Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research

ISSN No: 0975-7384
CODEN(USA): JCPRC5

J. Chem. Pharm. Res., 2011, 3(6):925-944

Importance of Microwave Reactions in the Synthesis of Novel Benzimidazole Derivatives: A Review

[1*]Anshul Chawla, [1]Ramandeep Kaur and [2]Anju Goyal

[1]CT Institute of Pharmaceutical Sciences, Shahpur, Jalandhar(Punjab) INDIA
[2]Chitkara College of Pharmacy, Chitkara University, Rajpura(Punjab)-INDIA

ABSTRACT

Benzimidazoles belonging to the fused heterocyclic system prepared from amino acids are associated with diverse pharmacological activities such as antimicrobial, antiviral, antidiabetic and anticancer activity. This review deals with the review of an efficient "green" synthesis of benzimidazole derivatives by microwave induced reactions.

Keywords: Benzimidazoles, Green synthesis, microwave reactions.

INTRODUCTION

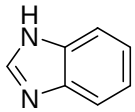
Benzimidazole nucleus is an important heterocyclic ring because of its synthetic utility and broad range of pharmacological activities. Some benzimidazole derivatives with different pharmacological effects, including antifungal [**1**], anti-helmintic [**2**], anti-HIV [**3**], antihistaminic [**4-6**], antiulcer [7-**8**], cardio tonic [**9**], antihypertensive [**10-11**] and neuroleptic [**12**] are in clinical use. Extensive biochemical and pharmacological studies have confirmed that these molecules are effective against various strains of microorganisms. It has earned an important place in the list of chemotherapeutic agents. The biological significance of benzimidazoles is due to its close relationship with structure of purines. The vital role of purines in the biological system was established and it was discovered that 5, 6-dimethyl-1- (α-D-ribofuranosyl) benzimidazole is an integral part of structure of Vit.B_{12}.

Microwave chemistry is the science of applying microwave irradiation to chemical reactions. Microwaves act as high frequency electric fields and will generally heat any material containing mobile electric charges, such as polar molecules in a solvent or conducting ions in a solid. Polar solvents are heated as their component molecules are forced to rotate with the field and lose energy in collisions. Microwave heating is able to heat the target compounds without heating the

entire furnace or oil bath, which saves time and energy. It is also able to heat sufficiently thin objects throughout their volume, in theory producing more uniform heating **[13-16]**. Microwave-assisted organic synthesis is an enabling technology for accelerating drug discovery and development processes. Microwave assisted reactions have received great interest because of their simplicity in operation, enhanced reaction rates, products with high purity and better yields compared to those conducted by conventional heating. Microwave instruments are used principally in three areas of drug research: the screening of organic drug formulae, peptide synthesis, and DNA amplification. Microwave-assisted organic synthesis in aqueous medium has resulted in the development of relatively sustainable and environmentally benign protocols for the synthesis of drugs and has emerged as a tool towards green chemistry. Microwave-assisted synthesis under controlled conditions has many applications in the field of medical chemistry and pharmaceutical research. This technology has made an impact in several areas of drug discovery related to organic synthesis **[17]**. Thus, we became interested in the study of synthesis of substituted benzimidazoles by using microwave technique.

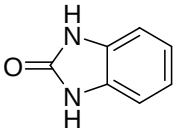
Chemistry of Benzimidazoles

The benzimidazoles contain a phenyl ring fused to an imidazole ring, as indicated in the structure for benzimidazole (1)

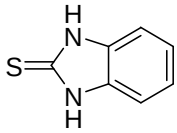


(1)

The benzimidazoles are also known as benzimidazoles or benzoglyoxalines. They have been named also as derivatives of *o*-phenylenediamine, especially in the early literature. Thus, benzimidazole according to this nomenclature would be called methenyl-*o*-phenylenediamine and 2-methylbenzimidazole would be called ethenyl-*o*-phenylenediamine. Also, they have been named as derivatives of the grouping composing the imidazole portion of the ring. Thus, for example, benzimidazole has also been called *o*-phenyleneformamidine and 2 (3H)-benzimidazolone (2) and 2 (3H) benzimidazolethione (3) are known also as *o*-phenyleneurea and *o*-phenylenethiourea, respectively.

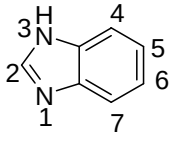


(2)



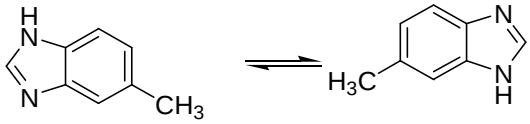
(3)

The numbering system for the benzimidazoles is as follows:
Occasionally, the 2-position is designated as the μ-position.



(4)

Benzimidazoles which contain a hydrogen atom attached to nitrogen in the 1-position readily tautomerize. This tautomerism is analogous to that found in the imidazoles and amidines. The benzimidazoles, in fact, may be considered as cyclic analogs of the amidines [**18**]. Because of this tautomerism in benzimidazoles certain derivatives which appear at first to be isomers are in reality tautomers; although two non-equivalent structures can be written, only one compound is known. This may be illustrated with 5(or 6)-methylbenzimidazole.



(5) (6)

Thus, 5 methylbenzimidazole (5) is a tautomer of 6-methylbenzimidazole (6) and both structures (4 and 5) represent the same compound. In designating such tautomeric compounds two numbers or sets of numbers are usually given designating the positions of the substituent group (or groups), the second number or group of numbers being placed in parentheses. In Table **1** the equivalent tautomeric pairs in benzimidazole derivatives are illustrated.

Table 1 Equivalent tautomeric pairs in benzimidazole derivatives

Position of substituent group(s) In first tautomer	Position of substituent group(s)In second tautomer	Designation
		4 (or 7)
4	7	5 (or 6)
5	6	2,4 (or 2,7)
2,4	2,7	2,5 (or 2,6)
2,5	2,6	4,5 (or 6,7)
4,5	6,7	4,6 (or 5,7)
4,6	5,7	2,4,5 (or 2,6,7)
2,4,5	2,6,7	2,4,6 (or 2,5,7)
2,4,6	2,5,7	4,5,6 (or 5,6,7)
4,5,6	5,6,7	4,5,7 (or 4,6,7)
4,5,7	4,6,7	2,4,5,6 (or
2,4,5,6	2,5,6,7	2,5,6,7)
2,4,5,7	2,4,6,7	2,4,5,7 (or
		2,4,6,7)

When the group attached to the nitrogen in the l-position is larger than hydrogen, such tautomerism is not indicated and isomeric forms exist. Thus, 1, 5-dimethylbenzimidazole (7) and 1,6-dimethylbenzimidazole (8) are separate and distinct compounds.

(7) (8)

The benzimidazoles are predominantly basic compounds having the ability to form salts with acids. Benzimidazole (pK α 5.5) is a basic considerably weaker than the imidazole (pK α7.0). This difference in the basic strength is a reflection of the conjugation between the imidazole and benzene rings. Conjugation increases the number of contributing states in the resonance sense, thus enhancing the chemical stability of the molecule [**19**].

Conventional method *vs.* Microwave method

Conventional methods of synthetic reactions need longer heating time, elaborate and tedious apparatus set up which result in higher cost and environmental pollution. Pharmaceutical laboratories use large quantities of toxic chemicals and solvents to perform reactions exposing laboratory persons including students and environment to related hazards. Reaction under microwaves is an effort toward "green chemistry" with low-boiling solvents at high temperature in closed vessels. Effects of microwaves in dry media organic reactions have shown synthetic utility for the preparation of biodynamic heterocycles. The probable mechanisms involved in

microwave heating are dipolarization, Ohmic heating, interfacial polarization *etc* [2**0**]. Capabilities for rapid heating and cooling, concurrent heating and cooling and differential heating facilitated novel chemical reactions and processes. Commercial microwave systems based on these developments are available. Time required for conventional reactions typically are decreased by 2-3 orders of magnitude. Green processes also have resulted through use of less or no catalyst, readily recyclable solvents, or media and yields that are often higher than normal. Complementary interactive software for calculating optimal conditions was developed [**21**]. The reaction rate of microwave induced organic reaction increases ten to thousand times and the yield of the product increases by 10-30 % compared to that by the conventional methods.

Procedure:

The microwave technique was performed in domestic microwave oven (SUNFLAME) for synthesizing selective heterocyclic molecules. Similarly, the conventional synthesis of same were performed and compared with microwave induced synthesis method. It was found that the reaction time was comparatively less from hr to min and the % yield were found to be higher when compared to conventional method. During our synthetic studies, it was observed that the conventional method of synthesising selected heterocyclic molecules such as phenytoin, acridone, coumalic acid, benzimidazole, *N*-phenylphthalimide and 2,3-diphenyl quinoxaline. Each reaction was repeated at least three times (different time intervals) and the products by studying their melting point and percentage yield the comparative results were tabulated in the Table No: 1

Scheme for the synthesis

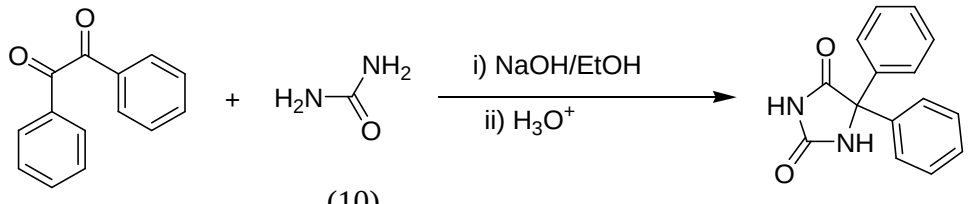
i) Phenytoin

Conventional method [22]:

A mixture of benzil (9) and urea (10) were refluxed in the presence of *aq.* sodium hydroxide and ethanol. The mixture was cooled to room temperature and the solution was poured into water and mixed thoroughly. The solution was filtered under suction and filtrate was made strongly acidic with *conc.* hydrochloric acid, cooled in ice water, then filtered the phenytoin (11) and recrystallised from industrial spirit.

Microwave method:

A mixture of benzil (9), urea (10), *aq.* sodium hydroxide and ethanol were taken in a beaker. The beaker was then placed in a domestic microwave oven (SUNFLAME). Then the mixture was cooled to room temperature and poured into water. The solution was filtered under suction and filtrate was made strongly acidic with *conc.* hydrochloric acid, cooled in ice water, filtered and recrystallized from industrial spirit.



