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Microwave-assisted one-pot syntheses of 4-aminoquinazolines

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Abstract: A simple, environmentally friendly, one-pot method for the synthesis of 4-aminoquinazolines using microwave irradiation has been developed. Structures of derivatives **3**, **4**, and **5** were confirmed by single-crystal X-ray diffraction. The *in vitro* cytotoxicity of each compound was investigated using an MTT assay with A549 and HepG2 cell lines to calculate half-maximal inhibitory concentrations.

Keywords: 4-aminoquinazoline; methodology; microwave assisted; one-pot syntheses.

4-Aminoquinazoline and its derivatives are known to have a wide range of useful biological and medicinal properties, including diuretic, antimicrobial, hypnotic, analgesic, and antihypertensive applications [1–3]. They are potent and powerful inhibitors of tyrosine kinases [4–7] and bind to epidermal growth factor receptors and vascular endothelial growth factor receptor 2. These receptors are often overexpressed or deregulated in many solid tumors, including those of the head, neck, lung, and breast, and have been linked to a poor prognosis [8]. Several small molecule inhibitors containing a 4-aminoquinazoline moiety have been developed and approved as anticancer drugs (Figure 1). Because of their pharmaceutical value, 4-aminoquinazolines are worthy of further investigation.

Traditional preparations of 4-aminoquinazolines involve substitution of 4-chloroquinazolines or *N*′-(2-cyanophenyl)-*N*,*N*-dimethylformamidine with an appropriate aniline [9–11]. However, these multistep reactions can be lengthy, use large volumes of organic solvent, and are performed under harsh conditions. Although several different methods have been investigated to overcome these problems, a simple, environmentally friendly reaction has not yet been developed [12, 13]. The method developed by Yoon et al. is performed at a high temperature (160°C), with acetonitrile as the solvent, and requires multiple purification steps [3]. Zhu et al. developed a method for synthesizing 4-anilinoquinazolines using a palladium catalyst [14]. Recently, Wu and coworkers developed a method for the synthesis of 4-aminoquinazolines with a Fe/Cu catalyst [15]. However, their protocol was long (10–12 h), required a high temperature (110°C), and involved multiple purification steps. Therefore, a simple and environmentally friendly synthesis for 4-aminoquinazolines is required. Organic reactions assisted by microwave irradiation have attracted considerable attention in recent years [16–19].

Modern scientific microwave equipment can be used to accurately control many reaction parameters, including temperature, pressure, and reaction time. Compared with conventional thermal heating, microwave-assisted organic synthesis of classical reactions (i.e. Michael additions, acylation, and alkylation reactions, condensations) can result in shorter reaction times, improved yields, and reduced formation of by-products [20–22]. Microwave reactions are useful in both drug discovery and process chemistry.

Converting a multistep reaction to a one-pot synthesis saves time and energy [23–26]. It also reduces the volume of waste solvent because no intermediate purification steps are required. Therefore, one-pot syntheses are environmentally friendly and economically viable for organic synthesis [23–26]. In our previous work [27–29], we successfully synthesized a series of novel asymmetric tripodal ligands using microwave irradiation in a one-pot synthesis. It has also been shown that dimethylformamide dimethyl acetal (DMF-DMA) can be used as the ring-closing agent in a one-pot synthesis of 1,3,5-triarylbenzene derivatives [30]. Kim et al. reported a synthesis of *N*-methyl-*N*-tosyl allylic amines from Baylis-Hillman adducts of *N*-tosylimines, with the aid of DMF-DMA. Tsou et al. also used DMF-DMA as a reactant and solvent [31]. In

