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Sonogashira cross-coupling reaction in 4-chloro-2-trichloromethylquinazoline series is possible despite a side dimerization reaction

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ABSTRACT

We studied the Sonogashira coupling reaction between 4-chloro-2-trichloromethylquinazoline and various terminal alkynes, mainly in phenylacetylene series. A brief review of the literature shows that mono- or polybromo/chloromethylated substrates, especially in aromatic series, are very rarely compatible with the achievement of Sonogashira reactions. Thus, although the 4-chloroquinazoline scaffold is a very good substrate for this palladium-catalyzed reaction, the typical behavior of the trichloromethyl group in reductive media leads to the competitive formation of undesirable reduced homodimers in high yields. However, by closely examining all the Sonogashira reaction parameters, we developed a specific operating procedure, using $Pd(OAc)_2$, Cs_2CO_3, and DMF, which resulted in the synthesis of 14 original coupling products in 10–70% yield, depending on the alkyne used.

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1. Introduction

In 1975, Kenkichi Sonogashira and co-workers reported a palladium-catalyzed substitution of acetylenic hydrogen with haloalkenes, haloarenes, and halopyridines.[1] Today, the Sonogashira cross-coupling reaction between haloaryl derivatives and terminal alkynes has become the most commonly used reaction for functionalizing aromatic scaffolds with alkynyl groups. This reaction, operated in mild conditions, has a wide compatibility with most functional groups and can easily be extended to numerous commercial terminal alkynes.

Among the heteroaromatic rings with pharmaceutical potential, quinazoline is a key nucleus encountered in several major drug-compounds used in the treatment of prostatic hypertrophy (doxazosine, alfuzosine, terazosine), hypertension (prazosine) and in oncology (erlotinib, gefitinib, lapatinib and vandetanib). In attempts to discover new anticancer agents, quinazolines bearing an alkynyl group at position 4 or 6 were prepared by different research teams, appearing very promising because of their excellent EGFR or Aurora A kinase inhibition activity.[2,3]

In recent years, as part of our search for new bioactive compounds,[4–6] our research group has been synthesizing and developing original quinazolines bearing an aryl-,[7] aniline-,[8,9] phenoxy-,[10] thiophenoxy-,[11] nitrobenzylic-[12] or arylsulfamide-group[13] at position 4 of the quinazoline ring. Thus, several new antiplasmodial hit-compounds were identified, sharing a 4-substituted-2-trichloromethylquinazoline scaffold. In each bioactive series, the key role of the trichloromethyl group in antiplasmodial activity was demonstrated.

In addition to its biological interest, the trichloromethyl group has long been known as a valuable synthetic precursor for the preparation of carboxylic acids, amides and more specifically, amidines, vinylic chlorides, α-chloroketones, and trifluoromethylated compounds.[14–17]

As a complement to our antiplasmodial pharmacomodulation study, we decided to explore the Sonogashira coupling reaction between various terminal alkynes and 4-chloro-2-trichloromethylquinazoline **1**, taking into account that this substrate had already been successfully involved into Suzuki–Miyaura palladium-catalyzed coupling reactions with boronic acids.[7]

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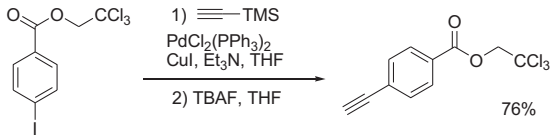
From a bibliographical point of view (Scifinder® substructure search, November 30th 2012), it rapidly appeared that, concerning Sonogashira reactions between aromatic halomethylated substrates (−CCl_3, −CBr_3, −$CHCl_2$, −$CHBr_2$, −CH_2Cl, −CH_2Br) and terminal alkynes, very few references were reported, only with chloromethylated substrates.[18] Thus, for example, the Sonogashira reaction between 1-bromomethyl-2-iodobenzene and various alkynes was presented as unsuccessful, requiring that the Sonogashira reaction be achieved on the 2-iodophenylmethanol before the bromomethyl group was re-introduced.[19] In aliphatic series, more references about Sonogashira reactions performed on chloro- or bromomethylated substrates are available, mainly using Pd(II) containing catalysts.[20] More specifically, concerning trichloromethylated substrates involved into Sonogashira coupling reactions, there is only one reference available,[21] in which the trichloromethyl group belongs to an aliphatic chain (Scheme 1).

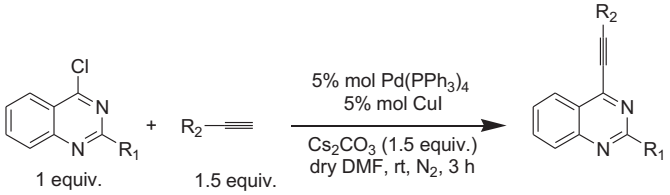


Scheme 1. Single example (reported by Christensen and co-workers) of a Sonogashira cross-coupling reaction involving a trichloromethyl-containing substrate.[21]

This brief review of the literature showed that the Sonogashira reaction may have a poor compatibility with the use of aromatic (mono or poly) halomethylated substrates, as one of the main limitations of this palladium-catalyzed coupling reaction.

2. Results and discussion

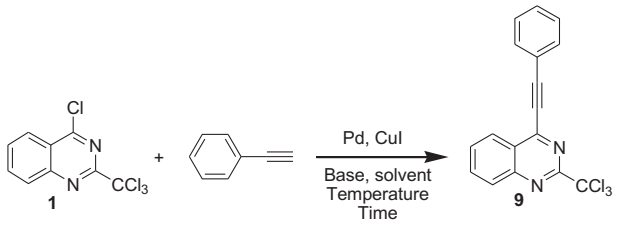
Effectively, our first attempts to perform a Sonogashira coupling reaction between 4-chloro-2-trichloromethylquinazoline **1** (whose microwave-assisted preparation was previously reported[22]) and cyclopropylacetylene or phenylacetylene, using classical reaction conditions (nitrogen atmosphere, TEA as a base, $Pd(PPh_3)_4$ as catalyst, CuI as co-catalyst, and THF as solvent), were unsuccessful and did not allow LC/MS detection of the expected coupling products in the reaction media. In order to show that the presence of a trichloromethyl group at position 2 was responsible for this reaction failure, we carried out some Sonogashira coupling reactions from 4-chloroquinazoline analogs bearing a hydrogen atom, a methyl or a trifluoromethyl group at position 2. For this purpose, 4-chloro-2-methylquinazoline **2** was prepared as previously reported.[23] After a few brief operating procedure adjustments, the corresponding 4-alkynylquinazolines (**3**–**8**) were obtained in good to excellent yields, using 5 mol % $Pd(PPh_3)_4$, 5 mol % CuI, 1.5 equiv of Cs_2CO_3 in dry DMF, under nitrogen atmosphere, at room temperature for 3 h (Scheme 2). It should be noted that these Sonogashira coupling reactions involving non-trichloromethylated quinazolines did not work when using Pd(II)-containing catalysts. We were thus able to conclude that the trichloromethyl group was effectively disturbing the Sonogashira coupling reaction.



3: R_1 = CH_3; R_2 = Ph 90%
4: R_1 = CH_3; R_2 = Cyclopropyl 98%
5: R_1 = H; R_2 = Ph 95%
7: R_1 = CF_3; R_2 = Ph 75%
8: R_1 = CF_3; R_2 = Cyclopropyl 60%
6: R_1 = H; R_2 = Cyclopropyl 72%

Scheme 2. Sonogashira coupling reactions in CCl_3-free 4-chloroquinazoline series.

We then extensively explored the Sonogashira coupling reaction between 4-chloro-2-trichloromethylquinazoline **1** and phenylacetylene, closely investigating each of the reaction parameters in turn, in order to try to identify favorable conditions to obtain the desired 4-phenylethynyl-2-trichloromethyl-quinazoline **9** (Scheme 3).



Scheme 3. General scheme for the study of the Sonogashira coupling reaction between 4-chloro-2-trichloromethylquinazoline **1** and phenylacetylene.

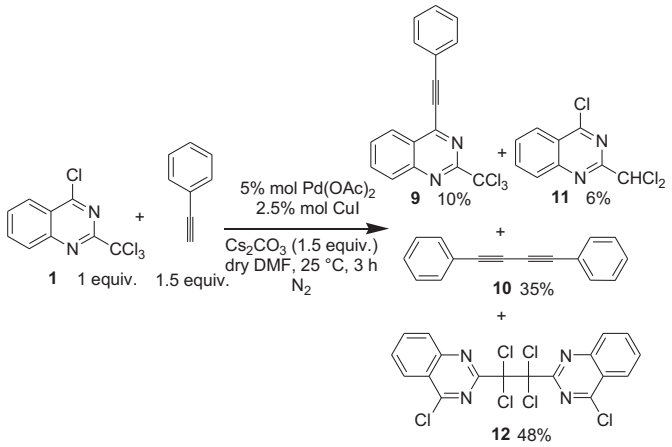
All 110 assays were done in small sealed reactors and the evolution of the reactions was monitored by LC/MS. We found that certain reaction conditions allowed the formation of compound **9**. The tested parameters and the best combination obtained are presented in Table 1.