(9) (10) (11)

Scheme 1

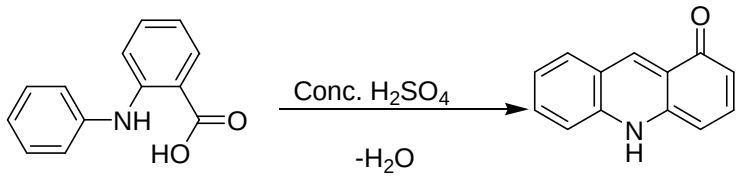
ii) Acridone

Conventional method [23]:

A mixture of *N*-Phenyl anthranilic acid (12) and conc. sulphuric acid was heated on a steam bath. The hot dark green solution was poured slowly and continuously into boiling water. Then the mixture was boiled and filtered. The crude product, acridone (13) was washed with hot water and recrystallized from acetic acid using charcoal.

Microwave method:

A mixture of *N*-Phenyl anthranilic acid (12) and *conc.* sulphuric acid was taken in a conical flask and the reaction mixture was kept in a domestic microwave oven. The hot dark green solution was poured slowly and continuously into boiling water. The mixture was boiled and filtered. The crude product was washed with hot water and recrystallized from acetic acid, using charcoal.



(12) (13)

Scheme 2

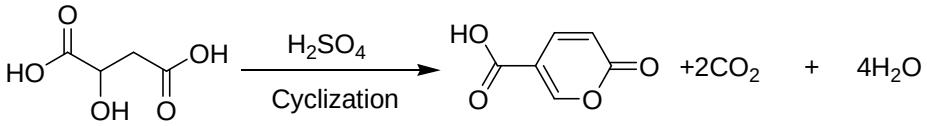
iii) Coumalic acid

Conventional method [24]:

Sulphuric acid was added to malic acid (14) in three portions. A slight exothermic reaction occurred with the steady evolution of gas. The mixture was heated on a water bath, then cooled and poured into ice. The mixture was then kept aside in a refrigerator, filtered the crude coumalic acid (15) and washed with small portions of ice water. The crude product was recrystallized from methanol.

Microwave method:

A mixture of malic acid (13) with *conc.* sulphuric acid was added. The beaker was placed in a domestic microwave oven. Then, adequate amount of ice was added and kept in the refrigerator. The product was filtered and recrystallized from methanol.



(14) (15)

Scheme 3

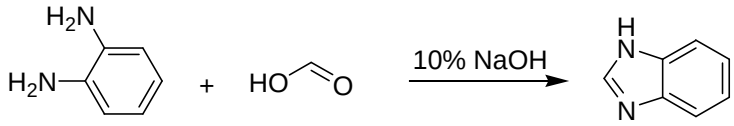
iv) Benzimidazole

Conventional method [25]:

A mixture of *o*-Phenylene diamine (16) and formic acid (17) was refluxed thermally. The reaction mixture was cooled and sodium hydroxide solution was added and then the crude product, benzimidazole (18) was washed with ice cold water and dissolved in boiling water for recrystallization, filtered and dried.

Microwave method:

A mixture of *o*-Phenylene diamine (16) and formic acid (17) was placed in a domestic microwave oven. The reaction mixture was cooled and sodium hydroxide solution was added. The crude product was washed with ice cold water, dissolved in boiling water for recrystallization, filtered and dried.



(16) (17) (18)

Scheme 4

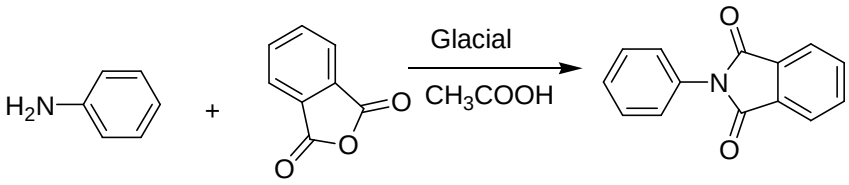
v) N-Phenyl Phthalimide

Conventional method [26]:

A mixture of aniline (19) and phthalic anhydride (20) was dissolved in glacial acetic acid. The solution was refluxed. The crude product, *N*-Phenyl phthalimide (21) was separated, filtered and recrystallized from ethanol.

Microwave method:

A mixture of aniline (19) and phthalic anhydride (20) was dissolved in glacial acetic acid contained in a domestic microwave oven. The crude product was separated, filtered and recrystallized from ethanol.



(19) **(20)** **(21)**

Scheme 5

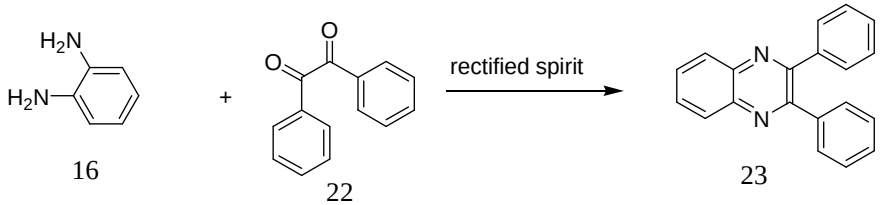
vi) 2, 3-Diphenyl Quinoxaline

Conventional method [27]:

Benzil (22) was dissolved in warm rectified spirit and transferred into *o*-Phenylene diamine (16) dissolved in rectified spirit. The mixture was refluxed and water was added. The crude product, 2, 3-diphenyl quinoxaline (23) was filtered and recrystallized from rectified spirit.

Microwave method:

Benzil (22) was dissolved in warm rectified spirit and transferred into *o*-Phenylene diamine (16) dissolved in rectified spirit. The beaker was placed in a domestic microwave oven. Then water was added and the crude product was filtered and recrystallized from rectified spirit.



16 22 23

Scheme 6

Above synthesis required a conventional reaction time of 2-15 hours while the yields were always poor (<50%) therefore it was felt worth while to study these reactions under microwave-induced technique with the aim of decreasing the reaction time and increasing the yield. The experiment like determination of saponification value, degradation of atropine, analysis of loss on drying could be performed within minutes (8-9 min.) with the help of microwave assisted technique and are being used for routine practical classes. Each time the products were isolated,

the % yield and quality of the products was compared with the one obtained by conventional method.

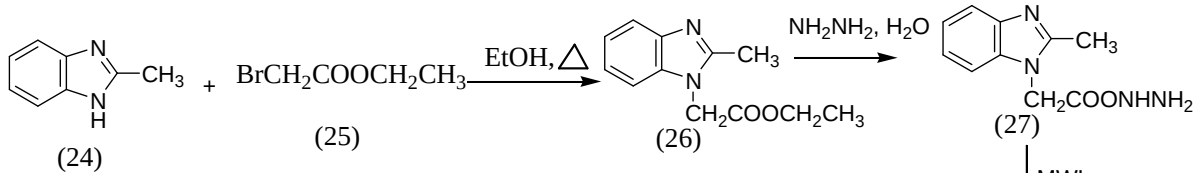
Table-1: Physical data of heterocyclic molecules and comparative study of conventional *vs.* microwave method

Compound	MP(° C)	Conventional Method		MP(° C)	Microwave Method	
		Time (hours)	% yield		Time (hours)	% yield
Phenytoin	294-299	2-2.5	75	295-297	6	80
Acridone	295-300	1.5-2	70	296-298	4	85
Coumalic acid	206-208	2-2.5	62	206-208	4	80
Benzimidazole	168-173	2-2.5	85	170-172	6	94
N-Phenylphthalimide	185-205	1-1.5	80	190-202	4	92
2,3-Diphenyl quinoxaline	110-114	1-1.5	75	111-113	4	85

Synthesis of benzimidazole derivatives using microwaves

The synthetic process involving the use of microwave radiations is green, mild and inexpensive. Its main advantages are excellent chemo selectivity and excellent yields. The groups of Gedye and Geigure / majetich in, 1986 first reported on the use of microwave heating to accelerate organic chemical transformations. Since the last few years, high speed microwave synthesis is being practiced owing to its vitality in organic synthesis procedures. **[28]**

Somani *et al* (2010) reported the synthesis of Schiff's base (28) from 2-methyl benzimidazole (24) (Scheme 7) which involved three steps [**29**]. In the first step, 2-methyl benzimidazole (0.10 mole) (24) was refluxed with ethyl bromoacetate (0.12 mole) (25) in ethanol as a solvent containing dry anhydrous K_2CO_3 for 20-22 h resulting in the formation of product ethyl-2-(2-methyl-1H-benzimidazol-1-yl)-acetate (26). 2-(2-methyl-1H-benzimidazol-1-yl) – acetohydrazide (27) was formed on refluxing ethyl-2-(2-methyl-1H-benzimidazol-1yl) (0.10 mole) (26) with hydrazine hydrate (0.15 mole) for 8-10 h in ethanol. The final step involved the use of microwave irradiation for synthesising the final compound (28) in which 0.01 mole of 2-(2-Methyl-1H-benzimidazol-1-yl)-acetohydrazide (27) was refluxed with 0.012 moles of various aldehydes under microwave in ethanol (10 mL) in the presence of glacial acetic acid as a catalyst for 30-40 minutes.



