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SYNTHESIS OF NOVEL 1-ALKYL-1,2-DIHYDRO-2-IMINO-4-QUINAZOLINAMINES BY TANDEM REACTION OF THE THREE COMPONENTS

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Abstract–A novel and efficient synthesis of quinazoline derivatives involving copper-catalyzed Ullmann-type coupling reaction was developed. These reactions were performed under mild conditions without the addition of a ligand. The coupling reaction and the subsequent cyclization reaction in series gave rise to the formation of intermolecular C-N bond and intramolecular C-N bond and synthesized novel *N,N′*-disubstituted 1,2-dihydro-2-imino-4-quinazolinamines in moderate to high yields simultaneously.

INTRODUCTION

It is known that quinazoline molecules have diverse and promising medicinal and biological activities, mainly including the powerful inhibiting activities on the epidermal growth factor receptors of tyrosine kinase (EGFR-TK), vascular endothelial growth factor receptors (VEGFR), and nerve growth factor receptors (NGFR). In addition, they also work as cell phosphorylation inhibitors,[1] ligands for benzodiazepine and GABA receptors in the central nervous system (CNS)[2,3] against neurological disorders[4,5] or as DNA binders.[6] Quinazoline core structures exist in a number of natural or synthetic compounds.[7] It is a very important unit of many therapeutic agents on the market or in the clinical trials,[8] such as Erlotinib (Tarceva) working as a EGFR-TK antagonist to treat locally advanced or metastatic non-small cell lung cancer (NSCLC),[9] Prazosin acting as an α-adrenergic blocker,[10] Iressa accomplishing the targeted therapy by inhibiting EGFR,[11,12] Tempostatin (an agent in phase II trials for bladder cancer), and Ispinesib (an agent in phase II trials for solid tumors). In addition, quinazolines displayed many other

remarkable and multiple activities, including anticonvulsant, antitussive, antihypertensive, antibacterial, antidiabetic, anti-inflammatory, and antimalarial properties etc.[13-15] So it is very significative to prepare the quinazoline molecules especially the novel derivatives. The development of green chemistry provides the conditions for the search of environmentally benign synthetic methods for their preparations.[16-21]

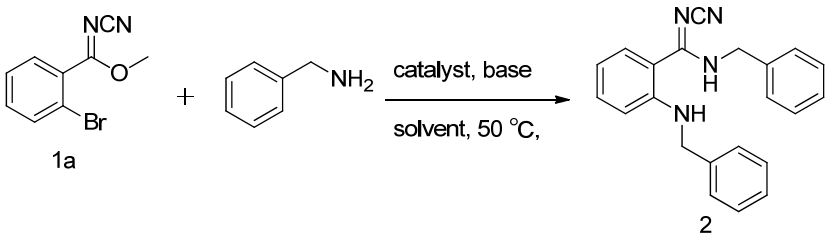
Many methods for the synthesis of quinazoline derivatives have been developed by far.[22-29] The Ullmann-type cross-coupling reactions generally used in C-N, C-O, and C-C bond formations[30] are common approaches to build the quinazoline structures.[31,32] Since Ullmann reactions were born in 1901,[33] for more than a century they were applied widely in the synthesis of some compounds which were intermediates in the life sciences and polymer industries.[34] The applications of Ullmann-type cross-coupling reactions, however, are frequently limited by their harsh reaction conditions such as high temperature[35] or the need of ligands.[36-38] Our group recently described the synthesis of cyanoimidate derivatives from aldehydes by using NBS as an oxidant.[39] Cyanoimidate derivatives have been widely used as precursors for the synthesis of heterocyclic compounds.[40-44] We decided to use the cyanoimidates as the starting materials to prepare quinazoline derivatives. Here we report a novel type of quinazoline derivatives *N,N′*-disubstituted 1,2-dihydro-2-imino-4-quinazolinamines which were prepared according to an efficient, original and mild copper-catalyzed Ullmann-type coupling method and a simple cyclization in series starting from methyl *o*-bromo-*N*-cyanobenzenecarboximidate. Different from other Ullmann-type coupling reactions, this coupling reaction proceeded in ligand-free manner, generating chemo- and regioselective intermolecular C-N bond product. To the best of our knowledge, this is the first report of these *N,N′*-disubstituted 1,2-dihydro-2-imino-4-quinazolinamines and the corresponding synthetic route.

