Research Paper

Volume : 4 | Issue : 9 | Sept 2015 • ISSN No 2277 - 8179

Microwave – A Magical Tool

Pharma

KEYWORDS :

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INTRODUCTION:

Albeit domiciliary microwave ovens have been widely used since the 1970s, the first reports that these energy sources were also befitted for accelerating organic reactions did not emerge until 1986. Microwave-assisted organic synthesis was firstly demonstrated independently in the research labs of Giguere and Gedye. Both demonstrated that the use of microwave ovens dramatically accelerated the rate of numerous organic reactions. Thereafter, microwave heating has been enforced not only to reduce reaction times but also to improve yields and selectivity[5].

Microwave-assisted heating under controlled conditions is an invaluable technology for medicinal chemistry and drug discovery applications because it often stunningly reduces reaction times, typically from days or hours to minutes or even seconds. Compound libraries can then be promptly synthesized either in a parallel or sequential (automated)format. In addition, MAOS technology often eases the discovery of novel reaction pathways, because the extreme reaction conditions feasible by microwave heating sometimes lead to anamalous reactivity that cannot always be reproduced by conventional heating. Microwave synthesis has the dynamism to influence medicinal chemistry efforts in at least three major phases of the drug discovery process: generation of a discovery library; hit-to-lead efforts; and lead optimization.

Microwave irradiation[3]:

Electro magnetic irradiation in the frequency range of 0.3–300 GHz, corresponding to wavelengths of 1 cm–1 m. All microwave reactors for chemical synthesis run at a frequency of 2.45 GHz (corresponding to a wavelength of 12.25 cm) to bypass intervention with telecommunication and cellular phone frequencies.

Theory[3]: MAOS is primarily based on the efficient heating of materials by 'microwave dielectric heating'effects. Microwave dielectric heating is reliant on the capacity of a specific material to absorb microwave energy and transform it to heat. Microwave irradiation generates heating by two main mechanisms: dipolar polarization and ionic conduction. Whereas the dipoles in the reaction mixture (for example, the polar solvent molecules) are involved in the dipolar polarization effect, the charged particles in a sample (usually ions) are affected by ionic conduction. When irradiated at microwave frequencies, the dipoles or ions of the sample alienate in the applied electric field. As the applied field oscillates, the dipole or ion field tries to realign itself with the alternating electric field and, in the course, energy is lost in the mode of heat through molecular friction and dielectric loss. The extent 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.

When comparing the ability of different solvents to interact with microwave radiation, two important considerations are (1) the solvent's ability to absorb microwave energy and (2) its ability to mutate the absorbed energy into heat. The interaction of a solvent with microwave irradiation is highly complicated. As well as being dependent on the solvent's dielectric properties, which are in turn dependent on the temperature of the solvent and the frequency of the applied radiation, the interaction is also dependent upon the viscosity of the solvent (which is also temperature dependent). The best similarity for the correlation of different solvents is to compare their loss tangent values. The loss tangent (tanδ) is defined as the tangent of the loss angle which is the fraction between the dielectric constant, ε′ (which describes the solvent's ability to absorb microwave energy) and the loss factor, ε′′ (which quantifies the efficiency with which the absorbed energy is converted to heat).

Table1: values of solvent loss tangents[2]

Solvent	Dielectric constant(εσ)[a]	Loss tangent(tanδ)[b]
Hexane	1.9	-
Benzene	2.3	-
Carbon tetrachloride	2.2	-
Chloroform	4.8	0.091
Acetic acid	6.1	0.174
Ethyl acetate	6.2	0.059
THF	7.6	0.047
Methylene chloride	9.1	0.042
Acetone	20.6	0.054
Ethanol	24.6	0.941
Methanol	32.7	0.659
Acetonitrile	36.0	0.062
Dimethyl formamide	36.7	0.161
Dimethyl sulfoxide	47.0	0.825
Formic acid	58.0	0.722
Water	80.4	0.123

a The dielectric constant, εs, equals the relative permittivity, ε′, at room temperature under the influence of a static electric field.

b Values determined at 2.45 GHz and room temperature.

Abbreviation: THF, tetrahydrofuran.

When the dielectric properties of the sample are too low to allow efficient heating by microwave radiation, the addition of traces of additives (e.g. ionic salts) that have large loss tangent values can significantly overcome these problems and empower adequate heating of the whole mixture. This often provides a promising way of using non polar solvents for running syntheses using microwave radiation.

Non polar molecules such as toluene, carbon tetrachloride, diethyl ether, and benzene are microwave-inactive, while polar mol-

ecules such as DMF, acetonitrile, CH2Cl2, ethanol, and H2O are microwave-suitable (i.e., polar molecules can align themselves with the electric field).

Equipment Needed[3]:

There are two types of reactors for microwave-assisted organic synthesis: a multimode reactor and a monomode reactor The most frequently widely used apparatus is the multimode reactor.

All the specialized microwave reactors commercially available nowadays feature built-in magnetic stirrers, direct temperature control of the reaction mixture with the aid of fiber-optic probes or infrared sensors, and software that permits on-line temperature and pressure control by control of microwave power output.

B | Microwave reactor technology for high-throughput synthesis and scale-up. **Ba** | Automated single-mode

microwave synthesizer (Initiator 60; Biotage AB). A robotic gripper device moves the sealed reaction vessels

(0.2–20 ml) in and out of the microwave cavity. Up to 60 reactions can be processed in an automated sequential fashion. **Bb** | Continuous-flow single-mode microwave reactor (Voyager; CEM Corp.). Scale-up is achieved by pumping reaction mixtures in and out of an 80-ml sealed reaction vessel following a stop-flow processing regime. **Bc** | Set-up for parallel microwave synthesis (CombiCHEM system; Milestone Inc.). The barrel-type overhead rotor system (left) can hold up to two 96-deep-well microtitre plates (right) for parallel synthesis on a 0.5–4-ml scale. The set-up is irradiated in a multimode microwave reactor (not shown). **Bd** | Multimode microwave scale-up system for parallel batch processing (Synthos 3000; Anton Paar GmbH). Microwave synthesis is performed in multivessel rotors (8 or 16 vessels) with reaction volumes of up to one litre.

