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Microwave-assisted synthesis of N-heterocycles in medicinal chemistry

Davide Garella,[a] Emily Borretto,[a] Antonella Di Stilo,[a] Katia Martina,[a] Giancarlo Cravotto*[a] and Pedro Cintas[b]

The syntheses of almost all N-heterocycles have now been successfully performed under microwave irradiation and have provided significant improvements in the reaction time and efficiency. The peculiar properties of dielectric heating give it the ability to strongly promote cyclocondensation, cycloaddition and selective N-heterocycle functionalisation and it has, therefore, very much caught the attention of the medicinal chemistry community. In this work, we present an overview of recent literature and technical advances in this research field with the aim of providing insight into the applications of microwave-assisted synthesis in the preparation of the main drug categories that contain N-heterocycle scaffolds.

1 Introduction

Microwave-assisted organic synthesis in specially made equipment has grown into a mature technique that has been widely applied in the drug discovery field, thanks to enhanced reaction rates, high yields, improved purity and greener reaction conditions.1 The reader is referred to a series of recent general reviews2–5 and monographs6,7 for in-depth coverage of these subjects. Although readers are likely to be acquainted with the great potential of dielectric heating, the advantages and disadvantages of a particular device or the conditions needed to maximize the efficiency and functionality are often overlooked. In recent years a great deal of attention has been paid to the application of microwaves (MW) to heterocycle synthesis.8–13 Ever since Van Noorden's report in 2008 entitled "Microwaving myths",14 in which several experts described the current status of MW-assisted chemistry, was published, new technological advances have been made that have broadened the applications of this type of irradiation in synthetic medicinal chemistry. In this same reference J. Moseley (Astra Zeneca) is quoted as saying: "virtually all new compounds now have their first synthesis in a microwave" and this fact has acquired even more relevance four years on. One-pot, MW-assisted multi-component reactions receive a great deal of attention because of their ability to efficiently give access to complex heterocyclic structures. Eloquent examples are the Ugi reaction and several heterocycle-cyclizations.15

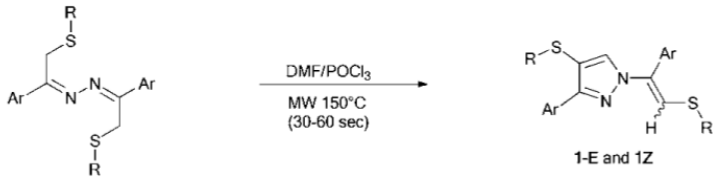
The latest generation of lab scale reactors offer high power density (1.5 kW L^{-1}), high temperature (up to 300°C), high pressure (up to 200 bar with gas inlets), multi-sample racks and extremely fast cooling when the reaction is complete.16 Impressive advances have been achieved on the "kilolab" scale, as recently reported by Morschh¨auser et al. (Clariant),17 thanks to a continuous flow MW-system that is based on a trans- mission line short-circuited waveguide reactor (2.45 GHz, max power 6 kW) which combines the benefits of existing mono- and multimode technologies. The present review will focus entirely on the pivotal role played by MW in the cyclization of N-heterocycles in the drug discovery field. To this end, we have brought together the expertise of synthetic organic chemists and medicinal chemists with the aim of highlighting relevant operative information on a target N-heterocycle and its biological/pharmacological activity. 60 different cyclizations are herein reported. Besides reactions performed in professional MW reactors, some examples refer to cyclization performed in poorly standardized apparatus (domestic MW ovens) in which the monitoring of the temperature was generally impossible. Instead of rejecting relevant findings in which cyclizations were performed in a domestic oven, these references were supported with additional reports that refer to the same selected cyclization but performed in a professional MW oven.

2 Antimicrobial activity

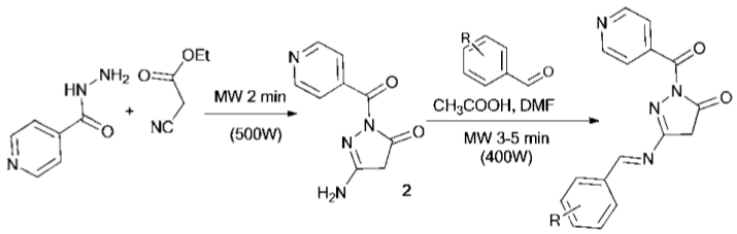
One of the earliest molecules used to treat tuberculosis was the pyridine derivative isoniazid which was o 鋡 en prescribed in combination with other drugs (ethanbutol, rifampin, streptomycin and pyrazinamide). The increasing drug-resistance of bacterial strains often requires the development of structural analogues or new derivatives, many of which bear pyrazole moieties that can boast strong activity and also play a vital role in biological systems.18 Several MW-assisted synthetic protocols have been described for the preparation of these N-heterocycles. Muthusubramanian et al. have described a fast MW procedure for the synthesis of arylthio/cyclohexylthio substituted pyrazoles (Scheme 1).19 The reaction of ω-arylthio substituted acetophenoneazines with Vilsmeier's reagent at 0°C gave complete conversion to the products 1. The cyclisation step was carried out under MW irradiation (CEM MW Synthesizer) at 150°C for 30–60 s. The E isomer was obtained as the main product, despite the fact that isomerisation side products were detected in some cases.

The antimycobacterial activity of the isomeric pyrazoles 1-E and 1-Z was screened and it was found that the first was the most active and that, in general, the cyclohexylthio substituted pyrazoles were more active than the arylthio derivatives.

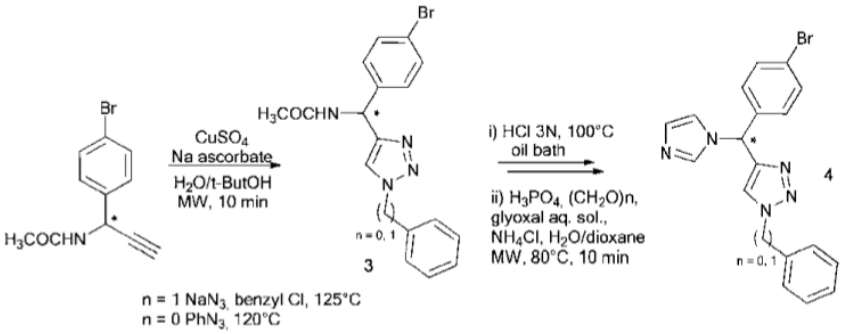
Sharma et al. have recently proposed a fast cyclisation reaction (only 2 min) between isonicotinhydrazide and ethyl 2-cyanoacetate that affords 3-amino-1-isonicotinoyl-1H-pyrazol- 5(4H)-one.20 The reaction was performed in a domestic MW oven, at 500 W with 30 s long intermittent bursts of radiation (product 2, Scheme 2). Product 3 was further functionalised with various substituted benzaldehydes to give a series of 3-(benzylideneamino)-1-isonicotinoyl-1H-pyrazol-5-(4H)-ones.



Scheme 1



Scheme 2



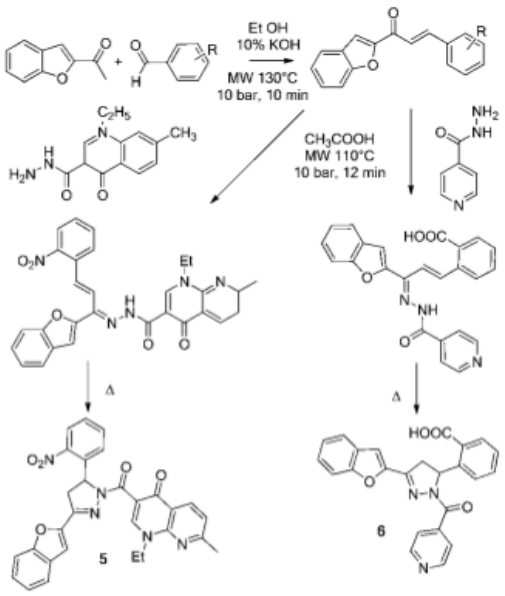
Scheme 3

All products were tested for in vitro antimicrobial activity and interesting results were found in the presence of –Cl, –F, $–NO_2$ and –OH substituent groups.

The determination of the Mycobacterium tuberculosis (MTB) genome sequence provided information which was crucial for the design of new drugs made to target this pathogen. Promising data have recently suggested that targeting MTB lipid metabolism pathways might provide an excellent route for attenuating or killing the bacterium. McLean and co-workers have demonstrated that some azole compounds are potent inhibitors of Mycobacterium bovis and Mycobacterium smegmatis (two mycobacterial species which closely resemble MTB) cell growth.21 By using these results, Botta et al. decided to more closely focus their attention on novel azole analogues with polycyclic structures which resemble typical antifungal/anti-bacterial azole drugs.22 An enantiopure form of arylpropargylamide was converted into 1,2,3-triazole via a MW-assisted click reaction in the presence of $CuSO_4$ and sodium ascorbate. The N-acetyl group was removed in the presence of 3 N HCl by heating in an oil bath at 100°C. The products obtained (3) were used in the next step without further purification (Scheme 3). The introduction of the imidazole ring from a primary amine was performed by a one-pot MW procedure at 80° C (H_3PO_4, para-formaldehyde, glyoxal aqueous solution (40%), NH_4Cl, H_2O/ dioxane, 10 min).

The products obtained were tested for their inhibitory activity toward MTB. The influence of different substituents on the phenyl rings and on the chirality of the synthesized products was studied. Although most of the compounds showed moderate activity, the bromo derivatives (4) showed excellent MIC values and the (R)-enantiomers, in particular, demonstrated very promising antimycobacterial activity and biological profiles that are similar to econazole and better than clo- trimazole. These results confirmed higher activity of enantiomerically pure compounds that is due to the specific interactions single enantiomers have with chiral biological systems.

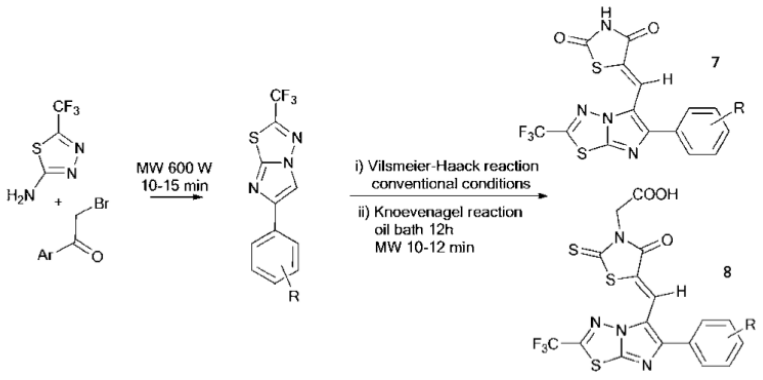
Several antimicrobial and antitubercular drugs bear pyridine or quinolone moieties. Manna and Agrawal have designed numerous benzofuranpyrazoline frameworks that contain both N-heterocycle rings and have evaluated their in vitro and in vivo antitubercular activity.23 In the first synthetic step, the chalcone was synthesized from 2-acetyl benzofuran using various aromatic aldehydes and MW irradiation (Synthos-3000, Anton Paar) for 10 min at 130° C and 10 bar (EtOH, 10% KOH) (Scheme 4). The product was further treated with two different hydrazides (isonicotinic acid hydrazide and nalidixic acid hydrazide) to give the final compounds 3-benzofuran-5-aryl-1-pyr- azolylcarbonyl-4-oxo-naphthyridins 5 (12 min, 110° C/10 bar) and 3-benzofuran-5-aryl-1-pyrazolyl-pyridylmethanones 6 (14 min, 120° C/10 bar). MW irradiation was employed in the final step of the reaction and provided rapid and efficient diazole cyclisation.



Scheme 4

The in vitro antitubercular activity was tested by measuring the growth of MTB in the Lowensteine Jensen medium. The naphthyridin ring is more favourable than the pyridinylcarbonyl ring for giving potent activity. The antitubercular activity may be due to the formation of the free isonicotinoyl-NAD complex, which might be responsible for the inhibition of cell wall biosynthesis in the mycobacterium. The highest activity was observed for the (o)-NO_2 substituent in compounds 5 and for the (o)-COOH substituent in 6. The carboxylic group contained in compound 6 seems to actively contribute to the formation of this complex and therefore was particularly active against multidrug-resistant MTB.

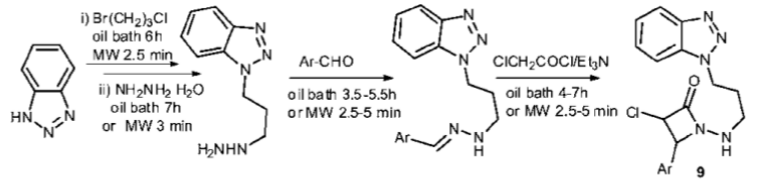
Analogously, with the aim of exploring the synergic antitubercular activity of two structures in the same framework, Alegaon et al. considered the functionalisation of imidazo[2,1-b]-[1,3,4]-thiadiazole with thiazolidine-2,4-diones and rhodanines,24 and these two derivatives showed very promising pharmacological activity. The core structure was synthesised under MW irradiation; previously prepared 5-(trifluoromethyl)- 1,3,4-thiadiazol-2-amine and multi-substituted α-haloaryl ketones were irradiated at 600 W for 10‑15 min (Scheme 5). The 2-(trifluoromethyl)-6-arylimidazo[2,1-b][1,3,4]-thiadiazoles were formylated at position 5 via the Vilsmeier‑Haack reaction and then subjected to Knoevenagel condensation which gave the desired products. All the reactions were carried out under both conventional and dielectric heating and results showed that MW irradiation dramatically cut down the reaction time to a few minutes. A weak antitubercular effect was observed with the thiazolidinedione moiety, while an enhanced activity was detected when the structure included rhodanine and even more so with rhodanine-3-acetic acid.