RESULTS AND DISCUSSION

Methyl 2-bromo-*N*-cyanobenzenecarboximidate (**1a**) and benzylamine were chosen as the model substrates for the optimization of the reaction conditions, including the catalysts, bases, and the solvents. As shown in Table 1, four catalysts were tested at 50 °C by using four equivalents of Cs_2CO_3 (relative to the amount of **1a**) as the base in DMF (Table 1, entries 1-4), and CuI showed the best activity. We also compared the effect of the solvents and DMF displayed to be the most suitable solvent (Table 1, entries 4-6). Several bases such as *t*-BuOK, K_3PO_4, K_2CO_3, Cs_2CO_3 were tested (Table 1, entries 4 and 7-9). Both Cs_2CO_3 and K_2CO_3 were satisfying. Whereas K_2CO_3 was a little better and cheaper than Cs_2CO_3 (Table 1, entries 4 and 9) and 4.0 equivalents was the most effective amount (Table 1, entries 9-11). After we decided the optimal base-solvent system, we tried the other two catalysts $CuSO_4$ and Cu_2O, but they did not perform well (Table 1, entries 12 and 13). Only trace amounts of the target compound (**2**) but many impurities were observed in such reaction conditions as the absence of catalyst, the absence of

nitrogen atmosphere, or in the aqueous environment (Table 1, entries 14-16). In summary, according to the optimal conditions (Table 1, entry 9), compound (**2**) could be easily synthesized by mild Ullmann coupling reactions in good yield without any ligand.

Table1. Copper-catalyzed coupling of methyl 2-bromo-*N*-cyanobenzenecarboximidate and benzylamine in different reaction conditions[a]



Entry	Catalyst	Base	Solvent	Yield%[b]
1	$Cu(OAc)_2$	Cs_2CO_3	DMF	63
2	CuBr	Cs_2CO_3	DMF	54
3	Cu	Cs_2CO_3	DMF	28
4	CuI	Cs_2CO_3	DMF	85
5	CuI	Cs_2CO_3	DMSO	30
6	CuI	Cs_2CO_3	MeCN	trace
7	CuI	*t*-BuOK	DMF	76
8	CuI	K_3PO_4	DMF	54
9	CuI	K_2CO_3	DMF	87
10	CuI	K_2CO_3[c]	DMF	56
11	CuI	K_2CO_3[d]	DMF	81
12	$CuSO_4$	K_2CO_3	DMF	66
13	Cu_2O	K_2CO_3	DMF	52
14	-	K_2CO_3	DMF	trace[e]
15	CuI	K_2CO_3	DMF	trace[f]
16	CuI	K_2CO_3	DMF	trace[g]

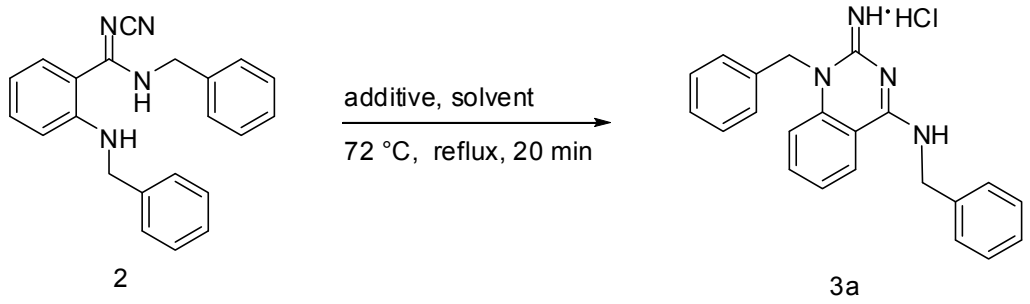
a) Reaction conditions: methyl 2-bromo-*N*-cyanobenzenecarboximidate (0.5 mmol), benzylamine (2.0 mmol), catalyst (0.05 mmol), base (2.0 mmol), solvent (4 mL) at 50 °C under nitrogen atmosphere; b) Yield of the isolated product; c) Base: (1.0 mmol); d) Base: (4.0 mmol); e) No addition of catalyst; f) Without nitrogen atmosphere; g) Aqueous environment. DMF = *N,N*-dimethylformamide; DMSO = dimethyl sulfoxide.

