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REVIEW ON MICROWAVE SYNTHESIS OF VARIOUS HETERO-CYCLIC NUCLEUS POSSESSING ANTI-INFLAMMATORY ACTIVITY

Chaganti Soujanya*, Karuna Devi Barla, Swathi Naraparaju, Saisree K., Sai Chandu A. and U V N Swamy D

Assistant Professor, Department of Pharmaceutical Chemistry, Gokaraju Rangaraju College of Pharmacy, Hyderabad-500090.

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***Corresponding Author**
Chaganti Soujanya
Assistant Professor,
Department of
Pharmaceutical Chemistry,
Gokaraju Rangaraju College
of Pharmacy, Hyderabad-
500090.

ABSTRACT

The review article aimed at presenting a few synthetic procedures for the preparation various anti-inflammatory heterocyclic nucleus using microwave methods. It has been observed that the recommendation of NSAIDS have been increasing in the treatment of different diseases associated with inflammation. Though researchers are constantly working towards developing new NSAIDS through various conventional procedures, not able to reach the demand because of various difficulties such as long reaction time, high cost and low yields. Hence, chemists have chosen microwave synthesis as a modern tool in the synthesis of NSAIDS as it is more convenient method in comparison to conventional method in terms of reaction time, cost and yields. Hence, in this review, presented a few procedures for the synthesis of NSAIDS by microwave to help out budding researchers in this area.

KEYWORDS: Microwave, NSAIDS, conventional, heterocyclic.

INTRODUCTION

The property of a medicine that lowers the inflammation is referred to as an anti-inflammatory agent. Anti-inflammatory drugs, as contrasted to opioids, which impact the central nervous system, account for about half of analgesics. They alleviate pain by lowering inflammation. Aspirin, ibuprofen, ketoprofen, diclofenac, and also naproxen are most of the

common effective anti-inflammatory medications. These chemicals are known as "non-steroidal anti-inflammatory drugs (NSAIDs)".[1] Anti-inflammatory agents contain various heterocyclic rings such as pyrazine, pyrimidine. acridine, thiazole, pyridazinone, pyrido imidazole, imidazolo quinoline, pyrazoline, quinoline, pyrrole, furan, diazole and imidazo thiadiazole.[2] which make their synthesis a difficult process for the research chemists. In search of convenient, affordable and suitable method for the synthesis of NSAIDS, microwave synthesis seems to be torch bearer as it is a convenient way toward the goal of green chemistry.[3] It can be used in chemical synthesis as a heat source which significantly reduce reaction times of numerous synthetically useful chemical transformations. The advantages of this enabling technology have more recently been exploited in the context of multistep total synthesis and medicinal chemistry/drug discovery and have additionally penetrated related fields such as polymer synthesis, material sciences, nanotechnology and biochemical processes.[2] A thorough literature search have been supported the chemist's hypothesis on utilising microwave for the synthesis of NSAIDS. Some of the successful synthetic procedures have been reported in this review to help out researchers to synthesize NSAIDS in less time with good yields conveniently.

1. Hany M. Abd El-Lateef et. al., reported the microwave synthesis of various novel 3-cyanopyridines with a solution of 4-formylphenyl-4-methylbenzenesulfonate (1); ethyl cyanoacetate(2 mmol, 0.22 mL); acetophenone derivatives, namely, acetophenone, 4-methylacetophenone, 4-methoxyacetophe-none, 4-aminoacetophenone, 4-chloroacetophenone, 4-bromoacetophenone, 4-nitroacetophenone, 1-acetylnaphthalene, 2-acetylthiophene, 2-acetylpyridine, 3-acetylpyridine, and 4-acetylpyridine; and ammonium acetate in molar ratio 1:1:1:2 in 5 mL of ethanol was allowed to irradiate in an MW oven for 2−7 min as shown in figure 1. All compounds synthesized were examined for their anti-inflammatory activity using diclofenac as a reference drug and showed promising anti-inflammatory activity.[4]

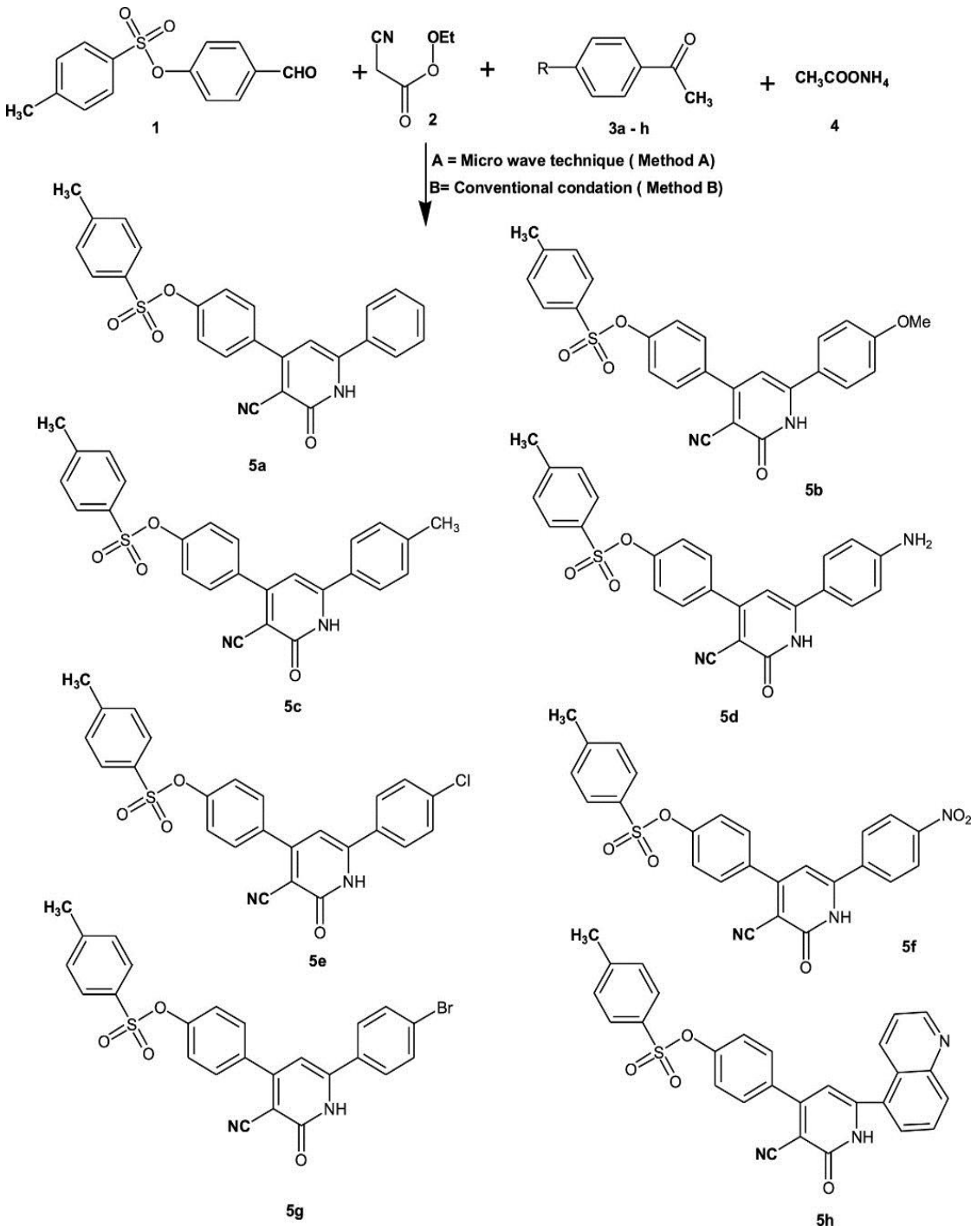


Figure 1: Synthesis of 3-Cyanopyridines.[4]

2. A cha Amira et.al., reported an eco-friendly and one-step microwave-assisted green synthesis of new functionalized bisphosphonates derivatives by a three-component reaction of aromatic sulfamide with triethyl orthoformate and diethyl phosphite as shown in figure 2. Initially, sulfamides 1(a–f) were prepared from the corresponding amines. When using microwave activation under solvent-free conditions at different temperatures and powers, bisphosphonate formation was achieved after 10 min at 150°C and power of 500 W. In

another experiment, an increase of the diethyl phosphite to 5 equivalents under similar conditions did not improve yield substituted with electron-donating and -withdrawing groups at different positions gave the corresponding products in reasonable to good yields in 10 to 20 min. The substitutions on aniline derivatives had no significant effect on the reaction time and product yield. The investigation showed remarkable *in vitro* and *in slico* activities, mainly the compound 4b has the highest anti-inflammatory activity suggesting synthesized target compounds could be used as a leads for new anti-inflammatory agents.[5]

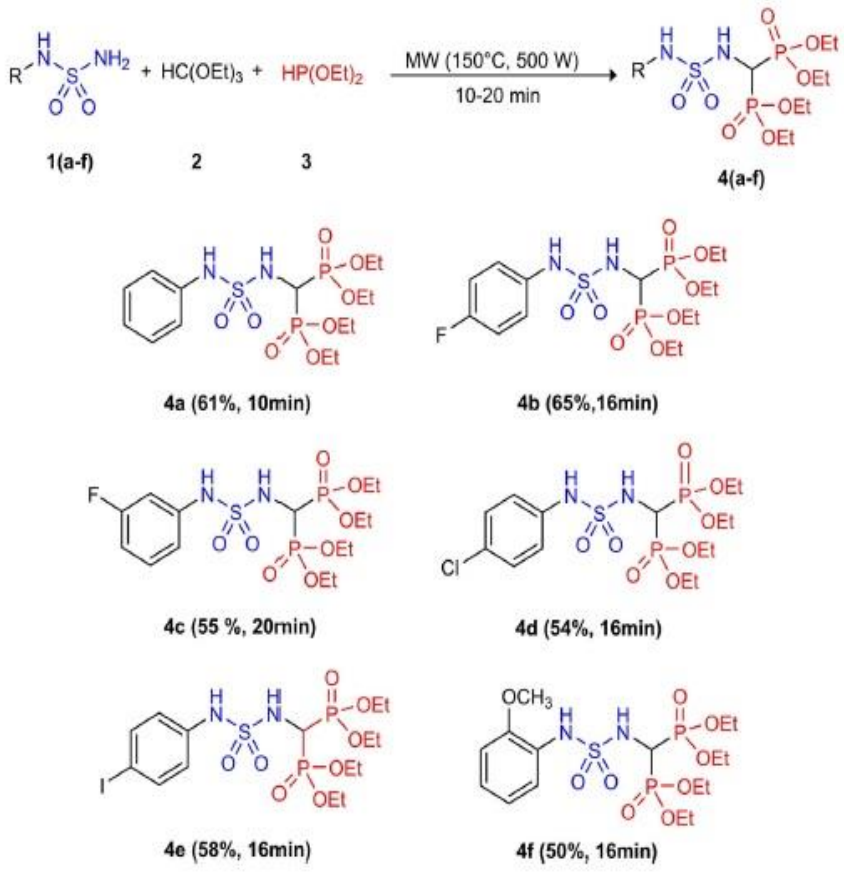
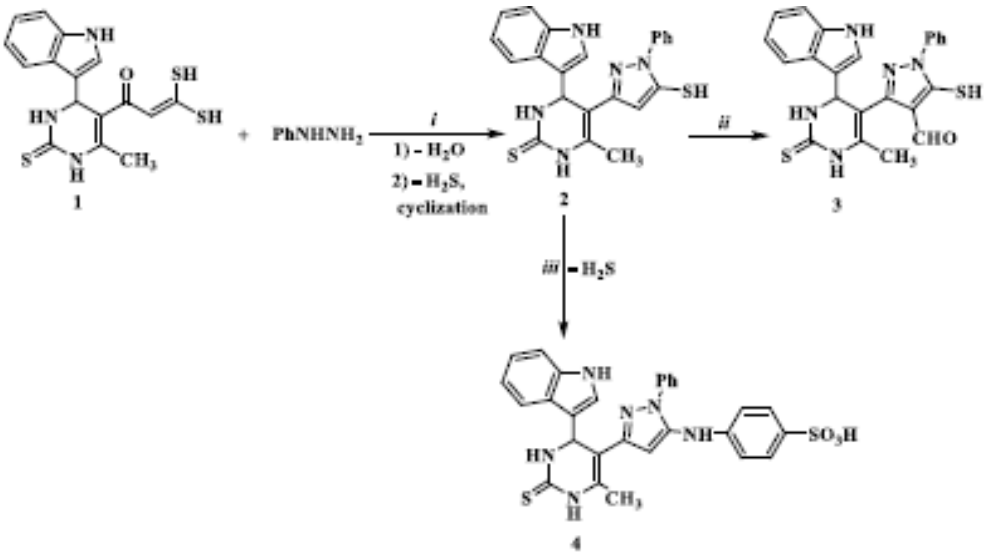


