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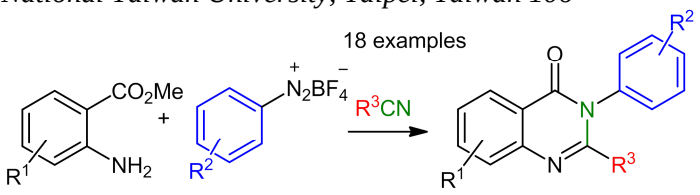

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Preparation of 4(*3H*)-quinazolinones from aryldiazonium salt, nitriles and 2-aminobenzoate *via* a cascade annulation

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ABSTRACT

One-pot synthesis of 3-aryl-4(*3H*)-quinazolinones has been realized through a cascade annulation. Reaction of aryldiazonium salt with a nitrile provides *in situ* generation of a reactive nitrilium ion, which is attacked by the amino group of 2-aminobenzoate followed by cyclization to deliver the desired product. This strategy offers a convenient and easy access to a wide range of functionalized quinazolinone.

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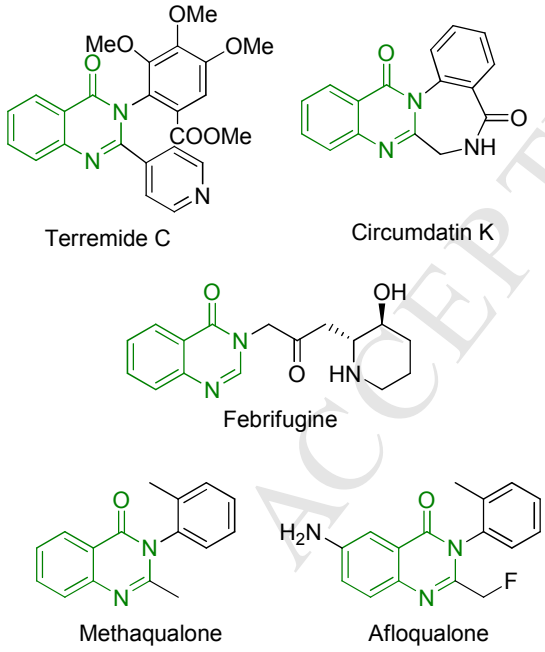
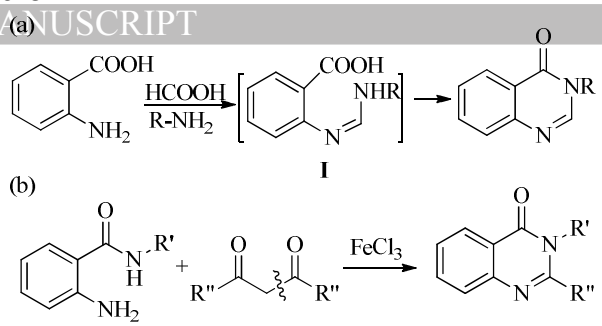
1. Introduction

Quinazolinones are prevalent structural units in a wide range of both natural products and pharmaceuticals.[1-2] Terremide C,[1a] Febrifugine,[1b-c] and Circumdatin K[1d] are naturally occurring alkaloids, whereas methaqualone[3] and afloqualone[4] are sedative and hypnotic medications (Scheme 1). In addition, quinazolinone derivatives exhibit wide spectrum of therapeutic activities such as anticancer,[5] hypotensive,[6] antiallergy[7] and protein tyrosine kinase inhibitory properties.[8] With the importance of quinazolinone derivatives in biological use, numerous synthetic approaches including methodologies with or without transition-metal catalysis leading to these heterocyclic structures have been disclosed and received significant attention. Quite a few review articles summarizing these methodologies have appeared.[9]

Methodologies for synthesis of quinazolinones are primarily based on condensation procedures. For example, microwave irradiation of a mixture of anthranilic acid, formic acid and primary amine provided 3-substituted quinazolin-4(3*H*)-ones (Scheme 2a). This reaction is believed to proceed through the amidine intermediate **I**, which subsequently underwent intramolecular amidation to yield the final product.[10a] It should be mentioned that most of these methods often require harsh reaction conditions and use of toxic and/or corrosive reagents such as PCl_3, $O{=}PCl_3$ or related reagents, which greatly affects the sensitive functional groups. On the other hands, transition metal catalysed synthesis offers various approaches to the desired product by using easily accessed starting materials due to the versatile activity and reaction types of metal complexes.[9] An interesting approach by Zhou and co-workers demonstrates that $FeCl_3$-catalyzed tandem reaction of 2-aminobenzamides with 1,3-diketones offers the quinazolinone products.[10b] This method involves a C-C bond cleavage pathway during the aromatization (Scheme 2b).

