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Review

Microwaves in drug discovery and multi-step synthesis

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Summary

The interest of microwaves in drug discovery and multi-step synthesis is exposed with the aim of describing our strategy. These studies are connected with our work on the synthesis of original heterocyclic compounds with potential pharmaceutical value. Reactions in the presence of solvent and solvent-free synthesis can be realised under a variety of conditions; for some of these selected results are given, and where available, results from comparison with the same solvent-free conditions but with classical heating are given.

Microwave-assisted reactions are now well established and have gained popularity, as indicated by the large number of papers currently published on this topic since 1986 [1]. The beneficial effects of microwave irradiation are finding an increased role in process chemistry, especially in cases when usual methods require forcing conditions or prolonged reaction times. Microwaves have also shown an advantage where processes involve sensitive reagents or when products may decompose under prolonged reaction conditions. In connection with these studies, the concept of speeding up resin-bound chemistry by microwave activation was also developed and has created a lot of interest, both from the academic and industrial communities. For all these reasons, the various possibilities offered by this technology are particularly attractive for multi-step synthesis and drug discovery processes where high yielding protocols and avoidance or facility of purification are highly desirable [1].

The main activity for our group consists of performing the synthesis of heterocyclic structures with potential pharmaceutical value. Our molecular targets are inspired by natural marine or terrestrial alkaloids in which interesting biological activity was detected. We describe the synthesis of new thiazole derivatives (I–IV) [2] derived from natural alkaloids extracted from marine organisms (e.g., dercitine and kuanoniamines) [3], or plants (e.g., ellipticine) [4] (Figure 1). In these studies, our strategy consisted of combining the thiazole ring with various heterocyclic structures in the hope of detecting interesting cytotoxicity profiles.

Fusion of the thiazole ring onto the heterocyclic skeletons suggested the use of imino-1,2,3-dithiazoles (e.g., **2** in Scheme 1) which have proved to be highly versatile intermediates in heterocyclic synthesis, undergoing a variety of reactions initiated by nucleophilic attack at different sites on the dithiazole ring (the driving force being the regeneration of the latent cyano group in the dithiazole ring, Scheme 1) [5].

The necessity of having high energy for such transformations led us to use microwaves, with the aim of improving the pharmaceutical development of our compounds. Here, we report the benefits associated with microwave methodology and we study the opportunity of using homogeneous or solvent-free conditions in order to achieve better yields and cleaner reactions than for the purely thermal processes. Two approaches were investigated: the first one involved the use of polar solvents which by themselves are good candidates for microwave heating; the

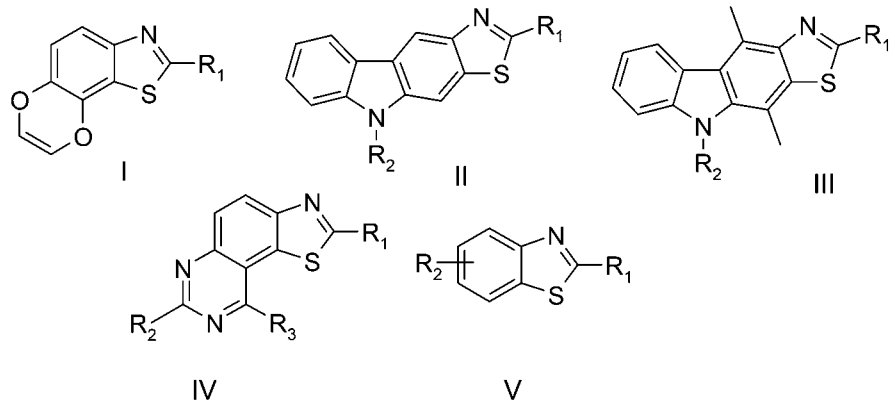
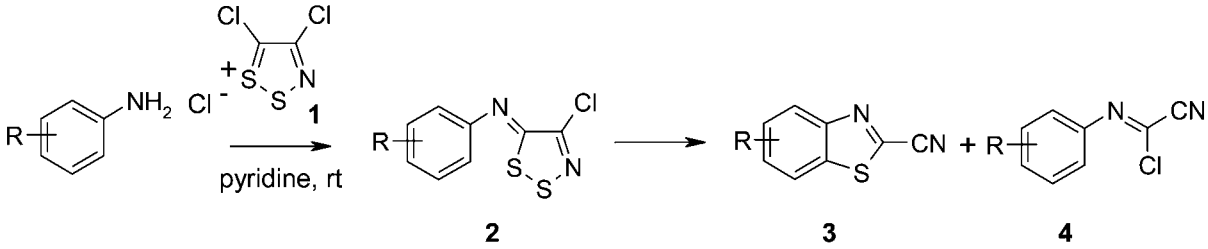