Figure 2: Synthesis of sulfamide-containing bisphosphonates esters under MW.[5]

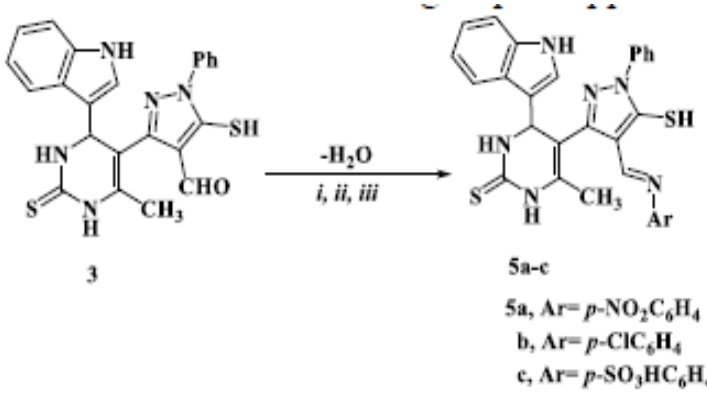
3. Entesar A. Hassan et.al., reported the microwave synthesis of some new mercapto pyrazolaldehyde bonded to indolyl dihydro pyrimidine thione derivatives. Synthesis of the pyrazole derivative **2** was achieved *via* the reaction between oxoketene *gem*-dithiol **1** and phenylhydrazine. Subsequently, the key synthon mercaptopyrazole derivative **2** was qualified to react with some reagents e.g. DMF/POCl3 and/or sulfanilic acid to afford pyrazolecarbaldehyde **3** and/or pyrazolyl aminobenzenesulfonic acid derivative **4**. as shown in figure 3a. The Schiff bases **5a-c** and/or the cyclic adducts **7**, **8a**, **b** and/or **9** resulted from the condensation of the formylated adduct **3** with the appropriate substituted amines such as

p-nitroaniline, *p*-chloroaniline, sulfanilic acid, guanidine sulfate, thiourea and/or acetophenone. as shown in figure 3b and 3d respectively. The celecoxib analog **6** was obtained by the condensation of the terminal sulfonic acid group in the adduct **4** with 4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one as shown in figure 3c. In addition, the compounds were screened *in vivo* and *in vitro* for their anti-inflammatory and microbiological activities and they gave satisfactory results.[6]



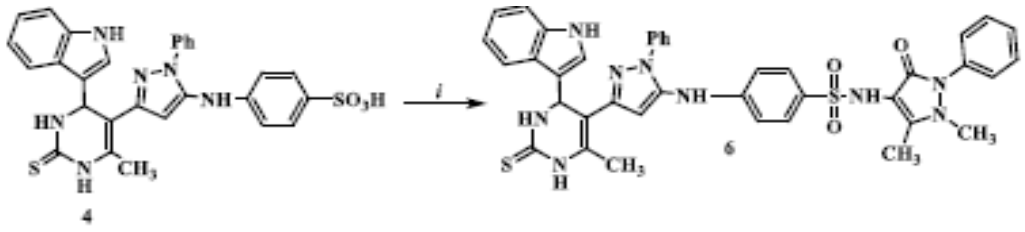
Scheme 1 Synthesis of 2-4
Reagents and conditions
i, EtOH/AcOH/reflux 5 h or EtOH/AcOH/MW 6 min.
ii, DMF/aq. K_2CO_3, $POCl_3$, stirr. 3 h.
iii, Sulfanilic acid, EtOH/Pip./reflux 6 h or sulfanilic acid, EtOH/Pip./MW 5 min.

Figure 3a: Synthesis of compounds 2-4.[6]



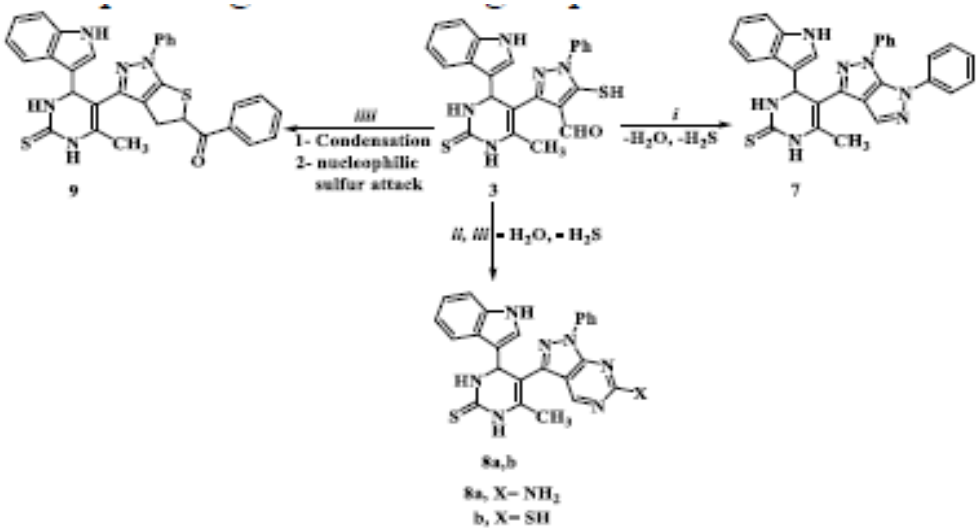
Scheme 2 Synthesis of 5a-c
Reagents and conditions:
5a, *i*, *p*-Nitroaniline, EtOH/Pip./reflux 5 h or *p*-nitroaniline, EtOH/Pip./MW, 5 min.
5b, *ii*, *p*-Chloroaniline, EtOH/Pip./reflux 5 h or *p*-chloroaniline, EtOH/Pip./MW, 6 min.
5c, *iii*, Sulfanilic acid, EtOH/Pip./reflux 5 h or sulfanilic acid, EtOH/Pip./MW, 6 min.

Figure 3b: Synthesis of compounds 5(a-c).[6]



Scheme 3 Synthesis of 6
Reagents and conditions:
i, 4-Amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one, EtOH/Pip/reflux 6 h or
4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one, EtOH/Pip/MW 5 min.

Figure 3c: Synthesis of compound 6.[6]



Scheme 4 Synthesis of 7-9
Reagents and conditions:
i, Phenylhydrazine, EtOH/Pip./reflux 4 h or phenylhydrazine, EtOH/Pip./MW, 5 min.
8a, *ii*, Guanidine sulfate, EtOH/Pip./reflux 5 h or guanidine sulfate, EtOH/Pip./MW, 5 min.
8b, *iii*, Thiourea, EtOH/Pip./reflux 5 h or thiourea, EtOH/Pip./MW, 6 min.
iiii, Acetophenone, MeOH/KOH/reflux 6 h, or acetophenone, MeOH/KOH//MW, 5 min.

Figure 3d: Synthesis of compound 7,8(a,b) and 9.[6]

4. Ankita V. Chitruk et. al., reported the general method for the synthesis of novel 1,2,4-triazole derivatives as shown in the figure 4. Firstly, a mixture of substituted benzhydrazide (2g) and carbondisulphide (1.5ml) was irradiated for 15 min at 340watt under microwave; monitored using chloroform: methanol (9:1) as mobile phase in TLC. Then the product of 2-(substituted)hydrazine carbodithioic acid was added in hydrazine hydrate (2ml) and methanol (10ml) and mixture was irradiated for 20min at 340 watt under microwave; monitored by TLC using butane: chloroform: water(7:2:1) as mobile phase. The solid product was washed with water and recrystallized with methanol. The pharmacological evaluation of 1,2,4-triazole derivatives revealed that, among all the compounds screened compound 2b showed leading antibacterial activity against the selected pathogenic strains of bacteria and compound 2e were found to have promising anti-inflammatory activity.[7]

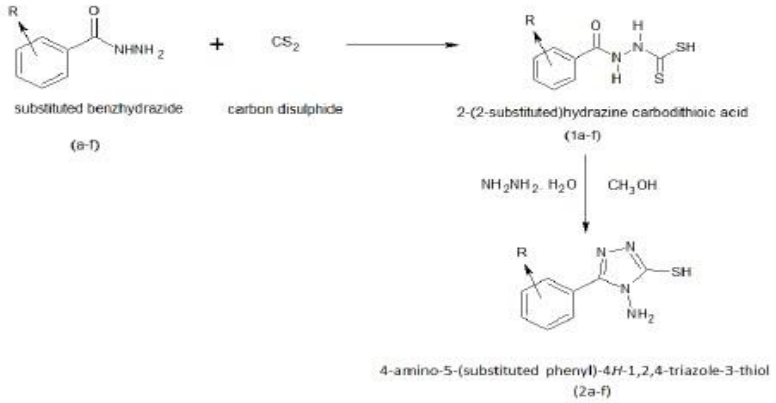


Figure 4: Synthesis of novel 1,2,4-triazole derivatives.[7]