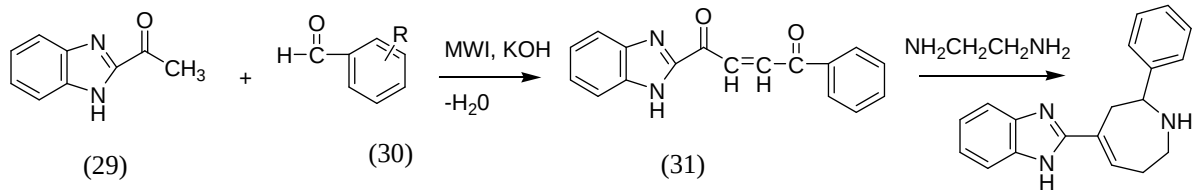
(24) (25) (26) (27) (28)

Compound	Ar
4a	Phenyl
4b	2-Hydroxyphenyl
4c	2-Chlorophenyl
4d	3-Methoxy-4-Hydroxyphenyl
4e	4-Hydroxyphenyl
4f	4-Methoxyphenyl
4g	3-Nitrophenyl
4h	Cinnamyl

Scheme 7

Srivastava *et al* (2010) synthesised 2-(7-phenyl-2,2,6,7-tetra hydro-1*H*-1,4-dizepine-5-yl)-1*H*-benzimidazole (32) (scheme 8) [**30**]. 2-acetyl benzimidazoles (0.01 mol) (29) reacted with substituted aldehydes (0.02 mol) (30) in methanol in presence of base (potassium hydroxide) in microwave oven for 30 seconds to 2 minutes at 300 watts power which resulted in corresponding

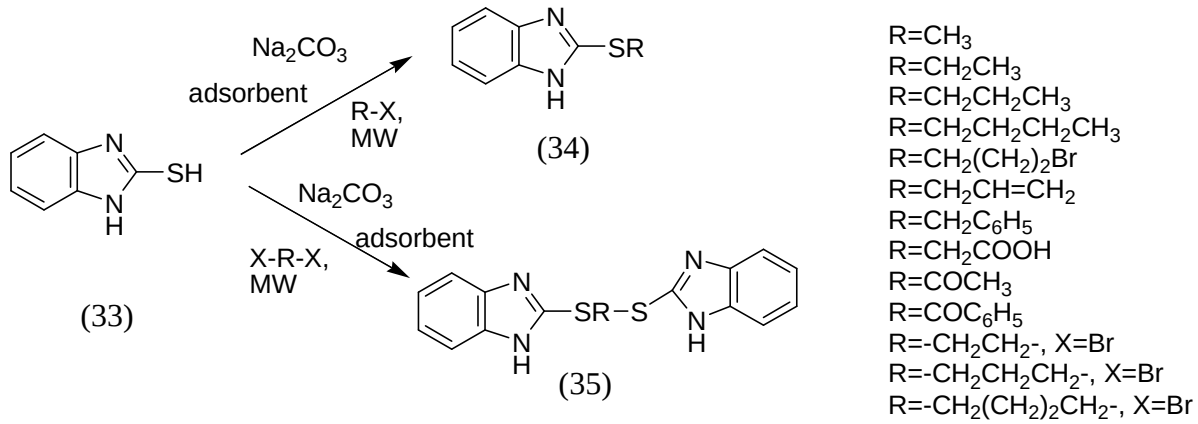
benzimidazolyl chalcones (31). Compound (31) (0.001 mol) on treatment with ethylenediamine (0.001) gave the final compound (32) under microwave induced condition (4 to 6 min at 800 watts).



(29) (30) (31) (32)

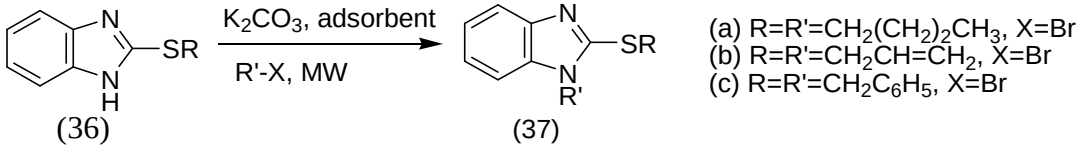
Scheme 8

Narkhede *et al* (2008) reported the synthesis of derivatives of 2-Mercaptobenzimidazole (34, 35) using an adsorbent [**31**]. Mercaptobenzimidazole (33) was dissolved in aqueous solution of sodium carbonate (5ml, 2N). Then adsorbent was added to it and stirred well. Then the mixture was evaporated for complete removal of water in MW oven. Then aryl halide or acid chloride (10mmol) or α, ω-dibromoalkane (5mmol) was added to the above mixture and irradiated in MW oven at 270 W at a pulse of 30 sec for 1-5 min. After the reaction was complete as monitored by TLC, the reaction mixture is cooled to room temperature. The reaction mixture was then extracted with dichloromethane (2x25 ml). The extract was dried over anhydrous sodium sulphate, filtered and removed the solvent to afford the desired products (34, 35) (scheme 9). The mercaptobenzimidazole derivative (36) reacted with alkyl halides under the similar conditions afforded product (37) (scheme 10).



(33) (34) (35)

Scheme 9

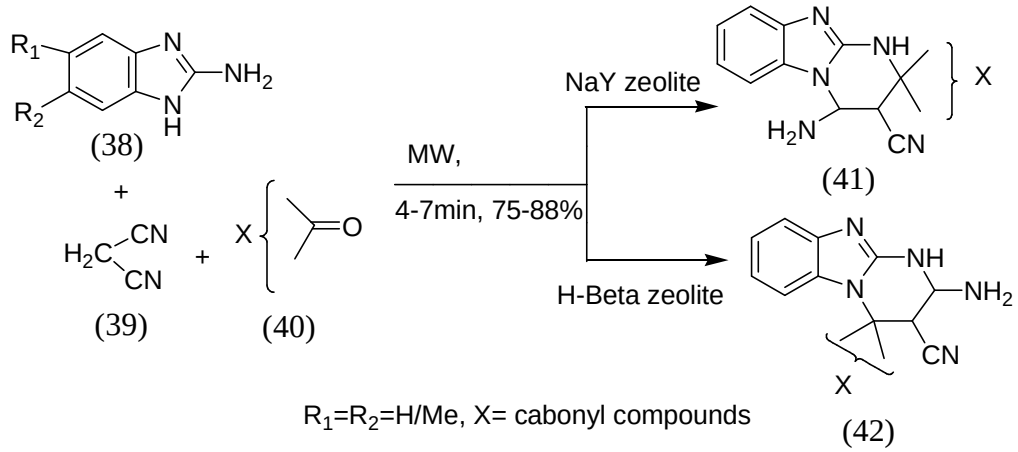


(36) (37)

Scheme 10

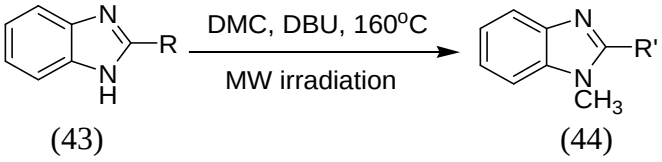
Arya *et al* (2009) synthesised 4'-amino-1'*H*-spiro [cyclohexane-1,2'-(pyrimido[1,2-a]benzimidazole)]-3'-carbonitrile (41) and 7'-amino-8'H-spiro [cyclohexane-1,5'-pyrimido[1,2-a]benzimidazole]-6'-carbonitrile (42) with regioselectivity (scheme 5) [**32**]. Substituted aminobenzimidazole (38), malononitrile (39) and carbonyl compound (40) were dissolved in 50 ml anhydrous benzene. To this solution, 2-4 g of mineral support (NaY and HY zeolite) was

added under stirring. After solvent evaporation under low pressure, the obtained solid was exposed to microwaves for appropriate time (3-10 min at 140°C). The activated solid was cooled and washed several times with 10 ml of benzene. Then, the solvent was evaporated and the products (41, 42) purified by methanol recrystallization.



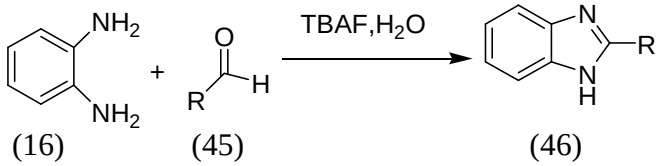
Scheme 11

Shieh *et al* (2001) reported a typical procedure for methylation of benzimidazoles [**33**]. A solution containing a substrate (43), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (1 equiv), Dimethyl carbonate (DMC), 1 equiv of tetrabutylammonium iodide (TBAI), a phase-transfer catalyst (PTC) and a solvent (either CH_3CN or DMF) was circulated by a pump through the microwave reactor which was preheated to 160 °C at 20 bar by microwave irradiation resulting in the desired product (44) (scheme 12).



Scheme 12

Joshi *et al* (2010) employed microwave method for synthesising 2-Arylbenzimidazole (scheme 13) [**34**]. A mixture of substituted aldehyde (10 mmol) (45), *o*-phenylene diamine (10 mmol) (16) and TBAF (5 mole %) was dissolved in minimum quantity of water with constant stirring and was irradiated under ultrasonic irradiation at ambient temperature for appropriate time. The progress of reaction was monitored by TLC. After the completion of reaction, mixture was extracted with ethyl acetate (2 × 25 ml) and dried under vacuum. The residue was subjected to column chromatography (60-120 mesh size silica gel, eluted with hexane-ethyl acetate (80:20) to obtain the pure product (46).

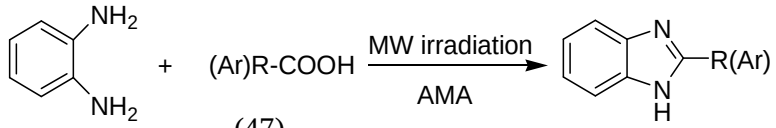


Scheme 13

Niknam *et al* (2007) reported microwave irradiation method as the best method for the synthesis of 2-substituted benzimidazoles (48) and bis benzimidazoles (50) from the direct reaction of phenylenediamine (16) and dicarboxylic acid (49) in the presence of alumina-methanesulfonic acid (AMA) as a catalyst with good to excellent yields (scheme 15) [**35**].

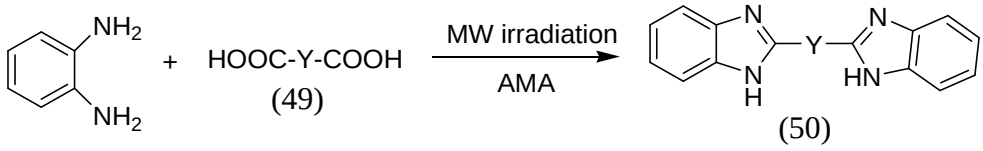
In a typical procedure, a mixture of 1, 2-phenylenediamine (5 mmol) (16), carboxylic acid (3.75 mmol) (47), alumina (0.5 g) and methanesulfonic acid (12 mmol) was subjected to microwave irradiation (900 W, with a frequency 2450 MHz) at 20% power for times specified. The progress

of the reaction was followed by TLC. After completion of the reaction, water was added to the reaction mixture, filtered, and washed with warm water to separate the alumina. The combined aqueous extracts were neutralized by sodium bicarbonate. The precipitates were then filtered, washed with water (2 × 15 ml) and air dried to afford the desired product in satisfactory purity. The precipitated products with lower purity were further purified by recrystallization from ethanol.