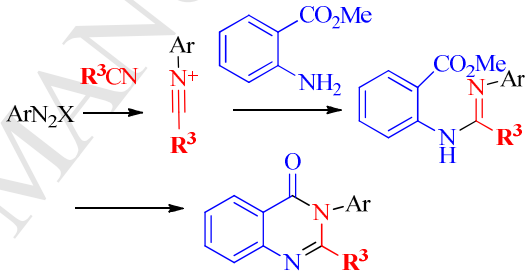


Scheme 1. Some derivatives of quinazolin-4-(3*H*)-ones



Scheme 2. Preparation of quinazolin-4(3*H*)-ones by (a) a condensation pathway and (b) a transition-metal catalysis

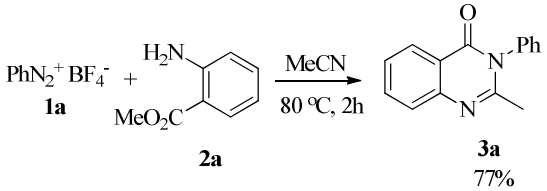
In recent studies, we have found that aryldiazonium salts can be used as the precursor for the preparation of various heterocycles.[11] In these syntheses, the key intermediate is *N*-arylnitrilium ion generated *in situ* from the reaction of the arenediazonium salt with a nitrile molecule.[12] Such an intermediate could further react with nucleophiles to construct the heterocycles in a cascade reaction fashion. Herein, we report a mild and transition metal-free synthesis of quinazolin-4(*3H*)-ones (Scheme 3). We envision that the reactive *N*-arylnitrilium intermediate could react with methyl anthranilate followed by cyclization to afford the desired product directly without the use of phosphorus trichloride or related reagents.



Scheme 3. Our approach in preparation of quinazolin-4(*3H*)-ones.

2. Results and discussion

To validate the hypothesis, we chose the reaction of phenyl-diazonium tetrafluoroborate (**1a**) with methyl anthranilate (**2a**) in acetonitrile as the model example (Eqn 1). After several trials by varying the temperature, the desired product **3a** was obtained in 77% yield by carrying out the reaction at 80 °C. Running the reactions at either higher or lower temperature resulted in a lower yield of the product. Efforts to reduce the quantity of nitrile in the presence of co-solvents such as dichloroethane, toluene and methanol led to poor yields. For example, carrying out this reaction in toluene with 10 equivalent of nitrile provided the target molecule in 52% yield. In these studies, we learned that the reaction requires to proceed under anhydrous conditions. Otherwise, *N*-phenyl acetamide was obtained as the major product, presumably due to the hydrolysis of nitrilium ion.

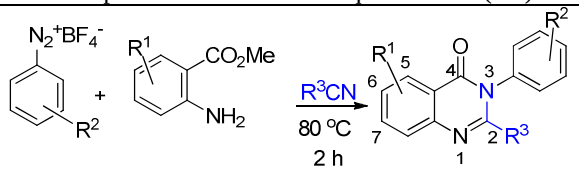


(Eqn. 1)

With this optimal condition in hand, we systematically examined this annulation toward functionalized 3-aryl-4(3*H*)-quinazolinones by reacting various aryldiazonium salts, nitriles and substituted anthranilates. Gratifyingly, aryldiazonium salts

with common substitutions such as, 4-Me, 3-Me, 4-OMe, 4-*t*Bu readily reacted with **2a** to give the corresponding quinazolinones in moderate to good yields (Table 1, entries 1-5). It is worth noting that this reaction could tolerate the presence of functional groups such as halogens and esters (**3f**-**3g**), providing ample potential for further synthetic elaborations. Notably, aryldiazonium salts with sterically demanding 2,4,6-trimethyl and 3,4,5-trimethoxy substituents were also found to be amenable substrates for this reaction, furnishing the multi-substituted quinazolinones in moderate yields (Table 1, entries 9-10). In addition, this annulation protocol was found to proceed well with various readily available aliphatic, aromatic and benzylic nitriles and delivered the corresponding 2-substituted quinazolin-4(3*H*)-ones in moderate yields (Table 1, entries 11-14). Unfortunately, malononitrile and 3-bromopropionitrile were failed to give the desired products. On the other hand, scope of this reaction was contemplated with various anthranilates. Utilization of anthranilates with diverse substitutions such as, 5-Me, 4-Br and 4,5-dimethoxy groups smoothly participated in the transformation and provided the corresponding quinazolinones in good yields (Table 1, entries 15-17).

