Synthesis of C6-Substituted Isoquinolino[1,2-*b*]quinazolines via Rh(III)-Catalyzed C–H Annulation with Sulfoxonium Ylides

Jin Zhang,[†,§,*] Xiaogang Wang,[†,§] Di Chen,[†,‡] Yifan Kang,[†] Yangmin Ma,[†,*] Michal Szostak[†,‖,*]

[†]College of Chemistry and Chemical Engineering, Shaanxi Key Laboratory of Chemical Additives for Industry, Shaanxi University of Science and Technology, Xi'an 710021, China

[‡]School of Food and Biological Engineering, Shaanxi University of Science and Technology, Xi'an 710021, China

[‖]Department of Chemistry, Rutgers University, 73 Warren Street, Newark, New Jersey 07102, United States

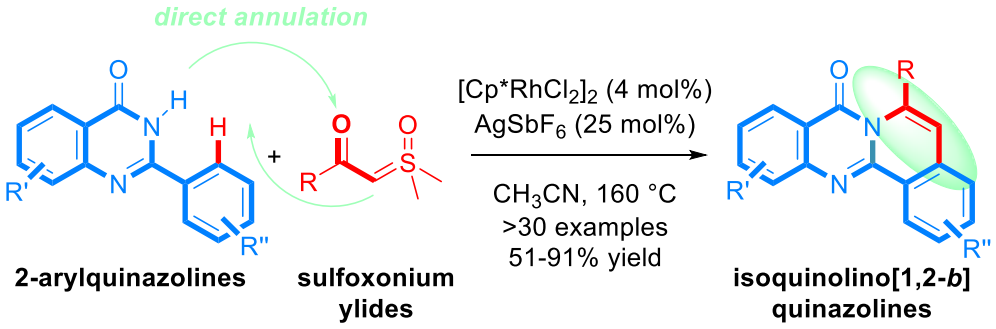
Corresponding author

zhangjin@sust.edu.cn

mym63@sina.com

michal.szostak@rutgers.edu

ABSTRACT



We report the synthesis of C6-substituted isoquinolino[1,2-*b*]quinazolinones via rhodium(III)-catalyzed C–H annulation with sulfoxonium ylides and evaluation of the cytotoxic activity of the scaffold. This C – H activation approach enables the most straightforward and convergent synthesis of C6-substituted isoquinolino[1,2-*b*]quinazolines reported to date. This operationally-simple method is compatible with a wide variety of the sulfoxonium ylide and arene C–H activation coupling partners, permitting access to diverse isoquinolino[1,2-

b]quinazolines. The method shows high atomy economy generating H_2O and DMSO as by-products. The method is scalable and operates with exquisite N-lactam cyclization selectivity, thus enabling expedient access to new heterocyclic analogues featuring promising cytotoxic properties.

1. INTRODUCTION

Isoquinolino[1,2-*b*]quinazolinones represent a class of high value, privileged heterocycles in natural products, drug discovery and advanced organic materials as electroluminescent dopants for light emitting devices (Figure 1).[1–3] However, the efficient synthesis of C6-substituted isoquinolino[1,2-*b*]quinazolinones has been severely underdeveloped to date. The classic way to construct C6-substituted isoquinolino[1,2-*b*]quinazolinones has relied on a sequential N-acylation/condensation of 2-aminopyridines with 2-fluorobenzonitriles and derivatives (Scheme 1A).[4] However, this route is limited by the ability to access functionalized 2-aminopyridine condensation partners, and cannot be used for convergent synthesis required for screening of biological properties.

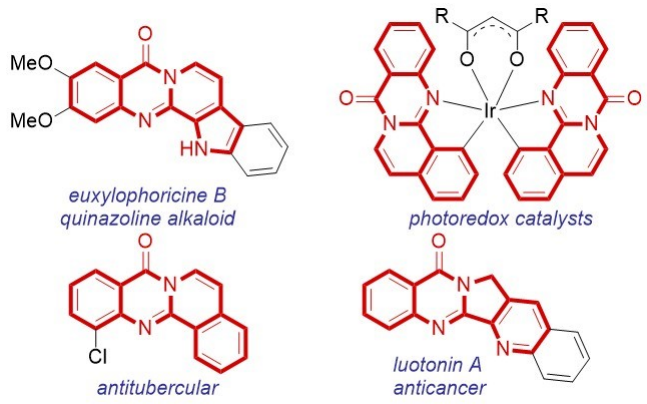
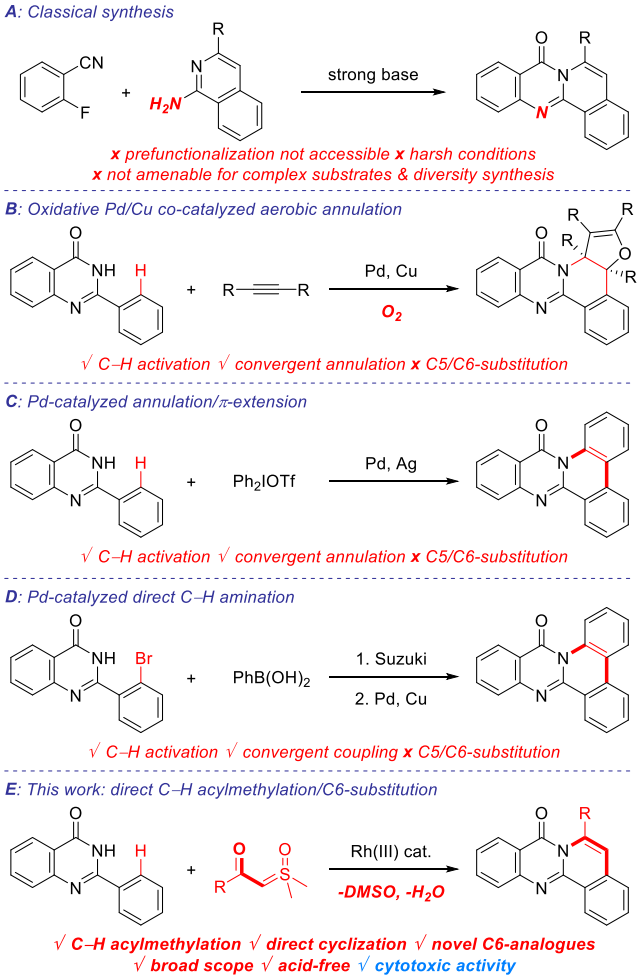


Figure 1. Examples of isoquinolino[1,2-*b*]quinazolines and representative related scaffolds. Note that C6-substituted isoquinolino[1,2-*b*]quinazolines are underrepresented due to the lack of methods for rapid synthesis.

At present, the emergence of powerful cross-coupling and C–H activation reactions has opened up new opportunities to efficiently generate novel heterocycles;[5] however, methods for the efficient, convergent and waste-minimized synthesis of C6-substituted isoquinolino[1,2-*b*]quinazolinones remain unknown.

In the context of the synthetic approaches to isoquinolino[1,2-*b*]quinazolinones, several recent reports have described methods based on annulation of 2-arylquinazolin-4(3*H*)-ones as a privileged heterocyclic motif.[6a] A Pd/Cu-co-catalyzed oxidative annulation in the presence of oxygen delivers C5/C6-dihydrofuran-fused isoquinolino[1,2-*b*]quinazolinones (Scheme 1B).[6b] A Pd-catalyzed annulation of 2-phenylquinazolin-4(3*H*)-ones with diaryliodonium salts furnishes C5/C6-benzene-fused isoquinolino[1,2-*b*]quinazolinones (Scheme 1C).[6c] A Pd-catalyzed direct C–H amination of 2-biphenylquinazolin-4(3*H*)-ones provides access to C5/C6-benzene fused isoquinolino[1,2-*b*]quinazolinones (Scheme 1D).[6d] Methods based on Pd- Pd/Ag-co-catalyzed C–H carbonylation,[6e] Pd-catalyzed intramolecular C–H activation,[6f] Ru-catalyzed C–H allylation/hydroamination,[6g] oxidative Ru(II)-catalyzed annulation,[6h] Ir-catalyzed C–H alkynylation/electrophilic cyclization[6i] and Cu-mediated C–H amination[6j] have accelerated the synthesis of isoquinolino[1,2-*b*]quinazolinones. However, none of these approaches allows for the construction of C6-mono-substituted isoquinolino[1,2-*b*]quinazolinones, a scaffold which has been essential in the development of new anticancer therapeutics.