High-throughput microwave synthesis[3]:

High-speed MAOS is applicable to a wide variety of synthetic transformations. It is becoming evident that microwave approaches often providing faster reactions and improved yields can probably be developed for most chemical transformations that require heat. Whereas in the past microwave chemistry was often applied only to a difficult or slow reaction step, today the number of examples in which microwave heating is used for many, if not all, of the reactions in a multistep synthesis is rapidly growing.

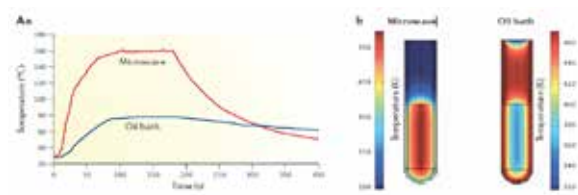
Advantages of microwave synthesis[3]

- Higher reaction temperatures can be obtained by connecting rapid microwave heating with sealed-vessel (autoclave) technology
- In many examples significantly reduced reaction times, higher yields and precise reaction profiles will be experienced, allowing for more hasty reaction optimization and library synthesis.
- Solvents with lower boiling points can be used under pressure (closed vessel conditions) and be heated at temperatures markedly higher than their boiling point.
- Microwave heating helps direct 'in core' heating of the reaction mixture, which results in a faster and more uniform heating of the reaction mixture
- Specific microwave effects(defined as accelerations in rate that cannot be attained or created by conventional heating, but that are essentially still attributed to thermal effects) that cannot be reproduced by conventional heating can be exploited for instance, the selective heating of strongly microwave-absorbing catalysts.
- Easy on-line regulation of temperature and pressure profiles is possible, which leads to more consistent reaction conditions.
- Microwave heating is more energy conserving than classical oil-bath heating because of direct molecular heating and inverted temperature gradients.
- Can easily be fitted to automated sequential or parallel synthesis.

Economics of Microwave Systems:

Several criteria for effective microwave drying systems are related to reduced cost. Cost saving may be realized through:

1. Energy conserving
2. Faster batch conversions
3. Operational efficiencies
4. Improved throughput
5. Labor reduction
6. Reduction in heat load in the plant
7. Reduced maintenance expenditure
8. Cut short in product fouling
9. Less floor occupancy needed



Differences between conventional and microwave heating, and examples of microwave reactor

technology. Aa | Variation in temperature profiles for a 5-ml sample of ethanol (boiling point 78 °C) heated under single-mode, sealed-vessel microwave irradiation (maximum set temperature 160 °C) and open-vessel oil-bath conditions (oil-bath temperature 100 °C) for 3 minutes. Dielectric heating with microwave energy is momentously more rapid than heating in an oil-bath by convection currents. Both experiments were performed in the same reaction vessel with stirring using an internal fibre-optic temperature-monitoring device. Using sealed-vessel microwave irradiation, a significantly higher temperature can rapidly be reached, compared with the oil-bath experiment, which was carried out under standard open-vessel reflux conditions. After the set temperature of 160 °C is reached in the microwave experiment (~100 s), an algorithm controlled by feedback with the temperature-monitoring device regulates the microwave power to maintain the set temperature. Active gas-jet cooling (180–400 s) then briskly cools the reaction mixture after microwave irradiation. **Ab** | Inverted temperature gradients in microwave versus oil-bath heating. Temperature profiles (modelling) 1 minute after heating by microwave irradiation (left) compared with treatment in an oil-bath (right). Microwave irradiation raises the temperature of the whole volume concurrently(bulk heating), whereas in the oil-heated tube the reaction mixture in contact with the vessel wall is heated first. Temperature scale in Kelvin.

ROLE OF MICROWAVE IN 3 MAJOR PHASES OF DRUG SYNTHESIS:[2]

The drug discovery process:

MAOS can cause impact in certain areas of drug discovery and is not only restrained to areas related to organic synthesis. Microwave technology is also being used in target discovery, screening, pharmacokinetics and in the clinic too.

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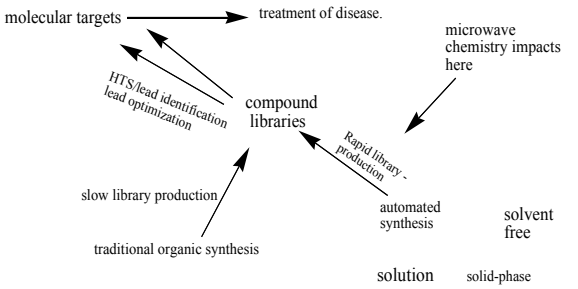
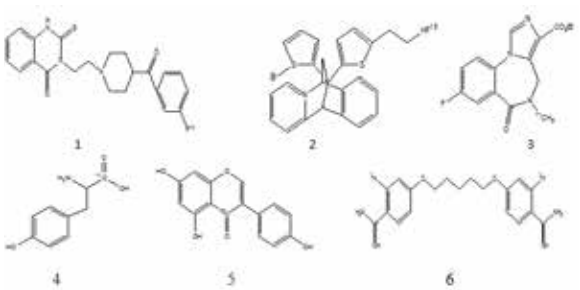


