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# Microwave-accelerated Dimroth rearrangement for the synthesis of 4-anilino-6-nitroquinazolines. Application to an efficient synthesis of a microtubule destabilizing agent

Alicia Foucourt [a], Carole Dubouilh-Benard [a], Elizabeth Chosson [a], Cécile Corbière [b], Catherine Buquet [b], Mauro Iannelli [c], Bertrand Leblond [d], Francis Marsais [e], Thierry Besson [a,*]

[a] Université de Rouen, CNRS UMR 6014—C.O.B.R.A. & FR3038, I.R.C.O.F. rue Tesnière, F-76130 Mont Saint-Aignan, France
[b] Université de Rouen, EA 3829, UFR Médecine-Pharmacie, 22 Boulevard Gambetta, 76183 Rouen cedex 1, France
[c] Milestone S.r.l., Via Fatebenefratelli, 1/5, 24010 Sorisole (BG), Italy
[d] ExonHit Therapeutics, 65 Boulevard Masséna, F-75013, Paris, France
[e] INSA de Rouen, CNRS UMR 6014—C.O.B.R.A. & FR3038, I.R.C.O.F. rue Tesnière, F-76130 Mont Saint-Aignan, France

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ABSTRACT

A useful and rapid access to 4-anilino-6-nitroquinazolines was investigated in a multi-gram scale via microwave-accelerated condensation and Dimroth rearrangement of the starting anilines with imines obtained by reaction of anthranilonitriles with formamide dimethylacetal. A novel short and efficient route to Azixa™ (EPi28495, MPC-6827), a microtubule destabilizing agent and apoptosis inducer, was performed with success demonstrating that well controlled parameters offer comfortable using of microwave technology with safe and environmental benefits.



## 1. Introduction

The use of adapted reactants and techniques offering operational, economic and environmental benefits over conventional methods is becoming crucial in the preparation and development of biologically active molecules. Recently, the use of clean and more efficient technologies, like microwaves, has become a major stimulus for both industry and academia as it was found to be an effective heating source applicable to a wide range of reactions.[1,2] Novel commercial microwave systems specific for synthesis offer improved opportunities for reproducibility, rapid synthesis, fast reaction optimization and potential discovery of new chemicals.[3]

Our research project consists in developing an easy access to heterocyclic molecules with pharmaceutical interest and we are particularly interested in finding a rapid preparation method of the quinazoline skeleton.[4] This ring is a building block for approximately 150 naturally occurring alkaloids. Their synthetic analogous possess a variety of biological activities, including antimalarial,[5] anticonvulsant,[6] antibacterial,[7] antidiabetic[8] and anticancer.[9] It is now assumed that the biological activity of various quinazolines depends on the type and the position of the substituents in their skeleton. Out of the wide known substitution pattern, 4-aminoquinazolines and their *N*-anilino derivatives were found to be potent and selective ATP competitive tyrosine kinase inhibitors for the treatment of EGFR-associated cancer types (for example Iressa™—gefitinib and Tarceva™—erlotinib, which are used for treatment of non-small-cell lung cancer).[10] More recently 6-thioureido-[11] and 6-ureido-4-[12] anilinoquinazolines have been designed for antimalarial or anticancer activity. In all of these studies 4-anilino-6-nitro-quinazolines are key precursors allowing access to a wide range of N-substituted 4-aminoquinazolines. In our hands, the synthesis of such intermediates proved to be quite difficult and complicated. Applying usual processes,[4] 6-nitroquinazolin-4-ones were treated with thionyl chloride or phosphoryl oxychloride to get the intermediates 4-chlororo-6-nitroquinazolines, which are very unstable and decompose on storage. To overcome this instability problem and in connection with our work on the application of microwave irradiation in organic chemistry,[13] we decided to focus our efforts on the access to 4-substituted 6-nitroquinazolines from 5-nitroanthranilonitrile, with the aim to obtain efficient and adapted conditions with operational and environmental benefits.

The developed microwave-assisted method was then applied to the synthesis of Azixa™ (EPi28495, MPC-6827),[14] a 4-anilinoquinazoline derivative that acts as a microtubule disrupting agent, causing

* Corresponding author. Tel.: +33 235 592 904/148 399; fax: +33 235 148 423; e-mail address: thierry.besson@univ-rouen.fr (T. Besson).

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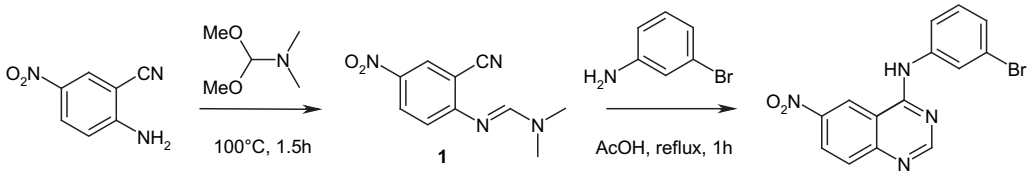
cell cycle arrest and apoptosis in cancer cells. Azixa™ has also been shown to be a vascular disrupting agent. Thus, Azixa™ has a dual mode of action; it induces apoptosis and reduces blood supply to the tumour and is actually in phase II clinical studies in patients with glioblastoma multiform and metastatic melanoma.[15] This paper describes our most recent findings in this field and allows us to present and discuss the mechanism of this chemical reaction.

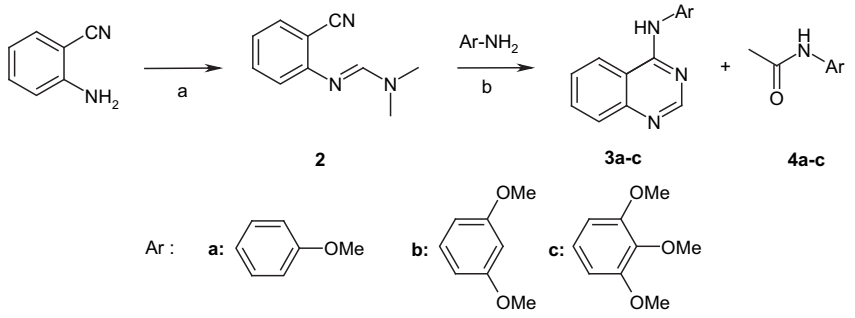
## 2. Results and discussion

Due to the diverse range of the pharmacological activities of quinazolines and their derivatives, there are numerous methods available for their synthesis.[4,13] One of the main route described for 4-anilino-6-nitroquinazolin-4-ones consists of reacting anilines with 4-chloro-6-nitroquinazolines obtained by chlorination with phosphorus oxychloride of the corresponding 6-nitroquinazolinone, which, in turn, is prepared by heating 5-nitroanthranilate with formamide (Niementowski reaction[16]). Nitration of the ring can also be performed after formation of the nude quinazolin-4-one from anthranilate. In our microwave-assisted experiments chlorination step of the nitrated ring was fairly painstaking and required relatively high temperatures. We often observed hydrolysis of a large part of the 4-chloro-6-nitroquinazoline into the starting quinazolin-4-one. Nitration of the 4-chloroquinazoline is also difficult and yielded mainly to the 6-nitroquinazolin-4-one. Checking literature data we observed that 4-chloro-6-nitroquinazoline is normally used without purification for the condensation with aromatic amines, confirming its instability.[4,17]

Looking for an efficient method allowing incorporation of the 4-anilino group during ring cyclisation, Tsou and co-workers[17] have reported the synthesis of a 6-nitro-4-(3-bromophenylamino)quinazoline performed in only two steps via condensation of 3-bromoaniline with an intermediate *N*-(2-cyano-4-nitrophenyl)-*N*,*N*-dimethylimidoformamide (**1**). This compound was obtained by reaction between the commercial 5-nitroanthranilonitrile and DMF-dimethylacetal (Scheme 1).