Scheme 1. Previous studies and this work.



As a part of our program on the synthesis of heterocycles[7] and C–H activation,[8] herein. we report the synthesis of C6-substituted isoquinolino[1,2-*b*]quinazolinones via Rh(III)-catalyzed C–H activation of 2-arylquinazolin-4(3*H*)-ones with sulfoxonium ylides and evaluation of the cytotoxic activity of the scaffold (Scheme 1E). Most crucially, the method allows for the most straightforward and convergent synthesis of C6-mono-substituted isoquinolino[1,2-b]quinazolines reported to date, thus enabling expedient access to new heterocyclic analogues featuring promising cytotoxic properties.

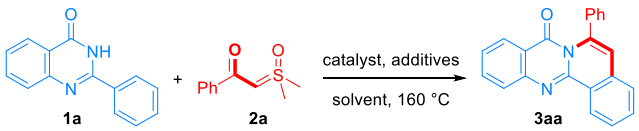
2. RESULTS AND DISCUSSION

The recent years have witnessed significant progress in the development of new C–H activation methods to form C–C(sp^3) bonds.[9,10] Our interest was piqued by the metal-carbene

insertion methods using sulfoxonium ylides.[11–13] These carbene precursors offer several advantages over α-diazo carbonyls, including safe handling, ease of preparation from the corresponding acyl halides using Corey-Chaykovsky reagent,[14] and high reactivity in acylmethylation.[15,16] We hypothesized that following the regioselective C–H acylmethylation, the pendant acyl moiety could be engaged in dehydrative N to C(O) condensation using the amide bond nitrogen to rapidly construct the isoquinolino[1,2-*b*]quinazolinone scaffold. This formal 1C homologation/acylative C–C(sp^3) bond formation would provide a new route to C6-mono-substituted isoquinolino[1,2-*b*]quinazolinones that thus far have been elusive using other C–H activation methods.[1–6]

At the outset of our studies, we investigated the reaction between 2-phenylquinazolin-4(3*H*)-one (**1a**) and sulfoxonium ylide (**2a**) to optimize the reaction conditions (Table 1). To our delight, we found that the catalyst formed from the rhodium dimer $[Cp^*RhCl_2]_2$ (4 mol%) and $AgSbF_6$ (25 mol%) promoted the coupling of (**1a**) and (**2a**) in DCE at 160 °C for 24 h to deliver the desired product (**3aa**) in promising 11% yield in the absence of any other additives (Table, entry 1). With this catalyst system in hand, various solvents were investigated, including EtOH, *n*-PrOH, CH_3CN, *n*-C_3H_7CN (Table 1, entries 2-5), and CH_3CN gave the best results (entry 4). With this solvent, the reaction proceeded efficiently to afford (3aa) in 85% yield (entry 4). Interestingly, reactions performed with other catalysts, such as $Pd(OAc)_2$ and $[Ru(p\text{-cym})Cl_2]_2$ were ineffective (entries 6-7). Other additives to form the cationic Rh(III) also resulted in lower reaction efficiency (entries 8-9). Furthermore, high temperature is required for the efficient reaction (entry 10, 140 °C <10% yield). The use of protic acid additives such as PivOH or $PhCO_2H$ to promote the C–H activation process was unsuccessful (entries 11-12, 24-25% yield).

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

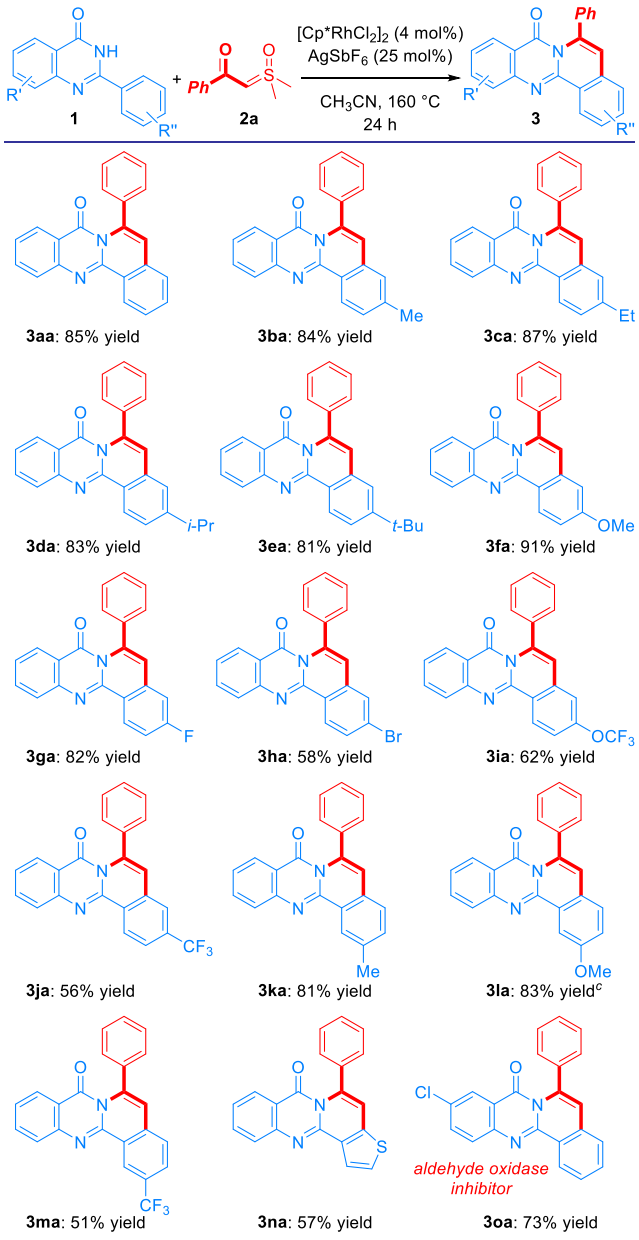
entry	catalyst	additive	solvent	yield (%)
1	$[Cp^*RhCl_2]_2$	$AgSbF_6$	DCE	11
2	$[Cp^*RhCl_2]_2$	$AgSbF_6$	EtOH	35
3	$[Cp^*RhCl_2]_2$	$AgSbF_6$	*n*-PrOH	<5
4	$[Cp^*RhCl_2]_2$	$AgSbF_6$	CH_3CN	85
5	$[Cp^*RhCl_2]_2$	$AgSbF_6$	n-C_3H_7CN	72
6	$Pd(OAc)_2$	$AgSbF_6$	CH_3CN	<5
7	[Ru(*p*-cym)Cl_2]$_2$	$AgSbF_6$	CH_3CN	<5
8	$[Cp^*RhCl_2]_2$	$AgNTf_2$	CH_3CN	65
9	$[Cp^*RhCl_2]_2$	AgOTf	CH_3CN	61
10[b]	$[Cp^*RhCl_2]_2$	$AgSbF_6$	CH_3CN	<10
11[c]	$[Cp^*RhCl_2]_2$	$AgSbF_6$	CH_3CN	24
12[d]	$[Cp^*RhCl_2]_2$	$AgSbF_6$	CH_3CN	25

[a]Conditions: **1a** (1.0 equiv), **2a** (1.2 equiv), catalyst (4 mol%), additive (25 mol%), solvent (0.05 M), 160 °C, 24 h. [b]140 °C. [c]With 1.0 equiv PivOH. [d]With 1.0 equiv $PhCO_2H$.

