Microwave-assisted synthesis of quinazolinone derivatives by efficient and rapid iron-catalyzed cyclization in water†

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A green, rapid, and efficient method was developed for synthesizing quinazolinone derivatives from substituted 2-halobenzoic acids and amidines *via* microwave-assisted iron-catalyzed cyclization with or without ligand in water (methods A and B) or DMF (methods C and D). With these methods, moderate to high yields of the desired products can be obtained from even inactive substrates, such as guanidines. To the best of our knowledge, this is the first report on the synthesis of N-heterocyclic compounds by iron-catalyzed C–N coupling in aqueous media.

Introduction

The concept of green chemistry[1] and its application[2] in synthetic chemistry has emerged as a major solution for the development of cleaner and more benign chemical processes. As part of this green concept, "water" and "microwaves" have become very popular and received substantial interest.[3] Water is environmentally benign, abundant and a cheap solvent, and can undoubtedly be considered as the cleanest solvent available for chemists.[3] In addition, it often exhibits unique reactivity and selectivity that cannot be attained in conventional organic solvents.[4] In most chemical processes, major adverse effects towards the environment are due mainly to the consumption of energy for heating.[3] To overcome this problem, it is highly desirable to develop efficient methods that use alternative energy sources such as microwave irradiation to facilitate chemical reactions. Recently, various methodologies and routes have been developed based on green chemistry.[3,5]

Quinazolinone derivatives are an important class of heterocyclic compounds that occur in many natural and synthetic products.[6–8] These compounds exhibit remarkable antitubercular, antifungal, antimalarial, antidiabetic, anti-inflammatory, and antitumor activities.[9,10] In addition, some quinazolinone derivatives are already being used and some are being tested in clinical trials for the treatment of cancer, which are expected to be promising candidates for facile and practical approaches for the synthesis of cancer therapy in the future.[11]

Generally, quinazolinone derivatives are synthesized using *ortho*-amino or *ortho*-nitro benzoic acid derivatives as starting materials.[9] The first synthesis of a quinazolinone scaffold from anthranilic acid and cyanogens was carried out by Griess,[7] and later, von Niementowski optimized the reaction involving the fusion (130–150 °C) of anthranilic acid analogs with amides.[12] Vanelle *et al.* reported the microwave-assisted synthesis of new quinazoline derivatives from 2-aminobenzamide and chloroacetyl chloride.[3b] However, the feasibility of this method was limited due to the difficult preparation of the starting materials.[9,13] Recently, CuI-catalyzed coupling of 2-bromobenzoic and 2-iodobenzoic derivatives with amidines to form quinazoline derivatives has been reported.[14] Despite the efficiency of the above mentioned protocols in terms of conversion, the development of less expensive and environmentally more benign catalysts is a major goal for organic synthesis. In this respect, iron-catalyzed reactions offer attractive industrial prospects in terms of sustainable chemistry, and hence must be studied in detail.[15] In the past few years, tremendous efforts have been made in the iron-catalyzed organic reactions with regard to C–N bond formation.[16–18] Taillefer and co-workers reported an economically competitive system that enable N-arylations by iron–copper cooperative catalysis.[16] Bolm *et al.* subsequently reported the first genuine iron-catalyzed N-arylation of N-nucleophiles.[17] We have recently described an efficient method of Fe_2O_3-catalyzed N-arylation of aryl halides with various amines using L-proline as the ligand.[19] The approach employs an environmentally friendly and economically competitive catalytic system and is tolerated with a broader scope of substrates, including both aliphatic and aromatic amines and various substituted aryl halides. Besides, microwave-assisted transition metal catalyzed C–N coupling reactions for the synthesis of N-heterocycles have been developed in our group,[20] which proved to be a green and rapid route in organic synthesis.[3] Prompted by these results, in this study, we wish to report an efficient iron-catalyzed synthesis of a series of quinazolinone derivatives in both H_2O and DMF under microwave irradiation. In comparison with the existing methods, the present approach has several distinguishing features that are worth mentioning: (i) it is environmentally friendly and cost-effective with readily available iron salts as catalysts, (ii) it proceeds faster and

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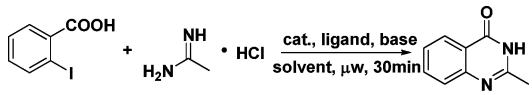
Table 1 Optimization of the reaction conditions (also see Table S1, ESI†)[a]



