



The Impact of Microwave Irradiation Reaction in Medicinal Chemistry: (A Review)

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ABSTRACT

The present review collects an update of the reactions in the area of medicinal chemistry using microwave irradiation. This review come up with an overview of most salient reactions performed under microwave irradiation in the field of drug discovery. Moreover, chemists are preferring to use this reaction rapidly in the academic as well as pharmaceutical laboratory during their drug discovery and making library of compounds. This reaction is much greener using less amount and readily recyclable solvents or sometimes reaction process without solvents and product become much cleaner, often yields are better than the conventional heating. Microwave irradiation is now very robust instrument used in company in the field of drug discovery, due to reduce the reaction time from hour to minute or even second and efficiently creation of compound libraries through combinatorial methodology associated with drug discovery so that new therapeutic agents bring to the market quicker. Hopefully, we will observe in the future the use of microwave irradiation drugs for the patients and this technology will utilize increase in number extensively in the field of medicinal chemistry. As this is an exceedingly rapid evolution area, this review offers significant expertise to the interested readers.

Keywords: Microwave irradiation, Drug discovery, Conventional method robust instrument.

INTRODUCTION

Microwave is an electromagnetic radiation. In the electromagnetic spectrum the microwave radiation is located between IR and Radio wave. Microwave has wave lengths 1 mm–100 km, frequencies 300 GHz–3 KHz and energy 1.24×10^{-3} – 1.24×10^{-6} eV.^{1,2}

These are non-ionizing invisible short wave length radiation travel with the velocity of light. Direct chemical reaction like UV-Visible radiations in

photochemical reaction microwave is not sufficiently energetic to cleave C-C bond to initiate chemical reaction. But surprisingly microwave radiated reaction is faster than that conventional chemical reaction. It was well known that microwaves heated water quickly. In organic synthesis microwave radiations have made its position as a non-conventional energy source as an alternative source of energy.

Microwaves are produced in magnetron. In 1920s it was discovered by an American engineer A. W. Hull and in the 1940s cooking food using



microwaves irradiation was invented by accident by another American engineer Percy Spencer. When he was working on active radar set he observed that a peanut chocolate bar in his pocket started to melt. He understands that radar had helped to melt his chocolate bar. Then popcorn was the first cooked deliberately with Spencer's microwave, and egg was the second experiment that blows up in the face when one experimenter worked on it. In 1947, for food processing microwave appliances "Radarange" come on to the market and in the 1950s both domestic and mercantile gadget started to appear for boiling, grilling, heating,

roasting and making of foods. First microwave oven was launched in the 1955s by Tappan but in the 1970s and 1980s frequently used domestic microwave ovens come about. In 1970s, the building of the microwave generator was improved and simplified and the price of the domestic used microwave oven drop dramatically. After that the oven chamber grill changes significantly higher or bigger size to smaller according to demand. Use of microwave irradiations in organic synthesis (MIOS) has made its position as a non-conventional energy source. In 1986 the first article was published related to MIOS.

Table 1: Wave length, frequency and energy of electromagnetic radiation: 1 eV = 3.8 x 10⁻²³ KCal

	Radiation type	Wave length	Frequency	Energy	
1	Gamma rays	<10 picometer	>10 ¹⁹ Hz	>100 KeV	Ionizing radiation
2	X-rays	0.01-210 nm	3x10 ¹⁹ – 3x10 ¹⁶ Hz	102KeV-124 eV	
3	Far Ultraviolet rays	10-200 nm	3x10 ⁷ – 1.5x10 ⁶ GHz	124 – 6.2 eV	
4	Ultraviolet rays	200-400 nm	1.5x10 ⁶ – 7.5x10 ⁵ GHz	6.2 – 3.1 eV	Non-Ionizing radiation
5	Visible rays	400-800 nm	7.5x10 – 3.7x10 ⁵ GHz	3.1 – 1.5 eV	
6	Near IR	0.8- 2.5 m	3.7x10 ⁵ – 1.2x10 ⁵ GHz	1.5 – 0.5 eV	
7	IR	2.5- 15 m	2.0x10 ⁴ – 3.0x10 ² GHz 7.5x10 ⁵ – 3.7x10 ⁵ GHz	0.5 – 0.08 eV	
8	Far IR	15-1 mm	300 GHz – 3 KHz	0.08 – 1.24x10 ⁻³ eV	
9	Microwave	1mm -1 m		1.24 x 10 ⁻³ – 1.24 x 10 ⁻⁶ eV	
10	Microwave and Radiowave	1 mm to 100 km		1.24 x 10 ⁻³ – 1.24 x 10 ⁻¹¹ eV	

Magnetron consists of a heated cathode a solid metal rod acts at the center and a ring shaped anode having holes called resonant cavities and a powerful magnet whose magnetic field surrounding the cathode. From the heated cathode energized electrons from cathode try to move towards anode in a straight line, but due to presence of strong magnetic field, the moving electrons are encountered both by the electric and magnetic fields and the electron experience a force to follow a curved path and move fast around the space between the anode and cathode. As the electron nip past the cavities, the cavities resonate and emit microwave radiation. The electron pass the cavities, it transfers energy to the cavity and making cavity resonate like someone blowing flute on the open end produces sound to generate microwave wave instead of sound wave.

At present, in chemical reactions two types of heating was used:

Conventional heating

Heating in this method is slow, non-selective, and less dependent and the outer surface is heated

first then heated inside the reaction system. Heat is introduced into the reaction solvents, reagents, and substance come after the walls of the vessel.

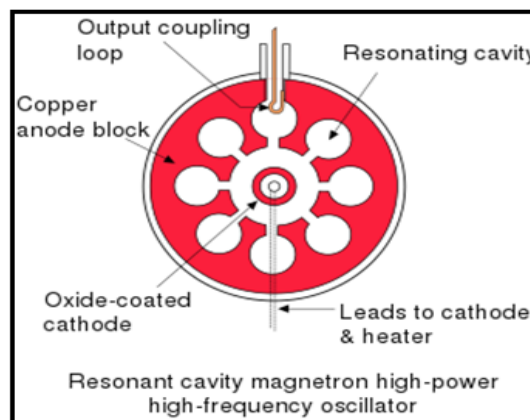


Fig. 1. Source: Biotage

Microwave heating

In the beginning microwave-assisted synthesis was observed that rate of heating is faster and selective absorption by polar compounds and sometimes altered product distributions contrast to conventional heating experiments by the use

of oil bath have led to speculation on the existence of so-called “specific” or “non-thermal” microwave effects. When a synthesis accomplished under MW irradiation was initiated completely different results from that of the conventionally heated with the identical conditions. According to most of the chemists the rate of amplification was observed during the MW irradiation is absolutely kinetic or thermal effect.

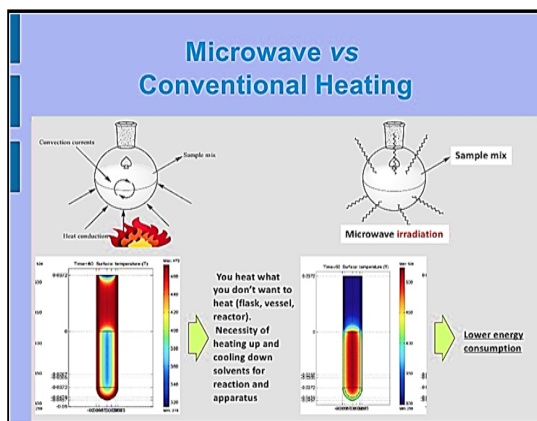


Fig. 2: Source: Biotage Left image = oil bath, both taken after 1 min of heating, right image = microwave heating

Unlike the high energy radiations like γ -rays, X-rays, UV-Visible radiations, MW radiations are non-ionizing radiations as they are not

energetic enough to ionize an atom or a molecule. So MW cannot cleave a chemical bond to initiate a chemical reaction directly unlike photochemical reactions where UV-Visible radiations are used to initiate reaction.

The given temperature of a reaction system is able to reach quickly by the microwave irradiation with a very short induction period as a result the reaction reaches the desired temperature quickly and the reaction starts immediately, which is beneficial in cases where the catalyst/reagents is not stable. The microwave heats the reaction system direct and uniform way, with respect to conventional heating where the glass is heated first and in turn the glass heats the solution.

In microwave reactions the vials are used as sealed and reactions are carried out in closed systems which means in addition to temperature, reactions are carried out under increased pressure and the reaction is allowing to be heated high up the boiling point of the solvent being used therefore reaction time is reduced compared to classical procedure. Reactions under microwave conditions are much cleaner with easy work up improved yield with less side effects.

Table 2: Frequency of various

Radiation type	Frequency (MHz)	Quantum energy (ev)	Bond type	Bond energy (ev)
Gamma rays	3.0×10^{14}	1.24×10^6	C-C single bon	3.61
X-rays	3.0×10^{13}	1.24×10^5	C=C double bond	6.35
Ultraviolet	1.0×10^9	4.1	C-O single bond	3.74
Visible light	6.0×10^8	2.5	C-O double bond	7.71
Infrared light	3.0×10^6	0.012	C-H bond	4.28
Microwave	2450	0.0016	OH bond	4.8
Radiofrequencies	1	4.0×10^{-9}	Hydrogen bond	0.04-0.44

Interaction of microwave with material

Microwave interacts with substances depending on the nature of the substance and the type of interactions may be reflection, transmission or absorption. On irradiation by microwave a metal strip generates spark on the surface of the metal. An electric conductive material reflects MW. Whereas, insulators, which are contemplated as substances with high dielectric properties like quartz, glass or polytetrafluoroethylene allows the transmission of most of the waves causing no heat. But the lossy dielectrics, which are substances that show dielectric losses and materials having permanent dipole moment, absorb most of the incident microwaves

and convert them into heat. Only polar molecule can absorb MW radiation and get heated whereas the non-polar compounds do not absorb MW and are transparent to MW i.e., substance having permanent or induced dipole moment are microwave active.

How does heat generate by absorbing MW radiation: Microwaves interrelate straight with the compounds of the whole reaction mixture cause to a quick jump up in the temperature. The process is not restricted by the thermal conductivity of the reaction tube, the consequence is an instantaneous confine superheating of any

material that will respond to either dipole orient or ionic conductivity. In the reaction tube both contents and vessel heated with better homogeneity and selective heating of polar molecules might be realized.

Use of microwave the acceleration of chemical reactions outcomes from the interactions between electromagnetic field and the material leading to the thermal and specific (non-thermal) effects. The compound must possess a dipole moment for microwave irradiation. A dipole is orients itself with an oscillating electric field and the electric field inverses in its every oscillation when a dipole is exposed to an alternating current and the dipole also rearrange itself to follow inverse electric field. The induced or permanent dipole respond to electric field and transfer power from electric field to the dielectrics and the dielectrics possess some residual energy as the polarization cannot follow an extremely rapid reversal pathway which is known as the hysteresis loss. The remaining energy induces heating in the dielectric material. This phenomenon is known as dielectric heating. The number of reversal of the dipole of the dielectric is related to the frequency of the electromagnetic radiation and in every reversal of the dipole there will be hysteresis loss. So a household microwave oven commonly used irradiation frequency (2450 MHz) oscillates $2 \times 2450 \times 10^6$ times per second and each oscillation is associated with a residual hysteresis loss and this total energy is transformed into the heat energy.²⁻⁵

Kappe⁶ and Von Hippel.⁷ reported some values for the dissipation factor and based on the values are showed in Table 3.

