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Pd-Catalyzed Regioselective Mono-Arylation: Quinazolinone as the Inherent Directing Group for C(sp^2)-H Activation

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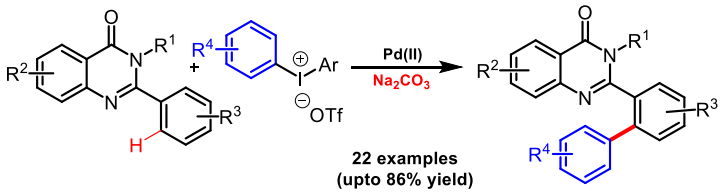


ABSTRACT: The Pd-catalyzed quinazolinone-directed regioselective mono-arylation of aromatic rings by C-H bond activation is developed. A broad substrate scope is demonstrated for both quinazolinone as well as diaryliodonium triflates. Use of base was found to be crucial for this transformation, unlike the known nitrogen-directed arylations. All the novel quinazolinones of biological interest were synthesised by using operationally simple Pd(II)-catalyzed arylation reaction.

INTRODUCTION

Over 70% of the top branded drugs contain at least one heterocyclic nucleus as a part of its overall skeleton. In particular, many synthetic drugs, bioactive natural products, and agrochemicals encompassing nitrogen-heterocyclic scaffolds are most common.[1] Quinazolinones are one of the important nitrogen-containing heterocyclic motifs found in more than 200 natural products as well as in several drugs (Figure 1).[1b,2] The quinazolinone derivatives possess wide range of pharmacological activities such as antimalarial, anticancer, antimicrobial, anti-diabetic, anti-inflammatory, antihypertensive, anticonvulsant, diuretic etc.[1-3] The synthesis of various

natural, and synthetic derivatives of quinazolinones has acquired immense attention by the scientific community because of their wide range of biological properties.[1-3]

The application of C-H bond functionalization to form new carbon-carbon (C-C) and C-heteroatom (C-X) bonds in the synthesis of structurally complex natural or unnatural compounds has emerged as a powerful tool, and it is an area of contemporary interest.[4] It provides direct access and delivers more atom economical paths in the synthesis of complex structures as compared to the traditional organic synthesis. Until now several C-H activation reactions in the organic compounds have been developed with or without directing groups.[4] The metal-catalyzed inter- or intramolecular aromatic C-H arylation is one of the widely used key-step in the total synthesis of several natural products,[4h] and the late-stage derivatization of bioactive molecules.[4g]

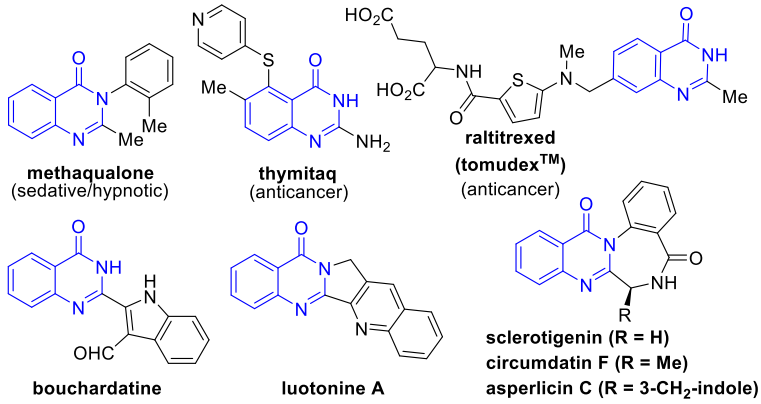


Figure 1. Selected quinazolinone drugs, and natural products.[1,2]

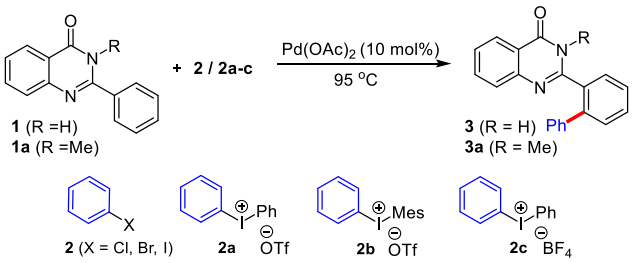
Due to the extensive occurrence of quinazolinone nucleus in bioactive organic compounds, we envisioned that the quinazolinone core could be exploited as the inherent directing group for the metal-catalyzed regioselective arylation, which would afford novel quinazolinones for structure-activity-relationship (SAR) studies. In this context, the literature survey revealed that, although there are several classical methods available for the synthesis of novel quinazolinone derivatives,[2,5] but there are only a few reports in the literature where quinazolinone compounds

itself were functionalized by metal catalysis. Pd-catalyzed oxygenations,[6] and oxidative C-H aminations[7] was reported by Reddy, and Wu et al. respectively. Besson, and co-workers reported regioselective arylation of (2H)-quinazolin-4-ones.[8] Pd-catalyzed syntheses of phenanthridine/benzoxazine fused quinazolinones were reported by using three different approaches; intramolecular C-H activation with bromoarenes,[9] intramolecular oxidative C-H amination,[10] and cascade C–H/N–H arylation.[11] Few other metal catalysts were utilized in the quinazolinone/quinazoline functionalization such as rhodium-catalyzed regioselective direct C-H amidation,[12] copper-catalyzed cascade amination,[13] and Ru/Rh-catalyzed annulation reactions.[14] Nevertheless, to the best of our knowledge, quinazolinone-directed intermolecular arylation of quinazolinone compounds is not known until now.

RESULTS AND DISCUSSION

Herein, we report a protocol for the arylation of various quinazolinones. The optimization of the protocol was carried out by screening various reaction parameters. Initial attempts on N-H free quinazolinone **1** as the substrate with various halo-benzenes **2** failed to produce coupling product **3**. Hence, we planned to study the protocol on various *N*-substituted quinazolinones. The *N*-methyl substituted quinazolinone substrate **1a** on treatment with halo-benzenes **2**, Pd-catalyst, and other additives did not furnish the expected product **3a** under various reaction conditions (Table 1). These observations suggest that more activated arylation reagent was necessary for this transformation. Diaryliodonium salts are well-known compounds as an arylation reagent due to their easy accessibility, and high reactivity.[15] Because of their highly electron-deficient nature, and good leaving group aptitude, they serve as versatile arylation agents with various metal catalysts.[16] Hence, we changed the phenyl source from halo-benzenes to diphenyliodonium triflate **2a**, and to our delight expected product **3a** was formed in 35% yield (entry 2).