1a 2a 3a

Entry	Catalyst	Ligand	Base	Temp (°C)	Solvent	Yield (%)[b]
1	—	—	Cs_2CO_3	100	DMF	Trace
2	$FeCl_3$	—	Cs_2CO_3	100	DMF	75
3	$FeCl_3$	L-Pro	Cs_2CO_3	100	DMF	84
4	$FeCl_3$	DMEDA[c]	Cs_2CO_3	100	DMF	79
5	$FeCl_3$	TMEDA[d]	Cs_2CO_3	100	DMF	Trace
6	$FeCl_3$	L-Pro	DBU	100	DMF	76
7	$FeCl_3$	L-Pro	NaO*t*Bu	100	DMF	71
8	$FeCl_3$	L-Pro	Cs_2CO_3	100	Toluene	73
9	$FeCl_3$	L-Pro	Cs_2CO_3	100	Dioxane	78
10	$Fe_2(acac)_3$	DMEDA	Cs_2CO_3	100	DMF	85
11	$FeCl_3$	L-Pro	Cs_2CO_3	100	H_2O	73
12	$FeCl_3$	L-Pro	Cs_2CO_3	120	H_2O	81
13	$FeCl_3$	L-Pro	Cs_2CO_3	150	H_2O	79
14	Fe_2O_3	L-Pro	Cs_2CO_3	120	H_2O	51
15	$Fe_2(acac)_3$	L-Pro	Cs_2CO_3	120	H_2O	61
16	$FeCl_3$	—	Cs_2CO_3	120	H_2O	78
17	$FeCl_3$	DMEDA	Cs_2CO_3	120	H_2O	75
18	$FeCl_3$	TMEDA	Cs_2CO_3	120	H_2O	Trace
19	$FeCl_3$	L-Pro	DBU	120	H_2O	63
20	$FeCl_3$	L-Pro	NaO*t*Bu	120	H_2O	71

[a] Reaction conditions: 2-iodobenzoic acid (1.0 mmol), acetamidine hydrochloride (1.5 mmol), catalyst (0.1 mmol), ligand (0.2 mmol), base (2 mmol), solvent (6 mL) with microwave-assisted under a nitrogen atmosphere. [b] Yield of isolated product. [c] DMEDA = N,N′-dimethylethanediamine. [d] TMEDA = tetramethylethylenediamine.

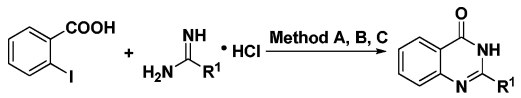
affords good to excellent yields within minutes under microwave irradiation, (iii) it is applicable to a broader range of substrates, including aliphatic, aryl, heterocyclic amidines, guanidyl, and various substituted 2-halobenzoic acids, (iv) it can take place in aqueous media, (v) it can take place in the ligand-free condition.

Results and discussion

We selected 2-iodobenzoic acid (**1a**, 1.0 equiv.) and acetamidine hydrochloride (**2a**, 1.5 equiv.) as the model substrates for the optimization of the reaction conditions, which included the catalyst, ligand, base, temperature, time, and solvent. The results are summarized in Table 1 (also see Table S1 ,ESI†). Only a trace product was observed in the catalyst and ligand-free condition (Table 1, entry 1). However, in the presence of $FeCl_3$ (10% mmol) without ligand in DMF at 100 °C under microwave heating for 30 min, we observed the formation of the expected product in 75% yield (Table 1, entry 2). It proved that this reaction can also be conducted in a ligand-free catalytic system. In order to obtain higher yields, L-proline (20% mol) was used as the ligand. As expected, the product yield improved to 84% (Table 1, entry 3, method C), which indicated that the ligand is of benefit to the reaction. Next, we screened ligands, such as DMEDA and TMEDA (Table 1, entries 3–5), but no results were superior than L-proline. This catalytic system was selected to examine the effect of bases, and Cs_2CO_3 was proven to be more effective than 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or NaO*t*Bu (Table 1, entries 3, 6 and 7). Finally, we probed the solvent effect and found that DMF was considerably superior to dioxane or toluene (Table 1, entries 3, 8 and 9). Following the above procedure, we also examined other iron catalysts, such as $Fe_2(acac)_3$ (10% mol) and Fe_2O_3 (10% mol) (see Table S1, ESI†). The preliminary results showed that the combination of $Fe_2(acac)_3$ and DMEDA (Table 1, entry 10, method D) also gave a high yield of 85%. In order to obtain greener methods, we conducted the reaction in water with the combination of $FeCl_3$ and L-proline at 100 °C under microwave heating for 30 min. To our delight, the desired product **3a** was formed in 73% yield (Table 1, entry 11). We then increased the temperature (Table 1, entries 11–13), and found that 120 °C is the most efficient to afford 81% product yield, which is comparable to that of methods C and D (Table 1, entry 12, method B). As examples of iron-catalyzed C–N coupling reaction in water are sparse,[18,20] we further optimized the reaction conditions including catalyst, ligand, and base in water, which produced lower yields of the desired products (Table 1, entries 14–20). We found that when the reaction was conducted in water, it can also give good yields up to 78% without ligands (Table 1, entry 16, method A). Finally, four independent optimized conditions (methods A, B, C, and D) were chosen by us for the following reactions.