Table 3: Dissipation factors for some solvents and materials (3 GHz and 25°C)

Solvent	Tan δ	Material	Tan δ
Ethylene glycol	1	Nylon 6,6	$12.8 \cdot 10^{-3}$
Ethanol	0.25	Poly(vinyl chloride)	$5.5 \cdot 10^{-3}$
Methanol	0.64	Porcelain 4462	$1.1 \cdot 10^{-3}$
Acetic acid ^a	0.174	Borosilicate glass	$1.06 \cdot 10^{-3}$
Water	0.157	Ceramic F66	$0.55 \cdot 10^{-3}$
0.1 mol/l NaCl	0.24	Polyethylene	$0.31 \cdot 10^{-3}$
0.5 mol/l NaCl	0.63	PTFE-PFA	$0.15 \cdot 10^{-3}$
Toluene	0.040	Fused quartz	$0.06 \cdot 10^{-3}$

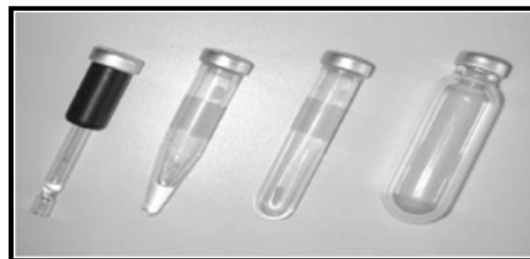


Fig. 3. Source: Biotage. Microwave irradiation tube

So the basic concept of heating is the ability of the radiation to introduce polarization of charges within the dielectric material. The amount of energy absorbed by a domain depends on the microwave intensity and the absorption cross section of the domain. Molecules possessing a large absorption cross-section are selectively heated and such molecules molecular radiators. To summarize, it is principal note that MW irradiation dielectric constant and dielectric loss both the properties are a function of microwave frequency. However, both laboratory and domestic used microwave gadget generally operate at 2.5 GHz to admit a deeper penetration MW into the substances, result a more uniform heating.

Conduction Mechanism

Ionic conduction of dissolved ions in solutions is familiar that increases with the rise in the temperature. The increase in the dielectric properties with temperature is especially important in the microwave heating of solids, as it introduces the phenomenon of thermal runaway. Dipole rotation influences the offering for heating in the starting of the process when submitting sample ions to MW irradiation. However, the ionic conduction dominates the heating process due to increase in temperature. The main limitation of this method is that it is not applicable for materials that have high conductivity, since such materials reflect most of the energy that falls on them.⁵

Microwave heating in organic Synthesis

It has been considered that MW is responsible for undergoing chemical reactions due to its thermal effect and non-thermal effect. When heat generated by MW is responsible for a chemical reaction, it is called thermal effect. When some other effect comes into play to accomplish a chemical reaction, it is considered as non-thermal effect. But the question arise that why MW-introduced reactions

are often faster than conventional heating? This is a burning question and many theories and postulates are published in the literature. A short discussion is made in this review.

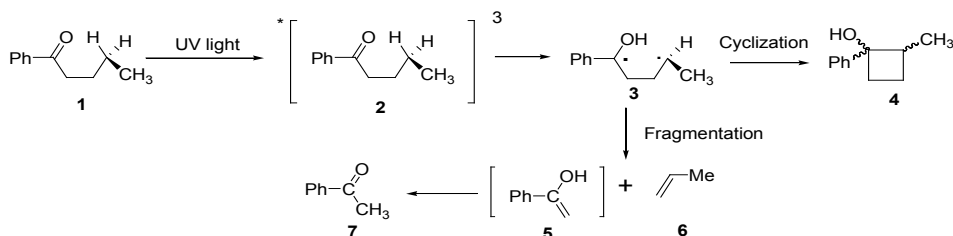
- A. Thermal effects which includes (i) Overheating, (ii) Hot spot, and (iii) selective heating of solvents, catalyst, reagents, and susceptors.
- B. Non-thermal effects of the highly polarizing field.

Overheating

When a liquid is heated by a normal oil bath, the liquid gets heated from the surface and gradually the whole liquid gets heated by convection and conduction process and finally reaches its boiling point when the vapour pressure of the liquid equals the atmospheric pressure and this observation is on the surface of the liquid. Interestingly, when a liquid is irradiated with microwave inverted heat transfer takes place from the interior of the irradiated medium to the exterior. When the boiling temperature reaches at the

surface, the internal temperature is higher than the boiling point by 13-26°C. In 1997 Mingos¹⁰ observed this effect in polar solvent on using microwaves, where overheating in the range 13–26 uC above the normal boiling point may occur (Figs 2).

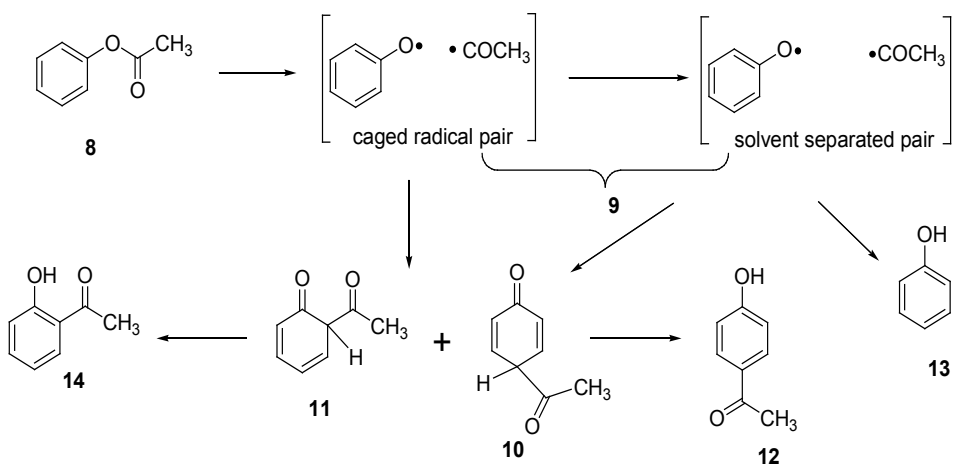
This overheating effect by MW in polar liquids by observing a temperature-dependent photochemical reaction was successfully justified by Klan *et al.*,¹¹ in 2001. Klan reported in a photochemical Norrish type II cleavage on valerophenone when irradiated in UV-light (Scheme 1) with both ketones (1:1) were irradiated with UV-light (at $\lambda > 280$ nm) in solvents (MeOH and CH₃CN) with similar photochemical environment for both substances. The fragmentation–cyclization ratio diversified from 5 to 8 and was attribute for given reaction conditions (Table 4). Commonly, by conventional heating, cyclization to cyclobutanol is a side reaction. But application of microwave irradiation increases the formation of cyclobutanol, which is more pronounced in acetonitrile.



Scheme 1. Norrish type II reaction reported by Klan

Klan reported the photo-Fries rearrangement of phenylacetate under MW irradiation as well as electrode less discharge lamp (EDL) which gives

two main products: 2- and 4-hydroxyacetophenone (Scheme 2). The formation of products are shown in Table 4.



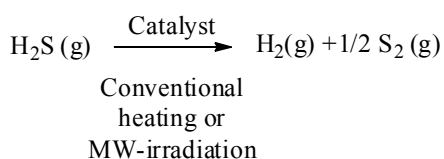
Scheme 2. Photo-Fries rearrangement reported by Klan.

Table 4: Product ratios under different reaction conditions

Solvent	Mode of heating	Reaction Temp (°C)	Overting (°C)	A:B
MeOH	Conventional	65	0	1.52
MeOH	microwave	75	10	1.32
CH ₃ CN	conventional	81	0	1.12
CH ₃ CN	microwave	90	0.09	0.9

Hot spots

Temperature of certain zones within the sample, solid or solution becomes very high, these zones are called hot spots. The temperatures at those zones are 100-200°C higher than the bulk temperature and sizes of the hot spots are around 100 μm. The difference in temperature was calculated by the help of some conversions observed, such as the conversion of γ - to α -alumina and the melting of MoS₂, that happen at temperatures much larger than the regular bulk temperature. The presence of hot spot was elaborated by Mingos studying the decomposition of H₂S over γ -Al₂O₃ or MoS₂- γ Al₂O₃.¹² The efficiencies of conversion was obtained to be better by MW irradiation over conventional heating. During the transformation by microwave irradiation γ -Al₂O₃ to α -Al₂O₃ was observed. The decomposition temperature of H₂S over γ -Al₂O₃ was 100-700°C. Phase transfer of γ -Al₂O₃ to α -Al₂O₃ takes place above 1000°C. The conversion of γ -Al₂O₃ to α -Al₂O₃ supports the formation of hot spots during microwave irradiation reaction.

**Scheme 3. The presence of hot spot was elaborated**

It is well known that the transformation efficiency using MW was established to be better compared to oil bath heating which is assigned as the presence of hot spots under microwave irradiation. During this transformation by MW-irradiation transition of γ -Al₂O₃ to α -Al₂O₃ was observed. The decomposition temperature of H₂S over γ -Al₂O₃ was 100–700°C. Phase transfer of γ -Al₂O₃ to α -Al₂O₃ takes place above 1000°C. The conversion of γ -Al₂O₃ to α -Al₂O₃ supports the formation of hot spots during MW-irradiation process. Similarly some molten molybdenum disulfide was obtained by MW-irradiation (m.p. of MoS₂ is 1185°C).

Hihn *et al.*,¹³ reported the temperature distribution during the synthesis of coumaran-2-one in absence of solvent in which the volume was divided into three different layers of equal thickness. Generation of hot spot was also described by Hallberg in the synthesis of β,β -diarylated aldehydes by the reaction of enol ethers in a two phase (toluene/aq. HCl) system.¹⁴ Marken *et al.*,¹⁵ reported that the effect of 2.45 GHz MW radiation on electro-organic reaction. The effect of MW was studied during the oxidation of ferrocene in acetonitrile (0.1 M nBu₄⁺Pf₆⁻) with a Pt-electrode. Increase in power of MW led to increase in limiting current. This effect qualitatively attributed to formation of hot spot near the electrode surface. The hot spot temperature was found to be 118°C which is considerably higher than both the boiling point of acetonitrile (81°C) and the electrode temperature (47°C). The solvent acetonitrile convection through the hot spot under these conditions becomes more effective for the process. So generation of hot spots can be considered in solid as well as in solution. They cannot be measured directly in that process.

Dabrowska *et al.*,¹⁶ was studied that laboratory reactors with microwave power capabilities of 600 W can heat 100 mL containers with water 100 times faster than convection heating and observed the overheating effects on reaction rates.

Selective heating

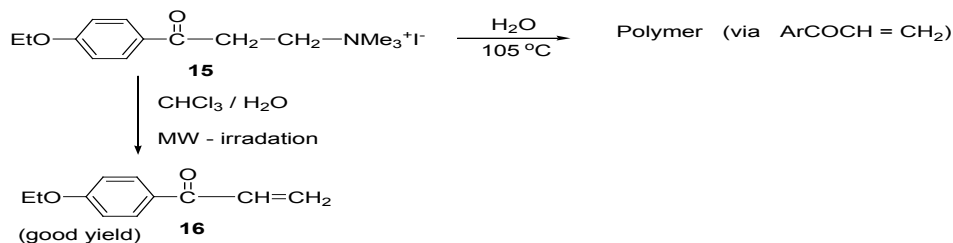
MW irradiation is a specific mode of heating. Fundamentally, MW irradiation give rise to quick intense heating of polar molecules while polar materials do not absorb the radiation and are not heated.¹⁷ Such selective heating may occur in any one or more components of a reaction system. In solvents, catalysts and reagents selective heating has been utilized.

