.
1.6.2 Medicinal Significance.

During the last two decades, several pyrimidines derivatives have been developed as chemotherapeutic agents and have found wide clinical applications.

1.6.2.1 Antineoplastic / Anticancer agents

There are a large number of pyrimidine-based anti metabolites. Usually, they are structurally related to the endogenous substrates that they antagonize. The structural modification may be on the pyrimidine ring or on the pendant sugar groups.

One of the early metabolites prepared was 5-fluorouracil (5-FU, 9a) \(^{184, 185}\), a pyrimidines derivative. 5-Thiouracil (9b) also exhibits some useful antineoplastic activities \(^{186}\). The antineoplastic compounds \(^{187}\) possessing the guanine nucleus (10) like azathioprine (11) \(^{188}\), mercaptopurine (12) \(^{189}\), thioguanine (13) \(^{190}\), tegafur (14) \(^{191}\), etc. were discovered after formulation of the antimetabolite theory by Woods and Fildes in 1940. These drugs prevent the utilization of normal cellular metabolites.
There are many more in recent times, like mopidamol (15)\textsuperscript{[192]}, nimustine (16)\textsuperscript{[193]}, raltitrexed (17)\textsuperscript{[194]}, uramustine (18)\textsuperscript{[195]} and trimetrexate (19)\textsuperscript{[196]}. 1-β-D-Arabinosylcytosine (Ara-C, 20)\textsuperscript{[197]} is also an example of a pyrimidine antimetabolite in which the sugar is arabinose having a beta configuration. It is mainly used as an anticancer agent and also exhibits significant therapeutic effects in patients with herpes virus infections and herpes encephalitis. Gemcitabine (21), a pyrimidine antimetabolite, shows excellent antitumour activity against murine solid tumours\textsuperscript{[198]}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chemical_structures.png}
\caption{Chemical structures of some drugs and metabolites.}
\end{figure}

**1.6.2.2 Drugs for Hyperthyroidism**

2-Thiouracil (9c) and its alkyl analogue, thiobarbital (9e) are effective drugs against hyperthyroidism. Propylthiouracil (9d) is used as a drug for hyperthyroidism with minimum side effects\textsuperscript{[199]}.
1.6.2.3  Antifolates, Antibacterial, & Antiprotozoals

In 1948, Hitchings made an important observation that a large number of 2,4-diaminopyrimidines and some 2-amino-4-hydroxypyrimidines are antagonists of folic acid \[200\]. Since then, a large number of 2,4-diaminopyrimidines have been synthesized as antifolates. It was eventually proved that these pyrimidines are inhibitors of the enzyme dihydrofolate reductase (DHFR) \[201, 202\]. Notable amongst the 2,4-diaminopyrimidine drugs are pyrimethamine (22), a selective inhibitor of the DHFR of malarial plasmodia; trimethoprim (23), an antibacterial drug which selectively inhibits bacterial DHFR and most importantly, the very potent but non selective DHFR inhibitors, methotrexate (24a) and aminopterin (24b), both used in cancer chemotherapy \[203\]. 3’,5’-dichloromethotrexate (24c), which is less toxic and more readily metabolized than methotrexate, has recently been introduced for anticancer therapy \[204\]. Brodimoprim (25) is also found to be an effective antibacterial compound \[205\].
1.6.2.4  **Sulfa Drugs**

Pyrimidine derivatives of sulfa drugs, namely sulfadiazine, sulfamerazine and sulfadimidine are superior to many other sulfonamides and are used in some acute UTIs, cerebrospinal meningitis and for patients allergic to penicillins \[^{206}\]. Sulfonamide–trimethoprim combinations are used extensively for opportunistic infections in patients with AIDS \[^{207}\]. Sulfadoxine (26a) \[^{208}\], a short and intermediate acting sulfonamide with a half-life of 7–9 days is used for malarial prophylaxis. Sulfisomidine (26b) with a half-life of 7 h is used as a combination sulfa therapy in veterinary medicine \[^{209}\]. Sulfadiazine (27a), sulfamerzine (27b) and sulfadimidine (27c) possess good water solubility and therefore carry minimum risk of kidney damage, which makes them safe even for patients with impaired renal functions.