With these optimal conditions in hand, we examined the feasibility of the use of amidines substrates for the synthesis of quinazolinones. We applied these methods to a variety of amidines substrates including aliphatic amidines, benzamidines, and heterocyclic amidines with 2-iodobenzoic acid. As shown in Table 2, moderate to good yields were obtained by methods A and B, and good to excellent yields were obtained with most of

Table 2 Iron-catalyzed forming quinazolinone derivatives of amidines substrates with 2-iodobenzoic acid[a]



1a 2a-2j 3a-3j

Entry	Products **3**	R_1	Yield (%)[f] A[b]	B[c]	C[d]	D[e]
1	**3a**	Me	78	81	84	85
2	**3b**	Cyclopropyl	74	77	82	81
3	**3c**	*t*-Bu	72	71	80	79
4	**3d**	Ph	74	79	81	86
5	**3e**	4-Me-Ph	63	69	82	82
6	**3f**	3,5-$(CF_3)_2$-Ph	45	41	55	54
7	**3g**	4-Cl-Ph	65	67	76	75
8	**3h**	Py-4-yl	73	70	82	81
9	**3i**	Morpholin-4-yl[g]	53	59	70	71
10	**3j**	NH_2	39	41	53	42

[a] Reaction conditions: 2-iodobenzoic acid (1.0 mmol), amidine hydrochloride (1.5 mmol), catalyst (0.1 mmol), ligand (0.2 mmol), base (2 mmol), solvent (6 mL) with microwave-assisted under a nitrogen atmosphere. [b] Method A: $FeCl_3$, Cs_2CO_3, H_2O. [c] Method B: $FeCl_3$, L-proline, Cs_2CO_3, H_2O. [d] Method C: $FeCl_3$, L-proline, Cs_2CO_3, DMF. [e] Method D: $Fe_2(acac)_3$, DMEDA, Cs_2CO_3, DMF. [f] Yield of isolated product. [g] Morpholine-4-carboximidamide hydroiodide.

the substrates when following methods C and D. All the aliphatic amidines studied herein afforded the product in good yields; however, steric hindrance affected the reaction to a certain extent (Table 2, entries 1–3). Quinazolinone derivatives were obtained in good yields from most of the benzamidines and substituted benzamidines studied herein (Table 2, entries 4–7). However, the yield obtained when using 3,5-bis-(trifluoromethyl)-benzimidamide (Table 2, entry 6) was less owing to the presence of two strong electron-withdrawing trifluoromethyl groups in this compound. Quinazolinone derivatives were obtained in good yields from heterocyclic amidines when using methods C and D and in moderate yields when using methods A and B. In particular, moderate to good yields of the product **3i** were obtained from morpholine-4-carboximidamide (Table 2, entry 9), which contained a guanidine moiety. Hence, we synthesized quinazoline derivatives from guanidine (Table 2, entry 10), and found that all the four above mentioned methods afforded the product in moderate yield.

We then investigated the scope of the process with respect to 2-halobenzoic acids (Table 3). We applied the new process for the synthesis of quinazoline derivatives from various substituted 2-halobenzoic acids with acetamidine and benzimidamide. Moderate to good yields were obtained by methods A and B, and good to excellent yields were obtained with most of the substrates when following methods C and D. The relative reactivity of substituted 2-halobenzoic acids was in the following order: aryl iodides > aryl bromides > aryl chlorides (Table 3, entries 1 and 9). The reactivity of the substituted 2-halobenzoic acids containing electron-donating groups was slightly higher than that of others. For example, the highest yield was obtained when using 2-iodo-4,5-dimethoxybenzoic acid (Table 3, entries 8 and 16).

Conclusion

In summary, we have developed a green, rapid, and highly efficient method for the synthesis of quinazolinone derivatives. The coupling reactions of 2-halobenzoic acid derivatives with amidines performed well under microwave heating with or without ligand in water or DMF. To the best of our knowledge, this is the first report of iron-catalyzed C–N coupling forming N-heterocycles in aqueous media. Even the non-active substrates, such as guanidines, gave moderate yields. The versatility, convenient operation, low cost, and environmental friendliness of this method, in addition to the high yields it provides, make it a practical method in preparing quinazolinone derivatives. Currently, we are exploring the scope and application of the proposed iron-catalyzed C–N coupling forming N-heterocycles with regard to the synthesis of pharmaceutical molecules.

Experimental

General experimental procedures

All reactions were carried out under nitrogen atmosphere. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of DMSO-d_6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, DMSO at 2.50 ppm; ^{13}C NMR: DMSO at 40.0 ppm).