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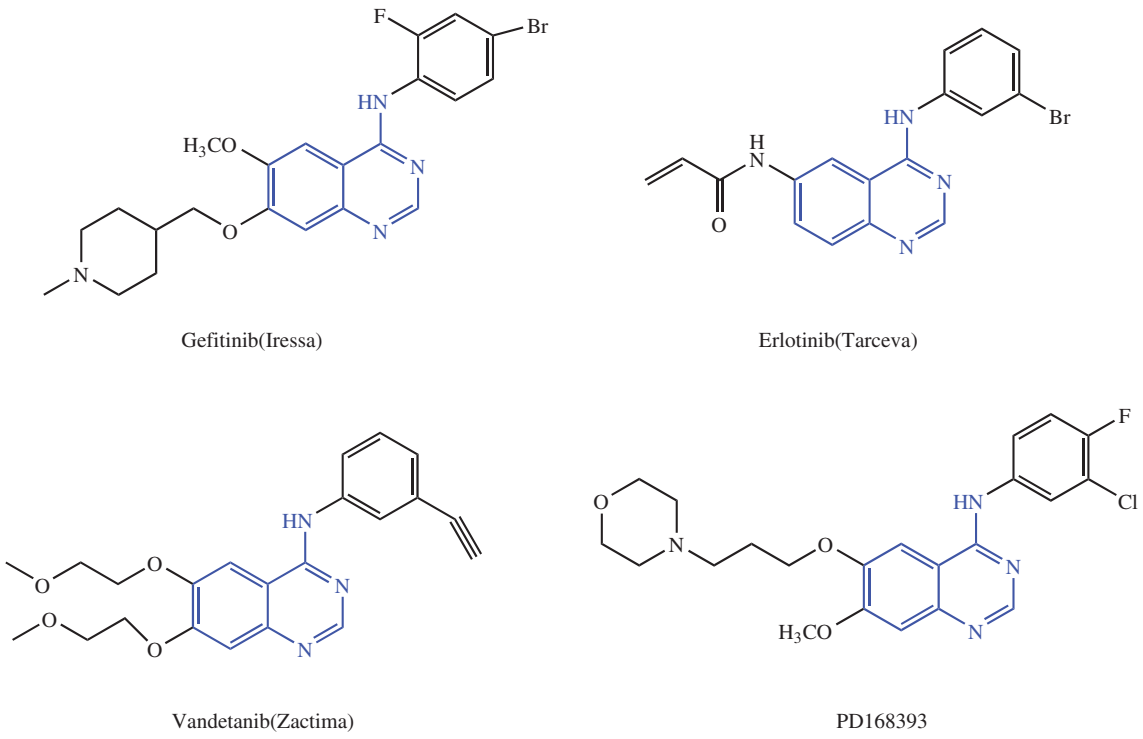
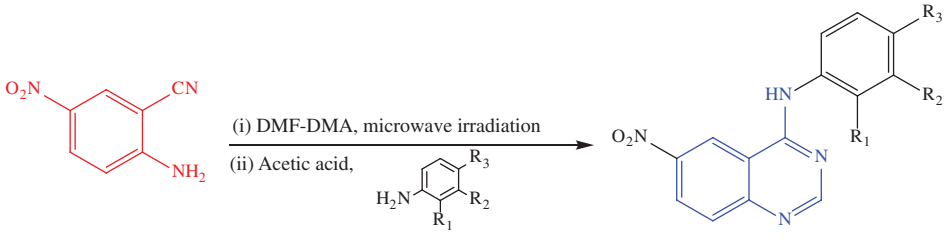


Figure 1: Chemical structures of several inhibitors containing 4-aminoquinazoline structure (shown in blue).

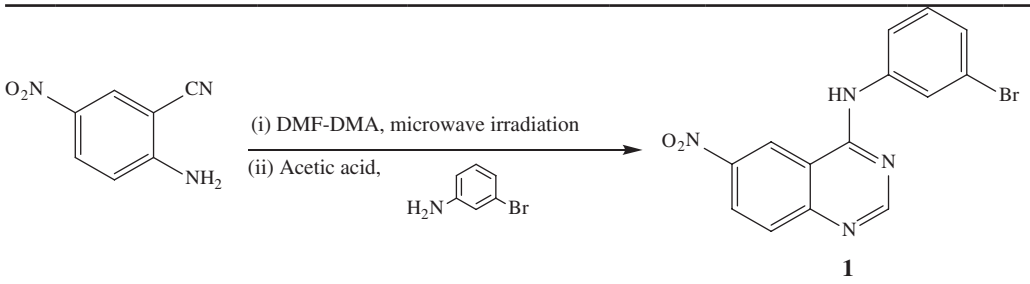
the present study, we applied this knowledge to the development of a one-pot synthesis for 4-aminoquinazolines (Scheme 1).