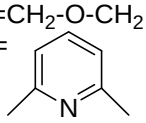
(16) (47) (48)

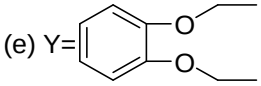
Scheme 14



(16) (49) (50)

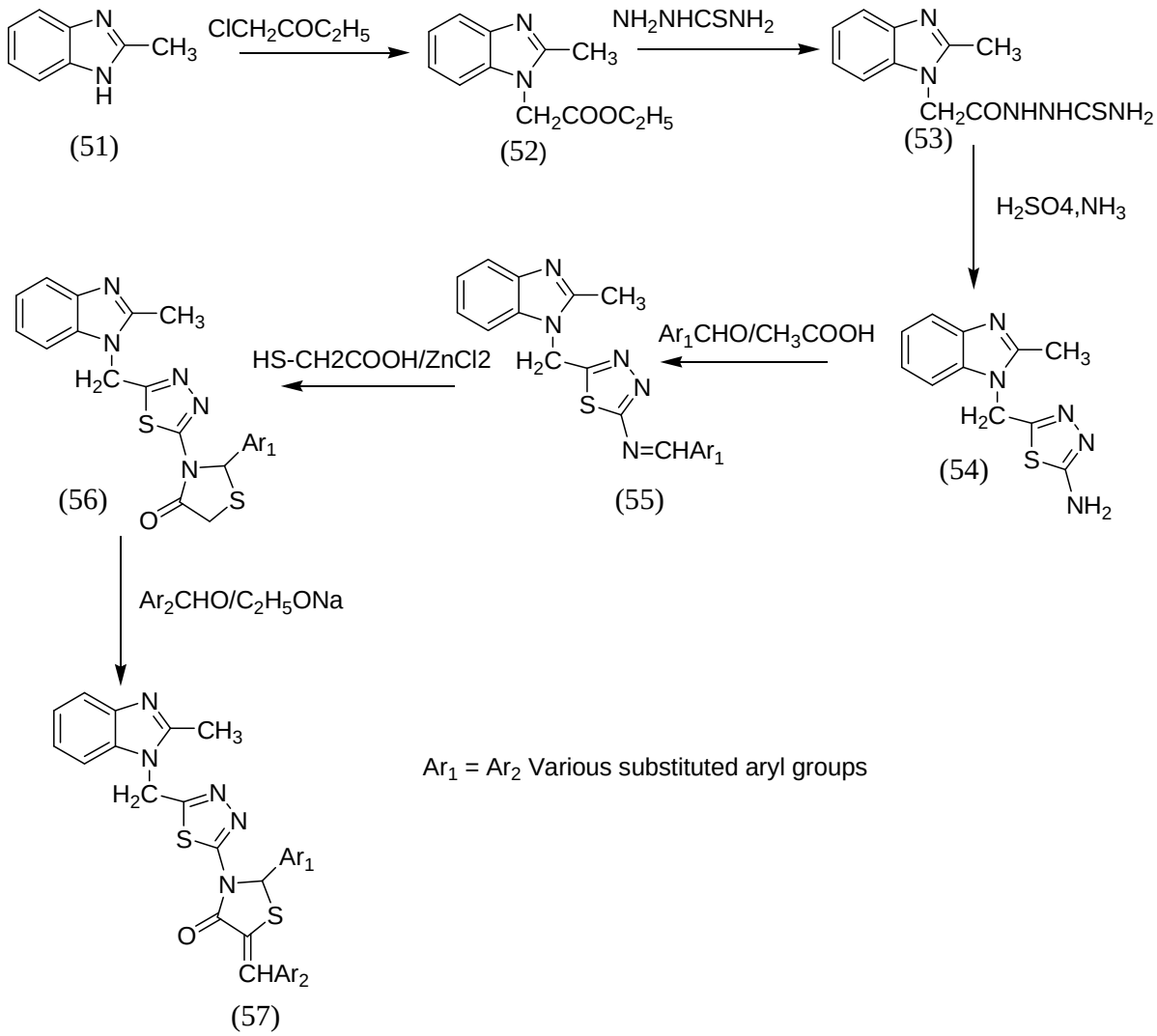
(a) Y=CH_2CH_2
(b)Y=CH_2-S-CH_2
(c) Y=CH_2-O-CH_2
(d) Y=





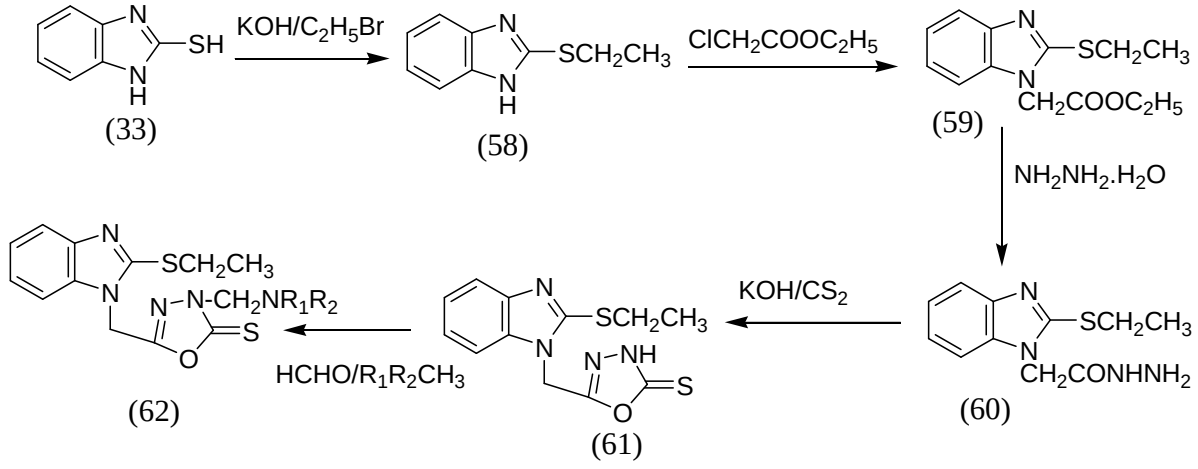
Scheme 15

Dua *et al* (2010) synthesised Substituted -4-Oxothiazolidine and their 5-Arylidene Derivatives of 2-Methyl-benzimidazole (57) from N1-Ethylacetate-2-methyl-benzimidazole (51) [**36**]. N1-Ethylacetate-2-methyl-benzimidazole (51) was formed from the reaction between 2-methyl-benzimidazole (0.30 mole) (24) and ethylchloroacetate (0.30 mole) with K_2CO_3 (6.168g) under microwave irradiation for 3 minutes (scheme 16). When a mixture of compound (51) (0.15 mole) and thiosemicarbazide (0.15 mole) was subjected to microwave irradiation at 160W for 5 min, N1-Acetylthiosemicarbazide-2-methyl-benzimidazole (52) was the product. N1–(2'-amino-5'-methylene) - 1', 3', 4'-thiadiazole-2—methyl-benzimidazole (53) was formed when compound (52) (0.10 mole) was dissolved in chloroform and concentrated H_2SO_4 (0.10 mole) and subjected to microwave irradiation in the resonance cavity of the microwave power system for 1.30 minutes and neutralized with concentrated liq. ammonia. When equimolar solution of compound (53) (0.0085 mole) and benzaldehyde (0.0085 mole) in methanol (20 ml) with 4-5 drops of glacial acetic acid was subjected to microwave irradiation in the resonance cavity of the microwave power system for 1.30 minutes, N1–(2-Benzylidene-imino-5'-methylene)-1', 3', 4'-thiadiazole]-2-methyl-benzimidazole (54) resulted. N'-[2'-{2-phenyl-1,3-thiazolidin-4-one}-5'-methylene-1',3',4'-thiadiazole]-2-methyl-benzimidazole (55) was formed when the equimolar solution of compounds (54) (0.005 mole) and mercaptoacetic acid (0.005 mole) with a pinch of anhydrous $ZnCl_2$ in methanol (30ml) was subjected to microwave irradiation for about 8 minutes. The equimolar solution of compound (55) (0.004 mole) and benzaldehyde (0.004 mole) in methanol (10 ml) in the presence of sodium ethoxide resulted in the product N1-[2'-{2-Phenyl-5-benzylidene-1, 3-thiazolidin-4-one}-5'-methylene -1', 3', 4'-thiadiazole]-2-methyl-1, 3-benzimidazole (57) under microwave irradiation at 300w for about 5 min.



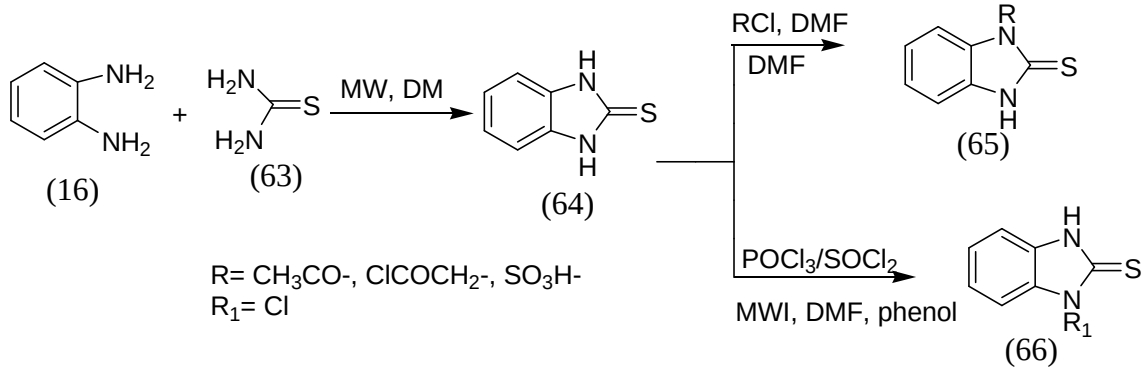
Scheme 16

Somani *et al* (2010) synthesised Mannich bases using benzimidazole derivative (33) [**37**]. The procedure involved the addition of formaldehyde (0.11 mole) and appropriate amines (0.11 mole) in a solution of thione (58) (0.1 mole) in ethanol (10 ml), and the mixture was heated in microwave at the power of 300 watts for 10 min. The mixture was kept overnight in refrigeration. The product (62) thus obtained was filtered and passed through column [silica gel, ethyl acetate: hexane (3:1)] to yield pure products (scheme 17).