We used to consider that the coupling reaction and the cyclization can happen in one step. In the optimization of this Ullmann-type coupling reaction, however, we found that the cyclization did not

succeed and only *N*-cyano-*N*′-(phenylmethyl)-2-(phenylmethylamino)benzenecarboximidamide (**2**) was synthesized. Therefore the cyclization was developed in the following step.

In the following step, *N*-cyano-*N*′-(phenylmethyl)-2-(phenylmethylamino)benzenecarboximidamide (**2**) was dissolved in the solvent and the additive was added. To set the model of this step, we screened the additives and the solvents as shown in Table 2. Ethanol, methanol, and xylene were tried to be the solvent respectively and methanol behaved the best (Table 2, entries 1-3). We used 6M hydrochloric acid as the additive and found that hydrochloric acid was significant to accelerate the ring-close reactions. But if there was excess hydrochloric acid, not the target compound but impurities increased (Table 2, entry 4). Finally, we obtained 1,2-dihydro-2-imino-*N*-(phenylmethyl)-1-(phenylmethyl)-4-quinazolinamine hydrochloride (**3a**) according to the optimal conditions (Table 2, entry 3). We also used one-pot reaction of Ullmann-type coupling and the cyclization to prepare the quinazolines (Table 2, entry 5), but the yield was very low.

Table 2. Cyclization of *N*-cyano-*N*′-(phenylmethyl)-2-(phenylmethylamino)benzenecarboximidamide (**2**) in different reaction conditions[a]



2 3a

Entry	Additive	Solvent	Yield%[b]
1	HCl	xylene	trace
2	HCl	EtOH	55
3	HCl	MeOH	93
4	HCl[c]	MeOH	43
5	HCl[d]	MeOH	30

a) Reaction conditions: *N*-cyano-*N*′-(phenylmethyl)-2-(phenylmethylamino)benzenecarboximidamide (0.1 mmol), additive (0.3 mmol), solvent (2 mL) at 72 °C; b) Yield of the isolated product; c) Additive (0.6 mmol); d) One pot reaction of Ullmann-type coupling and the cyclization reaction

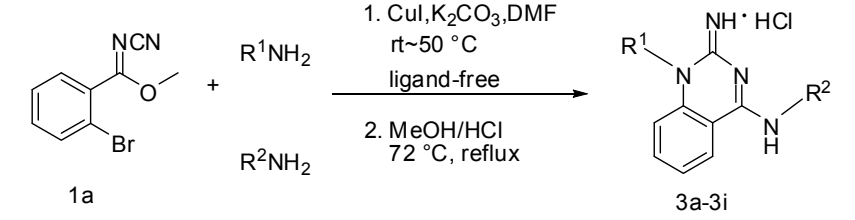
After determining the optimal conditions, we tested the scope of the coupling reaction of methyl 2-bromo-*N*-cyanobenzenecarboximidate with different amines. The results are summarized in Table 3. As

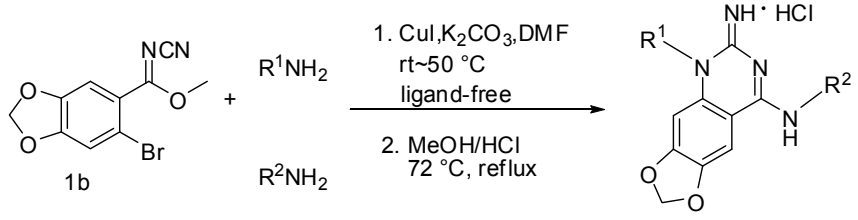
shown in Table 3, we used two *N*-cyanobenzenecarboximidates (**1a**) and (**1b**) as substrates and **1a** performed better. **1b** substituted by the electron-donating groups did not react in good yields (Table 3, entry 10). We also used methyl 2-bromo-*N*-cyano-4-nitrobenzenecarboximidate which is substituted by the electron-withdrawing group as substrate, but it did not apply to this model and it cannot even yield the target quinazoline molecular.

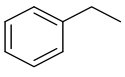
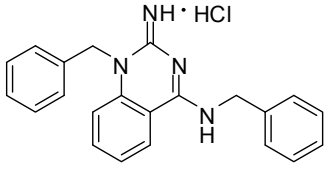
On the other hand, most of the examined amines provided moderate to good yields at 50 °C (Table 3). Moreover, the copper-catalyzed coupling reactions of some simple aliphatic amines such as methylamine and propylamine can carry out at room temperature (ca. 25 °C) (Table 3, entries 2 and 6). The reactivity of amine substituted by hydroxyl such as monoethanolamine was relatively weak to this method (Table 3, entry 9).