5. Gangadhara A et.al., reported an efficient microwave assisted synthesis of 2-substituted benzoxazole derivatives from anti-inflammatory drugs aceclofenac and mefenamic acid using amberlite-IRA-402 (OH) ion exchange resin as a base catalyst as shown in the figures 5a and 5b. The reaction was carried out in a microwave at an appropriate time leads to the formation of the products 4 and 7 with high yield and purity. The synergistic effect of both benzoxazole and anti inflammatory drugs (aceclofenac and mefenamic acid) significantly enhanced the pharmacological properties of compound 4 and 7. Molecular docking studies clearly revealed the anti-inflammatory efficacy of synthesized benzoxazole derivatives and their interaction with COX-2 protein.[8]

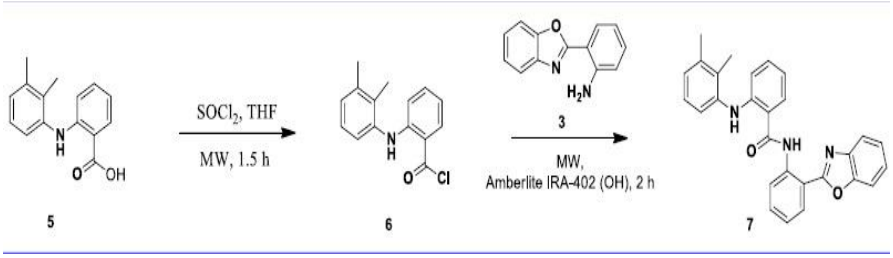


Figure 5a: Synthesis of 2-((2-(benzo[d]oxazol-2-yl)phenyl)amino)-2-oxoethyl 2-(2-((2,6-dichloro phenyl)amino)phenyl)acetate, 4.[7]

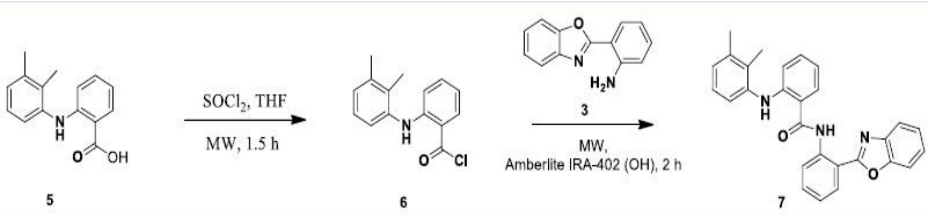


Figure 5b: Synthesis of N-(2-(benzo[d]oxazol-2-yl)phenyl)-2-((2,3-dimethylphenyl)amino) benzamide, 7.[8]

6. Patki Abhijeet S et.al., reported the synthesis of microwave assisted and eco-friendly synthesis of pyridine based chalcone and its derivatives as shown in the figure 6. A mixture of 2-acetyl Pyridene (0.01 mole) and aromatic aldehyde (0.01 mole) were mixed well in 20 ml of PEG-400 and then Aq. 30% KOH was added drop wise with continuous stirring and shaken well. The reaction mixture was put under microwave irradiation for 2-3 minutes.[9]

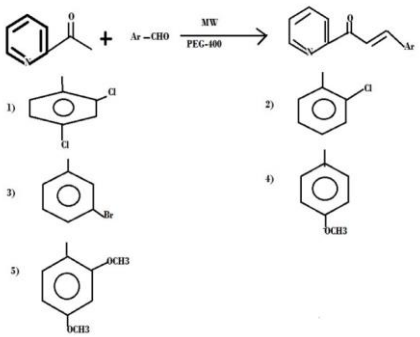


Figure 6: Synthesis of pyridine based chalcone and its derivatives.[9]

7. Kallappa M. Hosamani et. al., reported the synthesis of various novel (5Z)-3-(2-(2-oxo-2*H*-chromen-4-yloxy) ethyl)-5-benzylidenethiazolidine-2,4-dione derivatives through microwave irradiation by placing a mixture of benzylidene-thiazolidinones 2 (0.01 mol), various 4-(bromoethoxy)-2Hchromen-2-ones (0.01 mol) and powdered anhydrous K2CO3 (0.02 mol), into a 10 mL microwave pressure vial and irradiated in a microwave oven (model: CEM-Discover Focused Microwave system) under 100 W power at 50°C for 7-10 min in 5 mL acetone as shown in the figure 7. The data revealed that introduction of various thiazolidine-2,4-diones to coumarin derivatives influences the anti-inflammatory activity against the selected standard.[10]

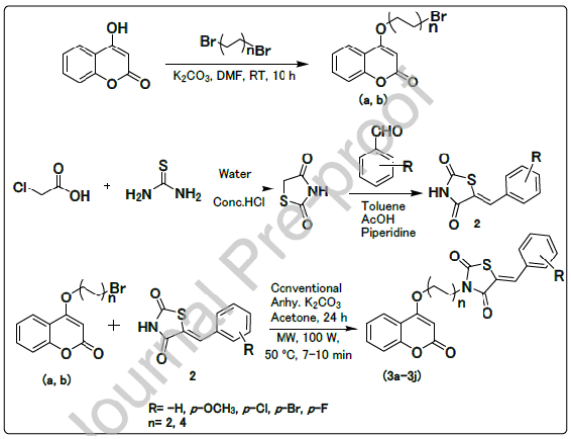


Figure 7: Synthetic route for the preparation of coumarin-thiazolidine-2,4dione derivatives.[10]

8. Yasir M. Kadhim et.al., reported the microwave synthesis studies of schiff bases. A finely ground mixture of compound (Yr 04, 0.01 mmol) was added in the irradiation tube, the appropriately substituted aromatic aldehyde (0.01 mmol) was added with 2 drops from glacial acetic acid and the reaction mix was irradiated in microwave synthesis reactor (450w) for a suitable time. Then, the reaction combination was cool to the room temperature, filtered, and the schiff base is collected. The product was recrystallized using absolute ethanol. The preliminary study of anti-inflammatory activity showed that compounds Yr 05 (a-j) have significantly more anti-inflammatory outcomes than sodium diclofenac.[11]

9. Sherri C. Young et.al., reported the synthesis of a series of novel *N*-benzylamide NSAID conjugates via a three-step process with a microwave-assisted bimolecular nucleophilic substitution as the final step. Formation of an acid chloride (**2**) was accomplished by reacting a carboxylic acid precursor containing a bromide leaving group beta to the carbonyl (**1**) with oxalyl chloride and one drop of *N*,*N*-dimethylformamide (DMF). A nucleophilic acyl substitution reaction was performed between **2** and benzylamine with base to form **3** in a moderate overall yield (43%). A bimolecular nucleophilic substitution (SN2) reaction between the NSAID carboxylate, either formed *in situ* or isolated/purchased in advance, was performed to generate the final conjugates as shown in the figure 9.[12]

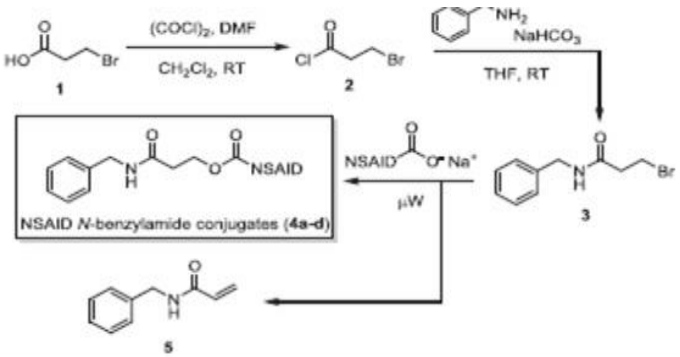


Figure 9: Synthesis of NSAID *N*-benzylamide conjugates 4a–d and an undesired elimination product (5).[12]

10. Anjan Kumar et.al., reported the microwave-irradiated synthesis and biological evaluation of 3,5-diaryl-1-phenyl-2-pyrazolines as antibacterial and anti-inflammatory agents. A series of 3,5-diaryl-1-phenyl-2-pyrazoline have been synthesized with excellent yields employing microwave techniques starting from substituted α, β-unsaturated carbonyl compounds which undergo cyclization reactions with phenylhydrazine as shown in the figure 10. The appropriate mixture of 1,3-diaryl prop-2-ene-1-one (0.1 mol), phenyl hydrazine (0.1

mol) and glacial acetic acid (20 mL) was subjected to microwave irradiation at 210 W, for 10–15 min to afford 2-pyrazolines. The reaction was monitor for completion using TLC. The product obtained was filtered and washed with warm methanol in order to remove adhered acetic acid and recrystallized from ethanol to get pure compounds. The synthesized compounds had shown good anti-inflammatory and found to be good inhibitor of pain. It was interesting to know that the compound **3h** which was found to be good anti-inflammatory agent, which was comparable with the standard drug diclofenac.[13]

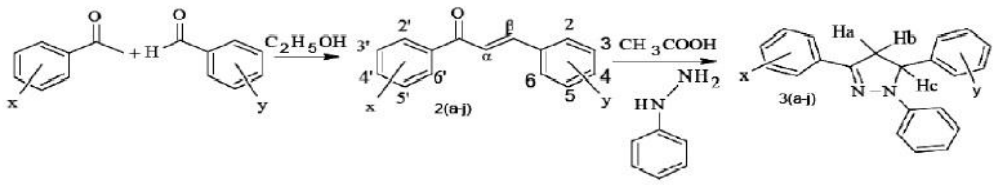


Figure 10: Synthetic route of 3,5-diaryl-1-phenyl-2-pyrazolines (3a-j).[13]

11. Muhammad Hanif et.al., reported the synthesis of a series of eight imine derivatives through microwave-assisted process. Schiff base formation by reacting 2-(4-methoxyphenyl) aceto hydrazide (3) and 4-amino-3-(4-methoxybenzyl)-1H-1,2,4-triazole-5(4H)-thione (6) with various substituted aldehydes. For the synthesis of Schiff base derivatives (7a – 7d), 4-amino-3-(4-methoxybenzyl)-1*H*-1,2,4-triazole-5(4*H*) thione **(6)** (0.125 mol, 1 eq) was dissolved in methanol (20 mL) and various substituted aldehydes (0.125 mol, 1 eq) were separately dissolved in methanol (20 mL). The two solutions were mixed together prior to exposure under microwave irradiation for 10 min with constant monitoring of the reaction progress by TLC at regular 2-min intervals as shown in the figure 11. Further, compounds **4a**, **4c**, **7a,** and **7c** significantly decreased the volume of rat paw edema ($P < 0.05$) and were screened as potent anti-inflammatory drugs among the series.[14]