Table 1. Preparation of substituted quinazolin-4(3*H*)-ones

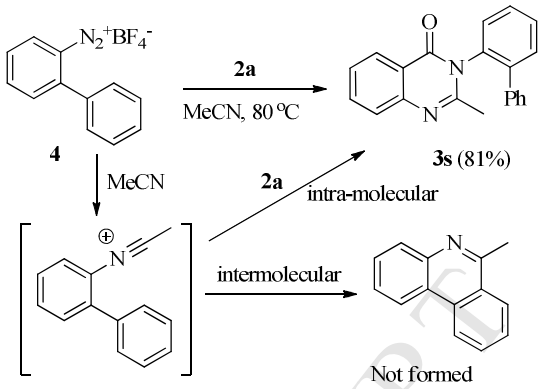


1 **2** **3**

Entry	Substituents in **3**	Yields[b]
1	**3a**, R^1 = H, R^2 = H, R^3 = CH_3	77%
2	**3b**, R^1 = H, R^2 = 4-Me, R^3 = CH_3	74%
3	**3c**, R^1 = H, R^2 = 3-Me, R^3 = CH_3	55%
4	**3d**, R^1 = H, R^2 = 4-OMe, R^3 = CH_3	53%
5	**3e**, R^1 = H, R^2 = 4-*t*-Bu, R^3 = CH_3	81%
6	**3f**, R^1 = H, R^2 = 4-Cl, R^3 = CH_3	33%
7	**3g**, R^1 = H, R^2 = 4-CO_2Et, R^3 = CH_3	44%
8	**3h**, R^1 = H, R^2 = 1-naphthyl, R^3 = CH_3	67%
9	**3i**, R^1 = H, R^2 =2,4,6-triMe, R^3 = CH_3	68%
10	**3j**, R^1 = H, R^2 =3,4,5-$(MeO)_3$, R^3 = CH_3	52%
11	**3k**, R^1 = H, R^2 = 4-Me, R^3 = $CH_3CH_2CH_2$	56%
12	**3l**, R^1 = H, R^2 = 4-Me, R^3 = $(CH_3)_2CH$	41%
13	**3m**, R^1 = H, R^2 = 4-Me, R^3 = C_6H_5	48%
14	**3n**, R^1 = H, R^2 = 4-Me, R^3 = $CH_2C_6H_5$	53%
15	**3o,** R^1 = 6-Me, R^2 = 4-Me, R^3 = CH_3	92%
16	**3p,** R^1 = 7-Br, R^2 = H, R^3 = CH_3	63%
17	**3q**, R^1 = 6,7-$(OMe)_2$, R^2 = H, R^3 = CH_3	68%

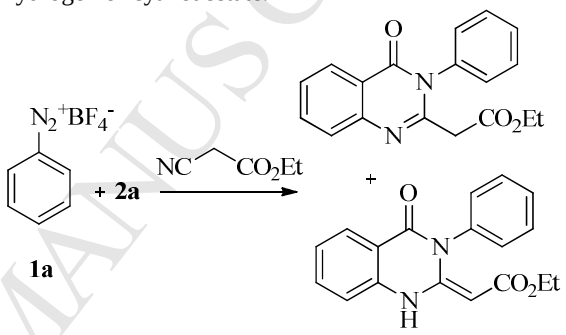
[a] Reaction conditions: aryldiazonium salt (100 mg) and **2** (1.1 eq) in nitrile (2 mL) was heated at 80 °C for 2 h. [b] isolated yields

Reaction of 2-phenyl substituted aryldiazonium salt (**4**) with methyl anthranilate (**2a**) under the standard conditions was investigated to study the competition of intra- versus inter-molecular pathway (Scheme 4). In contrast to our previous observations,[11c] aryldiazonium salt **4** was reacted with **2a** to furnish **3s** in excellent yields instead of the formation of 6-methylphenanthridine. Apparently, the intermolecular amination/cascade annulation of *N*-arylnitrilium ion is superior to the intramolecular arylation.



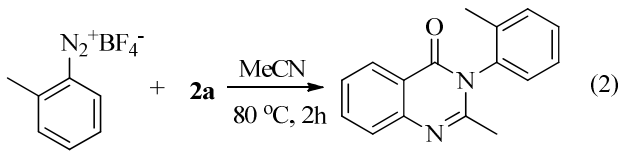
Scheme 4. Inter- versus intra-molecular pathway

On the other hand, reaction of ethyl cyanoacetate with **1a** and **2a** led to mixture of tautomers (**3t** and **3t'**) as an inseparable mixture (Scheme 5). This isomerization is due to the acidic hydrogen of cyanoacetate.