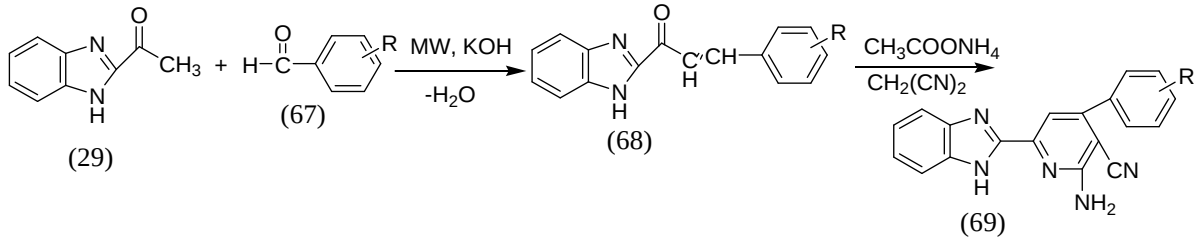
Scheme 17

Singh *et al* (2010) synthesised 1, 3 dihydrobenzimidazol-2-thione and its derivatives in two steps according to the following scheme 18 [**38**]. 1,3 Dihydro-Benzimidazol-2-thione (65) was formed by reacting *o*-phenylenediamine (16) (0.046 mole) and thiourea (63) (0.092 mol) in microwave at 40% intensity for 6 minutes 10 seconds till the colour changes to brown. Acetylchloride, chloroacetyl chloride and chlorosulfonic derivatives of 1,3, dihydro benzimidazol -2-thione (65) were synthesised from 1,3 Dihydro-Benzimidazol-2-thione (64). When the equimolar quantities (0.007 mol) of 1,3 dihydrobenzimadazole - 2 – thione (64) resulted acetylchloride derivative. Similarly, chloroacetyl chloride and chlorosulphonic derivatives of 1,3 Dihydro-Benzimidazol-2-thione (64) were synthesized by using chloroacetylchloride and chlorosulphonic acid in place of acetyl chloride. When a mixture of 1,3, dihydrobenzimidazol-2-thione (64) (0.007mol), (0.14 mol) of phophorousoxochloride/ thionyl chloride and a catalytic amount of phenol was subjected to microwave irradiation at 20% for 1 minutes 50 seconds, it afforded 2-chloro benzimidazole (66).



Scheme 18

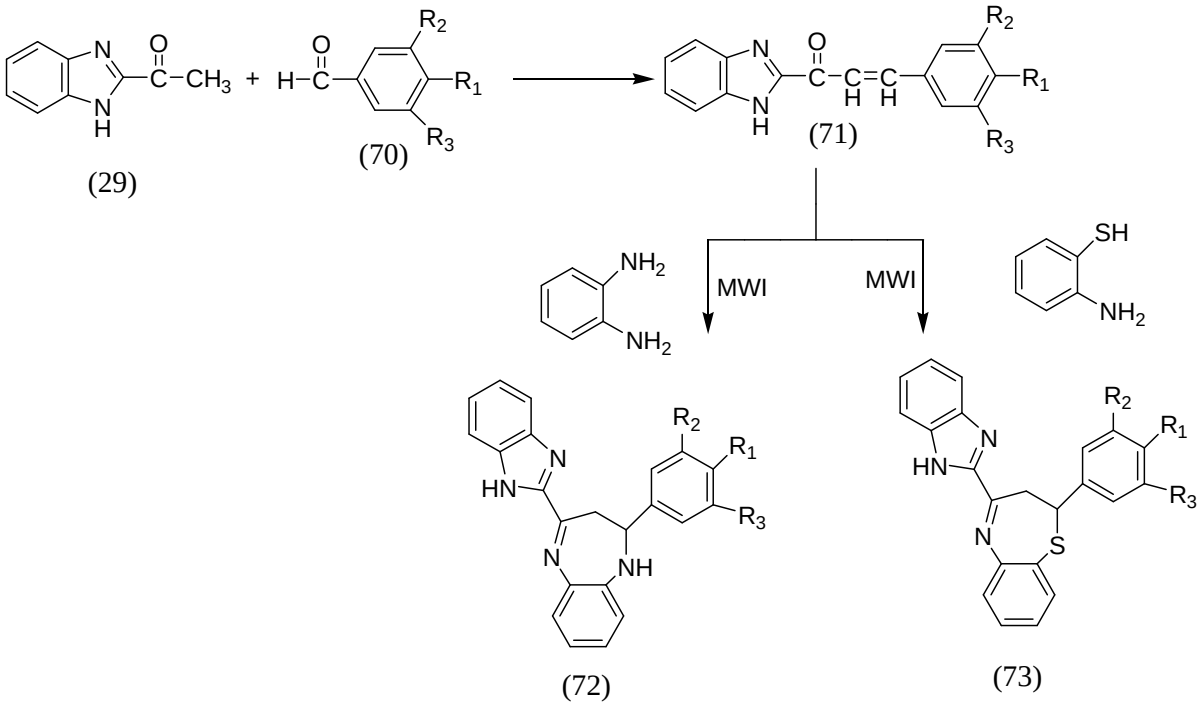
Yadav *et al* (2011) synthesised 2-subsituted benzimidazole derivatives carrying pyridine (69) [**39**]. The first step involved the synthesis of chalcones (68) by irradiating the mixture of 2-Acetyl benzimidazole (29) (0.01 mol) and variously substituted aryl aldehyde (67) (0.012 mol) in methanol in the presence of potassium hydroxide in microwave oven for 30 seconds to 3 minutes at 300 watts. In the second step, mixture of chalcone (68) (0.01 mol), malononitrile (0.01 mole) and ammonium acetate (0.08 mole) was irradiated in a microwave oven for 5 to 6 min at 800 watts and 2-amino-6-(1*H*-benzimidazol -2-yl)-4- phenyl pyridine -3- carbonitriles (69) was formed.



Scheme 19

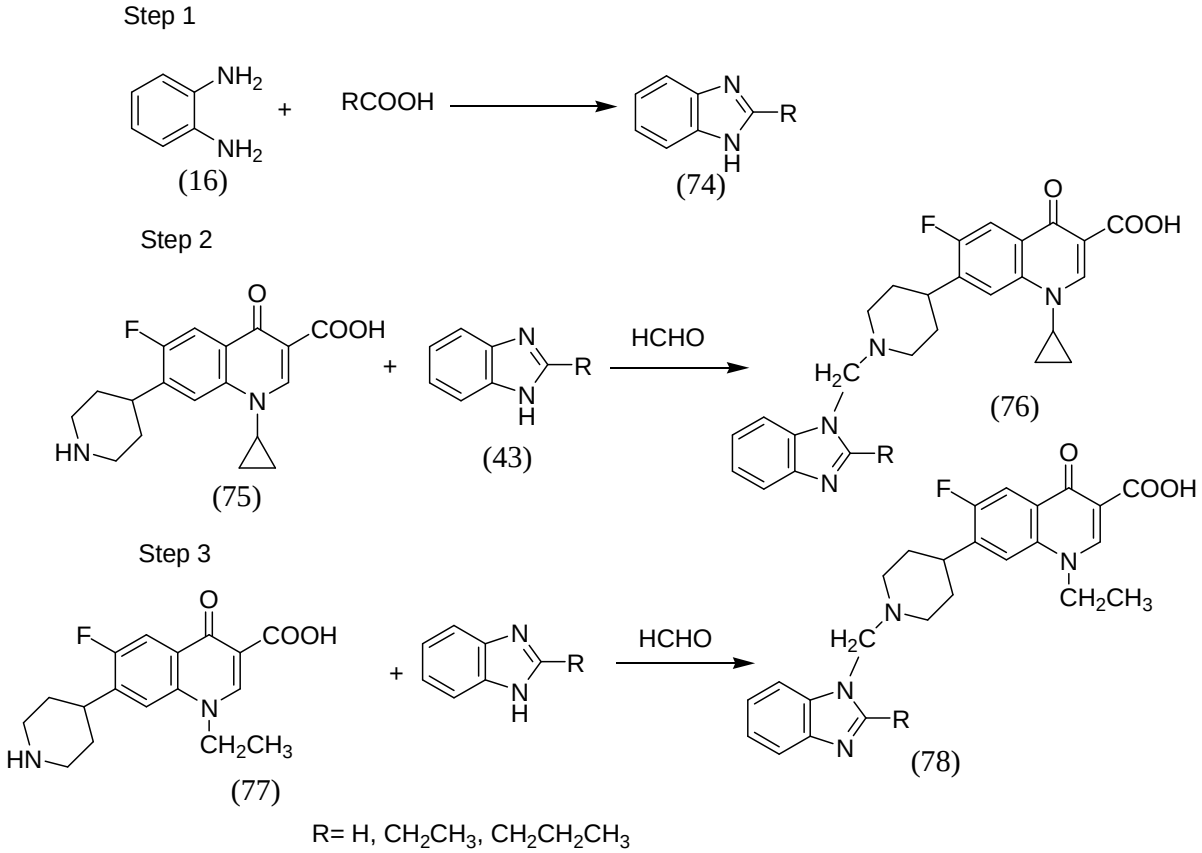
Srivastava *et al* (2011) reported synthesis of benzimidazole assembled 1, 5- benzodizepine and 1, 5-benzothiazepine derivatives [**40**]. In the first step, chalcones (71) were synthesised by irradiating A solution of 2-acetyl benzimidazole (29) (0.01 mole) and approximately aromatic aldehyde (70) (0.012 mole) in ethanol in the presence of sodium hydroxide (40%, 10ml) as a base in microwave oven for 30 seconds to 3 minutes at 300 watts. Then a mixture of chalcone (71) (0.01 mol), ortho phenylenediamine (0.01 mole) and glacial acetic acid in catalytic amount in DMF (10ml) was subjected to MWI for 4.50 to 5.30 min, resulted in synthesis of 4-(1*H*-benzimidazol-2-yl)-2-phenyl-2, 3-dihydro-1*H*-1,5-benzodiazepines (72). 4-(1*H*-benzimidazol-2-yl)-2-phenyl-2, 3-dihydro-1,5-benzothiazepines (73) was synthesised when An ultimate mixture

of chalcone (71) (0.01 mol), 2-amino thiophenol (0.01 mole) and catalytic amount of glacial acetic acid in dry benzene (10 ml) was subjected to microwave irradiation for 5 to 6 min.