In 1959, sulfadimethoxine (27d) \[^{210}\] was introduced with a half-life of approximately 40 h. The related 4-sulfonamidopyrimidine, sulfamethoxine (28) \[^{210}\] having two methoxy groups at 5 and 6 positions, has by far the longest half-life of about 150 h. Methyl diazine (27e) \[^{210}\] has a half-life of 65 h. Also, sulfamethoxy diazine (27f) \[^{210}\] possesses good half-life. A new broad-spectrum sulfonamide, sulfamethomidine (29) \[^{210}\] is relatively nontoxic and patients do not need extra fluid intake or alkalization. Sulfacytine (30) has been reported to be 3–10 times more potent than sulfaisoxazole and sulfisodimidine \[^{210}\].
1.6.2.5  Antivirals & Anti-AIDS

Recently, pyrimidine derivatives have generated widespread interest due to their antiviral properties. 5-Iododeoxyuridine (31) \(^{[211]}\) is an antiviral agent of high selectivity. IDU (5-iodo-2’-deoxyuridine) (32a) has been extensively utilized for viral infections. 5-Trifluromethyl-2’-deoxyuridine (F3 TDR, 32b) has been found useful against infections resistant to IDU therapy \(^{[211]}\). Ara-A, 9-\(\beta\)-D-arabinofuranosyl adenine (33), a relatively new antiviral drug, is effective against herpes infections of eye, brain and skin. It is especially effective against IDU-resistant herpes virus \(^{[211]}\).

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Some purine nucleosides are equally noteworthy. Retrovir (AZT-16, 34) is a potent inhibitor of the \textit{in vivo} replication and cytopathic effects of HIV and has been recently approved for use against AIDS and severe ARC \(^{[212]}\). At present, Acyclovir (35a) is the only remedy for genital herpes. The oral formulation of Acyclovir is effective against both first and second degree recurrence genital herpes with minimal
side effects. Ganciclovir (35b) has shown good in vivo activity against HCV1&2.

Several members of a series of acyclic nucleosides, which contain a fused pyrimidine ring (mainly purine), are found to be effective antivirals. Famiciclovir (35c) and valaciclovir (35d) are drugs used for several DNA viruses, including HSV types 1 and 2, Varicella-zoster virus and Epstein-Barr virus. Penciclovir (35e) is useful for topical treatment of recurrent herpes, Libialis. Cidofovir (36b), an antimetabolite for deoxycytosine triphosphate is used for the treatment of cytomegalovirus (CMV) in AIDS patients. Lamivudine (36a) is an effective antiviral...
AIDS drug when used in combination with zidovudine (37) \cite{216}. Zidovudine \cite{217} is an analogue of thymidine in which the azido group is substituted at the 3-position of the dideoxyribose moiety. It is active against RNA tumour viruses (retroviruses) that are the causative agents of AIDS and T-cell leukaemia. It is used in AIDS and AIDS related complex (ARC) to control opportunistic infections by raising absolute CD4+ lymphocyte counts. Also, zalcitabine (38) \cite{217} is another useful alternative drug to zidovudine. It is given in combination with zidovudine, when CD4+ cell count falls below 300 cells/mm3. Didanosine (39) \cite{218} is a purine dideoxynucleoside, which is an analogue of inosine. Didanosine inhibits HIV RT and exerts a virustatic effect on the retroviruses. Combined with zidovudine, antiretroviral activity of didanosine is increased. Stavudine (40) \cite{218} is a pyrimidine nucleoside analogue that has significant activity against HIV-1 after intracellular conversion of the drug to a D4T-triphosphate. It is more effective than zidovudine or didenosine for treatment in patients for delaying the progression of HIV infection. It is recommended for patients with advanced HIV infection. Abacavir sulfate (41) \cite{218} was approved in 1998 as a NRTI (Nucleoside Reverse Transcriptase Inhibitor) to be used in combination with other drugs for the treatment of HIV and AIDS. The major use of abacavir appears to be in combination with other NRTIs.

### 1.6.2.6 Antibiotics

There are few examples of pyrimidine antibiotics. The simplest of all is bacimethrin (5-hydroxymethyl-2-methoxypyrimidin-4-amine) (42), which is active against several staphylococcal infections \cite{219}. Gourgetin (43), a cytosine derivative is active against mycobacteria as well as several Gram-positive and Gram-negative bacteria \cite{220}. There are more derivatives of cytosine, namely amicetin (44) and plicacetin (45), which exhibit activity against acid fast and Gram-positive bacteria as well as some other organisms \cite{219}. Puromycin (46) has a wide spectrum of antitrypanosomal activity. Aminoglycoside antibiotics phleomycin (47a), bleomycin (47b) and related families are wide-spectrum antibiotics containing the pyrimidine ring. Another antibiotic tubercidine (48) is reported to exhibit antitumour properties \cite{220}. In addition, they have antineoplastic activity. Bleomycin is already in clinical use against certain tumours like Hodgkin’s lymphoma and disseminated testicular cancer \cite{221}.  

