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ARTICLE TYPE

Synthesis of 4-Alkynylquinazolines: Pd-Cu-cocatalyzed Coupling of Quinazoline-4-tosylates with Terminal Alkynes Using *N*-Heterocyclic Carbenes as Ligands

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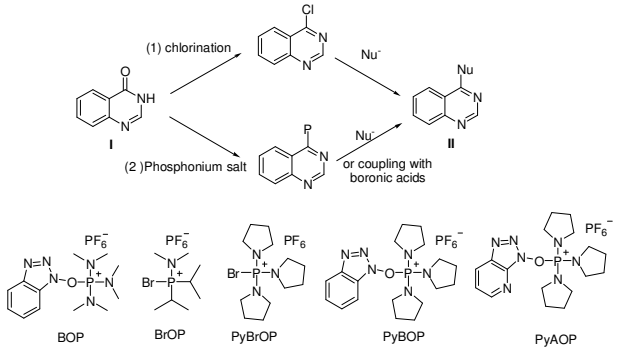
A Pd-Cu-cocatalyzed coupling reaction of quinazoline-4-tosylates with terminal alkynes using *N*-heterocyclic carbenes (NHC) as ligands is described, which providing 4-alkynylquinazolines in good to excellent yields. This transformation proceeds under mild conditions with high efficiency, which is attractive for focused compound library construction.

Introduction

During the last decade, *N*-Heterocyclic carbenes (NHCs) have been widely used as strong electronic donating ancillary ligands for organometallic chemistry and homogeneous catalysis.[1] Especially they serve as ligands in many catalytic coupling reactions,[2a] such as Suzuki,[2b-d] Heck,[2e] and Sonogashira reactions.[3] Sonogashira coupling is a classic method for the formation of a new C-C bond between aryl alkynes and aryl halides.[4] Recently, the reaction substrates have been expanded to aryl triflates,[5] aryl chlorides,[6] and aryl tosylates.[6g, 7,8,9]

On the other hand, quinazoline derivatives have been shown to be important in organic synthesis as well as in medicinal chemistry.[10] They exhibit remarkable biological activities, such as anticonvulsant, antibacterial, antidiabetic, and anticancer activities.[11] Among this class of molecules, the 4-functionalized quinazolines have been demonstrated as effective fungicides, anti-inflammatory, anti-cancer, anti-microbial and anti-hypertensive agents.[12,13] Consequently, considerable progress in synthetic methodology for 4-functionalized quinazoline derivatives have been made during the past decade.[14,15] Generally, two protocols have been developed for the synthesis of 4-functionalized quinazolines starting from 3*H*-quinazolin-4-one(4-quinazolinone) □ (Scheme 1): (1) Chlorination of 4-quinazolinone with reagents such as $SOCl_2$, $POCl_3$, and PCl_5, and then substitution with nucleophiles to afford the corresponding 4-functionalized quinazolines □.[13a-j,15b] (2) Activation of C-OH group with phosphonium salts (such as PyBroP, PyBOP, BroP, BOP), then substitution with nucleophiles or coupling with boronic acids to yield 4-functionalized quinazolines □.[16]



Scheme 1. protocols for the synthesis of 4-functionalized quinazolines

However most of these methods can only be applied to the preparation of quinazolines with 4-position heteroatoms (N, O, S) group. Relatively few examples concerning preparation for 4-C substituted quinazolines have been reported. To the best of our knowledge, there are only three examples concerning introduction of C– group at the 4-position of quinazoline core. Guiry described Pd-enhanced coupling reactions for synthesis of 4-arylquinazolines starting from arylboronic acid and 4-chloroquinazolines.[17a] Kitano reported that the 4-alkynylquinazolines were synthesized by a Sonogashira coupling reaction of 4-chloroquinazolines with terminal alkynes.[17b] Recently, we investigated the feasibility of one-pot palladium-catalyzed synthesis of 4-arylquinazolines from the reaction of 4-quinazolinones and arylboronic acid in the presence of TsCl.[17c] For 4-alkynylquinazolines could serve as potent EGFR tyrosine kinase inhibitors,[17b] the development of efficient routes for rapid access to 4-alkynylquinazolines under mild conditions is of high demand.