Table 1. Optimization Studies



entry[a, b]	**2/2a-c** (equiv)	additive (equiv)	solvent	yield (%)[c]
1	**2** (2)	AgOAc (2)	AcOH	N.R.
2	**2a** (1)	K_2CO_3 (1)	AcOH	35
3	**2a** (1)	K_2CO_3 (1)	toulene	N.R.
4	**2a** (1)	K_2CO_3 (1)	1,4-dioxane	N.R.
5	**2b** (1)	K_2CO_3 (1)	AcOH	30
6	**2c** (1)	K_2CO_3 (1)	AcOH	25
7	**2a** (1)	-	AcOH	N.R.
8	**2a** (2)	Na_2CO_3 (2)	AcOH	55
9	**2a (3)**	**Na_2CO_3 (2)**	**AcOH**	**71**
10	**2a** (3)	NaOAc (2)	AcOH	35
11	**2a** (3)	Na_2CO_3 (2)	PivOH	trace
12	**2a** (3)	Na_2CO_3 (2)	AcOH:PivOH	48

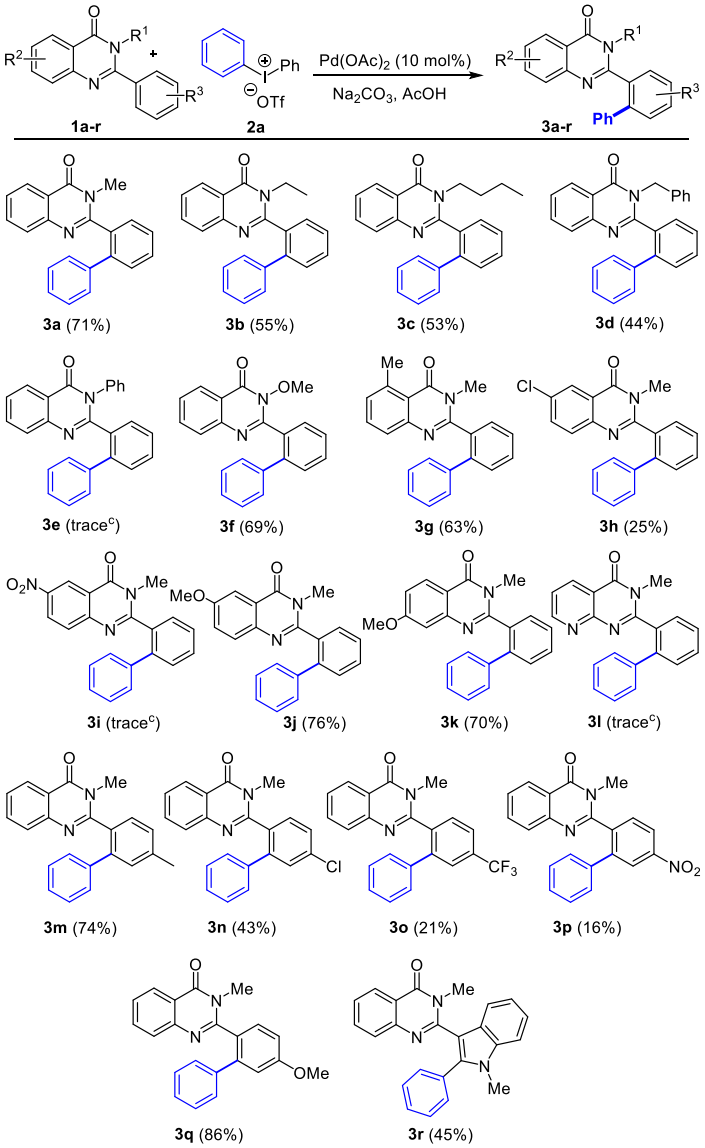
[a]Selected entries, [b]Reaction conditions: **1a**(0.2 mmol), AcOH (1 mL) in sealed tube for 36 h. [c]Isolated yield. N.R. = No reaction.

The variation in solvents did not show the formation of expected product (entries 3, 4). Also the use of unsymmetrical iodonium salt **2b** or iodonium salt **2c** having different counterion gave lower yields (entries 5, 6). We did not observe the expected product **3a** in the absence of base (entry 7), and the substrate **1a** was recovered unchanged, which suggests that the use of base is crucial for this reaction. This observation is in contrast to the reported Pd-catalyzed nitrogen-directed arylation by C-H activation using diaryliodonium salts.[4j,k] When two equivalents of the iodonium salt **2a** was used in combination with Na_2CO_3, we observed an improvement in the yield to 55% (entry 8). The highest possible yield of the product **3a** was 71% wherein three equivalent of salt **2a** was used (entry 9). Further, variation in the optimized conditions like a change in the base NaOAc (entry 10), solvent PivOH (entry 11), solvent combinations of

AcOH:PivOH (entry 12), and temperature, etc. resulted in either low or trace amount of product formation.

With the optimized conditions in hand, we next turned our attention to develop a general scope of the protocol. We planned to study the effect of substituent variation in the quinazolinone core on the arylation reaction (Table 2).

Table 2. Pd-Catalyzed Arylation of Various Quinazolinones[a,b]

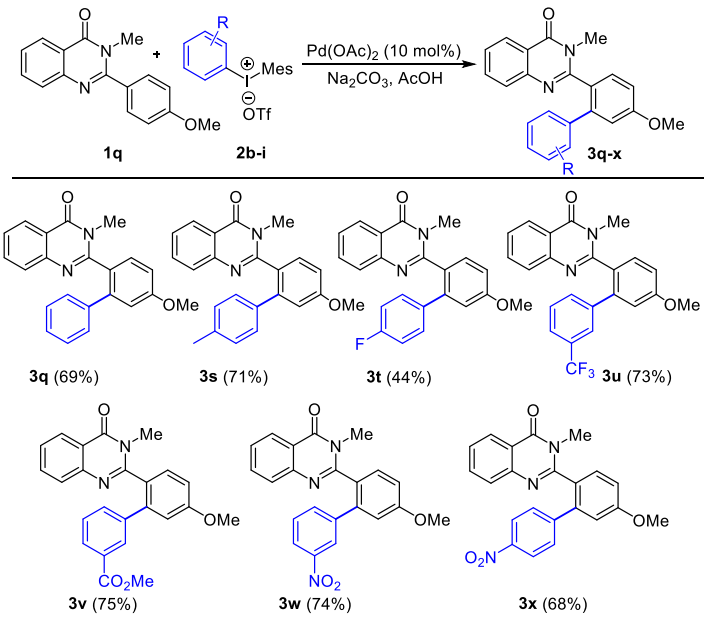


[a]Reaction conditions: **1a-r** (0.2 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), Na_2CO_3 (0.4 mmol), AcOH (1 mL), 30-36 h, 90-120 °C. [b]Isolated yield. [c]Trace product formation was confirmed by TLC, and HRMS.