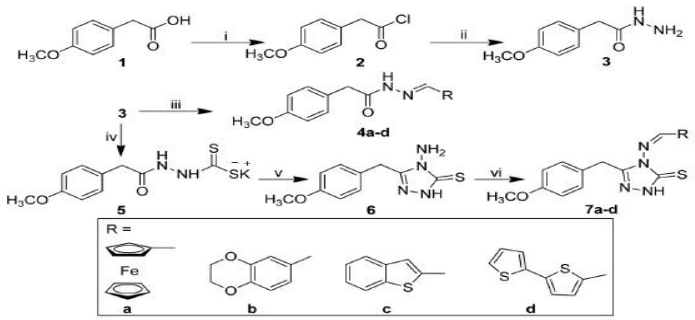
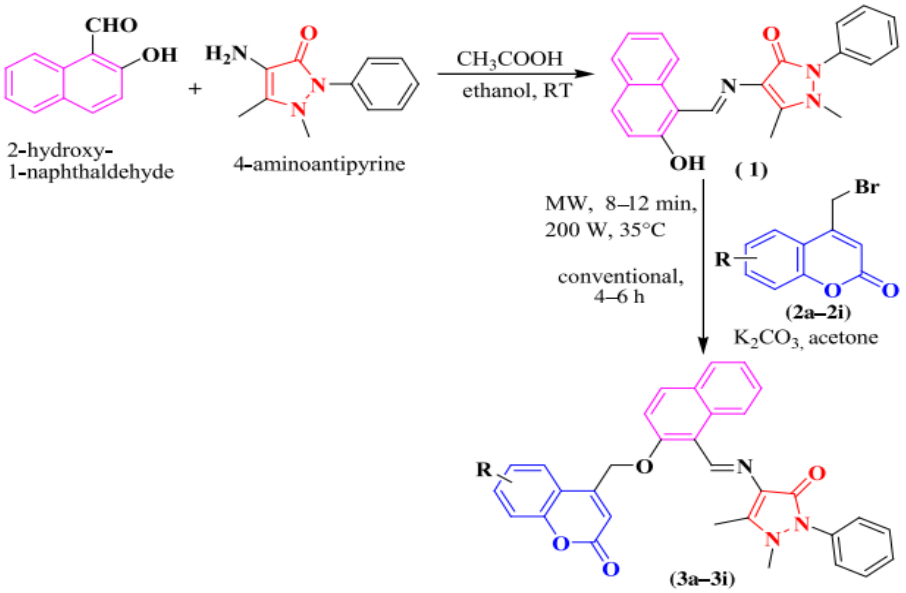


Figure 11: Synthesis of Schiff base derivatives 4a – 4d and 7a – 7d. Reagents and conditions: (i) $POCl_3$, $ClCH_2CH_2Cl$, reflux 3 h; (ii)hydrazine hydrate, TEA, MeCN, reflux 3

h; (iii)various substituted aldehydes, methanol, microwave pulses (10 min); (iv) CS2, KOH, methanol, stirring at 0°C, 1 h; (v) hydrazine hydrate (80 %), water, reflux, 10 – 12 h; (vi) various substituted aldehydes, methanol, microwave pulses (10 min).[14]

12. Rakesh R. Chavan et.al., reported the synthesis of (E)-1,5dimethyl-4-((2-((substituted-2-oxo-2H-chromen-4-yl)methoxy) naphthalen-1-yl)methyleneamino)-2-phenyl-1,2-dihydropyrazol-3-one derivatives **(3a–3i).** A mixture of anhydrous potassium carbonate (0.0025 mol) and (E)-4-((2-hydroxynaphthalen-1-yl)methyleneamino)-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-one (1) (0.001 mol) was taken in dry acetone (3 ml). To this, 4-bromomethyl coumarins (2a–2i) (0.001 mol) were added into 10 ml microwave pressure vial and irradiated in a microwave reactor (Model: CEM-Discover Focused Microwave system)under 200 W power at 35°C for 8–12 min as shoun in the fiure 12. The progress of reaction was monitored by TLC and the mixture was diluted with crushed ice. The synthesized compounds **(3a–3i)** were evaluated for their antibacterial activity by agar-well diffusion method and anti-inflammatory activity by egg albumin denaturation and results obtained are quite promising.[15]



R = (a) 5,7-diCH_3, **(b)** 6-ter-butyl, **(c)** 6-OCH_3, **(d)** 6-CH_3, **(e)** 6-Cl, **(f)** 7-OH, **(g)** 7-CH_3, **(h)** 5,6-benzo, **(i)** 7, 8-benzo .

Figure 12: Synthetic route to synthesize the title compounds (3a–3i).[15]

13. B. Sujatha et.al., developed an expeditious green synthetic approach was for the synthesis of α-aminophosphonates in good yields through one-pot three component reaction (Kabachnik-Fields reaction) of equimolar quantities of *N*-(4-amino-2-phenoxy

phenyl)methanesulfonamide, diethylphosphite and various aldehydes. A mixture of N-(4-amino-2-phenoxy phenyl)methanesulfonamide (2, 0.005 mol), diethylphosphite (3, 0.005 mol) and 4-fluorobenzaldehyde (4a, 0.005 mol) were taken in flat bottomed flask and irradiated with microwave radiations in a microwave oven at 490 W as shown in the figure 13. The reaction mixture was heated successively twice for 2-3 min period each time followed by a 1 min cooling interval between irradiations. This method was intended to avoid continuous overheating of the reactants. The reaction mixtures were kept under stirring to maintain the homogeneity of the irradiating field throughout the reaction. By monitoring with TLC, the reaction was stopped after 3-6 min. The obtained crude products were recrystallized from ethyl acetate to afford pure 5a-j as solids with 80.9-90.6% yield. Anti-inflammatory activity of newly synthesized compounds was evaluated *in vivo* using carrageenan-induced paw edema method in rats. Majority of the title compounds exhibited good anti-inflammatory activity when compared to the standard drugs.[16]

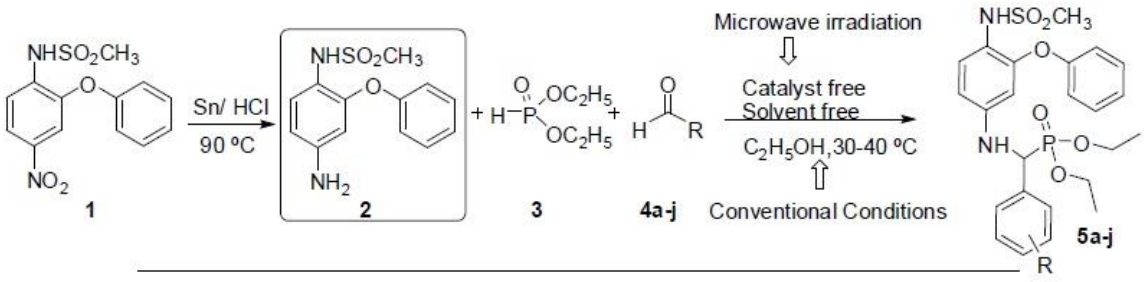


Figure 13: Microwave assisted synthesis of some novel α-aminophosphonates (5a-j).[16]

14. Deepak Swarnkar et. al., reported microwave-assisted synthesis of indole-based 4-dimethylamino-phenyl-n-methyl/phenyl-pyrazolidine pyrazole derivatives. A convenient route for the synthesis of *α,β*-unsaturated ketones (Chalcone) was achieved by the reaction of p-dimethylaminobenzaldehyde (1) (1.49 g, 0.01 mol) with appropriate ketone (2a-b) (0.01 mol) in the presence of piperidine (2 drops), under exposure to microwave at 200 W (95°C) intermittently with 5sec intervals with a specific reaction time of 2 min as shown in Figure 14.These compounds showed good anti-inflammatory activity in comparison with the standard drug diclofenac sodium.[17]

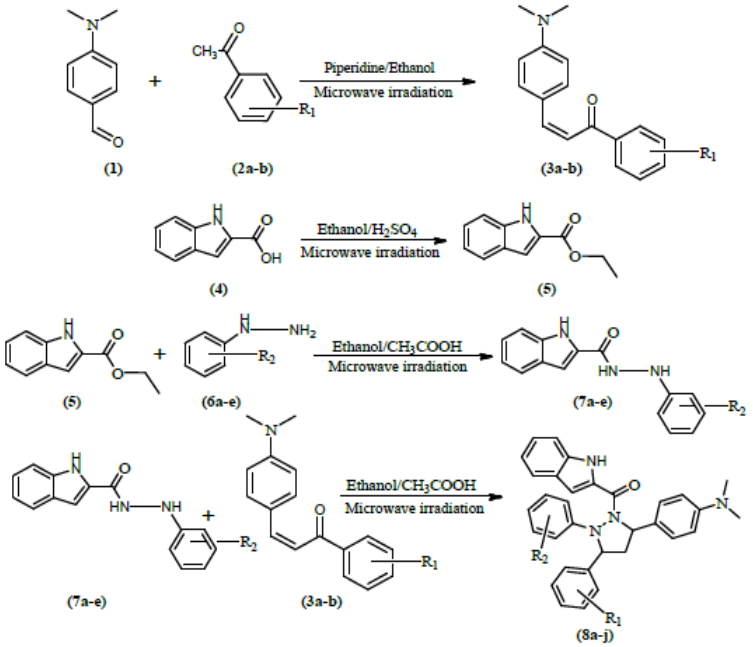


Figure 14: Synthesis of indole based 4-dimethylamino-phenyl-n-methyl/phenylpyrazolidine.[17]

15. Dongamanti Ashok et.al., synthesized a series of novel chroman scaffold incorporate spirochromanone derivatives 3a–i and 4a–i in two steps from 2-hydroxyacetophenone and cyclic alkanones under microwave irradiation in good yields. In the first step, the starting materials 2-hydroxy acetophenones 1a and 1b were prepared as per the literature (Kalena et al., 1997) shown in figure 15a. In the second step, a series of spirochromanones 3a–i and 4a–i by Kabbe condensation from 1-(7-hydroxy-2,2-dimethyl-chroman-6-yl)-ethanone 1a and 1-(5-hydroxy-2,2-dimethyl-chroman-6-yl)-ethanone 1b outlined in fihure 15b. These compounds are screened in vitro for their DPPH radical scavenging activity along with anti-inflammatory activity. In DPPH assay, compounds 3d, 3g, and 3h showed better radical scavenging activities than standard ascorbic acid. In addition, compounds 4a, 4b, 4c,4d, 4e, 4f, and 4g were found to be more potent DPPH radical scavenging activities. In anti-inflammatory activity, it can be seen that, compounds 3a, 3b, 3c, 4c, and 4d showed potent inhibitory activities.[18]

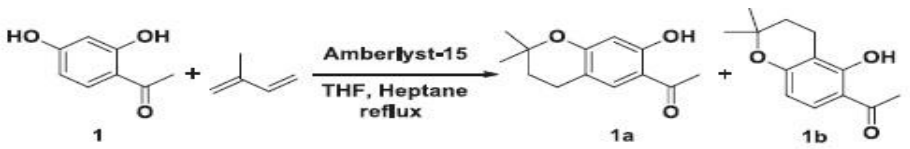


Figure 15a: Synthesis of 1-(7-hydroxy-2,2-dimethylchroman-6-yl)-ethanone (1a) and 1-(5-hydroxy-2,2-dimethylchroman-6-yl)-ethanone(1b).[18]