Scheme 5. Reaction of a nitrile with an active methylene unit

To further demonstrate the synthetic utility, we attempted the synthesis of methaqualone, a well-known sedative and hypnotic drug used for the treatment of insomnia (Eqn. 2).[13a-b] To our delight, treatment of 0.5 gram of **1k** with 2-methylanthranilate and anhydrous acetonitrile under the optimized conditions afforded the methaqualone in 78% isolated yield. Besides spectroscopic identification, structure of compound **3r** is further confirmed by X-ray crystallography (Figure 1).



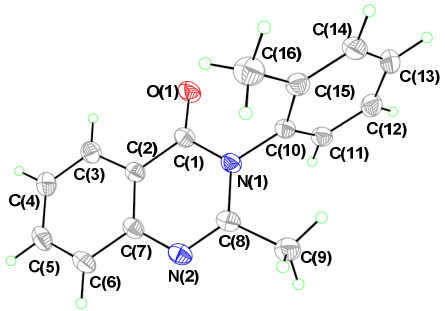


Figure 1. ORTEP plot of **3r** (30% probability ellipsoids)

In summary, we have disclosed a convenient and sustainable approach for the synthesis of quinazolin-4-(3*H*)-ones via a three-component intermolecular amination/tandem cyclization of *in situ* generated *N*-arylnitrilium ion intermediate. This method utilizes readily accessible aryldiazonium salts, nitriles and substituted anthranilates. Excellent functional group compatibility, mild reaction conditions and operational simplicity are the notable features of this report. Furthermore, this method provides an alternative to prepare diversified quinazolin-4-(3*H*)-one scaffolds without the use of toxic reagents such as phosphorus trichloride or related reagents.

3. Experimental section

^{1}H and ^{13}C NMR were recorded in a 400 MHz spectrometer in $CDCl_3$ and CD_3CN referenced to TMS. All the nitriles were dried over activated 4Å molecular sieves and solid nitriles were purchased and used without any purification. All the anilines were commercially purchased and used for diazotization. Flash chromatography was performed using silica gel 230-400 mesh. Aryldiazonium salts were prepared according to the literature procedure. In cases of known compounds, their ^{1}H and ^{13}C NMR values were compared with the literature values. For NMR data, only major product peaks are listed. Melting points were determined on a Fargo MP-1D instrument. Unless otherwise noted, all the reactions were performed without any special precautions.

*3.1. Typical Procedure for Preparation of **3**.*

A mixture of diazonium salt (100 mg, 1 eq) and methyl anthranilate (1.1 eq) dissolved in dry nitrile (2 mL) was placed in a sealed tube. Reaction mixture was heated to 80 ^{o}C with stirring for 2 h. Upon cooling, the reaction mixture was diluted with CH_2Cl_2 (20 mL) followed by an aqueous basic workup with aq. $NaHCO_3$ (5 mL). The crude product was purified by column chromatography with the eluent of ethyl acetate/ hexane (20% to 40% EtOAc:Hexane) to afford the pure product.

*3.1.1 2-Methyl-3-phenylquinazolin-4(3H)-one (**3a**)*[13b]

(94 mg, 77%)as a pale yellow solid; mp 143-144 ^{o}C; IR (CaF_2): 1742, 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.22 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.72 (ddd, *J* = 15.4, 7.8, 1.2 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.54-7.45 (m, 3H), 7.44-7.40 (m, 1H), 2.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.1, 154.1, 147.3, 137.6, 134.4, 129.9, 129.1, 127.9, 126.9, 126.6, 126.5, 120.6, 24.2; HRMS (ESI-TOF) calcd for $C_{15}H_{13}N_2O$ $[M+H]^+$ m/z = 237.1028, found 237.1030.

*3.1.2 2-Methyl-3-(p-tolyl)quinazolin-4(3H)-one (**3b**).*[10b]

(89.8 mg, 74%) as a pale yellow solid; mp 155-156 ^{o}C; IR (KBr): 1687, 1607 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.24 (d, *J* = 8.0 Hz, 1H), 7.79-7.74 (m, 2H), 7.49-7.45 (m, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 2.43 (s, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.0, 155.0, 146.5, 139.5, 134.7, 130.7, 127.6, 127.1, 126.8, 126.1, 120.6, 24.0, 21.2; HRMS (ESI-TOF) calcd for $C_{16}H_{15}N_2O$ $[M+H]^+$ *m/z* = 251.1184, found: 251.1193.