Scheme 5

Another combination of two active heterocycles was reported by Dubey and coworkers,25 who described the MW-assisted synthesis of some azetidinone derivatives that possess a benzotriazole moiety. The benzotriazole was first alkylated with 1- bromo-3-chloropropane and then rapidly converted to the hydrazine derivative under MW irradiation (3 min in a domestic MW oven) (Scheme 6).

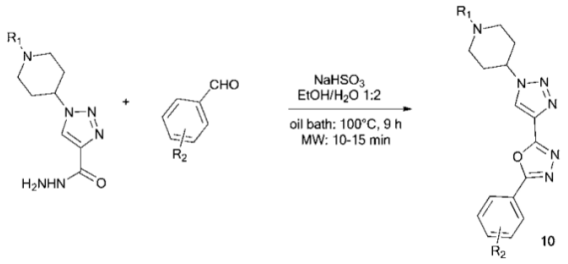
After chromatographic purification, the product was reacted with different benzaldehyde derivatives in the presence of a catalytic amount of glacial acetic acid to give the benzaldehydehydrazone derivative. The desired azetidinone derivatives of benzotriazole were eventually obtained via a reaction with $ClCH_2COCl$ in the presence of TEA. The extremely fast procedure (just a few minutes) gave yields that were 20% higher than that of the conventional method. Electron withdrawing groups on the Ar moiety generally provided higher antibacterial and antitubercular activity, while a marked antifungal activity was caused by the presence of electron donating substituents.



Scheme 6

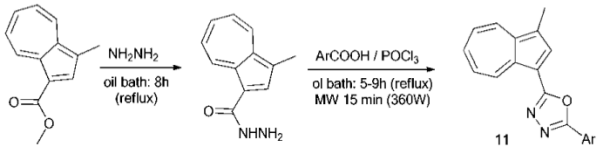
1,3,4-Oxadiazoles are considered to be an important class of heterocycles and are the core structure in many bioactive compounds.26 In particular 2,5-unsymmetrical disubstituted derivatives have considerable biological relevance,27 however, the syntheses of these spread heterocycles are anything but trivial. Fortunately, significant improvements in reaction rates and yields can be achieved under MW irradiation. By using one of their previous work as a base,28 Shinde et al. proposed a new synthetic method for 2,5-disubstituted 1,3,4-oxadiazoles under MW conditions (MicroSYNTH MW labstation) in the presence of sodium bisulfite.29 The MW-assisted reaction was carried out in ethanol by mixing the hydrazide and the aromatic aldehyde using sodium bisulphite as a catalyst (yield 95% in 10–15 min, 100°C). Under conventional heating, complete cyclisation required at least 9 hours (Scheme 7). All the products were tested for their in vitro antifungal activity. It was observed that functionalisation on the piperidine nitrogen and position 5 of the oxadiazole may dramatically change the activity. Compounds with a methyl sulphone group on the piperidine nitrogen and a Cl group on the phenyl moiety showed the same level of activity as miconazole against Fusariumoxysporum and Candida albicans. Replacing the Cl group with a hydroxyl group did

not affect the activity which was comparable with micona- zole against Candida albicans, Aspergillus flavus, and Aspergillus niger, and equipotent with miconazole against Fusariumoxysporum. Of all the compounds tested, the sulfonyl group in R1 and Cl or OH groups in R2 were the most active against the tested organisms. They can certainly be considered important pharmacophores for the design and development of new antifungal agents.



Scheme 7

Xu and co-workers have recently synthesised 1,3,4-oxadiazoles containing the azulene moiety. The solvent-less reaction mixture containing the azulenehydrazide, an appropriate carboxylic acid and a few drops of $POCl_3$ was irradiated under MW conditions (360 W) (Scheme 8).30

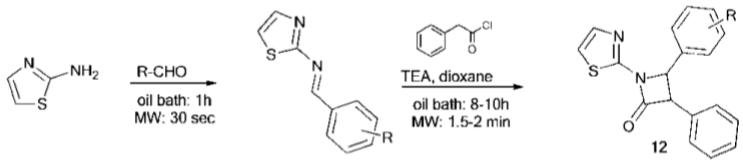


Scheme 8

The reactions proceeded slowly under reflux conditions (only 10–20% yields), whereas MW proved itself to be an excellent technique for the rapid, single step synthesis of the azulene moiety containing 2,5-disubstituted-1,3,4-oxadiazoles. Moreover, the intermediate can be considered an interesting synthon for the preparation of a variety of heterocycle-fused azulenes.

All the products obtained were tested for their antifungal activity and the best results were obtained with the p-chlorophenyl substituent. The compounds with substituents (i.e. $–C_6H_5$, 4-MeC_6H_4 and 4-Br-C_6H_4) showed enhanced activity against the fungus Aspergillus flatus and moderate activity against Penicillium, while other compounds with substituents (i.e. 4-OHC C_6H_4, 2-OHC C_6H_4, –C $C_6H_5CH]CH_2$, 4-MeC $C_6H_5CH]CH_2$) showed moderate activity against the fungi Penicillium and Trichophyton.

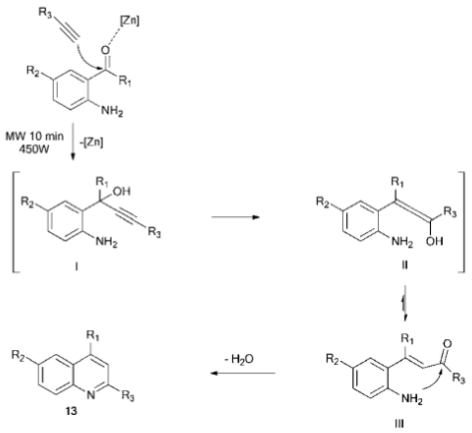
In the search for stronger antibacterial activity, Ali et al. incorporated 2-aminothiazole and azetidinone into a single molecular framework.31 The conventional heating and MW-assisted protocols (domestic MW oven) were compared. 2-Aminothiazole was reacted with a suitable aromatic aldehyde to rapidly achieve the respective imines (yield: MW 85–95%, oil bath 70–75%). These Schiff bases were then irradiated (1–2 min, 400 W) in the presence of phenylacetyl chloride under basic conditions (TEA) to afford the azetidinones 12 (MW: 85–95%; oil bath: 60–65%) (Scheme 9). It is important to highlight the fact that only a few minutes of MW irradiation were necessary to obtain the desired products in high yields, whereas even hours of conventional heating could not give the same results.



Scheme 9

Some of the synthesised compounds that contain more than one antibacterial pharmacophore site showed good antibacterial properties. Moreover, the β-lactam derivatives provide an interesting scaffold for structure–activity relationship studies (SAR). The modification of substituents and the O/N/S atoms of the pharmacophore groups had a favourable effect on the antiviral power and selectivity.

Perumal et al. proposed syntheses of quinoline and bis(in- dolyl)methanes via metal-catalysed coupling cyclisation with the aim of investigating new synthetic strategies.32 The reac- tions between 20 -aminoacetophenone and phenylacetylene in the presence of $Zn(OTf)_2$ (1 mol%) as the catalyst were carried out under MW irradiation (450 W for 10 min, in a domestic MW oven). All the reagents were stirred for 5 min and then transferred to a tube inserted in an alumina bath (100 g, 60 G_{245}, Fischer scientific bath). The proposed cyclisation mechanism is depicted in Scheme 10.



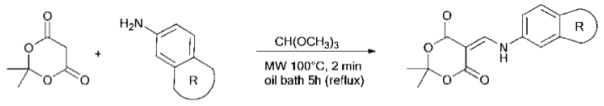
Scheme 10

The catalyst coordinates the carbonyl group allowing the terminal alkyne nucleophilic attack to form intermediate I, which undergoes a Meyer-Schuster rearrangement to form the corresponding allenol intermediate II, and then 20-aminochalcone III. The cyclocondensation of tautomer III leads to the elimination of water to form 2,4-disubstituted quinoline 13.

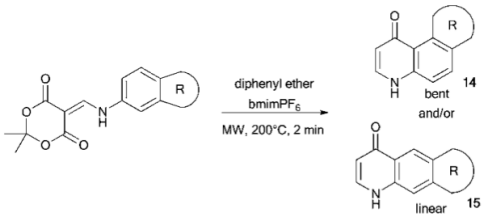
The same reaction conditions were employed for the synthesis of bis(indolyl)methanes from 2-phenylindole and a series of aldehydes. Both reactions were carried out under MW irradiation with low catalyst loading and afforded pure products. All products were screened for in vitro antibacterial and antifungal activity and the results showed that all compounds were active with comparable efficacy to reference drugs. Most of the bis(indolyl)methanes showed high antioxidant activity.

Quinolinone synthesis has been widely described in the literature. In fact, Azas et al. have reported a new protocol that involves a two-step MW procedure.33 In the first step, the Meldrum's acid intermediates were prepared and the conventional conditions were compared with MW irradiation (Scheme 11).

The derivatives obtained were converted into the respective bent or linear tricyclic quinolinones, depending on the starting heterocycle (Scheme 12). This step was further optimised by the use of ionic liquids ($BMImPF_6$) as solvents. The reaction proceeded to completion in only 3 minutes at 200° C under MW irradiation (mono-mode cavity Explorer CEM MW Synthesizer). The ionic liquid was recycled after product precipitation.



Scheme 11

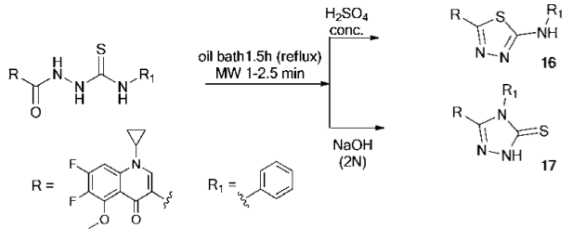


Scheme 12

Curiously, biological tests showed that the Meldrum's acid derivatives were more active and less toxic than the corresponding cyclised compounds. None of the cyclised products showed any antimalarial, antileishmanial or antimicrobial activity.

Thiodiazole and triazole derivatives bearing fluorinated quinolone were synthesized by Shelke et al.34 under conventional conditions as well as under ultrasound (US) and dielectric heating. In the first reaction step, the thiosemicarbazides, used as starting materials, were prepared following a conventional procedure in ethanol under reflux conditions (60 min). This intermediate underwent rapid internal cyclisation, affording azoles in good yields under suitable acidic or basic conditions. Thiodiazole 16 was obtained by irradiating (1–2.5 minutes at 300 W of power) the thiosemicarbazides together with concentrated H_2SO_4, while the respective triazole 17 was obtained by irradiating the mixture for 2.5 min at 300 W with NaOH (2 N) (Scheme 13). The reaction was completed in 1.5 hours under conventional heating, while the reaction in a domestic MW oven was much faster and gave higher yields.

Moreover, the fluorine substituent in the molecules provides the unique conditions of thermal stability and lipophilicity.35 All the compounds exhibit moderate to excellent antimicrobial activity against a range of bacterial and fungal strains.

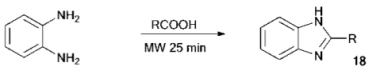


Scheme 13

Analogously Jubie and co-workers prepared a series of Mannich bases of Ciprofloxacin and Norfloxacin with various benzimidazoles under MW irradiation (domestic oven) with the aim of generating modified fluroquinolone rings.36 The substituted benzimidazoles 18 were prepared via irradiation of the o-phenylenediamine and an appropriate acid at 350 W for 25 minutes (Scheme 14).

The benzimidazole derivatives were suspended in an ethanolic solution of Ciprofloxacin (or Norfloxacin) and formaldehyde and irradiated for 3‑5 min to generate the corresponding benzimidazole substituted fluoroquinolones (Fig. 1). All the derivatives showed more highly marked activity with respect to the standards Norfloxacin and Ciprofloxacin, in particular when used against Candida albicans.

All the compounds obtained showed some antibacterial activity.



Scheme 14

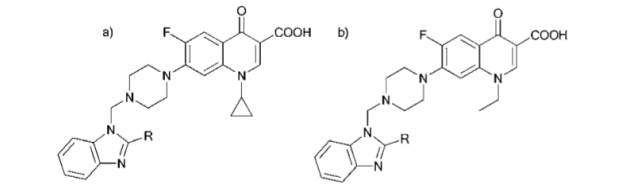
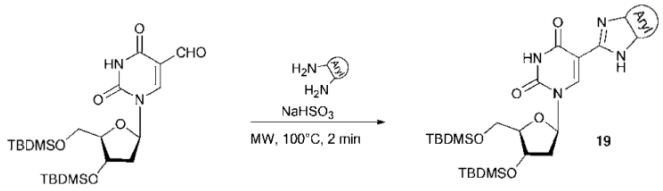


Fig. 1 Benzimidazole derivatives linked with Ciprofloxacin (a) and Norfloxacin (b)

Many nucleoside analogues that have been functionalised at the 5-position of pyrimidine nucleobases maintain the Watson– Crick base pairing37 and have shown potent activity against many viruses,38 and bacterial infections too.39 Krim et al. aimed to design a new class of fluorescent nucleosides with antibacterial activity and have performed the functionalisation of the benzimidazole ring (C-2) to the uridine (C-5).40 Benzimidazole was chosen for its wide spectra of biological activity, and attention was focused on the condensation step between o-phenylenediamine and 3,5-bis-O-(tert-butyldimethylsilyl)-5- (formyl)-2-deoxyuridine (Scheme 15).