**Scheme 1.** Reaction described by Tsou and co-workers in 2001.[17]




**Scheme 2.** Microwave-assisted synthesis of 4-anilinoquinazolines from anthranilonitriles. Reagents and conditions: (a) dimethylformamide dimethylacetal, 70 °C (800 W), 2 min, 94%; (b) acetic acid, 118 °C (600 W), 2 min, 93% (**3a**), 94% (**3b**) and 99% (**3c**).

Since 2001, this synthesis was very rarely used. In 2004, a paper from Han and co-workers[18] described a microwave approach for the second step performed in a parallel format. Working at 160 °C in pressurized vials and testing a number of aliphatic amines, it was possible to generate a small library in a short time (10 min). Different solvent conditions compared with the previous reported thermal procedure were also used. This approach was again recently used for the synthesis of intermediate 6-nitroquinazolines.[19]

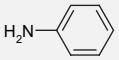
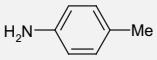
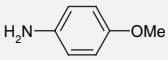
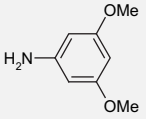
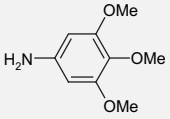
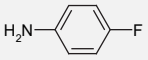
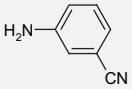
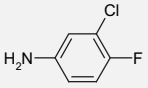
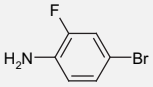
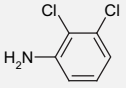
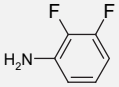
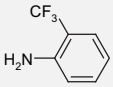
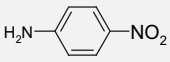
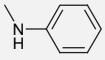
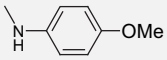
Persuaded that 4-anilino-6-nitroquinazolines would be more easily obtained from 5-nitroanthranilonitrile, our group decided to re-investigate the microwave conditions of the initial reaction described in 2001[17] with the aim to define a well established process allowing high level of reproducibility and also scaling-up for further developments. Our microwave experiments were performed under pressurized conditions using the novel 'hybrid' microwave platform MultiSYNTH (Milestone S.r.l. Italy) or at atmospheric pressure using the multimode platform START SYNHTH (Milestone s.r.l. Italy) equipped with an internal camera, which allows to observe general aspect of the mixture during the reaction (change of colour, formation of crystals, etc.). Reaction conditions were optimized varying applied power and temperature (measured by both, fibre-optic contact thermometer and infrared pyrometer).

Our study started with the synthesis of the intermediate *N*-(2-cyano-4-nitrophenyl)-*N*,*N*-dimethylimidoformamides (**1** and **2**). After optimization of the microwave conditions by varying reaction time, power input, temperature and pressure, we were able to obtain the expected product **1** at 70 °C in only 2 min of irradiation at atmospheric pressure, in almost quantitative yields (90–94% after purification) (Scheme 2). These yields were generally lower when the reaction was performed using longer heating times (more than 5 min) and in pressurized vials at higher temperatures (>130 °C). In this case large quantities of starting anthranilonitrile were recovered in combination with degradation products that were difficult to identify. This result suggested that hydrolysis of **1** can occurs more easily when effects of pressure and temperature are combined. In order to avoid probable by-products generated by this phenomenon, we decided to perform our experiments on the second step of the synthesis at atmospheric pressure in a range of temperature not exceeding 130 °C. It is important to notice that our atmospheric microwave-accelerated method allowed us to extend the scale of this synthesis using up to 70 g of the starting imine. Similar quantities of compound **2** were also prepared at 90 °C in only 15 min.

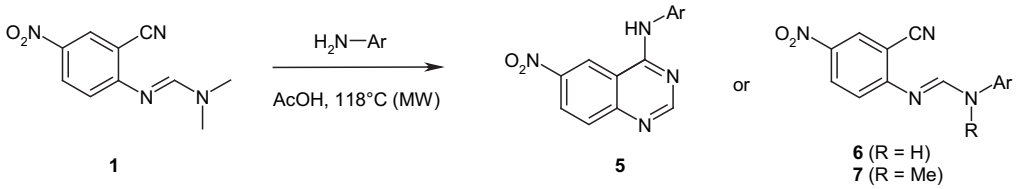
The second step of the synthesis consists in heating different anilines with **1** or **2** in the presence of acetic acid. Applying methods from the literature,[17–19] we firstly studied condensation of **2** with 1.1 or 1.2 equiv of nucleophilic anilines substituted by one, two or three methoxy groups. The evolution of all our experiments was followed by GC/MS chromatography. After various trials to optimize reaction time, temperature and power we were able to obtain, in 2 min, excellent yields (93–99%) of the expected 4-anilinoquinazolines (**3a**–**c**), which were often accompanied by small traces (1–2%) of the acetylated anilines (**4a**–**c**). These latest were easily eliminated by washing the crystallized major product with diethyl ether (Scheme 2). This result suggested us that, in our microwave conditions, acetic acid was able to react rapidly with aromatic amines to form the corresponding acetamides. In order to confirm this hypothesis we decided to observe evolution of the microwave heating of *p*-methoxyaniline alone in solution with acetic acid. After 2 min of irradiation the attempted acetamide was detected in a 28% yield and this value increased with time. Intrigued by this result we also compared our microwave experiments with traditional thermal heating in pre-heated oil bath and we observed that this phenomenon exists in the thermal processes but requires longer reaction time. Then, we may confirm that previous works published in the literature were not able to describe these by-products if the time used was inferior to 1 h. Quantitative yield of **3a** was obtained when 1 equiv of *p*-anisidine reacted with **2** under the condition given above (Scheme 2). In order to complete our study, the same experiment was performed with acetonitrile/acetic acid (7:3, v/v) as solvent.[18] In this case, product **3a** was isolated in 91% yield after 25 min of heating at 100 °C (this value is the highest temperature that can be reached in these conditions, at atmospheric pressure, whatever the value of the microwave power input). Comparing the two methods, we confirmed that the use of acetic acid as the single solvent gave cleaner raw mixtures easier to purify. Replacement of acetic acid by *N*-methylpyrrolidone (NMP) and PTSA (1.1 equiv) was also experimented with success (yield of **3a**: 83%) but in a longer reaction time (25 min) and at a higher temperature (160 °C). Purification of the attempted product was possible after several washing of the organic layer (ethyl acetate) with water followed by column chromatography.