Figure 1.



Scheme 1.

second, solvent-free approach included the use of support which allowed a rapid and safe heating of the reactants.

Microwave experiments in the presence of solvent

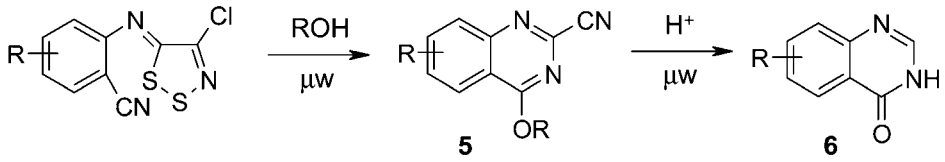
Although the use of solvents is not recommended for ecofriendly procedures and hazards are associated with microwave heating of organic solutions, we have previously showed that the use of homogeneous starting mixtures, in polar solvent, may have a beneficial effect on the scale-up of various reactions under atmospheric pressure. In order to avoid release of flammable and toxic vapours, our strategy consisted of using polar solvents, which possess a high boiling point and may be rapidly heated under microwave irradiation. Among all the solvents tested (e.g., *N,N*-dimethylformamide: DMF; *N,N*-dimethylacetamide: DMA; sulfolane; and 1-methyl-2-pyrrolidinone: NMP) the latter (bp: 202 °C) was defined as the best candidate: it is less toxic than DMF and DMA and, in comparison with sulfolane which is difficult to eliminate, it can be easily removed from the reaction mixture by washing with water.

Thermolysis of imino-1,2,3-dithiazoles into benzothiazoles (Scheme 1) [5]

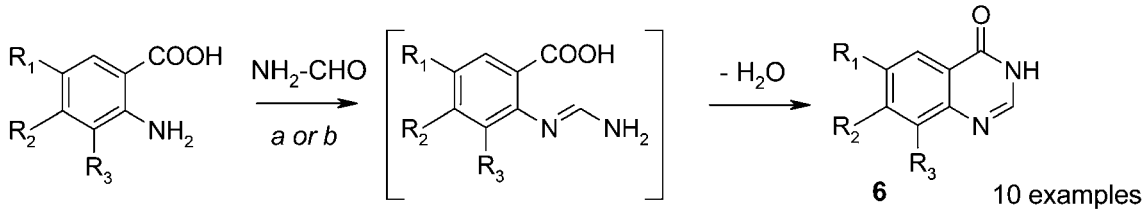
Studying the chemistry of Appel salt **1** and its derivatives, we previously showed that 5-(*N*-arylimino)-4-chloro-5*H*-1,2,3-dithiazoles **2**, which are stable crystalline solids, cyclised by vigorous heating to give sulphur, hydrogen chloride, and 2-cyanobenzothiazoles. It was also shown that electron releasing groups favoured formation of the benzothiazole **3** whilst a strong electron withdrawing group reduced the yield of **3** dramatically in favour of the cyanoimidoyl chloride **4**, which became the major product.

The traditional thermolysis procedures consisted of heating the neat imines **2** under argon at 200–250 °C with a metal bath for 1 or 2 min.