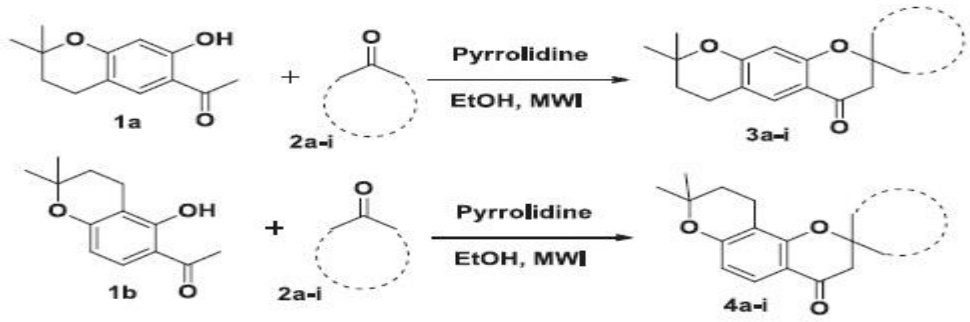


Figure 15b: Synthesis of Spirochromanones 3a–i and 4a–i.[18]

16. Abdel-Rhman B. A. El-Gazzar et.al., reported an efficient one-pot synthesis of 2-thioxopyrimido[4,5-*b*] quinoline **3a, b** from a three-component reaction of 6-aminothiouracil, cyclohexanone and aromatic aldehyde under microwave irradiation. Compound **3a, b** was used as a key intermediate for the synthesis of *S*- and *C*-nucleoside analogs of types, 5-(4-fluorophenyl / 4-anisyl)-2-*S*-(β-D-ribofuranosyl / arabinofuranosyl)-6,7,8,9-tetrahydro-3*H*pyrimido[4,5-*b*]quinolin-4-one (**6a**–**d**) and 5-(4-fluorophenyl / 4-anisyl)-2-*S*-(□-D-gluco / galactopyranosyl)-6,7,8,9-tetrahydro-3*H*-pyrimido[4,5-*b*]quinolin-4-one (**8a**–**d**). Also. the 2-hydrazino compounds **9a, b** were used for the synthesis of 3-(glycosyl)-6-(4-substituted phenyl)-7,8,9,10-tetrahydro[1,2,4] triazolo[4',3':1,2]pyrimido[4,5-*b*]quinoline-5-(1*H*)-one (**11a**–**d** and **13a**–**d**) as shown in the figure 16. The title compounds were investigated for anti-inflammatory and anticancer activities. Compounds **11a** exhibited the comparable anti-inflammatory activity (83.4 %) to the standard drug Indomethacin (85.2 %).[19]

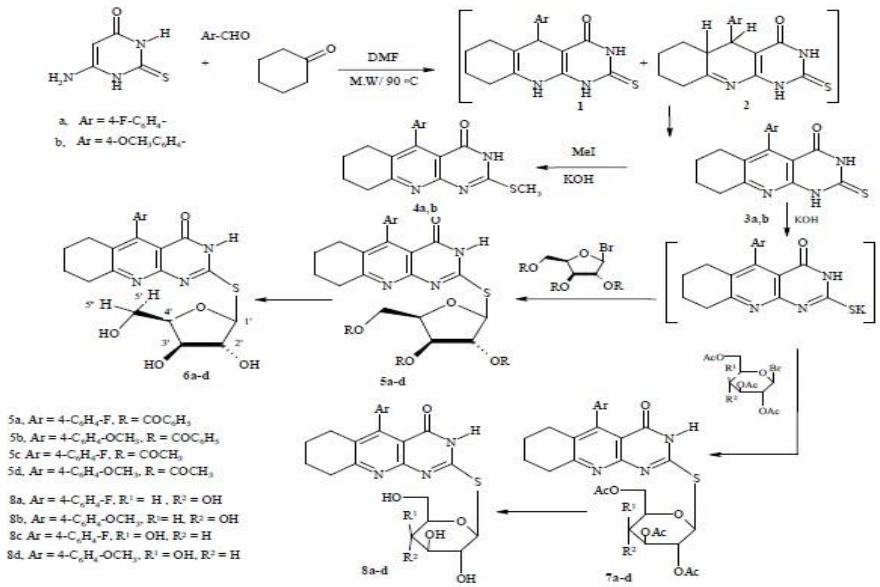


Figure 16: Synthesis of deacetylated *S*-glycosides of 5-aryl-6,7,8,9-tetrahydro-3*H*pyrimido-[4,5-*b*] quinolin-4-one 6a–d and 8a–d.[19]

17. Lata P. Kothapalli et.al., reported the microwave assisted irradiation of resorcinol and substituted aryl aldehydes using sulfamic acid as catalyst afforded novel 9-aryl-9H-xanthene-3,6-diol derivatives (1a–f) in good yields as shown in the figure 17. Resorcinol (2 mM) was reacted with various aromatic aldehydes (1 mM) and sulfamic acid (0.04 mM) as a catalyst in required quantity of water in a two necked round bottom flask (RBF). The mixtures were irradiated in a microwave attached with reflux condenser and constant stirring to avoid risk of high pressure development (Make-Raga's Scientific) at 350 W (110°C) till the completion of the reaction. The reaction was monitored by TLC (n-Hexane:Ethyl Acetate 1:1). After completion of the reaction, the reaction mixture was cooled to room temperature and ice was added along with stirring. The mixture was extracted with ethyl acetate two to three times in a separating funnel and the organic layer was evaporated to dryness. The crude products on recrystallisation from hot ethanol gave the pure 9-aryl xanthene derivatives (1a–f). Compounds 1e and 1f exhibited significant anti-inflammatory and analgesic activities as compared to standard drug. The study also revealed that compounds (1a–f) showed minimum or no ulcerogenicity in mice as that of the standard drug.[20]

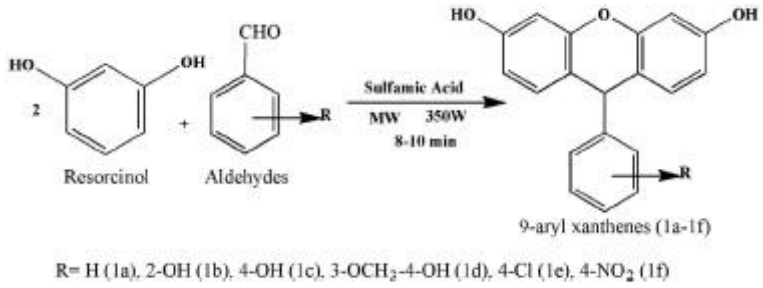


Figure 17: Synthesis of 9-aryl xanthene derivatives by microwave method.[20]

18. Mala Nath et.al., reported microwave-assisted reactions of triorganotin(IV)/diorganotin(IV) chlorides/oxides with hippuric acid(HHA), in 1:1 or 1:2 molar ratio resulted R3Sn(HA)(R = Ph (1b), n-Bu (2b), and Me (3b))/R2Sn(HA)2(R = n-Oct (4b), n-Bu (5b), and Me (6b)); (HA = anionof hippuric acid) General procedure for synthesis of triorganotin(IV)hippurates (method II)Trimethyltin(IV) chloride (1.00 g; 5 mmol) or tri-n-butyltin(IV) chloride (1.61 g; 5 mmol) or triphenyltin(IV)chloride (1.93 g; 5.0 mmol) was grounded with sodiumhippurate (1.01 g; 5 mmol) in a mortar to obtain a homogeneous mixture. To this reactant mixture, 1–2 mL of ethanol was added and subjected to microwave irradiationat 320 Watt for 2 min, and then cooled to room temperature and again irradiated for 1–2 min. This process was continued till the irradiation for required time was achieved.

The greasy products were scratched and washed with petroleum ether. Among the studied complexes, triphenyltin(IV) hippurate (1b) shows the highest anti-inflammatory activity.[21]

19. Kullampalayam Krishnasamy Sivakumar et.al., described an efficient synthesis of some mannich base of 5-methyl-2-[(2-oxo- 2H-chromen-3-yl) carbonyl]-2,4-dihydro-3H-pyrazol-3-one (**4a-j**) by using non-conventional (Microwave) techniques. Microwave assisted reactions showed that reaction happened in shorter time with good yield. The newly synthesized compounds were screened for their anti-inflammatory, analgesic activity, antioxidant, and antibacterial effects were compared with standard drug.[22]

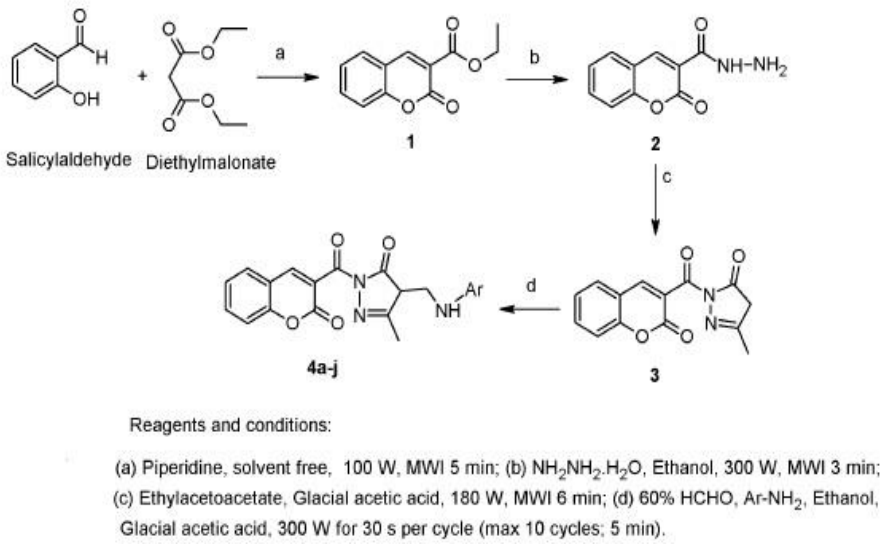
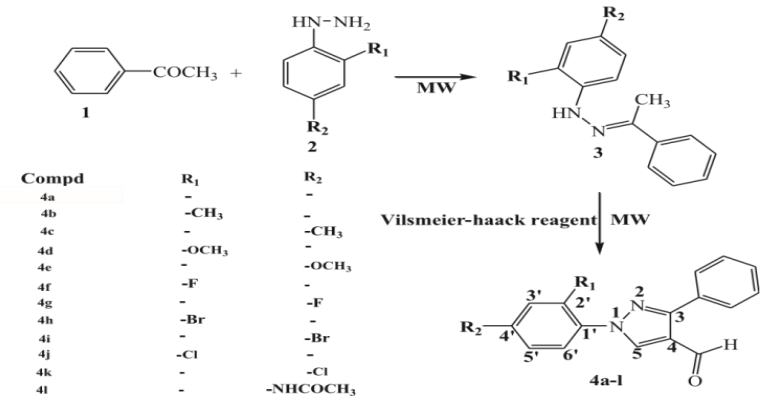