Taking into account these results we were able to optimize and perform the synthesis of a short library of 6-nitroquinazolines (**5a**–**k**) substituted in position 4, in short time and good yields (Scheme 3, Table 1). The reaction of 10 g of amidine **1** with substituted anilines was followed by GC/MS (reaction times given correspond to a complete disappearance of the starting compound **1**) and yields are given after purification. It was also possible to further extend the quantity of starting material up to 50 g. Here again working at atmospheric pressure allowed scaling-up of the reaction in very good conditions of quantities and time. It seems obvious that the result of the reaction depends on the nucleophilicity of the aniline and also on its accessibility in connection with the steric hindrance of the substituents. The presence of electron-attracting groups on the benzene ring and voluminous atoms or groups into the *ortho*-position of the aromatic amine involved an increase in reaction times and lowered the yields (see Table, products **5g**–**m**). Strong withdrawing groups, like nitro group, can stop the cyclisation process, leaving the acetamide as the main product. (e.g., **6** for *p*-$NO_2$). It is important to note that

**Table 1**

| Starting aniline | Reaction time (min)[a] | Product | Yield[b] (%) |
|---|---|---|---|
|  | 3 | **5a** | 88 |
|  | 2 | **5b** | 80 |
|  | 2 | **5c** | 99 |
|  | 2 | **5d** | 97 |
|  | 2 | **5e** | 89 |
|  | 5 | **5f** | 91 |
|  | 7 | **5g** | 82 |
|  | 10 | **5h** | 77 |
|  | 30 | **5i** | 70 |
|  | 90 | **5k** | 60 |
|  | 25 | **5l** | 74 |
|  | 210 | **5m** | 55 |
|  | 30 | **6** | 88 |
|  | 75 | **7a** | 50 |
|  | 45 | **7b** | 53 |

[a] Time for the complete disappearance of **2** (followed by GC/MS chromatography).
[b] After purification by crystallization and washing with diethyl ether.

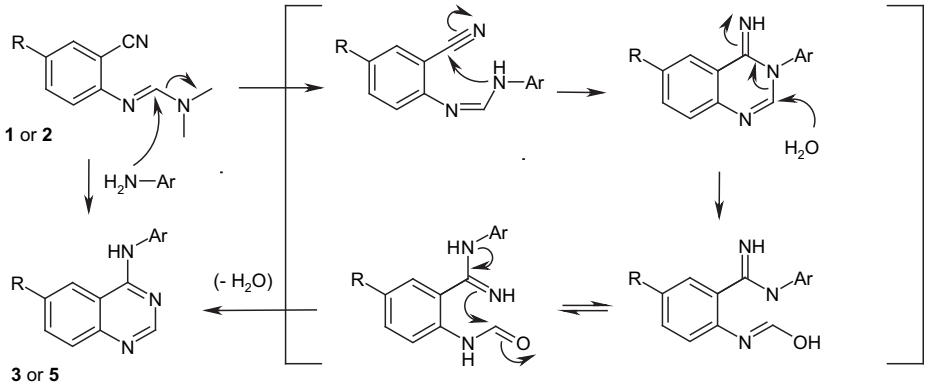



**Scheme 3.** Synthesis of 4-anilino-6-nitroquinazolines: for reaction times and yields see Table 1.

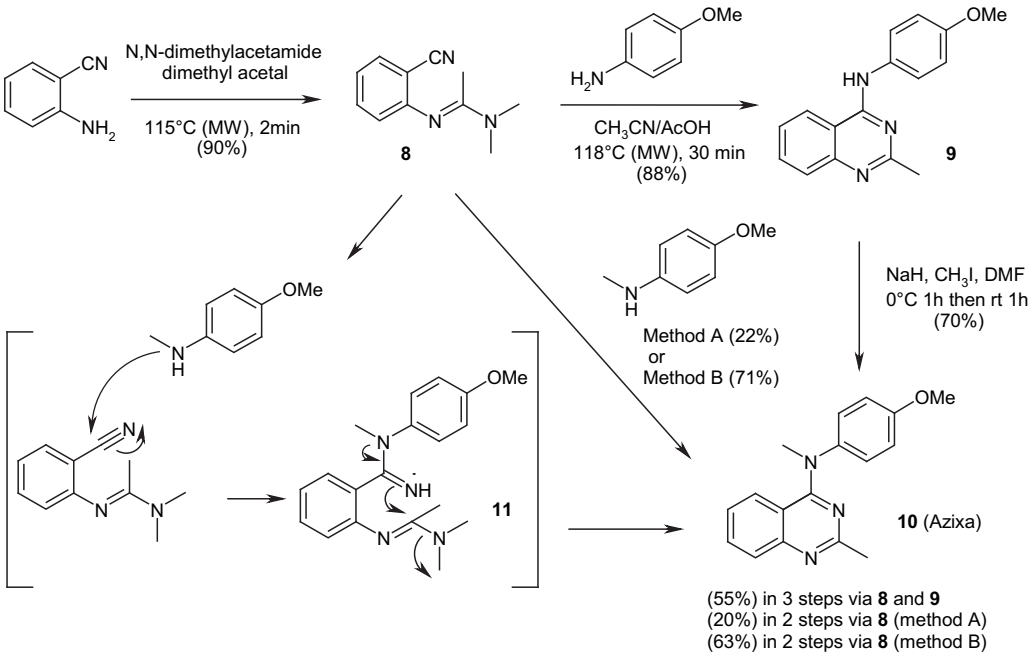
the camera equipped with the microwave was a real enhancement in the capabilities of the instrument; it allowed us to observe changes in the aspect of the mixture. Then, we observed that the reaction can be regarded as finished when crystals started to be formed in the flask.

Interestingly, the formation of compounds **7**, obtained when *N*-methylanilines were condensed with **2**, confirms the mechanism of the reaction which was rarely described in the literature until now.[20] We assume that the first attack of the aromatic amine takes place on the carbon of the *N*,*N*-dimethylamidine and result into ejection of dimethylamine. The intermediate aromatic amidine can then cyclise into a quinazoline skeleton in which the endocyclic and exocyclic nitrogen atoms switched place via a Dimroth rearrangement to afford the attempted 4-anilinoquinazoline (Scheme 4). If a first attack of the amine into the cyano group is possible in theory, it is more difficult in reality despite a probable catalytic action of acetic acid.

Azixa™ [*N*-(4-methoxyphenylamino)-*N*,2-dimethylquinazoline] (**10**) is a small-molecule inhibitor of microtubule formation and was identified as a potent apoptosis inducer.[13–15] Moreover, Azixa™ is not a substrate for Multiple Drug Resistance pumps and is able to cross the blood–brain barrier and accumulate in the brain.[15] These properties make Azixa™ a good candidate for primary and metastatic brain tumours for which treatment are actually limited. It is currently in phase II clinical studies in patients with glioblastoma multiform and metastatic melanoma. The synthesis of this 4-anilinoquinazoline substituted in position 2 by a methyl group was recently described in three steps from 2-aminobenzoic acid methyl ester and acetonitrile via an intermediate chloroimine, which was condensed with *N*-methyl-4-methoxyaniline in anhydrous propanol to give the final product with a total yield of 55%.[13,14] Our method starts from anthranilonitrile, which reacted with *N*,*N*-dimethylacetamide dimethylacetal. Compared the previously synthesized compounds (**1** and **2**) the synthesis of amidine **8** needed more energy due to the steric hindrance of the methyl group. It was obtained in good yield (90%) after 2 min of irradiation at 115 °C. Condensation of 4-methoxyaniline with **8** under the previous conditions described for products **5** needed a longer reaction time of 30 min to afford the quinazoline **9** in an average yield of 56%, together with a significant amount of by-products. In this case heating **8** in a mixture of acetonitrile/acetic acid (7:3, v/v) gave a very good yield (88%) of *N*-(4-methoxyphenylamino)-2-methylquinazoline (**9**). This latter could be further *N*-alkylated to give Azixa™ (**10**), which was purified twice by column chromatography in a good average yield of 55% from the starting anthranilonitrile (Scheme 5).