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Department of Chemistry, Saurashtra University, Rajkot 360 005
Part 1 “Investigations of some Aqua mediated as well as microwave assisted…”
1.6.2.7 Antifungals

Pyrimidines also exhibit antifungal properties. Flucytosine (49) \[222\] is a fluorinated pyrimidine used as nucleosidal antifungal agent for the treatment of serious systemic infections caused by susceptible strains of candida and Cryptococcus \[223\]. Hexetidine (50) \[224\] is mainly used for the treatment of aphthous ulceration.

![Chemical structures of Flucytosine and Hexetidine](image)

1.6.2.8 Anthelmentics

These drugs have the ability of ridding the body of parasitic worms. Pyrantel pamoate (51) is a depolarizing neuromuscular blocking agent that causes spastic paralysis in helminthes and is employed in the treatment of infestations caused by pinworms and roundworms \[225\].

![Chemical structure of Pyrantel pamoate](image)
1.6.2.9  Antitubercular Drug

![Chemical structure of Capreomycin]

Capreomycin (52) produced by *Streptomyces capreolus* is a second-line bacteriostatic antituberculin drug containing pyrimidine [226, 227].

![Chemical structure of Viomycin]

Viomycin (53) is more tuberculostatic than *p*-aminosalicylic acid. It is effective in the treatment of experimental tuberculosis.
1.6.2.10  CNS active agents

A. Sedative / Hypnotic / Antiepileptic agents

Agents of the anxiolytic, sedative and hypnotic group include a wide variety of barbiturates (54a–i) used as sedative and hypnotics and are classified as drugs having short, intermediate and long duration of action [228, 229]. Allobarbital (54a), aprobarbital (54b), pentobarbital (54e), phenobarbital (54g) and secobarbital (54i) are frequently used clinically as hypnotic barbiturates [230]. Hexobarbital (54c), cyclobarbital (54d) and propallylonal (54f) are some of the current drugs in the market used as sedative hypnotics [231]. Barbiturates as sedative hypnotics have a long and fascinating history. In fact Eli Lilly [232] patented secbutabarital (54h) in 1932, while barbitone (8), the first of the barbiturates was introduced in 1903.

B. Anxiolytic Agents

Few of the pyrimidine derivatives are also used as anxiolytics. Most important of these is buspirone (55), indicated in the management of anxiety disorders accompanied with or without depression. It lacks sedative, anticonvulsant and muscle relaxant effects and most importantly abuse potential [233]. Buspirone lacks affinity
to benzodiazepine receptors, but binds avidly to one subclass of serotonin receptors, the 5-HT1A subtype \[^{234, 235}\]. Ritanserin (56), a 5HT2 antagonist with anxiolytic activity is a pyrimidine derivative \[^{236}\]. A simple pyrimidine derivative, mezilamine (57) is classified as an antipsychotic agent \[^{237}\]. Risoperidone (58) is an antipsychotic drug, which is a structural hybrid of butyrophenone and can be used as anxiolytic, antidepressant and antiparkinsonian drug \[^{238}\].

### C. Pyrimidine Anaesthetics

Thimylal (59) is a short acting general anaesthetic drug, which is also a pyrimidines analogue \[^{239, 240}\].

Saxitoxin (60) is a naturally occurring pyrimidine containing anaesthetic agent, but is too toxic to be of clinical use. Saxitoxin is isolated from some marine dinoflagellates.
D. Diuretics & Uricosurics

Several xanthine derivatives (61) containing fused pyrimidine ring systems like caffeine (61a) \(^{[241]}\), etamiphylline (61b) \(^{[242]}\), lomiphylline (61c) \(^{[243]}\), etophylline (61d) \(^{[244]}\), theophylline (61e) and theodrendaline (61f) \(^{[245]}\) are known to promote a weak diuresis by stimulation of cardiac function and by a direct action on the nephron, acting as adenosine receptor antagonists.

There are a few examples of diuretics which contain a pyrimidine ring. Noteworthy are quinethazine (62a), metolazone (62b) \(^{[246]}\) and triamterene (63) \(^{[247]}\).
1.6.2.11 Cardiac Agents

A. Antihypertensive agents

Several pyrimidine ring-containing drugs have exhibited antihypertensive activity. Prazosin (64a), a quinazoline derivative, is a selective $\alpha_1$-adrenergic antagonist $[248, 249]$. Its related analogues bunazosin (64b) $[250]$, terazosin (64c) $[251]$ and trimazosin (64d) $[252]$ are potent antihypertensive agents. Another quinazoline derivative, ketanserin (65) $[253]$ having a similar effect is an antagonist of both $\alpha_1$-adrenergic and serotonin-S2 receptors. Its mechanism of action however is still controversial. A triaminopyrimidine derivative, minoxidil (66), whose mechanism of action and therapeutic action are similar to Prazosin, has been introduced in therapy for its side effects, in the treatment of alopecia, male baldness $[254]$. Besides these, some more pyrimidine derivatives given below were found to be antihypertensives $[255, 256]$. 