MOLECULAR TARGETS ⟶ TREATMENT OF AILMENTS

Figure1[5]: The drug discovery process and the foreseen impact of microwave chemistry on automated medicinal/combinatorial chemistry. Present day, novel therapeutic macromolecular targets are progressively being diagonised as drug targets. The urgency for new organic small molecules to feed the HTS facilities is, thence, acute in the pursuit of new hits. The lead generation and lead optimization processes must be hastened. Traditional and conventional methods of organic synthesis are honestly too slow to satisfy the forthcoming demand for compounds. Microwave-assisted chemistry is a craft that has the potential to accelerate the innovation of organic molecules

Screening and target discovery[2]:

One exotic application of activation by MAOS is in the preparation of radiopharmaceuticals that encompass isotopes with terse half-lives In these contexts, MAOS has been lucrative in abbreviating reaction times by up to 50% and has, in a few cases, doubled the radiochemical yield of the final product. Seemingly the primal use of microwave-enhanced radiochemistry was in the synthesis of positron emission tomography (PET) pharmaceuticals for expeditious use in human PET and *in vivo* rat imaging studies. The first use of microwaves in PET was reported in 1987.



Drug	Radio labelled atom	Type of receptor
Altanserine(1)	^{18}F	
New ligand (2)	^{18}F	NMDA
N-methyl flumazenil(3)	^{11}C	Benzodiazepine receptor antagonist
Tyrosine(4)	^{13}C	
Isoflavanoid phytooestrogen(5)	^{13}C	
Pentamidine(6)	^{3}H	

LEAD GENERATION AND ESCALATION[2]:
MICROWAVE ASSISTED PARALLEL SYNTHESIS:

In its most fertile form, MICROCOS uses multicomponent reactions for the synthesis of wide and diverse libraries. A library of 8000 cellulose-bound triazines (Fig. 2; **8**) has been produced by applying the spot-synthesis technique to a cellulose or polypropylene membrane . The decisive step in the production of this library was the microwave-assisted nucleophilic substitution of a membrane bound monochlorotriazine (Fig. 2; **7**). A distinction and extension to the **spot-synthesis technique** has been reported by Williams (Fig. 2). This new procedure combines synthesis, purification, analysis and screening of combinatorial libraries, all on a single thin-layer chromatography (TLC) plate. After spotting the reagents on the baseline, the plate was irradiated with microwaves for five minutes.(585 W) and cooled. The products were then eluted and isolated from the silica. A library of 40 *N*-substituted arylpiperazines (Fig. 2; **9**) was synthesized and purified for biological screening in 30 minutes. This methodology has been protracted to incorporate screening by bio-autographical agar overlay.

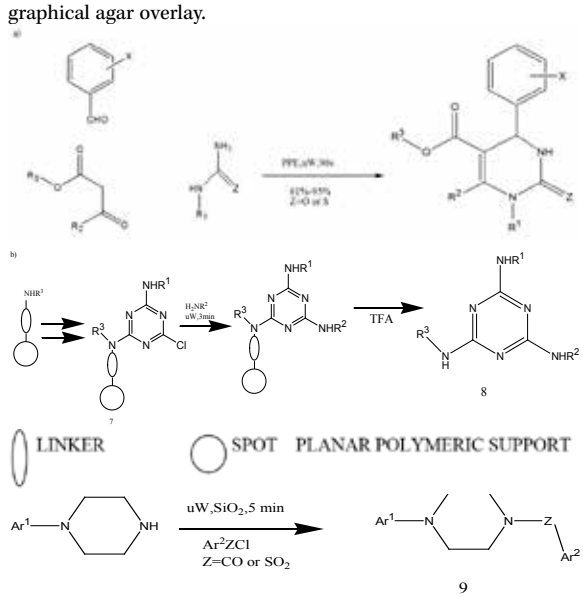


Figure 2[2]: Examples of microwave aided parallel synthesis. a)biginelli reaction b)cellulose and poly propylene spot synthesis C) silica spot synthesis. Ar^1 and Ar^2 are various substituted aromatics. Abbreviations: PPE-polyphosphoric acid, TFA-trifluoro acetic acid.

A recent concept in drug discovery is Diversity Oriented Synthesis (DOS), a high yield of the corresponding nitrogen heterocycle. Compared with classical thermal heating (8–24 hours,30–65% yields), there is a marked acceleration in the rate of the reaction. Protocols for the rapid preparation of diverse compilations of heterocyclic scaffolds from common 1,2-diketone intermediates (FIG. 3a) have been developed 35– 40 and simple, high-yielding microwave-assisted procedures have been reported for the preparation of diversely substituted 1,2,4-triazines, imidazoles, fused pyrazines (for example, quinoxalines), pyrazin- 2(1*H*)-ones38 and canthine derivatives (FIG. 3a). In most cases, condensation of a suitable 1,2-diketone building block, which serve as multifariousness elements, with the appropriate reaction partner(s) required only 5–10 minutes of microwave irradiation and resulted in a high yield of the corresponding nitrogen heterocycle. Compared with conventional thermal heating (8–24 hours, 30–65% yields), there is a notable acceleration in the rate of the reaction.

Based on the highly prolific microwave chemistry displayed in FIG. 3a, a series of potent and choosy allosteric AKT (also known as protein kinase B (PKB)) kinase inhibitors were developed. These inhibitors were derived from a 2,3-diphenylquinoxaline core and have an miraculous level of selectivity for

both AKT1 and AKT2. AKT is a serine/threonine kinase that has enticed a great deal of consideration as a promising molecular target for cancer therapy because of its crucial role as a regulator of the apoptotic machinery of cells. Both isozymes AKT1 and AKT2 are commonly over expressed or constitutively active in a large number of human cancers, including brain, gastric, colon, breast, lung and prostate carcinomas, and their activation corresponds with cancer progression[3].