**Scheme 4.** Mechanism of the reaction involved in the synthesis of 4-anilinoquinazolines from anthranilonitrile.




**Scheme 5.** Synthesis of Azixa™ and suggested mechanism via attack on the carbonitrile function. Method A: AcOH, 140 °C (MW), 6 h (22%); method B: $AlCl_3$ (1.5 equiv), NMP, 200 °C (MW), 2 h (63%).

One of our research activity consist in studying reactions, which need a high level of energy and to see if the intense heating available via microwaves may generate unexpected compounds or help underprivileged mechanisms.[21] Thus, we decided to heat amidine **8** with *N*-methyl-4-methoxyaniline, in the presence of acetic acid. Considering the mechanism described above, it was clear that nucleophilic attack of the secondary amine could be restricted by steric hindrance and we expected only formation of the cyano derivative (**11** in Scheme 5). Evolution of the reaction mixture was followed by GC/MS. Disappearance of the starting compound (**8**) was observed after 6 h (overall reaction time) of microwave heating in sealed vials. In the same time the starting *N*-methyl-*p*-anisidine was mainly transformed into its acetamide derivative. We also detected the carboxylic acid resulting from hydrolysis of the cyano group of **8** and we observed appearance of the starting anthranilonitrile due to its hydrolysis. Addition of 1 equiv of *N*-methyl-*p*-anisidine after 4 h of heating at 140 °C allowed to obtained, after a novel heating period of 2 h, a 22% yield of a compound identified as Azixa™ (**10**) by comparison of the physicochemical data (e.g., NMR, mass spectra, CG profile, mp). This surprising result suggests that the secondary aromatic amine has finally attacked the cyano group present in *ortho*-position of the amidine and that the intermediate compound (**11**) cyclised into the expected product (Scheme 5). To confirm this result, the same reaction was performed from **8** at 200 °C in NMP in the presence of 1.5 equiv of $AlCl_3$ a Lewis acid, which accelerate attack of the aromatic amine by activation of the carbonitrile function.[22] After 2 h of irradiation in a sealed vial, a good yield (71%) of the attempted *N*-(4-methoxyphenylamino)-*N*,2-dimethylquinazoline (**10**) was obtained after purification. This efficient microwave-assisted synthesis of Azixa™ was then performed in only two steps and in a good overall yield of 64%. This novel route provides many advantages over the conventional process,[14] it is more efficient, simple to purify and can be easily extended to a multigram-scale preparation.

## 3. Conclusion

In conclusion, we describe a very useful and rapid method for the synthesis of 4-anilino-6-nitroquinazolines via microwave assisted condensation of the starting anilines with imines obtained by reaction of anthranilonitriles with dimethylformamide dimethylacetal. All these results were applied to perform a novel, short and efficient route to Azixa™, a microtubule destabilizing agent, causing arrest of cell division and apoptosis in cancer cells and currently in phase II clinical studies. The information given in this paper is a further example that microwave heating is a very powerful tool for chemists. Well controlled parameters offer comfortable using of microwave technology with safe and environmental benefits; moreover it allows an easy scale-up to a multi-gram scale. These results are also in accordance with our recent works in which we demonstrated that the intense thermal effect of microwaves may generate underprivileged mechanisms and unexpected products.[21] During synthesis of Azixa™, the high level of energy rapidly available under microwaves allowed to bypass the main mechanism in favour of the unusual alternative, allowing access to the expected products. The strict control of the temperatures reached into the reactor is also a benefit to the overall management of the reaction.

## 4. Experimental section

### 4.1. General

All reactions were monitored by thin-layer chromatography with silica gel 60 $F_{254}$ pre-coated aluminium plates (0.25 mm). Melting points of solid compounds were measured on a WME Köfler hot-stage with a precision of ±2 °C and are uncorrected. IR spectra were recorded on a Perkin–Elmer IRFT 1650 spectrometer. Liquids were applied as a film between KBr windows and solids were dispersed in a KBr pellet. Absorption bands are given in $cm^{-1}$.

$^1H$, $^{13}C$ and $^{19}F$ NMR spectra were recorded on a Brucker DXP 300 spectrometer at 300, 75 and 282 MHz, respectively. Abbreviations used for peak multiplicities are s: singlet, d: doublet, t: triplet, q: quadruplet and m: multiplet. Coupling constants *J* are in Hertz and chemical shifts are given in parts per million and calibrated with DMSO-$d_6$ or $D_2O$ (residual solvent signals). Mass spectra analysis was performed by the Mass Spectrometry Laboratory of the University of Rouen. Mass spectra (EI) were recorded with a Waters LCP 1$^{er}$ XR spectrometer.

Microwave experiments were conducted in two commercial microwave reactors especially designed for synthetic chemistry. The 'hybrid' microwave platform MultiSYNTH™ (Milestone S.r.l. Italy) is a novel dedicated microwave system for synthetic applications. It allows a fast reaction optimization providing high energy density in a single-mode like configuration and an efficient scale-up (maximum working volume 300 mL) through parallel synthesis in a multi-mode configuration. The instrument features a special shaking system that ensures high homogeneity of the reaction mixtures. It is equipped with an indirect pressure-control through pre-calibrated springs at the bottom of the vessels shields and with both, contact-less infrared pyrometer (IRT) and fibre-optic contact thermometer (FO) for accurate temperature measurement. It is noteworthy that the IRT can be calibrated directly on the temperature read by the FO to ensure the highest accuracy and reproducibility.

START SYNTH (Milestone S.r.l. Italy) is a multimode cavity with a microwave power delivery system ranging from 0 to 1200 W. Open vessel experiments were carried out in a 250 mL round bottom flask fitted with a reflux condenser. The temperature was monitored via a fibre-optic contact thermometer protected in a Teflon coated ceramic well inserted directly in the reaction mixture. The vessel contents were stirred by means of an adjustable rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar inside the vessel. Temperature, pressure and power profiles were monitored in both cases through the EASY-Control software provided by the manufacturer.

*4.1.1. N′-(2-Cyanophenyl)-N,N-dimethylformamidine (**1**) (lit.[17]).* A suspension of anthranilonitrile (50.0 g, 0.42 mol) was suspended in dimethylformamide dimethylacetal (125 mL, 1.05 mol, 2.5 equiv) was irradiated at 90 °C (power input: 600 W) for 15 min. The resulting mixture was cooled to room temperature and purified by column chromatography over silica gel using $CH_2Cl_2$/EtOAc (8:2, v/v) as the eluent to give the desired compound **1** (68.0 g, 94% yield) as a pale yellow solid; mp 66 °C; IR (KBr) $\nu_{max}/cm^{-1}$ 2912, 2215, 1979, 1628, 1588, 1557, 1474, 1447, 1415, 1366, 1280, 1254, 1222, 1172, 1118, 1098, 969, 942, 870, 846, 758, 736; $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.91 (s, 1H, NC*H*N), 7.59 (dd, 1H, $J_1$=1.5 Hz, $J_2$=7.5 Hz, H-6), 7.49 (td, 1H, $J_1$=1.2 Hz, $J_2$=8.4 Hz, H-5), 7.14 (d, 1H, $J$=8.4 Hz, H-3), 7.02 (t, 1H, $J$=7.5 Hz, H-4), 3.06 (s, 3H, NC*H*$_3$), 2.98 (s, 3H, NC*H*$_3$); $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta$ 154.9, 154.5, 133.5, 132.8, 121.5, 118.8, 118.4, 105.9, 36.6, 33.9; HRMS calcd for $C_{10}H_{12}N_3$ $[M+H]^+$ 174.1031 found 174.1040.