Table 1
Sonogashira coupling reaction in 4-chloro-2-trichloromethylquinazoline series: reaction parameters studied

Parameters	Trials	Best reaction conditions
Solvent	THF; DMF; DMSO; TEA; acetonitrile; water	Dry DMF
Catalyst	$Pd(OAc)_2$; $PdCl_2$; $Pd(PPh_3)_2Cl_2$; $Pd(PPh_3)_4$	$Pd(OAc)_2$
Co-catalyst	None; 2.5 mol % CuI; 5 mol % CuI	2.5% CuI
Base	TEA; $NaHCO_3$; Na_2CO_3; Cs_2CO_3; $(Bu)_4N^+AcO^-$	Cs_2CO_3
Temperature	0 °C; 25 °C; 50 °C; 80 °C	25 °C
Time	Monitored by LC/MS	3 h
Catalyst (equiv)	1 mol %; 2.5 mol %; 5 mol %	5 mol %
Alkyne and base (equiv)	1 equiv; 1.5 equiv; 2 equiv	1.5 equiv

Not all the parameters studied had the same degree of effect on the reactivity of substrate **1** with phenylacetylene. Thus, presence or absence or amount of CuI, reaction temperature, reaction time and number of equivalents of either catalyst or alkyne did not have a major effect on the chromatogram profiles whereas solvent, catalyst, and base had a decisive impact on the reaction profile. Among the solvents, only dry DMF permitted the synthesis of **9**. Among all the palladium catalysts, only those containing Pd(II) allowed the formation of **9**, with very slight differences being noted between them. Contrary to the results previously obtained with non-trichloromethylated-4-chloroquinazolines, the use of $Pd(PPh_3)_4$ led to the detection of undesirable products only. Among the bases, only cesium carbonate and triethylamine appeared compatible with the production of **9**, cesium carbonate being slightly more favorable. Even without CuI, the reaction was able to take place. As for reaction temperature, slight heating to 50 °C, instead of room temperature, led to faster consumption of substrate **1** accompanied with greater quantities of by-products. Thus, by reacting **1** with 1.5 equiv of phenylacetylene for 3 h in dry DMF, using 1.5 equiv of Cs_2CO_3, 5 mol % of $Pd(OAc)_2$, and 2.5 mol % of CuI, at room temperature, under nitrogen atmosphere, coupling product **9** was only isolated in 10% yield (Scheme 4).

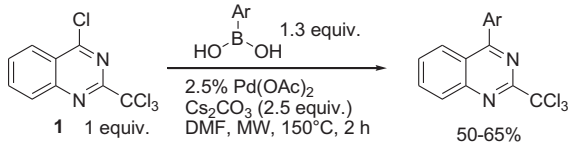
It should be noted that the reaction conditions allowing the formation of **9** appeared fully analogous to those which afforded the Suzuki–Miyaura cross-coupling reaction with boronic acids in



*Reaction yields of **9**, **11** and **12** were calculated from **1** while reaction yield of **10** was calculated from terminal alkyne*

Scheme 4. Sonogashira coupling reaction between **1** and phenylacetylene: isolation and characterization of reaction products.

the same 4-chloro-2-trichloromethylquinazoline series (Scheme 5).[7] It therefore appears that the combination of DMF/$Pd(OAc)_2$ was the most compatible with the preservation of the CCl_3 group in this series.

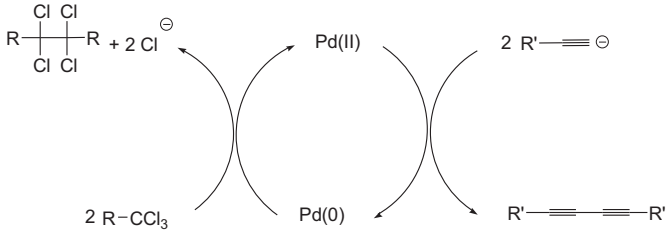


Scheme 5. Suzuki–Miyaura cross-coupling reaction conditions for the preparation of 4-aryl-2-trichloromethylquinazolines from **1**.[7]

Moreover, the first and unique example of a trichloromethyl-containing substrate involved in a Sonogashira coupling reaction[21] (Scheme 1) was also reported for a procedure using a Pd(II) containing catalyst, arguing for the crucial effect of the palladium oxidation state on compatibility with the trichloromethyl group in palladium-catalyzed coupling reactions.

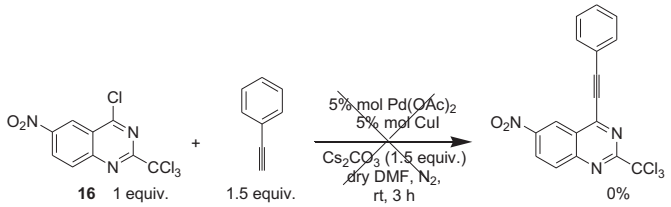
To examine the reasons leading to the low yield obtained in the synthesis of **9**, all reaction sub-products, which had been identified by LC/MS were isolated, in order to determine their respective yields (Scheme 4). This research showed that, in addition to coupling product **9**, the reaction of **1** with phenylacetylene gave three sub-products: alkyne dimer **10** in 35% yield, reduced dichloromethyl substrate-analog **11** in 6% yield and reduced dimerized-substrate **12** in high 48% yield. The exact structure of dimer **12** was determined according to both HSQC and HMBC 2D NMR experiments and identification of a typical fragment on mass spectrum ($C_8H_4ClN_2^+$). The dimerization of terminal alkynes in Sonogashira coupling reactions is a very well-known and frequently described undesirable competitive reaction corresponding to an oxidative dimerization of the copper(I) alkynyl salt.[24,25] Moreover, dimers analogous to compound **12** are reported in the literature when trichloromethylated molecules react with stoichiometric amounts of reductive agents such as iron(II)[26] or palladium(0).[27] This reaction corresponds to a reductive homocoupling of trichloromethylated molecules. Thus, the Sonogashira reaction medium could be a reductive medium in which trichloromethylated substrates undergo reductive homocouplings.

In order to clarify the mechanism of the reductive homocouplings of trichloromethylated species, two reaction assays were performed. Taking the appropriate Sonogashira coupling reaction conditions previously identified in the studied series, the first assay was performed without any palladium catalyst, while the second assay was performed without any base. None of these assays was able to produce a reaction, substrate **1** and terminal alkyne remaining unconsumed after several hours at either room temperature or 50 °C. These results indicate that, like the Sonogashira reaction, dimerization reactions require both the presence of palladium in the reaction medium and the preliminary formation of alkynyl salts. Moreover, when the reaction was carried out without CuI, both the Sonogashira coupling product **9** and homodimerized substrate **12** were still formed in the same proportions. Taken together, these findings therefore suggest that electrons coming from the oxidative dimerization of alkynyl salts in alkyne dimer may be transferred to trichloromethylated molecules, via a catalytic cycle of palladium allowing their reductive homodimerization and the liberation of chloride anions (Scheme 6). Thus the dimerization reaction of the trichloromethylated substrate in high yields remains possible even with catalytic amounts of palladium.



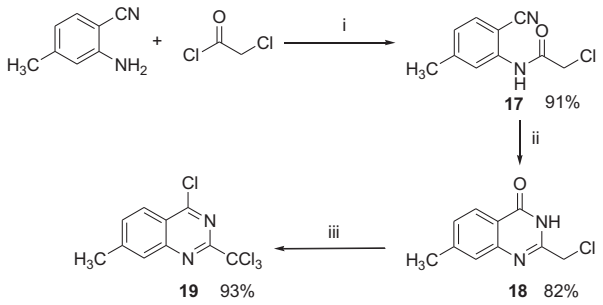
Scheme 6. Possible mechanism explaining the reductive homocoupling of **1** in the Sonogashira reaction medium.