Next, we explored the scope of this heterocycle synthesis using sulfoxonium ylide (**2a**) as a representative C–H acylmethylating reagent (Scheme 2). As shown, a variety of isoquinolino[1,2-*b*]quinazolinones could be constructed by this method. Crucially, in all cases, full C6-regioselectivity resulting from a nitrogen-directed C–H acylmethylation was observed, leading to a synthetically-useful process. Thus, 2-phenylquinazolin-4(3*H*)-one coupling partners bearing diverse electron-donating groups (**1a-1f**), halides (**1g-1h**), and electron-withdrawing substituents (**1i-1j**) at the para position of the 2-aryl ring worked well and furnished the corresponding products in good to excellent yields. Further, high selectivity at the less hindered site was observed using electronically-differentiated meta-substituted substrates (**1k-1m**),

which resulted in products (**3ka-3ma**) in 51-83% yields. Importantly, the method could also enable C–H annulation of five-membered heterocycles, such as thiophene (**3na**), as well as 6-chloroquinazolinones (**3oa**) that are known as aldehyde oxidase inhibitors.[17] At the present stage of reaction development C4 substituents OH, NH_2 and NO_2 have not been tested. The use of 2-vinylquinazolin-4(3*H*)-ones as substrates will be the subject of future studies.

Scheme 2. Scope of 2-Phenylquinazolin-4(3*H*)-ones.[a,b]

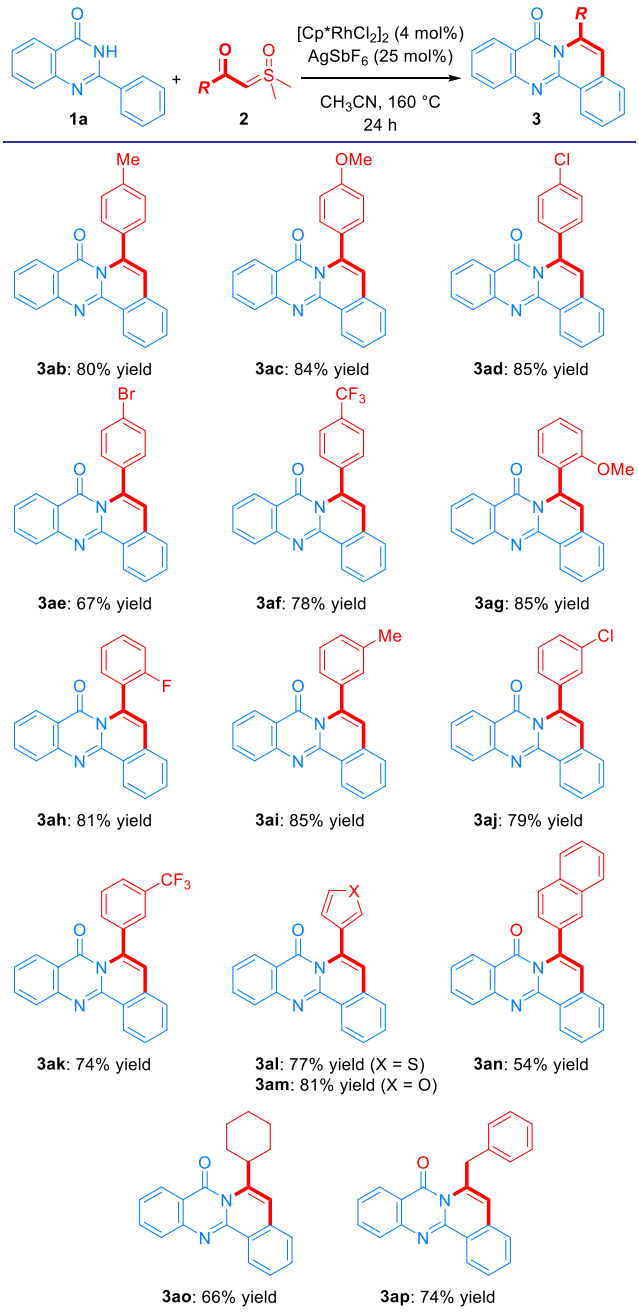


[a]Conditions: **1a** (1.0 equiv), **2a** (1.2 equiv), $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (25 mol%), CH_3CN

(0.05 M), 160 °C, 24 h. [b]Isolated yields. [c]5.3:1 regioisomers. See Supporting Information (SI) for details.

We next evaluated the scope of sulfoxonium ylides in this heterocycle synthesis (Scheme 3). In general, we found that the method is very broad with respect to the sulfoxonium ylide, attesting to the synthetic utility of sulfoxonium carbenes in C–C(sp^3) bond forming reactions.[11–13] Thus, ylides featuring various electron-donating groups (**3ab-3ac**), halides (**3ad-3ae**), and electron-withdrawing substituents (**3af**) enabled regioselective C–H activation and gave the desired products in high yields (67-85%). Furthermore, substitution at the sterically-hindered ortho-position was well-tolerated, affording the desired heterocycles in 81-85% yields (**3ag-3ah**). In addition, meta-substitution is well-compatible (**3ai-3ak**) as are other heterocyclic ring systems, such as thiophene and furan (**3al-3am**), and polyaromatic rings (**3an**), affording the desired products in good yields. Finally, we were pleased to find that the sulfoxonium ylide scope was not limited to aryl substitution, and the reaction also worked well when alkyl substituted sulfoxonium ylides were used (**3ao-3ap**). Overall, the method provides the most straightforward access to the isoquinolino[1,2-*b*]quinazolinone scaffold to date.[1–3] Especially noteworthy is broad scope with respect to both coupling partners and functional group tolerance to sensitive substituents that could be used for further functionalization by traditional cross-coupling methods.

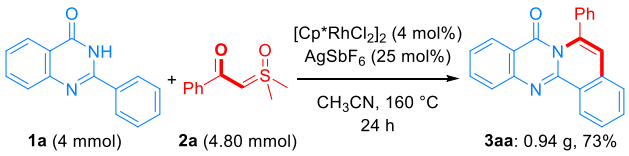
Scheme 3. Scope of Sulfoxonium Ylides.[a,b]



[a]Conditions: **1a** (1.0 equiv), **2a** (1.2 equiv), $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (25 mol%), CH_3CN (0.05 M), 160 °C, 24 h. [b]Isolated yields. See Supporting Information (SI) for details.

The practicality of the method was further evaluated in a gram-scale synthesis (Scheme 4), which produced the expected isoquinolino[1,2-*b*]quinazolinone product (**3aa**) in 73% yield.

Scheme 4. Gram-Scale Synthesis.



The parent 6-phenyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3aa**) was crystalline and we were able to confirm the amidic *N*-cyclization mode by X-ray crystallography (Figure 2). It is interesting to note that the amidic N–C(O) bond (1.421 Å) is only marginally shorter than the isoquinolino N–$C_{(Ar)}$ bond (1.431 Å). The C6 aromatic ring is practically half-twisted (τ = 42.5°) with respect to the isoquinolino[1,2-*b*]quinazolinone ring. Interestingly, the amide bond is moderately twisted (τ = 14.4°; χ_N = 5.6°), with the additive Winkler-Dunitz distortion parameter ($\tau+\chi_N$) of 20.0°.[20]