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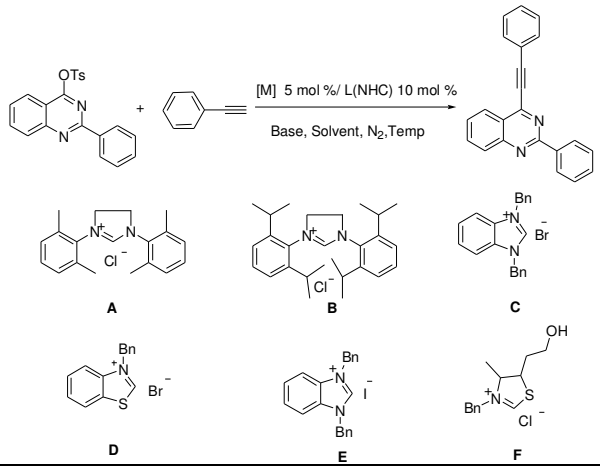
On basis of our recent work,[17c] we here reported that Pd-Cu-cocatalyzed coupling of quinazoline-4-tosylates with terminal alkynes for synthesis of 4-alkynylquinazolines using NHC as ligand.

Results and discussion

At the outset, 2-phenyl-quinazolin-4-tosylate **1a** and phenyl acetylene **2a** were employed as the substrates for reaction development. Firstly, the reaction was performed in the presence of 1.5 eq. DABCO and 5 mol% $Pd(OAc)_2$ in DCE at 60℃. Only trace amount of desired product 2-phenyl-4-(phenylethynyl)quinazoline **3a** was detected.

Table 1. Generation of 4-alkynylquinazolines via Pd-Cu-co-catalyzed coupling reactions of quinazoline-4-tosylates with terminal alkynes using NHC as a ligand



Entry	[M]	NHC	Base	Sovent	T (°C)	yield (%)[b]
1	$Pd(OAc)_2$	-	DABCO	DCE	60	Trace
2	$Pd(OAc)_2$	A	DABCO	DCE	60	18
3	$Pd(OAc)_2$	B	DABCO	DCE	60	Trace
4	$Pd(OAc)_2$	C	DABCO	DCE	60	30
5	$Pd(OAc)_2$	D	DABCO	DCE	60	35
6	$Pd(OAc)_2$	E	DABCO	DCE	60	Trace
7	$Pd(OAc)_2$	F	DABCO	DCE	60	26
8	$Pd(OAc)_2$	D	Cs_2CO_3	DCE	60	25
9	$Pd(OAc)_2$	D	K_2CO_3	DCE	60	18
10	$Pd(OAc)_2$	D	K_3PO_4	DCE	60	15
11	$Pd(OAc)_2$	D	Et_3N	DCE	60	trace
12	$Pd(OAc)_2$	D	DBU	DCE	60	3
13	$Pd(OAc)_2$	D	t-BuOK	DCE	60	trace
14	$Pd(OAc)_2$	D	DABCO	THF	60	35
15	$Pd(OAc)_2$	D	DABCO	Toluene	60	Trace
16	$Pd(OAc)_2$	D	DABCO	1,4-dioxane	60	38
17	$Pd(OAc)_2$	D	DABCO	DMF	60	32
18	$Pd(OAc)_2$	D	DABCO	H_2O	60	Trace
19	$Pd(OAc)_2$	D	DABCO	CH_3CN	60	55
20	$Pd(OAc)_2$	D	DABCO	CH_3CN	80	50
21	$Pd(OAc)_2$	D	DABCO	CH_3CN	100	30
22	$Pd(PPh_3)_2Cl_2$	D	DABCO	CH_3CN	60	75
23	$Pd(PhCN)_2Cl_2$	D	DABCO	CH_3CN	60	65
24	$Pd_2(dba)_3$	D	DABCO	CH_3CN	60	30
25	$PdCl_2$	D	DABCO	CH_3CN	60	65
26	$Pd(OAc)_2$+CuI	D	DABCO	CH_3CN	60	82
27	$Pd(PPh_3)_2Cl_2$ +CuI	D	DABCO	CH_3CN	60	89
28	CuI	D	DABCO	CH_3CN	60	-

