A new DMAP-catalyzed and microwave-assisted approach for introducing heteroarylamino substituents at position 4 of the quinazoline ring.

Armand Gellis, Charline Kieffer, Nicolas Primas, Gilles Lanzada, Michel Giorgi, Pierre Verhaeghe, Patrice Vanelle

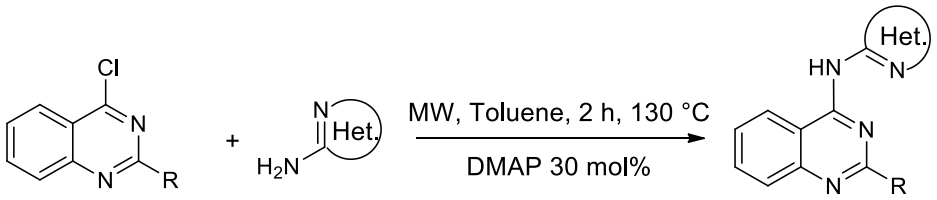
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

A new DMAP-catalyzed and microwave-assisted approach for introducing heteroarylamino substituents at position 4 of the quinazoline ring.

Leave this area blank for abstract info.

Armand Gellis[a], Charline Kieffer[a], Nicolas Primas[a], Gilles Lanzada[a], Michel Giorgi[b], Pierre Verhaeghe[c], Patrice Vanelle[a]



Tetrahedron Letters
journal homepage: www.elsevier.com

A new DMAP-catalyzed and microwave-assisted approach for introducing heteroarylamino substituents at position 4 of the quinazoline ring.

Armand Gellis[a], Charline Kieffer[a], Nicolas Primas[a], Gilles Lanzada[a], Michel Giorgi[b], Pierre Verhaeghe[c] and Patrice Vanelle[a] *

[a] *Aix-Marseille Université, CNRS, ICR, UMR 7273, Laboratoire de Pharmacochimie Radicalaire, Faculté de Pharmacie, 27 Bd Jean Moulin - CS30064, 13385 Marseille cedex 05, France.*
[b] *Aix-Marseille Université, CNRS, Spectropole FR 1739, 13397 Marseille cedex 20, France.*
[c] *Université Paul Sabatier, Faculté des Sciences Pharmaceutiques, Laboratoire de Chimie de Coordination UPR 8241 CNRS, 205 Route de Narbonne, 31400 Toulouse, France.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Quinazoline ring
Pharmaceutical chemistry
Heteroaryl moiety
DMAP
Microwave

ABSTRACT

We report herein a new methodology for synthesizing quinazoline derivatives bearing an heteroarylamino moiety at position 4 of the quinazoline ring. As an alternative to the Buchwald-Hartwig cross-coupling reaction which appears, until now, as the only efficient way to react 4-chloroquinazolines with numerous amino nitrogen-containing heterocycles displaying poor nucleophilicity, we developed a DMAP-catalyzed reaction involving microwave irradiation. Optimization of the reaction conditions led to the use of 30 mol% of DMAP in toluene, using a monomode microwave reactor and sealed vials. Moreover, the S_NAr reaction intermediate salt was isolated and fully characterized. Finally, the procedure was extended to two different 2-substitued-quinazoline series and also to various anilines, demonstrating that this approach was a general efficient way to access to such 4-substituted quinazoline scaffolds of high pharmaceutical interest.

1. Introduction

Quinazoline is the core ring of numerous drug compounds which scaffold always includes an amino or anilino substituent at position 4 of the quinazoline ring. Thus, prazosine, alfusozine, terazosine and doxazosine form an homogeneous group of α_1-receptor blockers used in the treatment of both benign prostatic hyperplasia and hypertension while erlotinib, gefitinib, lapatinib and vandetanib constitute a major subfamily of kinase inhibitor anti-cancer agents (Fig. 1).

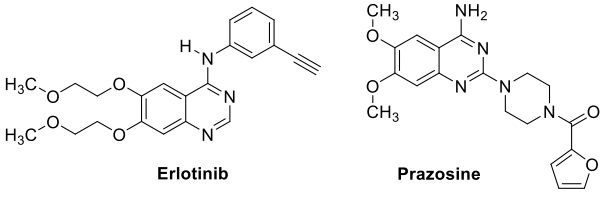


Figure 1. Typical structures of the quinazoline-containing drug-compounds erlotinib and prazosine.

Concerning the research for new kinase inhibitors, it was reported that quinazolines bearing an heteroarylamino moiety at position 4 were promising ALK5 (Activin A receptor type 2-Like Kinase) inhibitors (Fig. 2).[1]

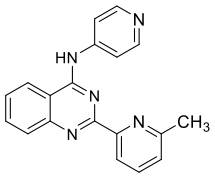


Figure 2. Structure of an ALK5 quinazoline inhibitor bearing an aminoheteroaryl moiety at position 4.

Among of our research activities centered on the synthesis of original molecules with anti-infective properties,[2-4] we developed various series of new quinazolines bearing an aryl-,[5] anilino-,[6] phenoxy-,[7] thiophenoxy-,[8] or sulfonamide substituents[9] at position 4 of the quinazoline ring. Through all studied series, the lead-compound belonged to the 4-anilinosubstituted one, presenting an inhibitory concentration 50% (IC_{50}) value of 0.4 µM on the W2 multi-resistant *Plasmodium falciparum* strain, an cytotoxic concentration 50% (CC_{50}) of 16 µM on the human HepG2 cell line and thus, a corresponding selectivity index (SI) of 40 (Fig. 3).[6]

* Corresponding author. Tel.:+ 33 4 9183 5580; fax:+ 33 4 9179 4677; e-mail address: patrice.vanelle@univ-amu.fr

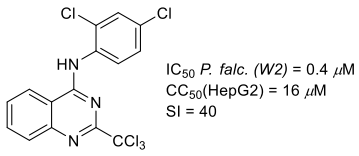
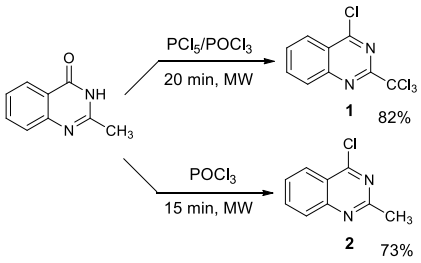


Figure 3. Antiplasmodial lead-compound in 4-substituted-2-CCl_3-quinazoline series.

Taking into account that the antiplasmodial mechanism of action of our lead-quinazoline could involve the inhibition of one of the parasite kinases, we decided to investigate the synthesis of new close structural analogues bearing an heteroarylamino moiety at position 4, in a view to identify more potent and selective antiplasmodial derivatives.

2. Results and discussion

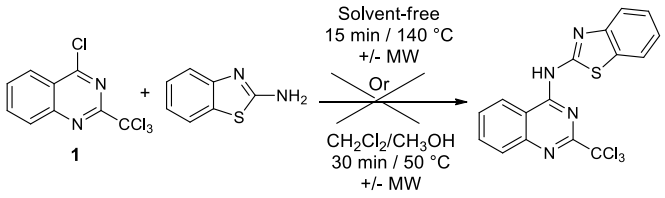
To access to the target 4-heteroarylamino quinazolines in a fast and efficient way, the synthesis pathway which was chosen consisted in a S_NAr reaction between 4-chloroquinazolines and diverse heterocyclic amines. Effectively, 4-chloroquinazolines and especially molecules such as compound **1**, bearing a strong electro-attracting group at position 2, display a good reactivity at position 4 toward most of nucleophilic reactants, including some carbanions.[10] For that purpose, quinazoline substrates **1** and **2** were prepared (Scheme 1) by using a microwave-assisted methodology which we previously reported.[11]



Scheme 1. Preparation of 4-chloroquinazoline substrates **1** and **2**.

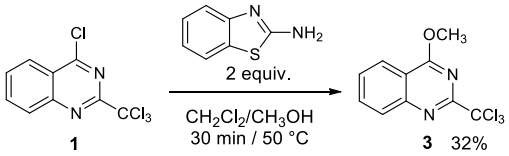
The use of microwave energy to heat and drive chemical reactions is growing at a rapid rate, with new and innovative applications in organic synthesis, continuously being reported in the literature. In many instances, microwave heating has been shown to dramatically reduce processing times, increase product yields and to enhance product purities or material properties compared to conventionally processed experiments.[12-17] Although a variety of different microwave reactors and processing options are available today,[18] the overwhelming majority of all currently published microwave synthesis protocols describe the use of this non-classical heating principle in conjunction with sealed reactors.[12,13]

Thus, substrate **1** was reacted with an excess of 2-aminobenzothiazole in various reaction conditions,[3] including microwave-assisted and solvent-free ones,[6] in both sealed reactors and open flasks. These trials appeared unsuccessful and did not allow any LC/MS detection of the expected product in the reaction media, while many resins were formed (Scheme 2).



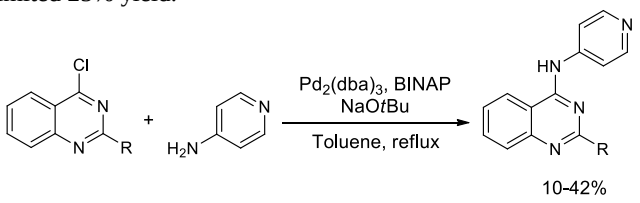
Scheme 2. Study of S_NAr reaction between substrate **1** and 2-aminobenzothiazole following previously described procedures.

Indeed, when substrate **1** was reacted with 2-aminobenzothiazole in a reaction medium containing methanol, the reaction product that we obtained resulted from the substitution of the chlorine atom by methanol. This result illustrates well the poor nucleophilicity of aminated nitrogen-containing heterocycles, in comparison with other amines including anilines, which easily undergo S_NAr reactions with 4-chloroquinazolines.[3, 6]



Scheme 3. Reaction of substrate **1** with 2-aminobenzothiazole in a mixture of dichloromethane and methanol.

