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Graphical Abstract

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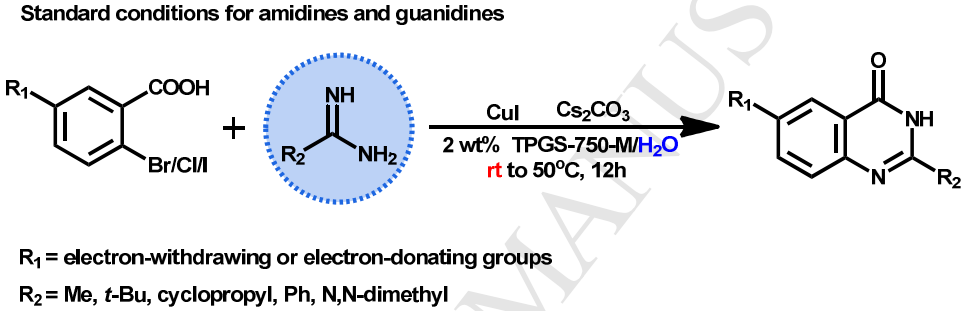

Tetrahedron

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A Convenient Aqueous Copper-Catalyzed Synthesis of Quinazolinones

Yulong Xu[a], Qiong Xie[a], Wei Li[a], Hongpeng Sun[a], Yonghui Wang[a.b] and Liming Shao*[a.b]

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ABSTRACT

A simple and highly efficient method for the aqueous copper-catalyzed coupling reactions with the aid of a commercially available surfactant (TPGS-750-M) is reported. In an aqueous micellar medium, 2-halobenzoic acids derivatives reacted with amidines and guanidines and generated the corresponding quinazolinone derivatives in good to excellent yields in the range of room temperature to, at most, 50°C. In addition, the reaction medium can be recycled, and this method led to a significant improvement of the E factors in comparison with the previously reported process.

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1. Introduction

Substituted quinazolinones are widely distributed in nature, and playing a vital role in the metabolism of all living cells.[1] Well known examples included luotonin A from *Peganum nigellastrum*[2], dictyoquinazol A from *Dictyophora indusata*[3], bouchardatine from *Bouchardatia neurococca*[4], (+)-febrifugine from *Hydrangea chinensis*[5], and chaetominine from *Adenophora axilliflora*[6] (Figure 1). Quinazolinone derivatives are now known to have a wide range of biological activities, *e.g.* anticancer, antiviral, anti-inflammatory, antifolate, antitumor, and many other activities.[7] Additionally, many marketed anticancer chemotherapeutic agents or sedative-hypnotic drugs and clinical development candidates utilize this core structure.[8] Recently, Fu's group discovered an efficient synthesis for quinazolinone derivatives by using mild copper-catalyzed conditions.[9] However, this method relying on organic solvents is still poorly adapted to fit the principles of green chemistry.[10] So, searching for new methodologies to synthesize quinazolinone derivatives in water remains as a focus point for chemists.

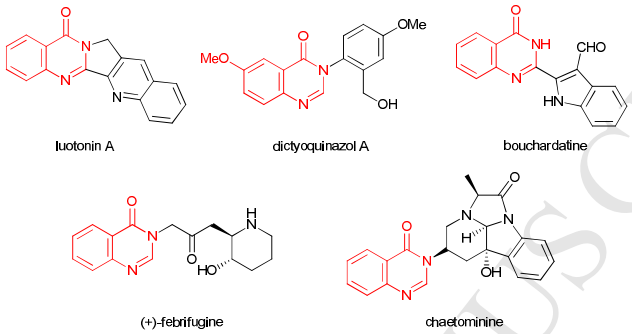


Figure 1. Structures of natural biologically important quinazolinones.

Replacing organic solvents with water for chemical process could have a number of potential benefits in terms of significant environmental impact, safety, cost and impurity profiles.[11] However, the low solubility of many organic compounds in water remains as a major hurdle for many aqueous organic reaction.[12] To address this issue surfactant additives may provide an efficient solution. In a series of publications, Lipshutz reported that using polyoxyethanyl-α-tocopheryl succinate (TPGS-750-M)[13] (Figure 2), a non-ionic amphiphile, allows important cross-coupling reactions such as metathesis, Suzuki-Miyaura, Heck, and Sonogashira reactions to be carried out in water.[14] To the best our knowledge, there is no example of copper-catalyzed coupling reactions using TPGS-750-M to construct N-heterocycles. Herein, we describe a procedure for the synthesis of quinazolinones under environmentally benign conditions and the aqueous reaction mixtures can be recycled several times.

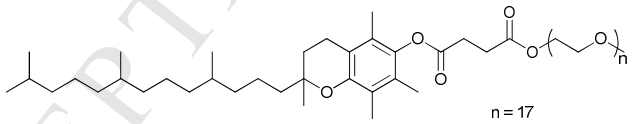
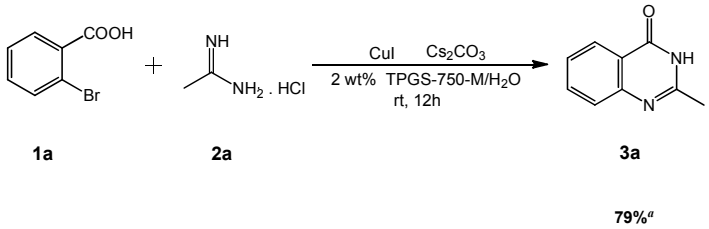


Figure 2. Structure of surfactant TPGS-750-M.

2. Result and discussion

In our initial prototype study, the reaction of 2-bromobenzoic acid (**1a**) and acetamidine hydrochloride (**2a**) were carried out by using Cs_2CO_3 and CuI in an aqueous solution of TPGS-750-M (2 wt%) (Scheme 1). The reaction was monitored by TLC and completed after 12 hours. After flash column purifiction, the quinazolinone (**3a**) was obtained in 79% yield. The result was encouraging and comparable to the method using organic solvent reported previously.[9]



Scheme 1. Initial example of copper-catalyzed coupling in water. Reaction conditions: 2-bromobenzoic acid (0.5 mmol), acetamidine hydrochloride (0.75 mmol), CuI (0.1 mmol), Cs_2CO_3 (1 mmol), TPGS-750-M/H_2O (2 wt%) at room temperature under a nitrogen atmosphere. [a]Isolated yield.

Replacement of the TPGS-750-M by other common nonionic amphiphiles showed much lower coupling yield and less than 30% of quinazolinone (**3a**) was obtained (Table 1). As previously reported, TPGS-750-M formed far larger particles[13] (*ca.* 50−60 nm) compared with other nonionic amphiphiles in water. Its big inner core space accommodates much better for the substrates/catalysts, and allowed high rates of couplings and high yields. Without any surfactant (entry 6), only 6% of quinazolinone was formed.

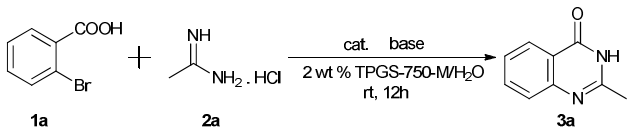
Table 1. Impact of the surfactant of the Copper-catalyzed coupling of 2-bromobenzoic acid with acetamidine hydrochloride.[a]

Entry	Surfactant	Yield[b] (%)
1	**TPGS-750-M**	**79**
2	Triton X 100	24
3	Brij-30	20
4	TPGS-1000	17
5	Tween 80	22
6	None	6

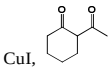
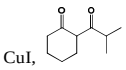
[a]Reaction conditions: 2-bromobenzoic acid (0.5 mmol), acetamidine hydrochloride (0.75 mmol), CuI (0.1 mmol), Cs_2CO_3 (1 mmol), surfactant/H_2O (2 wt%) at room temperature under a nitrogen atmosphere. [b]Isolated yield.

To optimize the copper-catalyzed coupling reaction, we further investigated the reaction conditions that include different catalysts and bases and their ratios. As shown in Table 2, when Cu or $CuSO_4$ was used in association with two equivalents of Cs_2CO_3 (relative to amount of **1a**) at room temperature, only 27% and 16% of the desired product were obtained after 12 h (entries 1 and 2). The use of CuBr led to 59% of **3a** after 12 h (entry 3). CuI was found to be the best catalyst for this reaction (79% yield, entry 4). The coupling yield decreased as the amount of base was reduced (46% yield, entry 5). However, increasing the amount of base gave a comparable yield (81% yield, entry 6). No desired product was observed when the reaction was run in the absence of the catalyst (entry 7). Among common inorganic bases, Cs_2CO_3 proved to be the most effective base, while K_2CO_3 and K_3PO_4 gave lower yields (67% and 41% yield, respectively. entries 8 and 9). Additionally, in the absence of the nitrogen atmosphere, only 14% of the desired product was obtained (entry 10). As we know, certain copper ligands are thought to increase catalyst stability and to prevent aggregation of the metal. Cyclic β-diketone ligand can be used for C-N bond formation with remarkable efficiency.[15] However, when commercially available 2-acetylcyclohexanone and 2-isobutyrylcyclohexanone were employed in the absence of the nitrogen atmosphere, the yield of desired product remained low at best (9% and 17% yield, respectively. entries 11 and 12).

Table 2. Copper-catalyzed coupling of 2-bromobenzoic acid with acetamidine hydrochloride: Optimization of the reaction conditions.[a]



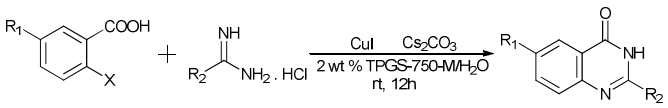
1a **2a** **3a**

Entry	Catalyst	Base	Yield[b] (%)
1	Cu	Cs_2CO_3 (1 mmol)	27
2	$CuSO_4$	Cs_2CO_3 (1 mmol)	16
3	CuBr	Cs_2CO_3 (1 mmol)	59
4	**CuI**	**Cs_2CO_3 (1 mmol)**	**79**
5	CuI	Cs_2CO_3 (0.5 mmol)	46
6	**CuI**	**Cs_2CO_3 (2.5 mmol)**	**81**
7	-	Cs_2CO_3 (1 mmol)	ND[c]
8	CuI	K_2CO_3 (1 mmol)	67
9	CuI	K_3PO_4 (1 mmol)	41
10	CuI	Cs_2CO_3 (1 mmol)	14[d]
11	CuI, 	Cs_2CO_3 (1 mmol)	9[d]
12	CuI, 	Cs_2CO_3 (1 mmol)	17[d]

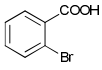
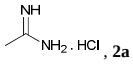
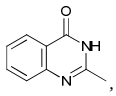
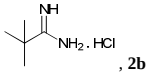
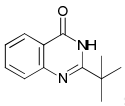
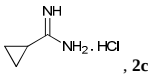
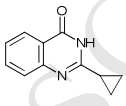
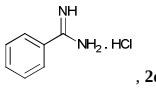
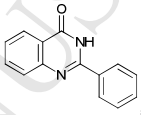
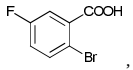
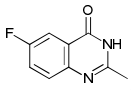
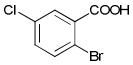
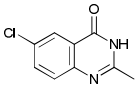
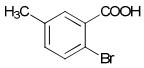
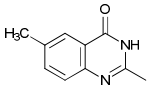
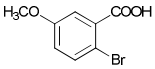
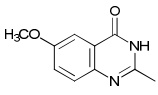
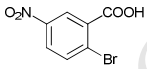
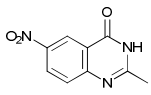
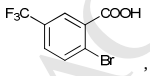
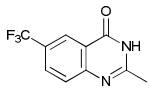
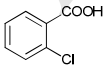
[a]Reaction conditions: 2-bromobenzoic acid (0.5 mmol), acetamidine hydrochloride (0.75 mmol), catalyst (0.1 mmol), base (1 mmol), TPGS-750-M/H_2O (2 wt%) at room temperature under a nitrogen atmosphere. [b]Isolated yield. [c]Not determined. [d]Without nitrogen atmosphere.