Initially, the effect of *N*-substitution was studied. *N*-Primary alkyl substituted quinazolinones furnished the expected products **3a-c** with moderate to good yields. We observed that with the increase in the chain length the yield of the respective product decreases. The quinazolinone substrate with *N*-benzyl substituent resulted in the moderate yield of **3d**. The *N*-Phenyl substituted quinazolinone provided only trace amount of product **3e**. The reason behind this observation might be the steric hindrance caused by the *N*-phenyl ring, which enforces the other phenyl ring out of the plane, thus inhibiting the formation of palladacycle. The quinazolinone substrate with *N*-methoxy substituent furnished **3f** in good yield. The *N*-methyl substituted quinazolinone provided better yield than the substrates with other *N*-substituents. Keeping the *N*-methyl substitution constant, the further scope of the arylation reaction with varyingly substituted quinazolinone core was explored. 5-Methyl substituted quinazolinone gave the corresponding arylated product **3g** in good yield, however, 6-chloro, and 6-nitro substituted quinazolinones resulted in low, and trace yield of products **3h**, and **3i** respectively. Most probably, the electron withdrawing substituents weakens the coordinating ability of these substrates with the metal catalyst, which resulted in lower yields. Electron rich substituents provided the arylated products **3j** and **3k** in very good yields. The heterocyclic substrate could only afford trace amount of product **3l** due to electron withdrawing effect of the pyridine ring. Furthermore, we began to explore the substrate scope of the aromatic ring attached to the quinazolinone core. The quinazolinone substrate with alkyl substituted aromatic ring resulted in the decent yield of product **3m**, however, as anticipated chloro, and other electron withdrawing substituents resulted in moderate to a low yield of products **3n-p**. Electron rich substituent enhanced the C-H activation process, and the product **3q** was obtained in excellent yield.

Pleasingly, the heterocyclic indole substrate could be arylated at the 2-position of indole to afford the product **3r**.

Table 3. Pd-Catalyzed Arylation with Various Diaryliodonium Triflates[a,b]



[a]Reaction conditions: **1q** (0.2 mmol), **2b-i** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), Na_2CO_3 (0.4 mmol), AcOH (1 mL), 30-36 h, 90-95 ^oC. [b]Isolated yield.

We also investigated the application of various diaryliodonium triflates in the developed arylation protocol (Table 3). The substrate **1q** was chosen for this purpose. It is well known that the sterically less hindered aryl group of diaryliodonum triflate undergoes metal-catalyzed coupling,[16d] hence we kept sterically hindered mesitylene as one of the substituent in the arylation reagent, and varied other aryl substituents. Various substituents on the arylation reagent were tolerated under the developed protocol. The arylated products such as unsubstituted **3q** and methyl substituted **3s** could be obtained in very good yields. The *para*-fluoro compound **3t** was obtained in moderate yield. The arylation reagents with electron withdrawing groups underwent smooth reactions under the developed protocol. The trifluoromethyl and ester groups at *meta*-position on arylation reagent were well tolerated, and expected products **3u**, and **3v** have been

synthesized in decent yields respectively. Nitro groups at *meta*- and *para*-positions of arylating reagents provided good yields of products **3w**, and **3x** respectively. Overall, it was observed that electron withdrawing groups on arylation reagents facilitates the reaction. It can be reasoned that the palladium insertion takes place promptly on more electron deficient coupling partner. As evident from the substrate scope study (Tables 2, and 3), the developed protocol is very general, and it will be suitable for generation of a library of compounds.

A plausible mechanism for the developed arylation protocol is depicted in Figure 2, based on the literature precedence.[4j,7,17]

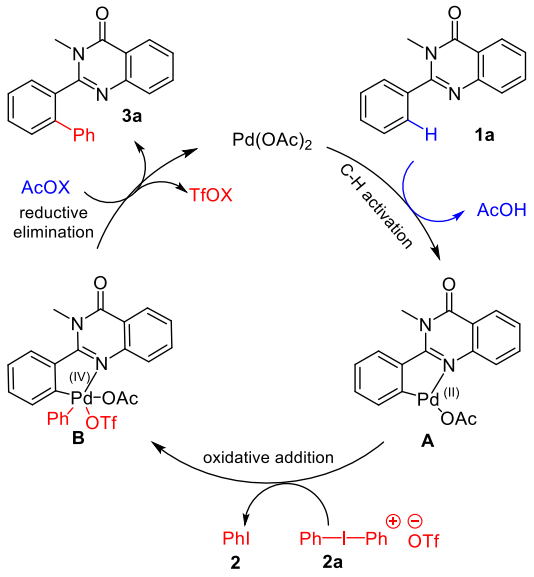


Figure 2. Proposed mechanism.

We believe that in the first step Pd(II) coordinates with the imine nitrogen of quinazolinone **1a**, and activates the proximal proton to form a five membered palladacycle **A**. Diphenyliodonium triflate **2a** oxidatively adds to the palladacycle **A** [Pd(II)] to form the palladacycle **B** [Pd(IV)]. Subsequently, base promoted reductive elimination affords product **3a**, and Pd(II) regenerates for the next catalytic cycles.

CONCLUSION

In summary, quinazolinone scaffold has been demonstrated as the inherent directing group in Pd-catalyzed intermolecular regioselective mono-arylation reaction. Diaryliodonium triflates have been used as arylation reagents in the C-H activation process, which provided the wide range of new quinazolinones. This novel protocol could be used for late-stage derivatisation of bioactive quinazolinones, and natural products for SAR studies. Screening the anticancer, and antimalarial properties of all the synthesized new quinazolinone compounds, and the work towards the development of quinazolinone as a directing group for other C-H activation processes is underway in our laboratory.

EXPERIMENTAL SECTION

General Information: All reagents and solvents were used as received from commercial sources unless and otherwise noted. All experiments were carried out under argon atmosphere in the sealed tube. Pre-coated plates (silica gel 60 PF254, 0.25 mm or 0.5 mm) were utilized for Thin Layer Chromatography (TLC). Column chromatographic purifications were carried out on flash silica-gel (240-400 mesh) using petroleum ether and ethyl acetate as eluents. The ^{1}H, ^{13}C NMR spectra were recorded on 200/400/500 MHz, and 50/100/125 MHz NMR spectrometer respectively in $CDCl_3$. Chemical shifts were reported as δ values from standard peaks. Melting points were recorded on Buchi instrument. Mass spectra were taken on LC-MS (ESI) mass spectrometer. High-resolution mass spectrometry (HRMS) was performed on a TOF/Q-TOF mass spectrometer. All diaryliodonium triflates[15c-d,18] and quinazolinone starting materials[19,20] were prepared according to well-known literature procedures.