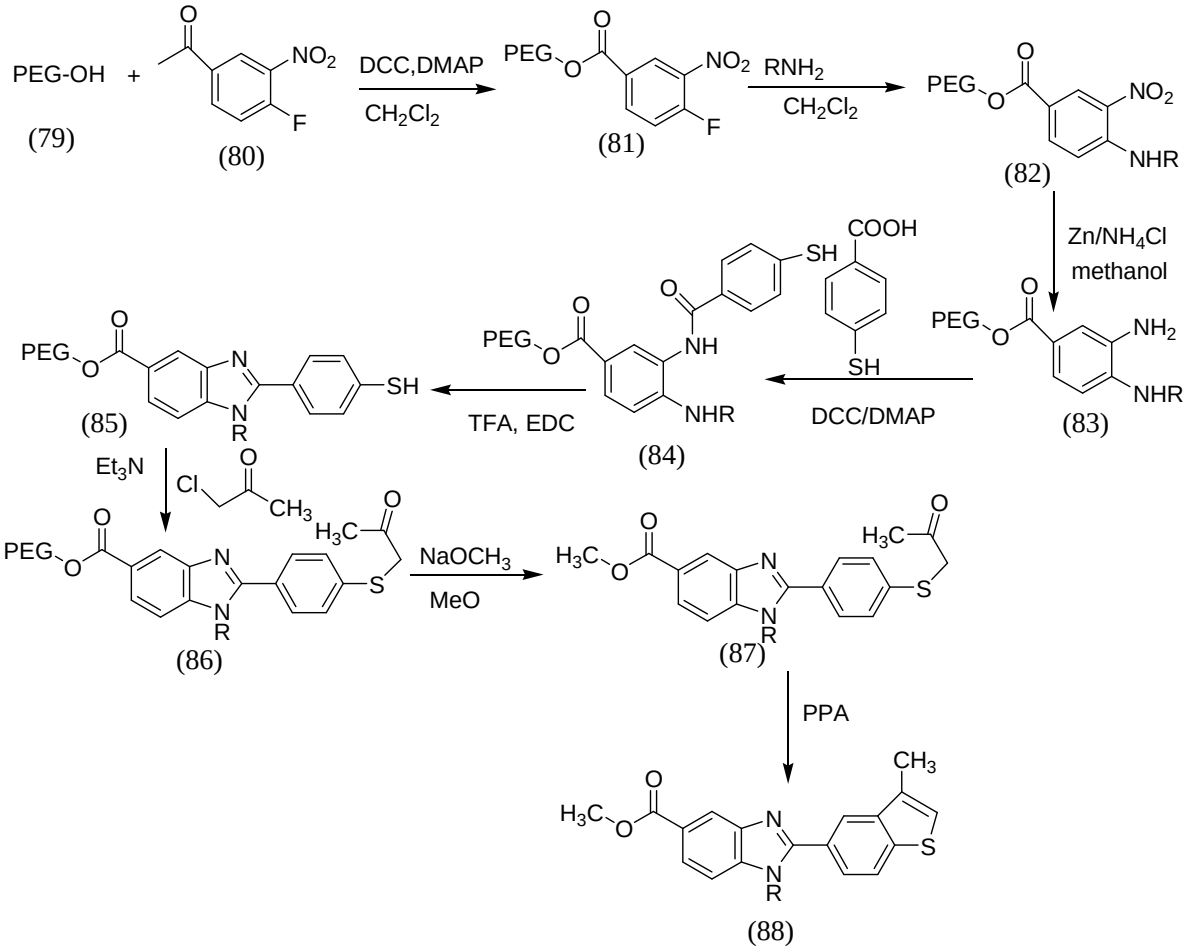
Scheme 20

Jubie *et al* (2010) synthesised benzimidazole substituted fluoroquinolones (76, 78) [**41**]. Benzimidazole derivatives were formed by subjecting a reaction mixture of *o*-phenylene diamine (0.01 mole) (16) and appropriate acid (0.01 mol) is to microwave irradiation at 350W for 25 minutes. The next step involved the synthesis of benzimidazoles substituted fluoroquinolones via Mannich reaction. A suspension of appropriate benzimidazole derivatives (46) (0.02 mole) in ethanol, ciprofloxacin & norfloxacin (0.02 mol) and 37% formaldehyde (0.5 ml) were irradiated in a microwave oven at an intensity of 80% with 3-5 min.



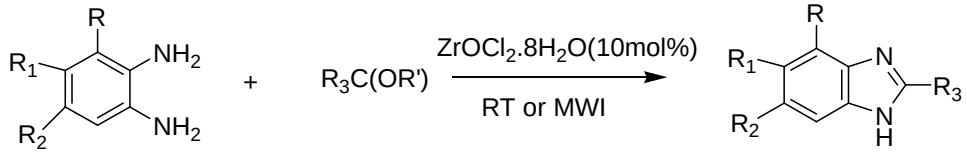
Scheme 21

Kini *et al* (2009) synthesised benzimidazolo benzothiophenes (88) by liquid phase combinatorial synthesis using soluble polymer support PEG 5000 (79) and 4-fluoro-3-nitrobenzoic acid (80) as starting materials with substituted primary amines (scheme 22) [**42**]. They first reacted the polymer bound diamino compound (83), dissolved in dichloromethane, with 1.2 mol of 4-mercaptobenzoic acid (MBA), 1.2 mol of DCC and a pinch of DMAP in the microwave for 20 min to afford PEG bound compound (83). The solution was filtered to remove the excess of DCC and DMAP salts. PEG bound 3-amino-4-mercapto benzene (84) was then treated with trifluoroacetic acid and ethylene dichloride in the ratio of 1:10 and was subjected to microwave irradiation for 20 minutes to precipitate the PEG bound 2-substituted benzimidazole (85).The solution of PEG bound mercaptobenzimidazole (85) was treated with chloroacetone (1.2 mol), triethylamine (1.2 mol) in dichloromethane and heated under microwave irradiation for about 10 min. After completion of the reaction, the reaction mixture was directly treated with cold diethyl ether to precipitate the product (86). The polyethylene glycol was cleaved from The PEG bound compound (86) using methanol and sodium methoxide to give compound (87). 1-Substituted–2-(4-aceto-methyl-thio-phenyl)-1*H*-benzoimidazole-5-carboxylic acid methyl ester (1.0 mol) (87) is treated with polyphosphoric acid (PPA) and heated on a water bath for 4 h to form 1-substituted-2-(3-methyl-benzo[b]thiophen-6-yl)-3H benzoimidazole- 5-carboxylic acid methyl ester (88).



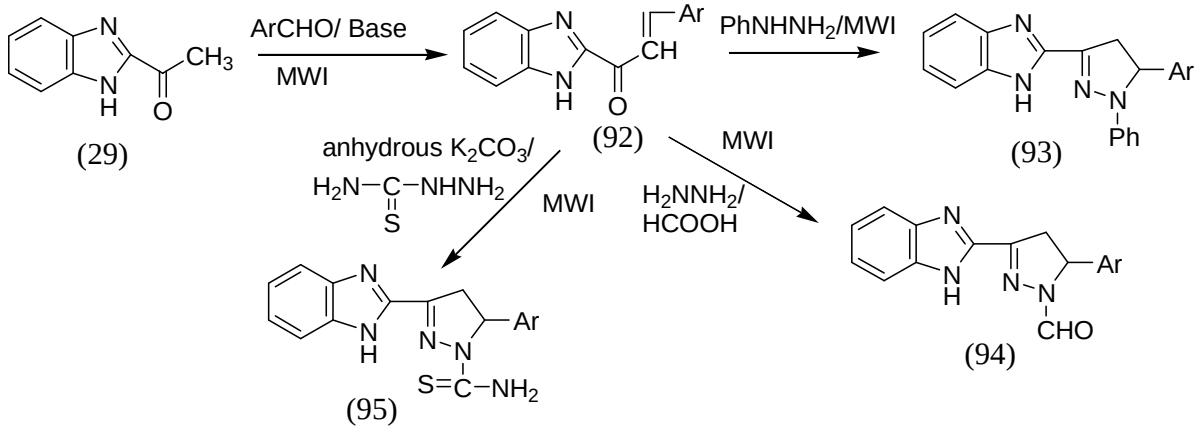
Scheme 22

Zhang *et al* (2007) reported the one pot synthesis of 2-substituted benzimidazoles (91) from the reaction of an appropriate *o*-phenylenediamine (89) (1.0 mmole), orthoester (90) (7.2 mmole) and $ZrOCl_2.8H_2O$ (10 mole%) under microwave irradiation at 160W for an appropriate time. (Scheme 23) [**43**].



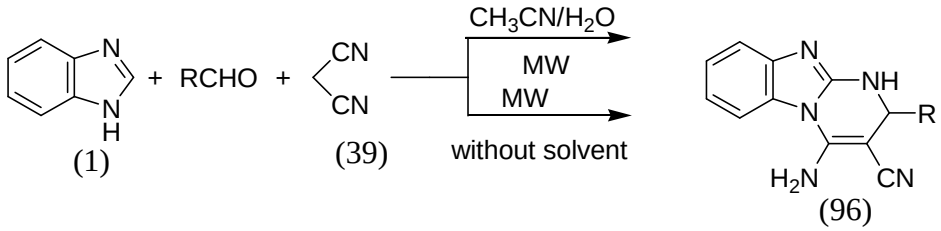
Scheme 23

Rajori *et al* (2007) Synthesised benzimidazolyl chalcones and pyrazolines using microwave irradiation. An intimate mixture of Compound (92) (0.01 mole) and phenyl hydrazones (0.012 mole) were subjected to microwave irradiation at 300 watt power for 4-6 min formation of 1-phenyl-3-benzimidazoleyl-5-aryl-2-pyrazolines (93) (scheme 24) [**44**]. An intimate mixture of compound (92) (0.01 mole), hydrazine hydrate (0.015 mole) and formic acid (15 mL) was subjected to microwave irradiation at 240 watt power for 4-6 min resulted in formation of 3-benzimidazolyl-5- aryl-2-pyrazolinyl-1- carboxaldehydes (94).An intimate mixture of compound (92) (0.01 mole), thiosemicarbazides (0.015 mole) and anhydrous K_2CO_3 (4g) under MW irriadiation at 300 watt power for 3-5 min resulted in the formation of 1-thiocarbamide-3-benzimidazolyl-5- aryl- pyrazolines (95).