Solvents

Strauss studied^{18,19} a Hoffmann elimination of β -aroyl ethyltrimethylammonium iodide under different condition (Scheme 4). It has been found that the polymerized product was generated when the reaction was transformed in water at 105°C. However, to avoid the polymerization reaction the synthesis was carried nicely by the help of MW irradiation in a two phase water/chloroform system when the temperatures of water and chloroform were 110 and 50°C, respectively. After completion of

the elimination reaction in aqueous phase at higher temperature, the formed phenyl vinyl ketone comes to

the lower chloroform layer, where the alkene survives from polymerization due to lower temperature.



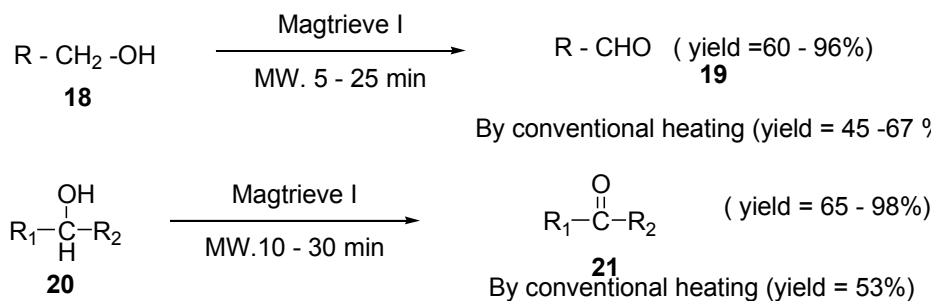
Scheme 4. Hoffmann elimination of β -arylethyltrimethylammonium iodide under different condition

To avoid polymerization this reaction was carried using two immiscible solvent systems like $\text{CHCl}_3/\text{H}_2\text{O}$ under microwave irradiation where phenyl vinyl ketone produced with high yield. The difference dielectric constants of CHCl_3 and H_2O are responsible for different temperature under microwave irradiation. The temperature organic phase and aqueous phase were 50°C and 110°C respectively. After the reaction the product phenyl vinyl ketone comes to the organic layer where the elimination product survives from polymerization due to lower temperature.²⁰

presence of a polar catalyst sometimes become the site of selective heating. For example, Bogdal^{21,22} experimented the oxidation of alcohols using a solid chromium dioxide catalyst Magtrieve I (Scheme 5). The microwave heating of Magtrieve I rapidly reaches its temperature up to 360°C within 2 minutes. When Magtrieve I and toluene were suspended into the reaction tube, the temperature of the catalyst becomes 140°C at the same time period. This shows that the temperature of the Magtrieve I can be higher than the bulk temperature of the reaction mixture, which suggests that MW irradiation process might be superior to other conventional processes.

Catalysts

In heterogeneous reactions mixture



Scheme 5. Heterogeneous reactions of alcohols using Magtrieve I

Auerbach²³ was explained the overheating effect through both the equilibrium and nonequilibrium molecular dynamics using zeolite-guest systems when Conner²⁴ completed his experimental work with that system. All atoms in zeolite-guest at equilibrium condition are at the same temperature however when Na-Y zeolite is irradiated to microwave in the methanol-benzene binary mixture, the effective steady-state temperature of Na atoms is considerably larger than that of the rest of the groundwork, suggesting a thermal energy distribution and found temperatures are different for each component of Tmethanol & Tbenzene, Tzeolite.

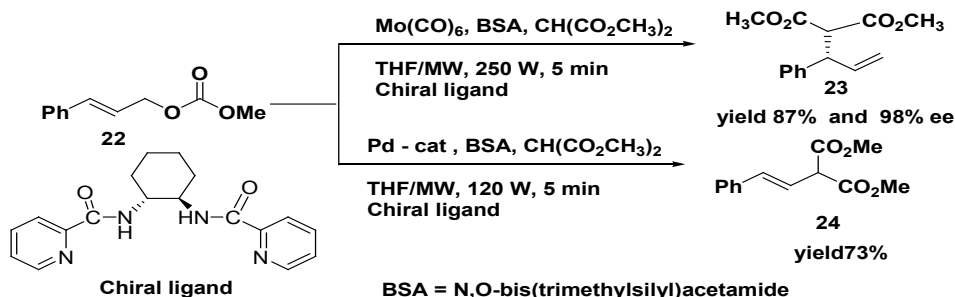
From this result it can be concluded that methanol dissipates energy to benzene, which is much slower approach to thermal equilibrium under steady-state conditions. Although, some disagreement also remains concerning the effects of MW heating in heterogeneous catalysis.²⁵ Another group of authors have showed the change of the catalyst's electronic properties upon exposure to MW irradiation²⁶⁻²⁸ during explain the superior catalytic properties of catalysts under these conditions.

Reagents and products

Larhed²⁹ studied the molybdenum and

palladium-catalyzed asymmetric allylic alkylation of (E)-3-phenyl-2-propenyl acetate using allylic carbonate. The reaction has been accomplished with complete conversion, good reproducibility, high yields (87%) and excellent regioselectivity (ee = 98%) within few minutes (Scheme 6) using

tetrahydro furan under microwave irradiation power of 250 W at 220°C. This high yield is clearly suggested that when MW heating is used there is a significant contribution from sustained overheating which is not only for the increased boiling points at elevated pressure.

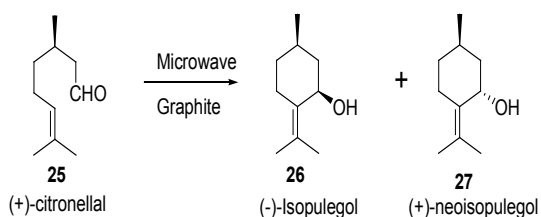


Scheme 6. Molybdenum and palladium-catalyzed asymmetric allylic alkylation of (E)-3-phenyl-2-propenyl acetate

Susceptors

When the reagents and solvents in a reaction medium do not absorb microwave radiation, a chemically inert substance in that medium but capable of absorbing MW radiation is used to facilitate the reaction, such substances are called susceptors. It transfers the thermal energy to another compound which itself cannot absorb the radiation. This method has an interesting advantage because it differs from a catalyst where the energy is focused on the reaction surface of the susceptor.

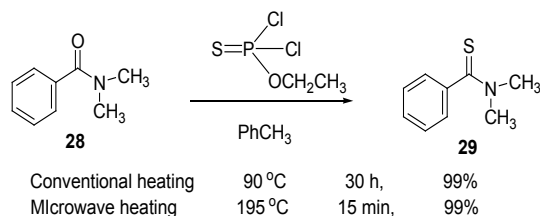
The cyclization reaction of (+)-citronellal to (-)-isopulegol and (+)-neoisopulegol in absence of solvent or heterogeneous conditions graphite acts as a susceptor studied by Garrigues³⁰ under MW heating (Scheme 7) in which the stereoselectivity of the transformation is changed. (-)-Isopulegol is all the time is the main diastereoisomer, although under conventional heating a trace amount of (+)-neoisopulegol was produced by the MW heating, it is formed in 30% yield.



Scheme 7. Graphite used as a susceptor

Ionic liquids (IL) act as a susceptor either in solution or under homogeneous conditions. Ley³¹ studied the reaction of amides to achieve thioamides

where toluene is not a good solvent to perform under microwave conditions, but reactions can occur under conventional heating condition. N,N-Dimethylbenzamide forms corresponding thioamide by heating with O-ethyl phosphorodichloridothioate [PS(OEt)Cl₂] for 30 h in toluene whereas using IL it can be performed in 15 mins under microwave irradiation (Scheme 8).



Scheme 8. Ionic liquids (IL) used as a susceptor for the preparation of thioamides from amides

Leadbeater³² determined to explain the above experimental result using ionic liquids as aids for the MW heating under nonpolar solvent (Table 5). This reaction transform in a quick period and polar solvents can be heated to much higher temperatures than the boiling point of the solvent used in sealed vessels using small quantity of an ionic liquid.

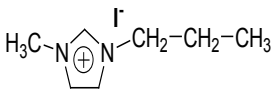
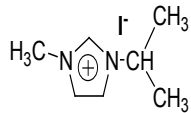
Non-thermal effects or specific MW effects

Non-thermal effect of microwave is still yet uncertain. Several theories have been postulated the presence of non-thermal effect along with the thermal effect of MW, whereas other group of scientists stick purely to the thermal effect of microwave which are only responsible for making a reaction faster or selective compared to oil bath heating methods.

Several theories and prediction have been made to explain the presence of non-thermal effect of microwave; at the same time other group of people

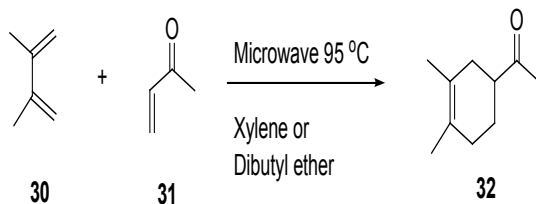
has tried to refute all these considerations. A brief discussion with some examples has been made in this review.

Table 5: Effect of ionic liquid

Ionic Liquid	Medium	Reaction temperature
	PhCH ₃ (bp 109 °C)	195 °C
	PhCH ₃ (bp 109 °C)	130 °C

Similar to thermal effects of microwave, non-thermal effect may arise during the interaction between MW and material. In fact it is very difficult to make a separation the thermal and non-thermal effects of MW in mechanistic studies. The MW effects are increased in reactions with polar transition states. Some scientists suggested that changes in the thermodynamic properties under MW irradiation are the cause of microwave effects. Berlan *et al.*,³³ reported the rate of cycloaddition reactions with 2,3-dimethyl-1,3-butadiene and methyl vinyl ketone carried out under reflux either in dibutyl ether or in xylene (Scheme 9) were always faster when irradiated under microwave than the conventional heating process. The observed acceleration is more pronounced in relatively polar solvent xylene where dielectric losses are small than dibutyl ether. It has been predicted due to modification in ΔG^* by the change of entropy of the system.

Gedye *et al.*,³⁴ studied the Diels Alder reaction between cyclopentadiene and methyl acrylate (Scheme 10) where microwave radiation does not change the endo/exo selectivity. Higher the yield and faster reaction than those taking place under reflux can be explained due to the fact that the reactions processed by the MW heating at higher temperatures.



Scheme 9. Cycloaddition reactions with 2,3-dimethyl-1,3-butadiene and methyl vinyl ketone under MW irradiation

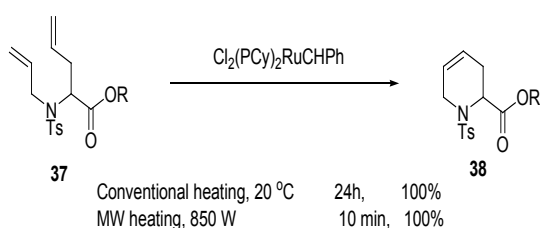
The rate of hydrolysis of adenosine triphosphate is 25 times faster under microwave irradiation than conventional heating at comparable temperature. The faster rate was attributed to direct absorption of radiation or by selective excitation of water of hydration over the bulk molecules. The rate enhancement may also be due to increase in kinetic energy of the solvent due to increase in kinetic energy of the solvent due to MW absorption. Bond³⁵ and Strauss^{36,37} reported individually the controlled systems esterification reactions either presence or absence of MW heating show identical and the yield of the final product depend only on the temperature profile—not on the mode of heating.