Then, we made a bibliographical search (Scifinder® substructure search May 27th 2014) concerning the reported reactions between 4-chloroquinazolines and heteroarylamines. Very few references were reported, all concerning the Pd-catalyzed Buchwald-Hardwig reaction. Thus, Gellibert *et al*, described a reaction with 4-aminopyridine and $Pd_2(dba)_3$ as catalyst, leading to coupled product in moderate yields (Scheme 4).[1] The same methodology and catalyst were also used in an analogous reaction reported in a patent by Suzuki *et al*, leading to a limited 25% yield.[19]



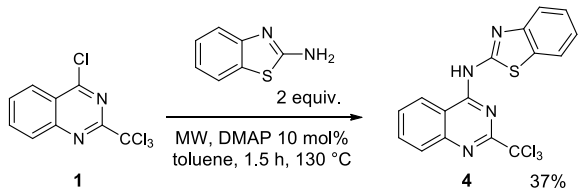
R_1 = phenyl, 3-chlorophenyl, 4-methyl-1,3-thiazol-2-yl, 6-methyl-2-pyridinyl

Scheme 4. Example of Buchwald-Hardwig cross-coupling reactions from 4-chloroquinazoline derivatives.

The Buchwald-Hardwig reaction is a rather expensive Pd-ligand requiring reaction. Moreover, the few examples reported in the literature show mild reaction yields for the coupling between 4-chloroquinazolines and heteroarylamines. Indeed, substrate **1** includes a trichloromethyl group at position 2 of the quinazoline ring, which can lead to competitive side-reactions when using Pd-catalyzed synthetic approaches. Effectively, probably because of the oxidant character of the trichloromethyl group, Pd-catalyzed reactions such as the Sonogashira reaction involving substrate **1** can lead to undesirable homodimeric quinazoline by-products, drastically decreasing the coupling reaction yield.[20]

In such a context, we decided to investigate another synthetic option to reach the target molecules in good yields and short reaction times: the use of 4-(dimethylamino)pyridine (DMAP). DMAP is known as an important and quite useful catalyst reagent in organic synthesis.[21] DMAP and its analogs have been widely used in many organic synthesis reactions, among which nucleophilic substitutions. Indeed, DMAP is an efficient catalyst for some nucleophilic aromatic substitution reactions, in particular to prepare 4-phenoxyquinolines from 4-haloquinolines and phenols.[22]

The reaction of substrate **1** with 2-aminobenzothiazole (2 equiv.) was then carried out in a sealed tube, under microwave irradiation, using 10 mol% of DMAP in toluene at 130 °C. For the first time, the awaited reaction did proceed and afforded the expected product in 37% yield, after 1.5 h (Scheme 5).



Scheme 5. Reaction of 4-chloro-2-trichloromethylquinazoline **1** and 2-aminobenzothiazole in presence of DMAP.

This experimental result prompted us to compare the efficacy of DMAP with other tertiary amine catalysts.[23,24] The use of 10 mol% of DABCO (1,4-diazabicyclo(2.2.2)octane), DBU (1,8-diazabicyclo(5.4.0)undec-7-ene) or TEA (triethylamine) were not successful (Table 1). Consequently, DMAP was kept as the reaction catalyst, and the optimization of the reaction was carried out.

Table 1. Reaction between substrate **1** and 2-aminobenzothiazole, depending on the tertiary amine catalyst used

Entry	Catalyst	Yield (%)
1	-	0
2	DMAP	37
3	DBU	0
4	DABCO	0
5	TEA	0

Table 2. Studied parameters for the DMAP-catalyzed reaction of **1** with 2-aminobenzothiazole, leading to **4.**

Entry	DMAP (mol%)	Reaction conditions	Amine (equiv.)	Solvent	Yield (%)
1	10	1.5 h, 130 °C/monomode MW	2	toluene	37
2	10	1.5 h, 150 °C/monomode MW	2	DMSO	8
3	10	1.5 h, 150 °C/monomode MW	2	DMF	7
4	10	1.5 h, 80 °C/monomode MW	2	THF	Traces (LC/MS)
5	20	1.5 h, 130 °C/monomode MW	2	toluene	61
6	20	2 h, 130 °C/monomode MW	2	toluene	65
7	30	1.5 h, 130 °C/monomode MW	2	toluene	75
8	40	1.5 h, 130 °C/monomode MW	2	toluene	75
9	**30**	**2 h, 130 °C/monomode MW**	**2**	**toluene**	**83**
10	40	2 h, 130 °C/monomode MW	2	toluene	80
11	30	3 h, 110 °C/monomode MW	2	toluene	62
12	40	0.5 h, 150 °C/monomode MW	2	toluene	52*
13	40	2 h, 800 W, 110 °C/multimode MW	2	toluene	39
14	40	36 h, 110 °C/classical conditions	2	toluene	78
15	30	2 h, 130 °C/monomode MW	3	toluene	82
16	30	2 h, 130 °C/monomode MW	1.2	toluene	51
17	30	2 h, 130 °C/monomode MW	1.5	toluene	62

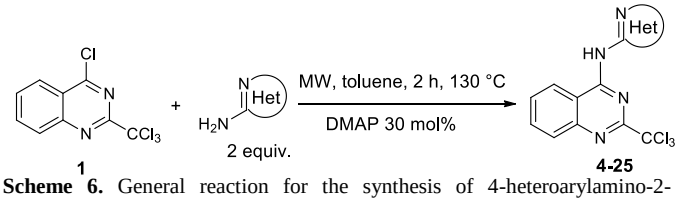
* Formation of resins

The monomode microwave oven used was a Biotage Initiator. The multimode microwave oven used was a Milestone SynthLab Station.

All parameters of the DMAP-catalyzed-reaction between quinazoline **1** and 2-aminobenzothiazole were investigated. The results are presented in Table 2. Concerning the solvent, THF, DMF, DMSO, and toluene were studied. Quinazoline **4** was obtained in very low 8 and 7% yields with DMSO and DMF, respectively, at 150 °C for 1.5 h while only traces of **4** were detected with THF at 80 °C, showing that toluene was, by far, the best tested solvent for the reaction to proceed. The amount of catalyst was then evaluated. With 20 mol% of DMAP, compound **4** was obtained in better yield, but initial product remained. A better reaction yield (75%) was obtained when using 30 mol% of DMAP, but the reaction was not complete after 1.5 h. When increasing to 40 mol% of DMAP, we obtained an analogous result, indicating that the optimal amount of DMAP was 30 mol%, leading to a 75% reaction yield. This last was slightly improved by increasing the reaction time to 2 h, leading to an optimal reaction yield of 83%. Heating the reaction mixture to 110 °C or 150 °C instead of optimal 130 °C (in a sealed reactor) lead to a significant decrease of the reaction yield. Curiously, when transposing the optimal reaction conditions used in entry 9 (monomode reactor) to a multimode microwave oven (entry 13) the reaction yield was drastically reduced. The explanation of this last result could come from the type of flask used: sealed vial in the monomode oven versus traditional open flask in the multimode oven, impacting on the reaction medium temperature which can be reached. Note that, in classical conditions (conventional heating), the reaction yield did not exceed 78% after a long 36 h reaction time (entry 14). Finally, the number of

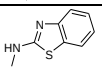
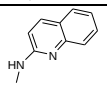
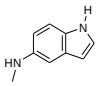
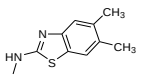
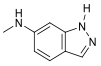
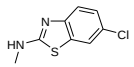
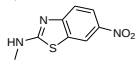
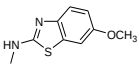
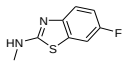
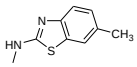
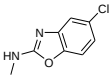
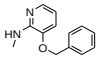
equivalents of 2-aminobenzothiazole was also studied, considering that some of heteroarylamines are expensive reagents. Optimal amount of the heterocyclic amine appeared to be 2 equivalents (entries 15-17).

After optimizing the reaction conditions, we investigated its extension to a broad spectrum of heteroarylamines, according to the general reaction presented in Scheme 6. We then synthesized a series of 22 new quinazolines (**4-25**), in moderate to good yields (31-83%) and short reaction time (2 h), under microwave irradiation. All assays were done in 5 mL sealed reactors and the evolution of the reactions was monitored by LC/MS. The results are presented in Table 3.

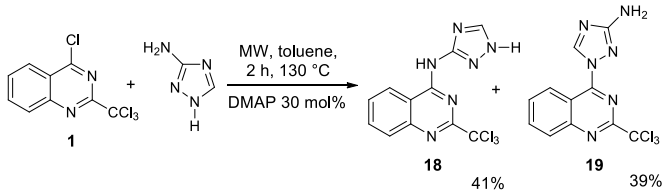


Scheme 6. General reaction for the synthesis of 4-heteroarylamino-2-trichloromethylquinazolines **4-25**.

Table 3. DMAP-catalyzed S_NAr for the formation of 4-heteroarylamino-2-trichloromethylquinazolines **4-25**.

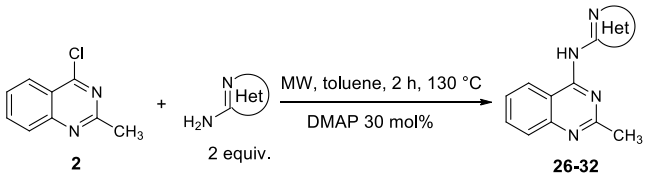
	N°	Yield (%)		N°	Yield (%)
	**4**	83		**15**	38
	**5**	77		**16**	51
	**6**	68		**17**	63
	**7**	71		**18**	41*
	**8**	49		**19**	39*
	**9**	76		**20**	30
	**10**	65		**21**	45
	**11**	61		**22**	60
	**12**	75		**23**	47
	**13**	63		**24**	41
	**14**	52		**25**	35

It should be noted that the reaction between 4-chloro-2-trichloromethylquinazoline **1** and 3-amino-1,2,4-triazole afforded two different products **18** and **19**, in respective 41 and 39% yields (Scheme 7).