Figure 19: synthesis of some mannich base of 5-methyl-2-[(2-oxo- 2H-chromen-3-yl) carbonyl]-2,4-dihydro-3H-pyrazol-3-one (4a-j).[22]

20. Theivendren Panneer Selvam et.al., reported the synthesis of Pyrazole-4-carbaldehyde derivatives. The synthetic strategy of the target compounds is illustrated in Figure 20. The acetophenone (0.01 mol), substituted phenyl hydrazine (0.01 mol) and DMF (0.5 mL) were exposed to microwave at 200 W intermittently at 10 s intervals. The specified reaction time of 3 min was observed of compound 1substituted phenyl-2-(1-phenylethylidene) hydrazine 3. The reaction mixture was cooled with cold water. The precipitate thus obtained was filtered, washed with water and purified by recrystallization from ethanol to furnish 3. The compound 3 (0.01 mol) was added portion wise with Vilsmeier-Haack reagent ($POCl_3$–DMF/SiO_2) (0.03 mol). After the addition was complete, the reaction flask was kept at room temperature for 5 min and silica gel 3 g was added and properly mixed with the help of a glass rod, till free flowing powder was obtained. The powder is then irradiated in a microwave oven at 400 W

intermittently at 30 s intervals. The specified reaction time of 5 min was observed of compound 4a–l. The reaction mixture was cooled and treated with cold water. The solid obtained by the neutralization of the filtrate with $NaHCO_3$ was filtered, washed with water and purified by recrystallization from methanol to afford 4a–l. The completion of reaction is monitored by TLC method [eluent: $CHCl_3$–MeOH (7:3)]. The newly synthesized compounds were evaluated for their anti-inflammatory and analgesic activities compared to Diclofenac sodium as standard drug. Compounds 4g, 4i and 4k exhibited the maximum anti-inflammatory and analgesic activities.[23]



Compd	R_1	R_2
4a	-	-
4b	$-CH_3$	-
4c	-	$-CH_3$
4d	$-OCH_3$	-
4e	-	$-OCH_3$
4f	-F	-
4g	-	-F
4h	-Br	-
4i	-	-Br
4j	-Cl	-
4k	-	-Cl
4l	-	$-NHCOCH_3$

Figure 20: Synthesis of Pyrazole-4-carbaldehyde derivatives.[23]

21. Ayşe Uzgören Baran reported synthesis of a series of potential biological active acyl hydrazone derivatives containing ibuprofen moiety (compounds **4a{4p**) by the condensation of ibuprofen hydrazone with aromatic aldehydes using conventional and microwave irradiation methods. The microwave method was found to be successful with nearly the same or higher yields and shorter reaction time, A mixture of 2-(4-i-butylphenyl)-propionic acid ester, **2** (1 g, 3.3 mmol), and hydrazine hydrate (3.0 mL, 61.73 mmol) in 3 mL of ethanol was placed in Teon microwave vessels. The system was heated in a microwave oven for 40 min at 100-W constant MW power and at variable temperature. After completion of the reaction (TLCmonitoring using ethyl acetate), the residue was treated with water. The separated solid was filtered and dried to give the desired product 3.[24]

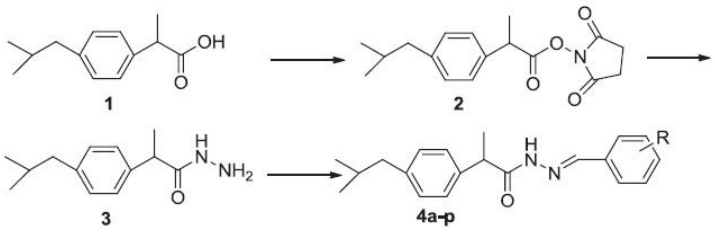


Figure 21: Synthetic pathways of ibuprofen-based acyl hydrazone derivatives.[24]

22. K. V. Sujith et al., proposed an efficient approach for the synthesis of triazolothiadiazole analogs of ibuprofen using microwave energy as depicted in the figure 22. Thus a series of 1,2,4-triazolo[3,4-b]-thiadiazoles 5 were synthesized starting from 4-amino-3-[1-(4-isobutylphenyl) ethyl]-5-mercapto-1,2,4-triazole 3 and different aromatic acids using phosphorous oxychloride as cyclizing agent by microwave. Microwave irradiation reduces both time and reaction endeavours along with reduced amount of phosphorous oxychloride. After optimization of the experimental conditions, 4-amino-3-[1-(4-isobutylphenyl)ethyl]-5-mercapto-1,2,4-triazole 3 was synthesized by following an easy one-pot protocol (Scheme1). Similarly 6-substituted-3-[1-(4-isobutylphenyl) ethyl] - 1,2,4-triazolo [3,4-b] - 1, 3, 4-thiadiazoles 5 were prepared by the reaction of equimolar mixture of ibuprofen substituted triazole 3 and aromatic acids 4 employing phosphorus oxychloride as cyclizing agent in microwave irradiation method. The main advantage of microwave-mediated method in this regard is the minimum use of the hazardous phosphorus oxychloride. Compounds 5a, 5d, 5f, and 5g were found to have significant anti-inflammatory properties comparable with the standard drugs.[25]

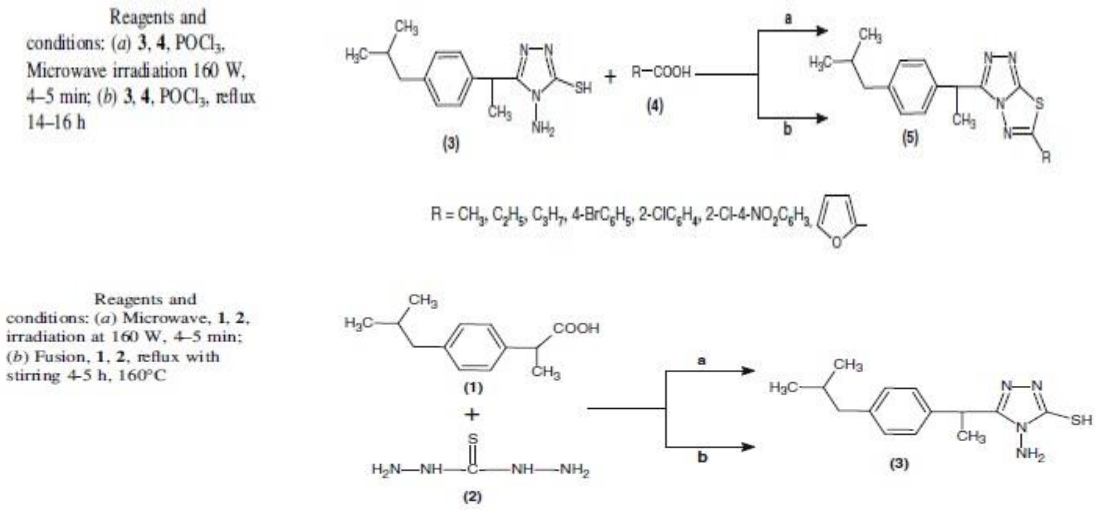


Figure 22: Synthesis of triazolothiadiazole analogs of ibuprofen.[25]

23. Biju CR et.al., aims at the development of a newer isoniazid-based oxadiazole ring system. 1,3,4-Oxadiazole derivatives as shown in the figure 23. Microwave-assisted synthetic procedure: *Step 1:* A mixture of (0.01 mole, 1.37 g) isoniazid, (0.01 mole) aromatic aldehyde and DMF (5 drops) was subjected to microwave irradiation at 300 w internally at 30-sec intervals for 3 min. The reaction mixture was cooled and treated with ice cold water. *Step 2:* To a solution of compound 1a (0.01 mole) in ethanol (15 ml), chloramine-T (0.01 mole) was added. The reaction mixture was exposed to microwave irradiation at 300W internally at 30-

sec intervals for 4 min. The reaction mixture was cooled and digested with cold water. Among the newly synthesized 1,3,4 oxadiazole analogues five were screened for analgesic and anti-inflammatory activity and three compounds showed good analgesic and anti-inflammatory activity.[26]

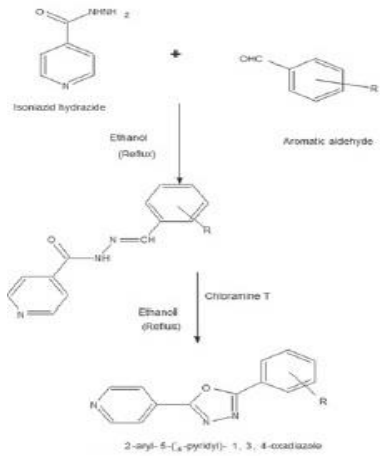


Figure 23: Synthetic scheme of 1,3,4 oxadiazole derivative.[26]

24. Vetrivel Nadaraj et.al., described the microwave-induced three-component one pot synthesis of 2-amino-3-carbethoxy-4-phenylpyrano[3,2-c] quinolin-5(6H)-ones (4a–l) from 4 hydroxyquinolin-2(1H)-ones, aromatic aldehydes and ethyl cyanoacetate as shown in the figure 24. A mixture of 4-hydroxyquinolin-2(1H)-one (0.6 mmol,0.100 g) or 6-methyl-4-hydroxyquinolin-2(1H)-one (0.6 mmol, 0.105 g), substituted aryl aldehyde (0.6 mmol) and ethyl cyanoacetate (0.6 mmol, 0.03 ml) was placed in a 100 ml beaker. Then, two drops of triethylamine was added and the reaction mixture was irradiated with microwaves at a power of 250 W at 120ºC for the specified time (5–12 min.). The reaction was monitored at intervals of 30 s by TLC and the mixture was poured into ice. The solid obtained was filtered, dried and purified by column chromatography using a mixture of petroleum ether and ethyl acetate (3:1) as the eluent. The pharmacological studies showed that all of the derivative compounds exhibited significant antibacterial and anti-inflammatory activity.[27]

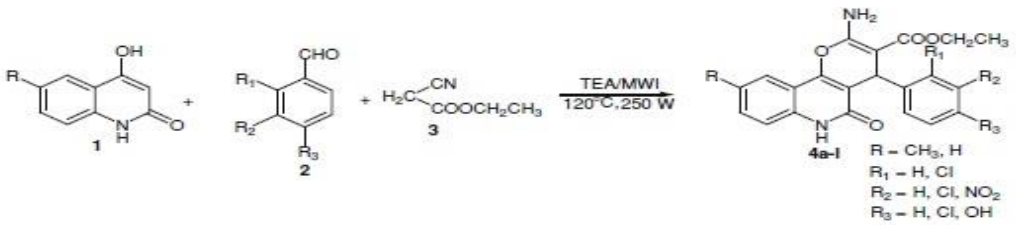


Figure 24: General synthetic scheme for the preparation of 2-amino-3-carbethoxy-4-(substituted phenyl) pyrano[3,2-c]quinolin-5(6H)-ones(4a–l).[27]