To support this mechanistic hypothesis, the Sonogashira reaction with phenylacetylene was then performed from 4-chloro-6-nitro-2-trichloromethyl-quinazoline **16** (prepared as previously described[28]), using the same Sonogashira reaction conditions. As presented in Scheme 7, no Sonogashira coupling product was obtained. Then, 4-chloro-7-methyl-2-trichloromethylquinazoline **19** was prepared in three steps[29] (Scheme 8) and reacted with phenylacetylene (Scheme 9) in the same conditions, affording the coupling product **20** in 15% yield. Thus, it appears that the redox potential of the 2-trichloromethylated quinazoline involved in the reaction has a great influence toward its reductive homodimerization, in competition with the Sonogashira coupling reaction. The most reducible substrate (**16**) does not allow any Sonogashira reaction (reaction yield=0%), intermediate substrate **1** affords a 10% Sonogashira coupling yield while less reducible substrate **19** can lead to the corresponding coupling product in 15% yield accompanied with smaller amount of substrate dimer **22** (25%). Then, among the parameters determining the feasibility of the Sonogashira coupling reactions on aromatic trichloromethylated substrates, the redox potential of these last may be a key criteria.



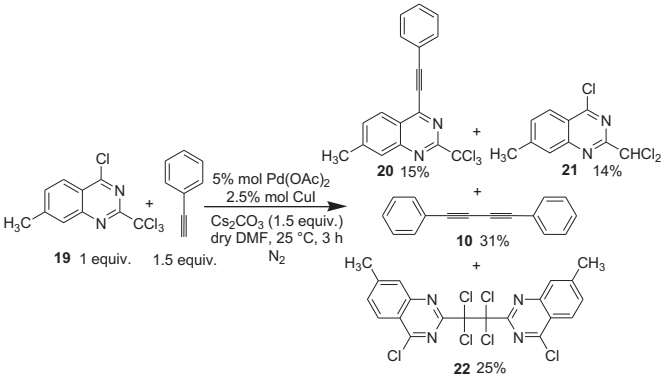
Scheme 7. Unsuccessful Sonogashira reaction between **16** and phenylacetylene.

Indeed, when the Sonogashira reaction of **1** with cyclopropylacetylene took place in the appropriate reaction conditions previously described, the expected coupling product **13** was obtained in 19% yield accompanied by both the alkyne dimer **14** in 24% yield and the coupling product dimer **15** in 4% yield (Scheme 10).



Reaction conditions: i) pyridine, DMF, MW, 150 W, 50 °C, 5 min; ii) H_2O_2, NaOH, EtOH/H_2O (2/1), 50 °C, 5 min; iii) PCl_5 (4 equiv.), $POCl_3$, 800 W, 110 °C, 30 min

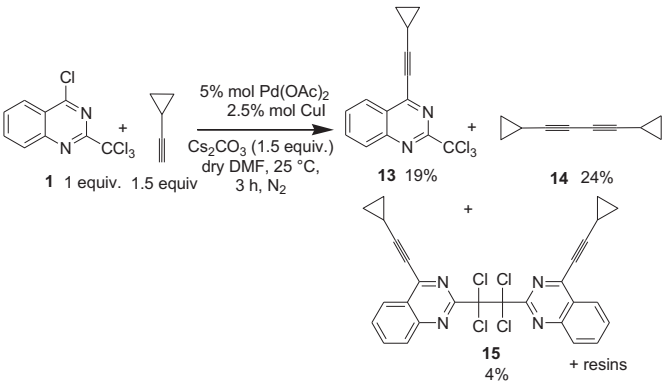
Scheme 8. Preparation of substrate **19**.



*Reaction yields of **20**, **21** and **22** were calculated from **19** while reaction yield of **10** was calculated from terminal alkyne*

Scheme 9. Reaction between **19** and phenylacetylene.

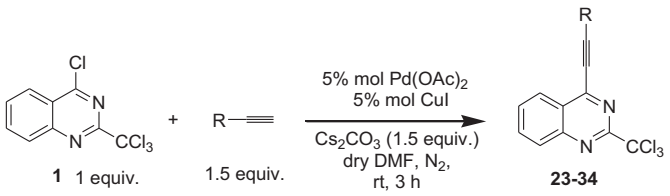
This last dimeric compound shows that reductive homocouplings of all trichloromethylated species present in the Sonogashira reaction medium are very problematic competitive reactions responsible for the difficulty in obtaining good yields of the expected Sonogashira coupling product.



*Reaction yields of **13** and **15** were calculated from **1** while reaction yield of **14** was calculated from terminal alkyne*

Scheme 10. Sonogashira coupling reaction between **1** and cyclopropylacetylene: isolation and characterization of reaction side products.

Despite the low reaction yields obtained for the synthesis of products **9** and **13**, since we needed to prepare small amounts of 4-alkynylsubstituted-2-trichloromethylquinazolines for our antiplasmodial pharmacomodulation study, we extended the Sonogashira coupling reaction to several terminal alkynes, mainly in phenylacetylene series. As presented in Scheme 11, we used the previously optimized reaction conditions.



Scheme 11. General reaction for the synthesis of 4-alkynyl-2-trichloromethylquinazolines **23**–**34**.

Thus, we synthesized a global series including 14 original derivatives bearing both a trichloromethyl group at position 2 and diverse alkynyl groups at position 4 of the quinazoline ring. For each of these 14 reactions, dimerized side products were only identified by LC/MS but not isolated. The X-ray diffraction analysis of compound **34** is presented in Fig. 1. To our surprise the reaction yields varied from 10 to 70%, depending only on the nature of the terminal alkyne used (Table 2). Overall when it comes to phenylacetylenes, the Sonogashira reaction appears favored when the phenyl ring is substituted by electron-donating groups such as methyl or methoxy groups, especially when several of these groups are present. In our case, the reaction did not work with phenylacetylenes bearing a fluorine atom on the phenyl ring.

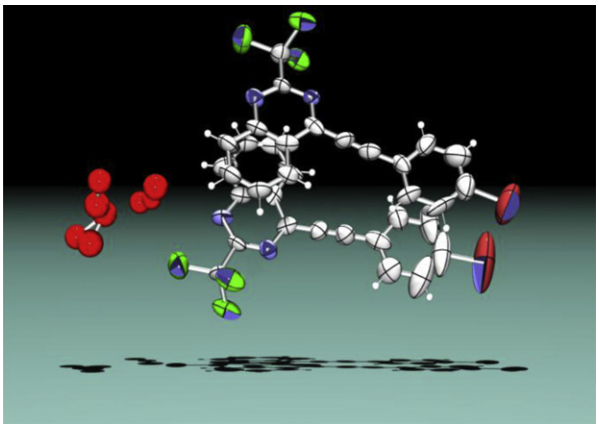
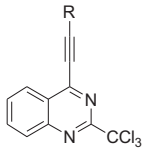


Fig. 1. X-ray structure of compound **34**.

These results are not in agreement with those previously obtained from the study of the Sonogashira coupling reaction between aryl bromides and phenylacetylenes,[30] which reported that the use of phenylacetylenes substituted by electron-withdrawing groups increases the Sonogashira coupling yield. At that stage, the only hypothesis, which could be made about such differences in reaction yields is that the value of the redox potential of the alkynyl-salt/alkyne couple versus the one of the Pd(II)/Pd(0) couple (E^0=0.98 V) would be key to the feasibility of the Sonogashira reaction with trichloromethylated substrates, by controlling the regeneration of Pd(0) responsible for the substrate reductive dimerization.

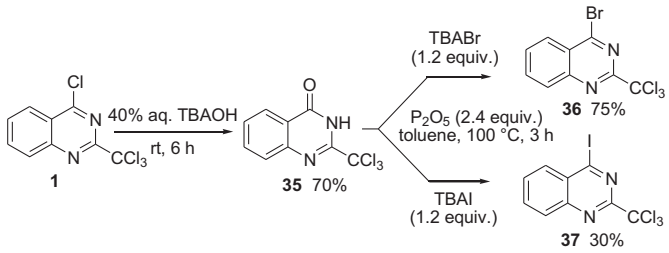
Lastly considering that our problem came from competition between two different reactions, we hypothesized that it might be possible to increase the Sonogashira coupling reaction yields by using brominated or iodinated derivatives **36** or **37** instead of 4-chloro-2-trichloromethylquinazoline **1**, to favor the Sonogashira coupling reaction. To evaluate this possibility, compounds **36** and **37** were prepared in two steps from **1** by successive S_NAr reaction

Table 2
Synthesized series of 4-alkynyl-2-trichloromethylquinazolines: reaction yields



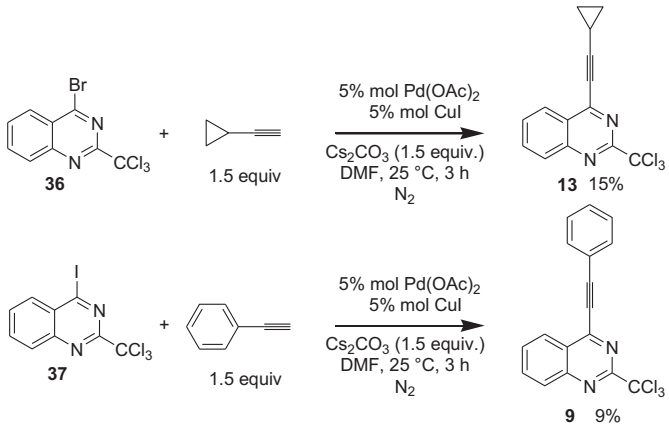
Compound	R–	Yields (%)
9	Ph–	10
13	Cyclopropyl–	19
23	Cyclopentyl–	11
24	4-CH_3–Ph–	21
25	3-CH_3–Ph–	20
26	2-CH_3–Ph–	41
27	2,3,4-CH_3–Ph–	70
28	4-*t*-Bu–Ph–	15
29	4-OCH_3–Ph–	18
30	3-OCH_3–Ph–	10
31	2-OCH_3-Ph-	18
32	(2-CH_3,4-OCH_3)–Ph–	45
33	2-Cl–Ph–	15
34	4-Br–Ph–	14
—	3-F–Ph–	0
—	4-F–Ph–	0

with TBAOH, affording lactam **35**, followed by reaction with either TBABr or TBAI, in the presence of P_2O_5 in toluene, as described in Scheme 12.