*4.1.2. N′-(2-Cyano-4-nitrophenyl)-N,N-dimethylformamidine (**2**) (lit.[17]).* A suspension of 5-nitroanthranilonitrile (70.0 g, 0.43 mol) in dimethylformamide dimethylacetal (129 mL, 1.08 mol, 2.5 equiv) was irradiated at 70 °C (power input: 800 W) during 2 min. The resulting mixture was cooled to room temperature and refrigerated overnight. The orange precipitate formed was filtered, washed with ethyl ether and dried to give **2** (87.9 g, 94% yield) as an orange solid; mp 148–150 °C dec; IR (KBr) $\nu_{max}/cm^{-1}$ 2971, 2901, 2224, 1623, 1593, 1558, 1499, 1414, 1374, 1310, 1280, 1170, 1141, 1076, 922, 888, 829, 776, 754, 726, 658; $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.42 (s, H-3), 8.24 (m, 2H, NC*H*N and H-5), 7.34 (d, 1H, $J$=9 Hz, H-6), 3.16 (s,

3H, NC$H_3$), 3.07 (s, 3H, NC$H_3$); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 161.0, 156.5, 139.9, 129.3, 128.5, 118.1, 116.8, 105.9, 40.4, 34.4; HRMS calcd for $C_{10}H_{11}N_4O$ $[M+H]^+$ 219.0882 found 219.0873.

### 4.2. Synthesis of the 4-arylaminoquinazolines (3a–c)

A mixture of *N*′-(2-cyanophenyl)-*N*,*N*-dimethylformamidine **1** (0.5 g, 2.89 mmol) and appropriate aniline (1.0 equiv) in acetic acid (3 mL) was irradiated at 118 °C (power input: 600 W) for 2 min. On completion, the reaction was cooled to ambient temperature. The resulting mixture was cooled to room temperature and purified by column chromatography over silica gel using $CH_2Cl_2$/EtOAc (80–20) as the eluent to give the desired compounds **4a**–**c**.

*4.2.1. N-(4-Methoxyphenyl)quinazolin-4-amine (**3a**).* Yield: 93%; yellow solid, mp 165 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3242, 3076, 2952, 2832, 1682, 1619, 1598, 1576, 1529, 1513, 1496, 1461, 1420, 1396, 1360, 1323, 1299, 1236, 1177, 1163, 1126, 1102, 1072, 1038, 974, 924, 857, 820, 778, 764, 753, 707, 683, 645, 629; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.74 (s, 1H, NH), 8.53 (d, 1H, *J*=9 Hz), 7.82–7.74 (m, 2H), 7.71 (d, 2H, *J*=8.7 Hz), 7.62 (t, 1H, *J*=7.5 Hz), 6.98 (d, 2H, *J*=8.7 Hz), 3.76 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 157.9, 155.9, 154.7, 149.6, 132.9, 131.9, 127.8, 126.1, 124.5, 122.9, 115.1, 113.7, 55.3; HRMS calcd for $C_{15}H_{14}N_3O$ $[M+H]^+$ 252.1137 found 252.1133.

*4.2.2. N-(3,5-Dimethoxyphenyl)quinazolin-4-amine (**3b**).* Yield: 94%; yellow solid, mp 142 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3380, 2945, 2836, 1699, 1609, 1573, 1529, 1501, 1476, 1457, 1427, 1388, 1356, 1234, 1205, 1155, 1078, 1052, 973, 932, 908, 855, 826, 800, 776, 680, 628, 602; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.67 (s, 1H, NH), 8.65 (s, 1H), 8.58 (d, 1H, *J*=8.1 Hz), 7.87–7.78 (m, 2H), 7.65 (t, 1H, *J*=7.2 Hz), 7.25 (s, 2H), 6.30 (s, 1H), 3.77 (s, 6H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 160.4, 157.8, 154.5, 149.7, 141.1, 132.9, 127.9, 126.2, 123.0, 115.4, 100.5, 95.5, 55.2; HRMS calcd for $C_{16}H_{16}N_3O_2$ $[M+H]^+$ 282.1243 found 282.1242.

*4.2.3. N-(3,4,5-Trimethoxyphenyl)quinazolin-4-amine (**3c**).* >Yield: 99%; white solid, mp 186 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3210, 3100, 3004, 2937, 2840, 2371, 1977, 1693, 1658, 1594, 1539, 1509, 1453, 1419, 1382, 1342, 1236, 1127, 1083, 1001, 871, 842, 824, 773, 689, 673, 608; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.69 (s, 1H, NH), 8.61 (s, 1H), 8.55 (d, 1H, *J*=8.1 Hz), 7.87–7.77 (m, 2H), 7.65 (t, 1H, *J*=7.2 Hz), 7.32 (s, 2H), 3.80 (s, 6H), 3.67 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 157.8, 154.6, 152.6, 149.6, 135.3, 133.9, 133.0, 127.9, 126.3, 122.9, 115.2, 100.3, 60.2, 55.9; HRMS calcd for $C_{17}H_{18}N_3O_3$ $[M+H]^+$ 312.1348 found 312.1368.

### 4.3. Synthesis of the 6-nitro-4-arylaminoquinazolines (5a–m)

A mixture of *N*′-(2-cyano-4-nitrophenyl)-*N*,*N*-dimethylformamidine **2** (1.0 g, 4.58 mmol) and appropriate aniline (1.0 equiv) in acetic acid (5 mL) was irradiated at 118 °C (power input: 600 W). On completion (followed by TLC or GC/MS chromatography), the reaction was cooled to ambient temperature. The separated solid was filtered and washed with diethyl ether to obtain the expected compounds **5a**–**m**, **6** and **7a**–**b**. Some of the reaction mixtures needed to be triturated in hexane/ethyl acetate (1:1, v/v) before crystallization and washing.

*4.3.1. 6-Nitro-N-phenylquinazolin-4-amine (**5a**) (lit.[12]).* Yield: 88%; yellow solid, mp 239 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3281, 3026, 1947, 1629, 1610, 1582, 1535, 1493, 1448, 1417, 1389, 1336, 1239, 1192, 1130, 1115, 932, 899, 853, 807, 755, 693, 633; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.4 (s, 1H, NH), 9.62 (d, 1H, *J*=2.1 Hz), 8.67 (s, 1H), 8.52 (dd, 1H, $J_1$=2.1 Hz, $J_2$=9.3 Hz), 7.89–7.81 (m, 3H), 7.45 (t, 2H, *J*=7.5 Hz), 7.21 (t, 1H, *J*=7.5 Hz); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 158.7, 157.7, 153.0, 144.4, 138.4, 129.4, 128.5, 126.5, 125.3, 124.5, 122.9, 120.8, 114.3; HRMS calcd for $C_{14}H_{11}N_4O_2$ $[M+H]^+$ 266.0811 found 266.0813.