[a] Isolated yield based on quinazoline-4-tosylate **1a**.

Gratifyingly, when 5 mol % NHC **A** was added, the yield of **3a** increased to 18%. Then, a series of NHCs ligand were screened, and NHC-D turned out to be the best one with the highest yield of 35%. Next, we examined the base effect on the reaction (Table 1, entries 8-13) and found that no better results were generated. Further screening of solvents revealed that the yield could be improved to 55% when the reaction was carried out in CH_3CN (entry 19). No better results were obtained when the reaction was performed at 80 °C or 100 °C. Finally, the catalyst screening results indicated that the output of the reaction could be raised to 75% when $Pd(PPh_3)_2Cl_2$ was used (entry 22). Further test indicated that added CuI as a co-catalyst could improve the yield, and $Pd(PPh_3)_2Cl_2$–CuI was the best combination (entry 27, yield 89%). The result is contrast to Buchwald, where in the presence of a copper cocatalyst has a deleterious effect on the coupling reaction.[6g] Control experiment showed that no reaction occurred use CuI as the catalyst (Table 1, entry 28).

With this promising result in hands, we started to explore the generality of this NHC-bimetal-co-catalyzed reactions of quinazoline-4-tosylates with alkynes under the optimized conditions highlighted above [5 mol% $Pd(PPh_3)_2Cl_2$ 5 mol% CuI, 10 mol% NHC, 1.5eq. DABCO, in CH_3CN at 60 °C]. The results are summarized in Table 2. To assess the impact of the structural and functional motifs on the reaction of **1a**, we tested a range of alkynes **2**. For all cases, compounds **1a** reacted with **2** leading to the corresponding 2-phenyl-4-alkynylqunazolines **3** in good to excellent yields (**3a**-**3h**). Both aryl and alkyl substituted acetylenes were demonstrated as good compatible in the transformation. Moreover, it was found that substrates with electron-withdrawing groups on R^3 were less reactive to some extent than those with the electron-donating groups when the R^3 group is phenyl. For example, the reactions of electron-withdrawing substituted substrates such as *p*-chloro or *m*-fluoro phenylacetylene gave the corresponding product **3b** or **3c** in 74% or 65% yield. While the reactions of electron-donating substituted substrates such as *p*-methoxyl, *p*-ethoxyl or *p*-ethylphenylacetylene afforded the corresponding product in 92%, 92% or 75% yields. We next examined the reactivity of quinazolinic tosylates **1** with different substituents on 2-position. As expected, the corresponding products were obtained in good to excellent yields when R^1 is aryl group (**3i**-**3o**). The reactions only gave moderate yields when R^1 is alkyl group (**3p**). Furthermore, when R^1 is hydrogen, no desired product was obtained (result is not list in the table), because the reactant was decomposed to the corresponding quinazoline under reaction conditions. It is noteworthy that substrates with electron-donating groups on the R^1 were more reactive to some extent than those with electron-withdrawing groups when the R^1 group was phenyl. For example, the reaction of 2-(*p*-methyl)phenyl quinazolin-4-tosylate or 2-benzo[1,3]dioxol-5-yl-quinazolin-4-tosylate with