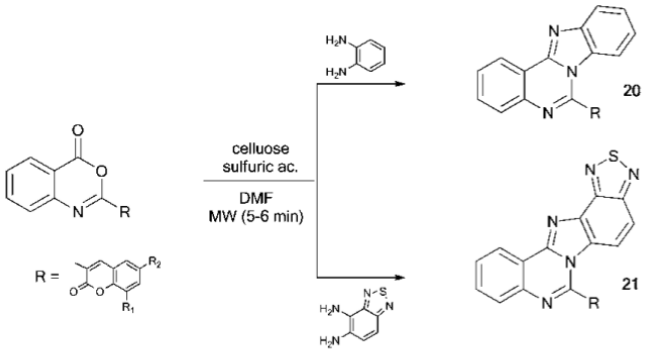


Scheme 15

The reaction was carried out neat, in the presence of $NaHSO_3$, under MW irradiation (100 °C for 2 min, mono-mode CEM-Discover); products 19 were obtained in good to excellent yields (67–90%). The functionalisation of the C-5 position with an aromatic structure ensured the desired fluorescence properties. Some products showed potential antibacterial activity, but no antiviral action was observed.

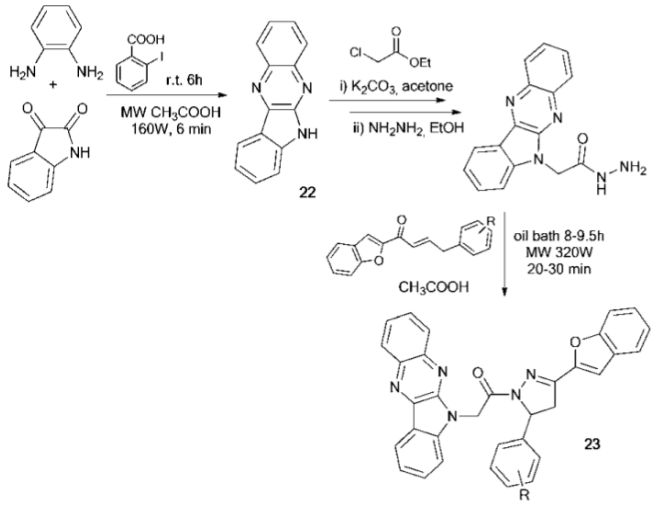
Coumarin and quinazoline rings were combined in a single scaffold in a new group of molecules designed by Rajitha et al.41 The appropriate previously prepared substituted 2-(2-oxo-2H- chromen-3-yl)-4H-benzo[d][1,3]oxazin-4-ones were either functionalised with o-phenylenediamine or with benzo[c][1,2,5] thiadiazole-4,5-diamine to form the desired products. The reactions were carried out under conventional conditions and dielectric heating; the results were compared and cellulose sulphuric acid was used as a green catalyst. The conditions are summarized in Scheme 16. MW condensation was particularly efficient; yields were increased in all cases and reaction times were drastically reduced from 5–6 hours under conventional heating to just a few minutes.

All the products were evaluated for their activity against a panel of bacterial and fungal strains and it was revealed that the highest activity occurred in products containing Br or Cl substituents in the R1 and R2 positions.



Scheme 16

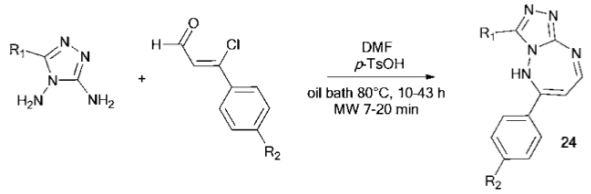
Benzofuran and pyrazoline derivatives are well known for their biological activity.42 The insertion of a second heterocyclic ring in their structure was used to boost the effect against multidrug resistant bacteria.43 Manna et al. described the synthesis of pyrazoline containing benzofuran using an indo- phenazine ring (Scheme 17).44



Scheme 17

The reactions were carried out and the classical synthetic route and the MW-assisted procedure (domestic MW oven) were compared. First of all, isatin and o-phenylenediamine were irradiated with MW for 6 minutes (160 W) providing indophenazine 22 in excellent yields (MW 97%, oil bath 70%). 6- Carbethoxymethyl indophenazine, previously synthesised from 22 and ethyl chloroacetate (yield: MW 88%; oil bath 64%), was treated in the presence of hydrazine hydrate in ethanol to generate pure indophenazine-6-acetic acid hydrazide in just a few seconds (yield: MW 94%; oil bath 66%). Benzofuranchalcones and indophenazine-6-acetic acid hydrazide were irradiated by MW (320 W) and very rapidly generated the desired products 23 in good to excellent yields (20–30 s vs. 8–9.5 h under conventional conditions). Five of the synthesised compounds (R 1/4 –OH (o), –NO_2 (m) and (o), –OCH_3 (p) and –H) showed good antibacterial activity (against Gram+ and Gram- bacteria) and low MIC values that are comparable with Sparfloxacin and Norfloxacin.

Gupta showed an interest in discovering the nature of any combined effect of having both triazepine and triazole moieties in a single framework on the physiological activity. The work reported a mild and rapid procedure for the synthesis of 3,6- diaryl-5H-[1,2,4]triazolo[4,3-b[1,2,4]triazepines from b-chlorocinnamaldehydes and 5-aryl-3,4-diamino-1,2,4-triazoles as outlined in Scheme 18.45



Scheme 18

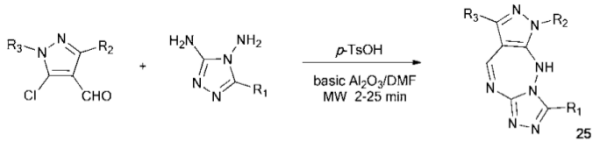
The cyclisation was carried out under dielectric heating (domestic MW oven at 640 W) in DMF using p-TsOH as the catalyst. For the sake of comparison with conventional heating, the reactions were also carried out in an oil bath using 80°C as the optimum reaction temperature. Some of the compounds obtained showed excellent antifungal activity against

Aspergillus niger and Penicillium species, and good to moderate activity against Aspergillus flavus and Rhizopus species.

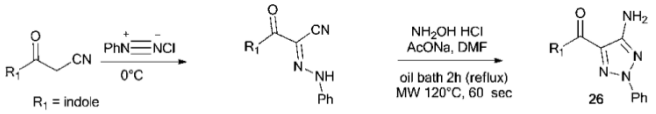
By using a similar MW procedure (640 W, domestic MW oven), the same author synthesised 1-substitued-8-aryl-3-alkyl/aryl-4H-pyrazolo[4,5-f][1,2,4]triazolo[4,3-b][1,2,4]triazepines (Scheme 19),46 using basic alumina as a solid support. The authors attribute the high yields and the rapidity of the reactions to the polar nature of the molecules and to their ability to interact with MW. The products obtained are made up of three heterocyclic moieties, each associated with a broad activity spectrum, while known for the antifungal activity when found together.

The synthesised compounds were evaluated for their antifungal activity against Aspergillus flavus, Aspergillus niger, Rhizopus species and Penicillium species and showed good activity.

Behbehani et al. performed 2-arylhydrazononitrile decoration using different techniques.47 The hydrazone derivative, prepared from the cyanoacetylindole, is an important synthon for the preparation of indolylheteroaromatic structures. In fact, when mixed with hydroxylamine hydrochloride and sodium acetate and irradiated for 60 seconds at 120°C (mono-mode cavity Explorer CEM MW Synthesizer) it afforded the 1,2,3-triazole 26 (Scheme 20).



Scheme 19

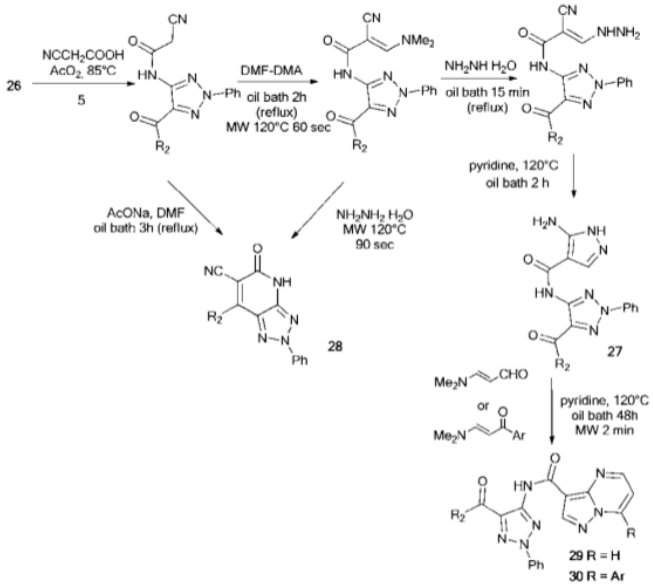


Scheme 20

The triazole was converted to the cyanoacetamide derivative and then to the corresponding enamines (E-isomer) in excellent yields after a few seconds of MW irradiation. Under conventional conditions the enamines, mixed with hydrazine hydrate in refluxing ethanol, yielded the acyclic hydrazine derivatives that underwent cyclization to form the corresponding amino- pyrazole 27, when stirred in refluxing pyridine (Scheme 21).

The same reaction, carried out under MW irradiation (120° C, 90 s), afforded the corresponding triazolo-pyridone derivatives 28. The reactivity seemed to be strongly influenced by the technique used for the reaction. The authors believe that upon the use of MW irradiation, the acyclic hydrazine derivatives tautomerize to produce a hydrazone intermediate that cyclises to generate 28. To achieve the same product it was necessary to stir the acyclic hydrazine in refluxing DMF with anhydrous sodium acetate (oil bath 3 h).

Pyrimidine rings were inserted into 27

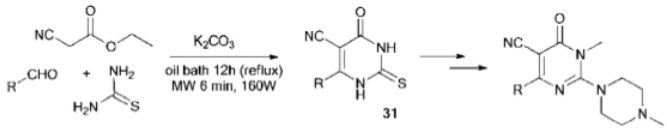


Scheme 21

by reacting these substances with 3-(dimethylamino)-acrolein. This process yiel- ded the corresponding pyrimidinopyrazole 29 (oil bath 48 h, MW 2 min at 120°C). In a similar manner, the reactions of 27 with enaminones, carried out either thermally (48 h) or under MW irradiation (2 min at 120°C), yielded the corresponding pyrazolo[1,5-a]pyrimidines 30. This strategy will be considered in the future for the preparation of pyridone-triazole; further optimisation is required, however.

All products were tested for antimicrobial activity and, in some cases, a significant activity against Gram-, Gram+ bacteria and yeast was found.

A three-component MW-assisted reaction was used by Basavaraja et al. for the synthesis of pyrimidine derivatives.48 The first step generated the pyrimidine core from ethyl cyanoacetate, thiourea and a suitable aldehyde under basic conditions (Scheme 22).



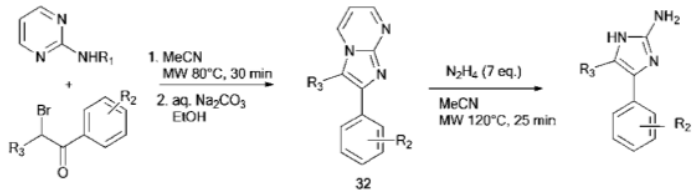
Scheme 22

While 12 hours were required for complete cyclisation under reflux conditions; MW dramatically reduced the reaction time and the desired products 31 were achieved in a few minutes (3 intermittent cycles of 2 min at 160 W).

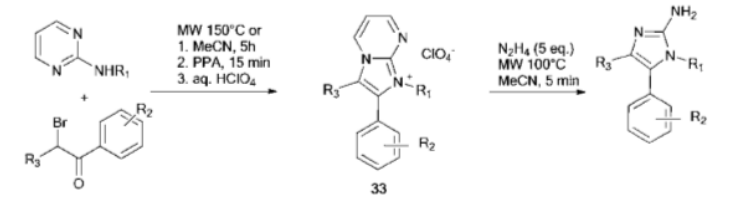
After preliminary methylation, intermediates 31 subsequently underwent an elimination reaction with heterocyclic secondary amines (piperazine, morpholine and N-methyl-piperazine) to generate various pyrimidine analogues. The biological profile of the synthesised pyrimidine showed moderate activity against Staphylococcus aureus and Bacillus subtilis, and significant antifungal activity against Candida albicans and Aspergillus niger.

De Keersmaecker et al. have recently proposed a procedure for the synthesis of substituted 2-amino-1H-imidazoles under MW irradiation.49 The protocol is based on the cyclocondensation of 2-aminopyrimidines and α-bromocarbonyl compounds, followed by the cleavage of the intermediary imidazo[1,2-a]pyrimidinium salts using an excess of hydrazine. This step was accurately studied, and MW and conventional procedures were compared under different conditions. Just a few minutes of MW irradiation at 80° C (multimode Milestone MicroSYNTH, equipped with a IR pyrometer and fiberoptic thermometer inside the reaction vial) were necessary to afford 2-amino-1H-imidazoles with increased yields of 10–15% (Scheme 23).50

The authors additionally proposed the synthesis of N1- substituted 2-aminoimidazoles from 2-amino-pyrimidines via N1-substituted imidazo[1,2-a]pyrimidinium salts.49,51 Harsh conditions and several steps were necessary to obtain the, mainly, hydroxy salts of the imidazo[1,2-a]pyrimidine when the reactions were carried out in an oil bath, whereas MW irradiation (150°C, 30 min) selectively afforded the imidazo[1,2-a]pyrimidinium salts, in a one-pot reaction, which underwent cleavage with hydrazine to form the desired products (Scheme 24).



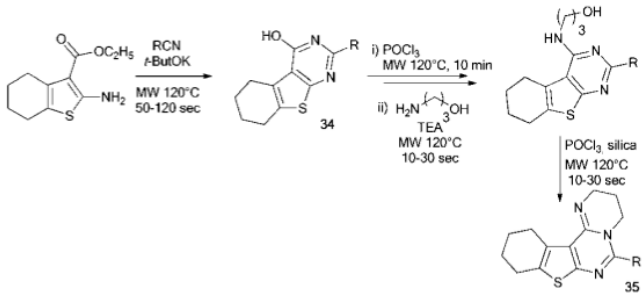
Scheme 23



Scheme 24

The 2-aminoimidazole derivative showed moderate biofilm inhibitory activity against Salmonella typhimurium and Pseudomonas aeruginosa, while the 4,5-disubstituted 2-amino-1H- imidazoles were in general more active against Salmonella typhimurium biofilm formation, but were also toxic to Salmo- nella. The inhibition of biofilm formation in Salmonella typhimurium and Pseudomonas aeruginosa was enhanced by inserting alkyl or cycloalkyl pendants (medium length) at the N1-position.