*4.3.2. N-(4-Methylphenyl)-6-nitro-quinazolin-4-amine (**5b**) (lit.[12]).* Yield: 79%; orange solid, mp 210 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3389, 3285, 3092, 3038, 1626, 1587, 1567, 1535, 1492, 1426, 1390, 1361, 1337, 1266, 1236, 1192, 1115, 1062, 975, 934, 900, 849, 810, 744, 677, 635, 618; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.4 (s, 1H, NH), 9.62 (d, 1H, *J*=2.3 Hz), 8.66 (s, 1H), 8.53 (dd, 1H, $J_1$=2.4 Hz, $J_2$=9.2 Hz), 7.89 (d, 1H, *J*=9.2 Hz), 7.70 (d, 2H, *J*=7.8 Hz), 7.23 (d, 2H, *J*=7.8 Hz), 2.32 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 158.8, 157.8, 153.1, 144.4, 135.8, 133.8, 129.4, 128.9, 126.6, 123.0, 120.9, 114.4; HRMS calcd for $C_{15}H_{13}N_4O_2$ $[M+H]^+$ 280.1003 found 280.1011.

*4.3.3. N-(4-Methoxyphenyl)-6-nitroquinazolin-4-amine (**5c**) (lit.[12]).* Yield: 99%; orange solid, mp 198–200 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3412, 3305, 3099, 1981, 1681, 1622, 1609, 1590, 1573, 1547, 1513, 1493, 1463, 1435, 1393, 1359, 1334, 1235, 1181, 1114, 1025, 943, 931, 899, 884, 847, 832, 808, 744, 679, 665, 625,624; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.3 (s, 1H, NH), 9.56 (d, 1H, *J*=2.1 Hz), 8.59 (s, 1H), 8.49 (dd, 1H, $J_1$=1.8 Hz, $J_2$=9.0 Hz), 7.85 (d, 1H, *J*=9.3 Hz), 7.68 (d, 2H, *J*=8.7 Hz), 6.99 (d, 2H, *J*=8.7 Hz), 3.77 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 172.1, 158.8, 157.9, 156.4, 153.1, 144.3, 131.2, 129.3, 126.4, 124.7, 120.8, 114.3, 113.7, 55.3; HRMS calcd for $C_{15}H_{13}N_4O_3$ $[M+H]^+$ 296.0913 found 296.0920.

*4.3.4. N-(3,5-Dimethoxyphenyl)-6-nitroquinazolin-4-amine (**5d**).* Yield: 97%; yellow solid, mp 220 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3372, 3079, 3005, 2939, 2841, 1694, 1621, 1586, 1531, 1494, 1462, 1409, 1385, 1362, 1327, 1289, 1225, 1202, 1154, 1111, 1072, 1051, 957, 932, 917, 900, 858, 846, 824, 810, 785, 746, 704, 676, 637, 620; $^{19}$F NMR (282 MHz, DMSO-$d_6$) $\delta$ −138.3, −142.6; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.2 (s, 1H, NH), 9.60 (d, 1H, *J*=1.8 Hz), 8.71 (s, 1H), 8.52 (dd, 1H, $J_1$=1.8 Hz, $J_2$=9.0 Hz), 7.89 (d, 1H, *J*=9.3 Hz), 7.16 (m, 2H), 6.31 (m, 2H), 3.76 (s, 6H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 160.3, 158.8, 157.6, 153.1, 144.6, 140.1, 129.6, 126.7, 120.8, 114.5, 101.0, 96.3, 55.3; HRMS calcd for $C_{16}H_{15}N_4O_4$ $[M+H]^+$ 326.1076 found 326.1070.

*4.3.5. 6-Nitro-N-(3,4,5-trimethoxyphenyl)quinazolin-4-amine (**5e**).* Yield: 89%; red solid, mp 258 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3426, 3075, 2994, 2933, 2838, 1620, 1574, 1539, 1517, 1486, 1461, 1446, 1433, 1406, 1388, 1361, 1351, 1332, 1246, 1224, 1192, 1131, 1113, 1071, 998, 934, 911, 888, 853, 831, 809, 794, 785, 746, 678, 651, 633, 619, 604; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.3 (s, 1H, NH), 9.58 (d, 1H, *J*=1.8 Hz), 8.69 (s, 1H), 8.52 (dd, 1H, $J_1$=1.8 Hz, $J_2$=9.0 Hz), 7.89 (d, 1H, *J*=9.3 Hz), 7.26 (m, 2H), 3.81 (s, 6H), 3.68 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 160.3, 158.6, 157.7, 153.0, 152.6, 144.4, 134.5, 134.4, 129.5, 126.5, 120.7, 114.4, 100.7, 60.2, 55.9; HRMS calcd for $C_{17}H_{17}N_4O_5$ $[M+H]^+$ 356.1188 found 356.1187.

*4.3.6. N-(4-Fluorophenyl)-6-nitroquinazolin-4-amine (**5f**) (lit.[12]).* Yield: 91%; yellow solid, mp 252 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3369, 3106, 3011, 1732, 1621, 1583, 1513, 1489, 1420, 1389, 1361, 1335, 1223, 1194, 1157, 1115, 928, 895, 869, 858, 827, 807, 796, 768, 746, 682, 653, 633; $^{19}$F NMR (282 MHz, DMSO-$d_6$) $\delta$ −117.8; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.48 (s, 1H, $_N$H), 9.63 (d, 1H, *J*=8.8 Hz), 8.69 (s,1H), 8.56 (dd, 1H, $J_1$=2.3 Hz, $J_2$=9.2 Hz), 7.93 (d, 1H, *J*=8.8 Hz), 7.81–7.86 (m, 2H), 7.28 (t, 2H, *J*=8.8 Hz); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 159.3, 158.1, 153.5, 144.9, 135.1, 129.9, 127.1, 125.4, 121.2, 115.8, 115.5, 114.7; HRMS calcd for $C_{14}H_{10}N_4O_2F$ $[M+H]^+$ 285.0786 found 285.0776.

*4.3.7. 3-(6-Nitroquinazolin-4-ylamino)benzonitrile (**5g**).* Yield: 82%; pale yellow solid, mp>260 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3349, 3273, 3089, 2228, 1755, 1724, 1627, 1581, 1542, 1495, 1474, 1443, 1411, 1388, 1361, 1338, 1251, 1146, 1113, 947, 925, 900, 857, 803, 745, 679, 631; $^1$H

NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.1 (s, 1H, NH), 9.36 (d, 1H, $J$=2.4 Hz), 8.84 (s, 1H), 8.63 (dd, 1H, $J_1$=2.4 Hz, $J_2$=9.0 Hz), 8.53 (s, 1H), 8.22 (m, 1H), 8.04 (d, 1H, $J$=9.3 Hz), 7.67–7.56 (m, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 159.7, 158.2, 154.2, 146.2, 140.8, 130.9, 130.7, 128.4, 127.5, 127.3, 125.9, 120.9, 119.3, 115.6, 113.3; HRMS calcd for $C_{15}H_{10}N_5O_2$ $[M+H]^+$ 292.0834 found 292.0833.

*4.3.8. N-(3-Chloro-4-fluorophenyl)-6-nitroquinazolin-4-amine (**5h**) (lit.[19a]).* Yield: 84%; yellow solid; mp>260 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 1736, 1624, 1585, 1572, 1536, 1510, 1495, 1485, 1423, 1364, 1340, 1263, 1216, 1115, 854, 808, 778, 746; $^{19}$F NMR (282 MHz, DMSO-$d_6$) $\delta$ −121.6; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.3 (s, 1H, NH), 9.47 (d, 1H, $J$=2.1 Hz), 8.66 (s, 1H), 8.46 (dd, 1H, $J$=6.6 Hz, $J$=2.1 Hz), 8.09 (dd, 1H, $J$=9.0 Hz, $J$=2.1 Hz), 7.82 (d, 1H, $J$=9.0 Hz), 7.78 (m, 1H), 7.4 (t, 1H, $J$=9.0 Hz); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 158.4, 157.4, 152.8, 144.5, 135.8, 129.5, 126.6, 124.1, 122.9, 120.6, 119.0, 118.8, 116.8, 116.5, 114.3; HRMS calcd for $C_{14}H_9N_4O_2FCl$ $[M+H]^+$ 319.0398 found 319.0382.