Scheme 7. Reaction between **1** and 3-amino-1,2,4-triazole.

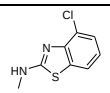
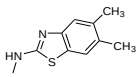
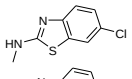
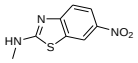
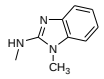
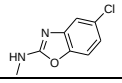
To demonstrate that this reaction could be generalized to other quinazoline substrates in which the reactivity of position 4 is not influenced by the presence of a trichloromethyl group at position 2, we carried out the same S_NAr reaction from substrate **2** (Scheme 8). The reaction yields, varying from medium to good, are presented in Table 4 and show that the reaction was not substrate-dependant in quinazoline series.



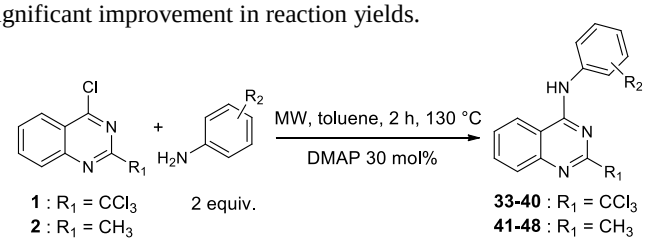
Scheme 8. General reaction for the synthesis of 4-heteroarylamino-2-trichloromethylquinazolines **26-32**.

Table 4. Reaction yields in DMAP-catalyzed S_NAr reactions between quinazoline substrate **2** and various 4-heteroarylamines.

	N°	Yield (%)
	**26**	87

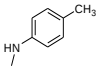
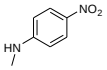
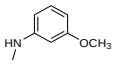
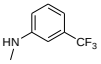
	**27**	81
	**28**	65
	**29**	72
	**30**	49
	**31**	83
	**32**	78

Moreover, we extended the reaction procedure to anilines (Scheme 9) in order to compare its efficiency with the one of the solvent-free procedure (method B) which we previously reported in 2-trichloromethylquinazoline series.[6] As presented in Table 5, in all cases, the DMAP-catalyzed procedure (method A) lead to a significant improvement in reaction yields.



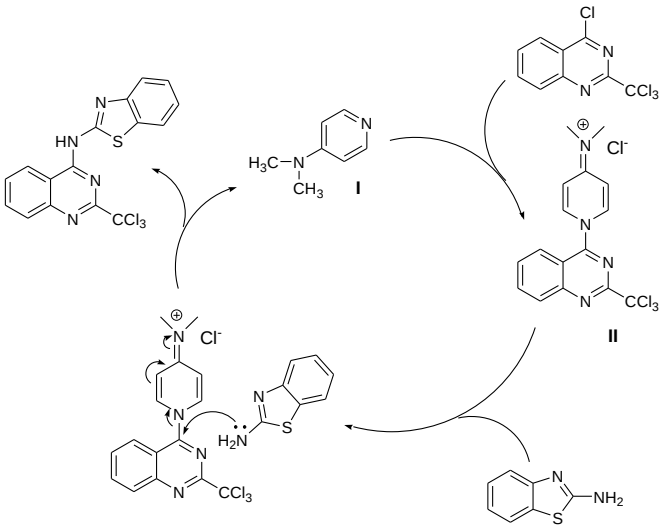
Scheme 9. General reaction for the synthesis of 4-arylamino-2-substituted quinazolines **33-48** DMAP-catalyzed.

Table 5. DMAP-catalyzed S_NAr for the formation of 4-arylaminoquinazolines.

	N°	Yield (%) $R_1 = CCl_3$ method A/B	N°	Yield (%) $R_1 = CH_3$ method A
	**33**	90/62	**41**	91
	**34**	85/66	**42**	92
	**35**	89/71	**43**	87
	**36**	96/77	**44**	97
	**37**	98/90	**45**	95
	**38**	97/90	**46**	97
	**39**	91/86	**47**	98
	**40**	82/75	**48**	96

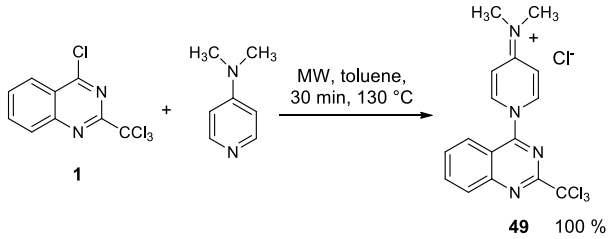
Method A: MW, DMAP 30 mol%, 2 equiv. of aniline reagent, toluene, 2 h, 130 °C. **Method B**: 3 equiv. of aniline reagent, solvent-free, 15 min., 140 °C.

The probable mechanism for the S_NAr reaction catalyzed by DMAP is shown in scheme 10. First, the nitrogen atom of the pyridine ring of DMAP (I) attacks the carbon at position 4 of quinazoline ring, to form the cationic quinazoline intermediate (II). Next, the heteroarylamine reacts with the intermediate (II) to afford the corresponding 4-heteroarylamino-quinazoline, and DMAP is regenerated to participate in a subsequent catalytic cycle (Scheme 10).



Scheme 10. Probable mechanism for the S_NAr reaction catalyzed by DMAP.

To support this mechanistic hypothesis, the quinazoline salt intermediate (II) was formed by reacting equimolar quantities of DMAP and substrate **1** in toluene. Chloride **49** was obtained with a quantitative yield (Scheme 11). This intermediate compound was isolated, NMR-characterized, and its structure was also confirmed by X-ray diffraction analysis (Figure 4).



Scheme 11. Reaction to isolate the intermediate coupling compound **49**.

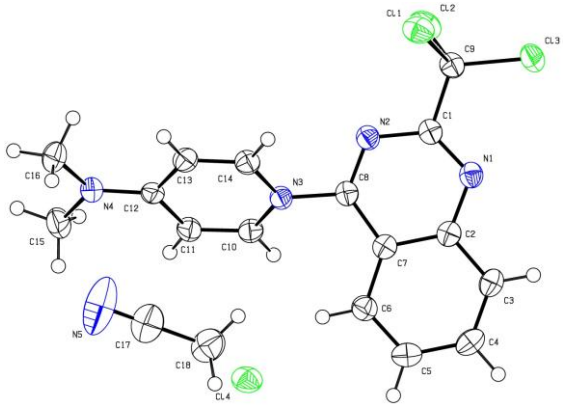


Figure 4. X-ray structure of intermediate salt **49** (crystal structure including 1 acetonitrile molecule from the crystallizing medium used)

3. Conclusion

Until now, the introduction of weakly nucleophilic heretoarylamines at position 4 of the 4-chloroquinazoline was carried out by using the Buchwald-Hartwig cross-coupling reaction. Because this particular reaction is rather expensive and also reported in a few bibliographical references as providing

moderate yields, we developed an efficient alternative synthetic procedure. After conducting a large study, focusing on each reaction parameter, the use of the DMAP catalyst, toluene as a solvent and microwave irradiation in a sealed vial, the reaction could be performed easily and rapidly. Moreover, the S_NAr reaction intermediate was isolated and fully characterized. Such a synthetic approach was extended to various quinazoline substrates and aniline derivatives, demonstrating its large interest for the preparation of molecules displaying pharmaceutical potential.

4. Experimental section

4.1. General

Melting points were determined on a Köfler melting point apparatus and are uncorrected. Elemental analyses and X-ray diffraction analysis were carried out at the Spectropole, Faculté des Sciences de Saint-Jêrome (Marseille) with a Thermo Finnigan EA1112 analyzer and a Brucker Nonius diffractometer. HRMS analyses were carried out at the Faculté de Pharmacie of Marseille on a QStar Elite (Applied Biosystems SCIEX) spectrometer or Electrospray MicrOTOF Q (Bruker, Daltonic), using PEG as the matrix. The experimental exact mass was given for the ion with the maximum isotopic abundance. Analysis of fragments was performed with a triple quadrupole LCMS-8030 Shimadzu at the Faculté de Pharmacie of Marseille. NMR spectra were recorded on a Bruker ARX 200 spectrometer at the Faculté de Pharmacie of Marseille (200 MHz ^{1}H NMR: reference $CHCl_3$ δ= 7.26, and 50 MHz ^{13}C: reference $CHCl_3$ δ= 76.9). The following adsorbent was used for column chromatography: silica gel 60 (Merck, particle size 0.063-0.200 mm, 70-230 mesh ASTM). TLC was performed on 5 cm x10 cm aluminum plates coated with silica gel 60F-254 (Merck) in an appropriate eluent. Visualization was performed with ultraviolet light (234 nm). Purity of synthesized compounds was checked by LC/MS analyses, which were realized at the Faculté de Pharmacie of Marseille with a Thermo Scientific Accela High Speed LC System® coupled using a single quadrupole mass spectrometer Thermo MSQ Plus®. The RP-HPLC column is a Thermo Hypersil Gold® 50x2.1 mm (C18 bounded), with particles of a diameter of 1.9 mm. The volume of sample injected on the column is 1 μL. Chromatographic analysis, total duration of 8 min, is on the gradient of the following solvents: t=0 min, water/methanol 50:50; 0<t<4 min, linear increase in the proportion of water to a water/methanol ratio of 95:5; 4<t<6 min, water/methanol 95:5; 6<t<7 min, linear decrease in the proportion of water to return to a water/methanol ratio of 50:50; 6<t<7 min, water/methanol 50:50. The water used was buffered with ammonium acetate 5 μM. The retention times (t_R) of the molecules analyzed are indicated in min. The microwave reactions were performed using multimode reactors: ETHOS Synth Lab station and MicroSYNTH® Lab terminal 1024 (Ethos start, Milestone Inc.); or monomode reactors: Biotage® Initiator classic in sealed vials

Crystal-Structure Analysis

The X-ray diffraction measurements were carried out on a Bruker-Nonius KappaCCD diffractometer at 223 K. Structures were solved using SIR92 and refinements calculations based on F^2 were performed using SHELXL-97. The compound **49** was crystallized in acetonitrile solution at 5 °C to provide desired single crystals.