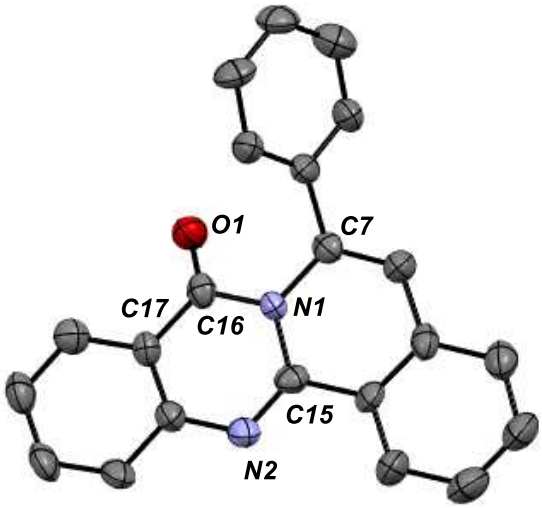


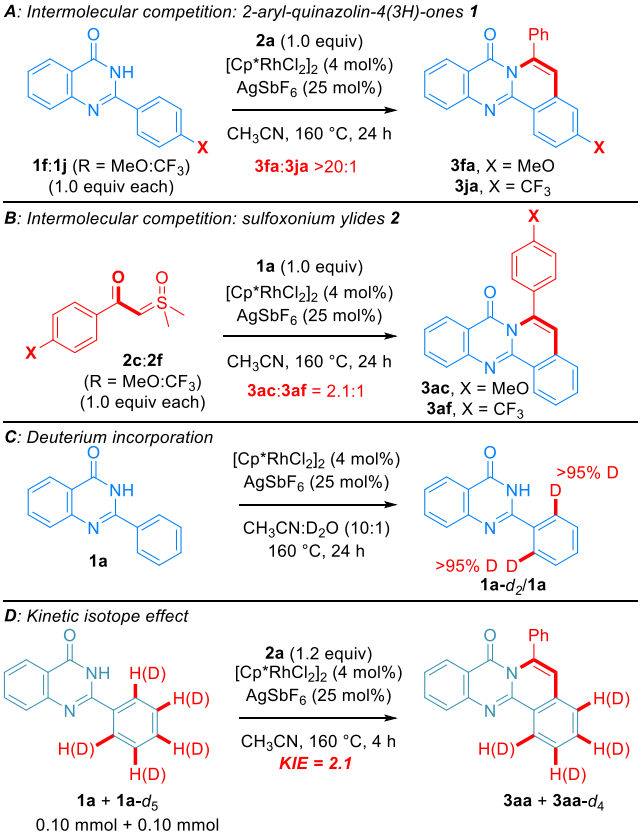
Figure 2. X-ray structure of (**3aa**). Crystallographic data, CCDC No. 1964235.

Next, we became interested to gain insight into the mechanism of this new method (Scheme 5). Intermolecular competition studies between differently substituted 2-phenylquinazolin-4(3*H*)-ones revealed that electron-rich arenes are inherently more reactive than their electron-deficient counterparts (Scheme 5A), consistent with an electrophilic rhodation pathway. Intermolecular competition studies between differently substituted sulfoxonium ylides revealed that electron-rich sulfoxonium ylides react preferentially (Scheme 5B). Deuterium incorporation

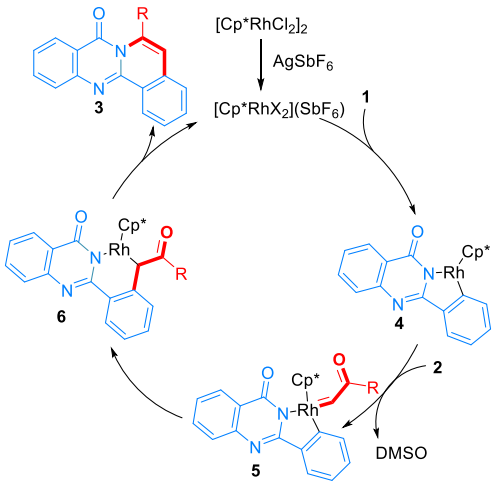
revealed that the cyclometallation step is reversible (Scheme 5C). Note that deuterium incorporation at other positions of the quinazoline ring was not observed. Kinetic isotope effect studies revealed a k_H/k_D value of 2.1 (18% conversion), indicating that the C–H bond cleavage may be involved in the rate-determining step (Scheme 5D). These studies indicate an electrophilic C–H functionalization pathway.[11a,h]

A plausible reaction mechanism is shown in Scheme 6. A cationic [Cp*Rh(III)] complex is generated in the presence of $AgSbF_6$. The N-directed C–H bond activation generates a rhodacyclic intermediate **4**. Coordination of sulfoxonium ylide and α-elimination of DMSO leads to the formation of species **5**. Migratory insertion of the Rh – carbene gives the six-membered metallacycle **6**. Protonolysis of the Rh–alkyl bond and amide N to CO condensation regenerates the active catalyst and delivers the condensation product **3aa**. We tentatively propose that the C–H acylmethylation proceeds via amidorhodium species **4**[18] with the electrophilic cyclodehydration facilitated by activation of the carbonyl group by Lewis acidic Rh(III) via the 6-membered intermediate;[19] however, at this stage imine-directed C–H activation followed by a nitrogen coordination switch cannot be excluded. Note that the reaction affords the linear fused isomer with exquisite selectivity (vs. angular).[5a] It is noteworthy that the reaction proceeds in the absence of additional additives.

Scheme 5. Mechanistic Studies.



Scheme 6. Proposed Catalytic Cycle.



Since the present method delivers isoquinolino[1,2-*b*]quinazolinones that constitute a class of privileged heterocycles well-known for their anticancer properties, we were keen on probing the cytotoxic activity of the synthetized compounds (Table 2). The synthesized products were tested against human lung cancer cells (A549), human breast cancer cells (MDA-MB-231) and

human prostate cancer cells (PC3) (see SI for details).[21] It is worth noting that all compounds showed very good solubility in DMSO; even after diluting by 100 times in water under the highest concentration insoluble residue was not observed. It is likely that the high solubility of these polyaromatics arises from the presence of polar nitrogen moieties. As summarized in Table 2, isoquinolino[1,2-*b*]quinazolinones **3ia**, **3af**, **3am** and **3an** showed promising growth inhibition, and compound **3an** shows a strong inhibitory effect on MDA-MB-231 in the range of cis-platin (**3an**: IC50 = 29.9 uM). Thus, these results highlight the potential of privileged C6-substituted isoquinolino[1,2-b]quinazolines[22] as cytotoxic agents.

Table 2. Cytotoxic Activity of **3aa**-**3ap**.

Entry	$IC_{50}(\mu M)$		
	A549	MDA-MB-231	PC3
3aa	106.6	121.0	161.3
3ba	156.3	>200	>200
3ca	>200	>200	>200
3da	>200	>200	>200
3ea	123.0	> 200	> 200
3fa	>200	154.1	>200
3ga	132.4	118.1	>200
3ha	>200	>200	>200
3ia	58.56	78.67	148.7
3ja	193.3	>200	>200
3ka	>200	>200	>200
3la	143.0	> 200	> 200
3ma	>200	>200	>200
3na	>200	>200	>200
3oa	161.5	> 200	153.5
3ab	137.2	172.6	>200
3ac	>200	>200	>200
3ad	105.2	128.7	>200
3ae	108.4	124.4	>200
3af	20.1	57.0	122.6

3ag	>200	>200	>200
3ah	>200	>200	>200
3ai	>200	>200	>200
3aj	129.1	>200	159.9
3ak	>200	>200	>200
3al	>200	>200	>200
3am	>200	99.42	89.52
3an	>200	29.90	>200
3ao	>200	>200	>200
3ap	>200	>200	>200
Cisplatin	4.969	12.15	70.40