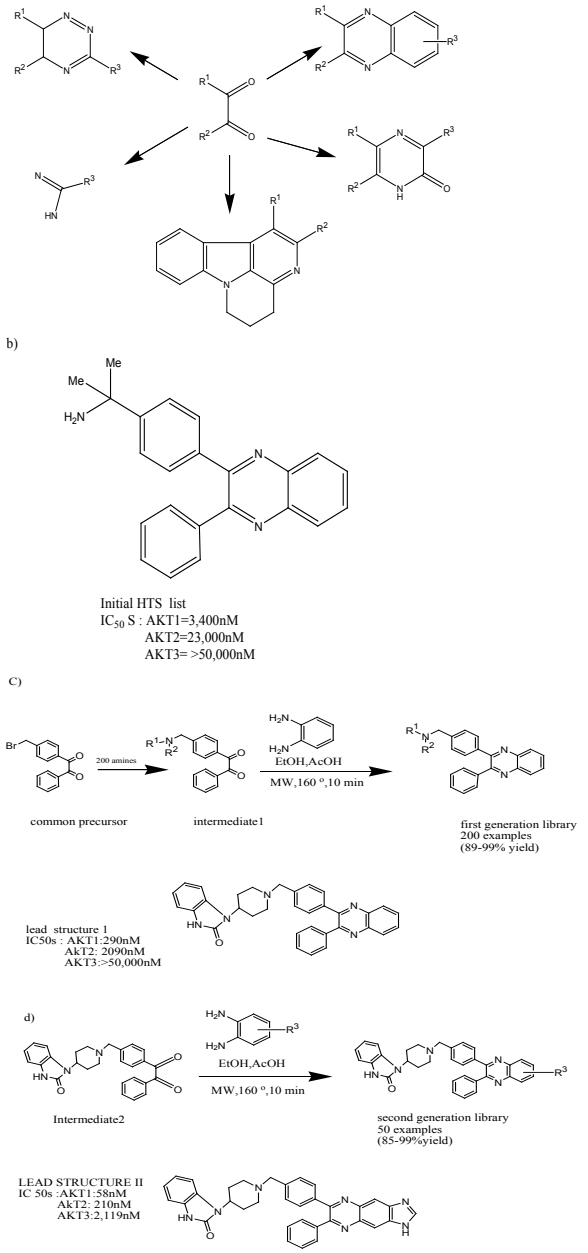


Figure 3[3] | **Lead generation and optimization of allosteric AKT kinase inhibitors derived from a 2,3-diphenylquinoxaline core. a** | Accelerated generation of heterocyclic scaffolds with potential biological activity using 1,2-diketones as common forerunners. In most cases, the final products were achieved within 10 minutes of microwave irradiation using suitable reaction partners. **b** | Original lead structure derived from high-throughput screening (HTS) showing modest AKTkinase inhibitory activity. **c** | First cycle of lead generation addressing the amine moiety. Automated sequential microwave synthesis led to 200 analogues in high yields, providing lead structure I with improved inhibitory activity. **d** | Second cycle of lead generation addressing the heterocyclic quinoxaline core. Microwave synthesis delivered 50 second-generation analogues, including a dual AKT1/AKT2 inhibitor with nanomolar activity (lead structure II).

Lead optimization of the malarial proteases plasmepsin I and II inhibitors [3]:

Microwave technology has also been applied in transition metal-catalysed reactions for the rapid optimization of inhibitors of the malarial proteases plasmepsin I and II (PlmI and PlmII, respectively). The recent publication of the genome of *Plasmodium falciparum*, the most devastating of the protozoan parasites causing malaria, has unfolded a number of new targets for drug intervention. Among these are the haemoglobin degrading aspartic proteases PlmI and PlmII. A few inhibitors for these proteases have been described in the biography. Nonetheless, selectivity towards the hugely autologous human aspartic cathepsin D (CatD) has been a trivial issue.

several focused libraries targeted for the inhibition of PlmI and PlmII were synthesized41 (FIG. 4). A hydroxyl ethylamine-based inhibitor (FIG. 4a) derived from a rational design approach was used as a starting point. To increase the structural diversity at the important P1′ side-chain of the inhibitor, a suitable aryl bromide-precursor was subjected to automated microwave-assisted Suzuki cross-coupling chemistry. The reaction with a diverse set of boronic acids under palladium catalysis allowed the production of a set of eight new inhibitors in moderate yields41. Among those, a lead structure with significantly improved potency with a benzofuran substructure was identified (lead structure III, FIG. 4b). In addition to the investigation of the P1′ side chain, substitution at the P3 position was also studied by reacting a diverse set of carboxylic acids with the primary amine. Next, the same microwave-assisted Suzuki arylation strategy was used to generate a second set of inhibitors that incorporated the biphenyl P1′ moiety from the original lead structure. From the nine new substances prepared by this method, lead structure IV was identified as one of the most active and selective inhibitors (FIG. 4c). Finally, a new eight-member library based on a combination of the most active P1′ and P3 side chains was prepared. The inhibitor with the highest activity and selectivity from this library was lead structure V, which showed some degree of selectivity for PlmI and PlmII versus CatD.