2-Methyl-4(3*H*)-quinazolinone were purchased from Sigma Aldrich.

4.2. Molecules prepared according to previously described procedures

4-Chloro-2-trichloromethylquinazoline **1** and 4-chloro-2-methylquinazoline **2** were prepared as described in the literature.[6, 11, 16, 20]

4.2.1. 4-Chloro-2-trichloromethylquinazoline (**1**) $C_9H_4Cl_4N_2$. MW: 282.18 g/mol. White solid (82%). mp 127 °C (lit. 127 °C).[16] ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.82-7.90 (m, 1H), 8.03-8.12 (m, 1H), 8.20-8.24 (m, 1H), 8.33-8.38 (m, 1H).

4.2.2. 4-Chloro-2-methylquinazoline (**2**) $C_9H_7ClN_2$. MW: 178.62 g/mol. White solid (73%). mp 86 °C (lit. 81.5-83 °C).[23] ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.75 (s, 3H), 7.48-7.56 (m, 1H), 7.75-7.86 (m, 2H), 8.05-8.09 (m, 1H).

4.2.3. 4-Methoxy-2-(trichloromethyl)quinazoline (**3**). MW: 277.53 g/mol. White solid (32%). mp 83 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/petroleum ether 5/5). ^{1}H ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.28 (s, 3H), 7.63-7.70 (m, 1H), 7.87-7.95 (m, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 8.21 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 54.9 (CH_3), 97.1 (C), 123.5 (CH), 128.5 (CH), 128.7 (CH), 134.3 (CH), 146.6 (C), 150.2 (C), 160.2 (C), 168.1 (C). LC-MS (ESI+) t_R 4.45 min, *m/z* $[M+H]^+$ 277.05/279.06/281.05. Anal. calcd. for $C_{10}H_7Cl_3N_2O$: C, 43.28; H, 2.54; N, 10.09. Found: C, 43.67; H, 2.83; N, 10.38.

*4.3. General procedure for the preparation of compounds **4** to **25***

A mixture of 4-chloro-2-trichloromethylquinazoline **1** (0.2 g, 0.71 mmol), DMAP (26 mg, 0.21 mmol, 0.3 equiv) and adequate heteroarylamine (1.41 mmol, 2 equiv) in toluene (3 mL) was introduced in miniaturized sealed reactor (5 mL). The reaction mixture was irradiated in a monomode microwave oven, for 2 h at 130 °C. After removal of the toluene under reduced pressure, the residue was purified by silica gel column chromatography and recrystallized from appropriate solvent.

4.3.1. N-(2-(trichloromethyl)quinazolin-4-yl)benzo[d]thiazol-2-amine (**4**) MW: 395.69 g/mol. Yellow solid (83%). mp 229 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 6.50 (br s, 1H), 7.27-7.34 (m, 1H), 7.42-7.50 (m, 1H), 7.64-7.68 (m, 1H), 7.75-7.83 (m, 1H), 7.95-8.07 (m, 3H), 8.71-8.75 (m, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 97.9 (C), 117.1 (C), 122.6 (CH), 124.0 (2CH), 124.8 (CH), 127.2 (CH), 128.8 (CH), 129.2 (CH), 129.3 (C), 130.7 (C), 135.1 (CH), 149.5 (C), 159.7 (C), 162.1 (C), 167.4, (C). LC-MS (ESI+) t_R 5.15 min, *m/z* $[M+H]^+$ 394.91/396.94/398.74. Anal. calcd. for $C_{16}H_9Cl_3N_4S$: C, 48.57; H, 2.29; N, 14.16. Found: C, 48.95; H, 2.49; N, 13.94 .

4.3.2. 4-Chloro-N-(2-(trichloromethyl)quinazolin-4-yl)benzo[d]thiazol-2-amine (**5**) MW: 430.14 g/mol. Yellow solid (77%). mp 255-256 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 6.42 (br s, 1H), 7.28-7.35 (m, 1H), 7.53-7.57 (m, 1H), 7.82-7.88 (m, 1H), 7.95-8.05 (m, 3H), 8.99-9.02 (m, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 97.4 (C), 120.8 (C), 120.9 (CH), 122.0 (C), 123.1 (CH), 123.3 (CH), 126.6 (CH), 127.0 (CH), 128.8 (CH), 130.9 (C), 136.1 (CH), 142.7 (C), 146.2 (C), 148.3 (C), 160.2 (C), 168.6 (C). LC-MS (ESI+) t_R 5.74 min, *m/z* $[M+H]^+$ 428.86/430.80/432.84. Anal. calcd. for $C_{16}H_8C_{l4}N_4S$: C, 44.68; H, 1.87; N, 13.03 . Found: C, 44.93; H, 1.81; N, 13.15.

4.3.3. 5,6-Dimethyl-N-(2-(trichloromethyl)quinazolin-4-yl)benzo[d]thiazol-2-amine (**6**) MW: 423.75 g/mol. Pale yellow solid (68%). mp 250 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.24 (s, 3H), 2.32 (s, 3H), 6.23 (br s, 1H), 7.24-7.27 (m, 1H), 7.43-7.50 (m, 1H), 7.56-7.62 (m, 1H), 7.79-7.86 (m, 1H), 8.03-8.07 (m, 1H), 8.17-8.23 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.9 (CH_3), 20.2 (CH_3), 97.5 (C), 119.8 (C), 122.6 (CH), 122.0 (C), 124.8 (CH), 128.7 (CH), 129.1 (CH), 132.3 (CH), 130.9 (C), 134.5 (C), 134.9 (CH), 136.0 (C), 143.4 (C), 149.5 (C), 159.8 (C), 166.3 (C). LC-MS (ESI+) t_R 5.67 min, *m/z* $[M+H]^+$ 422.93/424.90/426.85. Anal. calcd. for $C_{18}H_{13}C_{l3}N_4S$: C, 51.02; H, 3.09; N, 13.22. Found: C, 51.39; H, 2.91; N, 13.09.

4.3.4. 6-Chloro-N-(2-(trichloromethyl)quinazolin-4-yl)benzo[d]thiazol-2-amine (**7**) MW: 430.14 g/mol. Yellow solid (71%). mp 212 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.87 (br s, 1H), 7.32-7.36 (m, 1H), 7.51-7.66 (m, 2H), 7.89-7.97 (m, 2H), 8.12-8.16 (m, 1H), 8.23-8.27 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 97.2 (C), 113.9 (C), 120.5 (CH), 121.4 (CH), 121.6 (CH), 127.3 (CH), 129.3 (CH), 129.7 (C), 130.0 (CH), 133.9 (C), 134.8 (CH), 144.7 (C), 149.7 (C), 155.9 (C), 160.1 (C), 168.4 (C). LC-MS (ESI+) t_R 5.70 min, *m/z* $[M+H]^+$ 428.78/430.90/432.74. Anal. calcd. for $C_{16}H_8C_{l4}N_4S$: C, 44.68; H, 1.87; N, 13.03. Found: C, 44.29; H, 1.95; N, 13.28.

4.3.5. 6-Nitro-N-(2-(trichloromethyl)quinazolin-4-yl)benzo[d]thiazol-2-amine (**8**) MW: 440.69 g/mol. Yellow solid (49%). mp 260 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.1 (br s, 1H), 7.76-7.82 (m, 2H), 7.87-7.90 (m, 1H), 8.01 (t, *J* = 8.5 Hz, 1H), 8.17-8.21 (m, 1H), 8.29-8.41 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 92.9 (C), 117.3 (C), 120.1 (CH), 121.5 (CH), 123.4 (CH), 126.6 (CH), 128.8 (CH), 129.5 (CH), 131.4 (C), 135.8 (CH), 136.6 (C), 143.9 (C), 146.3 (C), 150.9 (C), 162.4 (C), 168.2 (C). LC-MS (ESI+) t_R 4.56 min, *m/z* $[M+H]^+$ 439.86/441.87/443.87. Anal. calcd. for $C_{16}H_8Cl_3N_5O_2S$: C, 43.61; H, 1.83; N, 15.89. Found: C, 43.26; H, 2.01; N, 15.48.

4.3.6. 6-Methoxy-N-(2-(trichloromethyl)quinazolin-4-yl)benzo[d]thiazol-2-amine (**9**) MW: 425.72 g/mol. Pale yellow solid (76%). mp 188 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.56 (br s, 1H), 3.82 (s, 3H), 7.04 (dd, *J* = 8.8 Hz, *J* = 2.5 Hz, 1H), 7.56-7.61 (m, 2H), 7.74-7.82 (m, 1H), 7.98-7.99 (m, 2H), 8.73-8.77 (m, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 56.2 (CH_3), 97.9 (C), 105.6 (C), 115.9 (2CH), 124.6 (CH), 128.6 (CH), 128.8 (CH), 129.2 (CH), 129.8 (C), 135.1 (CH), 141.3 (C), 149.4 (C), 156.6 (C), 156.8 (C), 159.6 (C), 168.7 (C). LC-MS (ESI+) t_R 4.86 min, *m/z* $[M+H]^+$ 424.95/426.92/428.94. Anal. calcd. for $C_{17}H_{11}Cl_3N_4OS$: C, 47.96; H, 2.60; N, 13.16. Found: C, 48.31; H, 2.49; N, 13.32.