3. **CONCLUSION**

In summary, we have developed a versatile method for the synthesis of C6-substituted isoquinolino[1,2-*b*]quinazolines via rhodium(III)-catalyzed C–H annulation with sulfoxonium ylides. The reaction enables the most straightforward and convergent route to C6-substituted isoquinolino[1,2-*b*]quinazolines reported to date. Further noteworthy features include high atom economy, with H_2O and DMSO by-products, high efficiency and broad scope with respect to both coupling components. Crucially, the potential of this approach for the synthesis of new cytotoxic compounds has been demonstrated. The mono C6-substituted isoquinolino[1,2-*b*]quinazolines show promising cytotoxic activity. Further investigation of the synthesis and biological properties of this class and related quinazolines are underway.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reagents were obtained commercially and used without further purification. Unless otherwise specified, all other reagents were purchased from Aldrich, Fisher or Energy and used without further purification. The NMR spectra were recorded on a Bruker MERCURY plus-400 (400 MHz, ^{1}H NMR; 101 MHz, ^{13}C NMR)

spectrometer with chemical shifts reported in ppm relative to the residual deuterated solvent and the internal standard tetramethylsilane (TMS). Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad singlet, coupling constant(s) in Hz, integration). Chromatography was carried out with silica gel (200-300 mesh) or neutral alumina (200-300 mesh) using mixtures of petroleum ether (b.p. 60-90 °C) and ethyl acetate as eluents. High resolution mass spectra (HRMS) were measured with a Waters Micromass GCT instrument and accurate masses were reported for the molecular ion $[M+H]^+$. The absorbance in each well was measured at 490 nm using an Epoch microplate reader (BioTek, Winooski, VT, USA). The melting point was determined by microscopic melting point meter SGW X-4B. 2-Arylquinazolin-4(3*H*)-ones (**1**)[23] and sulfoxonium ylides (**2**)[11c] were prepared using well-established methods. All Isoquinolino[1,2-*b*]quinazoline products **3** are new compounds unless stated otherwise.

General Procedure for Synthesis of sulfoxonium ylides (2). To a stirred solution of KO*t*-Bu (12.0 mmol) in THF (10 mL) was added trimethylsulfoxonium iodide (9.0 mmol) and the resulting mixture was refluxed for 3 h. The reaction mixture was then cooled to 0 °C, followed by addition of acyl chloride (3.0 mmol) in THF (5 mL). The mixture was warm up to room temperature and stirred for 3 h. Subsequently, the solvent was evaporated under reduced pressure and the reaction mixture was extracted with EtOAc/H_2O three times. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was pure by column chromatography using EtOAc/MeOH(95:5) to afford the sulfoxonium ylides **2**.

General Procedure for Synthesis of isoquinolino[1,2-*b*]quinazolinones. A pressure tube was charged with 2-phenylquinazolin-4(3*H*)-one **1** (0.10 mmol, 1.0 equiv), sulfoxonium

ylide **2** (0.12 mmol, 1.2 equiv), $[Cp^*RhCl_2]_2$ (0.004 mmol, 4 mol%), $AgSbF_6$ (0.025 mmol, 25 mol%) and CH_3CN (0.05 M). The reaction mixture was stirred at 160 °C for 24 h. After cooling to room temperature, the reaction mixture was filtered and volatiles were removed under reduced pressure. The residue was purified by silica gel chromatography using petroleum ether/ethyl acetate to afford the product.

Representative Procedure for Synthesis of Isoquinolino[1,2-*b*]quinazolinones. A pressure tube was charged with 2-phenylquinazolin-4(3H)-one **1a** (889.0 mg, 4.0 mmol, 1.0 equiv), sulfoxonium ylide **2a** (942.1 mg, 4.8 mmol, 1.2 equiv), $[Cp^*RhCl_2]_2$ (98.9 mg, 0.16 mmol, 4 mol%), $AgSbF_6$ (343.6 mg, 1.0 mmol, 25 mol%) and CH_3CN (80 mL, 0.05 M). The reaction mixture was stirred at 160 °C for 24 h. After cooling to room temperature, the reaction mixture was filtered and volatiles were removed under reduced pressure. The residue was purified by silica gel chromatography using petroleum ether/ethyl acetate to afford the product. Yellow solid (940 mg). Yield 73%. Characterization data are included in the section below.

Physical Properties and Characterization Data of the Synthesized Compounds. 6-Phenyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3aa)**, yellow solid (27.4 mg, 85% yield). *New compound.* Mp = 197 – 198 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.09 (d, *J* = 7.6 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.91 – 7.83 (m, 1H), 7.75 (t, *J* = 7.4 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.51 – 7.39 (m, 6H), 6.92 (s, 1H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.8, 147.6, 146.6, 138.3, 138.1, 134.5, 132.4, 132.2, 128.4, 128.0, 127.7 , 127.2, 127.1, 126.8, 126.5, 126.2, 125.7, 119.7, 118.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{15}N_2O^+$: 323.1179, found : 323.1175.

3-Methyl-6-phenyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ba)**, yellow solid (28.2 mg,

84% yield). *New compound.* Mp = 192 – 193 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.87 (d, *J* = 8.2 Hz, 1H), 8.22 (d, *J* = 7.9 Hz, 1H), 7.93 – 7.74 (m, 2H), 7.51 – 7.31 (m, 8H), 6.79 (s, 1H), 2.51 (s, 3H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.9, 147.8, 146.9, 143.0, 138.4, 138.1, 134.4, 132.4, 129.9, 128.0, 127.6, 127.2, 127.1, 126.7, 126.5, 126.1, 125.5, 124.9, 119.6, 118.1, 21.7. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{17}N_2O^+$: 337.1335, found : 337.1332.

3-Ethyl-6-phenyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ca)**, yellow solid (30.4 mg, 87% yield). *New compound.* Mp = 156 – 157 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.81 (d, *J* = 8.3 Hz, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 7.87 – 7.69 (m, 2H), 7.44 – 7.31 (m, 7H), 7.27 (s, 1H), 6.74 (s, 1H), 2.73 (q, *J* = 7.6 Hz, 2H), 1.28 (t, *J* = 7.6 Hz, 3H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.9, 149.0, 147.7, 146.9, 138.5, 138.0, 134.5, 132.5, 128.8, 128.0, 127.7, 127.3, 127.1, 126.7, 126.1, 125.4, 125.2, 125.1, 119.6, 118.3, 28.9, 15.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{24}H_{19}N_2O^+$: 351.1492, found : 351.1488.

3-Isopropyl-6-phenyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3da**), yellow solid (30.2 mg, 83% yield). *New compound.* Mp = 90 – 91 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.88 (d, *J* = 8.4 Hz, 1H), 8.21 (d, *J* = 8.6 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.81 – 7.74 (m, 1H), 7.48 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.38 (m, 7H), 6.82 (s, 1H), 3.05 (p, *J* = 6.9 Hz, 1H), 1.33 (d, *J* = 6.9 Hz, 6H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.9, 153.7, 147.8, 147.0, 138.5, 138.0, 134.4, 132.6, 128.0, 127.6, 127.5, 127.3, 127.1, 126.8, 126.1, 125.5, 125.3, 123.9, 119.6, 118.4, 34.3, 23.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{25}H_{21}N_2O^+$: 365.1648, found : 365.1643.

3-(*tert*-Butyl)-6-phenyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one(**3ea**), yellow solid (30.6 mg, 81% yield). *New compound.* Mp = 153 – 154 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.97 (d, *J* = 8.6 Hz, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 8.01 – 7.84 (m, 2H), 7.74 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.66 –

7.59 (m, 1H), 7.54 – 7.39 (m, 6H), 6.93 (s, 1H), 1.47 (s, 9H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.9, 156.0, 147.7, 147.0, 138.5, 138.0, 134.4, 132.3, 127.9, 127.6, 127.1, 127.1, 126.8, 126.4, 126.1, 125.4, 125.0, 122.8, 119.7, 118.6, 35.2, 31.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{26}H_{23}N_2O^+$: 379.1805, found : 379.1800.

3-Methoxy-6-phenyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3fa**), yellow solid (32.0 mg, 91% yield). *New compound.* Mp = 216 – 217 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.95 (d, *J* = 9.0 Hz, 1H), 8.24 (d, *J* = 7.8 Hz, 1H), 7.91 – 7.79 (m, 2H), 7.43 (m, 6H), 7.22 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.84 (s, 1H), 3.97 (s, 3H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 162.8, 160.9, 147.7, 147.1, 138.7, 138.3, 134.5, 134.3, 129.3, 128.0, 127.7, 127.1, 126.5, 126.1, 125.2, 120.7, 119.3 118.1, 117.3, 108.1, 55.6. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{17}N_2O_2^+$: 353.1285, found : 353.1280.