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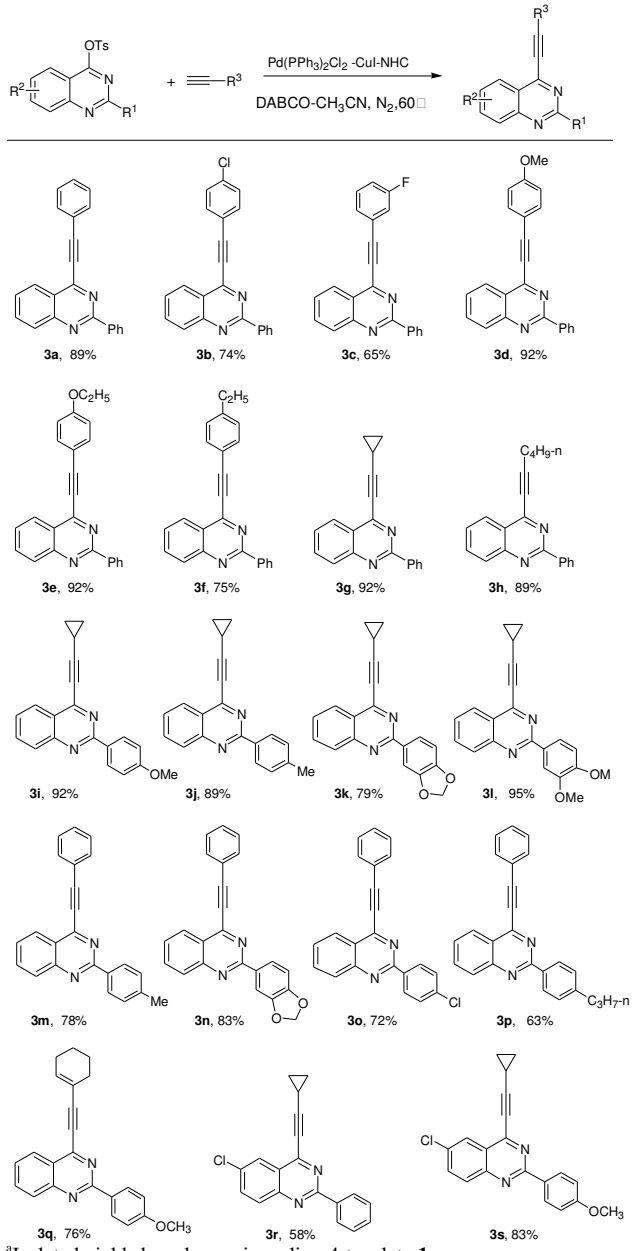
phenylacetylene gave rise to the desired product **3m** or **3n** in 78% or 83% yield, respectively. While for the reaction of 2-(4-chlorophenyl)quinazolin-4-tosylate with **2a** gave the corresponding yield of 72%. Vinyl substituted alkynes such as cyclohexenylacetylene was also studied, and gave the product **3q** in a yield of 76%. Finally, 6-chloro-quinazolin-4-tosylate was also assessed, and the results indicated that electron-withdrawing substituted on quinazoline core would suppress the reaction, however moderate to good yields were also obtained (**3r**, **3s**).

Table 2. Generation of 4-Alkynylquinazolines **3** via Pd-Cu-co-Catalyzed Coupling Reactions of Quinazoline-4-tosylates with Terminal Alkynes Using NHC as A Ligand [a]



[a]Isolated yields based on quinazoline-4-tosylate **1**.

Conclusions

In conclusion, we have developed an efficient reaction for synthesis of 4-alkynylquinazolines. The coupling reactions of quinazoline-4-tosylates with terminal alkynes cocatalyzed by $Pd(PPh_3)_2Cl_2$ and CuI with NHC as a ligand, affording 4-alkynylquinazolines in good to excellent yields. The transformation proceeded under mild conditions with high efficiency, which is attractive for further library construction.