In the present study, 2-amino-5-nitrobenzonitrile and DMF-DMA were used as the starting materials. No other organic solvent was required. In this reaction, DMF-DMA acted as both a reagent and the solvent. The reaction was performed under microwave irradiation for a set time (t_1). Then, 5 ml of an acetic acid solution of the appropriate aniline was added, and the mixture was irradiated again for a set time (t_2). The desired product was isolated in a satisfactory yield by recrystallization from dimethyl sulfoxide (DMSO). For this reaction, we investigated the impact of reaction time, molar ratio of 2-amino-5-nitrobenzonitrile:DMF-DMA:3-bromoaniline (1:1:1 and 1:1.2:1.2), microwave power, and reaction temperature on the yield of 4-aminoquinazoline **1** (Table 1, Table S1, and Table S2). With a reaction temperature of 70°C, the optimum molar ratio of 2-amino-5-nitrobenzonitrile:DMF-DMA:3-bromoaniline was 1:1.2:1.2, and the optimum microwave irradiation times were t_1=5 min and t_2=15 min. These conditions resulted in a 96% yield of the desired product (Table 1 entry 4, Table S2). Increasing the temperature to 80°C (Table 1, entry 5) and reducing the temperature (Table 1, entries 1–3) both affected the yield. Reducing the microwave power decreased the yield (Table 1, entries



Scheme 1: Synthesis of 4-aminoquinazoline structure derivatives **1–8**.

Table 1: Optimization of reaction conditions for one-pot synthesis **1**.[a]



1

Entry	Time (min), t_1, t_2	Temp. (°C)	Power (W)	Yield (%)
1[b]	5, 15	40	500	75.02
2[b]	5, 15	50	500	80.76
3[b]	5, 15	60	500	82.88
4[b]	5, 15	70	500	96.15
5[b]	5, 15	80	500	88.86
6[b]	5, 15	70	300	NR
7[b]	5, 15	70	400	63.16
8[b]	5, 15	70	500	96.15
9[b]	5, 15	70	600	90.26
10[b]	5, 15	70	700	90.55
11[c]	5, 15	70	500	93.85
12[d]	5, 15	70	500	91.16

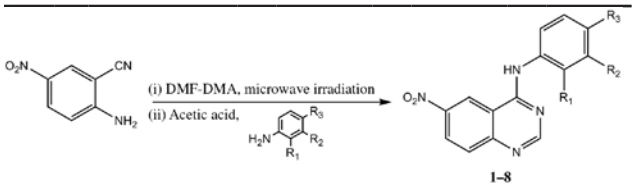
[a]Yield of isolated yields.
[b]2-Amino-5-nitrobenzonitrile (10 mmol), DMF-DMA (12 mmol), and aniline (12 mmol).
[c]Double.
[d]Quadruple.

7 and 8), and when a microwave power of 300 W was used, the product (**1**) was not obtained (Table 1, entry 6). Increasing the microwave power did not increase the yield (Table 1, entries 9 and 10), and some carbonization by-products were observed. Increasing the amount of the starting material to 20 mmol or 40 mmol led to minor decreases in the yield (Table 1, entries 11 and 12), but the yields were still satisfactory.

These results demonstrate that this simple one-pot approach can be used to obtain satisfactory yields with a short reaction time, simple postprocessing, and low volume of organic solvent (acetic acid and DMSO) (Table 1, entry 4). Using the optimum conditions established for the reaction, a series of anilines were studied for the synthesis of 4-aminoquinazolines (Table 2). All of the 4-aminoquinazolines were isolated in satisfactory yields (Table 2, entries 2–8). For comparison, entry 1 in Table 2 was conducted using a traditional heating method (air bath) under the same conditions for reaction time and temperature (see general procedure II in the ESI). The yield for this reaction was only 42%, which demonstrates that the microwave irradiation was superior.