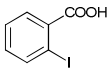
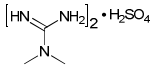
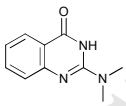
Using optimized reaction condition, we applied our methodology to synthesize quinazolinones. In the first place, the substituted 2-halobenzoic acids (**1**) and amidines/guanidines (**2**) in 2 wt % surfactant were added to a two-neck round bottom flask under nitrogen atmosphere and the reaction mixture was stirred for 10 minutes. Then Cs_2CO_3 (2 equiv.) was introduced and continue to stir for 15 min. Finally, CuI (0.2 equiv.) was added to the flask and the mixture was stirred under nitrogen atmosphere at the room temperature for 12 h. As shown in Table 3, the reactions took place smoothly, giving quinazolinone derivatives in good yields in all cases. The most probable reason for the higher reactivity of our catalyst system is that the larger particles of TPGS-750-M have greater amounts of lipophilic material in their inner cores, which can provide greater binding constants for substrates and reagents.[13] As expected, 2-chlorobenzoic acid showed lower reactivity than 2-iodo- and 2-bromobenzoic acids in the coupling reactions under the same reaction conditions due to the relatively higher C-Cl bond activation energy, while 2-iodobenzoic acid showed the highest reactivity (entries 15-18 vs. entries 1-4 and entries 11-14). To our delight, with increasing the temperature to 50°C, the reaction worked very well and the corresponding coupled products were obtained in 66-82% isolated yields (entries 11-14). However, increasing the reaction temperature to 80°C did not further improve yields (entry 11). Next, we tested the efficacy of this catalytic system with substituted 2-bromobenzoic acids. The reactivity was insensitive to the electronic properties of the groups on the phenyl ring of 2-bromobenzoic acids, whether electron-withdrawing or electron-donating groups (entries 5-10). In general, there was not much difference in reactivities of amidines. However, only trace amounts of desired product were observed in the couplings of N,N-dimethylguanidine with 2-iodobenzoic acids at room temperature. Surprisingly, a higher yield of 77% was obtained when the reaction temperature was raised to 50°C (entry 19).

Table 3. Copper-catalyzed synthesis of quinazolinone derivatives.[a]



1 2 3

Entry	1	2	Product, 3	Yield[b] (%)
1	 , **1a**	 , **2a**	 , **3a**	79
2	**1a**	 , **2b**	 , **3b**	73
3	**1a**	 , **2c**	 , **3c**	83
4	**1a**	 , **2d**	 , **3d**	83
5	 , **1b**	**2a**	 , **3e**	76
6	 , **1c**	**2a**	 , **3f**	81
7	 , **1d**	**2a**	 , **3g**	85
8	 , **1e**	**2a**	 , **3h**	84
9	 , **1f**	**2a**	 , **3i**	75
10	 , **1g**	**2a**	 , **3j**	78
11	 , **1h**	**2a**	**3a**	41 (82[c] 80[d])
12	**1h**	**2b**	**3b**	32 (66[c])
13	**1h**	**2c**	**3c**	40 (71[c])

14	**1h**	**2d**	**3d**	45 (75[c])
15	 , **1i**	**2a**	**3a**	92
16	**1i**	**2b**	**3b**	86
17	**1i**	**2c**	**3c**	91
18	**1i**	**2d**	**3d**	93
19	**1i**	 , **2e**[e]	 , **3k**	trace (77[c])

[a]Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), CuI (0.1 mmol), Cs_2CO_3 (1 mmol), TPGS-750-M/H_2O (2 wt%) at room temperature under a nitrogen atmosphere. [b]Isolated yield. [c]Reaction temperature of 50°C. [d]Reaction temperature of 80°C. [e]**2** (0.38 mmol).

Setup and workup of copper-catalyzed coupling reactions carried out in nanomicelles is simple. As illustrated in Figure 3, insolubility of substrates in water was observed (**P2**), and then the aqueous solution of TPGS-750-M (2 wt%) became clear as Cs_2CO_3 was added (**P3**). When CuI was added with good stirring, the reactions returned to heterogeneous (**P5**). Color changes after 12 hours widely depend upon the CuI present in the medium (**P6**). Then, minimal amounts of EtOAc were added to the flask, and after stirring, the layers separated for product isolation (**P7**, **P8**).

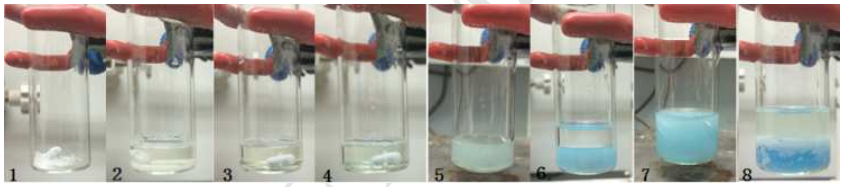
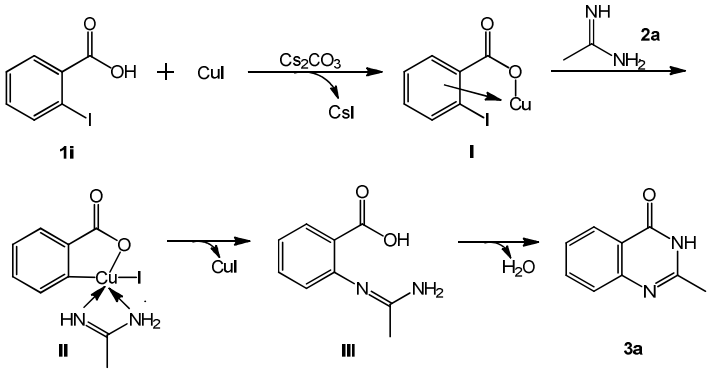


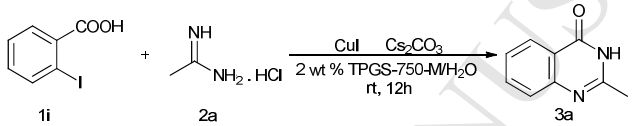
Figure 3. Appearance of a copper-catalyzed coupling reaction mixture over time. **P1**: Substrates, **P2**: TPGS-750-M/H_2O (2 wt%) added, **P3**: Cs_2CO_3 added, **P4**: CuI added, **P5**: after 6 hours, **P6**: after 12 hours and EtOAc added, **P7**: extraction solvent mixing, **P8**: extraction completed.

We also turn our attention onto the recycling of the aqueous media, which retains the surfactant TPGS-750-M. Results from a recycling study of the reaction of 2-iodobenzoic acid with acetamidine are shown in Table 4. Each cycle was followed by a standard in-flask extraction of the product using minimal amount of EtOAc (1 mL). Interestingly, according to the previously reported mechanism for the formation of quinazolinones[9] (Scheme 2), CuI was released to aqueous media in the process of reductive elimination, which can be reused for the next round of reaction after extraction (**II→III**). However, without addition of CuI in each recycle, the isolated yield associated with the 4th recycle dropped to 67% (column 3, Table 4). The most probable reason is that CuI was oxidized by air in the process of extraction of the product and addition of fresh substrates. When fresh substrates together with CuI (0.2 equiv.) were introduced to aqueous media in each recycle, after six recycles, a 77% yield of **3a** was obtained (column 4, Table 4).



Scheme 2. The previously reported mechanism for the formation of quinazolinone.

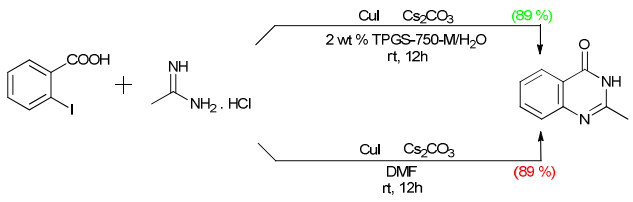
Table 4. Recycling of the aqueous reaction mixture.[a]



Entry	Cycle	Yield[b] (%)	Yield[b] (%)
1	1	92	89
2	2	96[c, d]	95[d]
3	3	85[c, d]	90[d]
4	4	67[c, d]	90[d]
5	5	-	87[d]
6	6	-	77[d]

[a]Reaction conditions: 2-iodobenzoic acid (0.5 mmol), acetamidine hydrochloride (0.75 mmol), CuI (0.1 mmol), Cs_2CO_3 (1 mmol), TPGS-750-M/H_2O (2 wt%) at room temperature under a nitrogen atmosphere. [b]Isolated yield. [c]Without addition of CuI. [d]Extracted with EtOAc; aqueous medium used for next reaction.

To quantify the "green-ness" of this process, we evaluated the environmental (E) factors[16], a green chemistry metric that measures the efficiency in a chemical process, based on organic solvent usage. Because of the complete absence of any organic solvent in the reaction medium, the E factors of our copper-catalyzed quinazolinone synthesis was only 12.6 (solvents used for purification were not taken into account), which is a significant improvement over the process with E factors 40 reported previously[9]. Taking limited amounts of water present as the medium into account, the E factors jump to 54.8, however, it dropped to 11.8 in the second cycle of the medium.



	based on	literature	this work	with recycle
E Factors	total organic solvent	**40**	**12.6**	**11.8**
	aqueous workup included	**40**	**54.8**	**11.8**

3. Conclusion

A simple and highly efficient method was developed for the copper-catalyzed coupling reactions of 2-halobenzoic acids derivatives with amidines and guanidines under green conditions. The reactions generated the corresponding quinazolinone derivatives in good to excellent yields. The aqueous micellar media can be recycled six times, and the associated E factors imply that this methodology increased overall level of greenness and provided an opportunity for the construction of diverse and useful molecules in environment-friendly conditions.

4. Experimental section

4.1. General

All reactions were carried out under a nitrogen atmosphere. All commercially available reagents were used without further purification unless otherwise stated. The aqueous solution of TPGS-750-M (2 wt %) is commercially available from Sigma-Aldrich. Analytical thin layer chromatography (TLC) was performed using Silica Gel GF254 plates (Rushan Taiyang Desiccant co, .ltd, 0.2 mm thick). Compounds were purified using smart flash AI-580S (YAMAZEN co, .ltd). ^{1}H and ^{13}C spectra were recorded on Varian 400 MHz and Bruker 600 MHz, respectively. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of DMSO-D6 (2.50 ppm). Data are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = Broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of DMSO-D_6 (40.0 ppm) on the δ scale. MS data was recorded on Agilent Technologies 6120 quadrupole mass spectrometer.

4.2. Surfactant screening

A two-neck round bottom flask was charged with a magnetic stirrer, evacuated and backfilled with nitrogen. 2-Bromobenzoic acid (**1a**, 0.5 mmol, 101 mg) and acetamidine hydrochloride (**2a**, 0.75 mmol, 71 mg) in 2 wt % surfactant (3 mL) were added under nitrogen atmosphere. After a 10-min stirring, Cs_2CO_3 (1 mmol, 326 mg) was added to the flask. 15 min later, CuI (0.1 mmol, 19 mg) was added to the flask. The mixture was allowed to stir under nitrogen atmosphere at the room temperature for 12 h. After completion of the reaction, the mixture was extracted with EtOAc (1 mL), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (1:1) as eluent to provide **3a**.