Scheme 12. Synthesis of 4-bromo-2-trichloromethylquinazoline **36** and 4-iodo-2-trichloromethylquinazoline **37** from 4-chloro-precursor **1**.

Then, these new substrates were involved in Sonogashira coupling reactions with phenylacetylene or cyclopropylacetylene. As presented in Scheme 13, the expected corresponding coupling products **9** and **13** were obtained in low yields (9 and 15%) even lower than those obtained by using substrate **1** (10 and 19%). These last results indicate that the Sonogashira coupling yield cannot be improved by changing the nature of the halogen atom at position 4



Scheme 13. Sonogashira coupling assays from brominated and iodinated analogs of **1**.

of the 2-trichloromethylquinazoline scaffold and that 4-chloro-2-trichloromethylquinazoline **1** is the most appropriate substrate in the studied series.

3. Conclusion

Despite the very good reactivity of the 4-chloroquinazoline scaffold toward the Sonogashira coupling reaction, the presence of a trichloromethyl group at position 2 of the same scaffold leads to the competitive formation of tetrachlorinated homodimers, responsible for global low Sonogashira coupling yields. These experimental results added to a review of the scientific literature show that the reducing character of the Sonogashira reaction medium is responsible for its poor compatibility with aromatic halomethylated substrates, which appears as one of the main limitations of this very useful palladium-catalyzed reaction. However, a detailed analysis of all the reaction parameters allowed us to determine specific reaction conditions using $Pd(OAc)_2$, DMF, and Cs_2CO_3, improving the preservation of the trichloromethyl group. Thus, a series of fourteen 4-alkynyl-2-trichloromethylquinazolines were synthesized, reaction yields varying from 10 to 70%, depending only on the alkyne used. The biological studies of the compounds described in this article are currently under investigation and will be published elsewhere.

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-Jérôme (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 ^1H 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×10 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® 50×2.1 mm (C18 bounded), with particles of a diameter of 1.9 μm. 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 mM. The retention times (t_R) of the molecules analyzed are indicated in min. The microwave reactions were performed in sealed vials, using a Biotage Initiator Microwave oven.

4-Chloroquinazolineand 2-methyl-4(3*H*)-quinazolinone were purchased from Sigma–Aldrich. 4-Chloro-2-trifluoromethylquinazoline was purchased from Alfa Aesar.

4.2. Molecules prepared according to previously described procedures

4-Chloro-2-trichloromethylquinazoline **1**, 4-chloro-2-methylquinazoline **2**, and 4-chloro-6-nitro-2-trichloromethylquinazoline **16**were prepared as previously described.[22,23,28]

*4.2.1. 4-Chloro-2-trichloromethylquinazoline (**1**).* $C_9H_4Cl_4N_2$. MW: 282.18 g/mol. White solid (75%). 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). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 95.9 (C), 122.9 (C), 126.0 (CH), 129.7 (CH), 130.6 (CH), 135.9 (CH), 150.2 (C), 159.9 (C), 164.0 (C).

*4.2.2. 4-Chloro-2-methylquinazoline (**2**).* $C_9H_7ClN_2$. MW: 178.62 g/mol. White solid (60%). 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). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.0 (CH_3), 121.8 (C), 125.7 (CH), 128.0 (2CH), 134.8 (CH), 151.5 (C), 162.1 (C), 163.5 (C).

*4.2.3. 4-Chloro-6-nitro-2-trichloromethylquinazoline (**16**).* $C_9H_3Cl_4N_3O_2$. MW: 326.95 g/mol. Beige solid (70%). Mp 95 °C (lit. 94–96 °C).[28] ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.38–8.43 (m, 1H), 8.80–8.86 (m, 1H), 9.25–9.26 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 29.8 (C), 95.4 (C), 122.7 (CH), 129.4 (CH), 132.1 (CH), 148.0 (C), 152.6 (C), 162.7 (C), 166.3 (C).

4.3. General procedure for the preparation of compounds 3–8

A mixture of appropriate quinazoline substrate (4-chloroquinazoline, or 4-chloro-2-trifluoromethylquinazoline or 4-chloro-2-methylquinazoline **1**) (500 mg, 1 equiv), tetrakis(-triphenylphosphine)palladium(0) (0.05 equiv), copper iodide (0.05 equiv), cesium carbonate (1.5 equiv), appropriate alkyne (1.5 equiv), and dry DMF (10 mL) was stirred under N_2 at room temperature for 3 h. Water was then added and the mixture was extracted with CH_2Cl_2 (2×20 mL). The organic layer was washed with water (5×200 mL), dried over Na_2SO_4, filtered, and evaporated. The crude residue was purified by column chromatography (silica gel, appropriate eluent) and washed with petroleum ether to give the corresponding coupling products (**3**–**8**).

*4.3.1. 2-Methyl-4-(2-phenylethynyl)quinazoline (**3**).* MW: 244.29 g/mol. Yellow solid (90%). Mp 98 °C (eluent column chromatography CH_2Cl_2/AcOEt 1:1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.91 (s, 3H), 7.39–7.47 (m, 3H), 7.58–7.66 (m, 1H), 7.71–7.76 (m, 2H), 7.83–7.97 (m, 2H), 8.33–8.37 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.5 (CH_3), 85.2 (CH), 98.1 (C), 121.1 (C), 123.2 (C), 126.4 (CH), 127.3 (CH), 128.0 (CH), 128.6 (2CH), 130.1 (CH), 132.5 (2CH), 134.3 (CH), 150.5 (C), 152.6 (C), 164.2 (C). LC/MS (ESI$^+$) t_R 3.93 min, m/z $[M+H]^+$ 245.47. HRMS (ESI$^+$) m/z 245.1074 $[M+H]^+$, calcd for $C_{17}H_{12}N_2$+H: 245.1073.

*4.3.2. 4-[2-(Cyclopropylethynyl)]-2-methylquinazoline (**4**).* MW: 208.26 g/mol. Beige solid (98%). Mp 48 °C (eluent column chromatography CH_2Cl_2/AcOEt 1:1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.84–0.88 (m, 4H), 1.41–1.54 (m, 1H), 2.67 (s, 3H), 7.34–7.38 (m, 1H), 7.57–7.71 (m, 2H), 7.94–7.88 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 0.2 (CH), 9.3 ($2CH_2$), 26.0 (CH_3), 72.3 (C), 104.3 (C), 122.7 (C), 126.0 (CH), 126.7 (CH), 127.4 (CH), 133.6 (CH), 149.8 (C), 152.6 (C), 163.5 (C). LC/MS (ESI$^+$) t_R 2.85 min, m/z $[M+H]^+$ 209.38. HRMS (ESI$^+$) m/z 209.1075 $[M+H]^+$, calcd for $C_{14}H_{12}N_2$+H: 209.1073.

*4.3.3. 4-(Phenylethynyl)quinazoline (**5**).* $C_{16}H_{10}N_2$. MW: 230.26 g/mol. Pale yellow solid (95%). Mp 66 °C (lit. 66–67 °C)[31] (petroleum ether) (eluent column chromatography CH_2Cl_2/AcOEt 9:1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.41–7.47 (m, 3H), 7.69–7.77 (m, 3H), 7.90–7.99 (m, 1H), 8.05–8.09 (m, 1H), 8.40–8.44 (m, 1H), 9.32 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 85.2 (C), 98.7 (C), 121.1 (C), 125.3 (C), 126.5 (CH), 128.4 (CH), 128.7 (2CH), 128.8 (CH), 130.3 (CH), 132.6 (2CH), 134.3 (CH), 150.2 (C), 152.6 (C), 155.0 (CH).