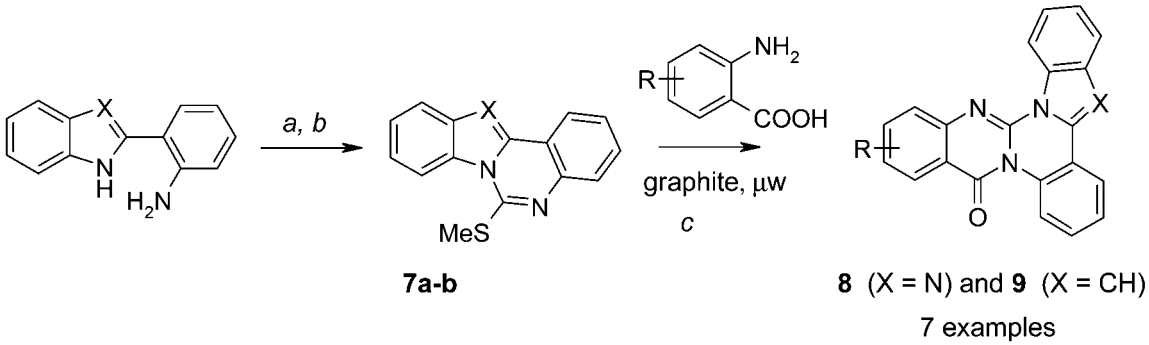
Various methodologies under conventional conditions or microwave (μw) irradiation were also developed in our group. Whatever method was used, the microwave procedures were more rapid than the purely thermal processes but the amount of the desired benzothiazoles **3** was constant (under 0.2 g of starting imine), and scaling-up (up to 0.2 g) the quantity of starting material led to lowest yields of products, ac-



Scheme 2.



Scheme 3. The Niementowski reaction: (a) Conventional conditions: 130–150 °C, average time 6 hr; (*b*) microwave conditions: μw (60 W), 150 °C, average time 20 min.



Scheme 4. Reagents and conditions: (a) CS_2, MeOH/KOH, reflux, μw, 55 min, 95%; (b) CH_3I, NaH/DMF, r.t., 5 min, 95%; (c) anthranilic acid, graphite, μw (120 W), 140 °C, 30 min.

Table 1. Microwave synthesis of benzothiazoles **3**. Method: **2** (1 g), *N*-methylpyrrolidin-2-one, μw (150 °C, 90 W)

Starting imine **2** (R)		Reaction time (min)	Product **3** (R)	Yield of **3** (%)
a	(H)	1	(H)	49
b	(4-CH_3)	2	(6-CH_3)	55
c	(4-OCH_3)	1	(6-OCH_3)	48
d	(2,5-diCH_3)	1	(4,7-diCH_3)	58
e	(2,5-diOCH_3)	3	(4,7-diOCH_3)	64

companied by complicated mixtures of carbonaceous compounds and impurities.

We have shown that the scale of the reaction could be extended to 5 g by heating of the starting imino-1,2,3-dithiazoles in the presence of NMP as solvent (Table 1) [6]. It allowed the obtaining of homogen-

Table 2. Synthesis of 3*H*-quinazolin-4-ones from various anthranilic acids

Starting material	R_1	R_2	R_3	Time (min)	Product	Yield (%)
a	H	H	H	20	**6a**	90[a]
b	Me	H	H	15	**6b**	75
c	Br	H	H	20	**6c**	75
d	NO_2	H	H	20	**6d**	87
e	OMe	OMe	H	40	**6e**	70
f	Br	H	Br	15	**6f**	78
g	OH	H	H	15	**6g**	86
h	OMe	OMe	OMe	40	**6h**	77
i	-C_2H_4-		H	15	**6i**	77
j	Pyridine[b]			20	**6j**	80

[a] A conventional thermal heating (oil bath) of this reaction at 150 °C for 6 hr led to the expected product in a 59% yield.
[b] Starting material: 2-aminonicotinic acid.

eous solutions which avoid the presence of carbonaceous compounds. The easiest purification of the crude product led to the attempted compound in better yields.

Synthesis of 4-alkoxyquinazoline-2-carbonitrile (Scheme 2) [7]

We have shown that introduction of a cyano group into the ortho position of the *N*-aryl group of the imines **2**, allowed formation of novel 4-alkoxyquinazolines by lengthy heating (40 hr) of the reactants. The yields of the quinazolines were improved in a shorter reaction time (2 hr) by microwave irradiation.