4.3. Reaction conditions optimization

A two-neck round bottom flask was charged with a magnetic stirrer, evacuated and backfilled with nitrogen (except for entry 10 in Table 2). 2-Bromobenzoic acid (**1a**, 0.5 mmol, 101 mg) and acetamidine hydrochloride (**2a**, 0.75 mmol, 71 mg) in 2 wt % TPGS-750-M (3 mL) were added under nitrogen atmosphere. After a 10-min stirring, base (1 mmol) was added to the flask (0.5mmol in entry 5 and 2.5mmol in entry 6, respectively). 15-min later, catalyst (0.1 mmol) was added to the flask (except for entry 7 in Table 2). The mixture was allowed to stir under nitrogen atmosphere at the room temperature for 12 h. After completion of the reaction, the mixture was extracted with EtOAc (1 mL), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (1:1) as eluent to provide **3a**.

4.4. Representative procedure

A two-neck round bottom flask was charged with a magnetic stirrer, evacuated and backfilled with nitrogen. Substituted 2-halobenzoic acid (**1**, 0.5 mmol) and amidine hydrochloride (**2**, 0.75 mmol) or bis(guanidine) sulphate (**2**, 0.38 mmol) in 2 wt % TPGS-750-M (3 mL) were added under nitrogen atmosphere. After a 10-min stirring, Cs_2CO_3 (1 mmol, 326 mg) was added to the flask. 15 min later, CuI (0.1 mmol, 19 mg) was added to the flask. The mixture was allowed to stir under nitrogen atmosphere at the shown temperature for 12 h. After completion of the reaction, the mixture was extracted with EtOAc (1 mL), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (3:1 to 1:1) as eluent to provide the desired product.

4.5. Recycling study

A two-neck round bottom flask was charged with a magnetic stirrer, evacuated and backfilled with nitrogen. 2-Iodobenzoic acid (**1i**, 0.5 mmol, 124 mg) and acetamidine hydrochloride (**2a**, 0.75 mmol, 71 mg) in 2 wt % TPGS-750-M (3 mL) were added under nitrogen atmosphere. After a 10-min stirring, Cs_2CO_3 (1 mmol, 326 mg) was added to the flask. 15 min later, CuI (0.1 mmol, 19 mg) was added to the flask. The mixture was allowed to stir under nitrogen atmosphere at the room temperature for 12 h. After completion of the reaction, the mixture was extracted with EtOAc (1 mL), and concentrated under reduced pressure. The residue

was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (1:1) as eluent to provide **3a**. (**1**) The aqueous reaction medium was then subjected to a subsequent identical reaction except for CuI, and the cycle repeated four times. (**2**) The aqueous reaction medium was then subjected to a subsequent identical reaction, and the cycle repeated six times.

4.6. E factors calculations

Note: Using the density of each liquid at 25°C; water = 1.00 g/ml; EtOAc = 0.897 g/ml; DMF = 0.948 g/ml.

Previous work:

Solvents: 3 ml DMF (2.844 g)

Product: 0.071g (89% yield)

$$\frac{2.844\,\text{g waste}}{0.071\,\text{g product}} = 40\,\text{E Factor}$$

This work:

□. Water NOT included as waste

Solvents: 1 ml EtOAc (897 mg)

Product:

First-cycle: 0.071g (89% yield)

Second-cycle: 0.076g (95% yield)

First-cycle

$$\frac{0.897\,\text{g waste}}{0.071\,\text{g product}} = 12.6\,\text{E Factor}$$

Second-cycle

$$\frac{0.897\,\text{g waste}}{0.076\,\text{g product}} = 11.8\,\text{E Factor}$$

□. Water included as waste

Solvents: 3 ml H_2O (3 g), 1 ml EtOAc (897 mg)

Product:

First-cycle: 0.071g (89% yield)

Second-cycle: 0.076g (95% yield)

First-cycle

$$\frac{3.897\,\text{g waste}}{0.071\,\text{g product}} = 54.8\,\text{E Factor}$$

Second-cycle

$$\frac{0.897\,\text{g waste}}{0.076\,\text{g product}} = 11.8\,\text{E Factor}$$

Acknowledgments

This work was financially supported by the National Basic Research Program of China (973 Program, 2015CB931804).

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Supplementary Material

Electronic Supplementary Information (ESI) available: Experimental procedures and details, ^{1}H and ^{13}C spectra.

A convenient aqueous copper-catalyzed synthesis of quinazolinones

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E-mail: limingshao@fudan.edu.cn (L. Shao)

Supporting Information

Supporting Information

I. General Information

All reactions were carried out under a nitrogen atmosphere. All commercially reagents were used without further purification unless otherwise stated. The aqueous solution of TPGS-750-M (2 wt %) is commercially available from Sigma-Aldrich. Analytical thin layer chromatography (TLC) was performed using Silica Gel GF254 plates (Rushan Taiyang Desiccant co, .ltd, 0.2 mm thick). Compounds were purified using smart flash AI-580S (YAMAZEN co, .ltd). ^{1}H and ^{13}C spectra were recorded on Varian 400 MHz and Bruker 600 MHz, respectively. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of DMSO-D_6 (2.50 ppm). Data are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = Broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of DMSO-D_6 (40.0 ppm) on the δ scale. MS data was recorded on Agilent Technologies 6120 quadrupole mass spectrometer. ESI-HRMS (high resolution mass spectrometry) spectra was obtained on AB SCIEX TRIPLE TOF 5600 mass spectrometer.

II. Standard Procedures

i. Surfactant screening

A two-neck round bottom flask was charged with a magnetic stirrer, evacuated and backfilled with nitrogen. 2-Bromobenzoic acid (**1a**, 0.5 mmol, 101 mg) and acetamidine hydrochloride (**2a**, 0.75 mmol, 71 mg) in 2 wt % surfactant (3 mL) were added under nitrogen atmosphere. After a 10-min stirring, Cs_2CO_3 (1 mmol, 326 mg) was added to the flask. 15 min later, CuI (0.1 mmol, 19 mg) was added to the flask. The mixture was allowed to stir under nitrogen atmosphere at the room temperature

for 12 h. After completion of the reaction, the mixture was extracted with EtOAc (1 mL), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (1:1) as eluent to provide **3a** (see Table 1 in text).

ii. Reaction conditions optimization

A two-neck round bottom flask was charged with a magnetic stirrer, evacuated and backfilled with nitrogen (except for entry 10 in Table 2). 2-Bromobenzoic acid (**1a**, 0.5 mmol, 101 mg) and acetamidine hydrochloride (**2a**, 0.75 mmol, 71 mg) in 2 wt % TPGS-750-M (3 mL) were added under nitrogen atmosphere. After a 10-min stirring, base (1 mmol) was added to the flask (0.5mmol in entry 5 and 2.5mmol in entry 6, respectively). 15-min later, catalyst (0.1 mmol) was added to the flask (except for entry 7 in Table 2). The mixture was allowed to stir under nitrogen atmosphere at the room temperature for 12 h. After completion of the reaction, the mixture was extracted with EtOAc (1 mL), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (1:1) as eluent to provide **3a** (see Table 2 in text).

iii. Representative procedure

A two-neck round bottom flask was charged with a magnetic stirrer, evacuated and backfilled with nitrogen. Substituted 2-halobenzoic acid (**1**, 0.5 mmol) and amidine hydrochloride (**2**, 0.75 mmol) or bis(guanidine) sulphate (**2**, 0.38 mmol) in 2 wt % TPGS-750-M (3 mL) were added under nitrogen atmosphere. After a 10-min stirring,

Cs_2CO_3 (1 mmol, 326 mg) was added to the flask. 15 min later, CuI (0.1 mmol, 19 mg) was added to the flask. The mixture was allowed to stir under nitrogen atmosphere at the shown temperature for 12 h (see Table 3 in text). After completion of the reaction, the mixture was extracted with EtOAc (1 mL), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (3:1 to 1:1) as eluent to provide the desired product.

iv. Recycling study

A two-neck round bottom flask was charged with a magnetic stirrer, evacuated and backfilled with nitrogen. 2-Iodobenzoic acid (**1i**, 0.5 mmol, 124 mg) and acetamidine hydrochloride (**2a**, 0.75 mmol, 71 mg) in 2 wt % TPGS-750-M (3 mL) were added under nitrogen atmosphere. After a 10-min stirring, Cs_2CO_3 (1 mmol, 326 mg) was added to the flask. 15 min later, CuI (0.1 mmol, 19 mg) was added to the flask. The mixture was allowed to stir under nitrogen atmosphere at the room temperature for 12 h. After completion of the reaction, the mixture was extracted with EtOAc (1 mL), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (1:1) as eluent to provide **3a**. **(1)** The aqueous reaction medium was then subjected to a subsequent identical reaction except for CuI, and the cycle repeated four times. **(2)** The aqueous reaction medium was then subjected to a subsequent identical reaction, and the cycle repeated six times, as summarized in Table 4 in text.

v. E factors calculations

Note: Using the density of each liquid at 25°C; water = 1.00 g/ml; EtOAc = 0.897 g/ml; DMF = 0.948 g/ml.

Previous work:

Solvents:
3 ml DMF (2.844 g)
Product:
0.071g (89% yield)

$$\frac{2.844\,\text{g waste}}{0.071\,\text{g product}} = 40\ \text{E Factor}$$

This work:
Water NOT included as waste

Solvents:
1 ml EtOAc (897 mg)
Product:
First-cycle: 0.071g (89% yield)
Second-cycle: 0.076g (95% yield)

First-cycle

$$\frac{0.897\,\text{g waste}}{0.071\,\text{g product}} = 12.6\ \text{E Factor}$$

Second-cycle

$$\frac{0.897\,\text{g waste}}{0.076\,\text{g product}} = 11.8\ \text{E Factor}$$

Water included as waste

Solvents:
3 ml H_2O (3 g)
1 ml EtOAc (897 mg)
Product:
First-cycle: 0.071g (89% yield)
Second-cycle: 0.076g (95% yield)

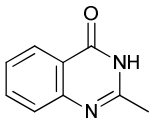
First-cycle

$$\frac{3.897\,\text{g waste}}{0.071\,\text{g product}} = 54.8\,\text{E Factor}$$

Second-cycle

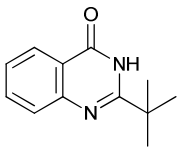
$$\frac{0.897\,\text{g waste}}{0.076\,\text{g product}} = 11.8\,\text{E Factor}$$

III. Compound Data



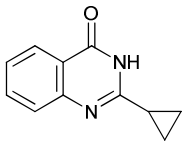
3a

2-Methylquinazolin-4(3H)-one (3a). Eluent: petroleum ether/ethyl acetate (1:1). Yield 33 mg (41% using 2-chlorobenzoic acid as the substrate); 66 mg (82% using 2-chlorobenzoic acid as the substrate at 50^{o}C); 64 mg (80% using 2-chlorobenzoic acid as the substrate at 80^{o}C); 63 mg (79% using 2-bromobenzoic acid as the substrate); 72 mg (90% using 2-iodobenzoic acid as the substrate). ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 12.19 (s, 1H), 8.05 (d, 1H, J=7.9Hz), 7.75 (t, 1H, J=7.7Hz), 7.55 (d, 1H, J=8.0Hz), 7.43 (t, 1H, J=7.5Hz), 2.33 (s, 3H). ^{13}C NMR (DMSO-*d*6, 600 MHz) δ 162.1, 154.7, 149.4, 134.7, 127.0, 126.3, 126.1, 121.1, 21.9. MS (ESI) *m/z* 161.1 $[M + H]^{+}$. Compound data match that previously reported.[1]



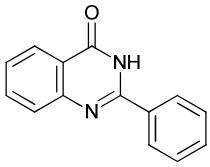
3b

2-(*tert*-butyl)quinazolin-4(3H)-one (3b). Eluent: petroleum ether/ethyl acetate (1:1). Yield 32 mg (32% using 2-chlorobenzoic acid as the substrate); 67 mg (66% using 2-chlorobenzoic acid as the substrate at 50^{o}C); 74 mg (73% using 2-bromobenzoic acid as the substrate); 87 mg (86% using 2-iodobenzoic acid as the substrate). ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 11.89 (s, 1H), 8.07 (d, 1H, J=7.6Hz), 7.76 (t, 1H, J=7.4Hz), 7.60 (d, 1H, J=7.9Hz), 7.46 (t, 1H, J=7.2Hz), 1.33 (s, 9H). ^{13}C NMR (DMSO-*d*6, 600 MHz) δ 163.1, 162.8, 148.8, 134.8, 127.8, 126.7, 126.1, 121.1, 37.7, 28.3. MS (ESI) *m/z* 203.1 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{12}H_{14}N_2O$, 203.1179; observed, 203.1181.