*4.3.4. 4-(Cyclopropylethynyl)quinazoline (**6**).* MW: 194.23 g/mol. Yellow oil (72%) (eluent column chromatography CH_2Cl_2/AcOEt 7:3). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.05–1.08 (m, 4H), 1.60–1.72 (m, 1H), 7.61–7.69 (m, 1H), 7.85–7.93 (m, 1H), 7.99–8.03 (m, 1H), 8.22–8.26 (m, 1H), 9.20 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 0.6 (CH), 9.7 ($2CH_2$), 72.7 (C), 105.3 (C), 125.4 (C), 126.6 (CH), 128.1 (CH), 128.6 (CH), 134.1 (CH), 149.9 (C), 153.0 (C), 154.8 (CH). LC/MS (ESI$^+$) t_R 2.38 min, m/z $[M+H]^+$ 195.24. HRMS (ESI$^+$) m/z 195.0926 $[M+H]^+$, calcd for $C_{13}H_{10}N_2$+H: 195.0917.

*4.3.5. 4-(Phenylethynyl)-2-trifluoromethylquinazoline (**7**).* MW: 298.26 g/mol. White solid (75%). Mp 162 °C (eluent column chromatography CH_2Cl_2/petroleum ether 1:1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.42–7.52 (m, 3H), 7.76–7.81 (m, 2H), 7.87–7.90 (m, 1H), 8.02–8.11 (m, 1H), 8.20–8.24 (m, 1H), 8.49–8.54 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 84.8 (C), 101.1 (C), 119.8 (q, J=275.0 Hz, C), 120.6 (C), 125.4 (C), 126.7 (CH), 128.7 (2CH), 129.4 (CH), 130.3 (CH), 130.7 (CH), 132.7 (2CH), 135.5 (CH), 149.8 (C), 152.1 (q, J=36 Hz, C), 154.0 (C). LC/MS (ESI$^+$) t_R 4.55 min, m/z $[M+H]^+$299.19. HRMS (ESI$^+$) m/z 299.0790 $[M+H]^+$, calcd for $C_{17}H_9F_3N_2$+H: 299.0790.

*4.3.6. 4-(Cyclopropylethynyl)-2-trifluoromethylquinazoline (**8**).* MW: 262.23 g/mol. White solid (60%). Mp 155 °C (eluent column chromatography CH_2Cl_2/petroleum ether 1:1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.12 (d, J=6.7 Hz, 4H), 1.66–1.77 (m, 1H), 7.75–7.83 (m, 1H), 7.97––8.05 (m, 1H), 8.14–8.18 (m, 1H), 8.31–8.35 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 0.8 (CH), 9.9 ($2CH_2$), 72.5 (C), 108.2 (C), 119.8 (q, J=275 Hz, C), 125.5 (C), 126.8 (CH), 129.3 (CH), 130.0 (CH), 135.2 (CH), 149.5 (C), 152.6 (q, J=36.6 Hz, C), 154.5 (C). LC/MS (ESI$^+$) t_R 3.78 min, m/z $[M+H]^+$263.24. Anal. Calcd for $C_{14}H_9F_3N_2$: C, 64.12; H, 3.46; N, 10.68%. Found: C, 64.69; H, 3.86; N, 10.17%.

4.4. General procedure for the preparation of compounds 9–15 and 20–34

To a sealed flask containing 1 g (3.54 mmol, 1 equiv) of 4-chloro-2-trichloromethylquinazoline **1**, palladium acetate (40 mg, 0.18 mmol, 0.05 equiv), copper iodide (33 mg, 0.177 mmol, 0.05 equiv), and cesium carbonate (1730 mg, 5.31 mmol, 1.5 equiv) were successively added. Then, under N_2 atmosphere, dry DMF (20 mL) and appropriate alkyne (1.5 equiv) were injected. The solution was stirred at room temperature for 3 h. Water was then added and the mixture was extracted with CH_2Cl_2 (2×30 mL). The organic layer was washed with water (5×100 mL), dried over Na_2SO_4, filtered, and evaporated. The crude residue was purified by column chromatography (silica gel, petroleum ether/CH_2Cl_2 1:1) and washed in petroleum ether to give the corresponding coupling products (**9**–**15** and **20**–**34**).

*4.4.1. 4-(Phenylethynyl)-2-trichloromethylquinazoline (**9**).* MW: 347.62 g/mol. Pale yellow solid (10%). Mp 203 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.43–7.49 (m, 3H), 7.78–7.86 (m, 3H), 7.99–8.07 (m, 1H), 8.18–8.22 (m, 1H), 8.46–8.50 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 85.0 (C), 95.9 (C), 100.4 (C), 120.8 (C), 124.2 (C), 126.6

(CH), 128.7 (2CH), 129.6 (CH), 129.9 (CH), 130.6 (CH), 132.7 (2CH), 135.2 (CH), 149.5 (C), 154.1 (C), 161.1 (C). LC/MS (ESI^+) t_R 5.10 min, m/z $[M+H]^+$ 347.19/349.10/351.11. HRMS (ESI^+) m/z 346.9903 $[M+H]^+$, calcd for $C_{17}H_9Cl_3N_2$+H: 346.9904.

*4.4.2. 1,4-Diphenylbuta-1,3-diyne (**10**).* $C_{16}H_{10}$. MW: 202.25 g/mol. yellow solid (35%). Mp 85 °C (lit. 85–87 °C).[32] ^1H NMR ($CDCl_3$, 200 MHz): δ 7.31–7.37 (m, 6H), 7.52–7.56 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 73.9 (2C), 81.5 (2C), 121.8 (2C), 128.4 (4CH), 129.2 (2CH), 132.5 (4CH).

*4.4.3. 4-Chloro-2-dichloromethylquinazoline (**11**).* $C_9H_5Cl_3N_2$. MW: 247.51 g/mol. White solid (6%). Mp 140 °C (lit. 135–137 °C).[33] ^1H NMR ($CDCl_3$, 200 MHz): δ 6.86 (s, 1H), 7.77–7.85 (m, 1H), 7.99–8.14 (m, 2H), 8.30–8.35 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 70.5 ($CHCl_2$), 123.3 (CH), 126.0 (CH), 129.2 (CH), 130.1 (CH), 135.7 (CH), 150.7 (C), 160.1 (C), 164.1 (C).

*4.4.4. 1,1,2,2-Tetrachloro-1,2-bis(4-chloroquinazolin-2-yl)ethane (**12**).* MW: 493.00 g/mol. Beige solid (48%). Mp 238 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.75–7.83 (m, 2H), 7.93–7.98 (m, 4H), 8.24–8.29 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 95.2 (2C), 122.6 (2CH), 125.7 (2CH), 129.4 (2CH), 130.2 (2CH), 135.3 (2CH), 150.3 (2C), 158.4 (2C), 161.6 (2C). LC/MS (ESI^+) t_R 5.22 min, m/z $[M+H]^+$ 490.66/492.70/494.72/496.70/498.46. HRMS (ESI^+) m/z 492.8920 $[M+H]^+$, calcd for $C_{18}H_8Cl_6N_4$+H: 492.8924. Typical fragment M=163 Da, $[C_8H_4ClN_2]^+$, was identified in ESI^+ at −30 V.

*4.4.5. 4-(Cyclopropylethynyl)-2-trichloromethylquinazoline (**13**).* MW: 311.59 g/mol. White solid (19%). Mp 180 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.10–1.13 (m, 4H), 1.62–1.74 (m, 1H), 7.72–7.79 (m, 1H), 7.94–8.02 (m, 1H), 8.13–8.17 (m, 1H), 8.28–8.32 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 0.8 (CH), 9.8 ($2CH_2$), 72.7 (C), 97.5 (C), 107.4 (C), 124.3 (C), 126.7 (CH), 129.5 (CH), 129.6 (CH), 135.0 (CH), 149.3 (C), 154.6 (C), 161.0 (C). LC/MS (ESI^+) t_R 4.58 min, m/z $[M+H]^+$ 311.05/313.07/314.95. HRMS (ESI^+) m/z 332.9720 $[M+Na]^+$, calcd for $C_{14}H_9Cl_3N_2$+Na: 332.9724.

*4.4.6. 1,4-Dicyclopropylbuta-1,3-diyne (**14**).* $C_{10}H_{10}$. MW: 130.19 g/mol. Colorless oil (24%).[34] ^1H NMR ($CDCl_3$, 200 MHz): δ 0.71–0.88 (m, 8H), 1.21–1.32 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 0.01 (2CH), 8.7 ($2CH_2$), 60.8 (2C), 80.0 (2C).