Condensed thienopyrimidines have shown some interesting biological activity as antimicrobial and non-steroidal antiinflammatory agents,52 and the drug design possibilities in this field led Prasad and Kishore to outline an efficient MW route for pyrimido[1,2-c]thieno[3,2-e]pyrimidine synthesis (Scheme 25).53 All reactions were performed in a CEM-Discover (reaction time ranged from 10 s to 10 min) under continuous internal temperature control.

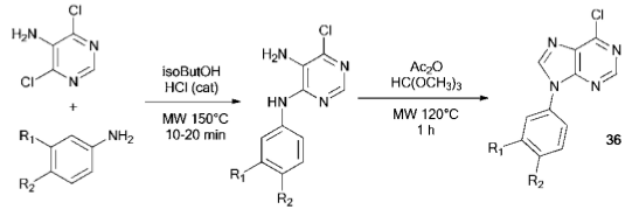


Scheme 25

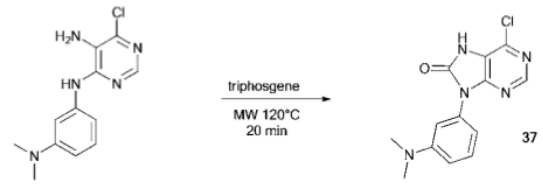
2-Amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo[b]thiophene was irradiated at 120°C (MW 50–120 s) with various aryl/alkyl nitriles with a catalytic amount of potassium t-butoxide to form the derivative 34. The hydroxyl group was converted to aminoalcohol via the chloro-derivative (MW 120°C 10–30 s). The last cyclisation of the aminopropanolic chain was also performed under MW irradiation in the presence of silica gel (60/120 mesh) and $POCl_3$ at 120°C (10–30 s). It is evident that all the crucial synthetic steps were strongly promoted by the use of MW.

P´erez et al. described the preparation of 9-aryl-6-chloropurines following alternative synthetic approaches.54 One of these procedures consisted of a two-step MW-assisted reaction (mono-mode Biotage Initiator 2.0). The aniline derivatives were first bound to dichloroaminopyrimidines and then cyclisation to 9-arylpurines was carried out under MW in the presence of trimethylorthoformate in acetic anhydride (120°C, 1 h) (Scheme 26).

Alternatively, the corresponding 8-oxopurine was obtained by irradiating the aminopyrimidine in the presence of triphosgene in THF (120°C, 20 min) (Scheme 27).

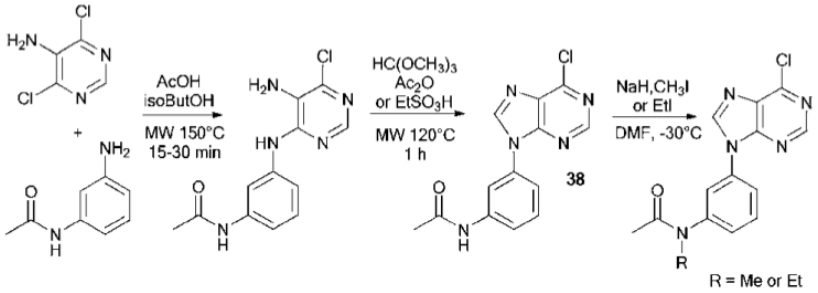


Scheme 26



Scheme 27

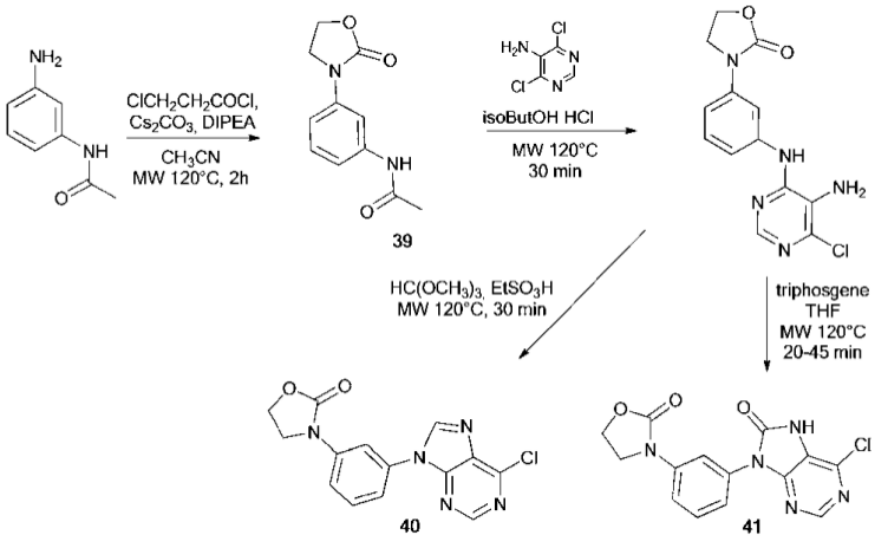
The same authors have described a series of compounds containing an acetanilide as their aryl substituent. The reactions were carried out with 30-amino-acetanilide and either dichloropyrimidine or its 2-methyl analogue in an acetic acid/isobutanol solvent mixture. The corresponding acetamide was obtained in good yields under MW irradiation (150°C for 15 min). The acetamide cyclisation was performed under dielectric heating with trimethylorthoformate and ethanosulphuric acid (120°C, 1 h) (Scheme 28). The N-alkylation of the purine 38 gave a compound which showed selective antiviral activity.



Scheme 28

A third series of analogues contain an oxazolidin-2-one on the aryl ring, part of more complex N-alkyl amide structure that underwent cyclization to a tetra-azabyciclic derivative. Oxazolidinone 39 was rapidly obtained (120°C, 2 h) in good yields under MW irradiation. The reaction was carried out by irradiating the 30-amino-acetanilide in the presence of 2-chloroethyl chloroformate, Cs_2CO_3 and DIPEA. The same reaction required 12 min in an oil bath.

The diaminopyrimidine derivative was obtained in moderate yields when compound 39 was irradiated together with dichloropyrimidines. These intermediates gave a purine 40 in the presence of trimethylorthoformate and ethanosulfonic acid under MW (120°C, 30 min). Alternatively, the use of triphosgene led to the 8-oxopurine 41 (120°C, from 20 to 45 min) (Scheme 29).

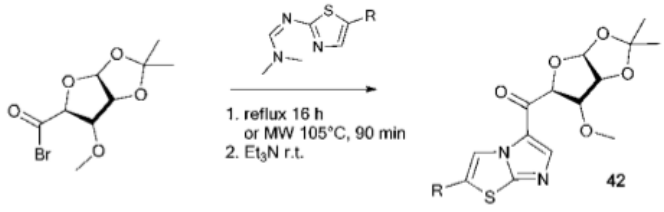


Scheme 29

Most of these compounds showed selective antiviral activity. The mechanism of action of 9-arylpurines was also investigated and preliminary results showed that these compounds stop infectious virus particles to assemble correctly.

D'Accorso et al. used an earlier report,55 as a base to develop a convergent procedure for the synthesis of imidazo[2,1-b]thiazoles.56 The cyclisation step between the carbohydrate and N-(5- arylthiazol-2-yl)-N,N-dimethyl formamidine was carried out under both conductive and dielectric heating (CEM-Discover).

With the non-conventional procedure, the reactions were carried out at 105° C for 90-150 min (Scheme 30), and although the yields were not significantly improved, the reaction was much faster. The coupled positions of the carbohydrate and the heterocyclic moieties were inverted (Scheme 31) with an eye for evaluating how the substituents in the heterocyclic ring could positively affect the antiviral activity. The reactions, in this case, were carried out by irradiating the mixture at 100°C for 90 minutes.



Scheme 30

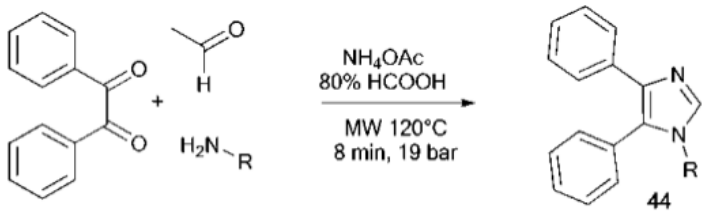
Scheme 31

All the derivatives exhibited a wide range of effective antiviral concentrations. Furthermore, brominated and chlorinated compounds showed enhanced antiviral activity and selectivity with respect to ribavirin, the only drug in clinical use for arena virus treatment, which was also evaluated as a reference substance.

3 Antinflammatory activity

The search for non-steroidal agents that possess both anti-fungal and anti-inflammatory activity has long been pursued. Of the arsenal of heterocyclic derivatives available, this dual effect is found in the drug imidazole. Several attempts to synthesise imidazoles and fused imizazole derivatives under MW irradiation have been described in the literature.

A multicomponent single step reaction was performed by Tripathy et al. to synthesise new analgesic and anti-inflammatory compounds made up of variously substituted imidazoles.57 All reactants were placed in a long necked glass vial and irradiated for 8 minutes at 120° C and 19 bar (Biotage, Emrys Optimizer) (Scheme 32).

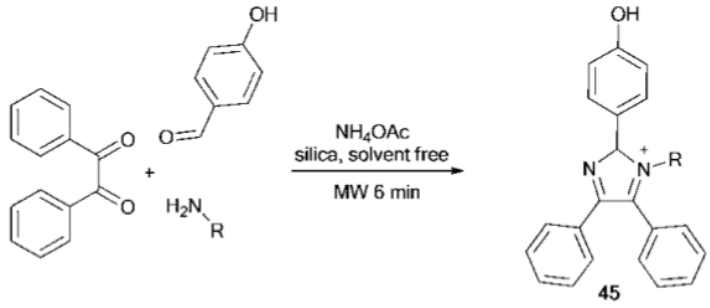


Scheme 32

In the first step, ammonium acetate released ammonia under hot, acidic conditions. Subsequently, the NH_3 reacted with an aldehyde to form an imine, while the other molecule interacts with the benzyl carbonyl group to form a second imine. The imidazole ring was synthesised via the cyclisation of the two imines, generated in situ, giving yields of 60–70%. The amines used for the reaction were aniline, p-isopropyl aniline, benzyl amine, p-chloro aniline, 1(H)-furfuryl amine and tryptamine, respectively.

All the products were screened for anti-inflammatory properties using the rat paw edema method and showed remarkable activity.

The same authors performed the one pot synthesis of tetra-substituted imidazoles (Scheme 33).58



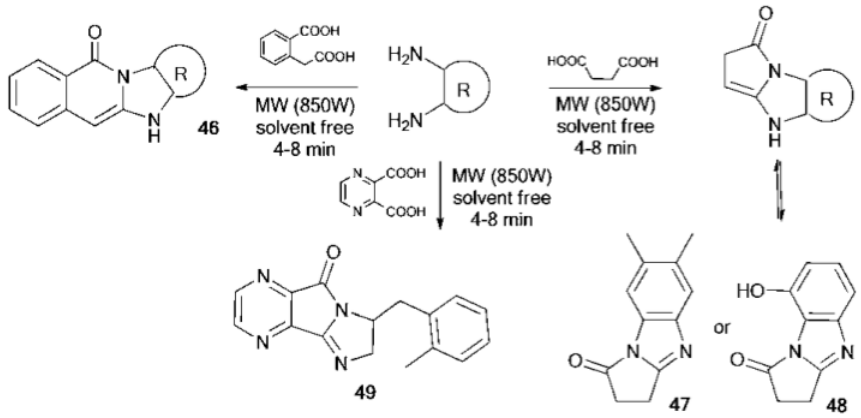
Scheme 33

The reaction proceeded via a four-component condensation reaction to form the imid- azole ring. MW enables easy access to several substituted imidazoles in short reaction times, high product purities and yields, whereas the same reactions proceeded very slowly under reflux

heating. Several amines were used for substitution at the imidazole ring position 1. It was observed that simple substituted anilines and alkylamines gave higher yields than complex heterocyclic amines. The 4-substituted anilines gave higher yields and easier purification. Five compounds were synthesised using various amines and p-hydroxybenzaldehyde (yields 80-85%). Two compounds were synthesised using amines and p-fluorobenzaldehyde (yields 75-80%), and seventeen compounds were synthesized using various amines and vanillin (yield 70-75%).

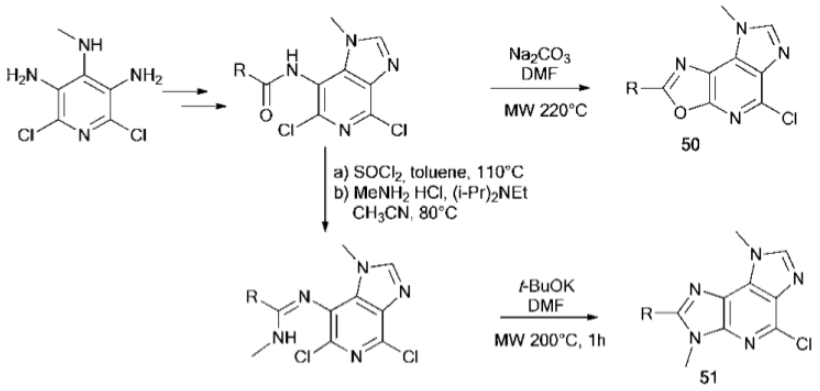
MW again strongly promoted the reactions and reduced the amount of solvent used. All compounds showed anti-inflammatory activity and significantly reduced the rat paw volume when administered orally.