![Chemical Structures of Antihypertensive Agents](image-url)
Alfuzocin (67), a prazosin analogue and an $\alpha_1$-adrenoceptor antagonist as well as urapidil (68) are used especially in urinary obstruction caused by benign prostate hyperplasia.

B. Vasodialators

A series of xanthine derivatives are used as peripheral and cerebral vasodilators. Especially, pentifylline (69a) and pentoxifylline (69b) are used in cardiovascular disorders [257]. Other derivatives like xantinol nicotinate (70b) [258], a vasodilator with general properties like nicotinic acid used in cerebral and peripheral vascular disorders and pimefylline (70a) and pyridofylline (70c) [259] are noteworthy. A new dopamine receptor stimulant, pirebidil (71) [260] is reported to have produced significant improvement in ADL (Activity of Daily Living) in patients suffering from Parkinson’s syndrome.

\[
\begin{align*}
(69a) \text{Pentifylline} & \quad \text{R} _1 \quad \text{R} _2 \quad \text{R} _3 \\
(69b) \text{Pentoxifylline} & \quad =O \quad \text{CH}_3 \quad \text{CH}_3 \\
(69c) \text{Propentofylline} & \quad -\text{H} \quad \text{CH}_3 \quad \text{CH}_3 \\
(70a) \text{Pimefylline} & \\
(70b) \text{Xantinol nicotinate} & \\
(70c) \text{Pyridofylline} & \quad \text{H}_2 \quad \text{O} \quad \text{SO}_3\text{H} \\
(71) \text{Pirebidil} & 
\end{align*}
\]

C. Cardiotonics / Bronchodilators

Several xanthine derivatives viz., theophylline (61e), aminophylline (72a) [261] and proxyphylline (72b) [261] exhibit good bronchodilator activity.
1.6.2.12 Antihistaminic Pyrimidines

Theophylline (73) is ten times more potent than either astemizole or terfenadine in its affinity for H1-histamine binding site and appears to be devoid of CNS activity [262]. Another pyrimidine containing antihistaminic drug, temelastine (73a) is comparable to mepyramine [263]. Radiolabelled studies have indicated that it does not penetrate the CNS appreciably. Icotidine (73b), a structural analogue of temelastine lacks CNS activity and is a dual antagonist of both H1 and H2 receptors [264].
Pemirolast (74)\textsuperscript{[265]}, a new oral nonbronchodilator antihistaminic agent is also a pyrimidine derivative. It has demonstrated sufficient antihistaminic activity to warrant its use in severe asthma. Another compound, piprinhydrinate (75)\textsuperscript{[266]} is also a pyrimidine derivative.

\textbf{1.6.2.13 \textit{Analgesics} / NSAID drugs}

Acetiamine (76a)\textsuperscript{[267]}, bentiamine (76b) and fursultiamine (76c)\textsuperscript{[268]} are new lipid-soluble forms of thiamine (vitamin B1) having therapeutic use in beriberi, polyneuritis, encephalopathy, pain, malnutrition and alcoholism and especially in the treatment of long-standing insulin-dependent diabetes mellitus. Fursultamine has been reported to inhibit the arachidonic acid cascade-line activation and reverse the increase in CBF (Coronary Blood Flow).

Afloqualone (77)\textsuperscript{[269]} has been evaluated as a successful anti-inflammatory agent with lower back pain patients. Epirizole (78)\textsuperscript{[270]}, another NSAID, is suggested to be a COX-2 inhibitor. Ademetionine (79)\textsuperscript{[271]} is primarily used in conjunction to glucosamine and chondroitin therapy. Octotiamine (80)\textsuperscript{[272]}, a vitamin B1 derivative also exhibits anti-inflammatory activity. Proquazone (81)\textsuperscript{[273]}, a condensed pyrimidin-2-one derivative has been reported to exhibit good NSAID potential.
1.6.2.14 **Metabolic Electrolytes**

Orotic acid (82)\(^{274}\), a simple pyrimidine derivative and its mineral forms are used in metabolic therapy, especially for cardiovascular patients to prevent heart failure in cardiomyopathy. Oroate is needed as a key intermediate in biosynthesis of pyrimidines nucleotides,\(^{275}\) which are building blocks for DNA and RNA required for the final protein synthesis.

1.6.3 **Conclusion.**

Pyrimidines occupy a distinct and unique place in our life. This heterocyclic moiety has great biological and medicinal significance. A large array of pyrimidine drugs possesses a variety of medicinal properties. These properties include anticancer, antibacterial, antiprotozoal, antimicrobial, antiviral, antihypertensive, antihistaminic, anti-inflammatory, analgesic, CNS-active to metabolic adjuvant.