4.3.7. 6-Fluoro-N-(2-(trichloromethyl)quinazolin-4-yl)benzo[d]thiazol-2-amine (**10**) MW: 413.68g/mol. Beige solid (65%). mp 249 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 5.74 (br s, 1H), 7.12-7.18 (m, 1H), 7.55-7.65 (m, 3H), 7.89-7.96 (m, 1H), 8.11-8.15 (m, 1H), 8.24-8.28 (m, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 97.7 (C), 109.1 (d, *J* = 26.5 Hz, CH), 115.0 (d, *J* = 23.1 Hz, CH), 116.0 (C), 124.6 (CH), 125.8 (C), 128.7 (C), 128.9 (CH), 129.3 (CH), 129.4 (CH), 135.4 (CH), 136.7 (C), 149.4 (C), 156.7 (C), 159.5 (C), 163.3 (d, *J* = 240.0 Hz, C). LC-MS (ESI+) t_R 4.95 min, *m/z* $[M+H]^+$ 412.98/414.85/416.81. Anal. calcd. for $C_{16}H_8Cl_3FN_4S$: C, 46.45; H, 1.95; N, 13.54. Found: C, 46.08; H, 2.04; N, 13.59.

4.3.8. 6-Methyl-N-(2-(trichloromethyl)quinazolin-4-yl)benzo[d]thiazol-2-amine (**11**) MW: 409.72 g/mol. Pale yellow solid (61%). mp 248 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.40 (s, 3H), 4.88 (br s, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 10.0 Hz, 1H), 7.75-7.83 (m, 2H), 7.96-8.05 (m, 2H), 8.73 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 21.39 (CH_3), 97.9 (C), 116.8 (C), 122.3 (CH), 124.8 (CH), 128.4 (CH), 128.8 (CH), 129.1 (CH), 129.5 (CH), 132.0 (C), 133.6 (C), 135.8 (CH), 146.3 (C), 149.5 (C), 159.7 (C), 162.4 (C), 167.4 (C). LC-MS (ESI+) t_R 5.58 min, *m/z* $[M+H]^+$ 408.96/411.08/413.06. Anal. calcd. for $C_{17}H_{11}Cl_3N_4S$: C, 49.83; H, 2.71; N, 13.67. Found: C, 50.17; H, 2.63; N, 13.89.

4.3.9. 5-Chloro-N-(2-(trichloromethyl)quinazolin-4-yl)benzo[d]oxazol-2-amine (**12**) MW: 411.95 g/mol. Beige solid (75%). mp 264 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.07 (br s, 1H), 7.23-7.28 (m, 1H), 7.37-7.47 (m, 2H), 7.66-7.74 (m, 1H), 7.87-8.05 (m, 2H), 8.73 (dd, *J* = 1.0 Hz, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 95.4 (C), 111.2 (CH), 114.7 (CH), 120.6 (C), 124.3 (CH), 125.9 (CH), 128.7 (CH), 129.1 (CH), 130.4 (C), 134.9 (CH), 135.7 (C), 144.1 (C), 148.2 (C), 154.1 (C), 159.7 (C), 162.4 (C). LC-MS (ESI+) t_R 5.33 min, *m/z* $[M+H]^+$ 412.95/414.88/416.84. Anal. calcd. for $C_{16}H_8Cl_4N_4O$: C, 46.41; H, 1.95; N, 13.53 . Found: C, 46.53; H, 1.92; N, 13.67 .

4.3.10. N-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-(trichloromethyl)quinazolin-4-amine (**13**) MW: 392.67 g/mol. Yellow solid (63%). mp 244 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.84 (s, 3H), 4.90 (br s, 1H), 7.28-7.33 (m, 2H), 7.55-7.70 (m, 3H), 7.82-7.88 (m, 2H), 8.63 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (DMSO-*d6*, 50 MHz): δ 28.5 (CH_3), 98.6 (C), 109.0 (CH), 111.2 (CH), 120.6 (C), 123.2 (CH), 123.3 (CH), 125.6 (CH), 127.3 (CH), 128.1 (CH), 128.5 (C), 130.5 (C), 133.3 (CH), 149.8 (C), 151.8 (C), 159.9 (C), 165.0 (C). LC-MS (ESI+) t_R 5.55 min, *m/z* $[M+H]^+$ 392.01/393.94/396.04. Anal. calcd. for $C_{17}H_{12}Cl_3N_5$: C, 52.00; H, 3.08; N, 17.84. Found: C, 52.39; H, 3.01; N, 18.13.

4.3.11. N-(1H-benzo[d]imidazol-2-yl)-2-(trichloromethyl)quinazolin-4-amine (**14**) MW: 378.64 g/mol. Pale yellow solid (52%). mp 231 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.11 (br s, 1H), 5.99 (br s, 1H), 6.91-7.09 (m, 1H), 7.23-7.31 (m, 3H), 7.51-7.57 (m, 1H), 7.73-7.81 (m, 1H), 8.09-8.38 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 96.8 (C), 110.5 (CH), 114.8 (CH), 120.2 (C), 121.4 (CH), 124.0 (CH), 125.9 (CH), 129.7 (CH), 131.4 (CH), 132.2 (C), 137.5 (CH), 138.9 (C), 152.5 (C), 153.0 (C), 157.0 (C), 160.1 (C). LC-MS (ESI+) t_R 4.20 min, *m/z* $[M+H]^+$ 378.02/379.97/382.11. Anal. calcd. for $C_{16}H_{10}Cl_3N_5$: C, 50.75; H, 2.66; N, 18.50. Found: C, 50.61; H, 2.70; N, 18.63.

4.3.12. N-(quinolin-2-yl)-2-(trichloromethyl)quinazolin-4-amine (**15**) MW: 389.67 g/mol. Yellow solid (38%). mp 205 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 7.54 (t, *J* = 7.5 Hz, 1H), 7.72-7.81 (m, 2H), 7.90-8.01 (m, 4H), 8.41-8.45 (m, 1H), 8.58-8.62 (m, 1H), 8.86-8.90 (m, 1H), 11.26 (br s, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 98.1 (C), 115.2 (C), 117.7 (CH), 124.6 (CH), 124.7 (CH), 126.2 (CH), 128.5 (CH), 128.8 (C), 129.1 (CH), 129.3 (CH), 131.2 (CH), 135.3 (CH), 136.3 (C), 139.3 (CH), 149.6 (C), 152.3 (C), 159.7 (C), 159.8 (C). LC-MS (ESI+) t_R 5.20 min, *m/z* $[M+H]^+$ 388.97/391.03/393.05. Anal. calcd. for $C_{18}H_{11}Cl_3N_4$: C, 55.48; H, 2.85; N, 14.38. Found: C, 55.86; H, 2.74; N, 14.17.

4.3.13. N-(1H-indol-5-yl)-2-(trichloromethyl)quinazolin-4-amine (**16**) MW: 377.66 g/mol. Pale yellow solid (51%). mp > 350 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 6.42 (m, 1H), 7.33-7.48 (m, 2H), 7.58-7.76 (m, 2H), 7.85-7.92 (m, 2H), 8.20-8.22 (m, 1H), 8.73 (d, *J* = 8.2 Hz, 1H), 10.23 (br s, 1H), 11.16 (br s, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 98.7 (C), 101.8 (CH), 111.4 (CH), 113.9 (C), 114.4 (CH), 117.8 (CH), 118.9 (CH), 123.9 (CH), 126.5 (CH), 128.3 (CH), 128.8 (CH), 130.7 (C), 133.7 (C), 139.3 (C), 149.2 (C), 158.9 (C), 161.3 (C). LC-MS (ESI+) t_R 3.64 min, *m/z* $[M+H]^+$ 377.02/379.00/381.11. Anal. calcd. for $C_{17}H_{11}Cl_3N_4$: C, 54.07; H, 2.94; N, 14.84. Found: C, 54.46; H,2.89; N, 14.69.

4.3.14. N-(1H-indazol-6-yl)-2-(trichloromethyl)quinazolin-4-amine (**17**) MW: 378.64 g/mol. Pale yellow solid (63%). mp 230 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 5.20 (br s, 1H), 7.60-7.82 (m, 3H), 7.91-8.01 (m, 3H), 8.60-8.62 (m, 1H), 8.80 (d, *J* = 8.2 Hz, 1H), 10.39 (br s, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 98.5 (C), 102.8 (CH), 114.6 (C), 117.0 (CH), 120.01 (C), 120.5 (CH), 124.3 (CH), 128.5 (CH), 129.0 (CH), 133.6 (CH), 134.6 (CH), 137.4 (C), 140.7 (C), 149.5 (C), 158.9 (C), 160.7 (C). LC-MS (ESI+) t_R 3.68 min, *m/z* $[M+H]^+$ 378.04/380.06/382.06. Anal. calcd. for $C_{16}H_{10}Cl_3N_5$: C, 50.75; H, 2.66; N, 18.50. Found: C, 50.98; H, 2.57; N, 18.46.

4.3.15. N-(1H-1,2,4-triazol-3-yl)-2-(trichloromethyl)quinazolin-4-amine (**18**) MW: 329.57 g/mol. Beige solid (41%). mp 217 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.58 (br s, 1H), 7.75-7.83 (m, 1H), 7.98-8.06 (m, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 9.28 (s, 1H), 9.58 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 96.4 (C), 114.6 (C), 127.6 (CH), 129.5 (2CH), 129.9 (CH), 135.6 (CH), 144.7 (CH), 153.2 (C), 153.6 (C), 159.5 (C). LC-MS (ESI+) t_R 3.80 min, *m/z* $[M+H]^+$ 328.99/330.93/333.05. Anal. calcd. for $C_{11}H_7Cl_3N_6$: C, 40.09; H, 2.14; N, 25.50. Found: C, 40.37; H, 2.08; N, 25.32.

4.3.16. 1-(2-(trichloromethyl)quinazolin-4-yl)-1H-1,2,4-triazol-3-amine (**19**) MW: 329.57 g/mol. Yellow solid (39%). mp 257 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.83-7.92 (m, 1H), 8.02 (s, 1H), 8.06-8.14 (m, 1H), 8.26 (d, *J* = 8.3 Hz, 1H), 8.40 (br s, 2H), 9.63 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 96.2 (C), 115.0 (C), 128.3 (CH), 130.0 (CH), 130.5 (CH), 136.0 (CH), 145.7 (CH), 152.8 (C), 155.6 (C), 155.5 (C), 158.1 (C). LC-MS (ESI+) t_R 4.26 min, *m/z* $[M+H]^+$ 328.94/330.94/332.94. Anal. calcd. for $C_{11}H_7Cl_3N_6$: C, 40.09; H, 2.14; N, 25.50. Found: C, 39.91; H, 2.10; N, 25.67.