A solvent free MW assisted method promoting cyclization of polycyclic benzimidazole derivatives was published by Sondhi et al. with the goal of identifying molecules with anticancer and anti-inflammatory activity.59 The cyclisation reactions were carried out by irradiating a mixture (1 : 1 molar ratio), previously mixed in a mortar, in a MW oven (4–8 min, 850 W) (Scheme 34). Various diamines were mixed with succinic acid to obtain tricyclic benzimidazole derivatives and with either 4-carboxyphenyl acetic acid or 2,3-pyrazinedicarboxylic acid to obtain tetracyclic derivatives. A number of tricyclic and tetracyclic benzimidazole derivatives were synthesised rapidly and in good yields (80–98%).



Scheme 34

All products were tested for anti-inflammatory and anticancer activity. Compounds 47 and 48 showed results that are comparable with the drug ibuprofen, whereas compound 49 showed interesting anticancer activity against human ovary and breast cancer cell lines. Burke has recently reported the identification of an imidazoquinoxaline based inhibitor of IkB kinase 2 (IKK2) as an orally active therapeutic agent for the treatment of inflammatory diseases.60 Despite promising in vitro efficacy studies in both acute and chronic preclinical inflammation models, the compound has relatively weak potency in vivo. Thiophene and pyrazolopurine chemotypes revealed themselves to be potent and selective inhibitors of IKK2, but their preparation was tedious, and pharmacokinetic profiles and chemotype diversification were quite poor. Kempson et al. aimed to improve the low metabolic stability of the pyrazolopurine and thiophene tricycles and developed a new synthetic route to block their metabolism sites.61 To test this hypothesis, a series of oxazole and imidazole tricycles were prepared under MW irradiation in the cyclisation step (Personal Chemistry Smith Synthesizer workstation) (Scheme 35).



Scheme 35

The oxazole was obtained from a penta-substituted pyridine. The reaction was carried out under MW irradiation (220°C) in the presence of sodium carbonate in DMF. The imidazole was obtained by converting the amide substituent into the corresponding chloroimidate with thionyl chloride, followed by subsequent displacement with methylamine. Ring closure was carried out under MW (200°C, 1 h) in the presence of potassium tert-butoxide affording 51 in good yields.

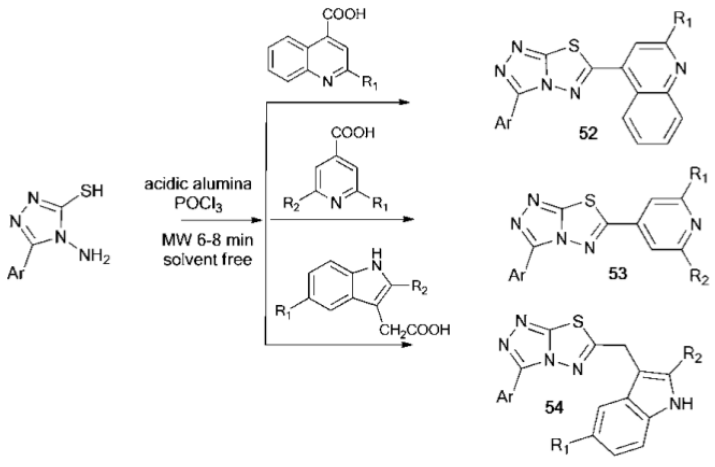
These intermediates were properly modulated and showed improved potency against IKK2, however, pharmacokinetic profiles were not improved.

Another example of MW promoted solvent free syntheses of new biologically active heterocycles has been published by Mathew et al.62 Their attention was focused on the 1,2,4-triazole and 1,3,4-thiadiazole structures which display analogies with numerous important biological compounds (i.e. thiosemicarbazide and biguanide).

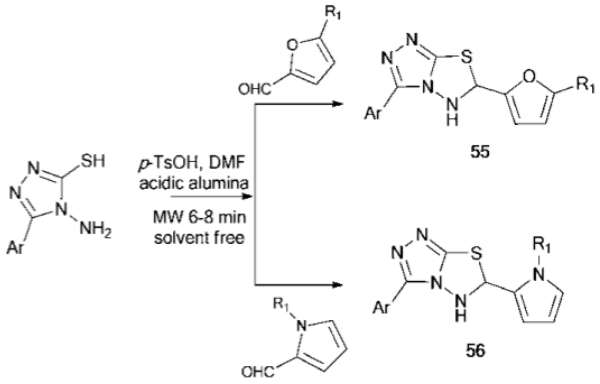
The synthesis enabled two important, biologically active nuclei to be incorporated into a triazolothiadiazole structure.

First of all, 4-amino-3-aryl/alkyl/heteroaryl substituted-5-mercapto-1,2,4-triazoles were prepared according to the Reid and Heindel procedure.63 A solution of the products obtained and their respective aromatic acids in $POCl_3$ were mixed, adsorbed, dried with alumina and irradiated for 30 seconds with MW (total irradiation 7–8 min) providing products 52–54 (Scheme 36).

The same procedure was used for the syntheses of the corresponding 5,6-dihydro triazolothiadiazoles 55 and 56. The corresponding products were obtained via the irradiation of the triazole with heteroaromatic aldehydes in the presence of p-TsOH in DMF for 6 minutes (Scheme 37).



Scheme 36

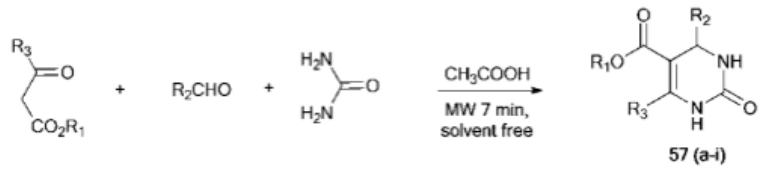


Scheme 37

The conventional synthetic reflux procedures required prolonged reaction times (6‑12 hours), while the reactions were faster and cleaner under MW irradiation, making the latter an all-round superior method.
The products obtained were subsequently screened for their biological activity. Compounds 55 gave the best results against both Gram+ and Gram- bacteria in antimicrobial tests. Compounds 56 showed good anti-inflammatory and analgesic activity. Maximum protection was observed in compounds with an indole ring at the 6 position of the triazolothiadiazole system 56, while introducing electron donating groups to the indole caused anti-inflammatory and analgesic activity to decrease.

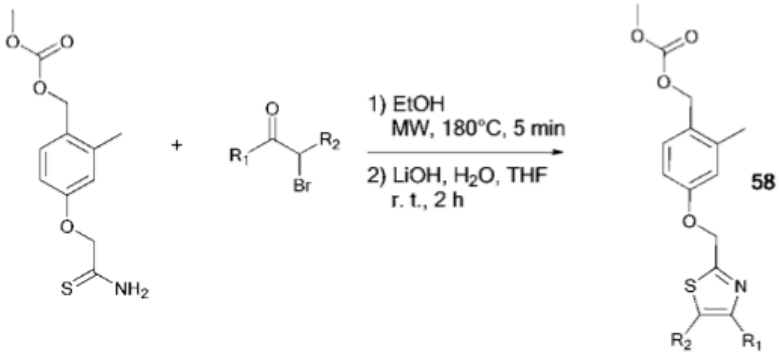
4 Drugs for cardiovascular diseases

Cardiovascular diseases have long been the main cause of death in many developing countries and of disability in industrialised areas. Furthermore, major heart diseases carry a mortality risk that is comparable to the worst malignancies. Many N-heterocyclic scaffolds that can be used in cardiovascular drug design have been obtained by MW-assisted synthesis.
Sujatha et al.64 presented MW-assisted synthesis of 3,4- dihydropyrimidinones (DHPMs) that can be seen in Scheme 38. DHPMs were easily prepared by heating 1,3-dicarbonyl compounds, urea and aromatic aldehydes in acetic acid under MW irradiation. Reactions were carried out in a modified domestic MW oven and monitored by TLC up to completion (time 5–7 min with a pulse rate of 40 s and power 30%). DHPMs, also called Biginelli products, possess interesting biological applications. The apparent structural similarities of DHPMs to the well-known Hantzsch-type dihydropyridines, which act as calcium channel modulators, can be considered as a very attractive feature in medicinal chemistry. Dihydropyridines are perhaps the most potent of Ca^{2+} channel blockers, although research into new drugs that may increase cardiac muscle contractility and show a broad therapeutic index is still ongoing. These authors presented the cardiotonic activity of DHPMs on an isolated perfused frog heart. The effects of DHPMs were evaluated on this model at various dose levels and compared with the activity of digoxin under identical experimental conditions. The results obtained clearly indicated that compounds 57a–f showed good cardiotonic activity, whereas compounds 57h and 57i showed themselves to be β-adrenergic receptor antagonists. Compound 57d appeared to be more effective than digoxin and the most interesting derivative in the series. In 5 minutes of MW irradiation (Emrys optimiser – Biotage AB) at 180°C Epple et al.65 obtained the thiazole ring via the Hantzsch condensation under MW from a thioamide intermediate and a wide range of R-bromoketones (Scheme 39).



57a R_1 = Et, R_2 = 3-HOC_6H_4, R_3 = CH_3
57b R_1 = Et, R_2 = isopropyl, R_3 = CH_3
57c R_1 = Ph, R_2 = 3-HOC_6H_4, R_3 = CH_3
57d R_1 = Et, R_2 = 4-HOC_6H_4, R_3 = CH_3
57e R_1 = Et, R_2 = 3-$MeOC_6H_4$, R_3 = CH_3
57f R_1 = Et, R_2 = biphenyl, R_3 = CH_3
57g R_1 = Et, R_2 = 2-$O_2NC_6H_4$, R_3 = CH_3
57h R_1 = Me, R_2 = 2-ClC_6H_4, R_3 = CH_3
57i R_1 = Et, R_2 = 2-ClC_6H_4, R_3 = CH_3

Scheme 38



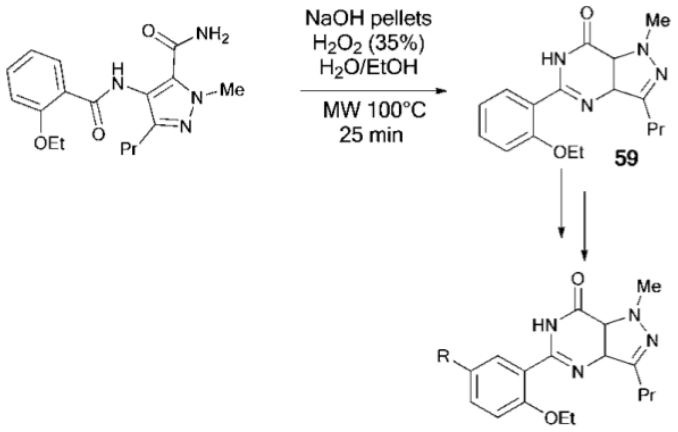
Scheme 39

It was demonstrated that the thiazole derivative was accommodated in a large hydrophobic pocket present in peroxisome proliferator-activated receptors (PPARs). These are key regulators of the genes involved in energy homeostasis and, as such, provide excellent targets for the potential treatment of metabolic syndrome, which significantly increases the chances of developing cardiovascular diseases. More than 150 analogues were synthesised according to the MW-assisted cyclisation protocol reported in Scheme 39, and were used, in turn, to synthesise a novel series of selective PPARd agonists. Several compounds are currently undergoing additional evaluation to further elucidate the role of PPARd in glucose and lipid metabolism and assess the potential of developing this series for treatment of diseases associated with metabolic syndrome.

Cyclic nucleotide phosphodiesterases (PDEs) are enzymes that catalyse the hydrolysis of cyclic nucleotides, cAMP and cGMP, to their respective 50-nucleoside monophosphates via the cleavage of the phosphodiester bond at the 30-position. The main therapeutic indications for PDE5 inhibitors are the treatment of erectile dysfunction and idiopathic pulmonary hypertension, although several other potential applications have been identified as well, such as for the treatment of systemic hypertension and prostate hyperplasia.

Sidelnafil is a well known phosphodiesterase 5 (PDE5) inhibitor, therefore, with the aim of obtaining analogues, Flores Toque et al.66 optimised MW-assisted cyclisation of 4-(2-ethoxy-benzamido)-1-methyl-3-propyl-1H-pyrazole-5-carboxamide to obtain the corresponding 1H-pyrazolo[4,3-d]pyrimidin-7(6H)- one 59 (Scheme 40). The synthesis was performed at 100° C in a multimode MW oven (300 W, ETHOS 1600, Milestone). The MW-assisted reaction was 6 times faster than the classical heating method, thus confirming the efficiency of MW flash-heating chemistry.

Many sildenafil analogues obtained from this intermediate were tested in vitro to evaluate the inhibition of PDE5 activity in human platelets, induced relaxation in rabbit corpora cavernosa and smooth muscle relaxation in isolated rabbit aortic rings.



Scheme 40

Several compounds exhibited good PDE5 inhibitory activity that was just as potent as sildenafil and may offer new leads for the development of novel drug analogues. Since these compounds are more lipophilic than sildenafil, they may show improved oral bioavailability and prolonged action in vivo. Further studies on the pharmacokinetic profile of these compounds are required to fully investigate their therapeutic potential.

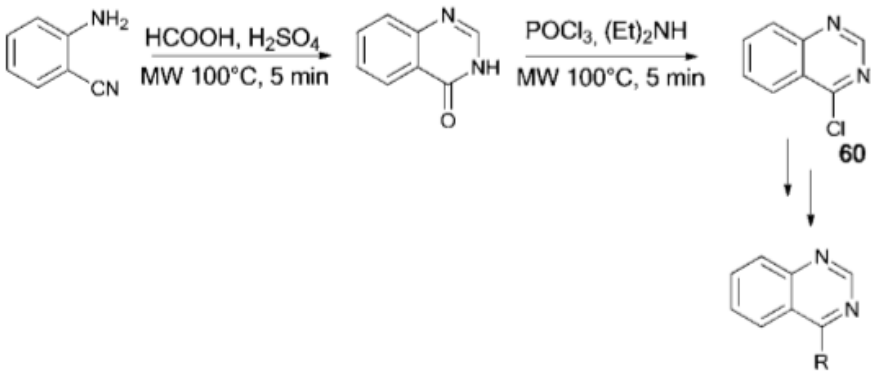
5 Drugs for central nervous diseases

Among the most frequently used therapeutic classes, CNS- acting drugs correspond to ca. 15% of the total. The remarkable ability of heterocyclic nuclei to serve as both biomimetics and active pharmacophores has largely contributed to their unique role as traditional key elements of numerous drugs. MW irradiation is clearly becoming a fundamental tool for optimising key steps in the syntheses involved in central nervous system drug design.