Experimental Section

General experimental procedure for synthesis of **3**. A mixture of 2-Aryl-*p*-methylbenzenesulfonatequinazoline **1** (0.20 mmol) and $Pd(PPh_3)_2Cl_2$ (5 mol %), NHC (D) (10 mol %), CuI (5 mol %), DABCO (0.3 mmol, 1.5 equiv) with alkyne **2** (0.3 mmol, 1.5 equiv) in CH_3CN (2.0 mL) were added subsequently. The mixture was stirred at 60 °C for 4 hours. After completion of the reaction as indicated by TLC, the solvent was evaporated. The residue was diluted with EtOAc (10 mL), washed with H_2O (10 mL), dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by purification on silica gel provided the corresponding product **3**.

2-Phenyl-4-(phenylethynyl)quinazoline (**3a**). white solid, mp: 112-113□; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.54 (m, 6H), 7.61 (t, J = 7.2 Hz, 1H), 7.77 (d, J = 7.2 Hz, 2H), 7.89 (t, J = 7.1 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.64 (d, J = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.7, 97.8, 121.4, 124.0, 126.5, 127.7, 128.6, 128.7, 129.1, 130.1, 130.7, 132.6, 134.2, 137.9, 151.0, 152.9, 160.9; HRMS calcd. for $C_{22}H_{14}N_2(M+H)^+$,307.1235; Found 307.1264.

2-Phenyl-4-((4-chlorophenyl)ethynyl)quinazoline (**3b**). White solid, mp: 118-119□; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 2H), 7.50-7.55 (m, 3H), 7.62 (t, J = 7.6 Hz, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.89 (t, J = 7.1 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 8.2 Hz, 1H), 8.63 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 86.5, 96.3, 119.8, 123.8, 126.3, 127.7, 128.6, 128.7, 129.1, 130.7, 133.8, 134.3, 136.4, 137.7, 151.0, 152.5, 160.9; HRMS calcd. for $C_{22}H_{13}ClN_2(M+H)^+$, 341.0846; Found 341.0858.

2-Phenyl-4-((3-fluorophenyl)ethynyl)quinazoline (**3c**). White solid, mp: 123-124□; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, J = 8.0 Hz, 1H), 7.4-7.58 (m, 6H), 7.68 (t, J = 7.6 Hz, 1H), 7.94 (t, J = 7.3 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.37 (d, J = 7.9 Hz, 1H), 8.64 (d, J = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.2, 95.9, 117.5 (d, $^2J_{CF}$ = 21.2 Hz), 119.3 (d, $^2J_{CF}$ = 23.1 Hz), 123.1 (d, $^3J_{CF}$ = 9.4 Hz), 123.9, 126.3, 127.8, 128.5 (d, $^4J_{CF}$ = 3.0 Hz), 128.6, 128.7, 129.1, 130.4 (d, $^3J_{CF}$ =8.5Hz), 130.7, 134.3, 137.7, 151.1, 152.4, 160.9, 161.2 (d, $^1J_{CF}$ = 246.1 Hz); HRMS calcd. for $C_{22}H_{13}FN_2(M+H)^+$, 325.1141; Found: 325.1140.

2-Phenyl-4-((4-methoxyphenyl)ethynyl)quinazoline (**3d**). White solid, mp: 178-179□; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 6.97 (d, J = 7.6 Hz, 2H), 7.49-7.58 (m, 3H), 7.61-7.67 (m, 1H), 7.73 (d, J = 7.6 Hz, 2H), 7.88-7.93 (m, 1H), 8.09 (d, J = 8.4 Hz, 1H), 8.39 (d, J = 7.6 Hz, 1H), 8.64 (d, J = 6.8 Hz, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 85.1, 98.7, 113.3, 114.4, 123.9, 126.5, 127.5, 128.6, 128.7, 129.0, 130.6, 134.1, 134.4,

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137.9, 150.9, 153.2, 160.9, 161.1; HRMS calcd. for $C_{23}H_{16}N_2O(M+H)^+$, 337.1341; Found 337.1335.