In well-controlled conditions this reaction was successfully extended to a larger scale without problems, allowing multigram (50 g in average) production of these useful heterocyclic intermediates.

Open microwave monomode reactors now available are especially designed for organic synthesis. In well-defined conditions (the concentration of starting materials may be important in homogeneous phase) many thermal reactions performed in the presence of solvent may be realised without drawbacks or hazards.

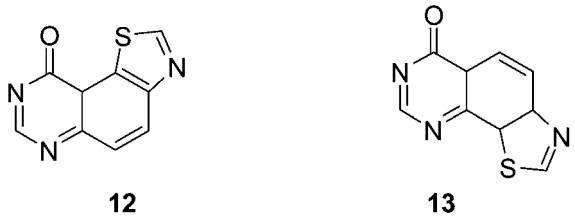
Microwave experiments in solvent-free conditions

Solvent-free synthesis can be realised under a variety of conditions; for some of these we reported selected results and, where available, results from comparison with the same solvent-free conditions but with classical heating are given.

Reactions without support: Re-investigation of the Niementowski reaction (Scheme 3 and Table 2) [8]

The most common synthetic method of the 3*H*-quinazolin-4-one ring is based on the Niementowski reaction, which involves the fusion of anthranilic acid (or a derivative, e.g., 2-aminobenzonitrile) with formamide and proceeds usually via an *o*-amidine intermediate (Scheme 3). This procedure usually needs high temperatures and requires lengthy and tedious conditions.

In order to improve the Niementowski method, several conditions were investigated [9]. Among the various combinations tested, the best results were obtained by treatment of the anthranilic acid with 5 equiv. of formamide with an irradiation programmed at 60 W and a fixed temperature (150 °C).



12 **13**

Figure 3.

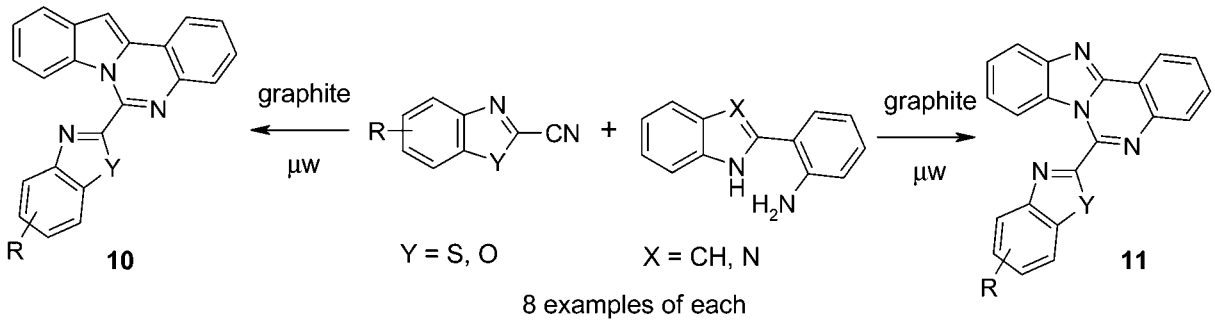
Again, the comparative study of this solvent-free procedure by classical heating (oil bath) and microwave irradiation showed that reaction time was reduced from several hours to a few minutes by using the latter technique. This process was extended and adapted to various anthranilic acids to give the desired products in very good yields.

Reactions with graphite as 'sensitizer' and support [10]

The solvent-free technique has been claimed to be particularly environmentally friendly, as it avoids the use of solvents, and has an easier work-up, if the support can be removed from the reaction mixture simply by filtration. Graphite is one of the solids most efficiently heated by microwaves [10] and is also known for its adsorbing properties of organic molecules. We recently showed that the strong thermal effect due to graphite/microwaves interaction can be efficiently used for the synthesis of various polyheterocyclic molecules, for which traditional methods failed or are less attractive.