Keeping in mind various biomedical applications and with a view to further assess the pharmacological profile of bi/tricyclic aromatic heterocycles related to pyrimidines, a new class of Chromeno Pyrimidinones have been synthesized in the frame work of this doctoral thesis.
1.7 THIAZOLIDINONE: A MAGIC MOIETY

Thiazolidinone, a saturated form of thiazoles with carbonyl group on fourth carbon, has been considered as a magic moiety (wonder nucleus) which posses almost all types of biological activities. This diversity in the biological response profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring. A lot of research work on thiazolidinones has been done in the past. The nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities. Numbers of methods for synthesis by using various agents are available in the references.

1.7.1 Chemistry of Thiazolidinone

Considerable confusion concerning the structure of 4-thiazolidinones exists in the early literature and noncyclic formulas were at first proposed for pseudothiohydantoin and for rhodanine \(^{[276]}\). 4-thiazolidinones are derivatives of thiazolidine with a carbonyl group at the 4 position \(^{[277]}\). Substitution is possible at 2, 3 and 5 position. Various optical and geometrical isomers are reported in the references \(^{[278]}\). A series of regioselective isomers has been reported in some works \(^{[279, 280]}\). The carbonyl group of 4- thiazolidinone is highly unreactive. But in few cases 4-thiazolidinone on reaction with Lawesson’s reagent gives corresponding 4-thione derivatives \(^{[281]}\). A detail study of tautomerism in 2-imnothiazolidine-4-one has been done by Akerblom E. \(^{[282]}\).

1.7.2 Synthesis of 4-Thiazolidinone

Several methods for syntheses are available in literature which involves conventional one pot, two pot synthesis \(^{[283]}\) and microwave as well as combinatorial syntheses methods. The dithiocarbamates formed by the reaction of primary amine with carbon disulfide in the presence of base react with haloalkanoic acid in the presence of NaHCO\(_3\) to give substituted 2-thiono-4- thiazolidinones as presented in the scheme 50.
The synthesis of 2-imino-4-thiazolidinones-4-14C has been reported by using thiourea and sodium salt of labeled monochloroacetic acid \[284\]. Another method of synthesis of 4-thiazolidinones is by use of thiocyanate, alkyl isothiocyanate with hydrazide/acetamide followed by the treatment with ethyl bromoacetate and sodium acetate \[285\]. Schiff’s bases obtained by the condensation of ketones and amines also react with mercaptoacetic acid to give 2,2-disubstituted-4-thiazolidinones \[286\]. Desai KR et al \[287\] has carried out the microwave assisted synthesis of thiazolidinone from the Schiff’s bases (scheme 51) by using thiolactic acid. The products were synthesized by conventional and microwave synthesis and the yield were compared with each other. They concluded that the percent yield with the microwave irradiated synthesis was better than the conventional.

One pot three component synthesis containing aldehyde, thiourea and chloroform (scheme 52) to give 2-amino-4-thiazolidinone derivatives was also reported \[288\]. Various imino thiazolidinones were developed by using different reagents with different reaction conditions.
Use of task specific ionic liquid as synthetic equivalent of ionic liquid phase matrices for the synthesis of small library of 4-thiazolidinone is also possible. Ethylene glycol is functionalized in good yields with 4- (formylphenoxy) butyric acid by using DCC/ DMAP catalyst. The synthesis was performed by one pot three component condensations under microwave dielectric heating [289, 290]. Lot of work has been done on the microwave dielectric heating based techniques either one step three components or two step processes [291-295]. Microwave method is easiest and rapid method of synthesis. The yield of product obtained is better than the conventional technique. Generally environmentally benign catalysts are used for the synthesis which helps in the less pollution and lower wastage of the reagents.

1.7.3 Pharmacological importance of 4-Thiazolidinone

A. Anti-HIV activity

The anti-HIV activity of several series of 2,3-diaryl-1,3-thiazolidin-4-ones (Fig.3) has been studied. Which are reported as a new family of antiviral agents acting as NNRTI’s with minimal cytotoxicity [296-298].
2-adamantyl-substituted thiazolidin-4-ones (Fig. 4) were synthesized and evaluated for activity against HIV-1 (IIIB) and HIV-2(ROD) in CEM cell cultures, by taking Nevirapine as reference compounds\[^{299}\].

Some researchers reported 2-(2,6-dibromophenyl)-3-heteroaryl-1,3-thiazolidin-4-one derivatives as shown in the Fig 5. A positive correlation between size of the halogen substituent and HIV-RT inhibitory activity was taken as logic for the synthesis\[^{300}\].