*4.3.9. N-(4-Bromo-2-fluorophenyl)-6-nitroquinazolin-4-amine (**5i**).* Yield: 70%; yellow solid, mp 212 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3385, 3030, 2359, 1621, 1585, 1568, 1525, 1494, 1480, 1413, 1387, 1362, 1345, 1316, 1229, 1185, 1129, 1112, 1079, 1056, 979, 931, 899, 874, 844, 807, 800, 781, 745, 677, 634; $^{19}$F NMR (282 MHz, DMSO-$d_6$) $\delta$ −115.0; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.6 (s, 1H, NH), 9.49 (d, 1H, $J$=1.5 Hz), 8.58 (s, 1H), 8.53 (dd, 1H, $J_1$=1.2 Hz, $J_2$=9.0 Hz), 7.91 (d, 1H, $J$=9.3 Hz), 7.69 (d, 1H, $J$=9.9 Hz), 7.54–7.46 (m, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 159.1, 158.2, 157.3, 154.9, 152.6, 144.5, 129.5, 129.2, 127.7, 127.6, 126.8, 125.9, 120.9, 119.7, 119.4, 118.7, 118.5, 114.3; HRMS calcd for $C_{14}H_9N_4O_2FBr$ $[M+H]^+$ 362.9893 found 362.9897.

*4.3.10. N-(2,3-Dichlorophenyl)-6-nitroquinazolin-4-amine (**5k**).* Yield: 60%; yellow solid, mp 182 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3408, 3087, 1682, 1622, 1585, 1537, 1488, 1450, 1431, 1415, 1389, 1362, 1337, 1297, 1196, 1121, 1063, 1042, 967, 945, 898, 884, 853, 809, 785, 743, 702, 692, 673, 633, 607; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.9 (s, 1H, NH), 9.46 (d, 1H, $J$=2.1 Hz), 8.54 (dd, 1H, $J_1$=2.7 Hz, $J_2$=9.3 Hz), 8.48 (s, 1H), 7.88 (d, 1H, $J$=9.3 Hz), 7.58–7.55 (m, 1H), 7.47–7.39 (m, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 151.9, 144.4, 132.2, 128.2, 127.3, 126.6, 120.8; HRMS calcd for $C_{14}H_9Cl_2N_4O_2$ $[M+H]^+$ 334.0029 found 334.0013.

*4.3.11. N-(2,3-Difluorophenyl)-6-nitroquinazolin-4-amine (**5l**).* Yield: 74%; yellow solid, mp 220 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3365, 3095, 3012, 2358, 1694, 1624, 1584, 1568, 1525, 1513, 1497, 1474, 1410, 1382, 1363, 1338, 1282, 1251, 1232, 1197, 1160, 1131, 1118, 1073, 1060, 1011, 923, 898, 858, 833, 811, 803, 771, 746, 723, 702, 683, 650, 631; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.7 (s, 1H, NH), 9.51 (d, 1H, $J$=1.8 Hz), 8.61 (s, 1H), 8.56 (dd, 1H, $J_1$=1.8 Hz, $J_2$=9.0 Hz), 7.93 (d, 1H, $J$=9.0 Hz), 7.35–7.26 (m, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 158.9, 157.3, 152.5, 152.1, 151.9, 148.9, 148.7, 146.7, 146.5, 144.5, 143.4, 143.2, 129.1, 128.7, 128.6, 126.8, 124.4, 124.3, 124.2, 124.1, 123.1, 123.0, 121.0, 114.8, 114.6, 114.5; HRMS calcd for $C_{14}H_9F_2N_4O_2$ $[M+H]^+$ 302.0609 found 302.0603.

*4.3.12. 6-Nitro-N-(2-(trifluoromethyl)phenyl)quinazolin-4-amine (**5m**).* Yield: 55%; yellow solid, mp 178 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3361, 3240, 3083, 1623, 1586, 1573, 1519, 1488, 1458, 1413, 1387, 1363, 1338, 1316, 1236, 1196, 1166, 1115, 1064, 1053, 1035, 933, 901, 865, 851, 812, 796, 767, 747, 737, 684, 663, 648, 633; $^{19}$F NMR (282 MHz, DMSO-$d_6$) $\delta$ −59.50; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.6 (s, 1H, NH), 9.62 (s, 1H), 8.55 (s, 1H), 8.49 (dd, 1H, $J_1$=1.7 Hz, $J_2$=9.1 Hz), 7.97 (d, 1H, $J$=8.9 Hz), 7.83–7.54 (m, 4H); HRMS calcd $C_{15}H_{10}F_3N_4O_2$ $[M+H]^+$ 334.0734 found 334.0725.

*4.3.13. N′-(2-Cyano-4-nitrophenyl)-N-(4-nitrophenyl)formamidine (**6**).* Yield: 88%; orange solid, mp>260 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3084, 2225, 1627, 1572, 1504, 1418, 1376, 1331, 1282, 1246, 1173, 1112, 1079, 923, 890, 850, 830, 810, 748; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.60 (d, 1H, $J$=2.7 Hz), 8.53 (s, 1H), 8.32 (dd, 1H, $J_1$=2.7 Hz, $J_2$=9.0 Hz), 7.69 (d, 1H, $J$=9.0 Hz), 7.45 (d, 2H, $J$=8.7 Hz), 7.10 (d, 2H, $J$=9.0 Hz); HRMS calcd for $C_{14}H_{10}N_5O_4$ $[M+H]^+$ 311.0701 found 311.0711.

*4.3.14. N′-(2-Cyano-4-nitrophenyl)-N-methyl-N-phenylformamidine (**7a**).* Yield: 49%; orange solid, mp 186 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3055, 2233, 1623, 1588, 1564, 1511, 1490, 1418, 1330, 1310, 1263, 1229, 1171, 1125, 1077, 1031, 985, 922, 908, 835, 760, 750, 729, 692, 665; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.62 (d, 1H, $J$=2.1 Hz), 8.58 (s, 1H), 8.34 (dd, 1H, $J_1$=2.1 Hz, $J_2$=9.0 Hz), 7.65 (d, 1H, $J$=9.0 Hz), 7.53–7.43 (m, 4H), 7.30 (t, 1H, $J$=7.2 Hz), 3.56 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 159.6, 154.6, 143.6, 141.5, 129.5, 129.2, 128.7, 125.6, 120.9, 120.2, 116.6, 106.8, 34.3; HRMS calcd for $C_{15}H_{13}N_4O_2$ $[M+H]^+$ 280.1048 found 280.1039.