4.3.17. N-(2-(trichloromethyl)quinazolin-4-yl)thiazol-2-amine (**20**) MW: 345.63 g/mol. Beige solid (30%). mp 175 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.08 (br s, 1H), 7.20 (d, *J* = 4.1 Hz, 1H), 7.57 (d, *J* = 4.1 Hz, 1H), 7.78-7.89 (m, 1H), 7.96-8.04 (m, 1H), 8.14-8.18 (m, 1H), 8.71 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 98.0 (C), 107.4 (CH), 114.7 (C), 124.6 (CH), 128.8 (CH), 128.9 (CH), 134.8 (CH), 139.5 (CH), 149.2 (C), 158.8 (C), 163.5 (C), 169.3 (C). LC-MS (ESI+) t_R 4.32 min, *m/z* $[M+H]^+$ 344.98/346.98/348.98. Anal. calcd. for $C_{12}H_7Cl_3N_4S$: C, 41.70; H, 2.04; N, 16.21 . Found: C, 41.58; H, 2.17; N, 16.06 .

4.3.18. N-(pyridin-2-yl)-2-(trichloromethyl)quinazolin-4-amine (**21**) MW: 339.61 g/mol. Yellow solid (45%). mp 154 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.06 (br s, 1H), 7.05-7.11 (m, 1H), 7.61-7.70 (m, 1H), 7.80-7.92 (m, 2H), 8.05-8.14 (m, 2H), 8.30-8.33 (m, 1H), 8.90-8.95 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 97.6 (C), 114.1 (C), 116.1 (CH), 119.5 (CH), 121.6 (CH), 128.8 (CH), 129.7 (CH), 134.2 (CH), 139.9 (CH), 145.9 (CH), 149.7 (C), 151.5 (C), 157.4 (C), 160.2 (C). LC-MS (ESI+) t_R 4.27 min, *m/z* $[M+H]^+$ 339.06/340.99/343.04. Anal. calcd. for $C_{14}H_9Cl_3N_4$: C, 49.51; H, 2.67; N, 16.50. Found: C, 49.42; H, 2.61; N, 16.59.

4.3.19. N-(5-chloropyridin-2-yl)-2-(trichloromethyl)quinazolin-4-amine (**22**) MW: 374.05 g/mol. Yellow solid (60%). mp 196 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.68-7.97 (m, 3H), 8.04-8.13 (m, 2H), 8.30 (d, *J* = 2.5 Hz, 1H), 8.58 (br s, 1H), 8.94 (d, *J* = 8.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 97.3 (C), 113.9 (C), 116.6 (CH), 121.3 (CH), 126.7 (C), 129.1 (CH), 130.1 (CH), 134.5 (CH), 139.9 (CH), 144.6 (CH), 149.7 (C), 149.8 (C), 156.9 (C), 159.9 (C). LC-MS (ESI+) t_R 5.05 min, *m/z* $[M+H]^+$ 372.98/374.94/376.95. Anal. calcd. for $C_{14}H_8Cl_4N_4$: C, 44.95; H, 2.16; N, 14.98. Found: C, 45.12; H, 2.19; N, 14.79.

4.3.20. N-(pyridin-3-yl)-2-(trichloromethyl)quinazolin-4-amine (**23**) MW: 339.61 g/mol. Yellow solid (47%). mp 222 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 7.48 (dd, *J* = 8.3 Hz, *J* = 4.8 Hz, 1H), 7.76-7.84 (m, 1H), 7.93-8.04 (m, 2H), 8.36 (d, *J* = 3.9 Hz, 1H), 8.44-8.48 (m, 1H), 8.66-8.70 (d, *J* = 8.3 Hz, 1H), 9.19 (d, *J* = 2.1 Hz, 1H), 10.38 (br s, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 98.2 (C), 114.6 (C), 123.9 (CH), 124.1 (CH), 128.9 (CH), 129.2 (CH), 129.8 (CH), 135.0 (CH), 136.3 (C), 143.1 (CH), 144.7 (CH), 149.4 (C), 159.1 (C), 160.3 (C). LC-MS (ESI+) t_R 3.85 min, *m/z* $[M+H]^+$ 339.02/341.01/342.91. Anal. calcd. for $C_{14}H_9Cl_3N_4$: C, 49.51; H, 2.67; N, 16.50. Found: C, 49.69; H, 2.70; N, 16.44.

4.3.21. N-(pyridin-4-yl)-2-(trichloromethyl)quinazolin-4-amine (**24**) MW: 339.61 g/mol. Yellow solid (41%). mp 254 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 7.80-7.88 (m, 1H), 7.97-8.07 (m, 2H), 8.12-8.15 and 8.54-8.56 (2d, A_2B_2 Syst, 4H), 8.73 (d, *J* = 8.2 Hz, 1H), 10.47 (br s, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 97.9 (C), 114.9 (C), 115.8 (2CH), 124.3 (CH), 129.3 (CH), 129.4 (CH), 135.5 (CH), 147.7 (2CH), 149.0 (C), 149.7 (C), 159.1 (C), 159.9 (C). LC-MS (ESI+) t_R 4.01 min, *m/z* $[M+H]^+$ 339.08/341.07/343.07. Anal. calcd. for $C_{14}H_9Cl_3N_4$: C, 49.51; H, 2.67; N, 16.50. Found: C, 49.73; H, 2.62; N, 16.39.

4.3.22. N-(3-(benzyloxy)pyridin-2-yl)-2-(trichloromethyl)quinazolin-4-amine (**25**) MW: 445.73 g/mol. Yellow solid (35%). mp 130 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 5.07 (s, 2H), 6.93-6.98 (m, 2H), 7.06-7.10 (m, 2H), 7.35-7.41 (m, 1H), 7.59-7.82 (m, 3H), 7.91-7.95 (m, 2H), 8.07-8.10 (m, 1H), 8.55 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 69.8 (CH_2), 98.3 (C), 114.1 (C), 121.1 (CH), 123.7 (CH), 124.1 (CH), 127.1 (2CH), 128.1 (CH), 128.5 (2CH), 128.6 (CH), 128.8 (CH), 134.7 (CH), 136.9 (CH), 139.6 (C), 142.0 (C), 149.6 (C), 150.1 (C), 159.1 (C), 160.5 (C). LC-MS (ESI+) t_R 3.93 min, *m/z* $[M+H]^+$ 444.92/446.84/448.75. Anal. calcd. for $C_{21}H_{15}Cl_3N_4O$: C, 56.59; H, 3.39; N, 12.57. Found: C, 56.20; H, 3.49; N, 12.89.

*4.4. General procedure for the preparation of compounds **26-48***

A mixture of 4-chloro-2-methylquinazoline **2** (0.2 g, 1.12 mmol), DMAP (41 mg, 0.34 mmol, 0.3 equiv) and adequate aromatic amine reagent (2.24 mmol, 2 equiv) in toluene (3mL) was introduced in miniaturized sealed reactor (5 mL). The reaction mixture was irradiated in a monomode microwave oven,

for 2 h at 130 °C. After removal of the toluene under reduced pressure, the residue was purified by silica gel column chromatography, and recrystallized**.**

4.4.1. N-(2-methylquinazolin-4-yl)benzo[d]thiazol-2-amine (**26**) MW: 292.36 g/mol. Yellow solid (87%). mp 268 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.68 (s, 3H), 7.29-7.33 (m, 1H), 7.39-7.54 (m, 2H), 7.64-7.82 (m, 4H), 8.53-8.57 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.8 (CH_3), 120.0 (C), 120.6 (CH), 121.4 (2CH), 123.8 (CH), 125.8 (CH), 126.3 (CH), 127.0 (CH), 132.2 (C), 134.2 (CH), 147.9 (C), 150.7 (C), 151.1 (C), 151.8 (C), 173.4 (C). LC-MS (ESI+) t_R 4.17 min, *m/z* $[M+H]^+$ 293.18. Anal. calcd. for $C_{16}H_{12}N_4S$: C, 65.73; H, 4.14; N, 19.16. Found: C, 65.51; H, 4.09; N, 19.31.

4.4.2. 4-chloro-N-(2-methylquinazolin-4-yl)benzo[d]thiazol-2-amine (**27**) MW: 326.80 g/mol. Yellow solid (81%). mp 266 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.70 (s, 3H), 7.26 (t, *J* = 7.9 Hz, 1H), 7.48-7.95 (m, 6H), 8.76 (br s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 24.8 (CH_3), 119.8 (C), 120.9 (CH), 121.0 (CH), 124.4 (CH), 124.5 (CH), 126.5 (CH), 127.1 (CH), 129.1 (C), 132.1 (C), 134.7 (CH), 135.1 (C), 145.9 (C), 156.0 (C), 158.2 (C), 167.4 (C). LC-MS (ESI+) t_R 5.12 min, *m/z* $[M+H]^+$327.01/328.98/331.22. Anal. calcd. for $C_{16}H_{11}ClN_4S$: C, 58.80; H, 3.39; N, 17.14. Found: C, 58.59; H, 3.44; N, 17.32.