2-Phenyl-4-((4-ethoxyphenyl)ethynyl)quinazoline (**3e**). Light yellow solid, mp: 132-133□; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, J = 7.0 Hz, 3H), 4.06 (m, 2H), 6.92 (d, J = 8.8 Hz, 2H), 7.50-7.56 (m, 3H), 7.61 (t, J = 7.1 Hz, 1H), 7.69 (d, J = 8.8 Hz, 2H), 7.87 (t, J = 7.0 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.36 (d, J = 8.2 Hz, 1H), 8.64 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 63.7, 85.1, 98.9, 113.1, 114.8, 123.9, 126.5, 127.5, 128.6, 128.7, 129.0, 130.6, 134.1, 134.4, 138.0, 150.9, 153.2, 160.6, 160.9; HRMS calcd. for $C_{24}H_{18}N_2O$ $(M+H)^+$, 351.1497; Found 351.1518.

2-Phenyl-4-((4-ethylphenyl)ethynyl)quinazoline (**3f**). White solid, mp: 136-137□; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J = 7.6 Hz, 3H), 2.73 (m, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.51-7.56 (m, 3H), 7.64-7.78 (m, 3H), 7.91 (t, J = 7.2 Hz, 1H), 8.11 (d, J = 8.3 Hz, 1H), 8.41 (d, J = 8.3 Hz, 1H), 8.64 (d, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 29.0, 85.3, 98.6, 118.5, 124.0, 126.6, 127.6, 128.3, 128.6, 128.7, 129.0, 130.7, 132.7, 134.2 137.8, 146.9, 150.9, 153.1, 160.9; HRMS calcd. for $C_{24}H_{18}N_2(M+H)^+$, 335.1548; Found 335.1553.

2-Phenyl-4-(cyclopropylethynyl)quinazoline (**3g**). White solid, mp: 108-109□; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01-1.15 (m, 4H), 1.68-1.70 (m, 1H), 7.45-7.60 (m, 4H), 7.85 (d, J = 7.5 Hz, 1H), 8.05 (d, J = 7.9 Hz, 1H), 8.22 (d, J = 7.8 Hz, 1H), 8.59-8.66 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 0.7, 9.6, 73.1, 104.3, 124.0, 126.6, 127.4, 128.5, 128.7, 128.9, 130.5, 134.0, 137.9, 150.8, 153.3, 160.8; HRMS calcd. for $C_{19}H_{14}N_2$ $(M+Na)^+$, 293.1055; Found 293.1075.

2-Phenyl-4-(butyl-ethynyl)quinazoline (**3h**). White solid, mp: 98-99□; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.44-1.53 (m, 2H), 1.64-1.70 (m, 2H), 2.55 (t, J = 7.2 Hz, 2H), 7.39-7.51 (m, 4H), 7.49 (t, J = 7.6 Hz, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 7.6 Hz, 1H), 8.52 (d, J = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.6, 18.5, 21.2, 29.2, 76.6, 99.7, 123.0, 125.5, 126.4, 127.5, 127.6, 127.8, 129.5, 133.0, 136.8, 149.8, 152.3, 159.7; HRMS calcd. for $C_{20}H_{18}N_2$ $(M+Na)^+$, 309.1348; Found 309.1368.

2-(4-Methoxyphenyl)-4-(cyclopropylethynyl)quinazoline (**3i**). White solid, mp: 112-113□; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90-1.05 (m, 4H), 1.54-1.60 (m, 1H), 3.77 (s, 3H), 6.92 (d, J = 8.6 Hz, 2H), 7.43 (t, J = 7.4 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 8.46 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.9, 9.8, 55.6, 73.4, 104.2, 114.1, 123.9, 126.8, 127.2, 128.9, 130.5, 130.8, 134.2, 151.1, 153.4, 160.8, 162.1; HRMS calcd. for $C_{20}H_{16}N_2O$ $(M+H)^+$, 301.1341; Found 301.1334.