*Preparation of novel tetraaza-benzo[a]indeno[1,2-c] anthracen-5-one derivatives (***8***) and triazabenzo[a] indeno[1,2-c]anthracen-5-ones (***9***)* [11, 12]
We have described the preparation of novel tetraazabenzo[*a*]indeno[1,2-*c*] anthracen-5-one derivatives (**8**) by fusion of the benzimidazo[1,2-*c*] quinazoline and quinazolin-4-one rings. Starting from 2-(2-aminophenyl)indole, we have also shown that novel triazabenzo[*a*]indeno[1,2-*c*]anthracen-5-ones **9** could quite easily be reached in three steps through a modified Niementowski reaction, which involves condensation of anthranilic acids with a *S*-alkylated-6-mercaptoindolo[1,2-*c*]quinazoline.

*Synthesis of novel indolo[1,2-c]quinazolines (***10***) and benzimidazo[1,2-c]quinazolines (***11***)* [13] (Table 3)
The products are obtained by condensation of the appropriate diamines (e.g., 2-(2-aminophenyl)indole



Scheme 5.

Table 3. Synthesis of indolo[1,2-*c*]quinazoline and benzimidazo[1,2-*c*]quinazoline derivatives

Starting material (R)		Product	Time (min)[a]	Yield (%)	Product	Time (min)[a]	Yield (%)
a	(H)	**10a**	135	64	**11a**	90	70
b	(6-F)	**10b**	240	53	**11b**	150	56
c	(6-CH_3)	**10c**	150	60	**11c**	60	71
d	(6-OCH_3)	**10d**	30	68	**11d**	10	73
e	(4,7-diCH_3)	**10e**	90	61	**11e**	65	65
f	(4,7-diOCH_3)	**10f**	115	54	**11f**	80	58
g	(6-NO_2)	**10g**	24 hr	12[b]	**11g**	10 hr	18[b]

[a] Time of microwave irradiation.
[b] P_2S_5, 1,2-dichlorobenzene reflux, μw heating (130 °C, 90 W).

or 2-(2-aminophenyl)benzimidazole) with 2-cyanobenzothiazoles. We showed that microwave irradiation (150 W) of the two starting compounds at 220 °C in the presence of graphite (10% by weight) afforded the indolo[1,2-*c*]quinazolines **10** and benzimidazo[1,2-*c*]quinazolines **11** good yields. Under similar experimental conditions (with the same quantity of starting material, graphite, and same reaction time), conventional heating allowed a small amount of the products (yields <35%).

Application to multi-step synthesis of polyheterocyclic systems

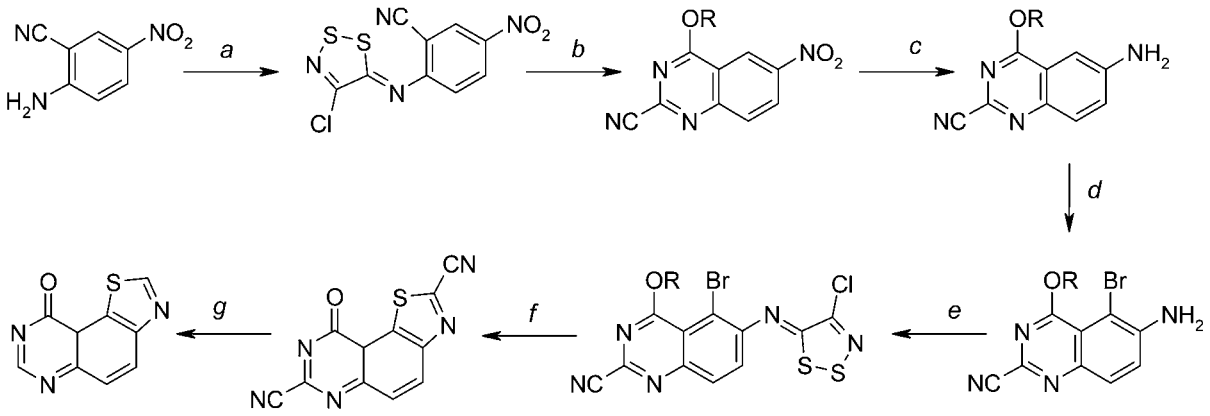
The examples described above clearly demonstrate that, with well-established experimental conditions, microwave irradiation can be used as a very useful alternative to classical methods, and it is now possible to combine drug discovery strategy with microwave heating for a rapid access to novel molecules with potent pharmacological value.