*4.4.7. 1,1,2,2-Tetrachloro-1,2-bis[4-(cyclopropylethynyl)-quinazolin-2-yl]ethane (**15**).* MW: 552.28 g/mol. Yellow solid (4%). Mp 185 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 0.91–1.03 (m, 8H), 1.46–1.57 (m, 2H), 7.63–7.71 (m, 2H), 7.80–7.85 (m, 4H), 8.18–8.22 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 0.6 (2CH), 9.5 ($4CH_2$), 72.5 (2C), 96.2 (2C), 105.6 (2C), 123.9 (2C), 126.2 (2CH), 129.0 (2CH), 129.2 (2CH), 134.1 (2CH), 149.2 (2C), 152.2 (2C), 159.3 (2C). LC/MS (ESI^+) t_R 5.01 min, m/z $[M+H]^+$ 551.90/553.90/555.91/557.51/558.93. HRMS (ESI^+) m/z 551.0355 $[M+H]^+$, calcd for $C_{28}H_{18}Cl_4N_4$+H: 551.0358.

*4.4.8. 7-Methyl-4-(phenylethynyl)-2-trichloromethyl-quinazoline (**20**).* MW: 361.65 g/mol. Beige solid (15%). Mp 174 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.65 (s, 3H), 7.43–7.51 (m, 3H), 7.61–7.66 (m, 1H), 7.75–7.80 (m, 2H), 7.99 (s, 1H), 8.33–8.37 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.3 (CH_3), 29.7 (C), 85.0 (C), 99.8 (C), 120.9 (C), 122.5 (C), 126.2 (CH), 128.5 (CH), 128.7 (2CH), 130.5 (CH), 132.1 (CH), 132.7 (2CH), 146.8 (C), 149.8 (C), 153.5 (C), 161.2 (C). LC/MS (ESI^+) t_R 5.37 min, m/z $[M+H]^+$561.07/363.02/365.06. HRMS (ESI^+) m/z 382.9877 $[M+Na]^+$, calcd for $C_{18}H_{11}Cl_3N_2$+Na: 382.9880.

*4.4.9. 4-Chloro-2-dichloromethyl-7-methylquinazoline (**21**).* MW: 261.53 g/mol. Beige solid (14%). Mp 182 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.63 (s, 3H), 6.83 (s, 1H), 7.60–7.64 (m, 1H), 7.88 (s, 1H), 8.17–8.21 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.2 (CH_3), 70.6 (CH), 121.4 (C), 125.6 (CH), 128.1 (CH), 132.3 (CH), 147.6 (C), 151.1 (C), 160.1 (C), 163.5 (C). LC/MS (ESI^+) t_R 3.89 min, m/z $[M+H]^+$261.13/263.24/265.05. HRMS (ESI^+) m/z 282.9570 $[M+Na]^+$, calcd for $C_{10}H_7Cl_3N_2$+Na: 282.9567.

*4.4.10. 1,1,2,2-Tetrachloro-1,2-bis(4-chloro-7-methylquinazolin-2-yl) ethane (**22**).* MW: 521.05 g/mol. Beige solid (25%). Mp 289 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.58 (s, 6H), 7.59–7.63 (m, 2H), 7.74 (s, 2H), 8.11–8.31 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.1 ($2CH_3$), 95.3 (2C), 120.8 (2C), 125.3 (2CH), 128.4 (2CH), 132.4 (2CH), 146.8 (2C), 150.5 (2C), 158.4 (2C), 161.1 (2C). LC/MS (ESI^+) t_R 5.56 min, m/z $[M+H]^+$518.56/520.53/522.49/524.82. Anal. Calcd for $C_{20}H_{12}Cl_6N_4$: C, 46.10; H, 2.32; N, 10.75%. Found: C, 46.51; H, 2.30; N, 10.69%.

*4.4.11. 4-(Cyclopentylethynyl)-2-trichloromethylquinazoline (**23**).* MW: 339.65 g/mol. Pale brown solid (11%). Mp 117 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.66–2.22 (m, 8H), 2.99–3.14 (m, 1H), 7.73–7.80 (m, 1H), 7.94–8.02 (m, 1H), 8.12–8.17 (m, 1H), 8.35–8.38 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.3 ($2CH_2$), 31.1 (CH), 33.5 ($2CH_2$), 76.7 (C), 97.0 (C), 108.1 (CH), 124.3 (CH), 126.7 (CH), 129.4 (CH), 129.7 (CH), 135.0 (CH), 149.3 (C), 154.8 (C), 161.0 (C). LC/MS (ESI^+) t_R 5.33 min, m/z $[M+H]^+$ 339.07/341.06/343.10. HRMS (ESI^+) m/z 339.0220 $[M+H]^+$, calcd for $C_{16}H_{13}Cl_3N_2$+H: 339.0217.

*4.4.12. 4-(4-Tolylethynyl)-2-trichloromethylquinazoline (**24**).* MW: 361.65 g/mol. Yellow solid (21%). Mp 177 °C (isopropanol). ^1H NMR ($CDCl_3$, 200 MHz): δ 2.44 (s, 3H), 7.28 (d, J=8.1 Hz, 2H), 7.68 (d, J=8.1 Hz, 2H), 7.78–7.86 (m, 1H), 7.97–8.03 (m, 1H), 8.18–8.22 (m, 1H), 8.46–8.51 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.8 (CH_3), 84.7 (C), 97.0 (C), 101.1 (C), 117.8 (C), 124.2 (C), 126.6 (C), 129.4 (2CH), 129.5 (CH), 129.8 (CH), 132.7 (2CH), 135.2 (CH), 141.2 (C), 149.5 (C), 154.3 (C), 161.1 (C). LC/MS (ESI^+) t_R 5.48 min, m/z $[M+H]^+$ 361.13/363.16/365.19. Anal. Calcd for $C_{18}H_{11}Cl_3N_2$: C, 59.78; H, 3.07; N, 7.75%. Found: C, 59.71; H, 3.01; N, 7.69%.

*4.4.13. 4-(3-Tolylethynyl)-2-trichloromethylquinazoline (**25**).* MW: 361.65 g/mol. Pale yellow solid (20%). Mp 175 °C (isopropanol). ^1H NMR ($CDCl_3$, 200 MHz): δ 2.42 (s, 3H), 7.34 (d, J=6.5 Hz, 2H), 7.60 (d, J=6.5 Hz, 2H), 7.77–7.82 (m, 1H), 7.99–8.06 (m, 1H), 8.18–8.23 (m, 1H), 8.46–8.51 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.2 (CH_3), 84.7 (C), 97.0 (C), 100.8 (C), 120.6 (C), 124.2 (C), 126.6 (CH), 128.6 (CH), 129.6 (CH), 129.9 (2CH), 131.5 (CH), 133.2 (CH), 135.2 (CH), 138.5 (C), 149.5 (C), 154.3 (C), 161.1 (C). LC/MS (ESI^+) t_R 5.44 min, m/z $[M+H]^+$ 361.15/363.16/365.15. Anal. Calcd for $C_{18}H_{11}Cl_3N_2$: C, 59.78; H, 3.07; N, 7.75%. Found: C, 59.80; H, 2.98; N, 7.70%.

*4.4.14. 4-(2-Tolylethynyl)-2-trichloromethylquinazoline (**26**).* MW: 361.65 g/mol. Yellow solid (41%). Mp 179 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.68 (s, 3H), 7.31–7.44 (m, 3H), 7.73–7.86 (m, 2H), 7.98–8.07 (m, 1H), 8.18–8.23 (m, 1H), 8.47–8.51 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.1 (CH_3), 88.7 (C), 97.0 (C), 99.4 (C), 120.7 (C), 124.2 (C), 126.0 (CH), 126.5 (CH), 129.6 (CH), 129.9 (2CH), 130.6 (CH), 133.3 (CH), 135.1 (CH), 141.5 (C), 149.6 (C), 154.3 (C), 161.2 (C). LC/MS (ESI^+ESI^+) t_R 5.70 min, m/z $[M+H]^+$ 361.13/363.15/365.27. HRMS (ESI^+) m/z 361.0059 $[M+H]^+$, calcd for $C_{18}H_{11}Cl_3N_2$+H: 361.0060.

*4.4.15. 2-Trichloromethyl-4-[2(2,4,5-trimethylphenyl)-ethynyl]-quinazoline (**27**).* MW: 389.71 g/mol. Pale yellow solid (70%). Mp 234 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.27 (s, 3H), 2.30 (s, 3H), 2.61 (s, 3H), 7.09 (s, 1H), 7.53 (s, 1H), 7.76–7.85 (m, 1H), 7.97–8.05 (m, 1H), 8.17–8.21 (m, 1H), 8.47–8.51 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.0 (CH_3), 20.0 (CH_3), 20.5 (CH_3), 88.3 (C), 97.0 (C), 100.4 (C), 117.8 (C), 124.2 (C), 126.6 (CH), 129.5 (CH), 129.8 (CH), 131.3 (CH), 134.2 (CH), 134.4 (C), 135.0 (CH), 139.0 (C), 140.0 (C), 149.5 (C), 154.5 (C), 161.2 (C). LC/MS (ESI^+) t_R 5.70 min, m/z $[M+H]^+$

389.02/391.04/393.08. HRMS (ESI^+) m/z 411.0192 $[M+Na]^+$, calcd for $C_{20}H_{15}Cl_3N_2$+Na: 411.0193.