Halogenation of alkene in different solvents with tetrahalomethane under homogeneous conditions with MW-irradiation was studied by Hajek in 1997³⁸ and it was observed that polar solvent works better because of dielectric heating effect resulting from the effective coupling of MW with polar solvent. Whereas, under heterogeneous reaction conditions the presence of hot spot and selective heating as discuss earlier are responsible for observed acceleration in reaction rate.



Scheme 10. MW-irradiation was observed that polar solvent works better

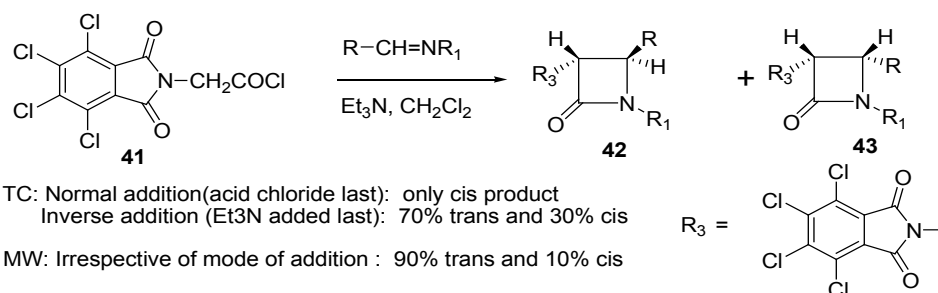
Some authors^{39,40} have described the direct activation either one or both reagents in the ring closing metathesis process is predicted that the rate increased in MW irradiation may be due to absorption of MW by the olefin as Kappe showed that absorption of MW heating by Grubb,s catalyst was little and the olefin acts as molecular radiator (Scheme 11). However, by conducting experiments under conventional heating conditions it was reported that it is less important whether a particular reactant gains the energy or the energy is transferred to the bulk solvent by the MW heating.⁴¹



Scheme 11. MW radiation by Grubb,s catalyst

On the basis of some model experiment Miklavc⁴² calculated the rotational dependence of O+HCl (DCI) A OH (OD)+Cl reactions which is predicted marked accelerations in transformation may take place via the rotational excitation on collision geometry. Earlier Berlinb⁴³ and Strauss¹⁸ proposed that the internal energy is distributed among translational, vibrational and rotational energies regardless of the mode of heating, since the dielectric heating increases the temperature of the system. Molecular agitation and mobility are also factors to consider MW effects.

During the decomposition of NaHCO₃ by classical oil bath heating and by MW-irradiation, the activation energy of decomposition was found to be smaller in case of MW-irradiation. The application of MW field to dielectric materials induces quick rotation of polarized dipoles in the molecule. This evolve heat

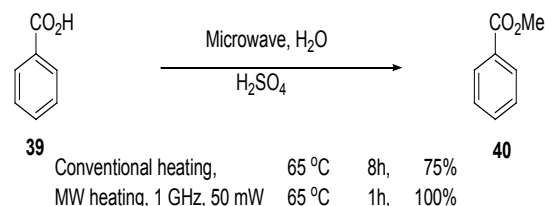


Scheme 13. [2+2] Cycloaddition reaction between acid chloride and a Schiff base

due to the friction while simultaneously increasing the probability of contact of molecules and atoms, thus decreases the activation energy and enhances reaction rate. In the Arrhenius pre-exponential factor 'A' which depends on the frequency of vibration of atoms at the reaction interface and this factor can be affected by MW without changing the activation energy. An increasing in 'A' alone may explain the acceleration of MW-induced reaction.

One instance which cannot be described by thermal effect⁴⁴ of MW is the mutarotaion of α -D-glucose. Pagnota⁴⁵ found that in ethanol-water (1:1), application of MW not only brings rapid equilibrium than conventional heating, but also changes the equilibrium proportion of the anomers and larger amount of α -D-glucose was found in the equilibrium than the thermal equilibrium.

Zhang⁴⁶ was reported another interesting study on esterification of benzoic acid in methanol. The reaction under MW radiation at a frequency of 1 GHz has no MW irradiation action but only athermal microwave effect. But the rate of reaction under these conditions is faster using MW irradiation (Scheme 12).



Scheme 12. Comparative study on esterification of benzoic acid in methanol

The study of [2+2] cycloaddition reaction between acid chloride and a Schiff base in presence of Et₃N was found to differ in conventional heating and by irradiation with MW (Scheme 13). Under thermal condition the mode of addition of reagents played a great role in determining the population of stereoisomers of the products, whereas under MW condition mode of addition has no effect on the population of the stereomers.^{47,48}

This reaction under MW irradiation no isomerization of the cis-product (the kinetically controlled product) to the thermodynamically controlled trans-product occur.

The drug discovery process using microwave irradiation

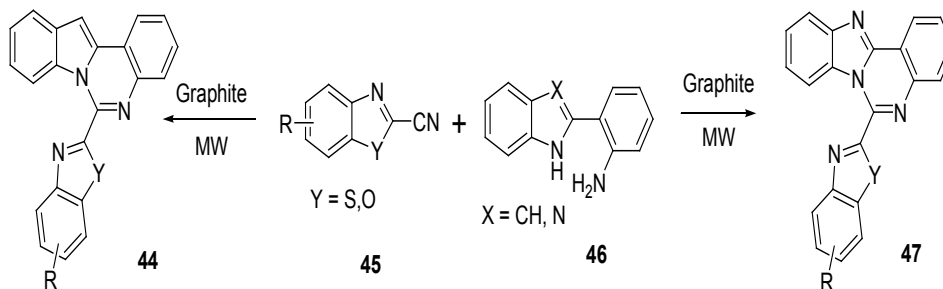
Microwave assisted organic synthesis (MAOS) have an impact in different field of drug discovery and this heating is also being used to produce library of compounds in target discovery, screening, pharmacokinetics and even in the clinic. The wide scope of MW irradiation is firmly illustrated by its use in several fields in drug discovery,⁴⁹ materials science, polymer chemistry,⁵⁰ nanotechnology,⁵¹ organic synthesis, and bioconjugation fields.⁵² This review outlines upto date some selected applications

with an attention on multistep microwave procedure in the drug discovery process.

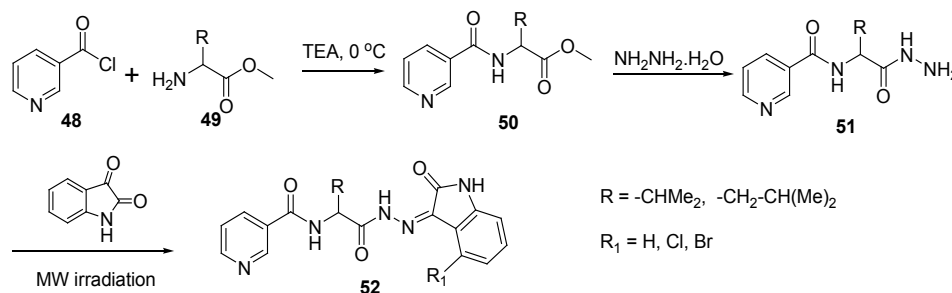
Antimicrobial drugs

Besson *et al.*, reported⁵³ some novel antimicrobial agents, indolo[1,2-c]quinazolines and benzimidazo[1,2-c]quinazolines. Condensation reaction of the appropriate diamines (e.g., 2-(2-aminophenyl) indole or 2-(2-aminophenyl)benzimidazole) with 2-yanobenzothiazoles under microwave irradiation (150 W) of the two starting compounds at 220°C in the presence of graphite produced very good yield other than normal condition (Scheme 14).

A.M. Naghla⁵⁴ reported library of antimicrobial compounds using microwave irradiation with good yields (Scheme 15).



Scheme 14. Synthesis of novel antimicrobial agents under microwave irradiation

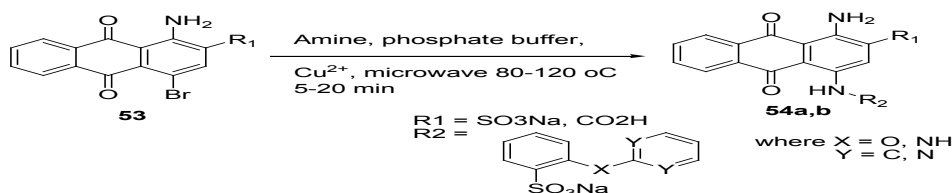


Scheme 15. Preparation of antimicrobial compounds using microwave irradiation

Anti-Thrombotic agents

Muller *et al.*, have reported⁵⁵ some anthraquinone derivatives as non-nucleotide-derived competitive antagonists of platelet P2Y₁₂ receptors. In the synthesis of the target compounds the key step was a copper(0)-catalyzed Ullmann

coupling reaction of 1-amino-4-bromoanthraquinone derivatives with anilines using microwave irradiation heating between 80–120°C for 5-20 min (Scheme 16). Following this approach, they prepared some non-nucleotide antagonists of human P2Y₁₂ receptor.

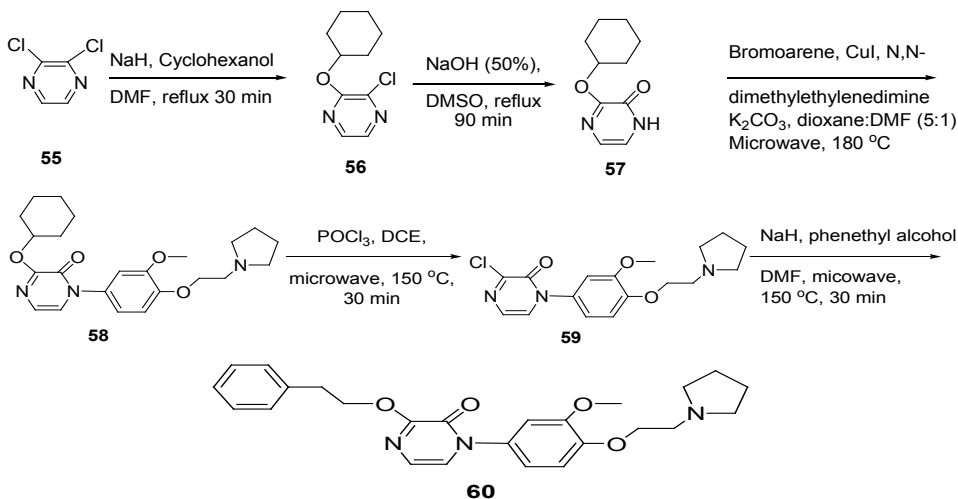


Scheme 16. Copper(0)-catalyzed Ullmann coupling reaction using microwave irradiation

Anti-obesity agents

Johnson and Johnson Pharmaceutical Research and Development have reported Melanin-concentrating hormone receptor 1 and prepared pyrazinone core which was performed

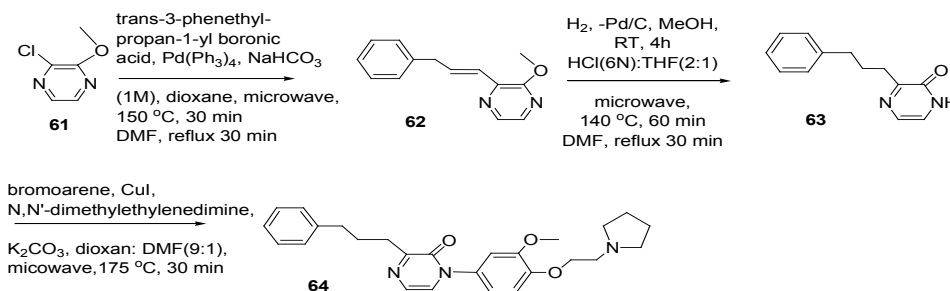
in a fast and efficient way using microwave irradiation and the whole reaction time was less than 3 h with five steps and out of five, three steps were carried out by microwave irradiation (Scheme 17).