Microwave-assisted synthesis of 2,3-diaryl-1,3-thiazolidin-4-ones (Fig.6) was performed in order to achieve striking reductions in reaction times, better yields, cleaner reactions\[^{301}\].
Recently prediction of Anti-HIV activity of 1,3,4-thiazolidinone derivatives were made on the basis of QSAR. CoMFA and CoMSIA were the two models used for the analysis. Based on the structures and biodata of previous thiazolidinone analogs, 3D-QSAR studies have been performed with a training set consisting of 96 molecules [302].

**B. Anticonvulsant activity**

Number of articles were found for the anticonvulsant potential of 4-thiazolidinones where substitution on 2,3 and 5 positions were done. Most of the compounds were found to exhibit protection against pentylentetrazole induced seizures [303-308]. Researchers reported the synthesis, characterization, and anticonvulsant evaluation of new N,N'-bis(arylidene)dihydrazide (Fig. 7) and bis(4-thiazolidinone) (Fig. 8) derivatives. Upto 90% protection was observed in the pentylentetrazole seizure [309].

Synthesis of newer thiadiazolyl and thiazolidinonyl quinazolin-4(3H)-ones was done in 2002 by kumar, A. [310]. The compounds were screened for their anticonvulsant activity and were compared with the standard drugs, phenytoin sodium, lamotrigine and sodium valproate. Out of the 30 compounds the most active compound was 3-({4-[2-(m-methoxy-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1,3,4-thiadiazol-2-yl}methylamino)-2-methyl-6-bromoquinazolin- 4(3H)-one.
Recently anticonvulsant activity of clubbed Thiazolidinone-barbituric acid and Thiazolidinone-triazole derivatives have been reported\(^{[311]}\). The compound in (Fig 9), substituted with different phenylthiazolidinonyl amino moieties at the 5 position of barbituric acid, has shown varying degrees of anticonvulsant activity. While 3-(2-chloroacetyl)-2- arylimino-5-[(Z)-arylmethylidene]-1,3-thiazolan-4-ones on treatment with 5-(1-phenoxyethyl)-4H-1,2,4-triazole-3-thiol in identical conditions provided a set of bulkier derivatives which have also shown the anticonvulsant potential (Fig 10).

C. Antimicrobial activity

Bhoot et al have synthesized 2-(ptolylimino)-3-(4-tolyl)-5-[5-(3,4-dichlorophenyl)-2-furylidene]-4-thiazolidinone (Fig. 11) and derivatives as an antimicrobial agents. Compounds were screened \textit{in vitro} for their antimicrobial activity towards variety of bacterial strains such as \textit{B. mega}, \textit{S. aureus}, \textit{E. coli}, \textit{P. vulgaris} and fungi such as \textit{Aspergillus niger} at a concentration of 40 µg. In conclusion remarkable inhibition was observed in compounds bearing R=phenyl, 2-methoxyphenyl, 2-methylphenyl, 3-methylphenyl 4-nitrophenyl substituents\(^{[312]}\).
Various 5-substituted 5-(N,N-disubstituted aminomethyl)-2-[4-carbethoxymethylthiazol-2-yl]imino]-4-thiazolidinones (Fig. 12) were synthesized by Altintas et al. Derivatives were screened for their in vitro antibacterial activity against Staphylococcus aureus ATCC 6538, Staphylococcus epidermidis ATCC 12228, Escherichia coli ATCC 8739, Klebsiella pneumoniae ATCC 4352, Pseudomonas aeruginosa ATCC 1539, Salmonella typhi, Shigella flexneri and Proteus mirabilis ATCC 14153 using disk diffusion [313].

Desai and Desai have synthesized five membered sulfur containing heterocyclic derivatives 2-(aryl)-3-[2-(benzothiazolylthio)-acetamidyl]-4-oxothiazolidines (Fig. 13). All the compounds have been screened for their antibacterial activity against Escherichia coli (Gram–ve), Staphylococcus aureus and Bacillus subtilis (Gram +ve) [314].
A series of 2-(substituted phenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl-ureido]-5H/methyl/carboxymethyl-4-thiazolidinones (Fig. 14) were prepared. All the derivatives were screened for antibacterial activity [315]. Number of other researchers also synthesized and screened 4-thiazolidinone derivatives for antimicrobial potential [316-322].

D. Follicle stimulating hormone (FSH) receptor agonist activity.

Follicle stimulating hormone (FSH) is a 38 kDa protein that triggers maturation of ovarian follicles in women and spermatogenesis in men. It is released from the anterior pituitary gland, following stimulation by gonadotropin releasing hormone (GnRH), and serves as the naturally occurring agonist of the FSH receptor.