3-Fluoro-6-phenyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ga**), yellow solid (27.9 mg, 82% yield). *New compound.* Mp = 208 – 209 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.03 (dd, *J* = 8.9, 5.6 Hz, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.84 (q, *J* = 8.5 Hz, 2H), 7.43 (m, 4H), 7.40 – 7.36 (m, 2H), 7.32 (td, *J* = 8.7, 2.4 Hz, 1H), 7.22 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.79 (s, 1H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 166.4, 163.9, 160.7, 146.8 (d, *J* = 45.5 Hz), 139.5, 137.9, 134.7, 134.5 (d, *J* = 10.0 Hz), 130.4 (d, *J* = 9.4 Hz), 128.1, 128.0, 127.1, 126.7, 126.1, 125.8, 123.7, 119.6, 117.1 (d, *J* = 2.9 Hz), 116.8 (d, *J* = 23.2 Hz), 111.9 (d, *J* = 22.4 Hz). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{14}FN_2O^+$: 341.1085, found : 341.1084.

3-Bromo-6-phenyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ha**), yellow solid (23.2 mg, 58% yield). *New compound.* Mp = 271 – 272 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.90 (d, *J* = 9.1 Hz, 1H), 8.25 (d, *J* = 7.9 Hz, 1H), 7.88 (q, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 7.7 Hz, 2H), 7.52 – 7.43 (m,

4H), 7.43 – 7.38 (m, 2H), 6.79 (s, 1H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.7, 147.2, 146.5, 146.5, 139.5, 137.8, 134.7, 133.8, 131.6, 129.0, 128.9, 128.1, 128.0, 127.2, 126.8, 126.1, 119.7, 116.6. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{14}BrN_2O^+$: 401.0284, found : 401.0282.

6-Phenyl-3-(trifluoromethoxy)-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ia**), yellow solid (25.2 mg, 62% yield). *New compound.* Mp = 203 – 204 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.99 (d, *J* = 8.9 Hz, 1H), 8.20 (d, *J* = 7.9 Hz, 1H), 7.80 (d, *J* = 5.8 Hz, 2H), 7.46 – 7.34 (m, 8H), 6.77 (s, 1H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.6, 151.9, 146.7, 146.5, 139.7, 137.8, 136.5, 134.7, 134.0, 129.8, 128.1, 128.0, 127.1, 126.9, 126.1, 126.0, 125.6, 124.3, 120.4 (q, *J* = 260.0 Hz), 116.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{14}F_3N_2O_2^+$: 407.1002, found : 407.0995.

6-Phenyl-3-(trifluoromethyl)-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ja**), yellow solid (21.8 mg, 56% yield). *New compound.* Mp = 243 – 244 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.11 (d, *J* = 8.3 Hz, 1H), 8.23 (d, *J* = 7.9 Hz, 1H), 7.92 – 7.79 (m, 4H), 7.52 – 7.36 (m, 6H), 6.87 (s, 1H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.6, 146.6, 146.3, 139.6, 137.7, 134.8, 133.7 (q, *J* = 33.0 Hz), 132.4, 129.9, 128.2, 128.1, 127.2, 127.0, 126.5, 126.1, 124.4 (q, *J* = 3.3 Hz), 123.6 (q, *J* = 273.8 Hz), 123.6 (q, *J* = 3.9 Hz), 120.0, 118.5, 117.0. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{14}F_3N_2O^+$: 391.1053, found : 391.1050.

2-Methyl-6-phenyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ka**), yellow solid (27.2 mg, 81% yield). *New compound.* Mp = 196 – 197 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.82 (s, 1H), 8.27 (d, *J* = 8.8 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.88 – 7.81 (m, 1H), 7.55 – 7.40 (m, 8H), 6.86 (d, *J* = 2.8 Hz, 1H), 2.60 (s, 3H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.9, 147.7, 146.8, 138.7,

138.4, 137.1, 134.5, 133.6, 130.1, 128.0, 127.6, 127.1, 127.1, 126.9, 126.7, 126.5, 126.1, 125.7, 119.7, 118.1, 21.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{17}N_2O^+$: 337.1335, found : 337.1332.

2-Methoxy-6-phenyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3la**) and 4-methoxy-6-phenyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3la'**). 5.3:1 mixture of regioisomers. Yellow solid (28.9 mg, 82% yield). Major isomer **3la**: *New compound.* Mp = 203 – 204 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.48 (d, *J* = 2.4 Hz, 1H), 8.29 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.89 – 7.83 (m, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.46 (m, 6H), 7.35 (d, *J* = 2.6 Hz, 1H), 6.88 (s, 1H), 4.09 (s, 3H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 161.0, 159.8, 147.4, 146.7, 138.5, 135.9, 134.4, 128.8, 128.1, 128.0, 127.5, 127.1, 126.8, 126.4, 126.2, 126.1, 125.7, 122.1, 119.7, 117.9, 108.1, 55.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{17}N_2O_2^+$: 353.1285, found : 353.1284.

6-Phenyl-2-(trifluoromethyl)-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ma**), yellow solid (19.9 mg, 51% yield). *New compound.* Mp = 245 – 246 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.28 (s, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 7.88 (m, 3H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.51 – 7.36 (m, 6H), 6.86 (s, 1H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.6, 146.7, 146.3, 140.4, 137.7, 134.9, 134.8, 130.2 (q, *J* = 33.2 Hz), 128.3 (q, *J* = 3.5 Hz), 128.2, 128.1, 127.5, 127.1, 127.0, 126.4, 126.1, 124.8 (q, *J* = 4.2 Hz), 123.8 (q, *J* = 273.6 Hz), 119.9, 116.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{14}F_3N_2O^+$: 391.1053, found : 391.1049.

5-Phenyl-7*H*-thieno[3',2':3,4]pyrido[2,1-*b*]quinazolin-7-one (**3na**), yellow solid (18.7 mg, 57% yield). *New compound.* Mp = 202 – 203 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 (d, *J* = 8.2 Hz, 1H), 7.80 (m, 3H), 7.49 – 7.37 (m, 6H), 7.33 (d, *J* = 5.1 Hz, 1H), 7.03 (s, 1H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.8, 147.3, 145.5, 139.9, 139.7, 138.4, 134.7, 133.6, 133.0, 128.0,

127.8, 127.3, 126.4, 126.1, 125.0, 124.7, 118.8, 114.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{13}N_2OS^+$: 329.0743, found : 329.0742.

10-Chloro-6-phenyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3oa**), yellow solid (26.0 mg, 73% yield). *New compound.* Mp = 248 – 249 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.03 (d, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 2.4 Hz, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.81 – 7.74 (m, 2H), 7.72 – 7.66 (m, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.50 – 7.40 (m, 5H), 6.94 (s, 1H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 159.9, 147.9, 145.3, 138.0, 134.9, 132.4, 131.2, 128.5, 128.5, 128.0, 127.8, 127.2, 126.6, 126.3, 126.1, 120.6, 118.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{14}ClN_2O^+$: 357.0789, found : 357.0787.

6-(*p*-Tolyl)-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ab**), yellow solid (26.9 mg, 80% yield). *New compound.* Mp = 189 – 190 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.02 (d, *J* = 8.0 Hz, 1H), 8.28 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.85 (dd, *J* = 8.2, 6.9 Hz, 1H), 7.70 (dt, *J* = 7.6, 1.9 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.58 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.34 – 7.25 (m, 4H), 6.87 (d, *J* = 2.1 Hz, 1H), 2.46 (s, 3H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 161.0, 147.7, 146.8, 138.1, 137.5, 135.4, 134.5, 132.5, 132.2, 128.8, 128.3, 127.3, 127.2, 127.1, 126.8, 126.5, 126.0, 125.7, 119.8, 117.8, 21.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{17}N_2O^+$: 337.1335, found : 337.1334.