Scheme 17. Preparation of pyrazinone core by microwave irradiation process

Second way of the synthesis this group was developed pyrazinone core 3-alkyl-1-aryl-

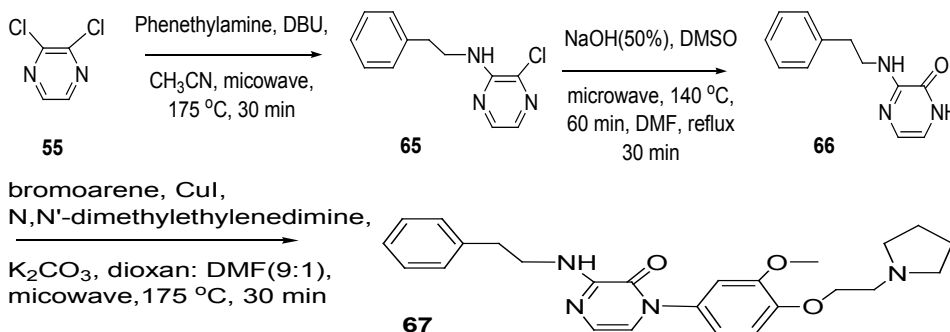
pyrazinone under microwave irradiations in all three steps with the reaction time of 4 h (Scheme 18).



Scheme 18. Second way preparation of pyrazinone core using microwave irradiation

This group was developed another way of the synthesis of 3-aminoalkyl-1-arylpyrazinones in three synthetic steps which was performed using microwave irradiation and a total reaction time of 70

min (Scheme 19). These synthetic routes are good example of use of microwave irradiation reaction can simplify chemistry and increase the efficiency of synthesis of potentially active compounds.

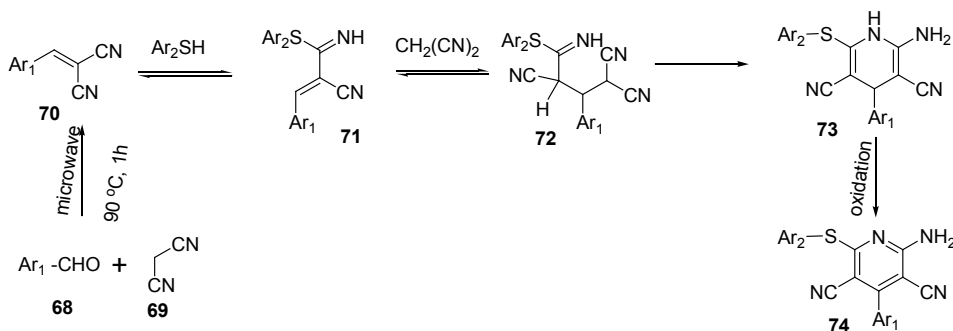


Scheme 19. Synthesis of 3-aminoalkyl-1-arylpyrazinones using microwave irradiation

Infectious diseases

Guo *et al.*, reported⁵⁷ the synthesis and biological studies of a set of pyridine dicarbonitriles as potential prion disease therapeutics and

reduced the reaction time from 24 h to 1 h at 90°C using microwave irradiation (Scheme 20) facilitating the purification and increasing the yield on an average by 15%.

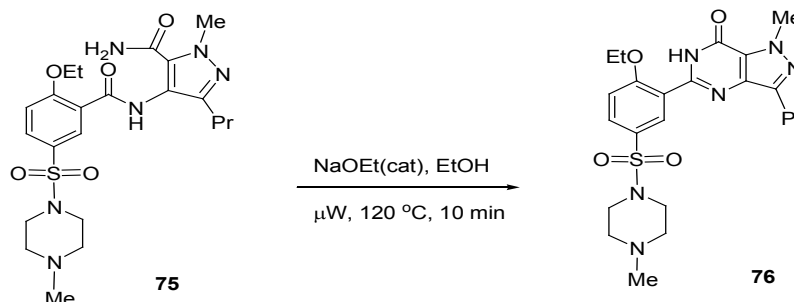


Scheme 20. Synthesis of pyridine dicarbonitriles using microwave irradiation

Erectile dysfunction

Flores-Togue *et al.*, have reported the efficiency of combining polymer-supported chemical

transformation with MAOS of the well-known commercially important pharmaceutical drug, sildenafil (Scheme 21).^{58,59}

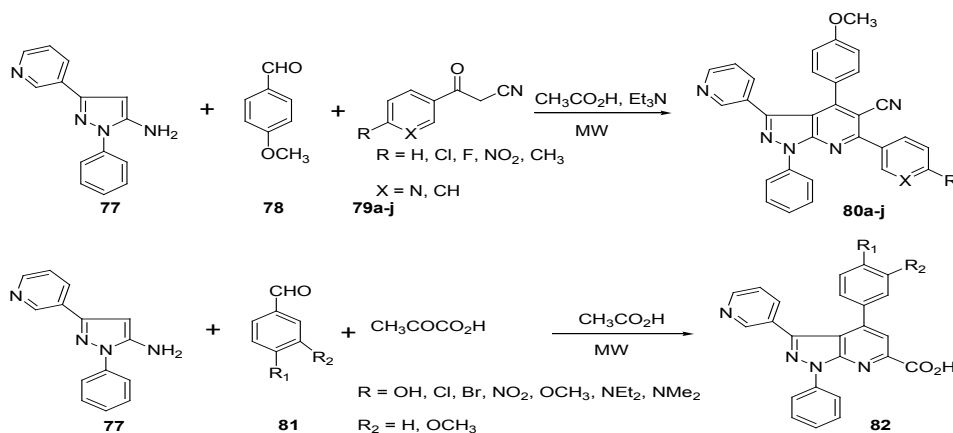


Scheme 21. Polymer-supported synthesis with microwave-assisted organic synthesis

Antitubercular, antibacterial and antitumor drugs

Rizk *et al.*, described⁶⁰ one-pot synthesis of pyrazolo[3,4-b]pyridine derivatives for antimicrobial, antibacterial⁶¹ and antitumor activities⁶² from the reaction of 5-amino-1-phenyl-3-(pyridin-3-yl)-1H-

pyrazole with 4-anisaldehyde and p-substituted β-ketonitriles or with pyruvic acid and some aromatic aldehydes in acetic acid medium using microwave irradiation in multi-component system (Scheme 22).

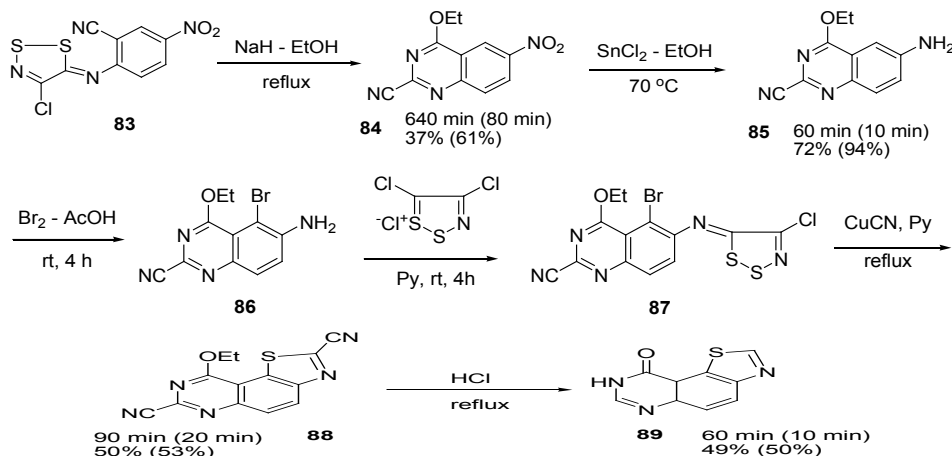


Scheme 22. Synthesis of pyrazolo[3,4-b]pyridine derivatives using microwave irradiation in multi-component system

Alzheimer's disease

The multicomponent synthesis of a thiazolo [5,4-f]quinazoline was recently synthesized⁶³

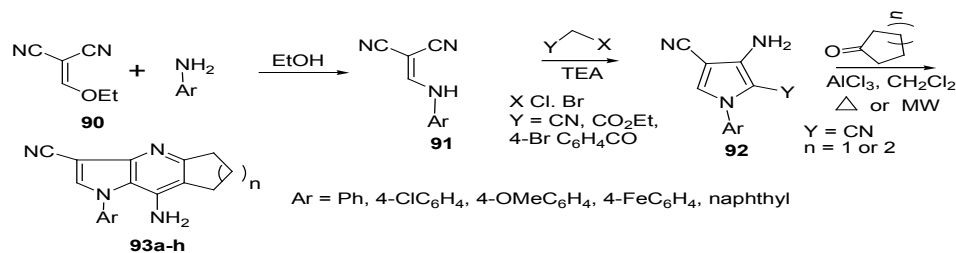
(Scheme 23) to improve yields with decrease reaction times and products that are more manageable to purification using MW heating.



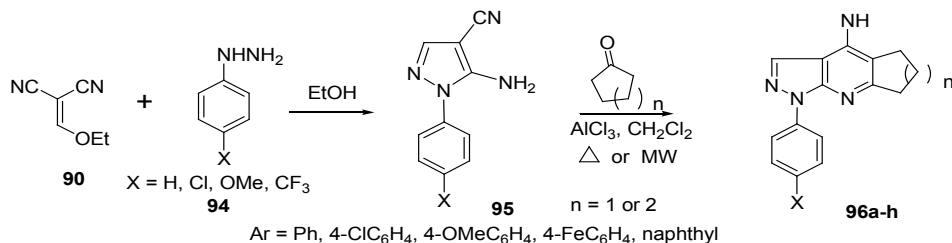
Scheme 23. Microwave assisted synthesis of a thiazolo[5,4-f]quinazoline

Mohamed *et al.*, reported number of fused five-membered aromatic ring analogues of tacrine containing halogens such as the pyrrolotacrine (Scheme 24), pyrazolotacrine

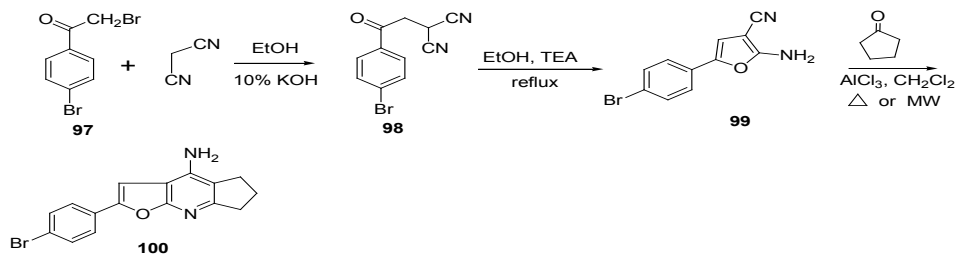
(Scheme 25), and furanotacrine (Scheme 26) heterocyclic ring systems in many ways using MW heating for the preparation of Anti-Alzheimer drug.