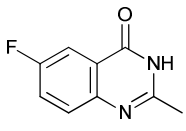
3c

2-Cyclopropylquinazolin-4(3H)-one (3c). Eluent: petroleum ether/ethyl acetate (2:1). Yield 37 mg (40% using 2-chlorobenzoic acid as the substrate); 66 mg (71% using 2-chlorobenzoic acid as the substrate at 50^{o}C); 77 mg (83% using 2-bromobenzoic acid as the substrate); 85 mg (91% using 2-iodobenzoic acid as the substrate). ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 12.41 (s, 1H), 8.03 (d, 1H, J=7.8Hz), 7.70 (t, 1H, J=7.6Hz), 7.46 (d, 1H, J=8.2Hz), 7.38 (t, 1H, J=7.5Hz), 1.94 (m, 1H), 1.04 (m, 4H). ^{13}C NMR (DMSO-*d*6, 600 MHz) δ 162.1, 159.5, 149.6, 134.7, 126.9, 126.2, 125.8, 121.1, 13.9, 9.9. MS (ESI) *m/z* 187.1 $[M + H]^+$. Compound data match that previously reported.[2]



3d

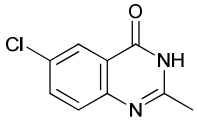
2-Phenylquinazolin-4(3H)-one (3d). Eluent: petroleum ether/ethyl acetate (3:1). Yield 50 mg (45% using 2-chlorobenzoic acid as the substrate); 83 mg (75% using 2-chlorobenzoic acid as the substrate at 50^{o}C); 92 mg (83% using 2-bromobenzoic acid as the substrate); 103 mg (93% using 2-iodobenzoic acid as the substrate). ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 12.54 (s, 1H), 8.16 (m, 3H), 7.83 (t, 1H, J=7.6Hz), 7.73 (d, 1H, J=8.1Hz), 7.55 (m, 4H). ^{13}C NMR (DMSO-*d*6, 600 MHz) δ 162.7, 152.8, 149.2, 135.1, 133.2, 131.9, 129.1, 128.2, 127.9, 127.1, 126.3, 121.5. MS (ESI) *m/z* 223.1 $[M + H]^{+}$, 245.0 $[M + Na]^{+}$. Compound data match that previously reported.[3]



3e

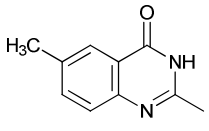
6-fluoro-2-methylquinazolin-4(3H)-one (3e). Eluent: petroleum ether/ethyl acetate (1:1). Yield 68 mg (76%). ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 12.32 (s, 1H), 7.72 (d, 1H, J=8.9Hz), 7.65 (t, 2H, J=8.8Hz), 2.32 (s, 3H). ^{13}C NMR (DMSO-*d*6, 600 MHz) δ 161.6, 160.8, 159.2, 154.2, 146.3, 129.9, 129.8, 123.3, 123.1, 122.3, 122.2, 110.8, 110.6, 21.8. MS

(ESI) *m/z* 179.1 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_9H_7FN_2O$, 179.0615; observed, 179.0614.



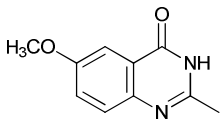
3f

6-Chloro-2-methylquinazolin-4(3H)-one (3f). Eluent: petroleum ether/ethyl acetate (1:1). Yield 79 mg (81%). ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 12.36 (s, 1H), 7.96 (s, 1H), 7.75 (d, 1H, J=8.7Hz), 7.55 (d, 1H, J=8.7Hz), 2.32 (s, 3H). ^{13}C NMR (DMSO-*d*6, 600 MHz) δ 161.2, 155.4, 148.1, 134.8, 130.5, 129.3, 125.1, 122.4, 21.9. MS (ESI) *m/z* 195.0 $[M + H]^+$. Compound data match that previously reported.[4]



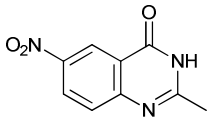
3g

2,6-dimethylquinazolin-4(3H)-one (3g). Eluent: petroleum ether/ethyl acetate (1:1). Yield 74 mg (85%). ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 12.10 (s, 1H), 7.84 (s, 1H), 7.56 (d, 1H, J=8.1Hz), 7.44 (d, 1H, J=8.1Hz), 2.39 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (DMSO-*d*6, 600 MHz) δ 162.1, 153.8, 147.5, 135.9, 135.8, 126.9, 125.5, 120.8, 21.8, 21.2. MS (ESI) *m/z* 175.1 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{10}H_{10}N_2O$, 175.0866; observed, 175.0867.



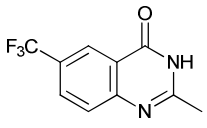
3h

6-methoxy-2-methylquinazolin-4(3H)-one (3h). Eluent: petroleum ether/ethyl acetate (1:1). Yield 80 mg (84%). ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 12.15 (s, 1H), 7.50 (d, 1H, J=8.8Hz), 7.44 (d, 1H, J=2.0Hz), 7.35 (m, 1H), 3.83 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (DMSO-*d*6, 600 MHz) δ 162.0, 157.6, 152.3, 143.9, 128.7, 124.2, 121.8, 106.2, 56.0, 21.7. MS (ESI) *m/z* 191.1 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{10}H_{10}N_2O_2$, 191.0815; observed, 191.0815.



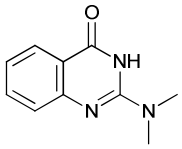
3i

2-Methyl-6-nitroquinazolin-4(3H)-one (3i). Eluent: petroleum ether/ethyl acetate (1:1). Yield 77 mg (75%). ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 8.69 (d, 1H, J=2.4Hz), 8.45 (m, 1H), 7.69 (d, 1H, J=9.0Hz), 2.37 (s, 3H). ^{13}C NMR (DMSO-*d*6, 600 MHz) δ 161.4, 158.9, 153.6, 144.8, 128.8, 128.7, 122.3, 121.1, 22.2. MS (ESI) *m/z* 206.0 $[M + H]^+$, 227.9 $[M + Na]^+$. Compound data match that previously reported.[5]



3j

2-methyl-6-(trifluoromethyl)quinazolin-4(3H)-one (3j). Eluent: petroleum ether/ethyl acetate (1:1). Yield 83 mg (73%). ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 8.27 (s, 1H), 8.02 (d, 1H, J=8.6Hz), 7.72 (d, 1H, J=8.6Hz), 2.36 (s, 3H). ^{13}C NMR (DMSO-*d*6, 600 MHz) δ 161.5, 157.6, 151.9, 130.7, 128.6, 126.4, 126.2, 125.3, 123.6, 121.1, 22.1. MS (ESI) *m/z* 229.0 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{10}H_7F_3N_2O$, 229.0583; observed, 229.0585.



3k

2-(dimethylamino)quinazolin-4(3H)-one (3k). Eluent: petroleum ether/ethyl acetate (2:1). Yield 73 mg (77% using 2-iodobenzoic acid as the substrate at 50^{o}C). ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 11.04 (s, 1H), 7.88 (d, 1H, J=7.8Hz), 7.54 (t, 1H, J=7.6Hz), 7.29 (s, 1H), 7.09 (t, 1H, J=7.3Hz), 3.08 (s, 6H). ^{13}C NMR (DMSO-*d*6, 600 MHz) δ 163.5, 151.7, 151.4, 134.7, 126.3, 125.0, 121.9, 116.8, 37.8. MS (ESI) *m/z* 190.1 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{10}H_{11}N_3O$, 190.0975; observed, 190.0975.

IV. References

[1] a) I. K. Kostakis, A. Elomri, T. Besson, *Tetrahedron Lett.* **2007**, *48*, 6609-6613; b) R. D. Richardson, M. Desaize, T. Wirth, *Chem. Eur. J.* **2007**, *13*, 6745-6754.

[2] Liu, X.; Fu, H.; Jiang, Y.; Zhao, Y. *Angew. Chem.* **2009**, *121*, 354.

[3] a) A. K. Tiwari, V. K. Singh, A. K. Mishra, *Eur. J. Med. Chem* **2007**, *42*, 1234-1238; b) D. J. Connolly, P. M. Lacey, P. J. Guiry, *J. Org. Chem.* **2004**, *69*, 6572-6589.

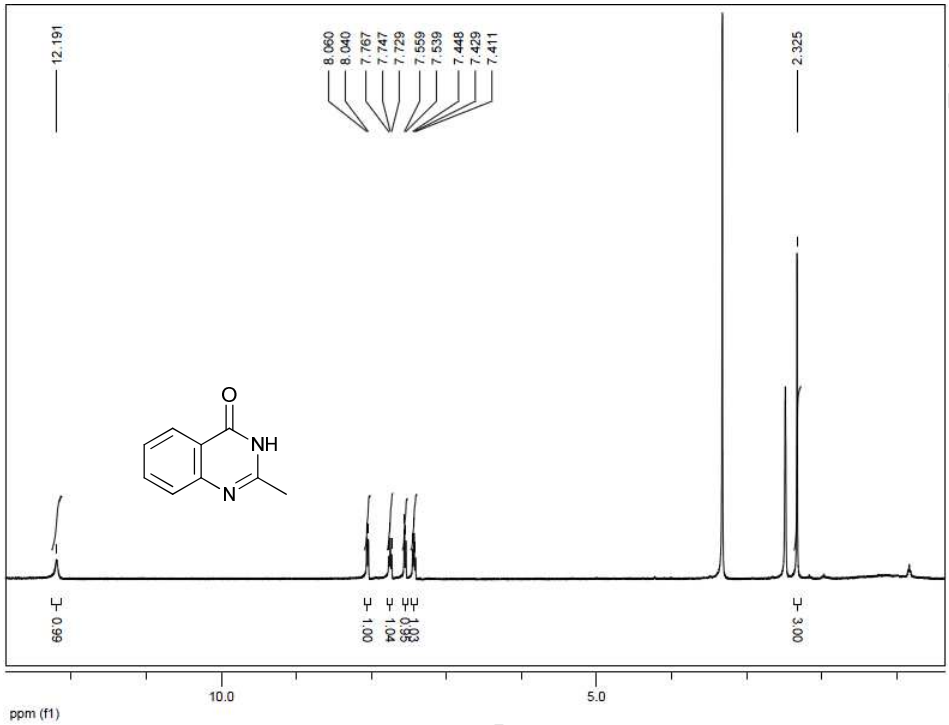
[4] J. B. Jiang, D. P. Hesson, B. A. Dusak, D. L. Dexter, G. J. Kang, E. Hamel, *J. Med. Chem.* **1990**, *33*, 1721-1728.