*4.4.16. 4-[2-(4-tert-Butylphenyl)ethynyl]-2-trichloromethyl-quinazoline (**28**).* MW: 403.73 g/mol. Yellow solid (15%). Mp 153 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.36 (s, 9H), 7.46–7.50 (m, 2H), 7.70–7.86 (m, 3H), 7.99–8.02 (m, 1H), 8.18–8.22 (m, 1H), 8.46–8.50 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 31.1 ($2CH_3$), 35.1 (2C), 77.3 (CH_3), 84.7 (C), 97.0 (C), 101.2 (C), 117.8 (C), 124.3 (C), 125.8 (2CH), 126.7 (CH), 129.7 (CH), 129.8 (CH), 132.6 (2CH), 135.2 (CH), 149.5 (C), 154.3 (C), 161.1 (C). LC/MS (ESI^+) t_R 5.67 min, m/z $[M+H]^+$ 403.04/404.98/407.10. HRMS (ESI^+) m/z 425.0353 $[M+Na]^+$, calcd for $C_{21}H_{17}Cl_3N_2$+Na: 425.0349.

*4.4.17. 4-[(4-Methoxyphenyl)ethynyl]-2-trichloromethyl-quinazoline (**29**).* MW: 377.65 g/mol. Yellow solid (18%). Mp 162 °C (isopropanol). ^1H NMR ($CDCl_3$, 200 MHz): δ 3.89 (s, 3H), 6.96–7.00 (m, 2H), 7.72–7.85 (m, 3H), 7.98–8.06 (m, 1H), 8.17–8.21 (m, 1H), 8.46–8.50 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 55.5 (OCH_3), 84.6 (C), 96.4 (C), 101.5 (C), 112.7 (C), 114.4 (2CH), 124.1 (C), 126.6 (CH), 129.5 (CH), 129.7 (CH), 134.6 (2CH), 135.1 (CH), 149.4 (C), 154.4 (C), 161.1 (C), 161.5 (C). LC/MS (ESI^+ESI^+) t_R 5.11 min, m/z $[M+H]^+$ 377.10/379.09/381.15. HRMS (ESI^+) m/z 377.0009 $[M+H]^+$, calcd for $C_{18}H_{11}Cl_3N_2O$+H: 377.0009.

*4.4.18. 4-[(3-Methoxyphenyl)ethynyl]-2-trichloromethyl-quinazoline (**30**).* MW: 377.65 g/mol. Pale yellow solid (10%). Mp 173 °C (cyclohexane). ^1H NMR ($CDCl_3$, 200 MHz): δ 3.88 (s, 3H), 7.03–7.09 (m, 1H), 7.29–7.32 (m, 1H), 7.37–7.39 (m, 2H), 7.79–7.87 (m, 1H), 7.99–8.07 (m, 1H), 8.19–8.23 (m, 1H), 8.46–8.50 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 55.5 (OCH_3), 84.7 (C), 96.9 (C), 100.3 (C), 117.3 (CH), 117.4 (CH), 121.8 (C), 124.2 (C), 125.3 (CH), 126.6 (CH), 129.6 (CH), 129.8 (CH), 129.9 (CH), 135.3 (CH), 149.5 (C), 154.1 (C), 159.5 (C), 161.1 (C). LC/MS (ESI^+) t_R 5.37 min, m/z $[M+H]^+$ 377.07/379.11/381.13. Anal. Calcd for $C_{18}H_{11}Cl_3N_2O$: C, 57.25; H, 2.94; N, 7.42%. Found: C, 57.04; H, 3.00; N, 7.85%.

*4.4.19. 4-[(2-Methoxyphenyl)ethynyl]-2-trichloromethyl-quinazoline (**31**).* MW: 377.65 g/mol. Beige solid (18%). Mp 180 °C (cyclohexane). ^1H NMR ($CDCl_3$, 200 MHz): δ 4.03 (s, 3H), 6.98–7.07 (m, 2H), 7.43–7.52 (m, 1H), 7.70–7.85 (m, 2H), 7.97–8.05 (m, 1H), 8.16–8.20 (m, 1H), 8.66–8.70 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 55.9 (OCH_3), 89.3 (C), 96.2 (C), 98.1 (C), 110.2 (C), 110.8 (CH), 120.8 (CH), 124.4 (C), 127.2 (CH), 129.4 (CH), 129.8 (CH), 132.3 (CH), 134.3 (CH), 135.0 (CH), 149.5 (C), 154.5 (C), 161.1 (C), 161.5 (C). LC/MS (ESI^+) t_R 5.12 min, m/z $[M+H]^+$ 376.91/378.01/379.81. HRMS (ESI^+) m/z 377.0008 $[M+H]^+$, calcd for $C_{18}H_{11}Cl_3N_2O$+H: 377.0009.

*4.4.20. 4-[2-(4-Methoxy-2-methylphenyl)ethynyl]-2-trichloromethyl-quinazoline (**32**).* MW: 391.68 g/mol. Pale yellow solid (45%). Mp 204 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.66 (s, 3H), 3.86 (s, 3H), 6.77–6.84 (m, 2H), 7.67–7.83 (m, 2H), 8.00 (t, J=7.2 Hz, 1H), 8.18 (d, J=8.3 Hz, 1H), 8.47 (d, J=8.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.4 (CH_3), 55.4 (OCH_3), 88.3 (C), 97.0 (C), 100.5 (C), 111.8 (CH), 112.9 (C), 115.6 (CH), 124.1 (C), 126.6 (CH), 129.5 (CH), 129.7 (CH), 135.0 (CH), 135.1 (CH), 143.8 (C), 149.5 (C), 154.5 (C), 161.2 (C), 161.4 (C). LC/MS (ESI^+) t_R 5.12 min, m/z $[M+H]^+$ 391.04/392.95/395.07. HRMS (ESI^+) m/z 412.9983 $[M+Na]^+$, calcd for $C_{19}H_{13}Cl_3N_2O$+Na: 412.9985.

*4.4.21. 4-[2-(2-Chlorophenyl)ethynyl]-2-trichloromethyl-quinazoline (**33**).* MW: 382.07 g/mol. Beige solid (15%). Mp 168 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.31–7.56 (m, 3H), 7.80–7.88 (m, 2H), 8.00–8.08 (m, 1H), 8.18–8.23 (m, 1H), 8.64–8.69 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 89.5 (C), 96.4 (C), 96.9 (C), 121.1 (C), 124.3 (C), 126.9 (CH), 129.5 (CH), 129.7 (CH), 130.1 (CH), 131.6 (CH), 133.6 (C), 134.6 (CH), 135.3 (CH), 137.2 (CH), 149.6 (C), 153.8 (C), 161.1 (C). LC/MS (ESI^+) t_R 5.54 min, m/z $[M+H]^+$ calcd 380.96/382.90/383.89. HRMS (ESI^+) m/z 402.9332 $[M+Na]^+$, calcd for $C_{17}H_8Cl_4N_2$+Na: 402.9334.

*4.4.22. 4-[2-(4-Bromophenyl)ethynyl]-2-trichloromethyl-quinazoline (**34**).* MW: 426.52 g/mol. Pale brown solid (14%). Mp 188 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.57–7.67 (m, 4H), 7.78–7.87 (m, 1H), 7.99–8.08 (m, 1H), 8.18–8.23 (m, 1H), 8.41–8.46 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 77.2 (C), 85.9 (C), 98.9 (C), 119.7 (C), 124.1 (C), 125.3 (C), 126.4 (CH), 129.6 (CH), 130.0 (CH), 132.1 (2CH), 134.0 (2CH), 135.3 (CH), 149.6 (C), 153.8 (C), 161.1 (C). LC/MS (ESI^+) t_R 5.14 min, m/z $[M+H]^+$ 424.85/426.83/428.86. HRMS (ESI^+) m/z 446.8833 $[M+Na]^+$, calcd for $C_{17}H_8BrCl_3N_2$+Na: 446.8829.