Synthesis of thiazolo[5,4-f]quinazolin-9-ones **12** *and thiazolo[4,5-h]quinazolin-6-ones* **13** (Figure 3) [14]

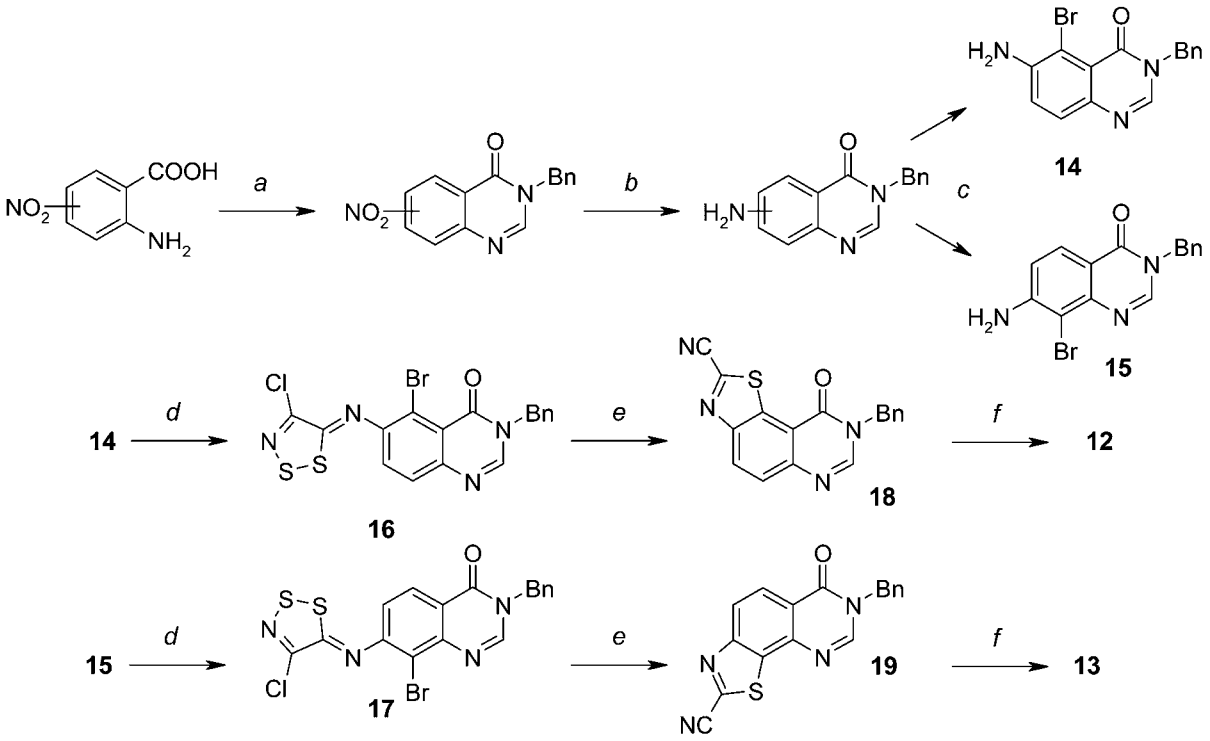
Inspired by previous work describing the synthesis and biological activity of a linear 7*H*-thiazolo[5,4-*g*]quinazolin-8-one, we recently studied the preparation of the angular 8*H*-thiazolo[5,4-*f*]quinazolin-9-one ring **12** via another route, using Appel's salt (4,5-dichloro-1,2,3-dithiazolium chloride) chemistry.

The thiazolo-quinazoline ring was performed in six steps from commercially available 2-amino-5-nitrobenzonitrile (Scheme 6). Comparison of conventional heating (oil or metal bath) and microwave irradiation demonstrates that the overall time for the synthesis was considerably reduced, the reactions were cleaner, and the products rapidly purified.