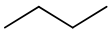
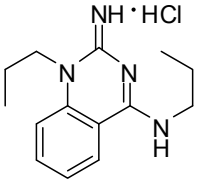
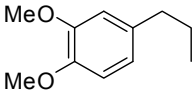
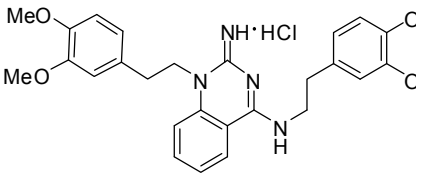
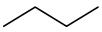
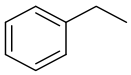
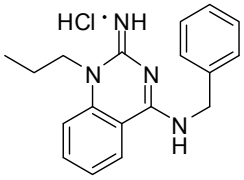
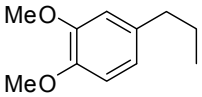
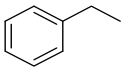
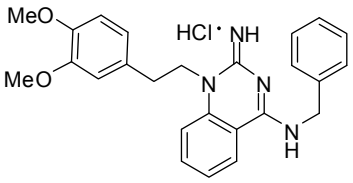
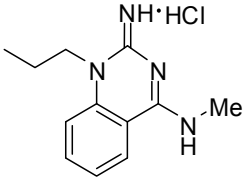
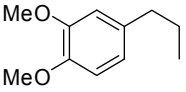
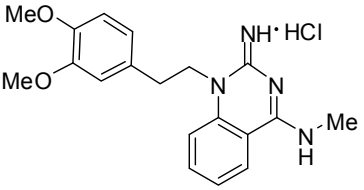
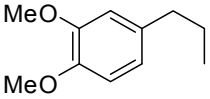
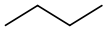
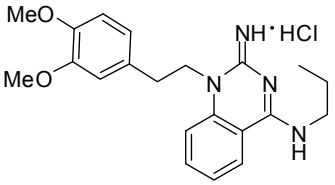
With two different amines, the regioselective coupling reaction can be achieved based on the different activity of methyl *N*-cyanocarboximidate and 2-Br or 6-Br of **1a**,**b**. Because methyl *N*-cyanocarboximidate was more active than 2-Br or 6-Br, R^1NH_2 which was added first reacted with methyl *N*-cyanocarboximidate prior. After consumption of the substrate, R^2NH_2 was added then and R^2NH_2 reacted with only 2-Br or 6-Br. So we can get regioselective compounds according to the different activity of methyl *N*-cyanocarboximidate and 2-Br or 6-Br and the addition of R^1NH_2 and R^2NH_2 step-by-step (Table 3, entries 4-10).

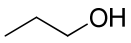
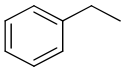
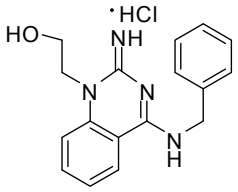
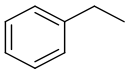
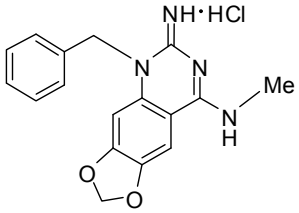
Table 3. Ullmann-type synthesis of quinazoline derivatives in two steps[a]





Entry	Amines	Product	Yield 1%[b]	Yield 2%[c]
1	R^1=R^2= 	 3	87	quantitative

2	R^1=R^2= 	 3b	81[d] (75[e])	98
3	R^1=R^2= 	 3c	74	90
4	R^1=  R^2= 	 3d	91	79
5	R^1=  R^2= 	 3e	80	89
6	R^1=  R^2= Me—	 3f	88[d] (77[e])	62
7	R^1=  R^2= Me—	 3g	84	54
8	R^1=  R^2= 	 3h	74	78

9	R^1=  R^2= 	 3i	47	56
10	R^1=  R^2= Me—	 4a	37	52

a) Reaction conditions: (first step) *N*-cyanobenzenecarboximidate (0.5 mmol), R^1NH_2 (0.5 mmol), R^2NH_2 (1.5 mmol), CuI (0.05 mmol), K_2CO_3 (2 mmol), DMF (4 mL) at 50 °C under nitrogen atmosphere; (final step) *N*-cyanobenzenecarboximidamide derivative (0.5 mmol), methanol (10 mL), 6M hydrochloric acid (1.5 mmol) at 72 °C; Substrate: **1a** for entries 1-9; **1b** for entry 10; b) The first step yield of the isolated intermediate; c) The final step yield of the isolated product; d) Reaction temperature of 50 °C; e) Reaction temperature of room temperature (ca. 25 °C).