2-(*p*-Tolyl)-4-(cyclopropylethynyl)quinazoline (**3j**). White solid, mp: 97-98□; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98-1.14 (m, 4H), 1.62-1.68 (m, 1H), 2.42 (s, 3H), 7.31 (d, J = 7.3 Hz, 2H), 7.54 (t, J = 6.9 Hz, 1H), 7.82 (t, J = 6.5 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H), 8.18 (d, J = 7.7 Hz, 1H), 8.49 (d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.6, 9.5, 21.5, 73.1, 104.0, 123.8, 126.5, 127.1, 128.6, 128.7, 129.2, 133.9, 135.1, 140.7, 150.7, 153.1, 160.7; HRMS calcd. for $C_{20}H_{16}N_2$ $(M+Na)^+$, 307.1211; Found 307.1198.

2-(Benzo[d][1,3]dioxol-5-yl)-4-(cyclopropylethynyl)quinazoline (**3k**). White solid, mp: 125-126□; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02-1.14 (m, 4H), 1.64-1.71 (m, 1H), 6.02 (s, 2H), 6.92 (d, J = 8.2 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 8.09 (s, 1H), 8.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.5, 9.5, 72.9, 101.3, 103.9, 108.0, 108.6, 123.5, 123.6, 126.4, 126.9, 128.5, 132.2, 133.8, 148.0, 149.7, 150.6, 152.9, 160.0; HRMS calcd. for $C_{20}H_{14}N_2O_2$ $(M+Na)^+$, 337.0953; Found 337.0976.

2-(3,4-Dimethoxyphenyl)-4-(cyclopropylethynyl)quinazoline (**3l**). White solid, mp: 128-129□; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04-1.08 (m, 4H), 1.64-1.71 (m, 1H), 3.95 (s, 3H), 4.06 (s, 3H), 6.98 (d, J = 8.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.1 Hz, 2H), 8.24 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.2, 9.2, 55.5, 55.6, 72.7, 103.6, 110.4, 110.8, 121.8, 123.3, 126.1, 126.5, 128.2, 130.3, 133.5, 148.5, 150.3, 150.9, 152.6, 159.9; HRMS calcd. for $C_{21}H_{18}N_2O_2$ $(M+H)^+$, 331.1447; Found 331.1476.

2-(*p*-Tolyl)-4-(phenylethynyl)quinazoline (**3m**). White solid, mp: 125-126□; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.34 (d, J = 7.6 Hz, 2H), 7.45 (m, 3H), 7.61 (t, J = 7.4 Hz, 1H), 7.77 (d, J = 6.5 Hz, 2H), 7.88 (t, J = 7.3 Hz, 1H), 8.07 (d, J = 8.3 Hz, 1H), 8.36 (d, J = 8.1 Hz, 1H), 8.54 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 85.8, 97.7, 121.4, 123.9, 124.8, 126.4, 127.4, 128.6, 128.7, 129.4, 130.1, 132.6, 134.2, 135.1, 140.9, 151.0, 152.8, 161.0; HRMS calcd. for $C_{23}H_{16}N_2$ $(M+H)^+$, 321.1392; Found 321.1394.

2-(Benzo[d][1,3]dioxol-5-yl)-4-(phenylethynyl)quinazoline (**3n**). White solid, mp: 153-154□; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (s, 2H), 6.95 (d, J = 8.2 Hz, 1H), 7.43-7.46 (m, 3H), 7.60 (t, J = 7.5 Hz, 1H), 7.77 (d, J = 6.0 Hz, 2H), 7.87 (t, J = 7.6 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 8.14 (s, 1H), 8.26 (d, J = 8.2 Hz, 1H), 8.35 (d, J = 8.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 85.7, 97.6, 101.4, 108.3, 108.8, 121.4, 123.7, 126.4, 127.3, 128.6, 128.8, 130.1, 132.3, 132.6, 134.2, 148.2, 150.0, 151.0, 152.7, 160.3; HRMS calcd. for $C_{23}H_{14}N_2O_2$ $(M+H)^+$, 351.1134; Found 351.1140.