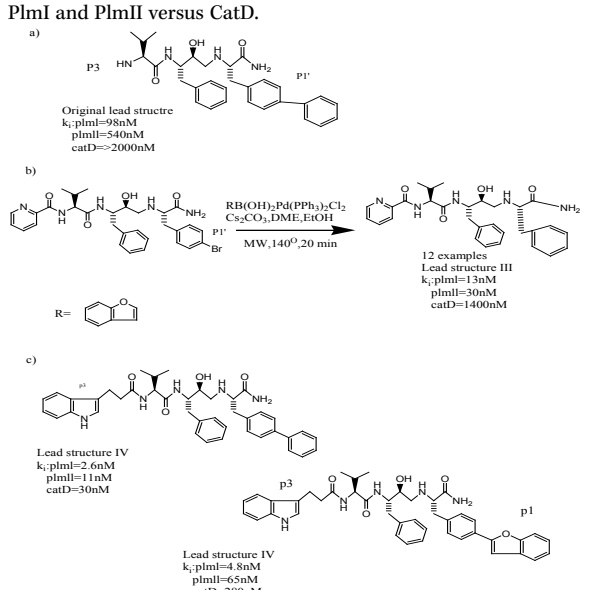


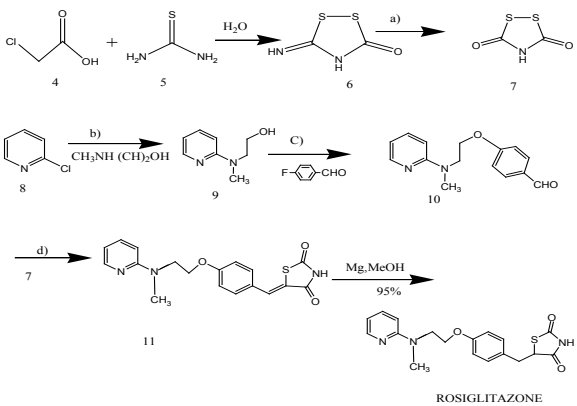
Figure 4[3] | **Lead optimization of the malarial proteases plasmepsin I and II inhibitors. a** | Original hydroxyl ethyl amino based lead structure derived by rational design46. The important amino-acid side-chains for optimization are marked as P1′ and P3. **b** | Microwave-assisted Suzuki arylations with sets of boronic acids for the genesis of analogues with modified P1′ side chain.

Volume : 4 | Issue : 9 | Sept 2015 • ISSN No 2277 - 8179

c | Lead structures derived by microwave-assisted Suzuki reactions with modified P3 side chain (lead structure IV) and combined P1′/P3 side chains exhibiting optimum inhibitory activity (lead structure V)..

MICROWAVE ASSISTED SYNTHESIS OF VARIOUS DRUGS:

a)ROSIGLITAZONE[7]:



Scheme:1 synthesis of rosiglitazone

Thiazolidine-2,4-dione (7) A mixture of monochloroacetic acid (4, 1.03 g, 10.9 mmol) and thiourea (5, 829 mg, 10.9 mmol) in water (2 ml) was introduced into a CEM Discover microwave reaction vessel equipped with a magnetic stirrer. The ves sel was sealed and the reaction mixture was stirred for 1 h at RT, successively irradiated by 250W microwave for 5 min at 140 ^{o}C and performed twice successively, cooled to RT and further stirred for 1 h. The formed solid was filtered and recrystallized from hot water to yield 7 (1.15 g, 90%).

2-(Methyl-pyridin-2-ylamino)ethanol (9)

A mixture of 2-chloropyridine (8, 506 mg, 4.46 mmol),2-(Nmethylamino) and ethanol (673 mg, 8.96mmol) was introduced into a CEM discover vessel equipped with a magnetic stirrer. The vessel was sealed and the reaction mixture was irradiated by 300W microwave for 10 min at 140 _C twice successively. The completion of the reaction was monitored by TLC (toluene–ethyl acetate, 1:1). The reaction mass was cooled to RT, diluted with 2 ml water, and extracted into 10 ml ethyl acetate twice. The combined ethyl acetate layer was washed with water, saturated brine, dried over anhyd Na2SO4 and concentrated in vacuum to give 9 (621 mg, 92%) as a pale yellow oil.

4-[2-(Methyl-pyridin-2-ylamino)ethoxy]- benzaldehyde (10)

A mixture of 9 (512 mg, 3.36 mmol), 4-fluorobenzaldehyde (422 mg, 3.40 mmol), KOH powder (565 mg, 10.08 mmol), and TBAHS (114 mg, 0.336 mmol) in water (0.5 ml) and toluene (2 ml) was introduced into a CEM Discover microwave vessel equipped with a magnetic stirrer. The vessel was sealed and the mixture was irradiated by microwave for 20 min at 85^{o}C. The completion of the reaction was monitored by TLC (toluene–ethyl acetate, 1:1). The reaction mass was cooled and diluted with 5 ml water and extracted into 25 ml toluene twice. The combined toluene layer was washed with water, dried over anhyd Na2SO4, and concentrated in vacuum to give 10 (778 mg, 90%) as a pale yellow oil.

4-[2-(Methyl-pyridin-2-ylamino)ethoxy]- benzylidene}thiazolidine-2,4-dione (11)

A mixture of 10 (504 mg, 1.97 mmol) and 7 (243 mg, 2.07 mmol) in toluene (1 ml) containing piperidine (cat.), acetic acid (cat.), and silica gel (0.1 g) were introduced into a CEM microwave vessel equipped with a magnetic stirrer. The vessel was sealed and the mixture was irradiated by microwave for 20 min at 130 _C. The fulfilment of the reaction was monitored by TLC. The reaction mass was cooled, diluted with 2 ml water, and further cooled to 5–10^{o}C under stirring. The solid mass formed was filtered and dissolved in hot methanol (5 ml), and insolubles were removed by filtration. Methanol was removed in vacuum to give 11 (649 mg, 93%) as yellow solid.

5-{4-[2-(Methyl-pyridin-2-ylamino)ethoxy]benzyl}- thiazolidine-2,4-dione; rosiglitazone

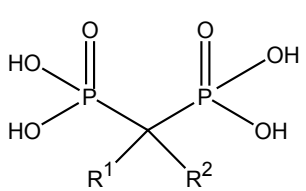
To a stirred suspension of alkene 11 (495 mg, 1.39 mmol) in methanol (10 mL) were added magnesium turnings (20 mg) and a pinch of iodine at RT, and the blend was stirred and warmed to commensate the reaction. Magnesium (50 mg) was added fraction wise for 30 min. On completion of the addition, the reaction mixture was stirred for 3 h at RT and dampened on ice water (10 mL). The pH was adjusted to 7.0–7.5 using 1 M hydrochloric acid and the mixture was extracted with dichloromethane (10 ml) twice. The combined organic extracts were washed with water (10 mL), dried over anhydrous Na_2SO4 and concentrated in vacuum. The residue was crystallized from boiling methanol to give ROSIGLITAZONE(470 mg, 95%) as a white solid.