*Crystal data for compound **34***: $C_{34}H_{18}Br_2Cl_6O_1N_4$, M=871.04, monoclinic, a=7.1122(3) Å, b=29.724(1) Å, c=17.6660(9) Å, α=90°, β=90.029(1)°, γ=90°, V=3734.6(3) Å^3, T=293(2) K, space group $P21/c$, Z=4, 17,982 reflections measured, 8349 independent reflections (R_{int}=0.1408). The final R_1 value was 0.0936 ($I>2\sigma(I)$). The final $wR(F^2)$ value was 0.1664 ($I>2\sigma(I)$). The final R_1 value was 0.4502 (all data). The final $wR(F^2)$ value was 0.2604 (all data). The goodness of fit on F^2 was 0.794.

4.5. Preparation of 2-chloro-*N*-(2-cyano-5-methylphenyl)-acetamide 17

To a flask containing 2-amino-4-methylbenzonitrile (5 g, 37 mmol, 1 equiv) and pyridine (9.2 mL, 111 mmol, 3 equiv), 2-chloroacetylchloride (3.6 mL, 62.9 mmol, 1.7 equiv), dissolved in DMF (50 mL), was added at 0 °C. The reaction mixture was microwave heated at 50 °C. After addition of water (100 mL), the solution was extracted with dichloromethane (3×50 mL). The organic layer was washed with water (3×100 mL), dried over sodium sulfate, and evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2) to give 2-chloro-*N*-(2-cyano-5-methylphenyl)-acetamide (**17**). MW: 208.64 g/mol. White solid (91%). Mp 132 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.42 (s, 3H), 4.23 (s, 2H), 7.04 (d, J=8.0 Hz, 1H), 7.49 (d, J=8.0 Hz, 1H), 8.19 (s, 1H), 8.79 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.2 (CH_3), 42.9 (CH_3), 99.9 (C), 116.1 (C), 121.6 (CH), 126.0 (CH), 132.1 (CH), 139.1 (C), 145.7 (C), 164.3 (C). LC/MS (ESI^+) t_R 0.96 min, m/z $[M+H]^+$ 209.40/211.36. Anal. Calcd for $C_{10}H_9ClN_2O$: C, 57.57; H, 4.35; N, 13.43%. Found: C, 57.87; H, 4.34; N, 13.31%.

4.6. Preparation of 2-chloromethyl-7-methylquinazolin-4(3*H*)-one 18

A mixture of 2-chloro-*N*-(2-cyano-5-methylphenyl)-acetamide**17** (4 g, 19.2 mmol, 1 equiv), ethanol (50 mL), and 8% H_2O_2 (50 mL) was cooled in a ice-bath. NaOH pellets (1.23 g, 30.7 mmol, 1.6 equiv) were then added. The mixture was stirred at room temperature for 15 min, then slowly heated to 50 °C until a homogeneous solution was obtained and then cooled down to room temperature. The solvent was removed in vacuo and the residue was suspended in water (250 mL), heated to 50 °C for 5 min, cooled down to room temperature, and acidified to pH 4 with a 1 M HCl solution. The resulting precipitate was collected by filtration and dried under reduced pressure to give **18**. MW: 208.64 g/mol. White solid (82%). Mp 276 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.51 (s, 3H), 4.57 (s, 2H), 7.35 (d, J=8.3 Hz, 1H), 7.50 (s, 1H), 8.19 (d, J=8.3 Hz, 1H), 10.03 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.5 (CH_3), 43.4 (CH_2), 119.0 (C), 125.9 (CH), 127.1 (CH), 128.8 (CH), 145.3 (C), 148.5 (C), 152.5 (C), 161.5 (C). LC/MS (ESI^+) t_R 1.47 min, m/z $[M+H]^+$ 209.33/211.30. Anal. Calcd for $C_{10}H_9ClN_2O$: C, 57.57; H, 4.35; N, 13.43%. Found: C, 57.33; H, 4.38; N, 13.09%.

4.7. Preparation of 4-chloro-7-methyl-2-trichloromethyl-quinazoline 19

Phosphorus pentachloride (12.0 g, 57.5 mmol, 4 equiv) and phosphorus oxychloride (20 mL, 218 mmol, 3.8 equiv) were added to 2-chloromethyl-7-methylquinazolin-4(3*H*)-one (**18**) (3 g, 14.4 mmol, 1 equiv). The reaction mixture was microwave-irradiated at 150 °C, for 30 min. After cooling, the mixture was alkalinized with NaOH pellets and extracted with CH_2Cl_2 (2×50 mL). The organic layer was washed with water (3×100 mL), dried over sodium sulfate, and evaporated. The crude product was purified by column chromatography (silica gel, petroleum ether/CH_2Cl_2 1:1) to give**19**. MW: 295.98 g/mol. White solid (93%). Mp 132 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.65 (s, 3H), 7.64–7.69 (m, 1H), 8.00 (s, 1H), 8.22 (d, J=8.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.2 (CH_3), 96.0 (C), 120.9 (C), 125.5 (CH), 128.6 (CH), 132.7 (CH), 147.6 (C), 150.3 (C), 159.8 (C), 163.3 (C). LC/MS (ESI$^+$) t_R 4.70 min, m/z $[M+H]^+$ 294.85/296.86/298.92. Anal. Calcd for $C_{10}H_6Cl_4N_2$: C, 40.58; H, 2.04; N, 9.46%. Found: C, 40.91; H, 2.02; N, 9.62%.

4.8. Preparation of 2-trichloromethylquinazolin-4(3*H*)-one 35

4-Chloro-2-trichloromethylquinazoline **1** (2 g, 7.6 mmol, 1 equiv) and 40% aqueous TBAOH in water (20 mL) were introduced in a flask. The suspension was stirred at room temperature for 6 h. The mixture was then extracted with EtOAc (2×30 mL) at pH=5 and washed three times with brine. The organic layer was dried with Na_2SO_4, filtered, and evaporated. The crude residue was purified by column chromatography (silica gel, petroleum ether/EtOAc 7:3) to give 2-trichloromethylquinazolin-4(3*H*)-one (**35**). MW: 263.50 g/mol. White solid (70%). Mp 215 °C (lit. 215 °C).[35] ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.58–7.66 (m, 1H), 7.80–7.90 (m, 2H), 8.33–8.37 (m, 1H), 11.01 (1H, br s). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 92.2 (C), 121.2, (C), 126.8 (CH), 128.9 (CH), 129.0 (CH), 135.4 (CH), 146.6 (C), 149.3 (C), 162.1 (C).

4.9. Preparation of compounds 4-bromo-2-trichloromethyl-quinazoline 36 and 4-iodo-2-trichloromethylquinazoline 37

2-trichloromethylquinazolin-4(*3H*)-one **35** (1 g, 3.8 mmol, 1 equiv) was dissolved in toluene (20 mL) in a flask, under nitrogen atmosphere. Phosphorus pentoxide (2.6 g, 9.12 mmol, 2.4 equiv) and TBABr (1.5 g, 4.6 mmol, 1.2 equiv) or TBAI (1.7 g, 4.6 mmol, 1.2 equiv) were added under nitrogen atmosphere and stirred for 3 h at 90 °C. After addition of water (100 mL), the mixture was alkalinized with a $NaHCO_3$ solution and extracted with AcOEt (2×50 mL). The organic layer was washed with water (2×50 mL), dried with Na_2SO_4, filtered, and evaporated. Crude residue was purified by column chromatography (silica gel, petroleum ether/CH_2Cl_2 1:1), affording **36** or **37**.

*4.9.1. 4-Bromo-2-trichloromethylquinazoline (**36**).* MW: 326.40 g/mol. White solid (75%). Mp 150 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.81–7.89 (m, 1H), 8.01–8.10 (m, 1H), 8.17–8.21 (m, 1H), 8.28–8.32 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 95.9 (C), 125.4 (C), 128.4 (CH), 129.9 (CH), 131.0 (CH), 136.0 (CH), 149.6 (C), 158.5 (C), 159.9 (C). LC/MS (ESI$^+$) t_R 4.02 min. LC/MS (ESI$^+$) t_R 4.45 min, m/z $[M+H]^+$ 324.06/326.23/328.86. HRMS (ESI$^+$) m/z 348.8516 $[M+Na]^+$, calcd for $C_9H_4BrCl_3N_2$+Na: 348.8516.

*4.9.2. 4-Iodo-2-trichloromethylquinazoline (**37**).* MW: 374.40 g/mol. White solid (30%). Mp 140 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.82–7.90 (m, 1H), 8.03–8.11 (m, 1H), 8.20–8.24 (m, 1H), 8.33–8.38 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 96.0 (C), 122.7 (C), 125.8 (CH), 129.6 (CH), 130.6 (CH), 135.9 (CH), 150.0 (C), 159.7 (C), 163.9 (C). HRMS (ESI$^+$) m/z 394.8375 $[M+Na]^+$, calcd for $C_9H_4Cl_3IN_2$+Na: 394.8375.

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