*3.1.3 2-Methyl-3-(m-tolyl)quinazolin-4(3H)-one (**3c**).*

(67.0 mg, 55%) as a pale yellow solid; mp 130-131 ^{o}C; IR (CaF_2): 1687, 1602 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.25 (d, *J* = 7.5 Hz, 1H), 7.76-7.71 (m, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.45-7.39 (m, 2H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 2.40 (s, 3H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.3, 154.3, 147.5, 140.1, 137.6, 134.5, 130.0, 129.7, 128.4, 127.0, 126.7, 126.5, 124.9, 120.8, 24.3, 21.3; HRMS (ESI-TOF) calcd. for $C_{16}H_{15}N_2O$ $[M+H]^+$ *m/z* = 251.1184, found 251.1193.

*3.1.4 3-(4-Methoxyphenyl)-2-methylquinazolin-4(3H)-one (**3d**).*[10b]

(63.8 mg, 53%) as a yellow solid; mp 181-182 ^{o}C; IR (CaF_2): 1683, 1611 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.26-8.23 (m, 1H), 7.76-7.72 (m, 1H), 7.67 (d, *J* = 8.0, 1H), 7.46-7.42 (m, 1H), 7.15 (d, *J* = 8.9, 2H), 7.01 (d, *J* = 8.9, 2H), 3.85 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.4, 160.0, 155.0, 147.0, 134.6, 130.1, 129.0, 127.1, 126.7, 126.5, 120.7, 115.2, 55.5, 24.3; HRMS (ESI-TOF) calcd for $C_{16}H_{15}N_2O_2$ $[M+H]^+$ *m/z* = 267.1134, found 267.1131.

*3.1.5 3-(4-t-Butylphenyl)-2-methylquinazolin-4(3H)-one (**3e**).*

(96 mg, 81%) as a pale yellow solid; mp 174-175 ^{o}C; IR (CaF_2):1742, 1699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.24 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.73 (ddd, *J* = 15.2, 7.6, 1.6 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.54-7.51 (m, 2H), 7.43 (ddd, *J* = 14.8, 7.2, 1.2 Hz, 1H), 7.17-7.13 (m, 2H), 2.23 (s, 3H), 1.35 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.2, 154.6, 152.3, 147.3, 134.9, 134.5, 127.3, 127.0, 126.9, 126.6, 126.5, 120.7, 34.8, 31.3, 24.4; HRMS (ESI-TOF) calcd for $C_{19}H_{21}N_2O$ $[M+H]^+$ *m/z* = 293.1654, found 293.1664.

*3.1.6 3-(4-Chlorophenyl)-2-methylquinazolin-4(3H)-one (**3f**).*[10b]

(40.2 mg, 33%) as a yellow solid; mp 175-176 ^{o}C; IR (CaF_2): 1685, 1604 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.26-8.23 (m, 1H), 7.78-7.74 (m, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.48-7.44 (m, 1H), 7.20 (d, *J* = 8.5 Hz, 2H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.2, 153.7, 147.4, 136.2, 135.4, 134.8, 130.3, 129.5, 127.1, 126.9, 126.8, 120.6, 24.4; HRMS (ESI-TOF) calcd. for $C_{15}H_{12}ClN_2O$ $[M+H]^+$ *m/z* = 271.0638, 273.0653; found 271.0637, 273.0652.

3.1.7 Ethyl 4-(2-methyl-4-oxoquinazolin-4-(3H)-yl)benzoate (***3g***).

(49.9 mg, 44%) as an orange solid; mp 188-189 ^{o}C; IR (CaF_2): 1722, 1693, 1596 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.25-8.22 (m, 3H), 7.79-7.75 (m, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.49-7.45 (m, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 2.23 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.4, 161.7, 153.7, 146.7, 141.3, 134.8, 131.5, 131.3, 128.2, 127.0, 126.9, 126.4, 120.4, 61.4, 24.0, 14.2; HRMS (ESI-TOF) calcd for $C_{18}H_{17}N_2O_3$ $[M+H]^+$ *m/z* =309.1239, found 309.1239.