Table 2[7]: conditions for scheme 1. Comparison of the cases of using microwave and conventional method for sheating.

Reaction	By microwave heating Conditions time yield	By conventional heating Conditions time yield
a)	H_2O 10 min 90 140^{o}	H_2O 12h 82 100^{o}
b)	Solvent free,140^{o} 20min 92	Solvent free,140^{o} 15h 85
c)	KOH,water,toluene, 20 min 90 TBAHS,85^{o}	DMF, NaH 8h 80 80^{o}
d)	Toluene,piperidine, CH_3COOH,SiO_2,130^{o} 10min 93	Toluene, piperidine, 15h 85 CH_3COOH,reflux

B) Nitrogen containing 1-hydroxymethylene bisphosphonate drugs[4]:

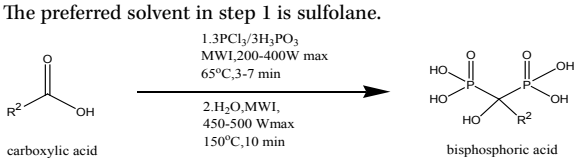
Bisphosphonate(BP) drugs carry a large affinity for bone and are effective for the treatment of diseases associated with bone mineralization, alike osteoporosis, Paget's disease, and hypercalcemia. In addition, certain BPs are effective against bone metastases in breast and prostate cancer.



General structure for methylenebisphosphonates

Method for the MAOS of 1-hydroxymethylenebis(phosphonic acids):

The preferred solvent in step 1 is sulfolane.



Scheme2 :. Modified method for the MAOS of 1-hydroxyme thylenebis(phosphonic acids). The preferred solvent in step 1 is sulfolane.

Table 3:Bisphosphonates synthesized via Scheme 2

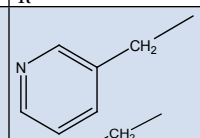
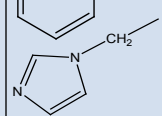
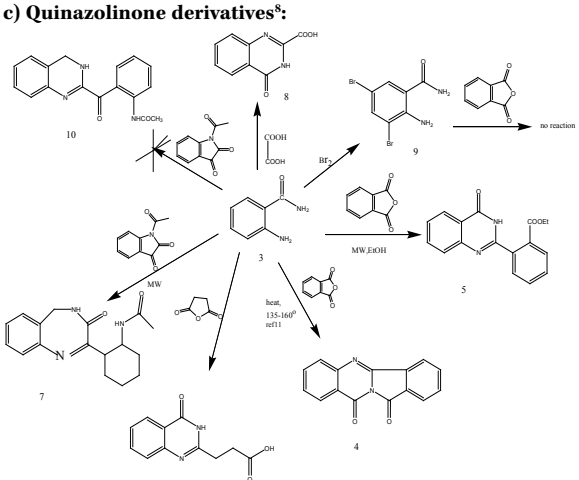
Compound	R^1	R^2
1. Risedronic acid	OH	
2.Zoledronicacid	OH	
3.pamidronic acid	OH	$H_2N(CH_3)_2$—
4.altendronic acid	OH	$H_2N(CH_3)_3$—
5.neridronic acid	OH	$H_2N(CH_3)_5$—

Table 4[4]:tMW synthesis of bis phosphate via scheme

compound	Time for MW synthesis of phosphorous intermediate	Time for MW hydrolysis (150°)	Isolated yied %	Isolated yield %, conventional heating(3.5 h at 65°,followed by refflux 6+h)
1	3min 15 sec	10 min	74	-
2	3 min 45 sec	10 min	70	67
3	3min 15 sec	10 min	64	72
4	7min	10 min	41	38
5	7min	10 min	53	-

c) Quinazolinone derivatives[8]:



Anthranilamide(3); ethyl 2-(4-oxo-3,4-dihydroquinazolin- 2-yl) benzoate(5); 3-(3,4-dihydro oxoquinazolin-2-yl) propanoic acid(6); N-(2-{(Z)-4,5-dihydro-3,5-dioxo-3Hbenzo[e] [1,4]diazepin-2-yl} phenyl) acetamide(7); 3,4-dihydro-4-oxoquinazoline-2- carboxylic acid(8), 2-amino-3,5-dibromobenzamide(9)

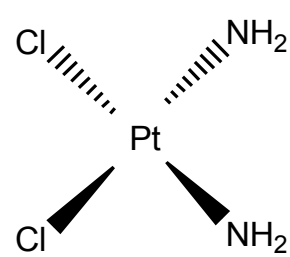
Quinazolinone derivatives are prominent for their distinct pharmacological (analgesic, anti-allergic, anticonvulsant, anti-depressant, anti-inflammatory, antimalarial, antimicrobial, hypotensive, sedative-hypnotic, etc) activities.

d) Microwave-assisted synthesis of the anticancer drug cisplatin, cis-[Pt(NH3)2Cl2]:

Originally synthesized by Peyrone in 1845,9,10 cisplatin can be synthesized using one of three basic methods, all of which use K2PtCl4 as the starting material. The Kauffman method uses a buffer solution of NH4OH–NH4Cl (pH ~ 8–9) as the reaction medium and the reaction is carried out in a refrigerator for 24–48 h.11 Synthesis by the Lebedinskii–Golovnya12 method (and the upgrade of this method by Kukushkin and co-workers13) employs an aqueous solution of NH4OAc : KCl at reflux for 2–3 h. Lastly, the Dhara method is a four-step process in which K2PtCl4 is first converted to K2PtI4 in situ, followed by the addition of NH4OH to produce cis-[Pt(NH3)2I2](s). Addition of AgNO3 converts cis-[Pt(NH3)2I2](s) to the diaqua species, cis-[Pt(NH3)2(H2O)2]2+ to which NaCl (or HCl) is added to obtain the final product, cis-[Pt(NH3)2Cl2]. World-wide, the Dhara method is the method of choice since it provides cisplatin in both high yield and high purity. Consequently, this method has been used many times to prepare 195mPt-labelled cisplatin.6,15,16 A minor time-related drawback to this method is that it requires 2–3 hours to complete.