Unfortunately, the pathway described in this case was not well adapted for easy introduction of various substituents onto the skeleton. Thus, in order to perform structure-activity studies we decided to re-investigate the synthetic approach to the planar compound **12**. At the same time we performed the synthesis of its novel regioisomer **13** (Figure 3), with the aim of allowing the presence of further substituents



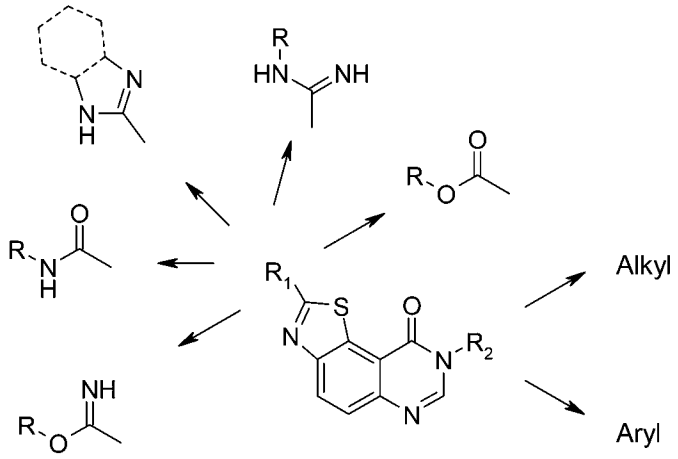
Scheme 6. (a) **1**, pyridine, CH_2Cl_2, room temp., 3 hr (78%); (b) NaH, EtOH, reflux (μw), 2 hr (61%); (c) $SnCl_2$,.$2H_20$, EtOH, μw, 70 °C, 10 min (94%); (d) Br_2, acetic acid, r.t., 4 hr; (e) **1**, pyridine, CH_2Cl_2, room temp., 4 hr (74%); (f) CuI, pyridine, reflux (μw), 15 min (53%); (g) HCl, reflux (μw), 10 min (50%).



Scheme 7. Reagents and conditions: (a) BnBr, NaH, DMF, μw, 70 °C, 15 min (80–95%); (b) ammonium formate/Pd/C, EtOH, μw, 65 °C, 10 min (75–92%); (c) Br_2, acetic acid, r.t., 2 hr; (d) **1**, pyridine, CH_2Cl_2, room temp., 3 hr (68–77%); (e) CuI, pyridine, reflux, μw, 15 min (75–83%); (f) Conc H_2SO_4, μw, 130 °C, 15 min (40%).

and then, to diversify the molecules studied (preliminary evaluations for *in vitro* antiproliferative activity of the 8*H*-thiazolo[5,4-*f*]quinazolin-9-ones **12** have shown that the final product is less active than its substituted precursors).

The pharmaceutical interest of the nude thiazoloquinazolinones **12** and **13** may be limited because of the lack of substituents, such as basic amino groups. The interest of the multi-step (7 steps from the nitroanilines) synthesis described here is to allow modulations of the ring in various positions. In particular,



Scheme 8. Studied modulations of the ring in various positions under microwave-accelerated conditions.

N-alkylations of the nitrogen in position 8, and transformations of the cyano group present in the thiazole moiety [2] are studied in order to generate novel series of bioactive molecules (Scheme 8).

Among all the reactions performed for the synthesis of such compounds, five were carried out with success to a focused microwave reactor. The short reaction times of these processes (10–40 min) and the purity of the products (generally observed compared to the purely thermal procedures) allowed a quick realisation of these multi-step syntheses.

Conclusion

In conclusion, successful studies are presented for the synthesis of novel heterocyclic structures. This work confirms that reaction mixtures exposed to microwaves allow an easy and rapid access to various original heterocycles, with potential pharmaceutical value.

We have also demonstrated that working under focused microwave irradiation needs special attention: (a) the ratio between the quantity of the material and the support (e.g., graphite) or the solvent is very important; (b) for solid starting materials, the use of solid supports offers operational, economical, and environmental benefits over conventional methods. In contrast, association of liquid/solid reactants on solid supports may involve uncontrolled reactions and is generally worse than comparative thermal reactions. In this case, simple fusion of the products or addition of an appropriate solvent may lead to more convenient mixtures or solutions for microwave applications.

The strategy described opens the door to wider application of microwaves in drug discovery strategies and is actually developed in our group. Scale-up and technical transposition to various multi-step syntheses are actually in progress and will be published at a later date.

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