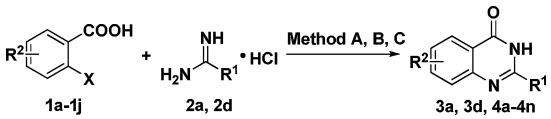
General procedure for synthesis of quinazolinone derivatives

Substituted 2-halobenzoic acid (**1**, 1.0 mmol) and amidines hydrochloride (**2**, 1.5 mmol) in water or DMF (6 mL) were added under nitrogen atmosphere. After 10 min stirring at room temperature, Cs_2CO_3 (2 mmol, 652 mg) was added to the solvent. $Fe_2(acac)_3$ (0.1 mmol, 35 mg) and DMEDA (0.2 mmol, 22 μL) or $FeCl_3$ (0.1 mmol, 16 mg) and L-proline (0.2 mmol, 23 mg) were added after 15 min to the reaction mixture. The reaction mixture was irradiated in a microwave oven at the shown temperature for 30 min (see Table 1 in text, and also Table S1, ESI†). After completion of the reaction, the mixture was filtered, and the solvent of filtrate was removed with the aid of a rotary evaporator. 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.

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

Eluent: petroleum ether : ethyl acetate (1 : 1). Yield 81% (2-iodobenzoic acid as the substrate, method A); 64% (2-bromobenzoic acid as the substrate, method A); 41% (2-chlorobenzoic acid as the substrate, method A). White solid, mp 239–241 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.20 (s, br, 1H), 8.04 (d, 1H, J = 6.9 Hz), 7.74 (t, 1H, J = 5.1 Hz), 7.54 (d, 1H, J = 6.0 Hz), 7.42 (t, 1H, J = 5.4 Hz), 2.32 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.8, 154.3, 148.9, 134.3, 126.5, 125.8, 125.6, 120.6, 21.5 ppm; MS (EI, m/z) 160 $[M]^+$; HRMS (EI) calcd for $C_9H_8N_2O$ $[M]^+$ 160.0637, found 160.0643.

Table 3 Iron-catalyzed forming quinazolinone derivatives of 2-halobenzoic acids with acetamidine and benzimidamide[a]



1a-1j 2a, 2d 3a, 3d, 4a-4n

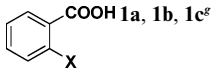
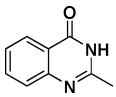
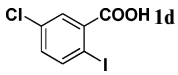
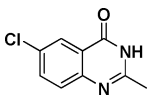
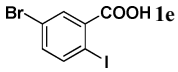
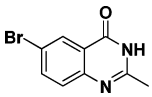
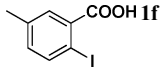
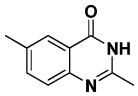
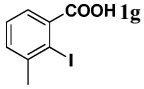
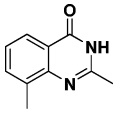
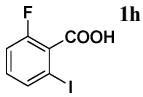
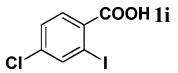
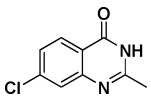
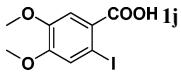
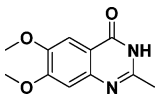
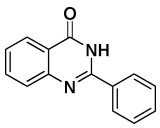
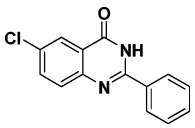
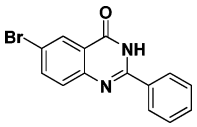
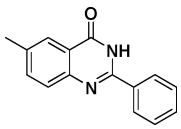
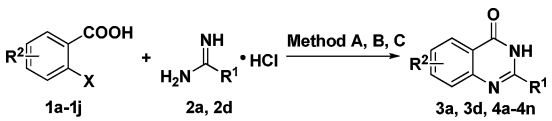
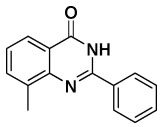
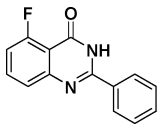
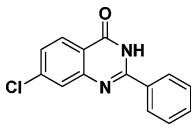
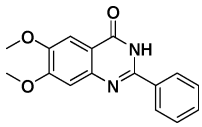
Entry	1	2	Product		Yield (%)[f] Method A[b]	Method B[c]	Method C[d]	Method D[e]
1	 **1a**, **1b**, **1c**[g]	**2a**		**3a**	I: 78 Br: 69 Cl: 38	I: 81 Br: 64 Cl: 41	I: 84 Br: 70 Cl: 47	I: 85 Br: 69 Cl: 51
2	 **1d**	**2a**		**4a**	58	52	81	84
3	 **1e**	**2a**		**4b**	54	53	80	86
4	 **1f**	**2a**		**4c**	59	67	82	79
5	 **1g**	**2a**		**4d**	59	65	83	81
6	 **1h**	**2a**		**4e**	49	51	71	74
7	 **1i**	**2a**		**4f**	53	50	81	83
8	 **1j**	**2a**		**4g**	76	71	83	89
9	**1a**, **1b**, **1c**	**2d**		**3d**	I: 74 Br: 61 Cl: 47	I: 79 Br: 68 Cl: 45	I: 81 Br: 73 Cl: 51	I: 86 Br: 71 Cl: 63
10	**1d**	**2d**		**4h**	61	64	80	85
11	**1e**	**2d**		**4i**	65	61	83	84
12	**1f**	**2d**		**4j**	61	59	79	81