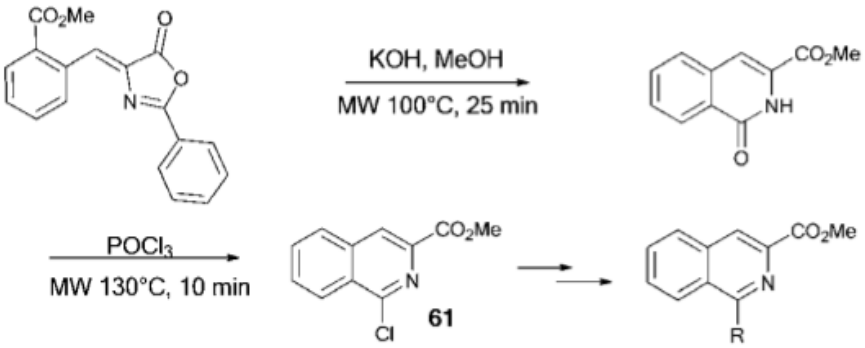
Saari et al.67 described an efficient MW-assisted cyclisation of quinazoline at 100°C (5 min in a Biotage Initiator 2.0).

Specifically, 4-chloroquinazoline 60 was prepared from the corresponding 2-aminobenzonitrile, which was first converted to quinazolin-4(3H)-one by acid-catalysed cyclisation with for- mic acid under MW irradiation. Treatment of the intermediate under MW with an excess of $POCl_3$ in N,N-diethylamine yielded the 4-chloroquinazoline 60 (Scheme 41).

Another MW-assisted cyclisation performed by the authors was the synthesis of an isoquinoline heteroaromatic system. The cyclisation of (Z)-methyl 2-[(5-oxo-2-phenyloxazol-4(5H)-ylidene)-methyl]-benzoate with KOH in MeOH at 100°C (Biotage Initiator 2.0) was complete in only 25 min, giving methyl 1-oxo-1,2-dihydroisoquinoline-3-carboxylate which was chlorinated, via treatment with POCl3, and aromatised to give methyl 1-chloroisoquinoline-3-carboxylate 61 (Scheme 42).



Scheme 41

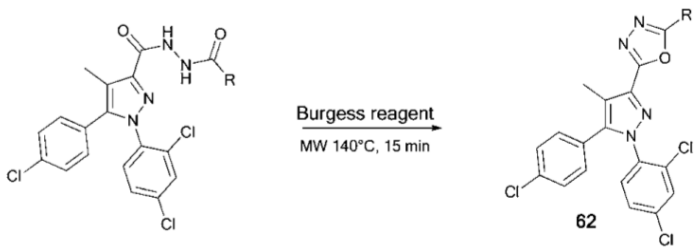


Scheme 42

The resulting quinolinic and isoquinolinic scaffolds were used to synthesise a series of quinolinyl, isoquinolinyl, quinoxalinyl and quinazoline phenyl amines as well as phenyl-sulfanylquinolines and phenoxyquinolines. MW irradiation was used both for their cyclisation, as mentioned above, and functionalisation. This compound library was screened for cannabinoid 2 receptor (CB2)-dependent G-protein activity, which was determined using the GTPcS binding assay. CB2 receptors have been recently identified in the brain and are thought to play a functional role in mental disorder and drug addiction. Recent investigations have demonstrated the therapeutic potential of selective CB2 receptor ligands. CB2 selective cannabinoids are expected to be devoid of undesired CB1-mediated psychotropic side effects and would be of therapeutic value in pain relief, inflammation, osteoporosis, and in the treatment of cancer and mental disorder such as Alzheimer's disease. These ligands serve as novel templates for the development of selective CB2 receptor agonists.

A series of biarylpyrazolyloxadiazole derivatives were investigated as antagonists to cannabinoid CB1 and CB2 receptors. The cyclization of substituted 1H-pyrazole-3-carbonyl-hydrazines was described by Lee et al.68 under MW.

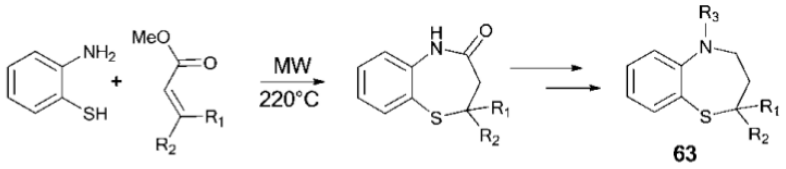
The reaction was performed at 140°C in the presence of a dehydrating agent (i.e., methyl N-(triethylammoniumsulfonyl)- carbamate, Burgess reagent) in 15 min of irradiation in a closed vessel (Biotage MW reactor) to give 1,3,4-oxadiazole 62 (Scheme 43).



Scheme 43

The study was aimed to validate the hypothesis that 1,3,4-oxadiazole could act as a bioisostere for the amide moiety because several compounds in this series exceeded the potency of known CB1 antagonists that bear an amide moiety. This class of compounds shows promising therapeutic potential as a CB1 receptor antagonist for the treatment of obesity.

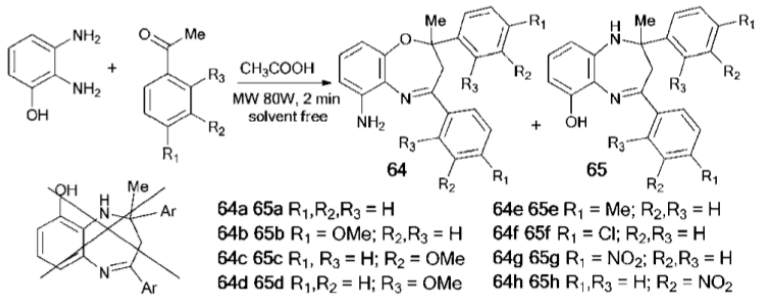
Wu et al.69 were interested in the identification of new antagonists for the NPY5 (Neuropeptide Y 5) receptor, which is involved in many different biological functions of the central and peripheral nervous systems. For example NPY5 antagonists may be useful in controlling food intake and treating obesity. Moderately potent NPY5 antagonists contain the benzothiazepinoneglycinamide scaffold, but these molecules have little stability and poor pharmacokinetic properties. The authors investigated a possible optimization of this scaffold in order to overcome these problems. They synthesised benzothiazepines using MW-assisted cyclisation. Specifically, the condensation of 2-aminothiophenol with methacrylate derivatives afforded benzothiazepinones which were reduced to benzothiazepines 63 (Scheme 44).



Scheme 44

Further functionalization of this moiety led to a series of compounds that have proven to be good NPY5 antagonists. The authors also reported a deep SAR study into their structure–activity relationship.

The benzodiazepine nucleus is perhaps better known. It is an important pharmacophore scaffold, which has a wide range of therapeutic and pharmacological properties. Many members of the benzodiazepine family are currently widely used as antianxiety, antidepressant, sedative, hypnotic, tranquilizing, anticonvulsant, antihistaminic, analgesic and anti-inflammatory agents. Because of their wide range of biological applications, the development of mild, efficient and environmentally friendly protocols continues to be a challenging endeavour for organic chemists. As a result, considerable attention has recently been drawn to new improved methods for the preparation of 1,5-benzodiazepines, including one-pot three-component reactions. Neochoritis et al.70 described a comparative study into the synthesis of 6-hydroxy-2,3-dihydro-1H-1,5- benzodiazepines and 6-amino-2,3-dihydro-1,5-benzoxazepines via the condensation of ketones with 2,3-diaminophenol in a one-pot MW assisted (Biotage Initiator 2.0) acid catalysed reaction without a solvent (Scheme 45).



Scheme 45

Table 1 Reaction conditions and products according to Scheme 45

Ketone	Time (min)	Power[a] (W)	**64** (%)	**65** (%)
a	2	80	35	59
b	3	240	—	88
b[b]	2	80	Traces	80
c	2	80	—	90
d	2	80	—	93
e	3	240	25	61
e[b]	2	80	81	Traces
f	2	80	41	56
g	3	240	81	Traces
h	5	80	47	30

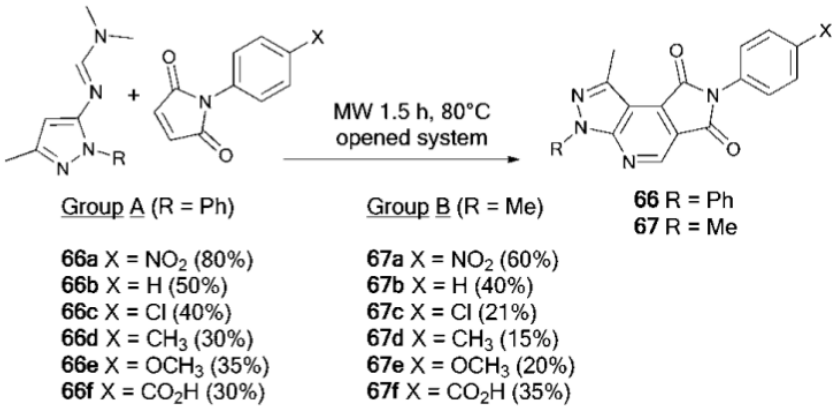
[a] Constant power. [b] With *p*-TSA as a catalyst.

From Scheme 45 and Table 1 it can be concluded that the presence of electron-withdrawing substituents in the acetophenone moiety stabilises the initially formed 1,5-benzoxazepines 64a–h and consequently facilitates their isolation. On the other hand, the presence of electron-releasing substituents means that the electron rich oxygen is easily protonated, resulting in the spontaneous transformation of benzoxazepines 64a–h into benzodiazepines 65a–h.

The synthesis of 6-hydroxybenzodiazepines was investigated and compared to that of their 6-aminobenzoxazepine counterparts. It was established that benzoxazepines are the kinetic products, whereas benzodiazepines are the thermodynamic ones.

Several new benzodiazepines and benzoxazepines have been synthesised with the aim of studying their antioxidant and anti-inflammatory activity. Novel compounds were tested with regard to their antioxidant ability as well as their potent lipid peroxidation (LPO) inhibitory activity. In terms of biological activity, the most interesting antioxidant derivatives were those with the benzoxazepine moiety and the amino group substituent.

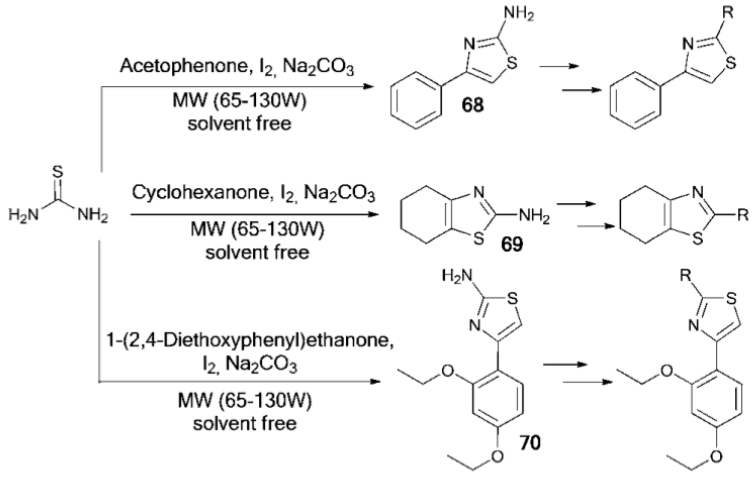
Nascimento-Ju´nior et al.71 used MW irradiation under solvent-free conditions to dramatically improve the process for obtaining new heterocyclic scaffolds, exploiting the aza-Diels–Alder reaction as the key-step. The classic synthesis of heterocyclic derivatives that include the pyrazolo[3,4-b]pyrrolo[3,4-d] pyridine scaffold gave poor yields (20–35%) even after 48 h heating in either AcOH or DMSO as a solvent. Easier access to these structures was achieved via MW-assisted hetero Diels–Alder reactions, improving yields and cutting down reaction times (Scheme 46). The method required irradiation at 80°C for 1.5 h in an open vessel (80 W in Discovery - CEM).



Scheme 46

Compounds containing the pyrazolo[3,4-b]pyrrolo[3,4-d] pyridine scaffold were described as displaying CNS action as muscarinic M1 receptor agonists. Although these heterotricyclic compounds presented a remarkable neuroactive profile (as sedatives and analgesic agents), further preclinical studies were strongly limited by the critical synthesis. The sedation produced by derivatives (66a–f and 67a–f) was investigated using locomotor activity tests in mice. Taken together, results showed that almost all of the N-methyl pyrazole derivatives (group A) are crucial in promoting the sedative effect.

Zhang et al.72 prepared 2-aminothiazole analogues in which the application of MW technology was used for the cyclisation reaction. The synthesis of 4,5-substituted-2-aminothiazole was in accordance with a published procedure, but improved by a MW-assisted cyclisation step (household oven, power 650 W), which gave results after a few minutes vs. 12 h under conven- tional thermal heating (Scheme 47).