Yanofsky SD et al. have shown the allosteric activation of FSH receptor, by screening unbiased combinatorial chemistry libraries of thiazolidinone derivatives (Fig. 14), using a cAMPresponsive luciferase reporter assay [323]. They also have shown that discrete modifications in the chemical structure of the thiazolidinone agonists produced compounds with different pharmacological properties [324]. This
was done by preparing substituted 5-alkyl \[^{325}\] Gama lactam substituted \[^{326}\] 4-thiazolidinone derivatives.

![Fig. 15](image)

**E. Anti cancer activity & Anti proliferative activity**

Ten cytoselective compounds have been identified from 372 thiazolidinone analogues (Fig. 16) by applying iterative library approaches. These compounds selectively killed both non-small cell lung cancer cell line H460 and its paclitaxel-resistant variant H460taxR at an IC50 between 0.21 and 2.93 \(\text{M}\) while showing much less toxicity to normal human fibroblasts at concentrations up to 195 \(\text{M}\). A pharmacophore derived from active molecules suggested that two hydrogen bond acceptors and three hydrophobic regions were common features \[^{327}\].

![Fig. 16](image)

Gududuru has synthesized a series of 2-aryl-4-oxothiazolidin-3-yl amides and were evaluated for ability to inhibit prostate cancer cells. Few potent compounds were detected, which were effective in killing prostate cancer cells with improved selectivity compared to serine amide phosphates \[^{328}\]. Various 4-thiazolidinone derivatives were synthesized for in vitro antiproliferative activity on five cell lines of human colon cancers, obtained from the American type culture collection \[^{329-333}\].
Thiazolidinone amides, carboxylic acids, serine amides were synthesized and tested for possible anticancer activity [334].

**F. Anti-inflammatory activity**

Sparatore has synthesized aromatic Schiff bases and 2,3-disubstituted-1,3-thiazolidin-4-one derivatives (Fig. 17) as anti-inflammatory agents. Both types of compounds displayed good level of activity against carrageenan induced edema in rat hind paw, while only moderate activity was observed in the writhing test in mice [335].

![Fig 17](image17)

Kumar A has synthesized 3-[4'-(p-chlorophenyl)-thiazol-20-yl]-2-[(substitutedazetidinone/thiazolidinone)-aminomethyl]-6-bromoquinazolin-4-ones (Fig. 18). Some of the compounds have shown satisfactory anti-inflammatory activity [336].

![Fig 18](image18)

A series of 4-thiazolidinone compounds, represented by LY178002 (5-[3,5-bis(1,1-dimethylethyl)- 4- hydroxyphenyl]methylene-4- thiazolidinone), have been described as potent inhibitors of cyclooxygenase and 5-lipoxygenase, also an
inhibitor of phospholipase A2 and cellular production of LTB4 by human polymorphonuclear leukocytes (PMNL). The results indicate that LY178002 is more effective in suppressing bone damage than the edema [337].

Ottana et al investigated 3,3’-(1,2-ethanediyl)-bis[2-aryl-4-thiazolidinone] derivatives, which showed interesting stereo selective anti-inflammatory/analgesic activities, suggesting that they might preferentially interact with inducible COX-2 isoform [338]. Synthesized 2-imino-4-thiazolidinones and 5-arylidene-2-imino-4-thiazolidinones were tested for in vivo anti-inflammatory activity in models of acute inflammation such as carrageenan-induced paw edema and pleurisy assay in rats [339, 340]. All derivatives exhibited significant activity levels. In addition, the ability of such a new class of anti-inflammatory agents to inhibit COX isoform was assessed in murine monocyte/macrophage J774 cell line assay.

Newbould studied the anti-inflammatory activity of 2-[(butoxycarbonyl)methylene]-4-thiazolidinone. The compound was found to be devoid of activity against most models of acute inflammation. However it partially inhibited Carageenan induced edema in the rat and prevented completely the development of secondary lesions in the rats injected with adjuvant in the footpad [341]. Geronikaki AA et al [342] has performed computer aided discovery of anti-inflammatory potential of 4-thiazolidinones by using PASS (Prediction of Activity Spectra for Substances), a tool for drug discovery.
G.  CFTR inhibitor

The cystic fibrosis trans membrane conductance regulator (CFTR) is a cAMP-regulated chloride channel, which when mutated can produce the hereditary disease cystic fibrosis. CFTR inhibition is a potential strategy for therapy of secretory diarrheas. Tonghui Ma have shown that the 4-thiazolidinones also have CFTR inhibitory potential. The purpose of the study was to identify high affinity CFTR inhibitors for application to studies of CF disease mechanisms and to the treatment of secretory diarrheas. The primary screening of 50,000 diverse compounds identified a small set of putative inhibitors of the 2-thioxo-4-thiazolidinone compound class. These compounds were unrelated structurally to known CFTR activators and to the CFTR inhibitors diphenylamine-2-carboxylate (DPC), 5-nitro-2(3-phenylpropyl-amino) benzoate (NPPB) and glibenclamide. The most potent CFTR inhibitor identified by screening of library of structural analogs had a K1 of about 300nM for inhibition of Cl-current in human airway cells. Inhibition was rapid, reversible and voltage dependant.