Table 3 *(Contd.)*



1a-1j 2a, 2d 3a, 3d, 4a-4n

Entry	1	2	Product		Yield (%)[f] Method A[b]	Method B[c]	Method C[d]	Method D[e]
13	**1g**	**2d**		**4k**	59	63	81	83
14	**1h**	**2d**		**4l**	48	52	81	79
15	**1i**	**2d**		**4m**	49	51	79	84
16	**1j**	**2d**		**4n**	73	70	84	88

[a] Reaction conditions: 2-iodobenzoic acid (1.0 mmol), amidine hydrochloride (1.5 mmol), catalyst (0.1 mmol), ligand (0.2 mmol), base (2 mmol), solvent (6 mL) with microwave-assisted under a nitrogen atmosphere. [b] Method A: $FeCl_3$, Cs_2CO_3, H_2O. [c] Method B: $FeCl_3$, L-proline, Cs_2CO_3, H_2O. [d] Method C: $FeCl_3$, L-proline, Cs_2CO_3, DMF. [e] Method D: $Fe_2(acac)_3$, DMEDA, Cs_2CO_3, DMF. [f] Yield of isolated product. [g] **1a**: X = I, **1b**: X = Br, **1c**: X = Cl.

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

Eluent: petroleum ether : ethyl acetate (1 : 1). Yield 77% (method A); 82% (method B); 81% (method C). White solid, mp 231–233 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.45 (s, br, 1H), 8.05 (d, 1H, J = 7.5 Hz), 7.72 (t, 1H, J = 8.4 Hz), 7.48 (d, 1H, J = 8.4 Hz), 7.40 (t, 1H, J = 7.5 Hz), 1.99–2.00 (m, 1H), 1.08–1.11 (m, 2H), 1.02–1.05 (m, 2H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.6, 159.1, 149.1, 134.3, 126.4, 125.7, 125.3, 120.6, 13.4, 9.5 ppm; MS (EI, m/z) 186 [M]$^+$; HRMS (EI) calcd for $C_{11}H_{10}N_2O$ [M]$^+$ 186.0793, found 186.0784.

2-*tert*-Butylquinazolin-4(3H)-one 3c

Eluent: petroleum ether : ethyl acetate (1 : 1). Yield 71% (method A); 80% (method B); 79% (method C). White solid, mp 206–208 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.07 (d, 1H, J = 7.8 Hz), 7.76 (t, 1H, J =7.5 Hz), 7.60 (d, 1H, J = 8.6 Hz), 7.46 (t, 1H, J = 7.5 Hz), 1.33 (s, 9H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.7, 162.3, 148.3, 134.4, 127.3, 126.3, 125.6, 120.7, 37.3, 27.8 ppm; MS (EI, m/z) 202 [M]$^+$; HRMS (EI) calcd for $C_{12}H_{14}N_2O$ [M]$^+$ 202.1106, found 202.1097.

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

Eluent: petroleum ether : ethyl acetate (3 : 1). Yield 79% (2-iodobenzoic acid as the substrate, method A); 68% (2-bromobenzoic acid as the substrate, method A); 45% (2-chlorobenzoic acid as the substrate, method A). White solid, mp 235–237 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.55 (s, br, 1H), 8.14–8.19 (m, 3H), 7.81–7.86 (m, 1H), 7.73–7.76 (m, 1H), 7.50–7.59 (m, 4H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.3, 152.4, 148.7, 134.7, 134.5, 132.7, 131.4, 128.6, 127.8, 126.6, 126.0, 121.0 ppm; MS (EI, m/z) 222 [M]$^+$; HRMS (EI) calcd for $C_{14}H_{10}N_2O$ [M]$^+$ 222.0793, found 222.0788.

2-*p*-Tolylquinazolin-4(3H)-one 3e

Eluent: petroleum ether : ethyl acetate (3 : 1). Yield 69% (method A); 82% (method B); 82% (method C). White solid, mp 261–263 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.50 (s, br, 1H), 8.10–8.17 (m, 3H), 7.82 (t, 1H, J = 6.9 Hz), 7.74 (d, 1H, J = 7.8 Hz), 7.52 (t, 1H, J = 7.2 Hz), 7.37 (d, 2H, J = 7.8 Hz), 2.41 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.2, 152.2, 148.8, 141.4, 134.6, 129.9, 129.2, 127.7, 127.4, 126.4, 125.8, 120.9, 21.0 ppm; MS (EI, m/z) 236 [M]$^+$; HRMS (EI) calcd for $C_{15}H_{12}N_2O$ [M]$^+$ 236.0950, found 236.0957.