The proposed mechanism for the reaction is shown in Scheme 2. First, the 2-amino-5-nitrobenzonitrile is converted into the corresponding formamidine cation **A** with DMF-DMA. Heating a solution of **A** and aniline in acetic acid induces reaction of the aniline with the carbon of the cyano group. Subsequent electrophilic attack of the nitrile nitrogen onto the enamine carbon leads to the

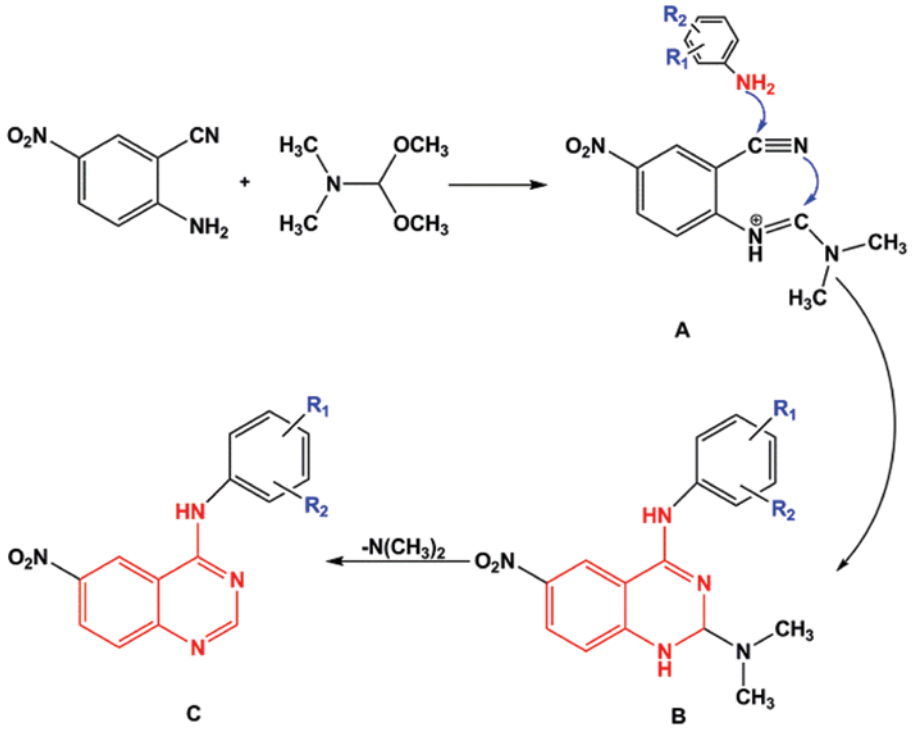
Table 2: One-pot synthesis of 4-aminoquinazolines **1–8**.[a]



1–8

Entry	Time (min), t_1, t_2	Temp. (°C)	Power (W)	Yield (%)
1[b]	5, 15	Yellow	500	96.15
2[b]	5, 15	Brick red	500	34.29
3[b]	5, 15	Yellow	500	66.63
4[b]	5, 15	Yellow	500	63.60
5[b]	5, 15	Orange	500	35.16
6[b]	5, 15	Orange	500	98.66
7[b]	5, 15	Yellow	500	98.86
8[b]	5, 15	Yellow	500	35.12

[a]Conditions: 2-amino-5-nitrobenzonitrile (10 mmol), DMF-DMA (12 mmol), and aniline (12 mmol).
[b]Yield of isolated yields.



Scheme 2: Proposed mechanism.

formation of the ring-closed product **B**. Aromatization and loss of the dimethylamino group provide the final product **C**.

All of the 4-aminoquinazolines were characterized by ^{1}H and ^{13}C NMR, FT-IR spectroscopy, and high-resolution mass spectrometry (Figs. S2–S33 in the ESI). Single crystals of **3**, **4**, and **5** suitable for X-ray diffraction were grown by slow evaporation from DMSO over a few days. The molecular structures of **3**, **4**, and **5** are shown in Figures 2 and 3. Crystal data and structure refinement details are given in Tables S4–S5 in the ESI. The structures of **3** and **4** belong to the monoclinic space group, $P21/c$, and **5** belongs to the triclinic space group, $P\bar{1}$. All three crystal structures contained one or two solvent molecules (DMSO). All bond distances and angles were within the normal ranges [32].