6-(4-Methoxyphenyl)-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ac**), yellow solid (29.5 mg, 84% yield). *New compound.* Mp = 218 – 219 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.03 (d, *J* = 8.0 Hz, 1H), 8.27 (d, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 7.72 (t, *J* = 7.4 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.86 (s, 1H), 3.89 (s, 3H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ

161.0, 159.1, 147.8, 146.7, 137.8, 134.5, 132.5, 132.2, 130.7, 128.2, 127.3, 127.2, 127.1, 126.8, 126.4, 125.7, 119.8, 117.6, 113.5, 55.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{17}N_2O_2^+$: 353.1285, found : 353.1285.

6-(4-Chlorophenyl)-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ad**), yellow solid (30.3 mg, 85% yield). *New compound.* Mp = 224 – 225 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.04 (d, *J* = 8.0 Hz, 1H), 8.26 (d, *J* = 8.8 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.90 – 7.84 (m, 1H), 7.75 (td, *J* = 7.5, 1.2 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.44 – 7.39 (m, 2H), 7.37 – 7.32 (m, 2H), 6.87 (s, 1H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.8, 147.5, 146.7, 136.8, 136.8, 134.7, 133.5, 132.4, 132.1, 128.7, 128.3, 127.4, 127.3, 127.1, 126.9, 126.6, 126.0, 119.6, 118.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{14}ClN_2O^+$: 357.0789, found : 357.0789.

6-(4-Bromophenyl)-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ae**), yellow solid (26.8 mg, 67% yield). *New compound.* Mp = 224 – 225 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.01 (d, *J* = 8.0 Hz, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 7.92 – 7.83 (m, 2H), 7.73 (t, *J* = 7.4 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.62 – 7.54 (m, 3H), 7.51 – 7.45 (m, 1H), 7.31 – 7.25 (m, 2H), 6.85 (s, 1H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.8, 147.4, 146.7, 137.3, 136.8, 134.7, 132.3, 132.1, 131.2, 128.7, 127.7, 127.4, 127.2, 127.0, 126.9, 126.6, 125.9, 121.6, 119.5, 118.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{14}BrN_2O^+$: 401.0284, found : 401.0281.

6-(4-(Trifluoromethyl)phenyl)-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3af**), yellow solid (30.4 mg, 78% yield). *New compound.* Mp = 215 – 216 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.02 (d, *J* = 8.0 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 7.86 (m, 2H), 7.74 – 7.63 (m, 4H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.47 (m, 3H), 6.85 (s, 1H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.7, 147.3, 146.8,

141.9, 136.6, 134.7, 132.3, 131.9, 129.5 (q, *J* = 32.8 Hz), 128.9, 128.7, 127.6, 127.3, 127.0, 126.7, 126.4, 126.0, 125.0 (q, *J* = 3.6 Hz), 124.1 (q, *J* = 273.1 Hz), 119.5, 118.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{14}F_3N_2O^+$: 391.1053, found : 391.1055.

6-(2-Methoxyphenyl)-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ag**), yellow solid (29.9 mg, 85% yield). *New compound.* Mp = 200 – 201 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.06 (d, *J* = 7.9 Hz, 1H), 8.27 (d, *J* = 8.8 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.88 – 7.81 (m, 1H), 7.72 (t, *J* = 7.3 Hz, 1H), 7.66 (t, *J* = 7.0 Hz, 1H), 7.63 – 7.55 (m, 2H), 7.49 – 7.41 (m, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.95 – 6.86 (m, 2H), 3.57 (s, 3H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.6, 155.8, 147.3, 146.8, 136.0, 134.2, 132.6, 132.0, 129.3, 128.3, 127.9, 127.6, 127.6, 127.2, 126.9, 126.8, 126.4, 125.5, 120.6, 119.5, 117.7, 109.7, 55.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{17}N_2O_2^+$: 353.1285, found : 353.1285.

6-(2-Fluorophenyl)-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ah**), yellow solid (27.5 mg, 81% yield). *New compound.* Mp = 174 – 175 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.07 (d, *J* = 7.9 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.88 – 7.82 (m, 1H), 7.73 (t, *J* = 7.3 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.45 (m, 2H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.14 – 7.07 (m, 1H), 6.91 (s, 1H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.7, 160.0, 157.5, 146.8 (d, *J* = 31.5 Hz), 134.6, 132.8, 132.2, 132.0, 129.6 (d, *J* = 8.2 Hz), 128.8, 128.1 (d, *J* = 3.2 Hz), 127.7, 127.4, 127.2, 126.9, 126.8, 126.5, 125.9, 124.0 (d, *J* = 3.4 Hz), 119.2, 118.8, 114.7 (d, *J* = 21.3 Hz). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{14}FN_2O^+$: 341.1085, found : 341.1082.

6-(*m*-Tolyl)-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ai**), yellow solid (28.5 mg, 85% yield). *New compound.* Mp = 168 – 169 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.02 (dd, *J* = 7.7, 4.0 Hz, 1H), 8.28 (d, *J* = 7.4 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.85 (dt, *J* = 8.2, 4.1 Hz, 1H), 7.70 (t, *J*

= 7.0 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.58 (t, *J* = 7.1 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.31 – 7.23 (m, 2H), 7.19 (d, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 5.1 Hz, 1H), 2.46 (s, 3H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.9, 147.7, 146.8, 138.3, 138.2, 137.7, 134.5, 132.4, 132.2, 128.6, 128.3, 127.9, 127.3, 127.2, 127.1, 126.8, 126.7, 126.5, 125.7, 123.3, 119.8, 117.9, 21.6. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{17}N_2O^+$: 337.1335, found : 337.1335.

6-(3-Chlorophenyl)-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3aj**), yellow solid (28.1 mg, 79% yield). *New compound.* Mp = 200 – 201 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.03 (d, *J* = 8.0 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 7.93 – 7.84 (m, 2H), 7.77 – 7.70 (m, 1H), 7.71 – 7.64 (m, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.44 (s, 1H), 7.37 (q, *J* = 7.9 Hz, 2H), 7.29 – 7.23 (m, 1H), 6.88 (s, 1H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.7, 147.4, 146.7, 140.0, 136.5, 134.7, 134.0, 132.4, 132.0, 129.2, 128.8, 127.7, 127.4, 127.3, 127.1, 126.9, 126.6, 126.1, 126.0, 124.5, 119.6, 118.5. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{14}ClN_2O^+$: 357.0789, found : 357.0790.

6-(3-(Trifluoromethyl)phenyl)-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ak**), yellow solid (28.1 mg, 79% yield). *New compound.* Mp = 194 – 195 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.04 (d, *J* = 8.0 Hz, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 7.89 (m, 2H), 7.77 – 7.65 (m, 4H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 6.0 Hz, 2H), 7.49 (t, *J* = 7.3 Hz, 1H), 6.89 (s, 1H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.7, 147.3, 146.7, 139.1, 136.4, 134.7, 132.4, 132.0, 130.5 (q. *J* = 32.5 Hz), 129.5, 128.9, 128.3, 127.5, 127.3, 127.0, 127.0, 126.7, 126.0, 124.3 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 273.6 Hz), 122.8 (q, *J* = 3.7 Hz), 119.5, 118.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{14}F_3N_2O^+$: 391.1053, found : 391.1055.

6-(Thiophen-3-yl)-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3al**), yellow solid (25.2 mg, 77%

yield). *New compound.* Mp = 188 – 189 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.99 (d, *J* = 8.0 Hz, 1H), 8.29 (d, *J* = 7.9 Hz, 1H), 7.92 – 7.80 (m, 2H), 7.74 – 7.67 (m, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.42 (d, *J* = 4.9 Hz, 1H), 7.16 – 7.08 (m, 2H), 7.03 (s, 1H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.7, 147.4, 146.5, 139.7, 134.5, 132.2, 132.0, 131.1, 128.7, 127.3, 127.6, 127.1, 126.8, 126.6, 126.6, 125.9, 125.5, 125.3, 119.9, 119.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{13}N_2OS^+$: 329.0743, found : 329.0741.