2-(3,5-Bis(trifluoromethyl)phenyl)quinazolin-4(3H)-one 3f

Eluent: petroleum ether : ethyl acetate (1 : 1). Yield 41% (method A); 55% (method B); 54% (method C). White solid, mp 268–270 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.91 (s, br, 1H),

8.82 (s, 2H), 8.32 (s, 1H), 8.15 (d, 1H, $J = 6.0$ Hz), 7.83 (t, 1H, $J = 6.3$ Hz), 7.80 (d, 1H, $J = 5.7$ Hz), 7.55 (t, 1H, $J = 5.1$ Hz) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.1, 149.8, 148.2, 135.2, 134.9, 131.2, 130.8, 130.5, 128.6, 127.8, 127.5, 125.9, 124.8, 121.8, 121.3 ppm; MS (EI, m/z) 358 $[M]^+$; HRMS (EI) calcd for $C_{16}H_8F_6N_2O$ $[M]^+$ 358.0541, found 358.0541.

2-(4-Chlorophenyl)quinazolin-4(3H)-one 3g

Eluent: petroleum ether : ethyl acetate (3 : 1). Yield 67% (method A); 76% (method B); 75% (method C). White solid, mp 298–300 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.63 (s, br, 1H), 8.18 (d, 2H, $J = 6.6$ Hz), 8.14 (d, 1H, $J = 5.7$ Hz), 7.83 (t, 1H, $J = 6.3$ Hz), 7.73 (d, 1H, $J = 5.7$ Hz), 7.61 (d, 2H, $J = 6.3$ Hz), 7.52 (t, 1H, $J = 5.4$ Hz) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.2, 151.3, 148.6, 136.3, 134.7, 131.6, 129.6, 128.7, 127.5, 126.8, 125.9, 121.0 ppm; MS (EI, m/z) 256 $[M]^+$; HRMS (EI) calcd for $C_{14}H_9ClN_2O$ $[M]^+$ 256.0403, found 256.0412.

2-(Pyridin-4-yl)quinazolin-4(3H)-one 3h

Eluent: petroleum ether : ethyl acetate (3 : 1). Yield 70% (method A); 82% (method B); 81% (method C). White solid, mp 281–283 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.80 (s, br, 1H), 8.80 (d, 2H, $J = 6.0$ Hz), 8.19 (d, 1H, $J = 7.5$ Hz), 8.12 (d, 2H, $J = 6.3$ Hz), 7.88 (t, 1H, $J = 8.4$ Hz), 7.79 (d, 1H, $J = 8.4$ Hz), 7.59 (t, 1H, $J = 7.2$ Hz) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 150.6, 150.3, 139.9, 134.8, 127.8, 127.4, 125.9, 121.6, 121.5 ppm; MS (EI, m/z) 223 $[M]^+$; HRMS (EI) calcd for $C_{13}H_9N_3O$ $[M]^+$ 223.0746, found 223.0749.

2-(4-Morpholino)quinazolin-4(3H)-one 3i

Eluent: petroleum ether : ethyl acetate (1 : 1). Yield 59% (method A); 70% (method B); 71% (method C). White solid, mp 289–291 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.90 (d, 1H, $J = 8.4$ Hz), 7.58 (t, 1H, $J = 8.1$ Hz), 7.37 (d, 1H, $J = 7.8$ Hz), 7.15 (t, 1H, $J = 7.8$ Hz), 3.64–3.65 (m, 8H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 133.0, 125.9, 123.3, 121.3, 117.6, 66.0, 45.0 ppm; MS (EI, m/z) 231 $[M]^+$; HRMS (EI) calcd for $C_{12}H_{13}N_3O_2$ $[M]^+$ 231.1008, found 231.1015.

2-Aminoquinazolin-4(3H)-one 3j

Eluent: petroleum ether : ethyl acetate (1 : 1). Yield 41% (method A); 53% (method B); 42% (method C). White solid, mp 313–315 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.88 (d, 1H, $J = 7.5$ Hz), 7.56 (t, 1H, $J = 8.1$ Hz), 7.20 (d, 1H, $J = 8.4$ Hz), 7.10 (t, 1H, $J = 7.5$ Hz) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.7, 150.5, 140.4, 134.0, 125.9, 121.5, 117.2 ppm; MS (EI, m/z) 161 $[M]^+$; HRMS (EI) calcd for $C_8H_7N_3O$ $[M]^+$ 161.0589, found 161.0596.

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

Eluent: petroleum ether : ethyl acetate (1 : 1). Yield 52% (method A); 81% (method B); 84% (method C). White solid, mp 292–294 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.39 (s, br, 1H), 7.99 (d, 1H, $J = 2.4$ Hz), 7.77–7.81 (m, 1H), 7.59 (d, 1H, $J = 8.7$ Hz), 2.34 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.7, 154.9, 147.7, 134.3, 130.0, 128.8, 124.6, 121.9, 21.4 ppm; MS (EI, m/z) 194 $[M]^+$; HRMS (EI) calcd for $C_9H_7ClN_2O$ $[M]^+$ 194.0247, found 194.0246.