[5] a) K. C. Patel, S. K. Patel, K. R. Desai, *Acta Ciencia Ind., Chem.* **1999**, *25*, 41-48; b) G. A. Showell, *Synth. Commun.* **1980**, *10*, 241-243.

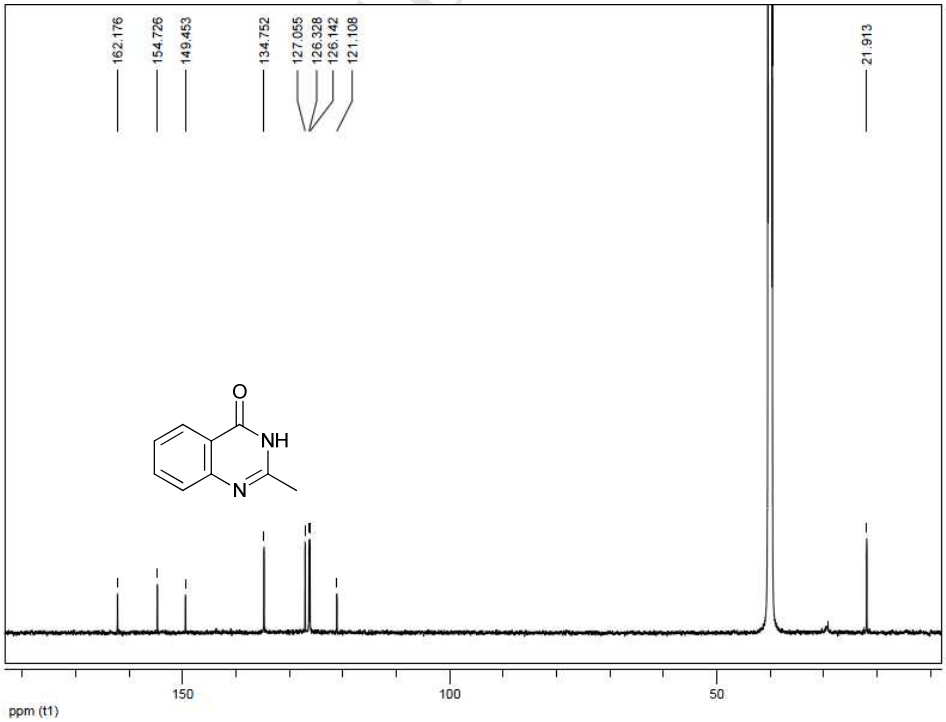
V. ^{1}H and ^{13}C NMR

2-Methylquinazolin-4(3H)-one (3a)

Proton NMR (DMSO-*d6*)

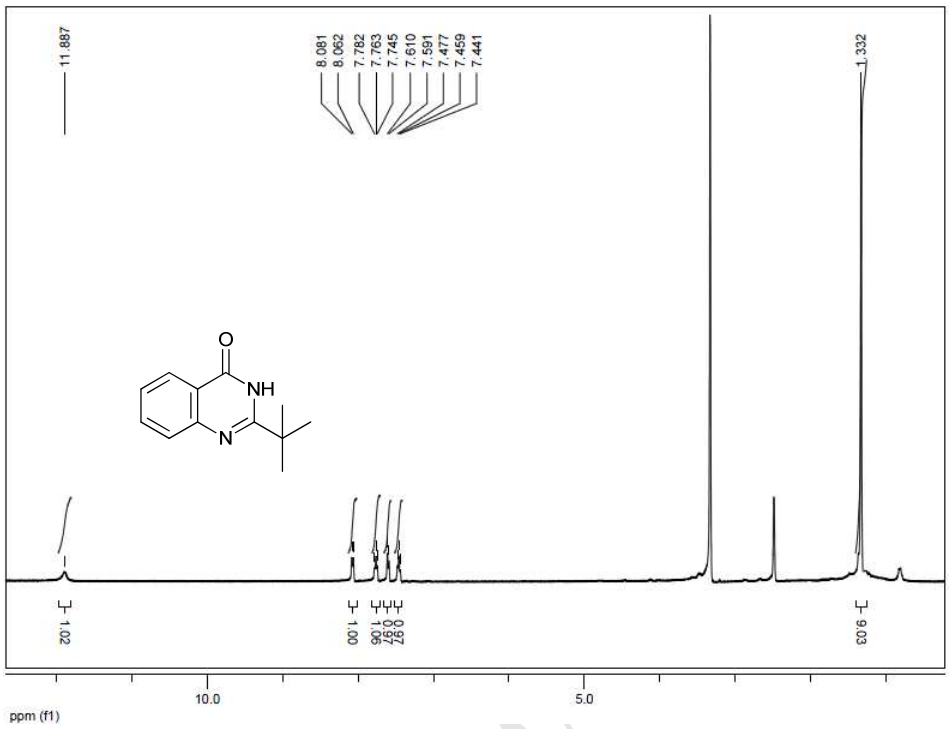


Carbon NMR (DMSO-*d6*)

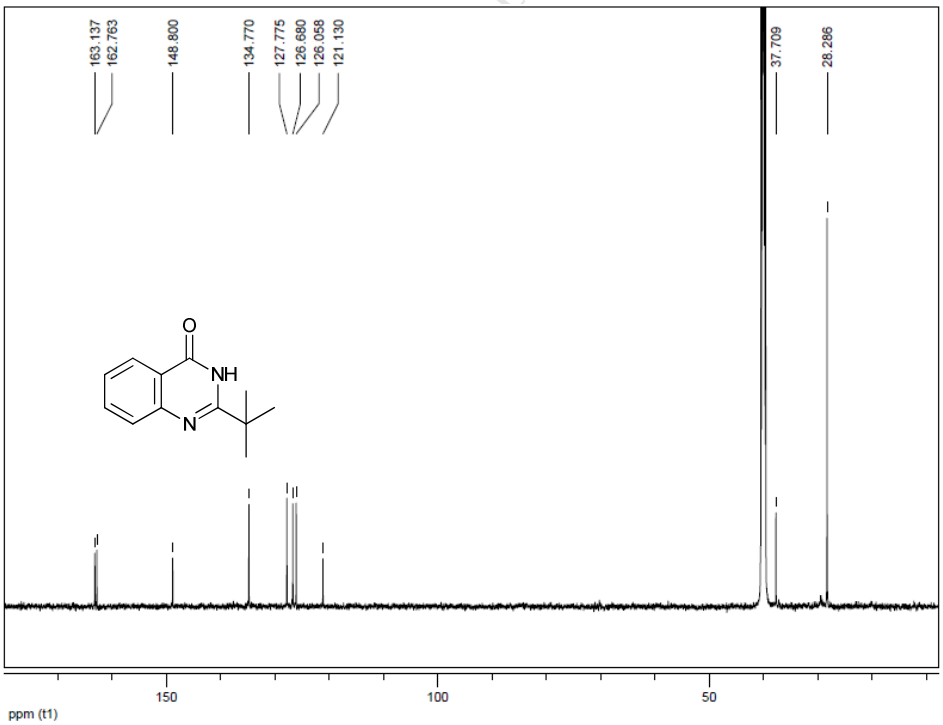


2-(*tert*-butyl)quinazolin-4(3H)-one (3b)

Proton NMR (DMSO-*d6*)

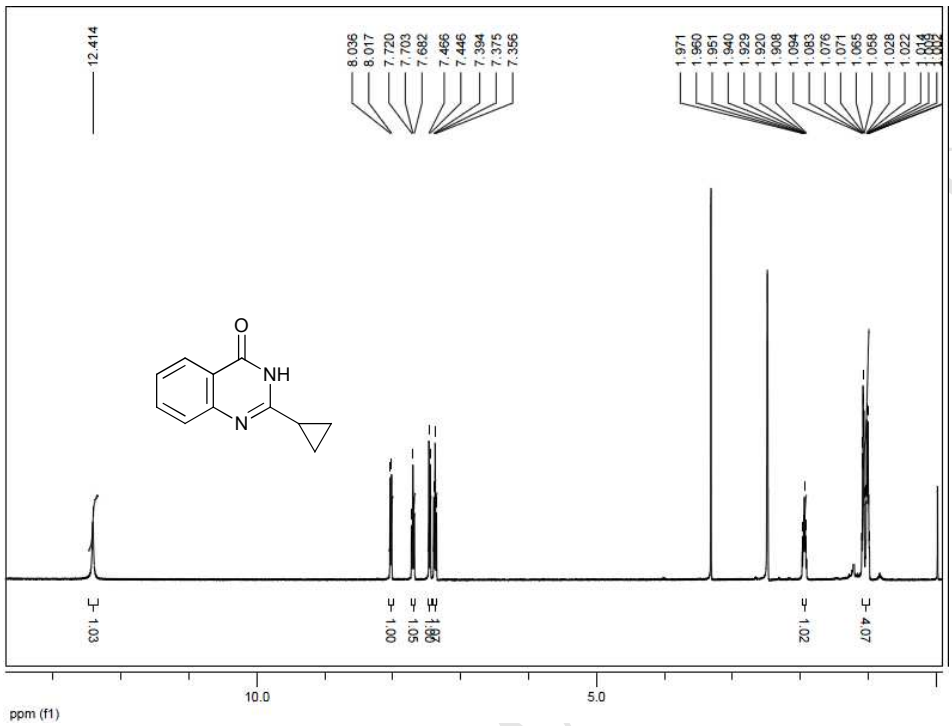


Carbon NMR (DMSO-*d6*)

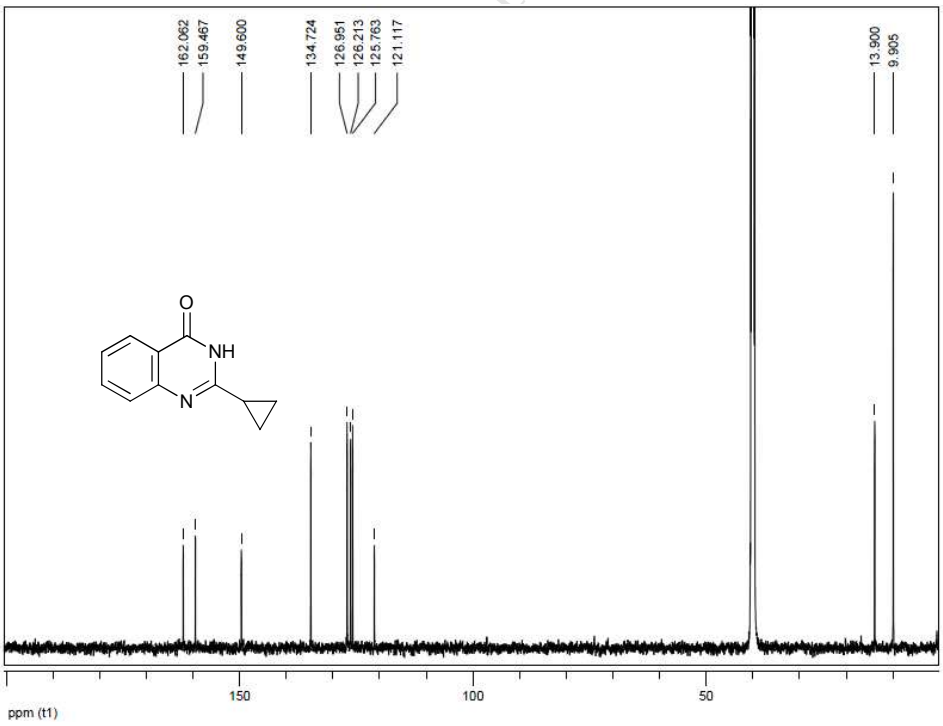


2-Cyclopropylquinazolin-4(3H)-one (3c)