Experimental Procedures for the Synthesis of Starting Materials:

Method A: The literature known procedure was followed.[19] *N*-Substituted anthranilamides (1.0 mmol; 1.0 equiv.), and aromatic aldehydes (1.2 mmol; 1.2 equiv.) were dissolved in DMSO (5 mL). Then, the reaction mixture was stirred at 120 ^{o}C in an open flask, and the progress was monitored by TLC. After complete consumption (48 h) of the starting materials, the reaction mixture was poured onto water and extracted with DCM. The organic layer was combined, dried over anhydrous sodium sulfate, and concentrated in *vacuo*. The crude mixture was purified by silica gel column chromatography using Pet. ether / EtOAc (5:1) as an eluent to afford 2,3-disubstituted-4(3H)-quinazolinones **1a-r**.

Method B: The literature known procedure was followed.[20] To the solution of *N*-substituted anthranilamides **4** (1 mmol) and *p*-TsOH (0.05 mmol) in THF (10 mL) was added aldehyde **5** (1.1 mmol) and the reaction mixture was then stirred at room temperature (RT) for 10 min., followed by portion wise addition of PIDA (1.5 mmol) over 5 min. After stirring for 1 h, the reaction mixture was diluted with EtOAc (20 mL), quenched with saturated aqueous $NaHCO_3$ solution (20 mL), and then extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (3 × 30 mL), dried over sodium sulfate and concentrated in *vacuo*. The crude mixture was purified by silica gel column chromatography using Pet. ether / EtOAc (5:1) as an eluent to afford 2,3-disubstituted-4(3H)-quinazolinones **1a-r**.

3-methyl-2-phenylquinazolin-4(3H)-one ***(1a)***.[19] Following the **Method A** procedure, **1a** was obtained as white solid (178 mg; 75% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.35 (dt, J = 7.9, 1.1 Hz, 1H), 7.80-7.73 (m, 2H), 7.63-7.43 (m, 6H), 3.51 (s, 3H).

*3-ethyl-2-phenylquinazolin-4(3H)-one (**1b**).*[21] Following the **Method A** procedure, **1b** was obtained as white solid (167 mg; 67% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.35 (dt, J = 7.9, 1.0 Hz, 1H), 7.80-7.72 (m, 2H), 7.59-7.47 (m, 6H), 4.05 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H).

*3-butyl-2-phenylquinazolin-4(3H)-one (**1c**).*[5b] Following the **Method A** procedure **1c** was obtained as white solid (122 mg; 44% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.34 (m, 1H), 7.79-7.70 (m, 2H), 7.56-7.46 (m, 6H), 4.05-3.92 (m, 2H), 1.65-1.50 (m, 2H), 1.28-1.08 (m, 2H), 0.78 (t, J = 7.1 Hz, 3H).

*3-benzyl-2-phenylquinazolin-4(3H)-one (**1d**).*[19] Following the **Method A** procedure, **1d** was obtained as white solid (119 mg; 38% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.43-8.34 (m, 1H), 7.83-7.73 (m, 2H), 7.59-7.50 (m, 1H), 7.50-7.31 (m, 5H), 7.26-7.15 (m, 3H), 6.99-6.87 (m, 2H), 5.29 (s, 2H).

*2,3-diphenylquinazolin-4(3H)-one (**1e**).*[19] Following the **Method A** procedure **1e** was obtained as white solid (203 mg; 68% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.37 (dt, J = 7.9, 1.0 Hz, 1H), 7.87-7.80 (m, 2H), 7.60-7.50 (m, 1H), 7.39-7.27 (m, 5H), 7.26-7.13 (m, 5H).

*3-methoxy-2-phenylquinazolin-4(3H)-one (**1f**).*[20] Following the **Method B** procedure, **1f** was obtained as white solid (163 mg; 65% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.36 (dt, J = 7.9, 1 Hz, 1H), 7.96-7.86 (m, 2H), 7.82-7.76 (m, 2H), 7.61-7.46 (m, 4H), 3.78 (s, 3H).

*3,5-dimethyl-2-phenylquinazolin-4(3H)-one (**1g**).* Following the **Method A** procedure, **1g** was obtained as white solid (113 mg; 45% yield). R*f*: 0.4 (1:4 EtOAc: Pet. ether); mp 105-107 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63-7.48 (m, 7H), 7.30-7.22 (m, 1H), 3.46 (s, 3H), 2.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.2, 155.8, 148.9, 140.9, 135.5, 133.4, 129.9,

129.5, 128.8, 127.9, 125.7, 119.1, 34.1, 23.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{15}N_2O$, 251.1179; found, 251.1181.

*6-chloro-3-methyl-2-phenylquinazolin-4(3H)-one (**1h**).* Following the **Method B** procedure, **1h** was obtained as white solid (192 mg; 67% yield). R*f*: 0.35 (1:4 EtOAc: Pet. ether); mp 126-128 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.30 (s, 1H), 7.78-7.64 (m, 2H), 7.62-7.45 (m, 5H), 3.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.7, 156.4, 145.8, 135.1, 134.7, 132.7, 130.2, 129.2, 128.9, 127.9, 126.0, 121.5, 34.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{12}N_2OCl$, 271.0633; found, 271.0636.

*3-methyl-6-nitro-2-phenylquinazolin-4(3H)-one (**1i**).*[22] Following the **Method A** procedure, **1i** was obtained as yellow solid (90 mg; 32% yield). ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 9.21 (d, *J* = 2.5 Hz, 1H), 8.55 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.64-7.57 (m, 5H), 3.57 (s, 3H).

*6-methoxy-3-methyl-2-phenylquinazolin-4(3H)-one (**1j**).*[23] Following the **Method A** procedure, **1j** was obtained as white solid (102 mg; 38% yield). ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.78-7.65 (m, 2H), 7.63-7.48 (m, 5H), 7.37 (dd, *J* = 9.0, 3 Hz, 1H), 3.95 (s, 3H), 3.52 (s, 3H).

*7-methoxy-3-methyl-2-phenylquinazolin-4(3H)-one (**1k**).*[23] Following the **Method A** procedure, **1k** was obtained as white solid (120 mg; 45% yield). ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.24 (d, *J* = 8.8 Hz, 1H), 7.61-7.48 (m, 5H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.09 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.91 (s, 3H), 3.49 (s, 3H).