4.4.3. 5,6-dimethyl-N-(2-methylquinazolin-4-yl)benzo[d]thiazol-2-amine (**28**) MW: 320.41 g/mol. Yellow solid (65%). mp 212 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.37 (s, 3H), 2.38 (s, 3H), 2.86 (s, 3H), 7.46-7.77 (m, 5H), 8.50-8.54 (d, *J* = 7.9 Hz, 1H), 14.58 (br s, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 20.1 (CH_3), 20.2 (CH_3), 22.8 (CH_3), 120.1 (C), 121.1 (CH), 121.5 (2CH), 125.7 (CH), 126.9 (CH), 129.5 (C), 133.1 (C), 134.1 (CH), 135.1 (C), 147.8 (C), 149.3 (C), 151.2 (C), 151.4 (C), 173.4 (C). LC-MS (ESI+) t_R 4.80 min, *m/z* $[M+H]^+$ 321.18. Anal. calcd. for $C_{18}H_{16}N_4S$: C, 67.47; H, 5.03; N, 17.49. Found: C, 67.19; H, 5.13; N, 17.65.

4.4.4. 6-Chloro-N-(2-methylquinazolin-4-yl)benzo[d]thiazol-2-amine (**29**) MW: 326.8 g/mol. Yellow solid (72%). mp 211 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.69 (s, 3H), 7.41-7.91 (m, 5H), 8.09 (d, *J* = 2.1 Hz, 1H), 8.62 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 24.9 (CH_3), 119.7 (C), 121.0 (CH), 121.7 (CH), 124.5 (CH), 126.9 (CH), 127.0 (CH), 127.8 (CH), 129.4 (C), 132.0 (C), 134.5 (CH), 135.3 (C), 146.2 (C), 156.4 (C), 158.6 (C), 167.2 (C). LC-MS (ESI+) t_R 4.60 min, *m/z* $[M+H]^+$ 327.13/329.23/330.68. Anal. calcd. for $C_{16}H_{11}ClN_4S$: C, 58.80; H, 3.39; N, 17.14. Found: C, 59.11; H, 3.41; N, 16.95.

4.4.5. N-(2-methylquinazolin-4-yl)-6-nitrobenzo[d]thiazol-2-amine (**30**) MW: 337.36 g/mol. Yellow solid (49%). mp 263 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.72 (s, 3H), 5.73 (br s, 1H), 7.60-7.90 (m, 4H), 8.22-8.26 (m, 1H), 8.60-8.63 (m, 1H), 8.93-8.94 (m, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 24.6 (CH_3), 119.6 (C), 119.0 (CH), 119.5 (CH), 119.8 (C), 122.2 (CH), 125.1 (CH), 127.1 (CH), 127.3 (CH), 133.9 (C), 134.8 (CH), 135.3 (C), 145.9 (C), 156.9 (C), 160.8 (C), 168.0 (C). LC-MS (ESI+) t_R 3.84 min, *m/z* $[M+H]^+$ 338.14. Anal. calcd. for $C_{16}H_{11}N_5O_2S$: C, 56.96; H, 3.29; N, 20.76. Found: C, 57.21; H, 3.25; N, 20.64.

4.4.6. 2-Methyl-N-(1-methyl-1H-benzo[d]imidazol-2-yl)quinazolin-4-amine (**31**) MW: 289.33 g/mol. Pale yellow solid (83%). mp 178 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.71 (s, 3H), 3.89 (s, 3H), 7.23-7.28 (m, 3H), 7.44-7.73 (m, 4H), 8.56 (d, *J* = 7.9 Hz, 1H), 14.56 (br s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 23.3 (CH_3), 28.7 (CH_3), 108.8 (CH), 116.4 (CH), 120.5 (C), 122.0 (CH), 122.2 (CH), 125.3 (2CH), 126.5 (CH), 133.0 (C), 133.7 (CH), 135.6 (C), 147.7 (C), 153.4 (C), 154.2 (C), 154.9 (C). LC-MS (ESI+) t_R 4.18 min, *m/z* $[M+H]^+$ 290.14. Anal. calcd. for $C_{17}H_{15}N_5$: C, 70.57; H, 5.23; N, 24.21. Found: C, 70.50; H, 5.27; N, 24.32.

4.4.7. 5-Chloro-N-(2-methylquinazolin-4-yl)benzo[d]oxazol-2-amine (**32**) MW: 310.74 g/mol. Beige solid (78%). mp 218 °C. (isopropanol). (eluent column chromatography CH_2Cl_2/AcOEt 9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.75 (s, 3H), 7.18-7.40 (m, 2H), 7.50-7.58 (m, 2H), 7.72-7.86 (m, 2H), 8.57 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.7 (CH_3), 110.7 (CH), 117.7 (CH), 119.7 (C), 123.8 (CH), 125.8 (2CH), 126.7 (C), 127.5 (CH), 129.6 (C), 135.05 (CH), 141.6 (C), 145.9 (C), 147.4 (C), 151.3 (C), 155.1 (C), 165.2 (C). LC-MS (ESI+) t_R 4.38 min, *m/z* $[M+H]^+$ 311.20/313.14. Anal. calcd. for $C_{16}H_{11}ClN_4O$: C, 61.84; H, 3.57; N, 18.03. Found: C, 61.97; H, 3.49; N, 17.89.

4.4.8. N-Phenyl-2-trichloromethylquinazolin-4-amine **(33)** [6] MW: 338.62 g/mol. Beige solid (90%). mp 150 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.15-7.23 (m, 1H), 7.40-7.48 (m, 2H), 7.62-7.71 (m, 2H), 7.84-7.88 (m, 1H), 7.93-7.99 (m, 3H), 8.07-8.11 (m, 1H).

4.4.9. N-(4-chlorophenyl)-2-(trichloromethyl)quinazolin-4-amine **(34)** [6] MW: 373.06 g/mol. Yellow solid (85%). mp 208 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.36-7.43 (m, 2H), 7.64-7.71 (m, 2H), 7.85-7.95 (m, 4H), 8.07-8.11 (m, 1H).

4.4.10. N-(p-tolyl)-2-(trichloromethyl)quinazolin-4-amine **(35)** [6] MW: 352.65 g/mol. Yellow solid (89%). mp 146 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.23 (s, 3H), 7.03-7.07 (m, 2H), 7.43-7.52 (m, 1H), 7.69-7.83 (m, 5H), 7.91-7.95 (m, 1H).

4.4.11. N-(4-nitrophenyl)-2-(trichloromethyl)quinazolin-4-amine **(36)** [6] MW: 383.62 g/mol. Yellow solid (96%). mp 294 °C. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 7.81-7.89 (m, 1H), 8.00-8.08 (m, 2H), 8.27-8.39 (m, 4H), 8.74 (d, *J* = 8.3 Hz, 1H), 10.65 (s, 1H).

4.4.12. N-(3-methoxyphenyl)-2-(trichloromethyl)quinazolin-4-amine **(37)** [6] MW: 368.64 g/mol. Yellow solid (98%). mp 142 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.89 (s, 3H), 6.71-6.76 (m, 1H), 7.14-7.33 (m, 2H), 7.66-7.70 (m, 2H), 7.84-7.93 (m, 2H), 8.05-8.12 (m, 2H).

4.4.13. N-(3-chlorophenyl)-2-(trichloromethyl)quinazolin-4-amine **(38)** [6] MW: 373.06 g/mol. Beige solid (97%). mp 174 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.11-7.17 (m, 1H), 7.25-7.37 (m, 1H), 7.63-7.75 (m, 3H), 7.85-7.95 (m, 2H), 8.06-8.11 (m, 1H), 8.21-8.23 (m, 1H).

4.4.14. 2-(trichloromethyl)-N-(3-(trifluoromethyl)phenyl)quinazolin-4-amine **(39)** [6] MW: 406.62 g/mol. Beige solid (91%). mp 139 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.41-7.58 (m, 2H), 7.66-7.74 (m, 1H), 7.82-7.96 (m, 1H), 8.00-8.13 (m, 4H), 8.53 (br s, 1H).

4.4.15. N-(2,4-dichlorophenyl)-2-(trichloromethyl)quinazolin-4-amine **(40)** [6] MW: 407.51 g/mol. White solid (82%). mp 204 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.40 (dd, *J* = 2.4 and 9.0 Hz, 1H), 7.48 (d, *J* = 2.4 Hz, 1H), 7.69-7.77 (m, 1H), 7.89-7.98 (m, 2H), 8.07-8.14 (m, 1H), 8.35 (br s, 1H), 9.10 (d, *J* = 9.0 Hz, 1H).

4.4.16. 2-methyl-N-phenylquinazolin-4-amine **(41)** [25] MW: 235.28 g/mol. Beige solid (91%). mp 166 °C (lit. 163-165 °C).[25] ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.65 (s, 3H), 7.32 (m, 1H), 7.49 (m, 2H), 7.77 (m, 4H), 8.15 (m, 1H), 8.59 (dd, *J* = 7.5 Hz, 1H).

4.4.17. N-(4-chlorophenyl)-2-methylquinazolin-4-amine **(42)** [26] MW: 269.73 g/mol. Pale beige solid (92%). mp 204 °C (lit. 203-205 °C).[26] ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.73 (s, 3H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.83 (m, 2H), 8.09 (t, *J* = 7.8 Hz, 1H), 8.61 (d, *J* = 8.3 Hz, 1H).

4.4.18. 2-Methyl-N-p-tolylquinazolin-4-amine **(43)** [26] MW: 249.31 g/mol. White solid (87%). mp 270 °C (lit. 265-268 °C).[26] ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.41 (s, 3H), 2.66 (s, 3H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.77 (m, 2H), 8.02 (m, 1H), 8.54 (m, 1H).

4.4.19. 2-Methyl-N-(4-nitrophenyl)quinazolin-4-amine **(44)** [26] MW: 280.28 g/mol. Pale yellow solid (97%). mp 141 °C (lit. 138-141 °C).[26] ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.74 (s, 3H), 7.84 (m, 2H), 8.15 (m, 3H), 8.36 (m, 2H), 8.60 (m, 1H).

4.4.20. N-(3-methoxyphenyl)-2-methylquinazolin-4-amine **(45)** [26] MW: 265.31 g/mol. Pale beige solid (95%). mp 218 °C (lit. 220-221 °C).[26] ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.72 (s, 3H), 3.85 (s, 3H), 6.30 (m, 1H), 7.40 (m, 3H), 7.82 (m, 2H), 8.09 (t, *J* = 7.5 Hz, 1H), 8.60 (d, *J* = 8.3 Hz, 1H).