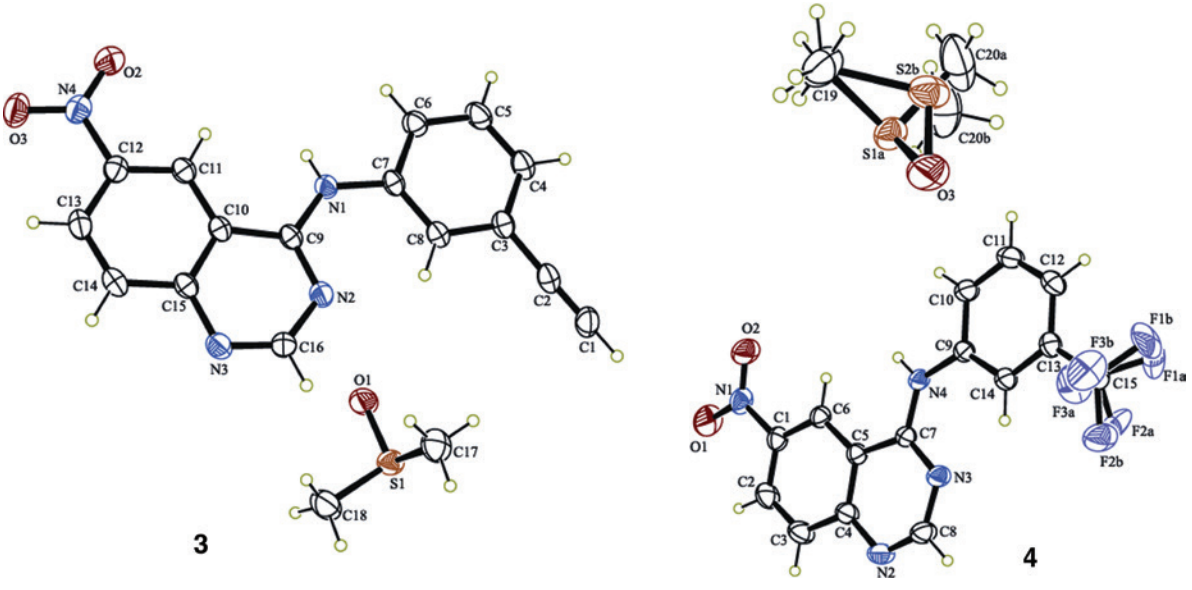


Figure 2: ORTEP crystal structure of **3** (left) and **4** (right); ellipsoids are drawn at 30% probability level and H atoms with arbitrary size.

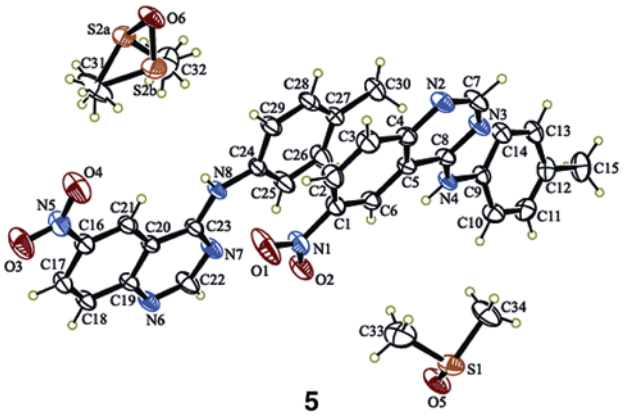


Figure 3: ORTEP crystal structure of **5**; ellipsoids are drawn at 30% probability level and H atoms with arbitrary size.

The *in vitro* cytotoxicity of each synthesized compound was examined using an MTT assay in A549 and HepG2 cell lines. The pharmacological screening results are presented in Table S3. None of the compounds showed obvious inhibitory activity on the two human cancer cells. Although these compounds show unsatisfactory cytotoxicity, further studies investigating derivatives of these compounds are now in progress.

In summary, an environmentally friendly, one-pot synthetic protocol with mild reaction conditions, convenient purification, and wide substrate scope was developed. This method will be useful for the synthesis of potentially biologically active 4-aminoquinazoline derivatives.

Supplemental material for this article is available online at http://www.degruyter.com/view/j/gps. The data are as follows: CCDC: 1425686 (for **3**), 1425687(for **4**), and 1425684 (for **5**), respectively. For ESI and crystallographic data in CIF or other electronic format.

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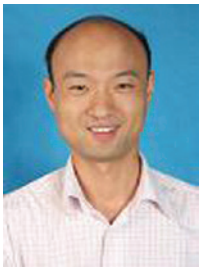

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