Proton NMR (DMSO-*d6*)

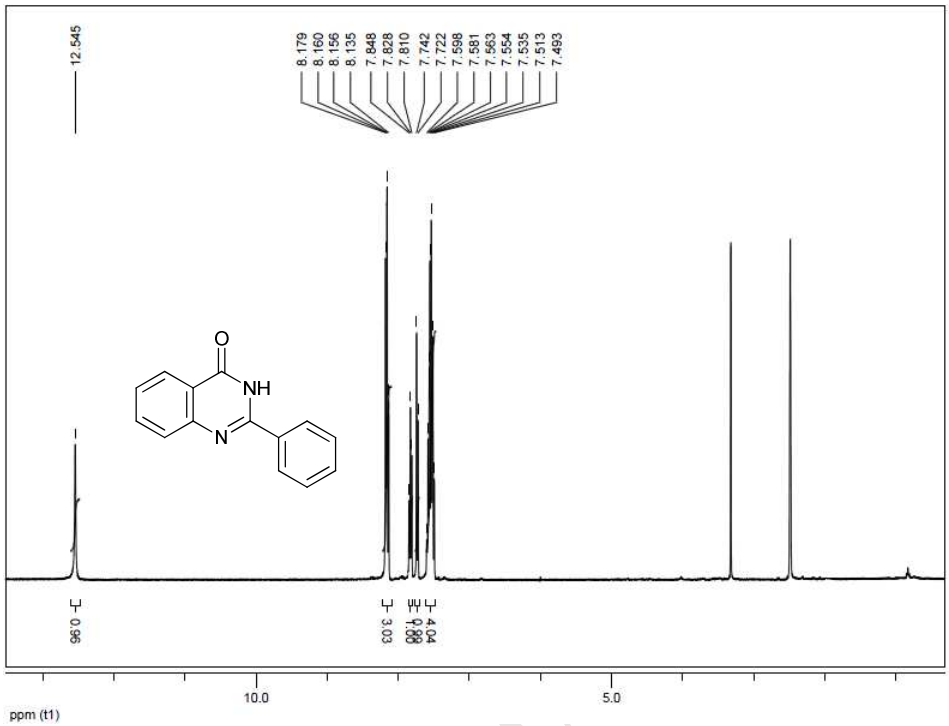


Carbon NMR (DMSO-*d6*)

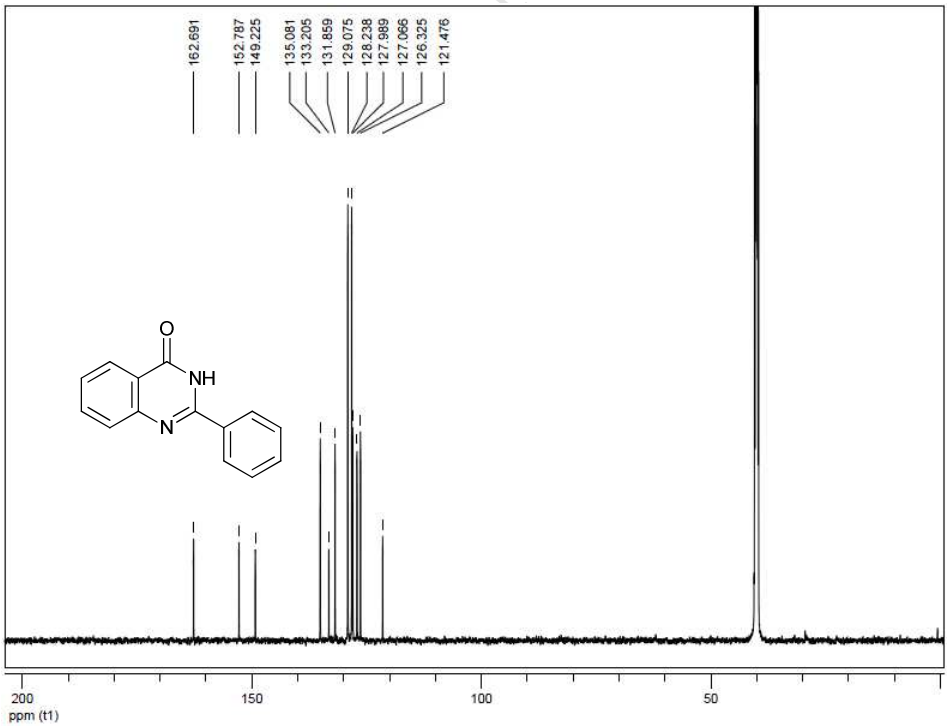


2-Phenylquinazolin-4(3H)-one (3d)

Proton NMR (DMSO-*d6*)

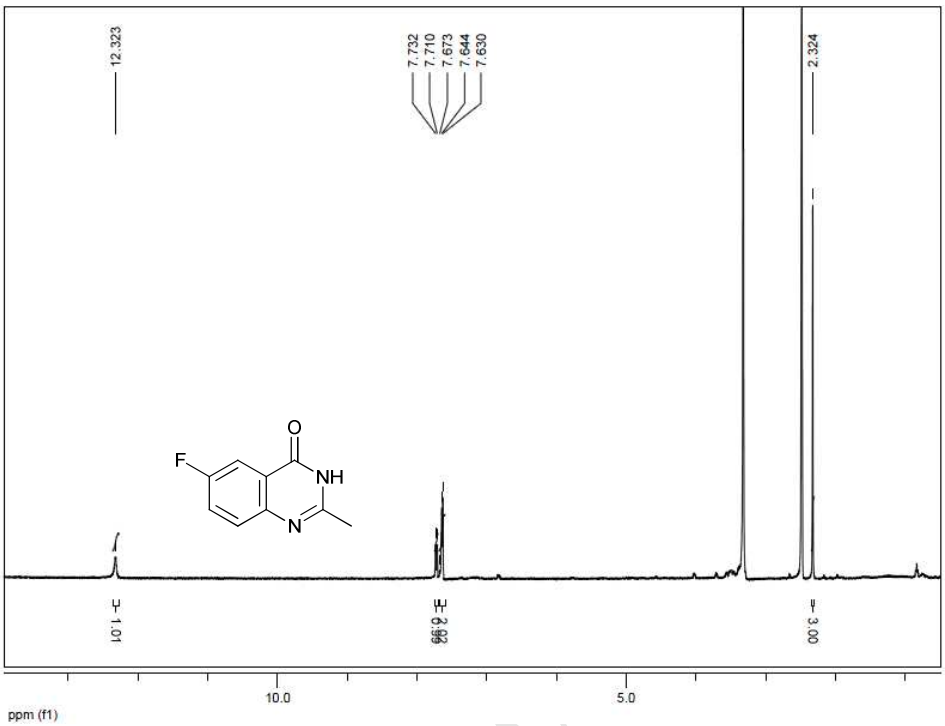


Carbon NMR (DMSO-*d6*)

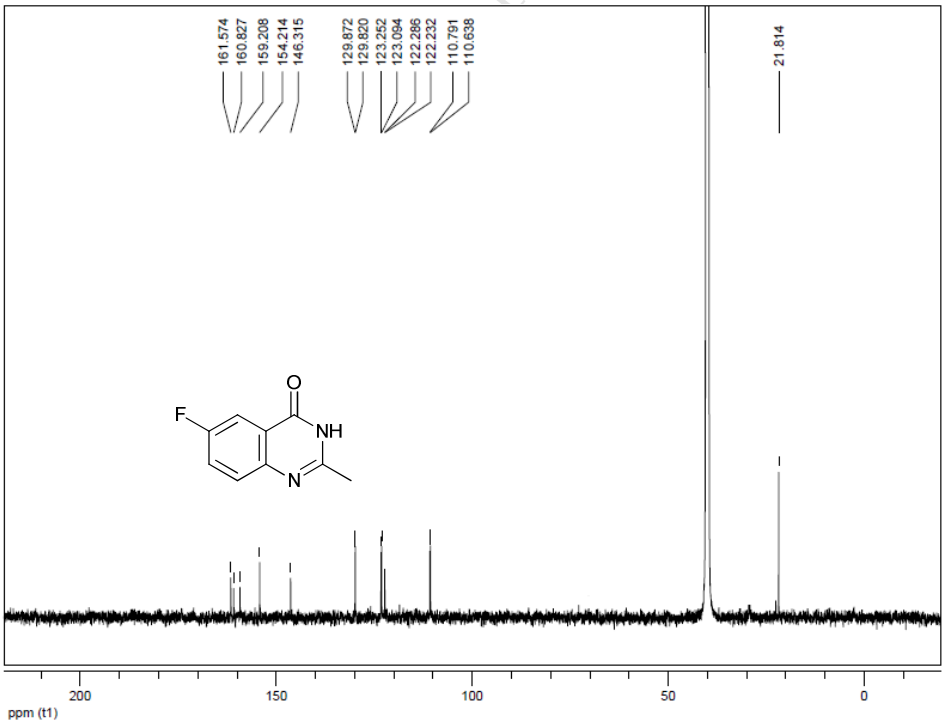


6-fluoro-2-methylquinazolin-4(3H)-one (3e)

Proton NMR (DMSO-*d6*)

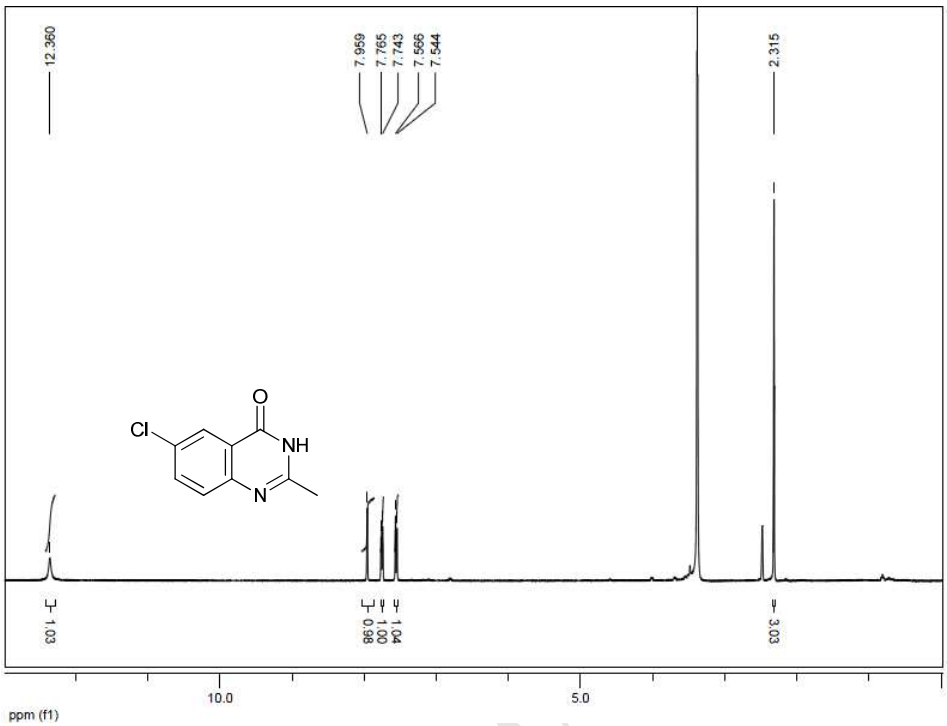


Carbon NMR (DMSO-*d6*)