*3.1.8 2-Methyl-3-(naphthalen-1-yl)quinazolin-4(3H)-one (**3h**).*

(80.1 mg, 67%) as a dark brown solid; mp 211-212 ^{o}C; IR (CaF_2): 1687, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.30-8.28 (m, 1H), 7.99 (d, *J* = 8.4, 1H), 7.94 (d, *J* = 8.4, 1H), 7.82-7.75 (m, 1H), 7.61-7.58 (m, 1H), 7.54-7.42 (m, 5H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.1, 155.0, 147.3, 134.7, 134.5, 134.1, 129.9, 129.6, 128.7, 127.9, 127.2, 126.8, 126.8, 126.7, 126.2, 125.6, 121.3, 120.6, 23.4; HRMS (ESI-TOF) calcd for $C_{19}H_{15}N_2O$ $[M+H]^+$ *m/z* = 287.1184, found 287.1181.

*3.1.9 2-Methyl-3-(2,4,6-trimethylphenyl)quinazolin-4(3H)-one (**3i**).*

(82 mg, 68%) as a white solid; mp 104-105 ^{o}C; IR (CaF_2): 1678, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.27 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.75 (ddd, *J* = 15.4, 7.8, 1.2 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.44 (ddd, *J* = 15.2, 7.8, 1.2 Hz, 1H), 7.01 (s, 2H), 2.33 (s, 3H), 2.13 (s, 3H), 2.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.2, 154.6, 147.7, 139.1, 134.6, 134.5, 133.3, 129.8, 127.2, 126.7, 126.4, 120.7, 23.1, 21.0, 17.5; HRMS (ESI-TOF) calcd for $C_{18}H_{19}N_2O$ $[M+H]^+$ *m/z* = 279.1497, found: 279.1493.

*3.1.10 2-Methyl-3-(3,4,5-trimethoxyphenyl)quinazolin-4(3H)-one **(3j)**.*

(60 mg, 52%) as a pale brown solid; mp 120-121 °C; IR (KBr): 1723, 1674 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.23 (d, *J* = 8.0 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 6.45 (s, 2H), 3.88 (s, 3H), 3.82 (s, 6H), 2.31 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.1, 154.5, 154.1, 147.0, 138.5, 134.7, 133.1, 127.0, 126.7, 126.5, 120.5, 105.1, 60.9, 56.2, 23.8; HRMS (ESI-TOF) calcd for $C_{18}H_{19}N_2O_4$ $[M+H]^+$ *m/z* = 327.1345, found: 327.1346.

*3.1.11 2-Propyl-3-(p-tolyl)quinazolin-4(3H)-one (**3k**).*

(76.2 mg, 56%) as a yellow solid; mp 151-152 °C; IR (CaF_2): 1682, 1594 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.24 (d, *J* = 8.0 Hz, 1H), 7.75-7.67 (m, 2H), 7.44-7.40 (m, 1H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 2.43-2.38 (m, 5H), 1.70 (q, *J* = 7.5 Hz, 2H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.5, 157.1, 147.4, 139.2, 134.6, 134.3, 130.4, 127.9, 127.0, 126.9, 126.4, 120.7, 37.6, 21.2, 20.5, 13.7; HRMS (ESI-TOF) calcd for $C_{18}H_{19}N_2O$ $[M+H]^+$ *m/z* = 279.1497, found 279.1501.

*3.1.12 2-Isopropyl-3-(p-tolyl)quinazolin-4(3H)-one **(3l)**.*

(55.2 mg, 41%) as an orange solid; mp 151-152 °C; IR (CaF_2): 1682, 1604 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.24 (d, *J* = 7.6 Hz, 1H), 7.78-7.74 (m, 2H), 7.45-7.41 (m, 1H), 7.33 (br, 2H), 7.13 (br, 2H), 2.7 (br, 1H), 2.4 (s, 3H), 1.24 (d, *J* = 2.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.6, 162.1, 147.3, 139.2, 134.6, 134.4, 130.5, 128.0, 127.0, 126.9, 126.5, 120.7, 32.3, 21.3; HRMS (ESI-TOF) calcd for $C_{18}H_{19}N_2O$ $[M+H]^+$ *m/z* = m/z 279.1497, found 279.1506.