CONCLUSION

In summary, a novel type of quinazoline substrates, *N,N′*-disubstituted 1,2-dihydro-2-imino-4-quinazolin-amine was synthesized according to an efficient, ligand-free and mild copper-catalyzed Ullmann-type coupling method and a simple cyclization step. The coupling reactions of methyl 2-bromo-*N*-cyanobenzenecarboximidate with amines performed well at room temperature to 50 °C without any ligand. The cyclization reaction could be completed in twenty minutes and hydrochloric acid is the key factor. Generally, the target compounds could be successfully obtained in moderate to good yields. We hope that these new quinazolines can provide a wider vision to build active molecules or effective drugs.

EXPERIMENTAL

^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard on Varian Mercury 400 MHz spectrometer. ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 100 Hz. The mass spectra (ESI/HRMS) were recorded on a Bruker Daltonics Data analysis 3.2 mass spectrometer. Unless noted otherwise, all solvents used for reactions are analytical grade and redistilled. The silica gel F254 plates were used for thin layer chromatography (TLC) and were examined by UV light at 254 nm. Column chromatography was performed on silica gel H. The *N*-cyanobenzenecarboximidates (**1a**,**b**) were

prepared according to the same procedure refered in our previous work.

General procedure for the synthesis of 1,2-dihydro-2-imino-*N*,*N*′-disubstituted-4-quinazolinamine 3a-3c from one kind of amine.

The *N*-cyanobenzenecarboximidate (0.5 mmol), amine (2.0 mmol), K_2CO_3 (2.0 mmol) and CuI (0.05 mmol) were dissolved in DMF (4 mL) and the mixture was stirred for 8 h at 50 °C under nitrogen atmosphere. The mixture was diluted with EtOAc (10 mL), then washed with brine (3 × 10 mL). The combined organic phase was evaporated in vacuo. The residue was purified by flash column chromatography using petroleum ether/EtOAc as eluant to give the *N*-cyanobenzenecarboximidamide derivative. The mixture of *N*-cyanobenzenecarboximidamide derivative (0.1 mmol), hydrochloric acid (0.3 mmol) and MeOH (2 mL) was refluxed at 72 °C. The reaction solution was concentrated in vacuo and then Et_2O was added to the residue to yield the quinazolines hydrochloride.

General procedure for the synthesis of 1,2-dihydro-2-imino-*N*,*N*′-disubstituted-4-quinazolinamine 3d, 3h, 3i from two kinds of amines (R^1NH_2, R^2NH_2).

The *N*-cyanobenzenecarboximidate (0.5 mmol) and amine (R^1NH_2) (0.5 mmol) were dissolved in DMF (1 mL) and the mixture was stirred at 50 °C until consumption of the substrates (monitored by TLC). Amine (R^2NH_2) (1.5 mmol), CuI (0.05 mmol), K_2CO_3 (2 mmol) and DMF (3 mL) were added in the former reaction solution and the mixture was stirred for 8 h at 50 °C under nitrogen atmosphere. The mixture was diluted with EtOAc (10 mL), then washed with brine (3 × 10 mL). The combined organic phase was concentrated under reduced pressure. The residue was purified by flash column chromatography using petroleum ether/EtOAc as eluant to give the *N*-cyanobenzenecarboximidamide derivative. The *N*-cyanobenzenecarboximidamide derivative (0.1 mmol), hydrochloric acid (0.3 mmol), and MeOH (2 mL) were heated at 72 °C. The reaction solution was concentrated in vacuo and Et_2O was added to the residue to yield the quinazolines hydrochloride.

General procedure for the synthesis of 1,2-dihydro-2-imino-*N*,*N*′-disubstituted-4-quinazolinamine 3e-3g, and compound 4a from two kinds of amines (R^1NH_2, R^2NH_2).