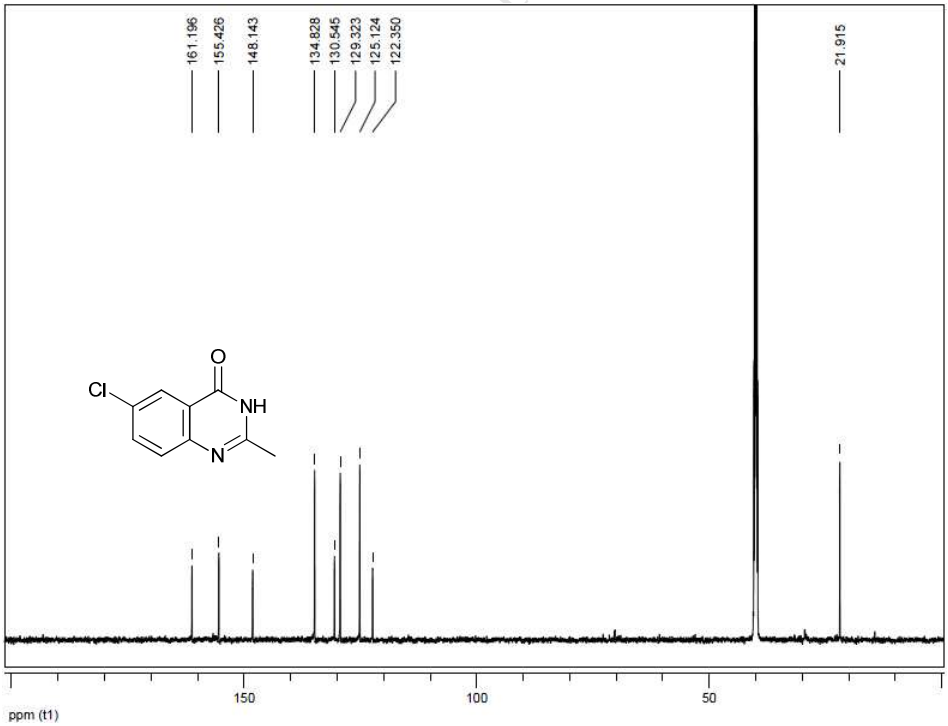


6-Chloro-2-methylquinazolin-4(3H)-one (3f)

Proton NMR (DMSO-*d6*)

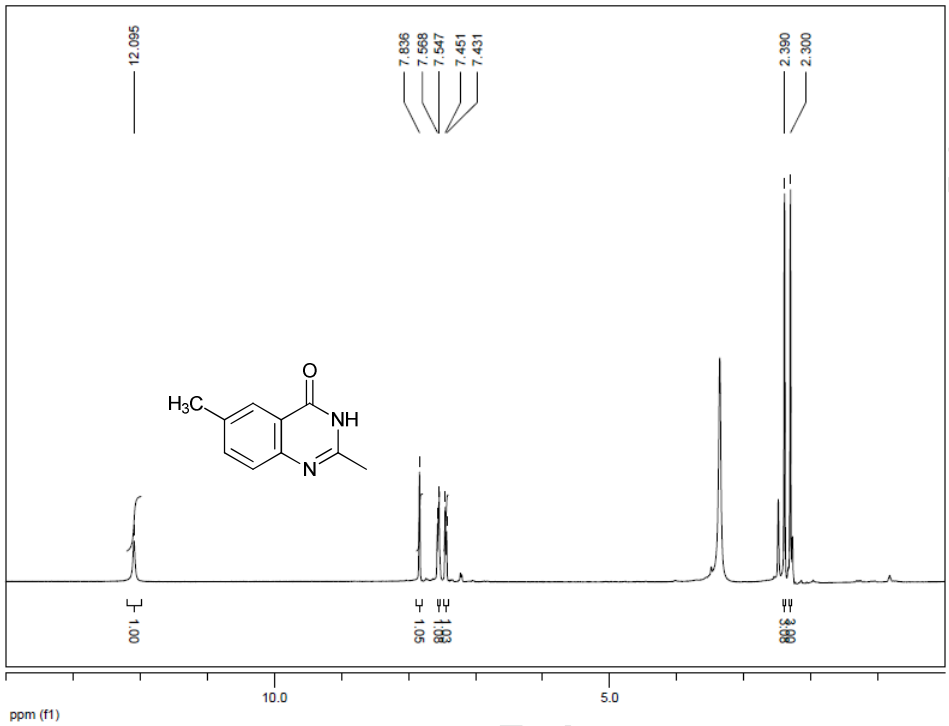


Carbon NMR (DMSO-*d6*)

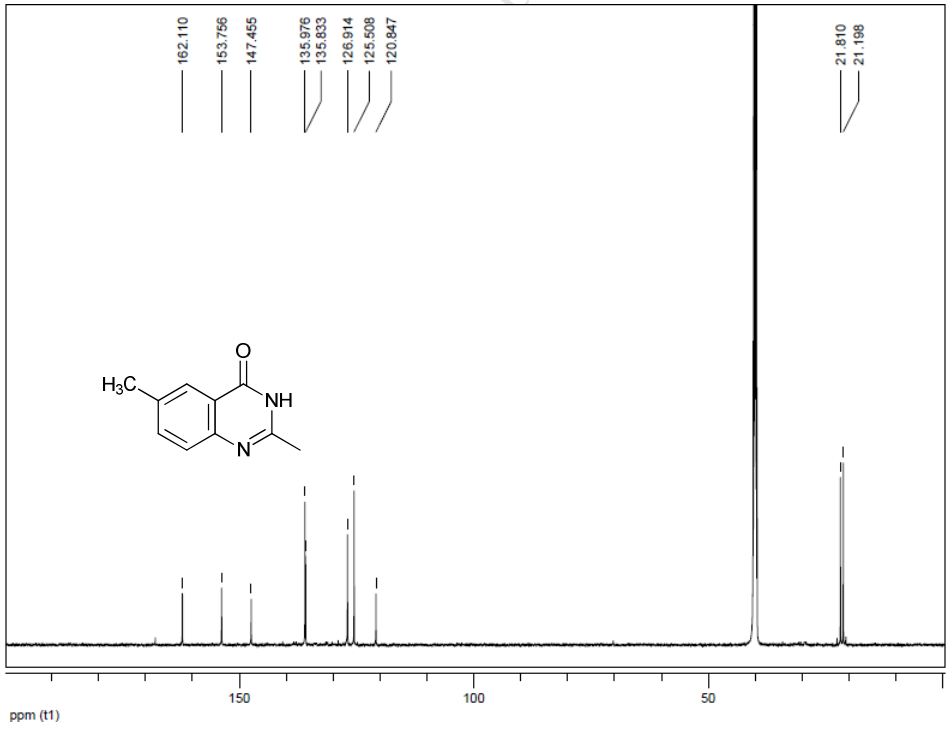


2,6-dimethylquinazolin-4(3H)-one (3g)

Proton NMR (DMSO-*d6*)

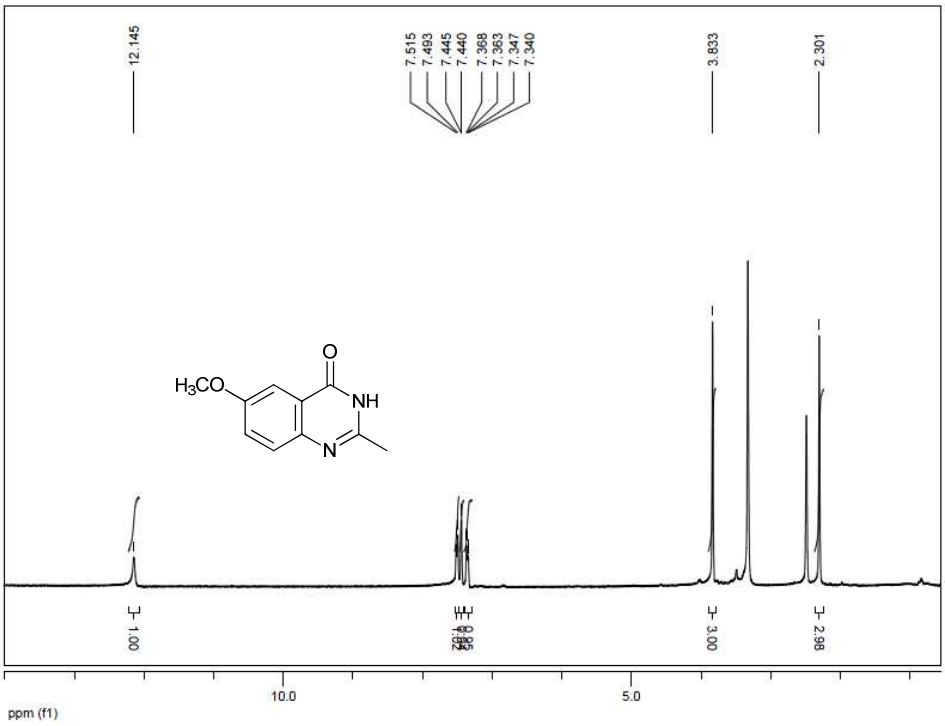


Carbon NMR (DMSO-*d6*)

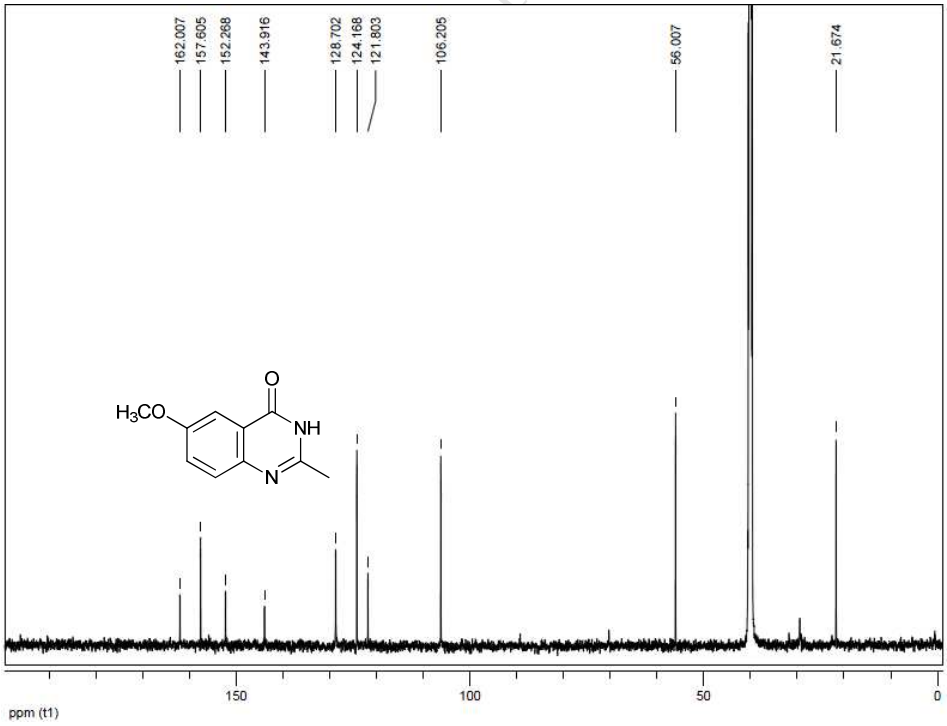


6-methoxy-2-methylquinazolin-4(3H)-one (3h)