6-Bromo-2-methylquinazolin-4(3H)-one 4b

Eluent: petroleum ether : ethyl acetate (1 : 1). Yield 53% (method A); 80% (method B); 86% (method C). White solid, mp 294–296 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.38 (s, br, 1H), 8.12 (d, 1H, $J = 1.8$ Hz), 7.88-7.90 (m, 1H), 7.50 (d, 1H, $J = 6.6$ Hz), 2.32 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.6, 155.1, 147.9, 137.1, 129.0, 127.8, 122.3, 118.1, 21.5 ppm; MS (EI, m/z) 238 $[M]^+$; HRMS (EI) calcd for $C_9H_7BrN_2O$ $[M]^+$ 237.9742, found 237.9759.

2,6-Dimethylquinazolin-4(3H)-one 4c

Eluent: petroleum ether : ethyl acetate (1 : 1). Yield 67% (method A); 82% (method B); 79% (method C). White solid, mp 246–248 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.11 (s, br, 1H), 7.86 (s, 1H), 7.55–7.58 (m, 1H), 7.46 (d, 1H, $J = 8.4$ Hz), 2.41 (s, 3H), 2.33 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.6, 153.2, 147.0 135.4, 135.3, 126.4, 125.0, 120.4, 21.3, 20.7 ppm; MS (EI, m/z) 174 $[M]^+$; HRMS (EI) calcd for $C_{10}H_{10}N_2O$ $[M]^+$ 174.0793, found 174.0795.

2,8-Dimethylquinazolin-4(3H)-one 4d

Eluent: petroleum ether : ethyl acetate (1 : 1). Yield 65% (method A); 83% (method B); 81% (method C). White solid, mp 247–249 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.16 (s, br, 1H), 7.89 (d, 1H, $J = 6.0$ Hz), 7.60 (d, 1H, $J = 5.4$ Hz), 7.30 (t, 1H, $J = 5.7$ Hz), 2.48 (s, 3H), 2.34 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.8, 154.1, 147.7, 134.5, 134.4, 125.0, 123.4, 120.5, 22.2, 17.4 ppm; MS (EI, m/z) 174 $[M]^+$; HRMS (EI) calcd for $C_{10}H_{10}N_2O$ $[M]^+$ 174.0793, found 174.0777.

5-Fluoro-2-methylquinazolin-4(3H)-one 4e

Eluent: petroleum ether : ethyl acetate (1 : 1). Yield 51% (method A); 71% (method B); 74% (method C). White solid, mp 251–253 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.25 (s, br, 1H), 7.69–7.76 (m, 1H), 7.37 (d, 1H, $J = 8.1$ Hz), 7.14–7.21 (m, 1H), 2.32 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.8, 159.2, 159.0, 155.4, 151.2, 134.8, 122.6, 112.2, 110.1, 21.2 ppm; MS (EI, m/z) 178 $[M]^+$; HRMS (EI) calcd for $C_9H_7FN_2O$ $[M]^+$ 178.0542, found 178.0536.

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

Eluent: petroleum ether : ethyl acetate (1 : 1). Yield 50% (method A); 81% (method B); 83% (method C). White solid, mp 291–293 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.35 (s, br, 1H), 8.05 (d, 1H, $J = 8.1$ Hz), 7.60 (d, 1H, $J = 2.1$ Hz), 7.45–7.49 (m, 1H), 2.35 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ161.1, 156.0, 150.0, 138.8, 127.7, 126.1, 125.7, 119.4, 21.5 ppm; MS (EI, m/z) 194 $[M]^+$; HRMS (EI) calcd for $C_9H_7ClN_2O$ $[M]^+$ 194.0247, found 194.0253.

6,7-Dimethoxy-2-methylquinazolin-4(3H)-one 4g

Eluent: petroleum ether : ethyl acetate (1 : 1). Yield 71% (method A); 83% (method B); 89% (method C). White solid,

mp 298–300 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.05 (s, br, 1H), 7.38 (s, 1H), 7.04 (s, 1H), 3.84–3.87 (m, 6H), 2.30 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.1, 154.4, 152.5, 147.9, 145.1, 113.4, 107.5, 104.8, 55.8, 55.6, 21.2 ppm; MS (EI, m/z) 220 [M]$^+$; HRMS (EI) calcd for $C_{11}H_{12}N_2O_3$ [M]$^+$ 220.0848, found 220.0843.

6-Chloro-2-phenylquinazolin-4(3H)-one 4h

Eluent: petroleum ether : ethyl acetate (3 : 1). Yield 64% (method A); 80% (method B); 85% (method C). White solid, mp 287–289 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.71 (s, br, 1H), 8.14–8.17 (m, 2H), 7.84–7.89 (m, 2H), 7.75–7.78 (m, 1H), 7.53–7.61 (m, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 168.0, 161.4, 152.9, 134.8, 134.3, 132.5, 131.7, 131.3, 128.7, 128.2, 127.9, 127.5, 124.9, 122.2 ppm; MS (EI, m/z) 256 [M]$^+$; HRMS (EI) calcd for $C_{14}H_9ClN_2O$ [M]$^+$ 256.0403, found 256.0406.