Scheme 24

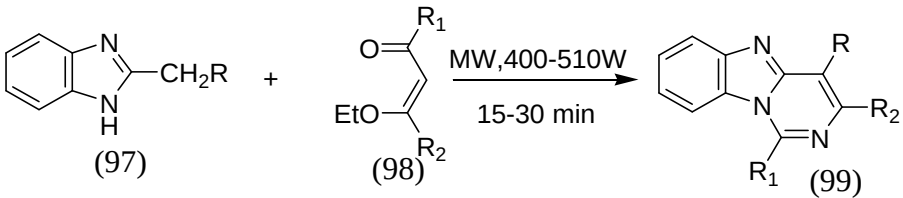
Kumbhare *et al* (2008), A variety of 1, 2-dihydropyrimido-[1,2-a]-benzimidazole-3-carbonitrile derivatives (96) were synthesized under microwave irradiation using water and acetonitrile as solvent system, as reported by [**45**]. A mixture of malononitrile (1 mmol), 2-aminobenzthiazole (1 mmol), benzaldehyde (1 mmol), and solvent mixture (1.5 mL, acetonitrile/water) were placed in a 10 mL pressure tube. The mixture was subjected to microwave irradiation (180 W, 250 psi, 80 ^{0}C) for 5 min and then diluted with dichloromethane (5 mL) and filtered. The solid was rinsed with dichloromethane (2x 5 mL) and the combined extracts were concentrated and purified by column chromatography to afford the corresponding pure product. The same compound was obtained in the absence of the solvent system.



R = 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-C_6H_5, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$

Scheme 25

Microwave energy has found application in the rapid synthesis of bridgehead nitrogen heterocycles under solvent-free conditions [**46**]. **Rahmouni *et al*. (1994)** have synthesised pyrimidino[1,6-*a*]benzimidazoles (99) (Scheme 46) under focused microwave irradiation in moderate yields from *N*-acylimidates (98) and activated 2-benzimidazoles(97).



R= CN, CO_2Me, CO_2Et

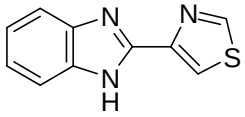
R_1, R_2 = alkyl

Scheme 26

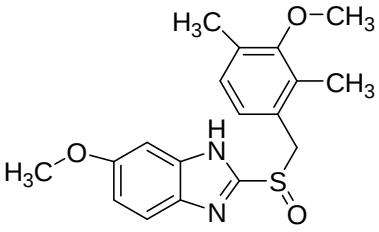
Pharmacological importance

The benzimidazole ring is an important pharmacophore in modern drug discovery. The compounds bearing benzimidazole moiety are reported to possess a number of interesting biological activities and the widespread importance of benzimidazole structure has extensive studies for practical synthetic method of heterocycles [47-51]. Benzimidazole derivatives have found the appreciation in diverse therapeutic areas including antimicrobial activity[52-56], the

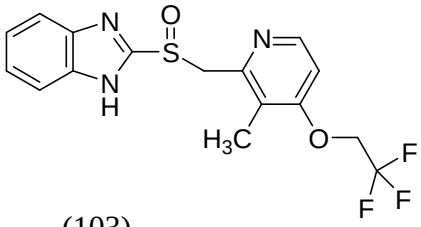
activity against several viruses such as HIV [57-59], antiallergic [60,61], antioxidant [62-64], antihistaminic [65], antitubercular [66,67], antiasthmatic [68], anti-diabetic [69,69a], anticancer [70- 74], antitumor [75-76], antiulcer [77,78], antihelmentic [79], HIV-1 reverse transcriptase inhibitors [80,80a], antiviral [81], anticoagulant [82], anti inflammatory [83], antibacterial [84,85], the series of biologically active benzimidazoles [86]. A variety of benzimidazoles are in use, like thiabendazole (100) and flubendazole (101) (anthelmintic), omeprazole (102) and lansoprazole (103) (antiulcerative) and astemizole (104) (antihistaminic) (figure 1). Some 1,5-bis(5-substituted benzimidazole)alkanes e.g. 1,5-Bis(5-nitro-1H-benzimidazole)pentane (105a), 1,6-Bis(5-nitro-1H-benzimidazole)hexane (105b), 1,6-Bis(5-amino-1H-benzimidazole)hexane (106a) & 1,6 -Bis(5-amino-2-methyl-1H-benzimidazole)hexane (106d) displayed good antileishmanial activity [87] (figure 1). 2-mercaptobenzimidazole derivatives exhibited significant analgesic activity when compared with standard drug, pentazocine [88] (Figure 1).



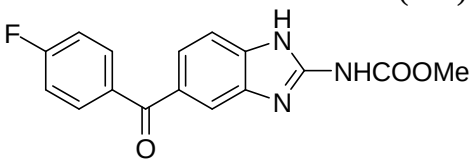
(100)



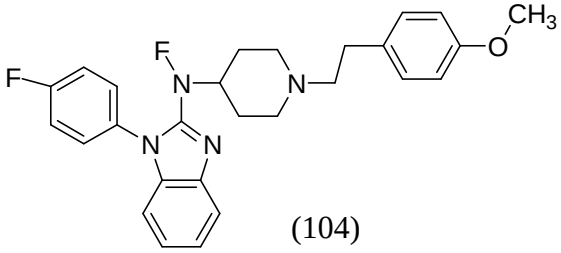
(102)



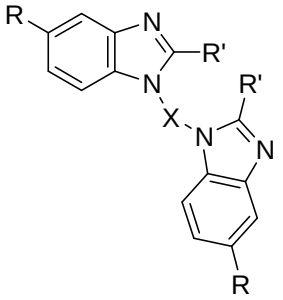
(103)



(101)

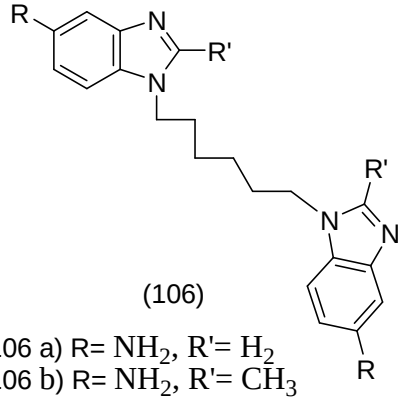


(104)



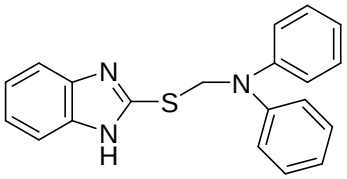
(105)

(105 a)R= NO_2, R'= CH_3
(105 b)R= NO_2, R'= H



(106)

(106 a) R= NH_2, R'= H_2
(106 b) R= NH_2, R'= CH_3



(107

Figure 1

CONCLUSION

The benzimidazole ring is an important pharmacophore in modern drug discovery. Attention has been increasingly given to the synthesis of benzimidazole derivatives by using microwave techniques. The benzimidazole derivatives are a resource for medicinal research. Benzimidazole derivatives having wide diverse of biological activity. The dynamic microwave power system employed offered an efficient heating of the material, thus reduced chemical reactions times and increased reaction yields were observed in most of the most of the literature quoted in this paper.

REFERENCES

[1] KH Berg; M Buchel; A Plempel; Zywietz; Mykosen. **1986**, 29, 221-229.
[2] AG Saimot; AC Cremieux; JM Hay; A Meulemans; MD Giovanangeli; B Delaitre; FP Coulaud. *Lancet*, **1983**, 17, 652-656.
[3] A Chimirri; S Grasso; AM Monforte; P Monforte; M Zappala. *I Farmaco*, **1991,** 46, 925-933.
[4] JE Niemegeers; F Awouters; AJ Janssen. *Agents and Actions*, **1986**, 18, 141-144.
[5] R Iemura; M Hori; H Ohtaka. *Chem. Pharm. Bull.*, **1989,** 37, 962- 966.
[6] J Benavides; H Schoemaker; C Dana;Y Claustre; M Delahaye; M Prouteau; P Manoury; JV Allen; B Scatton; SZ Langer; S Arbilla. *F Arzneim*. **1995,** 45, 551- 558.
[7] K Ishihara; T Ichikawa; Y Komuro; S Ohara; K Hotta; F Arzneim. *Drug Res.*, **1994**, 44, 827-830.
[8] DY Graham; A Mccullough; M Sklar; JS Sontag; WM Roufail; R Stone; RH Bishop; Gitlin; AJ Cagliola; RS Berman; T Humphries. *Digestive Diseases and Sciences*, **1990**, 35, 66-72.
[9] G Piazzesi; L Morano; JC Ruegg. Arzneim Forsch. *Drug Res.*, **1987**, 37, 1141-1143.
[10] Wiedemann; H Peil; H Justus; S Adamus; V Brantl; H Lohmann. Arzneim Forsch. *Drug Res*., 1985, 35, 964-969.
[11] K Kubo; Y Kohara; E Imamiya; Y Sugiura; Y Inada; Furukawa; K Nishikawa; Naka. *J, Med. Chem.*, **1993,** 36, 2182 – 2195.
[12] AJ Janssen; FTN Allewijn; F Arzneim. *Drug Res.*, **1968**, 18, 279-282.
[13] The Merck Index. *An Encyclopedia of chemicals, drugs and Biologicals*, **2001,** 13.
[14] A Loupy; VCH Wiley; Weinheim, **2006**.
[15] A Hoz; AD Ortiz; A Moreno. *Chem. Soc. Rev.*, **2005**, 164-178.
[16] C Strauss; R Trainor. *Aust. J. Chem.*, **1995**, 48, 1665.
[17] KK Rajasekhar; VA Shankar; TS Nithiyananthan; G Hareesh; P Naveen Kumar; RSP Reddy**.** *International Journal of ChemTech Research,* **2010,** 2, 592-597.
[18] AR Katritzky; AF Pozharski. *Handbook of Heterocyclic Chemistry,* **2000**, 2.
[19] BA Reddy. *J Biomed Sci and Res*., **2009**, 1, 27-32.
[20] JB Wright. The chemistry of the benzimidazoles. *Research Laboratories*.
[21] A Brett; Roberts; R Christopher; Strauss. Toward, **2004**.
[22] Vogel. Text book of practical organic chemistry. **1989,** 5, 1153.
[23] FG Mann; BC Saunders. **1986**, 4, 303.
[24] Vogel. *Text book of practical organic chemistry*. **1989,** 5, 1173.
[25] Vogel. *Text book of practical organic chemistry*. **1989**, 5, 1162.
[26] Vogel. *Text book of practical organic chemistry*. **1989**, 5, 1276.
[27] Vogel. *Text book of practical organic chemistry*. **1989**, 5, 1190.
[28] S Ganguli. *Pharma Times*. **2006**, 38(12), 26.
[29] R Somani; S Pawar; S Nikam; P Shirodkar; V Kadam. *International Journal of Chem Tech Research*, **2010**, 2(2), 860-864.
[30] JS Yadav; YK Srivastava. *Rasayan J. Chem*., **2010,** 3(4), 726-730.