2-(4-Chlorophenyl)-4-(phenylethynyl)quinazoline (**3o**). White solid, mp: 145-146□; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.51 (m, 5H), 7.66 (t, J = 7.5 Hz, 1H), 7.78 (d, J = 7.6 Hz, 2H), 7.92 (t, J = 7.6 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.39 (d, J = 8.0 Hz, 1H), 8.60 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.5, 98.1, 121.3, 123.9, 126.5, 127.8, 128.7, 128.8, 129.0, 130.1, 130.2, 132.6, 134.4, 136.3, 136.9, 150.9, 152.9, 159.9; HRMS calcd. for $C_{22}H_{13}ClN_2$ $(M+H)^+$, 341.0846; Found 341.0858.

2-Propyl-4-(phenylethynyl)quinazoline (**3p**). White solid, mp: 91-92□; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (t, J = 7.3 Hz, 3H), 1.93-2.03 (m, 2H), 3.11 (t, J = 7.8 Hz, 2H), 7.42-7.47 (m, 3H), 7.64 (t, J = 7.6 Hz, 1H), 7.76 (d, J = 7.5 Hz, 2H), 7.89 (t, J = 7.6 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 8.37 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.4, 41.9, 85.4, 97.9, 121.3, 123.4, 126.3, 127.3, 128.3, 128.6, 130.1, 132.5, 134.1, 150.5, 152.7, 167.4; HRMS calcd. for $C_{19}H_{16}N_2$ $(M+H)^+$, 273.1392; Found 273.1391.

2-(4-Methoxyphenyl)-4-(Cyclohex-1-enylethynyl)quinazoline (**3q**). Yellow white solid, mp: 123-125℃

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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 – 8.48 (m, 2H), 8.24 (d, *J* = 8.2 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.90 – 7.67 (m, 1H), 7.60 – 7.42 (m, 1H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.65- 6.46 (m, 1H), 3.89 (s, 3H), 2.53-2.26 (m, 2H), 2.25 -2.23 (m, 2H),, 2.06-1.63 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 160.6, 153.2, 150.9, 140.1, 133.9, 130.6, 130.3, 128.7, 126.9, 126.5, 123.6, 119.9, 113.8, 100.1, 83.6, 55.3, 28.8, 26.1, 22.1, 21.3. HRMS calcd. For $C_{23}H_{20}N_2O$ $(M+Na)^+$, 363.1473; Found 363.1478.

2-Phenyl-4-(cyclopropylethynyl)-6-chloro-quinazoline (**3r**). White solid, mp: 142-143□; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.09-1.11 (m, 4H), 1.68-1.73 (m, 1H), 7.49-7.51 (m, 3H), 7.77 (d, *J* = 8.9 Hz, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 8.17 (s, 1H), 8.57 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 0.2, 9.3, 72.3, 104.6, 124.0, 124.9, 128.1, 128.2, 130.1, 130.3, 132.6, 134.4, 137.0, 148.8, 151.9, 160.5; HRMS calcd. for $C_{19}H_{13}ClN_2$ $(M+Na)^+$, 327.0665; Found 327.0678.

2-(4-Methoxyphenyl)-4-(cyclopropylethynyl)-6-chloro-quinazoline (**3s**). White solid, mp: 119-120□; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.04-1.15 (m, 4H), 1.68-1.75 (m, 1H), 3.88 (s, 3H), 7.01 (d, *J* = 7.9 Hz, 2H), 7.75 (d, *J* = 9.1 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 8.15 (s, 1H), 8.53 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 0.4, 9.4, 55.1, 72.4, 104.4, 113.6, 123.9, 125.1, 129.8, 130.0, 130.1, 132.2, 134.5, 149.1, 152.0, 160.5, 161.7; HRMS calcd. for $C_{20}H_{15}ClN_2O$ $(M+H)^+$, 335.0951; Found 335.0972.

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