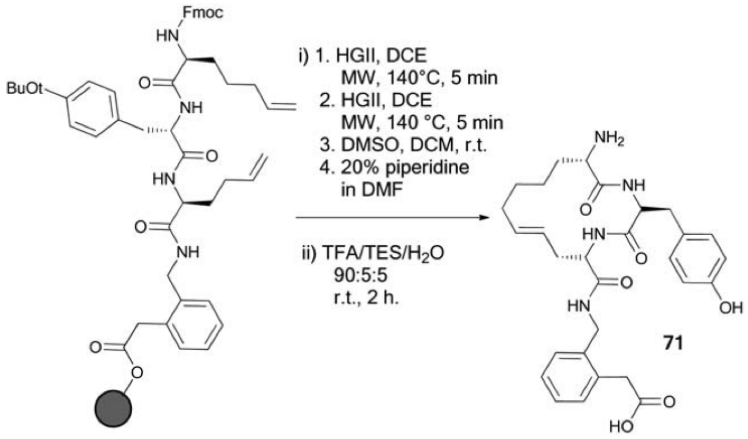
Scheme 47

This heterocycle is an attractive lead for the synthesis of new agents that can inhibit poly(ADP-ribose) polymerases (PARPs).

PARPs are known as nuclear enzymes that catalyse the poly-(ADP-ribosyl)ation of DNA-binding proteins, regulate immediate cellular response to DNA damage and facilitate DNA repair.

Because of its role in many common pathologies of various central nervous system diseases such as cell death, inflammatory responses, excitotoxicity and mitochondrial functional disorder, PARP-1 has attracted more and more attention as a suitable target for

neuroprotective agents. The 2-aminothiazole framework was singled out as a novel PARP-1 inhibitor scaffold via computer-aided drug design.
Andersson et al.73 employed the olefin ring-closing metathesis reaction (RCM) to perform a macrocyclisation and obtain a substituted dioxo-1,4-diazacyclotetradec-7-ene, compound 71.
Compounds were prepared by manual SPPS using the 9-fluorenylmethoxycarbonyl (Fmoc) protection strategy, followed by side chain to side chain cyclisation via RCM.
One example of a MW-assisted reaction is reported in Scheme 48 (Smith Synthesizer - Biotage).

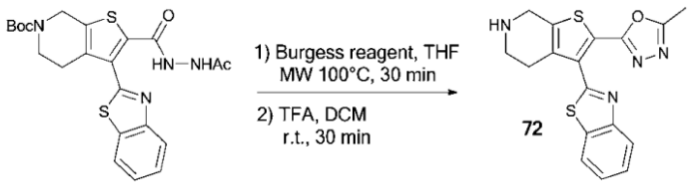


Scheme 48

The cyclisation was performed on a preparative scale using HGII (Hoveyda-Grubbs second generation catalyst) (0.15 equiv.) at 150° C for 5 min and repeated once after a second addition of the catalyst. This reaction provided potent inhibitors of insulin-regulated aminopeptidase (IRAP), which is an enzyme found in areas of the brain associated with memory and learning. The design, synthesis and biochemical evaluation of novel 13- and 14-membered macrocyclic tripeptide analogues of Angiotensin IV were presented. It was demonstrated that the replacement of a disulphide bridge with a carbon–carbon bridge in the N-terminal macrocyclic part was well tolerated. The most potent, selective and stable analogue in the series, 71 (Ki 1/4 4.1 nM), serves as a starting point for further optimisation.

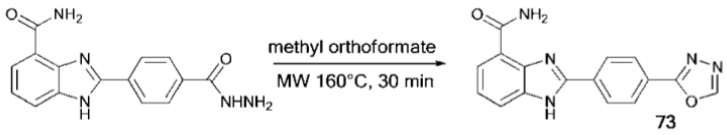
6 Anticancer activity

The burden of cancer continues to increase on a global scale, largely because of world population growth and aging, along-side the increasing adoption of cancer-causing behaviour particularly in economically developing countries. The effectiveness of chemotherapy is often limited by its toxicity to other tissues in the body. Research in the area never stops and MW-assisted synthesis may help find greener and faster access to libraries of N-heterocycle compounds to be screened as anti-cancer drugs.
Another example of 1,3,4-substituted oxadiazole synthesis via MW-assisted dehydrative cyclisation using the Burgess reagent was described by Rai et al.74 (Scheme 49).



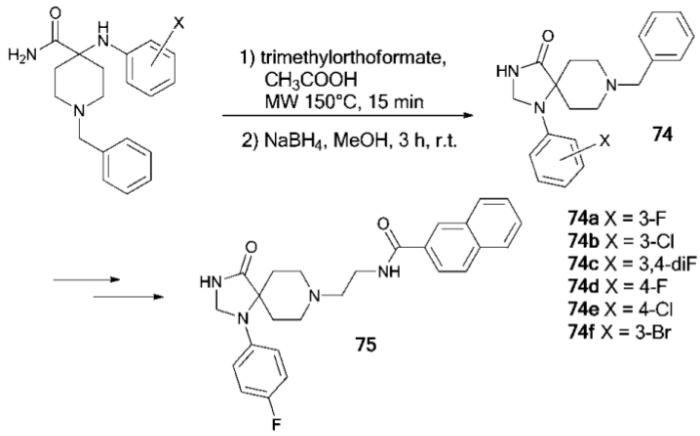
Scheme 49

The authors were interested in the optimization of apurinic/ apyrimidinic (AP) endonuclease 1 (APE1) inhibitors containing this N-heterocycle. APE1 is an attractive target in anticancer treatments and is the main enzyme responsible for the removal of a basic (or AP) sites in DNA in mammals. Indeed, APE1 is normally activated so it can cause DNA damage, therefore its inhibition may improve the activity of anticancer drugs that interact with DNA. MW-assisted syntheses of compound 72 and many other analogues have led to both an improvement in the potency of the initial lead compound and the discovery of new APE1 inhibitors. These small molecules exhibit activity against the purified APE1 enzyme. Moreover, this class of compounds possesses a generally favourable in vitro ADME profile, along with good exposure levels in plasma and the brain.
1,3,4-Oxadiazole derivatives were also obtained by Tong et al.75 from the corresponding benzohydrazide via condensation with methyl orthoformate at 160°C under MW irradiation for 30 min (Scheme 50) (Discover - CEM MW reactor).



Scheme 50

More than a decade ago, scientists from the University of Newcastle identified a class of benzoxazole-4-carboxamide compounds as weak poly(ADP-ribose) polymerase (PARP) inhibitors.76 The authors disclosed the development of a distinct class of inhibitors that had unsaturated heterocycles attached to the benzimidazole core. PARP-1 is a nuclear enzyme that is part of a larger family of PARP enzymes. DNA damage activates PARP-1, causing it to cleave its substrate nicotinamide adenine dinucleotide (NAD) and transfer ADP-ribose units to nuclear target proteins that can facilitate DNA repair. This mechanism allows cancer cells to escape apoptosis induced by DNA damaging treatments such as chemotherapy and radiation and enables cancer cells to repair the drug-induced DNA lesions. For this reason, the inhibition of PARP-1 has become an attractive strategy for anticancer therapy. A number of these inhibitors demonstrated high potency in both enzymatic and cellular assays; some of them also exhibited good pharmacokinetic properties and potent oral in vivo efficacy in potentiating the cytotoxic agent Temozolomide (TMZ) in a mouse xenograft model. Results show that the installation of an unsaturated heterocycle on the 2-phenyl group of the benzimidazole core proved to be another viable strategy for developing potent and orally efficacious PARP-1 inhibitors.
Lavieri et al.77 focused on the functionalisation of the 1,3,8- triazaspiro[4,5]decan-4-one scaffold with various halogens. In these syntheses, the closing of the spirocycli five-membered ring meant forcing MW conditions at 150° C for 15 min in AcOH (single mode Biotage Initiator-60), followed by reduction to provide the desired product (Scheme 51).



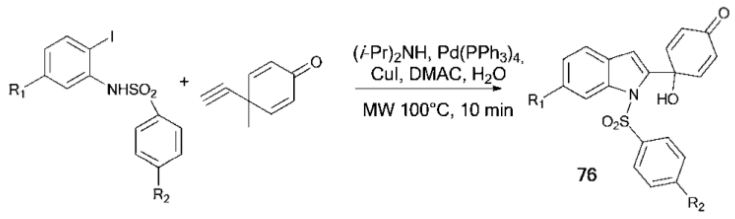
Scheme 51

A compound library was prepared, using this method, and tested for the PLD1 inhibiting activity. PLD (phospholipase D) catalyses the hydrolysis of phosphatidylcholine into the lipid second messenger phosphatidic acid and choline. Evidence from genetic and biochemical experiments indicates that PLD is an attractive target for cancer therapy.

The development of isoform-selective PLD inhibitors, specifically PLD2-selective inhibitors, may lead to a new class of cancer therapeutics. The authors reported the results of a matrix library approach to increasing PLD2 potency and selectivity within the 1,3,8-triazaspiro-[4,5]decan-4-one series.

All library members were evaluated for their ability to inhibit PLD1 and PLD2 in cellular and biochemical assays with recombinant PLD1 and PLD2 enzymes. The most potent (PLD2 IC50 1/4 20 nM) and selective (75-fold versus PLD1) PLD2 inhibitor was compound 75.

Quinols (4-hydroxycyclohexa-2,5-dien-1-ones) substituted with a heterocyclic fragment at the 4-position constitute a new pharmacophore in anticancer drug research. Classic quinol synthetic methods, however, have given variable yields, generally less than 40% and in some cases reactions have failed completely. Alkynyl-substituted quinol derivatives react with N-arylsulfonyl-2-iodoanilines under Sonogashira conditions as described by McCarroll et al.78 Best conditions were found to be MW irradiation of the homogeneous catalyst tetrakis-(triphenylphosphine)palladium and copper iodide in a diisopropylamine/aqueous DMAC medium at 100°C. The corresponding indoles were obtained in only 10 min and, therefore, it has been shown that MW-assisted Sonogashira coupling chemistry can be employed to construct a new series of indolylquinols (Scheme 52).

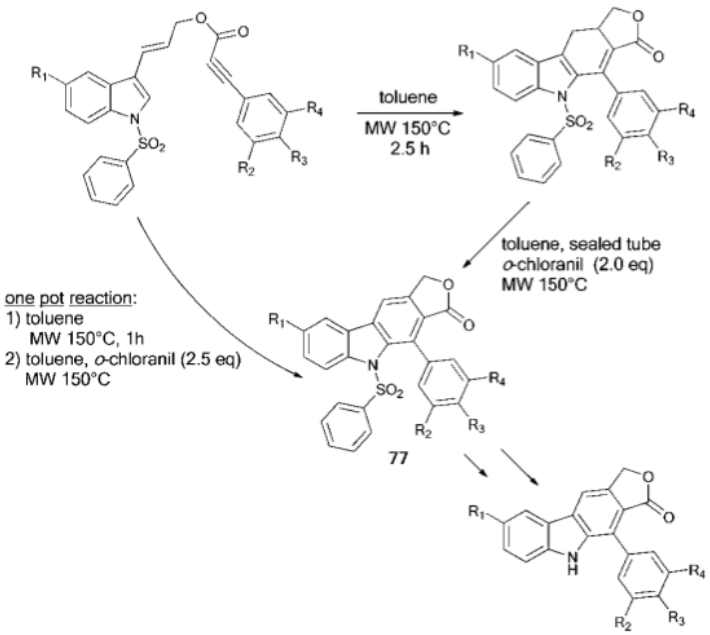


Scheme 52

These derivatives were tested and showed selective in vitro activity especially against cancer cells of colon, renal, and melanoma origin.

Hajbi et al.79 prepared new furocarbazoles from formylindoles and various benzaldehydes. Their straightforward and efficient synthesis gave access to esters which were then readily used in a 6p-electrocyclisation/aromatisation reaction. The one-pot Diels–Alder reaction was efficiently performed under MW irradiation (Biotage Initiator) (Scheme 53).

After furocarbazole deprotection and methyl ether cleavage, the compounds obtained were evaluated for the DNA top- oisomerase II inhibitor activity, although few promising candidates were discovered. This is possibly because they make use of different mode of action than etoposide, which is frequently prescribed in oncology and for which toxicities and resistance are known.



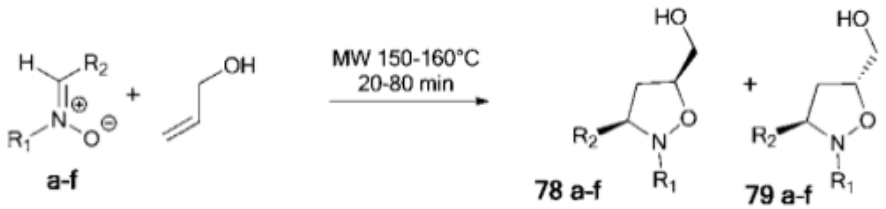
Scheme 53

Rescifina et al.80 reported the synthesis of isoxazolidinyl polycyclic aromatic hydrocarbons (isoxazolidinyl-PAHs), featuring the presence of an isoxazolidine ring on an aromatic planar system made up of an anthracene, a phenanthrene and a pyrene moiety. A marked improvement in the cycloaddition was obtained under MW irradiation, as in the case of nitrones, using a Discover reactor - CEM (Scheme 54, Table 2).

Table 2 Reactions of nitrones with allyl alcohol

Classical heating[a]				MW[b]		
Nitrone	R_1	R_2	Yield (%)	Yield (%)	Time (min)	78/79 ratio
a	Me	9-Anthryl	1	53	80	1.1 : 1.0
b	Me	9-Phenanthryl	30	83	20	1.3 : 1.0
c	Me	1-Pyrenyl	20	75	20	1.5 : 1.0
d	Bn	1-Pyrenyl	30	85	20	1.6 : 1.0
e	Bn	9-Phenanthryl	—[c]	39	20	1.5 : 1.0
f	Bn	9-Anthryl	—[c]	—[c]	80	—

[a] Solvent free; 1 : 200 dipole/dipolarophile; 130 °C 48 h. [b] Solvent free; 1 : 200 dipole/dipolarophile (power 90 W; temperature 150–160 °C). [c] No reaction.