General procedure (0.2 mmol scale). K2PtCl4 (83.0 mg, 0.2 mmol), KCl (30.0 mg, 0.4 mmol) and NH4OAc (62.0 mg, 0.8 mmol) were dissolved in water (1.0 mL) in the special microwave compatible test tube. The reaction mixture was stirred magnetically and brought to a reaction temperature of 100 °C within the first minute of reaction and then held at the same temperature for 14 min longer. The reaction mixture was then chilled to 0 °C in an ice-water bath, inducing precipitation of a yellow solid. Complete precipitation was assured by adding 4 volumes of ethanol (EtOH). The solid was collected by centrifugation and then treated with 2.0 mL N,N-dimethylacetamide (DMA) to extract the cisplatin. Following centrifugation, the DMA solution was removed and the remaining solid was leached with an additional 0.5 mL of DMA, and the

resulting solution was separated by centrifugation. The two DMA solutions were combined, followed by the addition of 3 volumes of EtOH to precipitate the crude cisplatin product. This crude product was collected by centrifugation, washed two times with EtOH, and then dried in vacuo at 45–50 °C for 15 min.



e) Aryl and hetero aryl chalcones[6]:

Chalcones (α, β – unsaturated ketones)enjoy a vast range of pharmacological activities such as antioncogenic1, anti-inflammatory, antiulcerative, analgesic, antiviral, antimalarial and antibacterial. The presence of a reactive α, β- unsaturated keto group in chalcones is found to be responsible for their respective pharmacological activities.

Volume : 4 | Issue : 9 | Sept 2015 • ISSN No 2277 - 8179

Various chalcones synthesized were:

1-(3′,4′-Dimethoxyphenyl)-3-phenyl-2-propen-1-one (C1), 1-(3′,4′-Dimethoxyphenyl)-3-(4”-methoxyphenyl) -2-propen-1-one (C2), 1-(3′,4′-Dimethoxyphenyl)-3-(3”,4”,5”-trimethoxyphenyl)-2-propen-1-one (C3), 1 (3′,4′-Dimethoxyphenyl)-3-(3”,5”-dimethoxyphenyl)-2-propen-1-one (C4), 1-(3′,4′-Dimethoxyphenyl)-3-(2”-chlorophenyl)-2-propen-1-one (C5), 1-(3′,4′-Dimethoxyphenyl)-3-(4”-chlorophenyl)-2-propen-1-one (C6), 1-(3′,4′ Dimethoxyphenyl)-3-(4”-fluorophenyl)-2-propen-1-one (C7), 1-(3′,4′-Dimethoxyphenyl)-3-(4”-hydroxyphenyl)-2-propen-1-one (C8), 1-(8′,9′-Benzo-1′,2′,3′-triazol-1′-yl)-3-(2”-chlorophenyl)-2-propen-1-one (C9), 1-(5′-Chloro-8′,9′-benzo-1′,2′,3′-triazol-1′-yl)-3-(2”-chlorophenyl)-2-propen-1-one (C10).

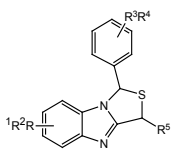
Compound	Reaction time		yield	
	Conv.(h)	MW(min)	Conv(%)	MW(%)
C1	3.00	6.00	76.3	89.5
C2	3.00	10.00	70.4	89.7
C3	3.00	5.00	73.4	92.7
C4	3.00	12.00	77.5	90.9
C5	3.00	20.00	75.2	91.9
C6	3.00	16.00	74.7	89.9
C7	3.00	18.00	85.9	88.7
C8	3.00	24.00	80.9	95.4
C9	8.00	30.00	66.8	88.6
C10	6.00	22.00	60.2	82.4

Microwave irradiation technique helped in minimizing the reaction time, improving the output and purity of the aryl and heteroaryl chalcones. Thus, it is the time conserving and efficient technique for the synthesis of chalcones.

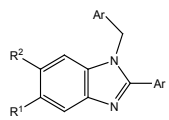
Four compounds(compounds **C3**, **C4, C7** and **C8**), showed good anti-inflammatory and antimalarial activities and reasonably good analgesic activity. Functional groups like methoxy (compounds **C3** and **C4**),fluoro (compound **C7**) and hydroxyl (compound **C8**), on the phenyl ring attached at position 3 of chalcones, were found to be essential for showing all the three activities.

Microwave-assisted synthesis of benzimidazole and thiazolidinone[1]:

microwave-assisted synthesis of 1*H*,3*H*-thiazolo[3,4- a]benzimidazoles, 2-aryl-1 benzyl benzimidazoles and 2,3-diaryl-1,3-thiazolidin-4-ones, which achieved reductions in reaction times, higher yields, cleaner reactions than for the previously described synthetic processes.