Scheme 24. Synthetic route of pyrazolotacrine derivatives



Scheme 25. Synthetic route for the preparation of pyrrolotacrine



Scheme 26. Synthesis of furanotacrine using MW irradiation

PET imaging agents

MAOS efficiently used to synthesize short-lived compounds with extremely short reaction times that could not be otherwise be prepared using classical methods due to decrease their continuous decaying radioactivity.⁶⁴ One most important application of activation by MAOS is in

the preparation of radiolabeled compounds for PET imaging agents for the treatment of cancer which contain short half-lives radioisotopes (Fig. 4; e.g.¹¹C,¹²²I and 18F). In all cases MAOS have reduced reaction times by up to 50% successfully and in some cases, the radiochemical yields of the final product become doubled.

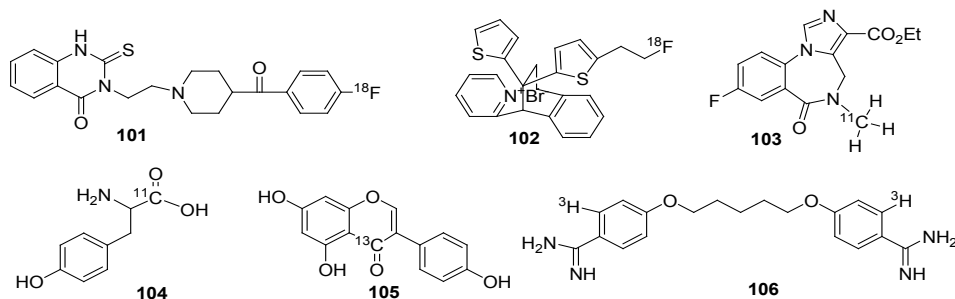
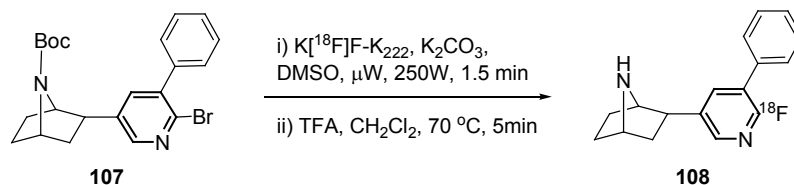


Fig. 4. Some PET with short half-lives compounds prepared using microwave irradiation

Dolle *et al.*,⁶⁵ used MW heating for the preparation of [¹⁸F]FPhEP, a novel α 4 β 2-selective antagonist for imaging nicotinic acetylcholine

receptors and the reaction time is reduced from 20 min to 90 s, to enhance the yield of the synthesis (Scheme 27).



Scheme 27. synthesis of [¹⁸F]FPhEP using microwave irradiation

MAOS have immense impact on medicinal chemistry. Kappe *et al.*, have reported⁶⁶ kinesin Eg5 inhibitor, monastrol (Fig.5 109), those were synthesized successfully under microwave conditions. They got a higher yield of the inhibitor with an improved purity compared to classing heating method using a MW-assisted Biginelli reaction. Kidwai *et al.*, have reported effectiveness in the synthesis

of the novel antibacterial β -lactams monastrol⁶⁷ with microwaves heating during the preparation of quinolones (Fig. 5; 110)⁶⁸ and cephalosporins (Fig. 5; 111).⁶⁹ The synthesis of anticarcinogenic isoflavones (Fig. 6; 113),⁷⁰ the antileukaemic alkaloid, convolutamydine-A (Fig. 6; 114)⁷¹ and the nitrogen mustard β -lactams and indoles⁷² have shown greater yield by microwave irradiation.

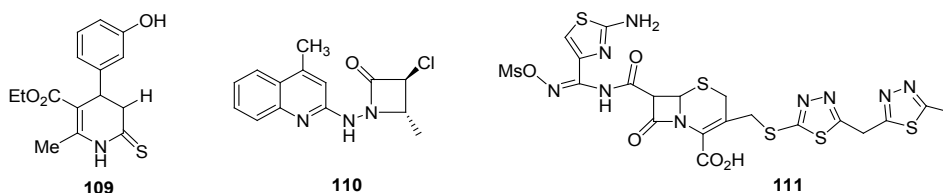


Fig. 5. Compound monastrol, quinolones, and cephalosporins

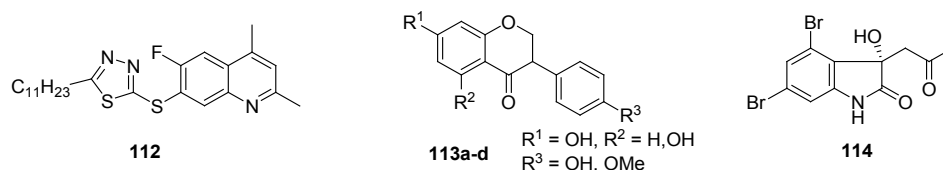


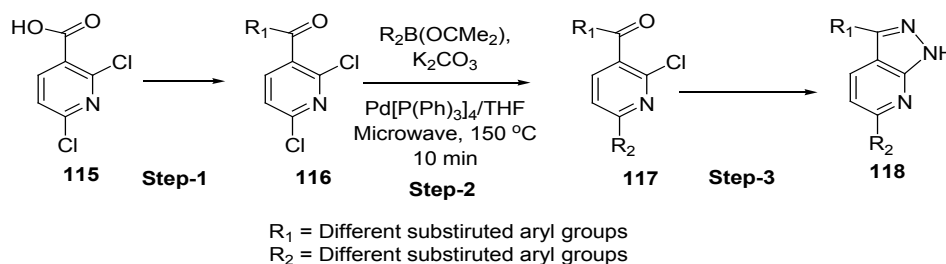
Fig. 6. Compound quinolones, anticarcinogenic isoflavones, convolutamydine-A

Medicinal and combinatorial chemistry

Hwang *et al.*, reported isotopically labelled compounds (e.g. ^{11}C , ^{122}I and ^{18}F) prepared by MAOS for PET imaging agent for cancer treatment which is required extremely short reaction time.⁷³

Bornmann *et al.*,⁷⁴ have synthesized a series of c-Kit molecules using MW-assisted reaction as an environmental friendly heating tool in multi-component system by the reaction of 2,6-dichloro

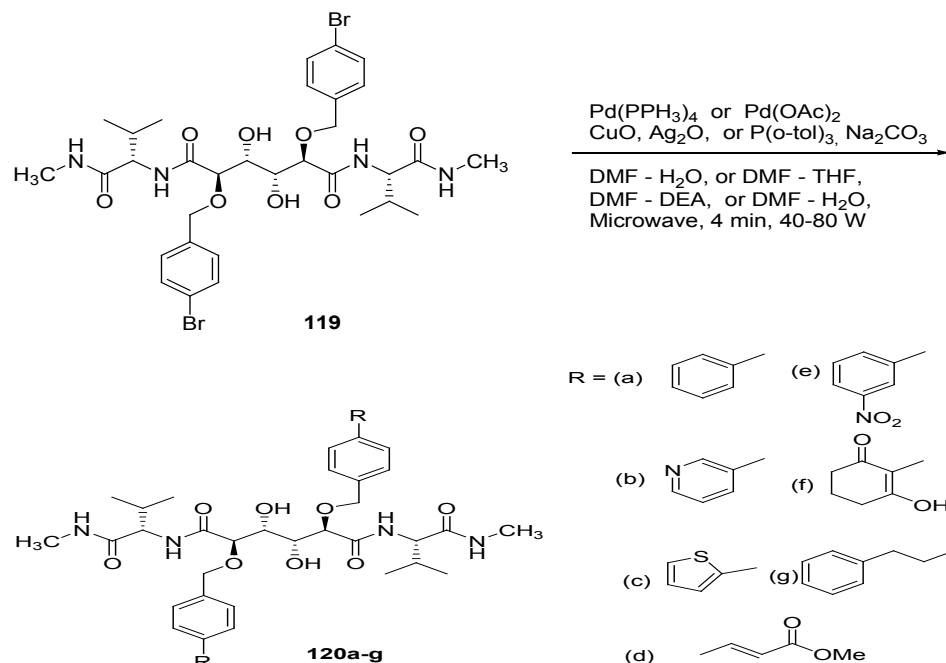
nicotinic acid chloride with the various zinc halides in presence of tetrakis(triphenylphosphine)palladium in 2 mL of THF. Suzuki coupling reaction were carried out under MW heating at 150°C for 5 to 10 min produced 24 compounds at a time using CEM microwave reactor and the yield of the reactions are more than 25 percentages where in conventional heating the reaction time is three days and the of the reactions are less than 15 percentages and needs more solvent.



Scheme 28. Synthesis of pyrazolo compounds under MW irradiation

Hallberg *et al.*, have reported their quick preparation of modified HIV⁻¹ protease inhibitors (Scheme 29; 120a-g) by the use of microwave-promoted coupling reaction. The commercially

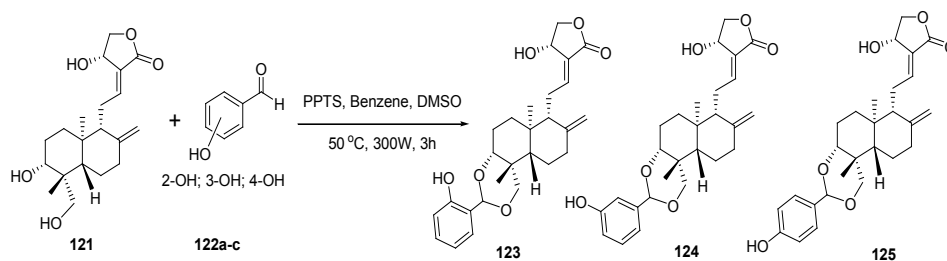
available aryl and heteroarylboronic acids and palladium-catalyst were used during coupling reaction (Scheme 29) under MW heating in which the yield of desired compounds is very high.⁷⁵



Scheme 29. Synthesis of HIV protease inhibitor

Levita *et al.*,⁷⁶ reported the semi-synthesis of andrographolide analogues of anti HIV⁻¹ drugs by modifying a synthesis method that has been

successfully carried out by Hadi Poerwono *et al.*, using microwave irradiation due to achieve several advantages.