*4.3.15. N′-(2-cyano-4-nitrophenyl)-N-(4-methoxyphenyl)-N-methylformamidine (**7b**).* Yield: 53%; orange solid, mp 132 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3008, 2939, 2837, 2228, 1620, 1589, 1561, 1496, 1442, 1417, 1333, 1292, 1261, 1247, 1228, 1187, 1171, 1128, 1074, 1029, 991, 969, 920, 905, 842, 828, 809, 786, 752, 735, 653; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.54 (d, 1H, $J$=2.7 Hz), 8.49 (s, 1H), 8.30 (dd, 1H, $J_1$=2.7 Hz, $J_2$=9.0 Hz), 7.60 (d, 1H, $J$=9.0 Hz), 7.44 (d, 2H, $J$=8.7 Hz), 7.02 (d, 2H, $J$=9.0 Hz), 3.77 (s, 3H), 3.51 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 159.7, 157.4, 154.7, 141.2, 136.9, 129.2, 128.7, 122.9, 119.9, 116.7, 114.6, 106.7, 55.5, 34.9; HRMS calcd for $C_{16}H_{15}N_4O_3$ $[M+H]^+$ 310.1155 found 310.1159.

### 4.4. Synthesis of *N*-(4-methoxyphenyl)-*N*,2-dimethylquinazolin-4-amine (10) (Azixa™)

*4.4.1. N′-(2-cyanophenyl)-N,N-dimethylacetamidine (**8**).* A suspension of anthranilonitrile (2.0 g, 16.9 mmol) in *N*,*N*-dimethylacetamide dimethylacetal (5.6 g, 42.3 mmol, 2.5 equiv) was irradiated at 115 °C (power input: 1000 W) for 2 min. The resulting mixture was cooled to room temperature and refrigerated overnight. The white precipitate that formed was filtered, washed with petroleum ether and dried to give **8** (2.8 g, 88% yield), as white needles; mp 68 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 2932, 2215, 1971, 1913, 1747, 1588, 1553, 1463, 1443, 1401, 1364, 1315, 1220, 1192, 1168, 1100, 1060, 1023, 960, 875, 839, 783, 756, 721; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.61 (d, 1H, $J$=7.5 Hz), 7.50 (t, 1H, $J$=7.5 Hz), 7.01 (t, 1H, $J$=7.8 Hz), 6.79 (d, 1H, $J$=8.1 Hz), 3.00 (s, 6H), 1.88 (s, 3H); HRMS calcd for $C_{11}H_{14}N_3$ $[M+H]^+$ 187.1179 found 187.1178.

*4.4.2. N-(4-Methoxyphenyl)-2-methylquinazolin-4-amine (**9**) (lit.[14b]).* *p*-Anisidine (0.18 g, 1.46 mmol, 1.1 equiv) was added to a suspension of *N′*-(2-cyanophenyl)-*N*,*N*-dimethylacetamidine **8** (0.25 g, 1.33 mmol) in AcOH/ACN (3:7, v/v). The resulting mixture was irradiated at 118 °C (power input: 600 W) for 60 min and cooled to room temperature. Purification by column chromatography over silica gel using $CH_2Cl_2$/EtOAc (1:1, v/v) as the eluent gave the desired compound **9** (0.31 g, 88% yield), as a white solid; mp 170 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$ 3053, 2958, 2837, 1619, 1598, 1573, 1513, 1464, 1422, 1386, 1354, 1293, 1238, 1182, 1170, 1132, 1104, 1032, 1001, 883, 825, 794, 770, 738, 681, 644, 628; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.58 (s, 1H, NH), 8.48 (d, 1H, $J$=8.1 Hz), 7.78–7.75 (m, 3H), 7.67 (d, 1H, $J$=8.1 Hz), 7.54 (t, 1H, $J$=7.5 Hz), 6.98 (d, 2H, $J$=8.7 Hz), 3.77 (s, 3H), 2.47 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 163.0, 157.7, 155.6, 150.2, 132.7, 132.3, 127.2, 125.1, 123.9, 122.8, 113.6, 113.2, 55.2, 26.3; HRMS calcd for $C_{16}H_{16}N_3O$ $[M+H]^+$ 266.1352 found 266.1308.

*4.4.3. N-(4-Methoxyphenyl)-N,2-dimethylquinazolin-4-amine (**10**) (Azixa™) (lit.[14b]).*

*4.4.3.1. From N-(4-methoxyphenyl)-2-methylquinazolin-4-amine **9**.* A suspension of *N*-(4-methoxyphenyl)-2-methylquinazolin-4-amine **9** (0.1 g, 0.38 mmol) in DMF (10 mL) was cooled to 0 °C. Then NaH (60% in mineral oil, 0.029 g, 0.76 mmol, 2.0 equiv) and $CH_3I$

(1.4 mL, 9.12 mmol, 24.0 equiv) were added. The reaction mixture was stirred at 0 °C for 1 h and warmed to room temperature (1 h). The reaction was quenched by adding 0.5 mL of water and diluted with ethyl acetate. The organic phase was washed with water and saturated NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by chromatography on silica gel with EtOAc as the eluent to afford **10** (0.074 g, 70%) as a pale yellow solid.

*4.4.3.2. From N′-(2-cyanophenyl)-N,N-dimethylacetamidine **8** in acetic acid.* *N*-Methyl-*p*-anisidine (0.20 g, 1.46 mmol, 1.1 equiv) was added to a suspension of *N′*-(2-cyanophenyl)-*N*,*N*-dimethylacetamidine **8** (0.25 g, 1.33 mmol) in AcOH (1.5 mL). The resulting mixture was irradiated at 140 °C (power input: 200 W) in a sealed tube for 4 h. (evolution of the reaction was estimed by GC/MS chromatography). *N*-Methyl-*p*-anisidine (0.20 g, 1.46 mmol, 1.1 equiv) was added to the reaction and the resulting mixture was irradiated again at 140 °C for 2 h. The reaction was cooled to ambient temperature and then solvent was evaporated under reduced pressure. The residue was purified by column chromatography over silica gel using $CH_2Cl_2$/EtOAc (20–80) as the eluent to give the desired compounds **10** (0.082 g, 22%) as a pale yellow solid.

*4.4.3.3. From N′-(2-cyanophenyl)-N,N-dimethylacetamidine **8** in NMP in the presence of $AlCl_3$.* To a suspension of *N′*-(2-cyanophenyl)-*N*,*N*-dimethylacetamidine **8** (0.25 g, 1.33 mmol) in NMP (1.5 mL) was added *N*-methyl-*p*-anisidine (0.27 g, 1.99 mmol, 1.5 equiv) and anhydrous aluminium chloride (0.26 g, 1.99 mmol, 1.5 equiv). The resulting mixture was irradiated at 200 °C (power input: 200 W) for 2 h and cooled to room temperature. The reaction mixture was diluted with ethyl acetate. The organic phase was washed with water and saturated NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by chromatography on silica gel with EtOAc as the eluent to afford **10** as a pale yellow solid (0.26 g, 71%); mp 86–90 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.53 (d, 1H, $J$=8.1 Hz), 7.57 (td, 1H, $J_1$=0.9 Hz, $J_2$=6.9 Hz), 7.20 (d, 2H, $J$=8.7 Hz), 7.05 (td, 1H, $J_1$=0.9 Hz, $J_2$=6.9 Hz), 6.99–6.94 (m, 3H), 3.77 (s, 3H), 3.48 (s, 3H), 2.58 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 162.3, 161.0, 157.6, 151.7, 141.0, 131.9, 127.5, 127.2, 125.7, 124.1, 115.3, 114.2, 55.4, 42.4, 26.2; HRMS calcd for $C_{17}H_{18}N_3O$ $[M+H]^+$ 280.3360 found 280.3357.

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