The *N*-cyanobenzenecarboximidate (0.5 mmol) and amine (R^1NH_2) (0.5 mmol) were dissolved in DMF (1 mL) and the mixture was stirred at 50 °C until consumption of the substrates (monitored by TLC). Amine (R^2NH_2) (1.5 mmol), CuI (0.05 mmol), K_2CO_3 (2 mmol) and DMF (3 mL) were added in the former reaction solution and the mixture was stirred for 8 h at 50 °C under nitrogen atmosphere. The mixture was diluted with EtOAc (10 mL), then washed with brine (3 × 10 mL). The combined organic phase was

concentrated under reduced pressure. The residue was purified by flash column chromatography using petroleum ether/EtOAc as eluant to give the *N*-cyanobenzenecarboximidamide derivative. The *N*-cyanobenzenecarboximidamide derivative (0.1 mmol), hydrochloric acid (0.3 mmol), and MeOH (2 mL) was heated at 72 °C. The reaction solution was concentrated in vacuo. And the residue was purified by flash column chromatography using CH_2Cl_2/MeOH as eluant to yield the quinazolines hydrochloride.

Methyl 2-bromo-*N*-cyanobenzenecarboximidate (1a)

White solid, Y: 76%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.0 Hz, 1H), 7.46-7.43 (m, 1H), 7.42-7.39 (m, 1H), 4.10 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 178.24, 133.53, 132.84, 132.47, 128.81, 127.57, 119.47, 112.49, 57.23. IR (KBr): v = 2203, 1607, 1585, 1344, 1035, 757 cm^{-1}. HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_9H_8BrN_2O$ 260.9642, found 260.9642.

Methyl 6-bromo-*N*-cyanobenzo[*d*][1,3]dioxole-5-carboximidate (1b)

White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.380 (s, 1H), 7.133 (s,1H), 6.166 (s, 2H), 2.850 (d, *J* = 4.0 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 169.87, 149.78, 147.28, 128.51, 117.13, 112.80, 110.99, 108.96, 102.88, 28.82. IR (KBr): v = 3234, 3113, 2186, 1604, 1571, 1480, 1409, 1244, 1041 cm^{-1}. HRMS-ESI: *m/z* [M] calcd for $C_{10}H_7BrN_2O_3$ 281.9640, found 281.9644.

***N*-Cyano-*N′*-(phenylmethyl)-2-(phenylmethylamino)benzenecarboximidamide (2)**

White solid, Y: 87%. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.48 (d, *J* = 8.0 Hz, 1H), 7.75-7.48 (m, 1H), 7.50-7.42 (m, 4H), 7.38-7.34 (m, 4H), 7.31-7.27 (m, 1H), 7.22 (d, *J* = 7.6 Hz, 2H), 5.51 (s, 2H), 4.85 (s, 2H), 4.04 (br, 1H).

1,2-Dihydro-2-imino-*N*-(phenylmethyl)-1-(phenylmethyl)-4-quinazolinamine hydrochloride (3a)

White solid, Y: 87%. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.15 (br, 1H), 8.45-8.43 (m, 1H), 7.80-7.76 (m, 1H), 7.49-7.47 (m, 4H), 7.38-7.35 (m, 4H), 7.31-7.28 (m, 2H), 7.20 (d, *J* = 7.2 Hz, 2H), 5,50 (s, 2H), 4.85 (s, 2H), 1.85 (s, 1H). ^{13}C NMR (100 MHz, CH_3OD): δ = 161.78, 157.94, 142.01, 139.71, 135.66, 131.10, 130.49, 129.97, 129.43, 127.79, 127.13, 126.23, 126.15, 118.33, 113.95, 50.91, 46.78. IR (KBr): v = 3440, 1326, 767, 700 cm^{-1}. HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{22}H_{21}N_4$ 341.1688, found 341.1756. Anal. Calcd for $C_{22}H_{21}ClN_4$ C: 70.11, H: 5.62, Cl: 9.41, N: 14.87. Found C: 69.28, H: 5.66, Cl: 9.46, N: 14.67.

1,2-Dihydro-2-imino-*N*-propyl-1-propyl-4-quinazolinamine hydrochloride (3b)

White solid, Y: 79%. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.89 (br, 1H), 8.63 (d, *J* = 8.0 Hz, 1H),

7.88-7.84 (m, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.48-7.44 (m, 1H), 4.15-4.11 (m, 2H), 3.54-3.50 (m, 2H), 1.71-1.62 (m, 4H), 1.10-0.01 (m, 3H), 0.94-0.90 (m, 3H).^{13}C NMR (100 MHz, CH_3OD): δ = 161.49, 157.12, 141.51, 137.36, 126.82, 126.18, 117.73, 113.84, 48.68, 45.22, 23.93, 22.04, 12.59, 11.62. IR (KBr): v = 3294, 2961, 2873, 1432, 1380, 1323 cm^{-1}. HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{14}H_{21}N_4$ 245.1688, found 245.1751.