1



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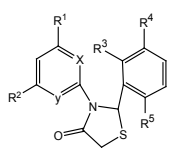
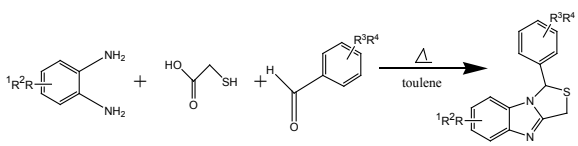


3

Synthesis of 1-aryl-1*H*,3*H*-thiazolo[3,4-a]benzimidazoles (1a-e):

1-(2,6-Difluorophenyl)-1*H*,3*H*-thiazolo-[3,4-a]benzimidazole (1a); 1-(3-Nitrophenyl)-1*H*,3*H*-thiazolo[3,4-a]benzimidazole (1b)**;** 1-(2,6-Difluorophenyl)-6,7-dimethyl-1*H*,3*H*-thiazolo[3,4-a] benzimidazole (1c); 1-(2,6-Difluorophenyl)-5-methyl-1*H*,3*H*-thiazolo[3,4-a]benzimidazole (1d); 1-(2,6-Difluorophenyl)-8-methyl-1*H*,3*H*-thiazolo[3,4-a]benzimidazole (1e).



toulene

1(a-e)

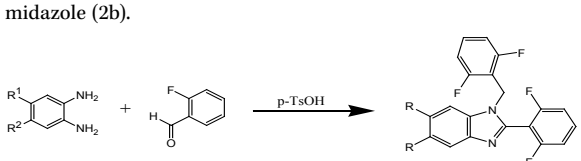
Compound	R^1	R^2	R^3	R^4	Reaction time		Yield	
					A	B	A	B
1a	H	H	2-F	6-F	48h	12 min	92	60
1b	H	H	3-NO_2	H	24h	12 min	25	50
1c	6-Me	7-Me	2-F	6-F	24h	12 min	36	40
1d	5-Me	H	2-F	6-F	48h	12 min	22	64
1e	8-Me	H	2-F	6-F	48h	12 min	5	16

A=conventional heating;B=microwave irradiation.

Synthesis of 2-aryl-1-benzylbenzimidazoles (2a-2b):

1-(2,6-Difluorobenzyl)-2-(2,6 difluorophenyl) -benzimidazole (2a);

1-(2,6-Difluorobenzyl)-2-(2,6-difluorophenyl)-5,6-dimethylbenzimidazole (2b).



p-TsOH

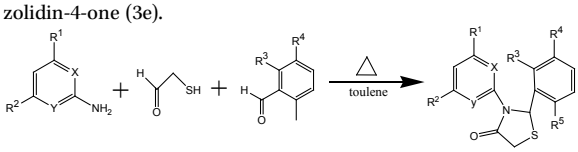
2(a-b)

Compound	R	Reaction time		Yield	
		A	B	A	B
2a	H	2h	6 min	20	70
2b	Me	2h	6 min	70	72

A=conventional heating; B=microwave irradiation.

Synthesis of 2,3-diaryl-1,3-thiazolidin-4-ones (3a-3e):

2-(2,6-Dichlorophenyl)-3-(3-methylphenyl)-1,3-thiazolidin-4-one (3a); 2-(2,6-Difluorophenyl)-3-(3-methoxyphenyl)-1,3-thiazolidin-4-one (3b); 3-(6-Bromopyridin-2-yl)-2-(2,6-difluorophenyl)-1,3-thiazolidin-4-one (3c); 2-(2-Chloro-6-fluoro-3-methylphenyl)-3-(4-methyl pyrimidin-2-yl)-1,3-thiazolidin-4-one (3d); 2-(2,6-Dichlorophenyl)-3-(4,6-dimethylpyrimidin-2-yl)-1,3-thiazolidin-4-one (3e).



toulene

3(a-e)

Compound	X	Y	R^1	R^2	R^3	R^4	R^5	Reaction time		Yield %	
								A	B	A	B
3a	CH	CH	Me	H	Cl	H	Cl	48h	12 min	65	72
3b	CH	CH	OMe	H	F	H	F	48h	12 min	16	46

Compound	X	Y	R^1	R^2	R^3	R^4	R^5	Reaction time		Yield %	
								A	B	A	B
3c	N	CH	Br	H	F	H	F	48h	12 min	60	85
3d	N	N	Me	H	Cl	Me	F	48h	12 min	38	65
3e	N	N	Me	Me	Cl	H	Cl	48h	12 min	38	56

A=conventional heating; B=microwave irradiation

Integration with other technologies[3]:

Not only can MAOS be practised to standard solution phase chemistry protocols, this technology can also be productively integrated into solid or fluorous-phase organic synthesis. Both of these technologies are designed to clear-cut product isolation and purification after synthesis.

A pivotal application of microwave-aided solid-phase synthesis approaches with implications for the drug discovery process is its novel use in the efficient preparation of both peptides and peptide analogues, besides the generation of combinatorial β-peptide libraries there are more than 40 marketed peptides worldwide, around 270 peptides in clinical-phase screening and about 400 in advanced preclinical phases. One of the stumbling blocks associated with peptides is that they are often challenging and pricey to synthesize. By using microwave heating, majority of the identified peptides could be prepared in momentously higher purity and yield than is feasible under current typical conditions. This will reward in the evolution of novel therapeutic peptides and in the bulk scale production of further important peptide products.

Conclusion :

From its inception as a tool in organic chemistry,Microwave served as a indispensible appliance in the Drug synthesis and Lead optimization. Its applications were proved in the synthesis of various classes of drugs ranging from Anti-diabetics (like Rosiglitazone, Thiazolidines), Antimalarial drugs and Chalcones. Besides being a unparallelised invention of mankind in the 20th century,it too has certain limitations for being extravagant and it needs a skilled operator to steer. Nevertheless, microwave serves as miraculous brainchild in the field of chemistry owing to its expedition and rapidity .

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