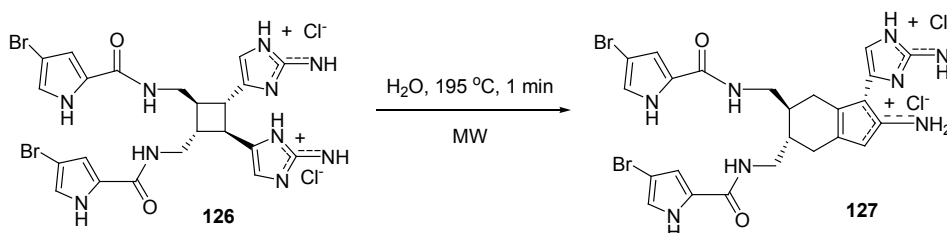


Scheme 30. The synthesis of 2-hydroxybenzylidene andrographolide (**123**), 3-hydroxybenzylidene andrographolide (**124**), and 4-hydroxybenzylidene andrographolide (**125**)

Antiviral drugs

Baran *et al.*, described the total synthesis of ageliferin, an antiviral marine alkaloid by a tautomerization/ring expansion reaction from sceptrin.⁷⁷ The product was successfully achieved

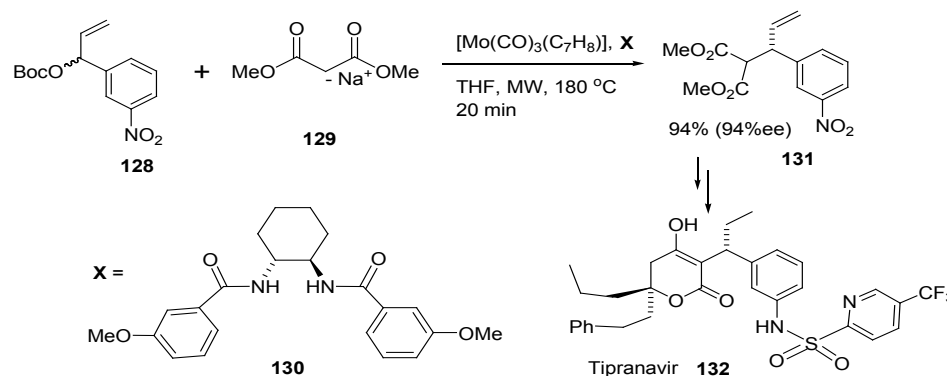
by MW heating only in water within a minute and the yield of the reaction is 40% (Scheme 31). Whereas by the use of conventional heating takes longer time and led to decompose the unstable compound.



Scheme 31. Microwave-assisted transformation of sceptrin into ageliferin

Trost and Andersen recently have applied⁷⁸ the concept in their approach to the orally bioavailable HIV inhibitor tipranavir (Scheme 32). Preparation of the key chiral intermediate **130** was obtained by asymmetric allylic alkylation beginning from carbonate **128**. The yield of the product was obtained about 94% by employing 10 mol% of the molybdenum

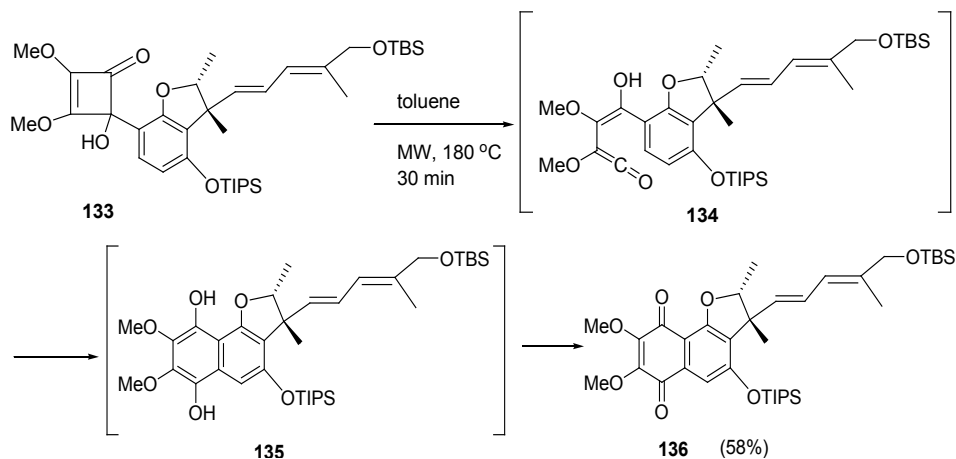
precatalyst and 15 mol% of the chiral ligand **131** with 2.0 equivalents of sodium dimethylmalonate as the additive. The synthesis was transformed under sealed-vessel MW heating at 180 °C for 20 min. Whereas classical heating (67 °C) required 24 h and produced almost same chemical yield of intermediate **130**, albeit with slightly higher enantiomeric purity (96% ee).



Scheme 32. Rearrangement of a squaric acid derivative to a vinylketene

Trost *et al.*, have synthesized successfully furaquinocin antibiotics by the microwave-assisted squaric acid/vinylketene rearrangement for the preparation of dimethoxynaphthoquinone **135** which is a protected analogue of furaquinocin E (Scheme 33).⁷⁹ The rearrangement reaction

from the compound **133** to **134** using oil bath heating was unsuccessful. The same conversion was attempted under MW irradiation at 180 °C in toluene led to complete conversion with an admissible yield of **136** (58%) after oxidation to the naphthoquinone.

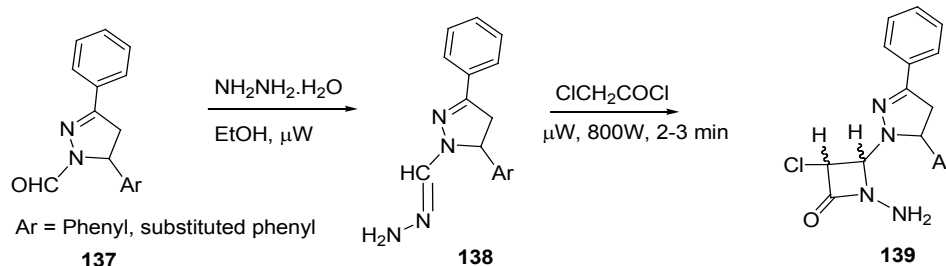


Scheme 33. Rearrangement reaction under MW irradiation from squaric acid derivative to a vinylketene

Anticancer agents

Banik *et al.*, described an efficient synthesis of 3-substituted-4-phenyl-1-(9,10-dihydrophenanthren-3-yl)azetidin-2-ones using Staudinger cycloaddition under microwave

irradiation.⁸⁰ The diastereoselectivity of the product formation depends on temperature, the nature of substituent on lactam nitrogen the power level of the microwave irradiation and the polarity of the solvent.



Scheme 34. Synthesis of β -lactam under MW irradiation

Gomha *et al.*, reported⁸¹ an efficient and a novel approach for the synthesis of some novel 4-heteroaryl-pyrazoles (Fig. 7), which have reported hitherto in a multicomponent synthesis under MW irradiation and to assess their

anticarcinogenic effects against hepatocellular carcinoma (HepG-2) and human lung cancer (A-549) cell lines and showed that oxazoles are the most active compounds against the lung carcinoma cell line (A549), compared with cisplatin.

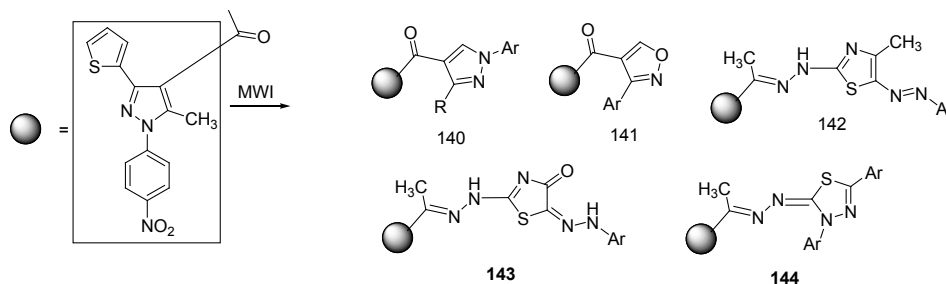
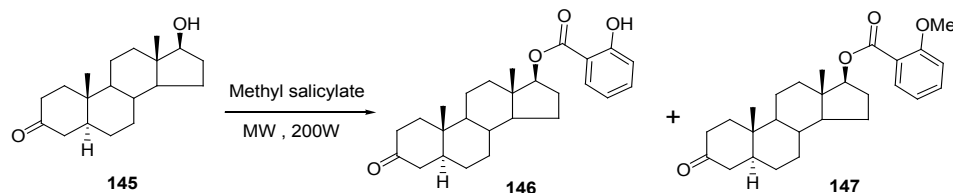


Fig. 10. Synthesis of some novel 4-heteroaryl-pyrazoles

Jovanovic-Santa *et al.*, reported⁸² an efficient microwave-assisted synthesis of 2-methoxybenzoyl ester without solvents which shows important potency against MDA-MB-231 cells

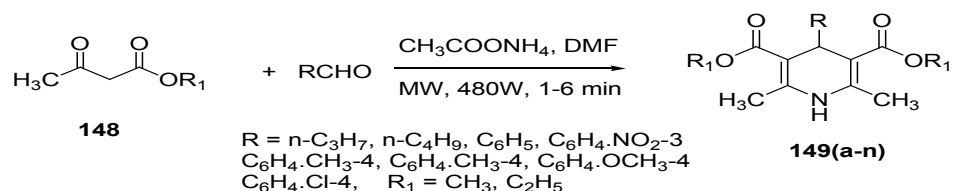
and maximum compounds are used to show their strong growth inhibition property against PC-3 cells. The most inhibition potency showed the salicyloyloxy stigmastane derivative (Scheme 35).



Scheme 35. Microwave-assisted synthesis of 2-Methoxybenzoyl ester

G. Achaiah, RV. Malla *et al.*, have been synthesized 83 fourteen new 4-alkyl/aryl/aryl-2,5-bis-(carbomethoxy/carbomethoxy)-1,4-dihydro-2,6-dimethyl pyridines carbomethoxy derivatives under conventional and MW irradiation from a one-pot three-component reaction mixture

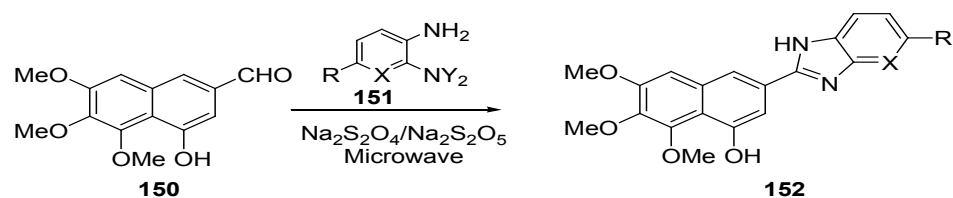
consisting of alkyl acetoacetate, aldehyde and ammonium acetate. All most all compounds revealed their cytotoxicity against MCF-7 and A549 cancer cell lines and exhibit moderate-to-good anticancer activity against these cell lines (Scheme 36).



Scheme 36. Synthesis of 1,4-dihydro-2,6-dimethyl pyridines under classical and MW heating method

H.T. Buu Bui and his coworkers reported⁸⁴ twelve novel 2-quinolizinybenzimidazole and 2-aphthalylbenzimidazole type compounds with molecular variation generates by the substituents at positions 5- and 6 (aza, H, CH₃, Cl, NO₂, NH₂, OCH₃), via the condensation

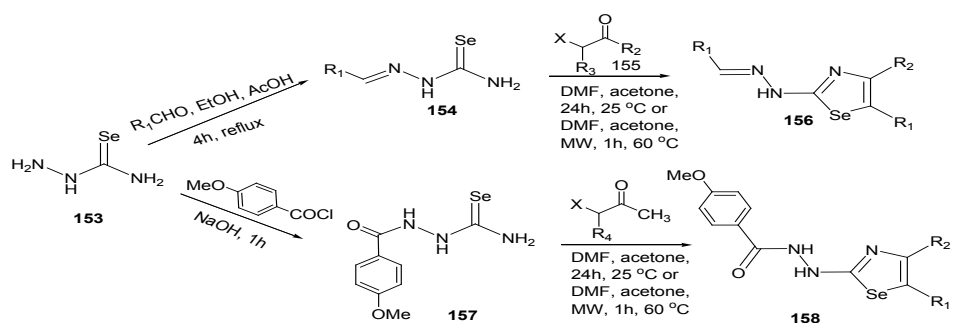
of 4-oxo-4H-quinolizinecarbaldehyde or naphthalenecarbaldehyde with substituted *o*-phenylenediamines, *o*-nitroaniline and 2,3-pyridinediamine and use of sodium metabisulfite or sodium hydrosulfite as catalyst by the MW condition (Scheme 37).