1,2-Dihydro-2-imino-*N*-[(3,4-dimethoxyphenyl)ethyl]-1-[(3,4-dimethoxyphenyl)ethyl]-4-quinazolinamine hydrochloride (3c)

Light yellow solid, Y: 67%. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.03 (s, 1H), 8.63 (d, *J* = 8.0 Hz, 1H), 7.84-7.80 (m, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.44-7.40 (m, 1H), 7.03 (s, 1H), 6.90 (s, 1H), 6.84-6.73 (m, 4H), 4.46 (s, 2H), 3.71-3.66 (m, 12H), 3.52 (s, 2H), 2.95-2.87 (m, 4H). ^{13}C NMR (100 MHz, CH_3OD): δ = 159.49, 155.20, 149.45, 149.28, 148.54, 148.04, 139.60, 135.36, 131.98, 129.70, 124.96, 124.36, 121.66, 121.43, 116.26, 113.16, 112.95, 112.11, 111.87, 55.60, 46.41, 43.12, 34.53, 32.28. IR (KBr): v = 3415, 1651, 1607, 1515, 1262, 1237, 1026, 768 cm^{-1}. HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{28}H_{33}N_4O_4$ 489.2424. Found 489.2493.

1,2-Dihydro-2-imino-*N*-(phenylmethyl)-1-propyl-4-quinazolinamine hydrochloride (3d)

White solid, Y: 72%. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.10 (s, 1H), 8.47 (d, *J* = 8.0 Hz, 1H), 7.92-7.88 (m, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.53-7.49 (m, 1H), 7.450 (d, *J* = 7.6 Hz, 2H), 7.370-7.33 (s, 2H), 7.29 (d, *J* = 7.2 Hz, 1H), 4.81 (d, *J* = 5.6 Hz, 2H), 4.12-4.08 (m, 2H), 1.70-1.65 (m, 2H), 1.02-1.00 (m, 3H). ^{13}C NMR (100 MHz, CH_3OD): δ = 161.53, 157.12, 141.65, 139.87, 137.52, 130.53, 130.01, 129.39, 126.88, 126.34, 117.78, 113.78, 48.76, 46.68, 22.01, 11.67. IR (KBr): v = 3462, 2966, 2882, 1448, 1378, 764, 706, 676 cm^{-1}. HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{18}H_{21}N_4$ 293.1688, found 293.1758. Anal. Calcd for $C_{18}H_{21}ClN_4$ C: 65.74, H: 6.44, Cl: 10.78, N: 17.04. Found C: 65.09, H: 6.43, Cl: 10.53, N: 16.85.

1,2-Dihydro-2-imino-*N*-(phenylmethyl)-1-[(3,4-dimethoxyphenyl)ethyl]-4-quinazolinamine hydrochloride (3e)

Light yellow solid, Y: 71%. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.16 (d, *J* = 7.6 Hz, 1H), 8.48 (d, *J* = 8.0 Hz, 1H), 7.90-7.86 (m, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.52-7.48 (m, 1H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.38-7.34 (m, 2H), 7.30-7.27 (m, 1H), 6.95 (s, 1H), 6.83-6.78 (m, 2H), 4.81 (d, *J* = 7.6 Hz, 2H), 4.44-4.41 (m, 2H), 3.69 (s, 6H), 2.93-2.90 (m, 2H). ^{13}C NMR (100 MHz, CH_3OD): δ = 159.67, 155.48, 149.51, 148.64, 139.96, 138.08, 135.47, 129.75, 128.74, 128.19, 127.66, 125.08, 124.29, 121.72, 116.38, 113.10, 112.23, 111.92, 55.60, 55.46, 46.32, 44.88, 32.23. IR (KBr): v = 3350, 1649, 1606, 1517, 1265, 1241,

1028, 763, 706 cm^{-1}. HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{25}H_{27}N_4O_2$ 415.2056, found 415.2127.