*3.1.13 2-Phenyl-3-(p-tolyl)quinazolin-4(3H)-one (**3m**).*[13c]

(72.6 mg, 48%) as a pale yellow solid; mp 185-186 °C; IR (CaF_2): 1685, 1604 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.26 (d, *J* = 7.9 Hz, 1H), 7.75-7.69 (m, 2H), 7.45-7.41 (m, 1H), 7.27-7.25 (m, 2H), 7.19-7.11 (m, 3H), 7.02 (d, *J* = 8.1 Hz, 2H), 6.94 (d, *J* = 8.2 Hz, 2H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.3, 155.3, 147.4, 138.2, 135.5, 134.9, 134.6, 129.6, 129.2, 128.9, 128.7, 127.9, 127.6, 127.1, 120.9, 21.1; HRMS (ESI-TOF) calcd for $C_{21}H_{17}N_2O$ $[M+H]^+$ *m/z* = 313.1341, found 313.1335.

*3.1.14 2-Benzyl-3-(p-tolyl)quinazolin-4(3H)-one (**3n**).*[13d]

(84.0 mg, 53%) as a yellow oil; IR (CaF_2): 1684, 1593 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.27-8.25 (m, 1H), 7.77-7.75 (m, 2H), 7.48-7.44 (m, 1H), 7.18-7.14 (m, 5H), 6.89-6.87 (m, 2H), 6.82 (d, *J* = 8.2 Hz, 2H), 3.90 (s, 2H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.6, 155.5, 147.4, 139.1, 135.4, 134.4, 134.2, 130.0, 128.6, 128.3, 128.3, 127.2, 127.0, 126.8, 126.8, 120.9, 42.6, 21.2; HRMS (ESI-TOF) calcd. for $C_{22}H_{19}N_2O$ $[M+H]^+$ *m/z* = 327.1497, found 327.1505.

*3.1.14 2,6-Dimethyl-3-(p-tolyl)quinazolin-4(3H)-one (**3o**).*

(118.1 mg, 92%) as a pale yellow solid; mp 121-122 °C; IR (KBr): 1676, 1596 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.00 (d, *J* = 0.6 Hz, 1H), 7.53-7.52 (m, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 2.43 (s, 3H), 2.40 (s, 3H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.3, 153.4, 145.4, 139.1, 136.5, 135.8, 135.1, 130.5, 127.6, 126.4, 126.3, 120.4, 24.2, 21.1(2C); HRMS (ESI-TOF) calcd. for $C_{17}H_{17}N_2O$ $[M+H]^+$ *m/z* = 265.1314, found 265.1354.

*3.1.15 7-Bromo-2-methyl-3-phenylquinazolin-4(3H)-one (**3p**).*

(103 mg, 63%) as a white solid; mp 173-174 °C; IR (KBr): 1682, 1585 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.01 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 1.6 Hz, 1H), 7.55-7.46 (m, 4H), 7.22 (d, *J* = 7.2 Hz, 2H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.7, 155.6, 148.4, 137.4, 130.0, 129.9, 129.5, 129.4, 129.2, 128.4, 127.8, 119.5, 24.4; HRMS (ESI-TOF) calcd. for $C_{15}H_{12}{}^{79}BrN_2O$ $[M+H]^+$ *m/z* = 315.0133, found 315.0135; HRMS (ESI-TOF) calcd. for $C_{15}H_{12}{}^{81}BrN_2O$ $[M+H]^+$ *m/z* = 317.0113, found 317.0122.

*3.1.16 6,7-dimethoxy-2-methyl-3-phenylquinazolin-4(3H)-one (**3q**).*

(105 mg, 68%) as a brown solid; mp 240-241 °C; IR (KBr): 1675, 1614 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.53-7.44 (m, 4H), 7.23 (d, *J* = 7.2 Hz, 2H), 7.06 (s, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.5, 155.1, 152.9, 148.8, 143.5, 137.8, 129.8, 129.1, 128.0, 113.8, 107.1, 105.9, 56.3, 56.2, 24.0; HRMS (ESI-TOF) calcd. for $C_{17}H_{17}N_2O_3$ $[M+H]^+$ *m/z* = 297.1239, found 297.1237.

*3.1.17 2-methyl-3-(o-tolyl)quinazolin-4(3H)-one (**3r**).*[13a]

(473 mg, 78%) as a white solid; mp 114-115 °C; IR (KBr): 1683, 1598 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.24 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.72 (ddd, *J* = 15.2, 7.6, 1.6 Hz, 1H), 7.65 (dd, *J* = 8.0, 0.4 Hz, 1H), 7.42 (ddd, *J* = 15.0, 7.6, 0.8 Hz, 1H), 7.37-7.30 (m, 3H), 7.12 (d, *J* = 7.2 Hz, 1H), 2.14 (s, 3H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.4, 154.1, 147.5, 136.6, 135.2, 134.4, 131.3, 129.4, 127.8, 127.5, 126.9, 126.6, 126.4, 120.6, 23.7, 17.2; HRMS (ESI-TOF) calcd. for $C_{16}H_{15}N_2O$ $[M+H]^+$ *m/z* = 251.1184, found 251.1181.