[31] HP Narkhede; UB More; DS Dalal; PP Mahulikar. *Journal of scientific & industrial research*, **2008**, 67, 374-376.
[32] K Arya; A Dandia; 13th international electronic conference on synthetic organic chemistry. **2009**.
[33] W Shieh; S Dell; O Repic. *Organic letters*, **2001,** 3(26), 4279-4281.
[34] RS Joshi; PG Mandhane; SK Dabhade; CH Gill. *Journal of the Chinese Chemical Society*, **2010,** 57, 1227-1231.
[35] K Niknam; Fatehi-Raviz A. *Journal of the Iranian Chemical Society*, **2007**, 4 (4), 438-443.
[36] R Dua; SK Sonwane; SK Srivastava; SD Srivastava. *Journal of Chemical and Pharmaceutical Research*, **2010,** 2 (1), 415-423.
[37] S Vijayaraghavan; RR Somani; PY Shirodkar; VJ Kadam. *Indian journal of chemistry,* **2010,** 49, 1130- 1134.
[38] A Singh; AC Rana. *International Journal of PharmTech Research*, 2(3), 1969-1977.
[39] JS Yadav; YK Srivastava. *Der Chemica Sinica,* **2011,** 2(1), 1-7.
[40] JS Yadav; YK Srivastava. *Der Pharmacia Lettre*, **2011**, 3(2) 284-291.
[41] S Jubie; R Rajeshkumar; B Yellareddy; G Siddhartha; M Sandeep; K Surendrareddy ; HS Dushyanth; K Elango. *J. Pharm. Sci. & Res*., **2010,** 2(2), 69-76.
[42] D Kini; H Kumar; M Ghate. *E-Journal of Chemistry*, **2009**, 6(S1), S25-S32.
[43] ZH Zhang; L Yin; YM Wang. *Catalysis communications,* **2007**, 8(7), 1126-1131.
[44] J Rajori; J Yadav; R Kumar; YK Shrivastva. *Indian journal of chemistry*, **2010,** 49, 989-993.
[45] RM Kumbhare; U Kosurkar; KV Kumar; T Dadmal; AK Tiwari. *Indian journal of chemistry*. **2008,** 47, 1154-1159.
[46] M Rahmouni; A Derdour; JP Bazureau; J Hamelin. *Tetrahedron Lett.*, **1994**, 35, 453.
[47] GL Gravatt; C Baguley; WR Wilson. *J. Med. Chem.*, **1994,** 37, 4338.
[48] P Tempest; V Ma; S Thomas; Z Hua; MG Kelly; C Hulme. *Tetrahedron Lett.* **2001,** 42,
[49] 4959-4962.
[50] R Trivedi; S K De; R A Gibbs. *J. Mol. Catal. A. Chem*., **2005,** 245, 8-11.
[51] LN Divaeva; TA Kuzmenko; AS Morkovnik; VN Komissarov. *Chem. Heterocyclic*
[52] *Compds.,* **2006,** 42, 463-468.
[53] A Davoodnia; M Roshani; E Saleh Nadim; M Bakavoli; N Tavakoli Hoseini. *Chin. Chem.*
[54] *Lett*. **2007,** 18, 1327-1330.
[55] C Kus; G Aylan-Kicigil; M Iscan. *Arch. Phar, Res.*, **2004,** 27, 156-163.
[56] AE Abdel-Rahman; AM Mahmoud; GM El-Naggar. *Pharmazie.*, **1983,** 38, 589-590.
[57] FSG Soliman; SM Rida; T Kappe. *Arch. Pharm*., **1984,** 317, 951-958.
[58] S Ozden; D Atabey; S Yildiz; H Goker. *Bioorg. Med. Chem*., **2005,** 13, 1587-1597.
[59] K Sztanke; K Pasternak; A Sidor-Wojtowicz; J Truchlinska; K Jozwiak. *Bioorg. Med.*
[60] *Chem*. **2006,** 14, 3635-3642.
[61] AR Porcari; RV Devivar; LS Kucera; JC Drach; LB Townsend. *J. Med. Chem*., **1998,**
[62] 41, 1251.
[63] M Roth; ML Morningstar; PL Boyer; SH Hughes; RW Bukheit; CJ Michejda. *J. Med.*
[64] *Chem*. **1997,** 40, 4199.
[65] R Samia; A Soda; M El-Hesham; TY Fahmy. *Arch. Pharm. Res.,* **2006,** 29, 826-833.
[66] T Fukuda; T Saito; S Tajima; K Shimohara; K Ito. *Arzneim.-Forsch./Drug Res.*, **1984,**
[67] 34, 805-810.
[68] H Nakano; T Inoue; N Kawasaki; H Miyataka; H Matsumoto; T Taguchi; N Inagaki;
[69] H Nagai; T Satoh. *Chem. Pharm. Bull*., **1999,** 47, 1573-1578.
[70] B Can-Eke;MOPuskullu; E Buyukbingol; M Iscan. *Chemico-Biological Interactions,*
[71] **1998,** 113, 65-77.
[72] C Kus; G Ayhan-Kilcigil; B Can-Eke; M Iscan. *Arch. Pharm. Res.*, **2004,** 27, 156-163.

[73] Ayhan-Kilcigil, G.; Kus, C.; Coban, T.; Can-Eke, B.; Iscan, M. *Journal of Enzyme*
[74] *Inhibition and Medicinal Chemistry*, **2004,** 19, 129-135.
[75] H Goker; G Ayhan-Kilcigil; M Tuncbilek; C Kus; R Ertan; E Kendi; S Ozbey; M Fort; C
[76] Garcia; AJ Farre. *Heterocycles*, **1999,** 51, 2561-2573.
[77] VL Khairnar; SR Lockhande; MR Patel; BG Khadse *Chemical Abstract*, **1981,** 95, 203.
[78] I Kuchkguzel; G Kuchkguzel; S Rollas; M Kiraz. *Bioorg. & Med. Chem. Lett.* **2001,** 11,
[79] 1703.
[80] E Souness; D Aldous; C Sargent. *Immunopharmacology*, **2004,** 47, 127.
[81] K Senten; PVV Venken; ID Meester; AM Lambeir; S Scharpe; A Haemers; K Augustyns. *J. Med. Chem.*, **2003,** 46, 5005.
[82] E Black; J Breed; AL Breeze; K Embrey; R Garcia; TW Gero; L Godfrey; PW Kenny; AD Morley; CA Minshull; A D Pannifer; J Read; A Rees; DJ Russell; D Toader; J Tucher. *Bioorg & Med. Chem. Lett.*, **2005,** 15, 2503.
[83] FD Popp. *J. Org. Chem*., **1980,** 26, 1566.
[84] FD Popp. *J. Med. Chem*., **1911**, 7, 210.
[85] LL Kruse; DL Ladd; PB Harrsch; FL McCabe; SM Mong; L Faucette; R Johnson. *J. Med. Chem*., **1989,** 32, 409-417.
[86] I Islam; EB Skibo; RT Dorr; DS Alberts. *J. Med. Chem*. **1991,** 34, 2954-2961.
[87] MM Ramla; MA Omar; H Tokuda; HI El.Diwani. *Bioorg. Med. Chem.* **2007,** 15, 6489-6496.
[88] WA Denny; GW Rewcastle; BC Bagley. *J. Med. Chem.*, **1990,** 33, 814.
[89] M Tatsuta; M Kataoka; K Yasoshima; S Sakakibara; M Shimazaki; T Yura; Y Li; N Yamamoto; J Gupta; K Urbahns. *Bioorg. Med. Chem. Lett.*, **2005,** 15, 2265-2269.
[90] E Carlsson; P Lindberg; S Unge. *Chem. Br*., **2002,** 5, 42.
[91] JE Richter; *Am. J. Gastroenterology*., **1997,** 92, 30-34.
[92] JC Hazelton; B Iddon; H Suschitzky; LH Woolley. *Tetrahedron*, **1995,** 51, 10771- 10794.
[93] K Karen, *Antiviral Res*.**, 2006,** 71, 154- 163.
[94] JM Gardiner; CR Loyns; A Burke; A Khan; N Mahmood. *Bioorg. Med. Chem. Lett.*, **2003,** 13, 657-660.
[95] YF Li; GF Wang; Y Luo; WG Huang; W Tang; CL Feng; LP Shi; YD Ren; JP Zuo; W Lu.
[96] *Eur. J. Med. Chem*. **2007,** 42, 1358-1364.
[97] WB Young; P Sprengeler; WD Shrader; Y Li; R Rai; E Verner; T Jenkins; P Fatheree; A
[98] Kolesnikov; JW Janc; L Cregar; K Elrod; B Katz. *Bioorg. Med. Chem. Lett.*, **2006,** 16, 710-713.
[99] A Mertens; B Muller-Beckmann; W Kampe; JP Holck; W Von der Saal. *J. Med. Chem*., **1987,** 30, 1279-1287.
[100] R Vinodkumar; SD Vaidya; BV Siva Kumar; UN Bhise; SB Bhirud; UC Mashelkar. *J. Med.*
[101] *Chem.*, **2008,** 43, 986-995.
[102] M Andrzejewska; LY Mulia; A Tapia; RC Rivera; AE Laudy; BJ Starosciak; Z Kazimierczuk. *Eur. J. Pharm. Sci.*, **2004,** 21, 323-329.
[103] AA Jafar; KN Vijayakumar; BR Venkatraman; G Venkatesh. *Orbital-Electronic J. Chem.*, **2009,** 1(4), 306-309.
[104] M Verma; A Bhandari; RK Nema. *J. Chem. Pharm. Res.*, **2010**, 2(3), 244-250.
[105] K Anandarajagopal; RN Tiwari; N Venkateshan; GV Pooshan; P Promwichit. *J. Chem. Pharm. Res.*, **2010**, 2(3):230-236.