1,2-Dihydro-2-imino-*N*-methyl-1-propyl-4-quinazolinamine hydrochloride (3f)

White solid, Y: 55%. ^1H NMR (400 MHz, DMSO-d_6): δ = 9.78 (br, 1H), 8.46 (d, *J* = 8.0 Hz, 1H), 7.90-7.86 (m, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.51-7.47 (m,1H), 4.14-4.10 (m, 2H), 3.05 (s, 3H), 1.70-1.64 (m, 2H), 1.02-1.00 (m, 3H). ^{13}C NMR (100 MHz, CH_3OD): δ = 159.26, 154.54, 139.19, 135.37, 124.59, 116.14, 114.49, 111.65, 52.06, 28.38, 20.03, 10.55. IR (KBr): v = 3489, 2967, 2876, 1485, 1443, 1404, 1371, 761, 672 cm^{-1}. HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{12}H_{17}N_4$ 217.1375, found 217.1446.

1,2-Dihydro-2-imino-*N*-methyl-1-[(3,4-dimethoxyphenyl)ethyl]-4-quinazolinamine hydrochlorid (3g)

Light yellow solid, Y: 45%. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.45 (d, *J* = 7.6 Hz, 1H), 7.85-7.82 (m, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.46-7.43 (m, 1H), 6.99 (s, 1H), 6.84-6.78 (m, 2H), 4.45-4.41 (m, 2H), 3.71 (d, *J* = 10.4 Hz, 6H), 3.04 (s, 3H), 2.92-2.88 (m, 2H). ^{13}C NMR (100 MHz, CH_3OD): δ = 161.82, 157.23, 151.29, 150.41, 141.37, 136.95, 131.52, 126.70, 125.85, 123.42, 118.01, 114.89, 113.96, 113.73, 57.28, 48.06, 34.02, 29.48. IR (KBr): v = 3380, 2959, 2836, 1443, 1398, 1268, 1235, 1027 cm^{-1}. HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{19}H_{23}N_4O_2$ 339.1743, found 339.1810.

1,2-Dihydro-2-imino-*N*-propyl-1-[(3,4-dimethoxyphenyl)ethyl]-4-quinazolinamine hydrochloride (3h)

White solid, Y: 58%. ^1H NMR (400 MHz, DMSO-d_6): δ = 9.61 (s, 1H), 8.44 (d, *J* = 7.4 Hz, 2H), 7.86-7.82 (m, 1H), 7.66 (d, *J* = 7.4 Hz, 1H), 7.48-7.45 (m, 1H), 6.92 (s, 1H), 6.83-6.74 (m, 1H), 4.41 (s, 2H), 3.69-3.68 (m, 6H), 2.89 (s, 2H), 1.68-1.63 (m, 2H), 0.93-0.90 (m, 3H). ^{13}C NMR (100 MHz, CH_3OD): δ = 161.44, 157.26, 151.28, 150.38, 141.56, 137.13, 131.63, 126.82, 126.23, 123.56, 118.14, 114.98, 113.97, 113.82, 65.19, 57.41, 45.24, 34.13, 24.00, 12.77. HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{21}H_{27}N_4O_2$ 367.2056, found 367.2128.

1,2-Dihydro-2-imino-*N*-(phenylmethyl)-1-(ethoxyl)-4-quinazolinamine hydrochloride (3i)

Oil liquid, Y: 26%. ^1H NMR (400 MHz, DMSO-d_6): δ = 10.37 (s, 1H), 8.57 (d, *J* = 8.0 Hz, 1H), 8.37 (s, 1H), 7.85 (d, *J* = 3.2 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.35-7.31 (m, 2H), 7.27 (d, *J* = 7.2 Hz, 1H), 5.31(s, 1H), 4.78 (d, *J* = 7.6 Hz, 2H), 4.34 (s, 2H), 3.76 (d, *J* = 4.8 Hz, 2H). IR (KBr): v = 3409, 1350, 1057, 1022, 761, 702 cm^{-1}.

5-Benzyl-6-imino-*N*-methyl-5,6-dihydro[1,3]dioxolo[4,5-*g*]quinazolin-8-amine hydrochloride (4a)

White solid, Y: 20%. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.76-7.74 (m, 2H), 7.68 (d, J = 6.0 Hz, 3H), 7.47 (d, J = 10.4 Hz, 2H), 6.39 (s, 2H), 3.99 (s, 2H), 3.60 (s, 3H), 1.85 (s, 1H).

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