*3-methyl-2-phenylpyrido[2,3-d]pyrimidin-4(3H)-one (**1l**).*[24] Following the **Method A** procedure **1l** was obtained as white solid (87 mg; 37% yield). ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 9.01

(dd, *J* = 4.6, 2 Hz, 1H), 8.66 (dd, *J* = 7.9, 2 Hz, 1H), 7.71-7.60 (m, 2H), 7.58-7.41 (m, 4H), 3.56 (s, 3H).

*3-methyl-2-(p-tolyl)quinazolin-4(3H)-one (**1m**)*.[25] Following the **Method A** procedure, **1m** was obtained as white solid (160 mg; 64% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.34 (d, *J* = 7.8 Hz, 1H), 7.70-7.69 (m, 2H), 7.56-7.41 (m, 3H), 7.33 (d, *J* = 8 Hz, 2H), 3.52 (s, 3H), 2.45 (s, 3H).

*2-(4-chlorophenyl)-3-methylquinazolin-4(3H)-one (**1n**)*.[21] Following the **Method A** procedure, **1n** was obtained as white solid (152 mg; 56% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.32 (d, *J* = 7.5 Hz, 1H), 7.83-7.67 (m, 2H), 7.60-7.45 (m, 5H), 3.50 (s, 3H).

*3-methyl-2-(4-(trifluoromethyl)phenyl)quinazolin-4(3H)-one (**1o**)*. Following the **Method B** procedure, **1o** was obtained as white solid (131 mg; 43% yield). R*f*: 0.35 (1:4 EtOAc: Pet. ether); mp 119-121 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.35 (d, *J* = 7.9 Hz, 1H), 7.88-7.69 (m, 6H), 7.54 (t, *J* = 7.3 Hz, 1H), 3.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.4, 154.7, 147, 138.7, 134.5, 132.1 (q, *J* = 33.1 Hz), 128.6, 127.5, 127.4, 126.8, 125.9 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 272 Hz), 120.6, 34.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{12}N_2OF_3$, 305.0896; found, 305.0893.

*3-methyl-2-(4-nitrophenyl)quinazolin-4(3H)-one (**1p**)*.[25] Following the **Method B** procedure, **1p** was obtained as yellow solid (129 mg; 46% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.43 (d, *J* = 8.8 Hz, 2H), 8.37 (d, *J* = 8.7 Hz, 1H), 7.87-7.74 (m, 4H), 7.63-7.51 (m, 1H), 3.51 (s, 3H).

*2-(4-methoxyphenyl)-3-methylquinazolin-4(3H)-one (**1q**)*.[21] Following the **Method A** procedure, **1q** was obtained as white solid (181 mg; 68% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.32

(d, *J* = 7.7 Hz, 1H), 7.78-7.68 (m, 2H), 7.59-7.44 (m, 3H), 7.08-6.98 (m, 2H), 3.88 (s, 3H), 3.54 (s, 3H).

*3-methyl-2-(1-methyl-1H-indol-3-yl)quinazolin-4(3H)-one (**1r**).* Following the **Method A** procedure, **1r** was obtained as white solid (130 mg; 45% yield). R*f*: 0.4 (1:1 EtOAc: Pet. ether); mp 194-196 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.35 (d, *J* = 7.3 Hz, 1H), 7.80-7.70 (m, 3H), 7.55 (s, 1H), 7.51-7.45 (m, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.27 (t, *J* = 7.9 Hz, 1H), 3.91 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.3, 152.1, 147.9, 136.8, 134.1, 130.6, 127.2, 126.6, 126.4, 126.2, 122.9, 121.2, 120.7, 120.1, 110.5, 109.9, 34.1, 33.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{16}N_3O$, 290.1288; found, 290.1293.

General Experimental Procedure for Arylations by C-H Activation:

A sealed tube was charged with quinazolinone **1a-r** (0.2 mmol), diaryl iodonium triflate **2a-i** (0.6 mmol), sodium carbonate (42 mg; 0.4 mmol) and $Pd(OAc)_2$ (4.5 mg; 10 mol%). To the above mixture AcOH (1 ml; 0.2M) was added and flushed twice with argon gas. The tube was packed with screw cap and placed in preheated oil bath at 90 ^{o}C-120 ^{o}C. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to RT after 30-36 h, diluted with ethyl acetate and evaporated under *vacuo* to dryness. After aqueous workup the residue was purified by column chromatography to afford pure quinazolinone **3a-x**.

*2-([1,1'-biphenyl]-2-yl)-3-methylquinazolin-4(3H)-one (**3a**).* Following the general experimental procedure, **3a** was obtained as a colorless solid (44 mg; 71% yield); Reaction Time: 36 h at 95 ^{o}C. R*f*: 0.4 (1:4 EtOAc:Pet. ether); mp 125-127 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.27 (d, *J* = 7.9 Hz, 1H), 7.84-7.76 (m, 2H), 7.67-7.57 (m, 2H), 7.56-7.47 (m, 3H), 7.37-7.30 (m, 2H), 7.27-7.22 (m, 3H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.1, 156.4, 147.1,

140.2, 139.4, 134.2, 134.1, 130.4, 130.2, 129.2, 128.7, 128.5, 128.1, 128, 127.5, 126.9, 126.7, 120.4, 32.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{17}N_2O$, 313.1335; found, 313.1337.

*2-([1,1'-biphenyl]-2-yl)-3-ethylquinazolin-4(3H)-one (**3b**)*. Following the general experimental procedure, **3b** was obtained as a colorless solid (36 mg, 55% yield); Reaction time: 36 h at 100 ^oC; R_f: 0.4 (1:4 EtOAc:Pet. ether); mp 137-139 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.27 (d, J = 7.93, 1H), 7.88-7.75 (m, 2H), 7.65-7.55 (m, 2H), 7.54-7.49 (m, 3H), 7.40-7.32 (m, 2H), 7.26-7.16 (m, 3H), 4.0-3.90 (m, 1H), 3.37-3.27 (m, 1H), 0.96 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.5, 156.1, 146.6, 140.0, 139.3, 134.3, 133.7, 130.4, 130.1, 129.2, 128.7, 128.6, 127.9, 127.8, 127.2, 127, 126.7, 120.8, 40.5, 13.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O$, 327.1492; found, 327.1495.