25. Rishikesh V. Antre et. al., reported the synthesis of various 4-(2-amino-6-(substituted) pyrimidin-4-yl)-3-methyl-1-(substituted)-1H-pyrazol-5(4H)-one (5a–5j) derivatives. The starting materials, 3-methyl-1-substituted-1H-pyrazol-5(4H)-ones (2a–2b), were obtained in high yields by the treatment of ethyl acetoacetate with 1-phenylhydrazine (1a)or 1-(2,4-dinitrophenyl)hydrazine (1b) using a microwave oven. The 4-acetyl-3-methyl-1-substituted-1H-pyrazol-5(4H)-ones (3a–3b) were prepared by the acylation of (2a–2b) with the corresponding acid chloride following Jensen's procedure (Jensen, 1959). The chalcone derivatives, 4-(3-(substituted)acryloyl)-3-methyl-1-(substituted)-1H-pyrazol-5(4H)-ones, (4a–4j), were prepared by reacting (3a–3b) with different substituted aromatic aldehydes by using 60% sodium hydroxide in ethanol. 4-(2-amino-6-(substituted)pyrimidin-4-yl)-3-methyl-1-(substituted)-1H-pyrazol-5(4H)-one (5a–5j) were prepared by reacting (4a–4j) with guanidine hydrochloride. Finally (5a–5j) were reacted with substituted aromatic aldehydes to give corresponding Schiff bases (6a–6j) in very good yields as depicted in the figure 25.Further, reported that out of ten compounds 5a, 5c–5f, 5h were found to have anti-inflammatory, analgesic and antipyretic activities near to the standard. The pharmacological studies suggested that the presence of 4-hydroxy, 4-methoxy, 4-(dimethylamino) and 2-hydroxy as electron releasing groups on phenyl ring at C6 of amino pyrimidine exhibit anti-inflammatory, analgesic and antipyretic activities nearly to the standard.[28]

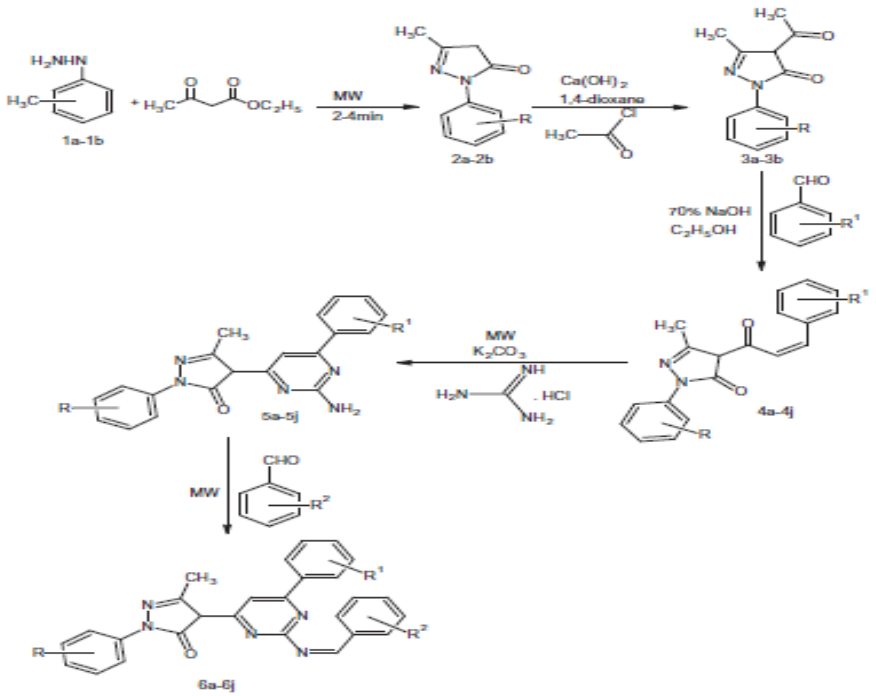


Figure 25: Synthesis of (6a–6e) using phenylhydrazine (1a) and 1-(2,4-dinitrophenyl)hydrazine (2b).[28]

26. Mymoona Akhter et.al., reported solvent-free microwave thermolysis of a series of some new benzoxazines derivatives as shown in the figure 26. It was observed that the solvent-free microwave thermolysis is a convenient, rapid, high-yielding, and environmental friendly protocol for the synthesis of benzoxazines. To synthesise compounds 2a-b, a solution of aromatic primary amine (0.025 mol) in methanol (0.05 mol), formaldehyde was added and the solution was refluxed for 10 min. To this solution, 4-hydroxy acetophenone (0.025 mol, 3.4 g) was added, and refluxing was continued for a specified period. The reaction was followed by TLC (toluene:ethylacetate:formicacid, 5:4:1), after the completion of reaction, excess of solvent was distilled off, and the reaction mixture was cooled to room temperature and poured onto crushed ice. The solid thus separated was filtered, dried, and crystallized from methanol. Compound 2a–b (0.01 mol) was titrated with two flakes of KOH in a pestle motor and (0.0l mol) of aromatic aldehydewas added. The contents were mixed throughly and transferred to a 25 ml beaker. The beaker was placed in a microwave oven for 4–6 min (900 W) (four pulses each of 1–1.5 min). The reaction conditions for a single reaction were optimized in terms of power, pulse (time), and cooling time of reaction mixture. The optimum time for microwave synthesis was found to be a cycle of 1–2 min of irradiation followed by 2 min off. The microwave irradiations were repeated 3–4 times giving a total time of 4–6 min to achieve the completion of the reaction. Further compound, 3f was found to be most active and safe anti-inflammatory and analgesic agents and could be used to develop more potent and safe anti-inflammatory and analgesic agents.[29]

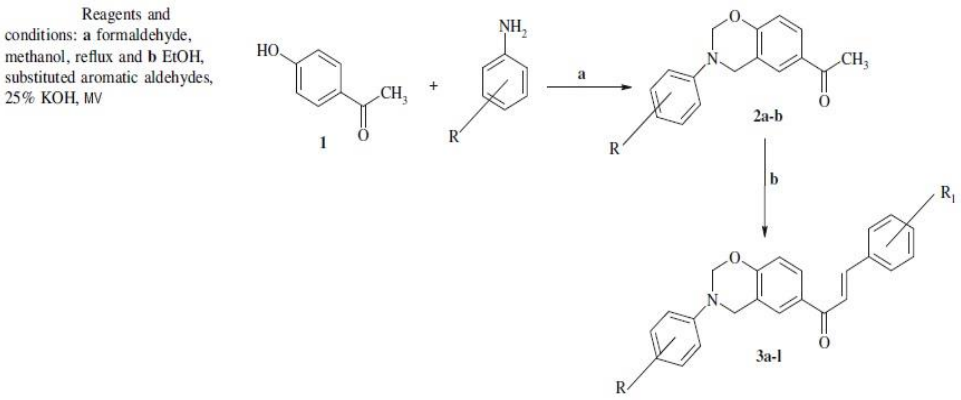


Figure 26: Synthesis of some new 3,4-dihydro-2H-1,3-benzoxazines.[29]

27. Subbu Perumal et.al., reported the synthesis of 2-aryl-3,4-dihydro-2H-thieno[3,2-b]indoles. In a typical reaction, the synthesis of 2-aryl-3,4-dihydro-2H-thieno[3,2-b]indoles 6 was effected by refluxing a mixture of 5-aryldihydro-3(2H)-thiophenones 4and arylhydrazine hydrochloride 5 (Figure 27) in a 1:1.3 molar ratio in ethanol for 30–70 min. The reaction

mixture reached a temperature of 80 C during reflux as measured by inserting a thermometer inside the reaction mixture. Work up of the reaction mixture after completion of the reaction (TLC) followed by crystallization afforded the product 6 in a pure state in good yields (80-95%).[30]

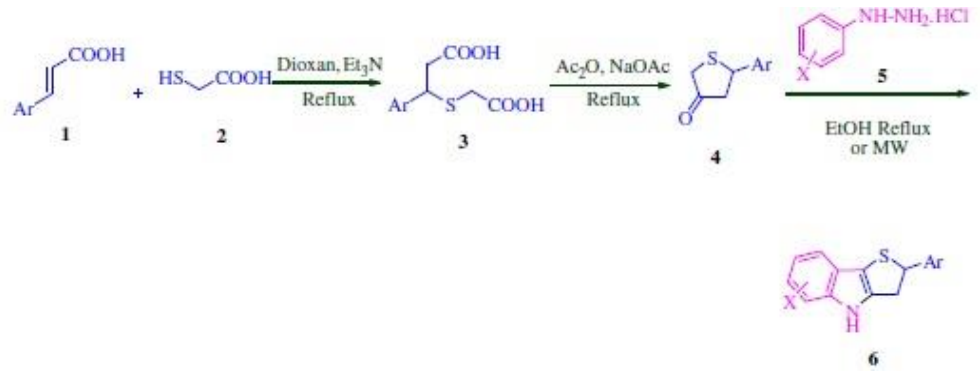


Figure 27: Synthesis of 2-aryl-3,4-dihydro-2H-thieno[3,2-b]indoles.[30]

28. Krishna Nand Singh et.al., reported the synthesis of 3'-(aryl/heteroaryl)-1-morpholinomethyl/piperidinomethylspiro[3H-indole-3,2'-thiazolidine]-2,4'(1H)-dioneshas been achieved in an open vessel. Isatins 1 undergo an easy condensation with various aryl/hetero aryl amines by MW using montmorillonite K10 clay as a solid support to afford Schiff bases 2, which subsequently undergosmooth cyclization with TGA under neat MW conditions to afford the spiro thiazolidinones 3. The spiro-compounds are made to react with morpholine/piperidine and formaldehyde to give the corresponding Mannich bases 4/5 in reasonably good yield.[31]

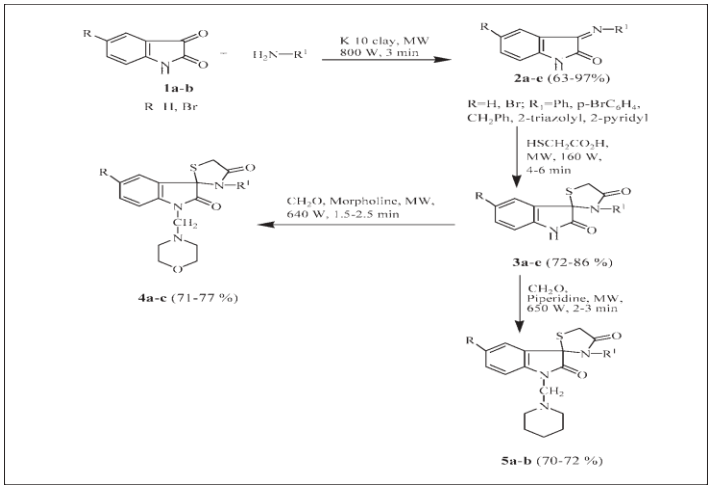


Figure 28: Synthesis of 3'-(aryl/heteroaryl)-1-morpholinomethyl/piperidinomethylspiro[3H-indole-3,2'-thiazolidine]-2,4'(1H)-diones.[31]