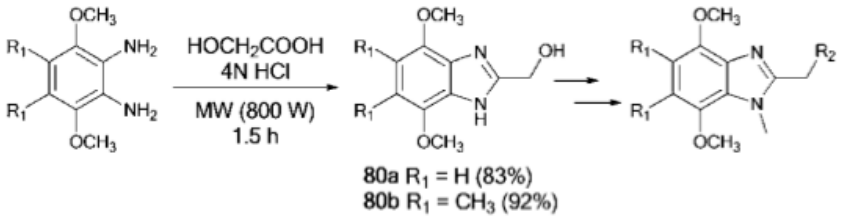


Scheme 54

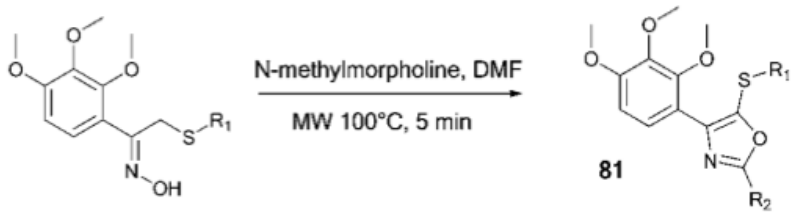
These isoxazolidinyl-PAHs were the first members of a new series of potential, non-ionic DNA intercalators.

Research into the development of non-peptide-based DNA interactive drugs has been intense, since such agents offer the potential to interact with their intended target without falling hostage to cellular peptidases. Of the established drug-DNA associative methods available, intercalation is one of the most predictable, and a variety of natural and synthetic agents that work using this strategy show excellent antitumour activity.

A new class of potential DNA intercalation agents, the isoxazolidinyl-PAHs, has been synthesised according to the 1,3- dipolar cycloaddition methodology and promoted by MW irra- diation. A systematic investigation into structural variations of the isoxazolidine nucleus was carried out to gain further details as to this template's potential as an antitumour agent.
New benzimidazole-4,7-diones, substituted at the 2-position, were synthesised via a MW-assisted reaction (multimode ETHOS, Milestone) by Gellis et al.81 (Scheme 55).
A series of variously substituted benzimidazole-4,7-diones were synthesised from this intermediate and tested for their antitumour activity. Substituents with different electronic and solubility characteristics were selected, while others were chosen for their alkylating properties. The aim here was to investigate the effects of substituents at the 2-, 5- and 6-position.
Their cytotoxicity was evaluated on colon, breast and lung cancer cell lines. One compound was shown to possess excellent cytotoxicity which was comparable to that of mitomycin C.
A series of 2,4,5-trisubstituted oxazole derivatives that contain a heterocyclic moiety were designed and synthesised by Liu et al.82 MW irradiation promoted the rapid O,N-acylation–cyclodehydration cascade reaction between oximes and acid chloride, and twenty novel 2,4,5-trisubstituted oxazole derivatives containing the heterocycle moiety were synthesised (Scheme 56).



Scheme 55



Scheme 56

In addition to much faster conversion, the major advantage of MW irradiation was a significantly increased yield, as can be seen in Table 3.

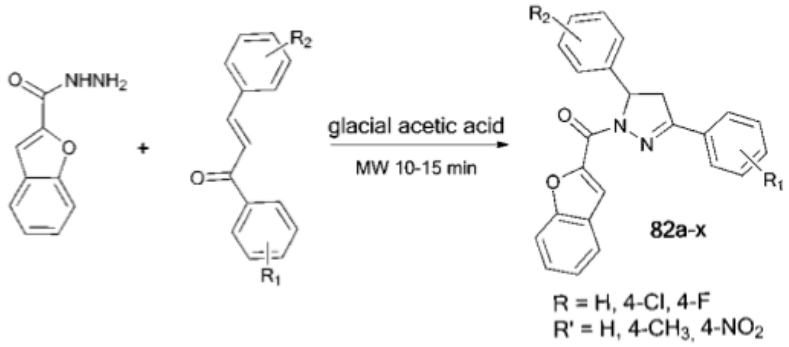
Table 3 Microwave promoted oxazole formation reaction

Solvent (v/v)	Conditions	Additive	Yield (%)
Pyridine/toluene (5.6 : 1)	120 °C, 18 h	—	—
Pyridine/toluene (5.6 : 1)	MW, 100 °C, 30 min	NMM[a]	—
DMF	MW, 120 °C, 15 min	NMM[a]	37.2
DMF	MW, 140 °C, 30 min	NMM[a]	22.3
DMF	MW, 100 °C, 10 min	NMM[a]	62.5

[a] 5 mol % of NMM was used.

Oxazoles are one of the key building elements of natural products. The oxazole ring is endowed with a number of interesting effects that set it apart from the numerous heterocyclic moieties of biological and pharmacological interest, one such effect is the antiproliferative activity.

Parekh et al.83 have synthesised some novel benzofuran functionalised pyrazole derivatives using MW irradiation (Scheme 57).

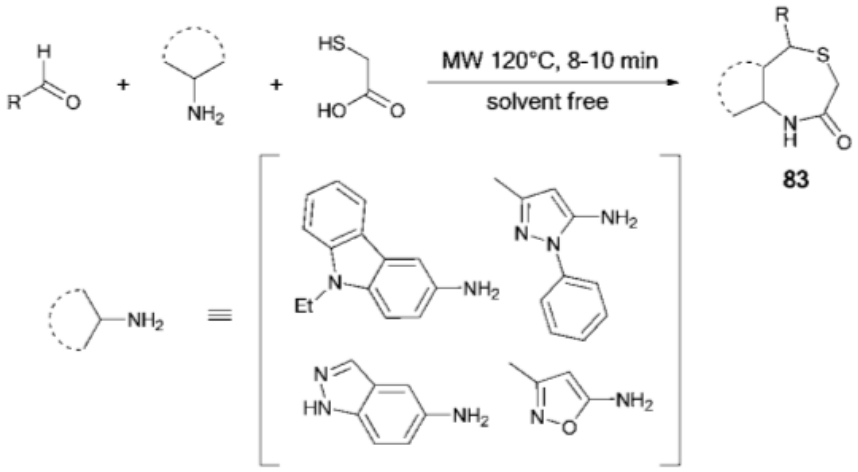


Scheme 57

They demonstrated some easy and fast benzofuran-2-yl- (4,5-dihydro-3,5-substituted diphenylpyrazol-1-yl)methanone syntheses under MW irradiation. All the synthesised compounds were examined for the antiproliferative activity.

One of the main problems currently facing the treatment of human neoplastic diseases is the phenomenon of multidrug resistance (MDR) to the many anticancer agents used in chemotherapy. Therefore, these compounds were also tested for their ability to reverse multidrug resistance in human MDR1- gene transfected mouse lymphoma cells in vitro. Compounds 82a-x were found to have a high inhibitory effect on the MDR reversal activity.

Shi et al.84 carried out the design and diversity-oriented synthesis of novel 1,4-thiazepine derivatives which were embedded with carbazole, pyrazole and isoxazole motifs in a solvent-free MW-assisted three-component reaction (10 min at 120°C, with a monomodal Emrys Creator – Biotage) (Scheme 58).



Scheme 58

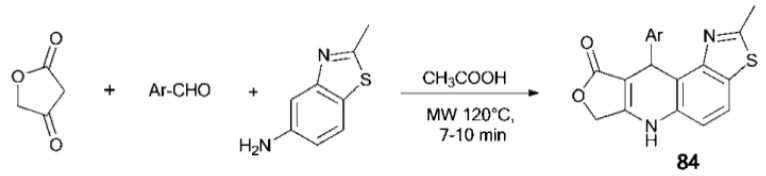
A number of heteroaromatic amines (containing carbazole, pyrazole and isoxazole skeletons) and various aldehydes (including electron rich and poor aromatic aldehydes and heteroaromatic aldehydes) were used to obtain target molecules in which each included one of the bioactive 1,4-thiazepine and carbazole, pyrazole and isoxazole units. The protocol is

applicable to a wide range of aldehydes and heteroaromatic amines and can provide a library of novel 1,4-thiazepine derivatives 83 in high yields (88–94%) and in short reaction times (8–10 min).

These new 1,4-thiazepine derivatives underwent cytotoxicity tests in the carcinoma cell line HCT 116 (ATTC CCL 247) and mice lymphocytes. They exhibited high selective cytotoxicity to HCT 116 cells. These results suggest that the 1,4-thiazepine derivatives 83 exhibit remarkable selective cytotoxicity to this carcinoma cell line.

This study has achieved a green and easy route to 1,4-thiazepine derivatives, which include bioactive heterocyclic skeletons, which may well find pharmaceutical applications after further investigation.

Shi et al.85 reported an efficient synthesis of new 4-aza-podophyllotoxin analogues that contain thiazole skeletons 84 via MW-assisted three-component reactions (in a monomodal Emrys Creator – Biotage) of aromatic aldehydes, tetronic acid and 2-methylbenzo[d]thiazol-5-amine (Scheme 59).



Scheme 59

A possible reaction mechanism may involve the Knoevenagel condensation between aldehydes and tetronic acid in the initial step. Next, the Michael addition of 2-methylbenzo[d]thiazol-5-amine to the first adduct may provide another open-chain intermediate, which may give rise to the final products 84 upon intramolecular cyclisation and dehydration.

Under these optimised conditions, a variety of substituted aromatic and heteroaromatic aldehydes were used as reactants (Table 4). Both aromatic aldehydes bearing either electron-donating groups (such as alkoxy and methyl) or electron-withdrawing groups (such as nitro or halide) and heterocyclic thiophene-2-carbaldehyde (84l) showed high reactivity and afforded good yields of 4-aza-podophyllotoxin analogues 84.

Table 4 Reaction time and yield according to Scheme 59[a]

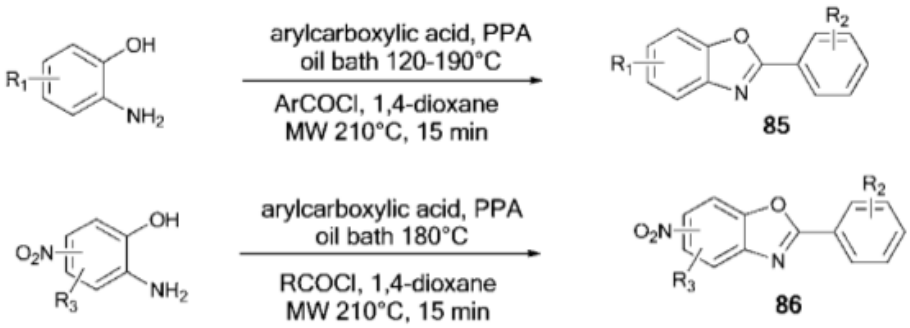
Product	Ar	Time (min)	Yield (%)
84a	4-FC_6H_4	8	80
84b	4-ClC_6H_4	8	82
84c	4-BrC_6H_4	8	83
84d	3-$NO_2C_6H_4$	7	78
84e	4-$NO_2C_6H_4$	7	82
84f	C_6H_5	10	79
84g	4-$CH_3C_6H_4$	8	80
84h	4-$OCH_3C_6H_4$	8	79
84i	2,4-$Cl_2C_6H_3$	8	81
84j	4-OH-3-$NO_2C_6H_3$	7	77
84k	3,4,5-$(OCH_3)_3C_6H_2$	10	73
84l	Thien-2-yl	10	70

[a] All the reactions were carried out in 1 mmol scale in 2 ml AcOH at 120 °C, under MW (100–150 W) and the ratio of starting materials was 1/1/1.

In vitro cytotoxicity tests on the malignant melanin carcinoma cell line M14, mammary carcinoma cell line MCF7 and colon carcinoma cell line SW1116 showed moderate to strong cytotoxicity to the three carcinoma cell lines, making these promising antitumour drug candidates that, however, require further structural modification and biological investigation.
This approach not only provides a valuable tool in the design and synthesis of new 4-aza-podophyllotoxin analogues, but it also has the advantages of atom-economy, environmental-friendliness, good yields and operational simplicity.

7 Other activities

There are a number of methodologies that allow access to the 2- aryl benzoxazole core. The most generally applicable synthetic route uses a cyclocondensation between an aminophenol and either a carboxylic acid, using polyphosphoric acid (PPA), or an acid chloride. While thermal activation of the reaction has often been the heating method of choice, MW irradiation has also proven to be an extremely effective accelerant, particularly in reactions that use an acid chloride.
Chancellor et al.86 have published the synthesis of a series of novel 2-arylbenzoxazoles 85 and 86. In some cases, the ben- zoxazole core was obtained via MW irradiation of the corre-sponding aminophenolic compound and the arylcarboxylic acid or chloride (Scheme 60). (Initiator - Biotage or Explorer - CEM).



Scheme 60

Benzoxazole was identified as a small molecule up-regulator of utrophin, a protein which is the autosomal paralogue of dystrophin. Up-regulation of utrophin has been proposed as a potential treatment paradigm for Duchenne muscular dystrophy (DMD), the most common form of muscular dystrophy in children and which has been linked to a mutation in the dystrophin gene.
A series of novel 2-arylbenzoxazoles was identified by the authors as potent up-regulators of utrophin production, as assessed by an H2K cell-based assay with a luciferase reporter readout. The most active examples have an in vitro potency of less than 1 mM and give in vitro and in vivo ADME profiles which warrant further investigation. Lead optimisation studies caused 2-arylbenzoxazolic derivatives to be identified as molecules for further investigation.

8 Conclusions

The use of MW irradiation in the preparation of heterocycle libraries has become increasingly popular in the pharmaceutical and academic fields. Of the many enabling technologies for drug discovery and development, MW irradiation has doubtlessly given the most impressive contribution. By taking advantage of this efficient energy source, compound libraries for lead generation and optimisation have been assembled in a fraction of the time required by classical thermal methods and often in much higher yields.

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