Proton NMR (DMSO-*d6*)

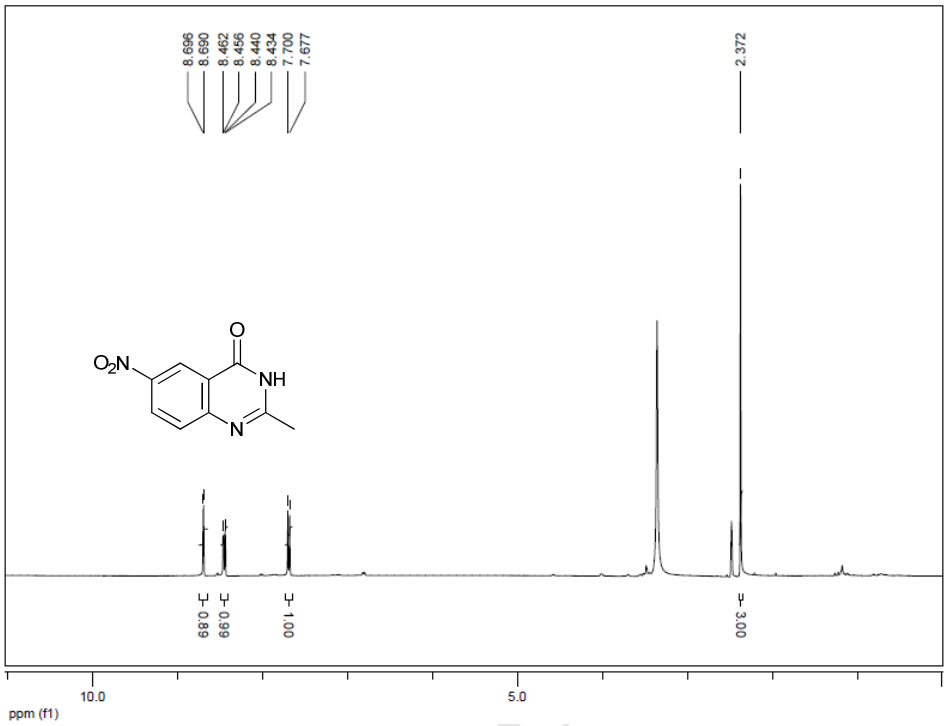


Carbon NMR (DMSO-*d6*)

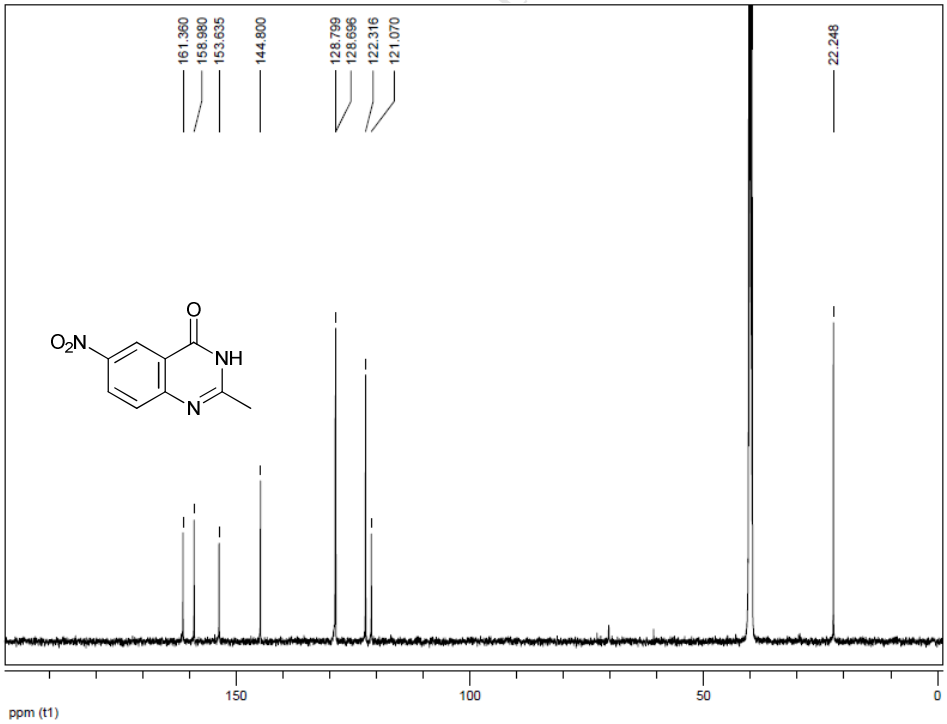


2-Methyl-6-nitroquinazolin-4(3H)-one (3i)

Proton NMR (DMSO-*d6*)

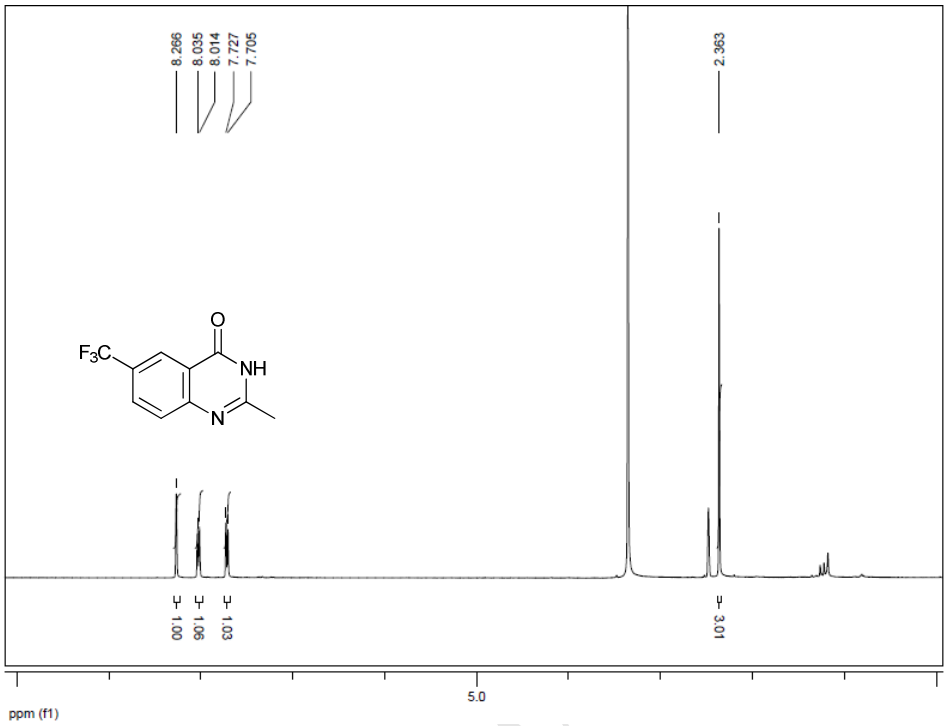


Carbon NMR (DMSO-*d6*)

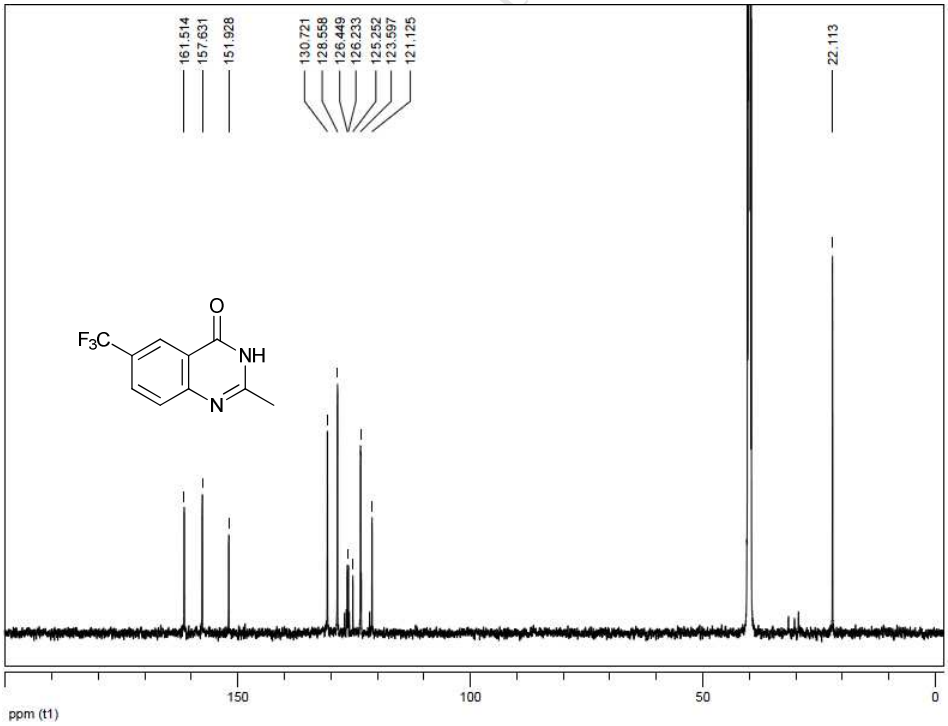


2-methyl-6-(trifluoromethyl)quinazolin-4(3H)-one (3j)

Proton NMR (DMSO-*d6*)

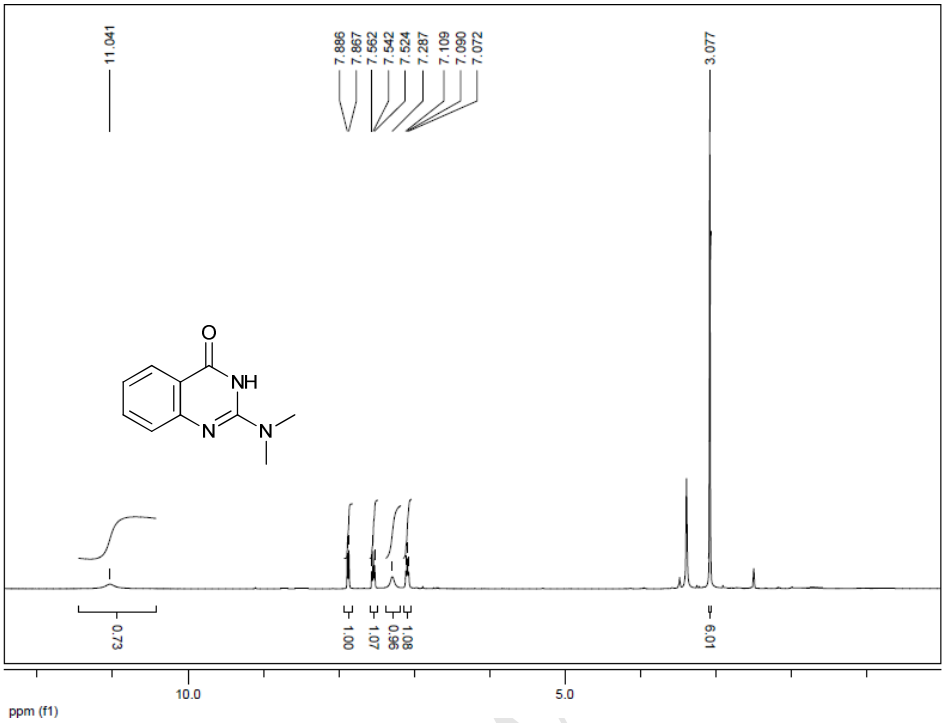


Carbon NMR (DMSO-*d6*)



2-(dimethylamino)quinazolin-4(3H)-one (3k)

Proton NMR (DMSO-*d6*)



Carbon NMR (DMSO-*d6*)