Sonawane ND88, has synthesized thiazolidinone 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone (CFTRinh-172) which inhibits cystic fibrosis trans membrane conductance regulator (CFTR) chloride channel conductance with sub-micromolar affinity and blocks cholera toxin-induced intestinal fluid secretion. Greatest CFTR inhibition potency was found for 3-CF3 and polar group-substituted-phenyl rings, and a thiazolidinone core. Two compounds with CFTR inhibition potency and solubility >180 lM (>10-fold more than CFTRinh-172) were identified: Tetrazolo-172, containing 4-tetrazolophenyl in place of 4-carboxyphenyl, and Oxo-172, containing thiazolidinedione in place of the thiazolidinone core. The same researchers and their co workers have shown the CFTR inhibitory activity of thiazolidinone derivatives using computational as well as conventional methods.

H.  Miscellaneous applications

Apart from pharmacological applications the 4-thiazolidinones have also been used in synthesis. One of the older uses was in the synthesis of merocyanine dyes which extend the sensitivity of silver halide emulsions to wavelengths within the...
visible region of the spectrum. Pawelczyk et. al. have synthesized the 4-thiazolidinone derivatives by microwave method as a new fragrant substances and unsaturated analogs of jasmines. The n-pentylamine was mixed with acetaldehyde. The mixture was stirred at room temperature under condenser. After 1 h ethyl thioglycolate (or thioglycolic acid) was added. Reagents were irradiated for 5 min with 160 W by microwaves in a flask with condenser and further treated with ethyl acetate.

\[ \text{Scheme-53} \]

I. Conclusion

The literature reveals that 4-thiazolidinone has diverse biological potential, and the easy synthetic routes for synthesis have taken attention of the chemists, pharmacologists and researchers. The anticancer and anti HIV activities are the most encouraging activities for the pharmacists. Also the research in anticonvulsant, FSH agonistic and CFTR inhibitory activity has given positive results. By the present scenario it can be concluded that 4-thiazolidinones have a great potential which remain to be disclosed till date.

Thus, keeping in mind this potential some novel thiazolidin-4-ones containing the indoline nucleus have been synthesized and their biological activity has also been checked.
REFERENCES

1. Dictionary.com


26. http://www.rsc.org/is/journals/current/green/greenpub.htm


34. Wool, R. P. Affordable Composites from Renewable Sources (ACRES). In The Presidential Green Chemistry Challenge Awards Program: Summary of 2000 Award Entries and Recipients; EPA744-R-00-001; U.S. Environmental
Part 1 “Investigations of some Aqua mediated as well as microwave assisted…”

Protection Agency, Office of Pollution Prevention and Toxics: Washington, DC, 2001; p 9


42. Meehan, N. J.; Sandee, A. J.; Reek, N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Poliakoff, M. Continuous, Selective Hydroformylation in


83. Monsanto Company. The Catalytic Dehydrogenation of Diethanolamine. In The Presidential Green Chemistry Challenge Awards Program: Summary of 1996 Award Entries and Recipients; EPA744-K-96-001; U.S. Environmental...
Part 1 “Investigations of some Aqua mediated as well as microwave assisted…”


Part 1 “Investigations of some Aqua mediated as well as microwave assisted…”


129. Single-mode cavities offer more consistent and predictable energy distribution. Single-mode instruments produce one homogeneous, intense pocket of energy that is highly reproducible. Due to their uniform energy distribution and higher power density, these systems typically couple more efficiently with small samples. Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002.
Part 1 “Investigations of some Aqua mediated as well as microwave assisted...”

173. For information on the combined microwave/ultrasound instrument, see: Peng, Y.; Song, G. Green Chem. 2001, 3, 302.


Part 1 “Investigations of some Aqua mediated as well as microwave assisted…”

244. Degussa, DE, 1 119 868, 1959.
266. Promonta, DE, 934 890, 1951.


283. Cunico W et al., One-pot synthesis of 2-isopropyl-3-benzyl-1,3-thiazolidin-4-ones and 2-phenyl-3-isobutyl-1,3-thiazolidin-4-ones from valine, arenealdehydes and mercaptoacetic acid. Tetrahedron letters, 2007; 48: 6217-6220.


330. NCI-Navy Medical Oncology Branch cell line supplement, *J Cell Biochem Suppl* 1996; 24

331. Miller et al., US 2007/ 0155807 A1,
Part 1 “Investigations of some Aqua mediated as well as microwave assisted…”