29. S. L. Gaonkar et.al., reported A series of N-substituted 2-butyl-5-chloro-3H-imidazole-4-carbaldehyde derivatives bearing potentially bioactive substituents were synthesized by microwave irradiation method in good yield. A 25-mL conical flask was charged with 2-butyl-5-chloro-3H-imidazole-4-carbaldehyde (1 g, 5.37 mmol), anhydrous K2CO3 (0.90 g, 6.52 mmol), 1-bromo-2- bromomethyl-4,5-dimethoxy-benzene (1.66 g, 5.35 mmol), and dimethylformamide (5 mL), mixed thoroughly, and then inserted into a microwave oven (KENSTAR) domestic type oven 800Wwith a frequency of 2,450 MHz) and irradiated for 50–60 s. After completion of the reaction (by TLC toluene–ethylacetate; 7:3), the dark red mass was diluted with 25mLwater and the product was extracted with dichloromethane (25mL). The extract was washed with water (10 mL) and then dried (Na2SO4). The solvent was evaporated and the remaining pale yellow oil was crystallized from ethanol. Compounds 6i and 6d exhibited anti-inflammatory activity that was comparable to that of the standard drug ibuprofen.[32]

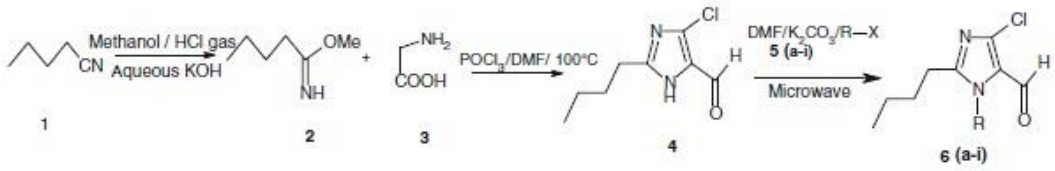


Figure 29: Scheme for the synthesis of N-substituted 2-butyl-5-chloro-3H-imidazole-4-carbaldehyde.[32]

30. Marcos A.P. Martins et.al., reported the synthesis of novel 3- or 4-substituted 5-trifluoromethyl-5-hydroxy-4,5-dihydro-1H-1-carboxyamidepyrazoles. A solution of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones 1(2 mmol) and semicarbazide hydrochloride (0.268 g, 2.4 mmol) in methanol/water 3:1 v/v (6 mL) and pyridine (2 mL) was stirred for a few minutes. The mixture was then irradiated in a microwave ETHOS 1 at 100 W, 2.2 bar of pressure for 4 min. The temperature was set to 70°C and the irradiation was automatically stopped at this temperature. After cooling to room temperature, the solution was extracted with chloroform (2 _ 20 mL) and ethyl acetate (2 _ 20 mL). The organic layers were washed with a solution of H2O/HCl (10:1) (2 _ 10 mL) and with distilled water (2 _ 10 mL). Finally, the organic layers were combined and dried with magnesium sulfate, the solvent was removed by rotatory evaporation; the 5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-1-carboxyamide pyrazoles 2aej were isolated. When necessary, the products were recrystallized from hexane. Further, suggested that the 5-hydroxy-5-trifluoromethyl-4,5-dihydro- 1H-1-

carboxyamidepyrazoles are promising candidates for the future development of novel drugs for the treatment of pain and inflammatory diseases.[33]

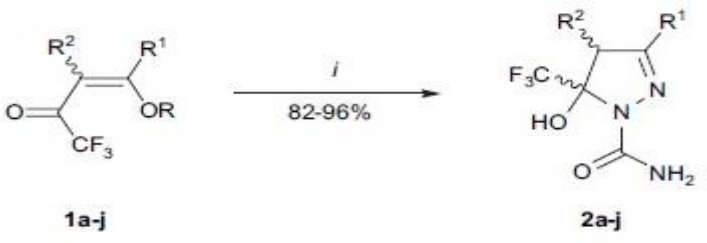


Figure 30: Synthesis of novel 3- or 4-substituted 5- trifluoromethyl-5-hydroxy-4,5-dihydro-1H-1-carboxyamidepyrazolesReagents and conditions: (i) $NH_2NHCONH_2.HCl$, $MeOH/H_2O$, Py, MW, 100 W, 70°C, 2.2 bar, 4 min.[33]

31.Sham M Sondhi et.al., reported the synthesis of microwave assisted synthesis of indole and furan derivatives possessing good anti-inflammatory and analgesic activity. Synthesis of N'-(phenylsulfonyl)-1H-indole-2-carbohydrazide, 1a Indole-2-carboxylic acid (322 mg, 2 mmol) and benzene sulfonyl hydrazide (344 mg, 2 mmol) were mixed thoroughly. This mixture was subjected to microwave irradiation (by keeping inside a microwave oven) for 2.0 min at 600 W power level and reaction progress was monitored by TLC. Synthesis of N'-tosyl-1H-indole-2-carbohydrazide,1b Indole-2-carboxylic acid (322 mg, 2 mmol) and p-toluenesulfonyl hydrazide (372 mg, 2 mmol) were mixed together and subjected to microwave irradiation for 5.0 min at 850 W power level as shown in the figure 31.[34]

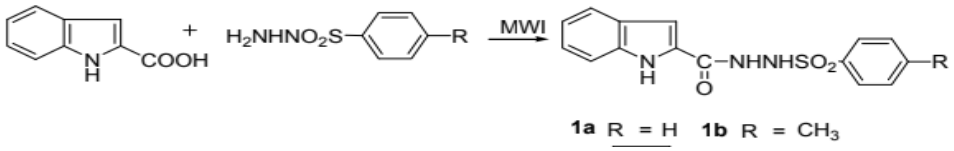


Figure 31: Synthesis of indole and furan derivatives.[34]

32. Mohammad mumtaz alam et.al., reported the microwave assisted one pot synthesis of some pyrazole derivatives as a safer anti-inflammatory agents. A mixture of 2-chloroquinoline-3-carbaldehyde (1 mmol) and 2,4-dinitrophenylhydrazine or semicarbazide (1.25 mmol) was refluxed in ethanol (20 mL). The reaction was monitored by TLC using toluene: ethyl acetate : formic acid (5 : 4 : 1, v/v/v). After completion of reaction, the ethanol was concentrated to half of its volume and poured into ice water. The precipitate obtained was filtered, washed with water and recrystallized from ethanol.[35]

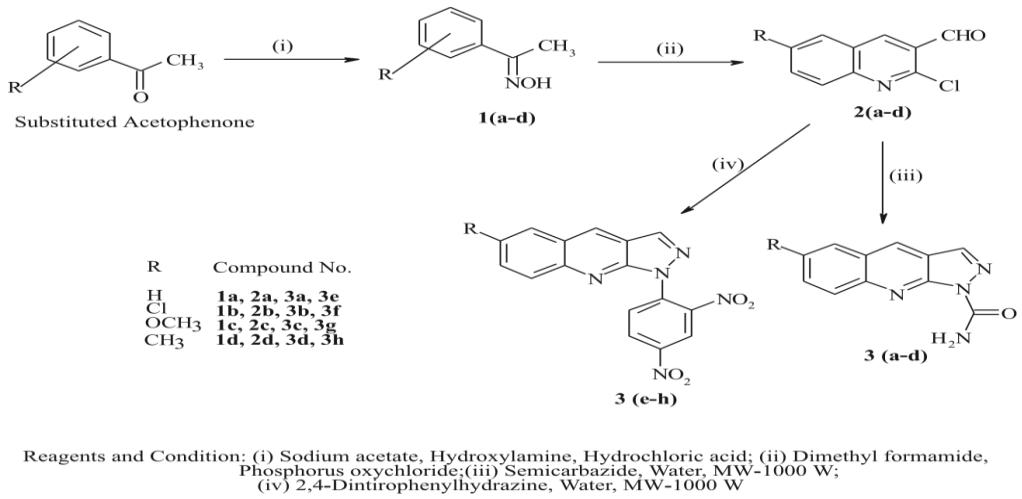
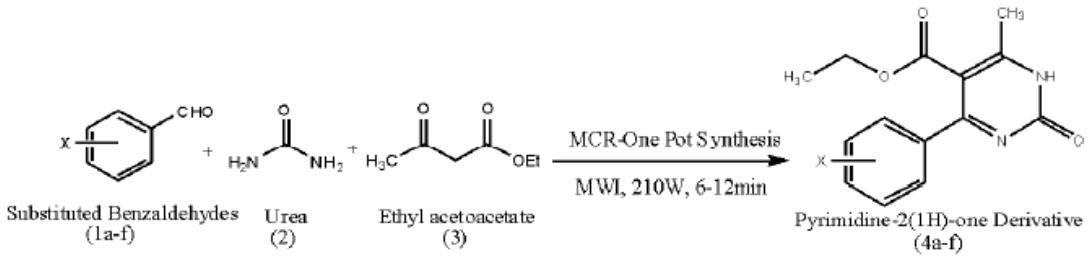


Figure 32: synthesis of some pyrazole derivatives as a safer anti-inflamatory agents.[35]

33. Biswa Mohan Sahooa et.al., has reported the synthesis of a new series of 4-(*p*-substituted phenyl)-5-ethoxy-carbonyl-6-methyl–pyrimidine-2(1*H*) one derivatives based on the protocol of Biginilli reaction. The mixture of urea, ethylacetoacetate and substituted benzaldehydes were allowed to react in presence of sodium ethoxide under microwave irradiation. Conventionally, equimolar mixture of substituted benzaldehydes (**1a-f**), urea (**2**) and ethylacetoacetate (**3**) in sodium hydroxide solution were refluxed on water bath for 2-4 h where as it took 6-12 min in microwave irradiation at power level-2 (210 W) with higher yields.[36]



Scheme 1. Synthetic route of the titled compounds (**4a-f**).

Figure 33: synthesis of a new series of 4-(*p*-substituted phenyl)-5-ethoxy-carbonyl-6-methyl–pyrimidine-2(1*H*) one derivatives.[36]

CONCLUSION

Upon a thorough literature search on the microwave synthesis of the NSAIDS, we finally able to provide a few procedures that can be applied in further synthesis of various heterocyclic nucleus having anti-inflammatory activities.

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