*3.1.18 3-([1,1'-biphenyl]-3-yl)-2-methylquinazolin-4(3H)-one (**3s**).*

(89 mg, 81%) as a colorless viscous oil; ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.29-8.26 (m, 1H), 7.69 (ddd, *J* = 15.6, 7.6, 1.6 Hz, 1H), 7.54-7.49 (m, 4H), 7.42 (ddd, *J* = 15.6, 7.4, 1.2 Hz, 1H), 7.29-7.25 (m, 3H), 7.21-7.18 (m, 3H), 2.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.9, 154.0, 147.4, 140.3, 137.8, 135.3, 134.4, 131.5, 129.7, 129.0, 128.8, 128.5, 128.1, 127.8, 127.1, 126.6, 126.4, 120.3, 23.9; HRMS (ESI-TOF) calcd for $C_{21}H_{17}N_2O$ $[M+H]^+$ m/z = 313.1341, found 313.1341.

3.1.19 ethyl 2-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl) acetate (**3t**) and ethyl 2-(4-oxo-3-phenyl-3,4-dihydroquinolin-*2(1H)-ylidene)acetate (**3t'**).*

(108 mg, 68%) as a pale yellow viscous oil; (**3t : 3t'**= 1: 0.33 inseparable mixture); Compound **3t**: ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.28-8.26 (m, 1H), 7.70 (ddd, *J* = 15.2, 7.6, 1.6 Hz, 1H), 7.71-7.69 (m, 1H), 7.56-7.53 (m, 1H), 7.52-7.51 (m, 1H), 7.51-7.50 (m, 1H), 7.49-7.48 (m, 1H), 7.27-7.25 (m, 1H), 7.24-7.23 (m, 1H), 4.07-4.03 (m, 2H), 3.58 (s, 2H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.8, 150.2, 147.2, 136.9, 134.6, 130.1, 129.9, 129.6, 128.5, 128.4 (2C), 127.2, 127.0, 61.5, 42.9, 14.0. Compound **3t'** ^1H NMR ($CDCl_3$, 400 MHz): δ = 12.15 (brs, 0.33 H), 8.05-8.03 (m, 0.33 H), 7.59-7.56 (m, 0.32 H), 7.47-7.46 (m, 0.62 H), 7.22-7.21 (m, 0.33 H), 7.11 (ddd, *J* = 15.2, 7.8, 1.2 Hz, 0.34 H), 7.06 (d, *J* = 8.4 Hz, 0.34 H), 4.11-4.08 (m, 0.67 H), 1.20 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.9, 162.2, 160.2, 153.6, 139.4, 135.7, 135.4, 129.3, 128.3, 127.3, 122.6, 121.1, 115.1, 114.8, 59.3, 14.4; HRMS (ESI-TOF) calcd for $C_{18}H_{17}N_2O_3$ $[M+H]^+$ m/z = 309.1239, found 309.1234.

3.2 Crysatllography.

Crystals suitable for X-ray determination were obtained for **3r** by slow evaporization of a chloroform solution at room temperature. Cell parameters were determined by a Siemens SMART CCD

diffractometer. Crystal data: $C_{16}H_{14}N_2O$, F_w = 250.29, Monoclinic, $P2_1/n$, a = 8.6926(5), b = 15.8320(5) Å, c = 10.0440(5) Å, α = 90, β = 110.282(6)°, γ = 90°, V = 1296.56(12) Å^3, Z = 4, D_{calcd} = 1.282 Mg/m^3, F(000) = 528, crystal size : 0.25 x 0.20 x 0.15 mm^3, 3.8290 to 28.7710°, 7038 reflections collected, 2887 reflections [R(int) = 0.0311], Final R indices [I>2sigma(I)]: R1 = 0.0559, wR2 = 0.1543, for all data R1 = 0.0799, wR2 = 0.1810, Goodness-of-fit on F^2 = 0.937. The structure was solved using the SHELXS-97 program[14] and refined using the SHELXL-97 program[15] by full-matrix least-squares on F2 values. CCDC 1880653 contain the supplementary crystallographic data for complexes **3r**, which can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

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Supplementary Material

Spectra of quinazolinones and crystal data of **3r** are deposited as supplementary material. Supplementary data related to this article can be found at https://doi.org/xxxxxxxxxxxx