*2-([1,1'-biphenyl]-2-yl)-3-butylquinazolin-4(3H)-one (**3c**)*. Following the general experimental procedure, **3c** was obtained as a colorless solid (37 mg, 53% yield); Reaction time: 30 h at 90 ^oC; R_f: 0.4 (1:4 EtOAc:Pet. ether); mp 108-110 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26 (d, J = 7.94, 1H), 7.83-7.76 (m, 2H), 7.63-7.56 (m, 2H), 7.55-7.48 (m, 3H), 7.37-7.32 (m, 2H), 7.26-7.21 (m, 3H), 3.87-3.77 (m, 1H), 3.27-3.17 (m, 1H), 1.45-1.32(m, 2H), 1.11-1.0(m, 2H), 0.66 (t, J = 7.32, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.8, 156.2, 147, 140, 139.4, 134.2, 134.1, 130.3, 130, 129.5, 128.6, 127.9, 127.8, 127.4, 126.8, 126.7, 120.9, 45, 30.1, 19.8, 13.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{23}N_2O$, 355.1805; found, 355.1806.

*2-([1,1'-biphenyl]-2-yl)-3-benzylquinazolin-4(3H)-one (**3d**)*. Following the general experimental procedure, **3d** was obtained as a colorless solid (34 mg, 44% yield); Reaction time: 36 h at 120 ^oC; R_f: 0.4 (1:4 EtOAc:Pet. ether); mp 84-85 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.29 (d, J = 7.94, 1H), 7.82 (d, J = 6.72 Hz, 2H), 7.59-7.50 (m, 3H), 7.40-7.28 (m, 5H), 7.27-7.20 (m, 2H),

7.16-7.09 (m, 3H), 6.77 (d, *J* = 7.32, 2H), 5.27 (d, *J* = 15 Hz, 1H), 4.30 (d, *J* = 15 Hz, 1H),^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162, 156.3, 146.8, 139.9, 139.4, 136.2, 134.5, 133.7, 130.4, 130, 129.9, 128.8, 128.7, 128.3, 128, 127.7, 127., 127.3, 127.1, 120.8, 47.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{21}N_2O$, 389.1648; found, 389.1648.

*2-([1,1'-biphenyl]-2-yl)-3-phenylquinazolin-4(3H)-one (**3e**)*. Following the general experimental procedure, **3e** was formed in trace amount by TLC analysis and also confirmed by LC-HRMS; Reaction time: 36 h at 120 ^{o}C; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{19}N_2O$, 375.1492; found, 375.1500.

*2-([1,1'-biphenyl]-2-yl)-3-methoxyquinazolin-4(3H)-one (**3f**)*. Following the general experimental procedure, **3f** was obtained as a colorless solid (45 mg; 69% yield); Reaction Time: 36 h at 90 ^{o}C. R*f*: 0.4 (1:3 EtOAc:Pet. ether); mp 101-103 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.28 (d, *J* = 7.9 Hz, 1H), 7.82-7.76 (m, 2H), 7.65 (d, *J* = 7.3 Hz, 1H), 7.61 (d, *J* = 7.3 Hz, 1H), 7.55-7.48 (m, 3H), 7.37-7.31 (m, 2H), 7.26-7.20 (m, 3H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.6, 156.5, 146.3, 141.6, 140.1, 134.4, 131.4, 130.5, 130, 129.1, 128.5, 128.4, 127.9, 127.5, 127.2, 127, 126.7, 122.7, 64; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{17}N_2O_2$, 329.1285; found, 329.1286.

*2-([1,1'-biphenyl]-2-yl)-3,5-dimethylquinazolin-4(3H)-one (**3g**)*. Following the general experimental procedure, **3g** was obtained as a colorless solid (41 mg; 63% yield); Reaction Time: 36 h at 95 ^{o}C. R*f*: 0.4 (1:4 EtOAc:Pet. ether); mp 124-126 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.66-7.49 (m, 6H), 7.39-7.32 (m, 2H), 7.29-7.23 (m, 4H), 2.95 (s, 3H), 2.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.7, 156.1, 148.8, 140.9, 140.2, 139.6, 134.2, 133.3, 130.3,

130.2, 129.5, 129.2, 128.7, 128.6, 128.1, 127.9, 125.7, 119, 32.5, 23.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O$, 327.1492; found, 327.1494.

*2-([1,1'-biphenyl]-2-yl)-6-chloro-3-methylquinazolin-4(3H)-one (**3h**)*. Following general experimental procedure **3h** was obtained as a colorless solid (17 mg; 25% yield); Reaction Time: 36 h at 120 ^oC. R*f*: 0.35 (1:3 EtOAc:Pet. ether); mp 129-131 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.22 (s, 1H), 7.76-7.69 (m, 2H), 7.66-7.60 (m, 1H), 7.59-7.51 (m, 3H), 7.34-7.29 (m, 2H), 7.27-7.21 (m, 3H), 3.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.1, 156.7, 145.6, 140.3, 139.3, 134.8, 133.8, 132.7, 130.6, 130.2, 129.2, 129.1, 128.8, 128.5, 128.1, 127.06, 126, 121.4, 32.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{16}N_2OCl$, 347.0946; found, 347.0951.

*2-([1,1'-biphenyl]-2-yl)-3-methyl-6-nitroquinazolin-4(3H)-one (**3i**)*. Following the general experimental procedure, **3i** was formed in trace amount by TLC analysis and also confirmed by LC-HRMS; Reaction time: 36 h at 120 ^oC; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{16}N_3O_3$, 358.1186; found, 358.1188.

*2-([1,1'-biphenyl]-2-yl)-6-methoxy-3-methylquinazolin-4(3H)-one (**3j**)*. Following the general experimental procedure, **3j** was obtained as a colorless solid (52 mg; 76% yield); Reaction Time: 36 h at 95 ^oC. R*f*: 0.35 (1:2 EtOAc:Pet. ether); mp 177-179 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.74 (d, J = 8.5 Hz, 1H), 7.65-7.48 (m, 5H), 7.39 (dd, J = 8.5, 2.4 Hz, 1H), 7.35-7.29 (m, 2H), 7.28-7.20 (m, 3H), 3.93 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162, 158.5, 154.2, 141.8, 140.3, 139.5, 134.1, 130.4, 130.1, 129.3, 129.1, 128.7, 128.5, 128.1, 127.9, 124.7, 121.2, 105.9, 55.8, 32.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O_2$, 343.1441; found, 343.1441.