Scheme 37. Synthesis of quinolizinybenzimidazole and 2-naphthalylbenzimidazole type compounds by the microwave condition

L. Gaina *et al.*, reported⁸⁵ some novel 1,3-selenazole compounds under microwave assisted Hantzsch condensation reactions. Anti-proliferative effects for these compounds were tested against

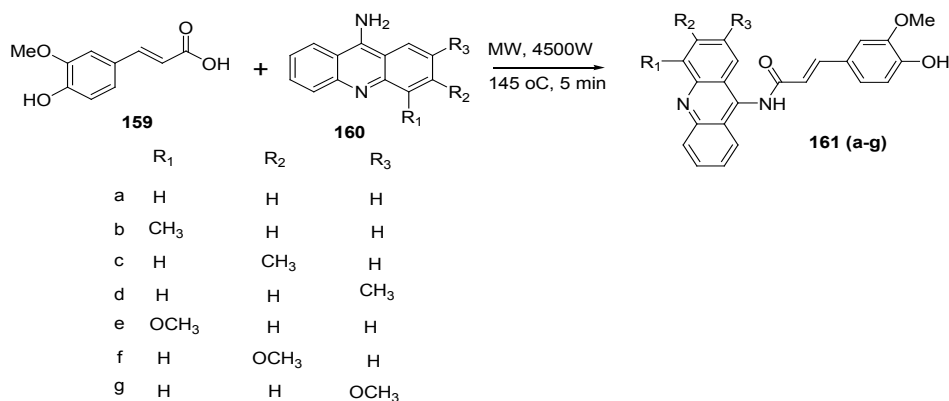
leukemia cell lines (HL60 and CCRF-CEM) and carcinoma cell lines (HCT116, MDA-MB231 and U87MG). The result showed moderate cytotoxicity for all the experimented cell lines (Scheme 38).



Scheme 38. Synthesis of 1,3-selenazole compounds under microwave assisted Hantzsch condensation reactions

N. Kumar *et al.*, designed and synthesized 86 three different series of amide derivatives of ferulic acid by MW heating in absence of solvent. All the compounds were found stable upto 100°C during their thermal stability test but at higher temperature these

compounds decomposed through single step. These compounds were tested their anticancer activity against breast (MDA-MB-231 and MCF-7), cervical (HeLa), lung (A549) and liver (HepG2) human cancer cell lines (Scheme 39) and these compounds exhibit noticeable activity.

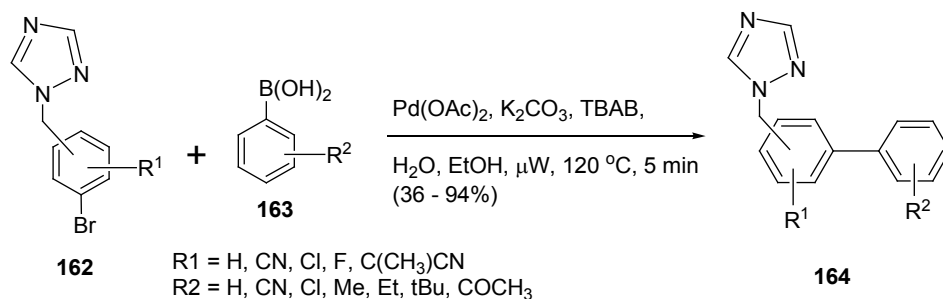


Scheme 39. Synthesis of a series of amide derivatives under microwave-assisted reaction

Aromatase inhibitors

Potter *et al.*, synthesized⁸⁷ a series of novel and potent aromatase inhibitors,

active heterocyclic compounds using Suzuki cross coupling methodology under microwave irradiation.



Scheme 40. Synthesis of a series of heterocyclic compounds by microwave-assisted reaction

Antiarrhythmic, anticonvulsant, antineuralgic, trigeminal neuralgia and skeletal muscle relaxant

Hydantoin compounds have showed a wide range of medicinal properties (Fig. 8), such as, phenytoin acts many purposes, like anticonvulsant, antiarrhythmic, trigeminal neuralgia, antineuralgic and skeletal muscle relaxant.⁸⁸ Sulfahydantoin has been identified on the respect of inhibition of

serineproteases.⁸⁹ The glucopyranosylidene-spirothiohydantoin is described⁹⁰ that it inhibits efficiently of muscle and liver glycogen phosphorilases.⁹¹ Mei-Jung Lin and Chung-Ming Sun⁹² have developed a hybrid strategy using both microwave irradiation and combinatorial approach. Thiohydantoin were synthesized by the following route is shown in Scheme 41.

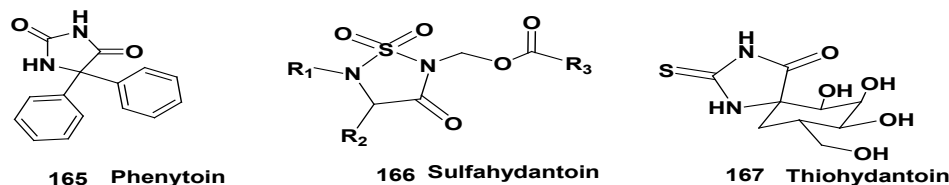
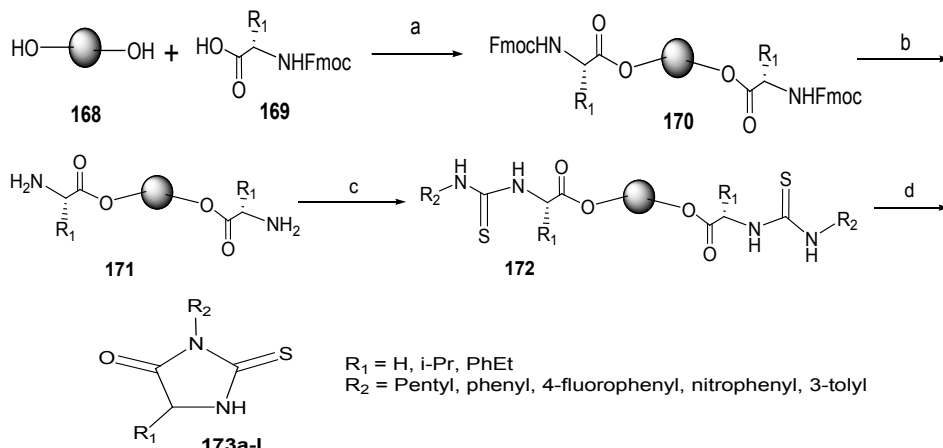


Fig. 8. Some medicinally interesting hydantoin analogs

Reagents and conditions

(a) DCC, DMAP, CH₂Cl₂, MW, 150 W, 14 min; (b) 10% piperidine, CH₂Cl₂, 25°C, 1 h; (c)

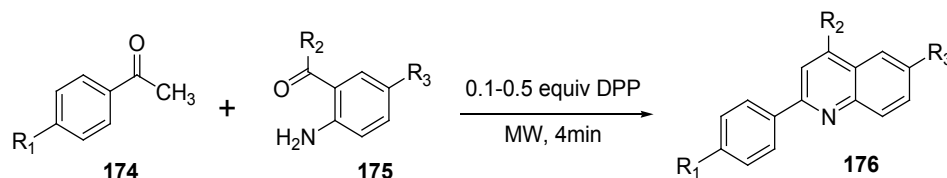
R₂NCS, CH₂Cl₂, MW, 150 W, 7 min; (d) K₂CO₃, CH₂Cl₂, MW, 150 W, 7 min (88-99%).



Scheme 41. The general synthetic route of thiohydantoin synthesis of by microwave-assisted reaction

Quinolines are well known for their salient biological activities and also for the development of polymers and conjugated molecules that integrate increased electronic or nonlinear optical properties with good instinctive properties. Kwon reported the synthesis of some quinoline derivatives using Friedlander coupling condensation between an

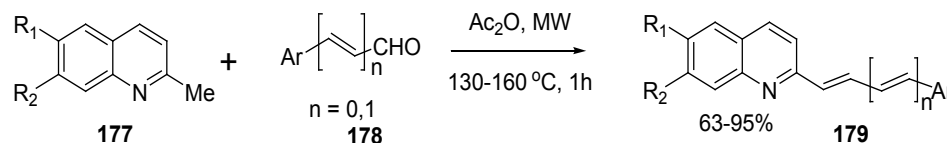
acetophenone and a 2-aminoacetophenone in the presence of diphenylphosphate (0.1–0.5 equiv.) within 4 min under MW irradiation in solvent free condition.⁹³ This yields of the products are up to 85% when MW irradiation technology is used, and the yield achieved not more than 24% with classical heating by the same conditions.



Scheme 42. Solvent free synthesis of quinoline derivatives under MW irradiation

Menéndez described solvent free microwave-assisted synthesis of 2-styrylquinolines by condensation of 2-methylquinolines with cinnamaldehydes or benzaldehydes in the presence

of acetic anhydride⁹⁴ (Scheme 43) which are valuable derivatives for Alzheimer patients as imaging agents for β -amyloid plaques on human brain sections.



Scheme 43. Preparation of 2-styrylquinolines using MW

CONCLUSION

In this review we tried to give an outline of microwave assisted synthesis and it has already exercised a huge impact on medicinal chemistry. Microwave dielectric heating has many advantages compared to conventional heating in the medicinal

synthesis. MW heating decreased reaction times from days to minutes, achieved higher yields, heating rates become higher than those achieved from classical heating. There is no direct touch between the energy source and the reacting substances. Sometime achieve magical transformation which is impossible to realize by oil bath heating. Microwaves

interacts selectively between the reactants and solvents and in many cases in the absence of solvents i.e. solvent free reactions, provides clean reactions without the formation side products which are impossible using conventional heating. Such an enormous superior new technology is engaged in the field of medicinal chemistry. This new technology can facilitate the bottlenecks within the drug discovery arena. Before chemists were used simple or 'adapted' domestic instruments for their reaction system. Last twenty years, the appearance of new several commercial instruments with advanced technology available to the bench of chemist. These facilities of new technology help to overcome the problems of reproducibility, controllability and safety experienced with the domestic microwaves during the transformation of reactions. This technology is utilized in the laboratory and helps on the fields of medicinal chemistry with screening and making library of compounds for the drug design and drug development. Though this modern technology has huge facility in the laboratory but the major drawbacks

of this relatively new technology is cost management of equipment. The recent price of microwave reactors for the reaction purpose is still many times higher than that of classically heating instruments though prices for microwave reactors have come down considerably since their first introduction in the late 1990s. Now be of the opinion that the use of microwave heating in medicinal chemistry will be normalized in the coming years since this technology assures the requirements of both the pharmaceutical laboratory and academic purpose.

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Conflicts of Interest

The authors announce that there is no conflict of interest.

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