4.4.21. N-(3-chlorophenyl)-2-methylquinazolin-4-amine **(46)** [6] MW: 269.73 g/mol. Beige solid (97%). mp 171 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.72 (s, 3H), 7.11 (dd, *J* = 0.9 and 8.0 Hz, 1H), 7.32 (dd, *J* = 8.0 and 8.2 Hz, 1H), 7.50 (dd, *J* = 0.9 and 8.0 Hz, 1H), 7.64–7.88 (m, 5H), 8.01 (br s, 1H).

4.4.22. 2-Methyl-N-(3-(trifluoromethyl)phenyl)quinazolin-4-amine **(47)** [7] MW: 303.28 g/mol. Beige solid (98%). mp 178 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.72 (s, 3H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.52 (dd, *J* = 7.3 and 7.7 Hz, 2H), 7.74–8.06 (m, 5H), 8.23 (br s, 1H).

4.4.23. N-(2,4-dichlorophenyl)-2-methylquinazolin-4-amine **(48)** [6] MW: 304.17 g/mol. Beige solid (98%). mp 154 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.75 (s, 3H), 7.32–7.38 (m, 1H), 7.45–7.46 (m, 1H), 7.52–7.60 (m, 1H), 7.77–7.85 (m, 1H), 7.90–7.94 (m, 2H), 8.19 (br s, 1H), 8.88 (d, *J* = 8.3 Hz, 1H).

4.5. Procedure for the preparation of N-methyl-N-(1-(2-(trichloromethyl)quinazolin-4-yl)pyridine-4(1H)-ylidene)methanaminium chloride **(49)**

A mixture of 4-chloro-2-trichloromethylquinazoline **1** (0.2 g, 0.71 mmol) and 1.0 equiv of DMAP (87 mg, 0.78 mmol) in toluene (3 mL) was introduced in miniaturized sealed reactor (5 mL). The reaction mixture was irradiated in a monomode microwave oven, for 30 min. at 130 °C. After removal of the toluene under reduced pressure, the residue was purified by silica gel column chromatography, using dichloromethane/ethyl acetate (7:3), afforded 0.28 g of compound **49**. White solid (100%), MW: 404.12 g/mol. mp 199 °C dec. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.55 (s, 6H), 7.64-7.68 (d, *J* = 7.8 Hz, 2H), 7.99-8.07 (m, 1H), 8.15-8.23 (m, 1H), 8.31-8.39 (m, 2H), 8.83 (d, *J* = 7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 41.4 ($2CH_3$), 95.4 (C), 109.5 (2CH), 115.9 (C), 123.6 (CH), 130.1 (CH), 132.0 (CH), 136.8 (CH), 140.7 (2CH), 152.6 (C), 157.5 (C), 158.6 (C), 159.5 (C). LC-MS (ESI+) t_R 3.24 min, *m/z* $[M+H]^+$ 367.04/369.10/371.12. HRMS (ESI+) *m/z* 367.0281 $[M+H]^+$, calcd. for $C_{16}H_{14}Cl_3N_4$: 367.0278.

Crystal data for compound ***49****:* $C_{18}H_{17}Cl_4N_5$, *M*=445.17, triclinic, *a*=9.0976 (3) Å, *b*=10.2471 (3) Å, *c*=12.0374 (4) Å, *α*=96.152 (3) °, *β*=111.436 (3) °, *γ*=97.826 (2) °, *V*=1019.73 (6) Å^3, *T*=223 K, space group *P* -1, *Z*=2.

Acknowledgements

This work was supported by the Centre National de la Recherche Scientifique (CNRS) and Aix-Marseille Université (AMU). C. Kieffer thanks the Assistance Publique-Hôpitaux de Marseille (AP-HM) for hospital appointment. The authors warmly thank Vincent Remusat for the ^{1}H and ^{13}C-NMR spectra recording.

References and notes

1. Gellibert, F.; Fouchet, M.-H.; Nguyen, V.-L. ; Wang, R. ; Krysa, G.; de Gouville, A.-C.; Huet, S.; Dodic, N. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 2277–2281.
2. Djekou, S.; Gellis, A.; Maldonado, J.; Crozet, M. P.; Vanelle, P. *Heterocycles*, **2001**, *55*, 535-544.
3. a) Kabri, Y.; Azas, N.; Dumètre, A.; Hutter, S.; Laget, M.; Verhaeghe, P.; Gellis, A.; Vanelle, P. *Eur. J. Med. Chem.* **2010**, *45*, 616-622; b) Curti, C.; Laget, M.; Carle, A. O.; Gellis, A.; Vanelle, P. *Eur. J. Med. Chem.* **2007**, *42*, 880-884.
4. a) Gellis, A.; Dumètre, A; Lanzada, G.; Hutter, S; Ollivier, E.; Vanelle, P.; Azas, N. *Biomed. Pharmacother*. **2012**, *66*, 339-347; b) Crozet, M. D.; Botta, C.; Gasquet, M.; Curti, C.; Remusat, V.; Hutter, S.; Chapelle, O.; Azas, N.; De Meo, M.; Vanelle, P. *Eur. J. Med. Chem.* **2009**, *44*, 653-659.
5. Verhaeghe, P.; Azas, N.; Gasquet, M.; Hutter, S.; Ducros, C.; Laget, M.; Rault, S.; Rathelot, P.; Vanelle, P. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 396.
6. Verhaeghe, P.; Azas, N.; Hutter, S.; Castera-Ducros, C.; Laget, M.; Dumètre, A.; Gasquet, M.; Reboul, J.-P.; Rault, S.; Rathelot, P.; Vanelle, P. *Bioorg. Med. Chem.* **2009**, *17*, 4313-4322.
7. Castera-Ducros, C.; Azas, N.; Verhaeghe, P.; Hutter, S.; Garrigue, P.; Dumètre, A.; Mbatchi, L.; Laget, M.; Remusat, V.; Sifredi, F.; Rault, S.; Rathelot, P.; Vanelle, P. *Eur. J. Med. Chem.* **2011**, *46*, 4184-4191.
8. Verhaeghe, P.; Dumètre, A.; Castera-Ducros, C.; Hutter, S.; Laget, M.; Fersing, C.; Prieri, M.; Yzombard, J.; Sifredi, S.; Rault, S.; Rathelot, P.; Vanelle, P.; Azas, N. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 6003-6006.
9. Primas, N.; Verhaeghe, P.; Cohen, A.; Kieffer, C.; Dumètre, A.; Hutter, S.; Rault, S.; Rathelot, P.; Azas, N.; Vanelle, P. *Molecules*, **2012**, *17*, 8105-8117.
10. Since, M.; Khoumeri, O.; Verhaeghe, P.; Maillard-Boyer, M.; Terme, T.; Vanelle, P. *Tetrahedron Lett*., **2011**, *52*, 3810-3813.
11. Verhaeghe, P.; Rathelot, P.; Gellis, A.; Rault; S.; Vanelle, P. *Tetrahedron*, **2006**, *62*, 8173-8176.
12. Kappe, C. O.; Dallinger, D. *Mol. Diversity*, **2009**, *13*, 71.
13. Caddick, S.; Fitzmaurice, R. *Tetrahedron*, **2009**, *65*, 3325.
14. Kabri, Y.; Verhaeghe, P.; Gellis, A.; Vanelle, P. *Molecules*, **2010**, *15*, 2949-2961.
15. Gellis, A.; Njoya, Y.; Crozet, M. P.; Vanelle, P. *Synth. Commun.*, **2001**, *31*, 1257-1262.
16. S. Djekou, S.; Gellis, A.; El-Kashef, H.; Vanelle, P. *J. Het. Chem.*, **2006**, *43*, 1225-1229.
17. Kabri, Y.; Gellis, A.; Vanelle, P. *Eur. J. Org. Chem.*, **2009**, 4059-4066.
18. Kappe, C. O.; Dallinger, D.; Murphree, S. S. *Practical Microwave Synthesis for Organic Chemists: Strategies Instruments and Protocols*, Wiley-VCH, Weinheim, **2009**.
19. Suzuki, M.; Kondo, K.; Kurimura, M.; Valluru, K.-R. ; Takahashi, A.; Kuroda, T.; Takahashi, H.; Fukushima, T.; Miyamura, S.; Ghosh, I.; Dogra, A.; Harriman, G.; Elder, A.; Shimizu, S.; Hodgetts K.; Newcom, J. Quinazolines as therapeutic compounds and related methods of use, U.S. Patent WO 2013/003586 A1, 2013.
20. Kieffer, C. ; Verhaeghe , P.; Primas , N.; Castera-Ducros , C.; Gellis , A.; Rosas , R.; Rault , S.; Rathelot , P.; Vanelle, P. Tetrahedron, 2013, 69, 2987-2995.
21. Murugan, R.; Sriven, E. F. V. *Aldrichimica Acta*. **2003**, *36*, 21.
22. Robey, R.L.; Alt, C.A.; DeAmicis, C.V. U.S. Patent 5,245,036, Sep 14, 1993; *Chem. Abstr*. **1994**, *120*, 30682n.
23. Shang, Y.; Wang, C.; He, X.; Ju, K.; Zhang, M.; Yu, S.; Wu, J. *Tetrahedron*, **2010**, *66*, 9629-9633.
24. Baidya, M.; Kobayashi, S.; Brotzel, F.; Schmidhammer, U.; Riedle, E.; Mayr, H. *Angew. Chem. Int. Ed.*, **2007**, *46*, 6176-6179.
25. Rocco, S.; Barbarini, J. E.; Rittner, R. *Synthesis* **2004**, 3, 429-435.
26. Kurteva, V. B.; Zlatanova, V. N.; Dimitrov, V. D. *Arkivoc*, **2006**, 46-56.