*2-([1,1'-biphenyl]-2-yl)-7-methoxy-3-methylquinazolin-4(3H)-one (**3k**)*. Following general experimental procedure **3k** was obtained as a colorless solid (48 mg; 70% yield); Reaction Time: 36 h at 95 ^{o}C. R*f*: 0.35 (1:2 EtOAc:Pet. ether); mp 197-199 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.15 (d, *J* = 8.6 Hz, 1H), 7.65-7.48 (m, 4H), 7.37-7.30 (m, 2H), 7.28-7.22 (m, 3H), 7.19 (d, *J* = 1.8 Hz, 1H), 7.08 (dd, *J* = 8.5, 1.8 Hz, 1H), 3.94 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.5, 161.7, 157.2, 149.3, 140.1, 139.4, 134.2, 130.4, 130.1, 129.1, 128.7, 128.5, 128.2, 128.03, 128, 117.2, 114, 107.8, 55.6, 32.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O_2$, 343.1441; found, 343.1432.

*2-([1,1'-biphenyl]-2-yl)-3-methylpyrido[2,3-d]pyrimidin-4(3H)-one (**3l**)*. Following the general experimental procedure, **3l** was formed in trace amount by TLC analysis and also confirmed by LC-HRMS; Reaction time: 36 h at 120 ^{o}C; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{16}N_3O$, 314.1288; found, 314.1286.

*3-methyl-2-(5-methyl-[1,1'-biphenyl]-2-yl)quinazolin-4(3H)-one (**3m**)*. Following the general experimental procedure, **3m** was obtained as a colorless solid (48 mg; 74% yield); Reaction Time: 36 h at 95 ^{o}C. R*f*: 0.4 (1:4 EtOAc:Pet. ether); mp 151-153 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26 (d, *J* = 7.9 Hz, 1H), 7.82-7.74 (m, 2H), 7.55-7.44 (m, 2H), 7.38-7.29 (m, 4H), 7.26-7.17 (m, 3H), 3.00 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.2, 156.6, 147.2, 140.5, 140.1, 139.6, 134.2, 131.4, 130.8, 129.1, 128.68, 128.66, 128.5, 127.8, 127.4, 126.8, 126.6, 120.4, 32.6, 21.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O$, 327.1492; found, 327.1494.

*2-(5-chloro-[1,1'-biphenyl]-2-yl)-3-methylquinazolin-4(3H)-one (**3n**)*. Following the general experimental procedure, **3n** was obtained as a colorless solid (30 mg, 43% yield); Reaction time:

30 h at 90 ^{o}C; R_f: 0.5 (1:2 EtOAc:Pet. ether); mp 148-150 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26 (d, J = 7.9 Hz, 1H), 7.83-7.75 (m, 2H), 7.58-7.48 (m, 4H), 7.34-7.29 (m, 2H), 7.29-7.21 (m, 3H), 2.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162, 155.4, 147, 142, 138.2, 136.4, 134.4, 132.6, 130.7, 130.1, 128.9, 128.5, 128.4, 128.1, 127.5, 127.1, 126.7, 120.5, 32.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{16}N_2OCl$, 347.0946; found, 347.0941.

*3-methyl-2-(5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)quinazolin-4(3H)-one (**3o**)*. Following the general experimental procedure, **3o** was obtained as a colorless solid (16 mg; 21% yield); Reaction Time: 36 h at 120 ^{o}C. R*f*: 0.35 (1:2 EtOAc:Pet. ether); mp 140-142 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.28 (d, J = 7.9 Hz, 1H), 7.85-7.70 (m, 5H), 7.54 (t, J = 7.3 Hz, 1H), 7.39-7.32 (m, 2H), 7.32-7.27 (m, 3H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.9, 155, 146.9, 141.2, 138, 137.3, 134.5, 132.6 (q, J = 33.1 Hz), 130, 129, 128.7, 128.4, 127.5, 127.3, 127.1 (q, J = 3.9 Hz), 126.8, 124.9 (q, J = 3.9 Hz), 123.6 (q, J = 272 Hz), 120.5, 32.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{16}N_2OF_3$, 381.1209; found, 381.1209.

*3-methyl-2-(5-nitro-[1,1'-biphenyl]-2-yl)quinazolin-4(3H)-one (**3p**)*. Following the general experimental procedure, **3p** was obtained as a colorless solid (11 mg; 16% yield); Reaction Time: 36 h at 120 ^{o}C. R*f*: 0.3 (1:2 EtOAc:Pet. ether); mp 215-217 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.43 (s, 1H), 8.39 (d, J = 8.6 Hz, 1H), 8.28 (d, J = 7.9 Hz, 1H), 7.87-7.75 (m, 3H), 7.56 (t, J = 7.3 Hz, 1H), 7.41-7.29 (m, 5H), 2.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.7, 154.3, 148.9, 146.8, 142.1, 139.7, 137.2, 134.6, 130.8, 129.2, 128.4, 127.56, 127.55, 126.8, 125.1, 122.8, 120.5, 32.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{16}N_3O_3$, 358.1186; found, 358.1185.

*2-(5-methoxy-[1,1'-biphenyl]-2-yl)-3-methylquinazolin-4(3H)-one (**3q**)*. Following the general experimental procedure, **3q** was obtained as a colorless solid (59 mg, 86% yield); Reaction time: 30 h at 90 ^{o}C; R_f: 0.5 (1:1 EtOAc:Pet. ether); mp 192-194 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (d, J = 7.94, 1H), 7.81-7.75 (m, 2H), 7.55-7.46 (m, 2H), 7.36-7.32 (m, 2H), 7.26-7.22 (m, 3H), 7.07-7.07 (m, 2H), 3.92 (s, 3H), 3.0 (s, 3H); ;^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.3, 161, 156.5, 147.2, 141.9, 139.5, 134.2, 130.8, 128.7, 128.4, 128.1, 127.4, 126.9, 126.8, 126.6, 120.4, 115.5, 113.4, 55.6, 32.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O_2$, 343.1441; found, 343.1443.

*3-methyl-2-(1-methyl-2-phenyl-1H-indol-3-yl)quinazolin-4(3H)-one (**3r**)*. Following the general experimental procedure, **3r** was obtained as a colorless solid (33 mg; 45% yield); Reaction Time: 36 h at 100 ^{o}C. R*f*: 0.5 (1:4 EtOAc:Pet. ether); mp 198-200 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.31 (d, J = 7.9 Hz, 1H), 7.79-7.72 (m, 2H), 7.64 (d, J = 7.9 Hz, 1H), 7.51-7.33 (m, 8H), 7.28-7.23 (m, 1H), 3.80 (s, 3H), 3.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163, 152.2, 147.8, 140, 137.5, 134, 130.6, 129.9, 129.02, 128.95, 127.5, 126.8, 126.6, 126.5, 123.1, 121.5, 120.4, 119.6, 110, 109.5, 32.9, 31.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{20}N_3O$, 366.1601; found, 366.1606.