6-Bromo-2-phenylquinazolin-4(3H)-one 4i

Eluent: petroleum ether : ethyl acetate (3 : 1). Yield 61% (method A); 83% (method B); 84% (method C). White solid, mp 284–286 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.73 (s, br, 1H), 8.23 (d, 1H, $J = 2.4$ Hz), 8.17 (dd, 2H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 7.98 (m, 1H), 7.70 (d, 1H, $J = 8.4$ Hz), 7.55–7.59 (m, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.2, 153.0, 147.8, 137.4, 132.5, 131.6, 131.2, 129.9, 128.7, 128.2, 127.9, 127.5, 122.6, 119.0 ppm; MS (EI, m/z) 300 [M]$^+$; HRMS (EI) calcd for $C_{14}H_9BrN_2O$ [M]$^+$ 299.9898, found 299.9892.

6-Methyl-2-phenylquinazolin-4(3H)-one 4j

Eluent: petroleum ether : ethyl acetate (3 : 1). Yield 59% (method A); 79% (method B); 81% (method C). White solid, mp 238–240 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.47 (s, br, 1H), 8.15 (d, 2H, $J = 5.1$ Hz), 7.94 (s, 1H), 7.63 (s, 2H), 7.51–7.56 (m, 3H) 2.44 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.1, 151.4, 146.7, 136.2, 135.8, 132.7, 131.1, 128.5, 127.6, 127.3, 125.2, 120.7, 20.8 ppm; MS (EI, m/z) 236 [M]$^+$; HRMS (EI) calcd for $C_{15}H_{12}N_2O$ [M]$^+$ 236.0950, found 236.0959.

8-Methyl-2-phenylquinazolin-4(3H)-one 4k

Eluent: petroleum ether : ethyl acetate (3 : 1). Yield 63% (method A); 81% (method B); 83% (method C). White solid, mp 237–239 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.55 (s, br, 1H), 8.21–8.25 (m, 2H), 7.99 (d, 1H, $J = 7.2$ Hz), 7.70 (d, 1H, $J = 7.2$ Hz), 7.56–7.59 (m, 3H), 7.40 (t, 1H, $J = 8.1$ Hz), 2.62 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.6, 151.1, 147.2, 135.6, 135.0, 133.0, 131.4, 128.7, 127.8, 126.1, 123.5, 120.9, 17.2 ppm; MS (EI, m/z) 236 [M]$^+$; HRMS (EI) calcd for $C_{15}H_{12}N_2O$ [M]$^+$ 236.0950, found 236.0956.

5-Fluoro-2-phenylquinazolin-4(3H)-one 4l

Eluent: petroleum ether : ethyl acetate (3 : 1). Yield 52% (method A); 81% (method B); 79% (method C). White solid, mp 308–310 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.58 (s, br, 1H), 8.18 (d, 2H, $J = 6.6$ Hz), 7.78–7.85 (m, 1H), 7.54–7.62 (m, 4H), 7.24–7.30 (m, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ161.8, 159.5, 153.3, 150.9, 135.2, 135.1, 132.2, 131.7, 128.6, 127.9, 123.6, 113.0, 112.8, 110.5 ppm; MS (EI, m/z) 240 [M]$^+$; HRMS (EI) calcd for $C_{14}H_9FN_2O$ [M]$^+$ 240.0699, found 240.0692.

7-Chloro-2-phenylquinazolin-4(3H)-one 4m

Eluent: petroleum ether : ethyl acetate (3 : 1). Yield 51% (method A); 79% (method B); 84% (method C). White solid, mp 286–288 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.71 (s, br, 1H), 8.17 (t, 3H, $J = 6.6$ Hz), 7.81 (d, 1H, $J = 1.8$ Hz), 7.55–7.63 (m, 4H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.6, 153.8, 149.9, 139.2, 132.4, 131.7, 128.6, 127.9, 126.8, 126.6, 119.8 ppm; MS (EI, m/z) 256 [M]$^+$; HRMS (EI) calcd for $C_{14}H_9ClN_2O$ [M]$^+$ 256.0403, found 256.0420.

6,7-Dimethoxy-2-phenylquinazolin-4(3H)-one 4n

Eluent: petroleum ether : ethyl acetate (3 : 1). Yield 70% (method A); 84% (method B); 88% (method C). White solid, mp 307–309 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.43 (s, br, 1H), 8.17 (d, 2H, $J = 6.0$ Hz), 7.49–7.55 (m, 4H), 7.22 (s, 1H), 3.90–3.93 (m, 6H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.9, 161.6, 154.8, 150.8, 144.8, 132.8, 131.2, 131.1, 128.6, 128.2, 127.5 114.0, 108.3, 105.0, 56.0, 55.7 ppm; MS (EI, m/z) 282 [M]$^+$; HRMS (EI) calcd for $C_{16}H_{14}N_2O_3$ [M]$^+$ 282.1004, found 282.1010.

Acknowledgements

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