*2-(5-methoxy-4'-methyl-[1,1'-biphenyl]-2-yl)-3-methylquinazolin-4(3H)-one (**3s**)*. Following the general experimental procedure, **3s** was obtained as a colorless solid (51 mg, 71% yield); Reaction time: 36 h at 95 ^{o}C; R_f: 0.5 (1:1 EtOAc:Pet. ether); mp 130-132 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26 (d, J = 7.93, 1H), 7.84-7.76 (m, 2H), 7.54-7.44 (m, 2H), 7.22 (m, J = 7.32, 2H), 7.08-7.00 (m, 4H), 3.91 (s, 3H), 2.99 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.3, 160.9, 156.7, 147.3, 141.9, 138, 136.6, 134.2, 130.8, 129.5, 128.2, 127.4,

126.8, 126.7, 126.6, 120.4, 115.4, 113.1, 55.5, 32.60 21.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{21}N_2O_2$, 357.1598; found, 357.1600.

*2-(4'-fluoro-5-methoxy-[1,1'-biphenyl]-2-yl)-3-methylquinazolin-4(3H)-one (**3t**)*. Following the general experimental procedure, **3t** was obtained as a colorless solid (32 mg, 44% yield); Reaction time: 36 h at 90 ^oC; R_f: 0.5 (1:1 EtOAc:Pet. ether); mp 155-157 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.26 (d, J = 7.62, 1H), 7.82-7.7.76 (m, 2H), 7.53-7.48 (m, 2H), 7.34-7.29 (m, 2H), 7.05 (dd, J = 2.7, 8.6 Hz, 1H), 7.01 (d, J = 2.7, 1H), 6.95 (t, J = 8.6 Hz 2H), 3.92 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 162.5 (d, J = 248 Hz), 162.2, 161, 156.2, 147.2, 140.8, 135.5 (d, J = 2.86 Hz), 134.3, 130.8, 130.1 (d, J = 7.63 Hz), 127.4, 126.9, 126.9, 126.7, 120.4, 115.8 (d, J = 21 Hz), 115.6, 113.4, 55.56, 32.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{18}N_2O_2F$, 361.1347; found, 361.1347.

*2-(5-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-3-methylquinazolin-4(3H)-one (**3u**)*. Following the general experimental procedure, **3u** was obtained as a colorless solid (60 mg; 73% yield); Reaction Time: 36 h at 95 ^oC. R*f*: 0.3 (1:2 EtOAc:Pet. ether); mp 142-144 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (d, J = 7.3 Hz, 1H), 7.83-7.72 (m, 2H), 7.68 (s, 1H), 7.57-7.45 (m, 4H), 7.35 (t, J = 7.3 Hz, 1H), 7.13-7.07 (m, 1H), 7.05 (d, J = 1.8 Hz, 1H), 3.94 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.2, 161, 155.6, 146.9, 140.21, 140.17, 134.3, 131.6, 131.1 (q, J = 32.4 Hz), 130.7, 129.2, 127.3, 127, 126.9, 126.6, 125.5 (q, J = 3.9 Hz), 124.7 (q, J = 3.9 Hz), 123.6 (q, J = 272.8 Hz), 120.3, 115.6, 113.9, 55.7, 32.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{18}N_2O_2F_3$, 411.1315; found, 411.1324.

*Methyl 5'-methoxy-2'-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)-[1,1'-biphenyl]-3-carboxylate (**3v**)*. Following the general experimental procedure, **3v** was obtained as a colorless solid (60 mg,

75% yield); Reaction time: 30 h at 90 ^{o}C.R_f: 0.4 (1:2 EtOAc:Pet. ether); mp 118-120 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (d, J = 7.94, 1H), 8.09 (s, 1H), 7.92 (d, J = 3.66, 1H), 7.78 (d, J = 3.66, 2H), 7.56-7.47 (m, 3H), 7.30 (d, J = 7.94, 1H), 7.11-7.06 (m, 2H), 3.93 (s, 3H), 3.72 (s, 3H), 3.0 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.4, 162.2, 161, 156, 147.1, 140.6, 139.56, 134.2, 132.6, 130.7, 129.6, 129.1, 128.8, 127.4, 126.9, 126.6, 120.4, 115.5, 113.8, 55.6, 52, 32.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{21}N_2O_4$, 401.1496; found, 401.1505.

*2-(5-methoxy-3'-nitro-[1,1'-biphenyl]-2-yl)-3-methylquinazolin-4(3H)-one (**3w**)*. Following the general experimental procedure, **3w** was obtained as a colorless solid (57 mg, 74% yield); Reaction time: 30 h at 90 ^{o}C; R_f: 0.5 (1:1 EtOAc:Pet. ether); mp 158-160 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.33 (s, 1H), 8.24 (d, J = 7.9 Hz, 1H), 8.12 (d, J = 7.9 Hz, 1H), 7.82-7.74 (m, 2H), 7.63 (d, J = 7.3, 1H), 7.55 (d, J = 8.5, 1H), 7.51 (t, J = 7.32, 1H), 7.39 (t, J = 7.93. 1H), 7.13 (d, J = 8.5, 1H), 7.07 (s, 1H), 3.95 (s, 3H), 3.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.2, 161.1, 155.2, 148.3, 146.9, 141.1, 139.2, 134.5, 134.3, 130.8, 129.7, 127.4, 127.2, 126.6, 126.7, 123.6, 122.9, 120.3, 115.8, 114.3, 55.7, 32.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{18}N_3O_4$, 388.1292; found, 388.1292.

*2-(5-methoxy-4'-nitro-[1,1'-biphenyl]-2-yl)-3-methylquinazolin-4(3H)-one (**3x**)*. Following general experimental procedure **3x** was obtained as a colorless solid (53 mg, 68% yield); Reaction time: 36 h at 90 ^{o}C; R_f: 0.5 (1:1 EtOAc:Pet. eher); mp 205-207 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26 (d, J = 7.94, 1H), 8.12 (d, J = 8.54, 2H), 7.82-7.72 , 2H), 7.58-7.49 (m, 4H), 7.13 (dd, J = 8.54, 1.83, 1H), 7.05 (s, 1H), 3.94 (s, 3H), 3.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.1, 161, 155.3, 147.3, 146.9, 146.1, 139.5, 134.5, 130.9, 129.4, 127.4,

127.3, 126.8, 126.7, 123.9, 120.3, 115.8, 114.4, 55.7, 32.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{18}N_3O_4$, 388.1292; found, 388.1298.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Spectroscopic data (^1H, ^{13}C and HRMS spectra) of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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