6-(Furan-3-yl)-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3am**), yellow solid (25.3 mg, 81% yield). *New compound.* Mp = 166 – 167 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.03 (d, *J* = 7.9 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 7.93 – 7.82 (m, 2H), 7.73 (t, *J* = 7.2 Hz, 1H), 7.67 (t, *J* = 7.3 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.55 (s, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.09 (s, 1H), 6.65 (d, *J* = 3.3 Hz, 1H), 6.57 (dd, *J* = 3.0, 1.9 Hz, 1H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.5, 150.6, 147.1, 146.6, 142.5, 134.6, 132.2, 131.9, 128.9, 128.0, 127.5, 127.4, 127.2, 126.9, 126.7, 125.9, 119.6, 118.3, 111.0, 107.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{13}N_2O_2^+$: 313.0972, found : 313.0970.

6-(Naphthalen-2-yl)-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3an**), yellow solid (20.0 mg, 54% yield). *New compound.* Mp = 216 – 217 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.11 (d, *J* = 7.7 Hz, 1H), 8.25 (d, *J* = 8.8 Hz, 1H), 7.98 (d, *J* = 13.1 Hz, 2H), 7.94 – 7.84 (m, 4H), 7.79 – 7.73 (m, 1H), 7.72 – 7.67 (m, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.42 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.02 (s, 1H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 160.8, 147.7, 138.0, 136.0, 134.7, 133.1, 132.7, 132.5, 132.5, 128.6, 128.2, 127.8, 127.4, 127.3, 127.2, 126.7, 126.6, 126.4, 126.2, 125.9, 124.8, 124.2, 119.6, 118.6. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{26}H_{17}N_2O^+$: 373.1335, found : 373.1335.

6-Cyclohexyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ao**), yellow solid (22.3 mg, 68% yield). *New compound.* Mp = 159 – 160 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.90 (d, *J* = 8.0 Hz, 1H), 8.37 (d, *J* = 8.0 Hz, 1H), 7.92 – 7.74 (m, 2H), 7.69 – 7.61 (m, 1H), 7.59 – 7.45 (m, 3H), 6.84 (d, *J* = 2.8 Hz, 1H), 4.01 (tt, *J* = 11.3, 2.7 Hz, 1H), 2.15 (d, *J* = 12.0 Hz, 2H), 1.93 – 1.76 (m, 3H), 1.61 – 1.45 (m, 2H), 1.39 – 1.23 (m, 3H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 162.7, 148.0, 146.5, 146.1, 134.3, 132.7, 131.9, 127.6, 127.1, 126.8, 126.9, 126.6, 125.8, 125.5, 120.2, 112.1, 39.5, 33.8, 26.7, 26.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{21}N_2O^+$: 329.1648, found : 329.1650.

6-Benzyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**3ap**), yellow solid (24.9 mg, 74% yield). *New compound.* Mp = 127 – 128 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.96 (d, *J* = 8.0 Hz, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 5.8 Hz, 2H), 7.72 – 7.63 (m, 1H), 7.59 (t, *J* = 7.0 Hz, 1H), 7.53 – 7.40 (m, 2H), 7.30 – 7.17 (m, 5H), 6.69 (s, 1H), 4.78 (s, 2H). ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ 162.1, 147.8, 146.4, 139.1, 138.5, 134.3, 132.4, 132.0, 129.0, 128.4, 128.0, 127.3, 127.3, 126.9, 126.7, 126.5, 125.8, 125.6, 120.0, 116.7, 41.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{17}N_2O^+$: 337.1335, found : 337.1335.

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra. MTT assay and mechanistic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

zhangjin@sust.edu.cn

mym63@sina.com

michal.szostak@rutgers.edu

Author Contributions

§These authors contributed equally to this work.

ACKNOWLEDGMENT

J.Z. thanks the China Scholarship Council (No. 201808610096). Financial support was provided by the Foundation for Young Scholars of Shaanxi University of Science and Technology (No. BJ12-26). M.S. thanks Rutgers University and the NSF (CAREER CHE-1650766).

REFERENCES

(1) (a) Mhaske, S. B.; Argade, N. P. The Chemistry of Recently Isolated Naturally Occurring Quinazolinone Alkaloids. *Tetrahedron* **2006**, *62*, 9787-9826. (b) Khan, I.; Ibrar, A.; Abbas, N.; Saeed, A. Recent Advances in the Structural Library of Functionalized Quinazoline and Quinazolinone Scaffolds. Synthetic Approaches and Multifarious Applications. *Eur. J. Med. Chem.* **2014**, *76*, 193-244. (c) Kshirsagar, U. A. Recent Developments in the Chemistry of Quinazolinone Alkaloids. *Org. Biomol. Chem.* **2015**, *13*, 9336-9352.

(2) (a) Rakesh, K. P.; Kumara, H. K.; Manukumar, H. M.; Gowda, D. C. Anticancer and DNA Binding Studies of Potential Amino Acids Based Quinazolinone Analogs: Synthesis, SAR and Molecular Docking. *Bioorg. Chem.* **2019**, *87*, 252-264. (b) Sen, T.; Neog, K.; Sarma, S.; Manna, P.; Boruah, H. P. D.; Gogoi, P.; Singh, A. K. Efflux Pump Inhibition by 11H-pyrido[2,1-*b*]quinazolin-11-one Analogues in Mycobacteria. *Bioorg. Med. Chem.* **2018**, *26*, 4942-4951. (c) Ortikov, I. S.; Turdibaev, Z. E.; Islamova, Z. I.; Elmuradov, B. Z.; Abdurazakov, A. S.; Bektemirov, A. M.; Osipova, S. O.; Khushbaktova, Z. A.; Syrov, V. N.; Shakhidoyatov, K. M. Search for Bactericides Among

Derivatives of Deoxyvasicinone, Mackinazolinone, and Thienopyrimidinones. *Pharm. Chem. J.* **2017**, *51*, 456-464. (d) Adepu, R.; Prasad, B.; Ashfaq, M. A.; Ehtesham, N. Z.; Pal, M. New MCR Based on Intramolecular Heck Reaction under Aerobic Conditions: a Direct Access to Cytotoxic Fused N-heterocycles. *RSC Adv.* **2014**, *4*, 49324-49328. (e) Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. Synthesis of Quinazolinones and Quinazolines. *Tetrahedron* **2005**, *61*, 10153-10202. (f) Witt, A.; Bergman, J. Recent Developments in the Field of Quinazoline Chemistry. *Curr. Org. Chem.* **2003**, *7*, 659-677. (g) Hour, M. J.; Huang, L. J.; Kuo, S. C.; Xia, Y.; Bastow, K.; Nakanishi, Y.; Hamel, E.; Ernest, L.; Kuo, H. 6-Alkylamino- and 2,3-Dihydro-3'-methoxy-2-phenyl-4-quinazolinones and Related Compounds: Their Synthesis, Cytotoxicity, and Inhibition of Tubulin Polymerization. *J. Med. Chem.* **2000**, *43*, 4479-4487. (h) Kametani, T.; Chu, V. L.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. IminoKetene Cycloaddition. 2. Total Syntheses of Arborine, Glycosminine, and Rutecarpine by Condensation of Iminoketene with Amides. *J. Am. Chem. Soc.* **1977**, *99*, 2306-2309.

(3) (a) Stoessel, P.; Breuning, E.; Joosten, D. Cyclometalated Pyrimido[2,1-*a*]isoquinoline and Imidazo[2,1-*a*]isoquinoline Metal Complexes as Electroluminescent Dopants for Organic Light-emitting Devices. WO2011044988 **2011**, Apr 21, 2011. (b) Takeuchi, H.; Watanabe, O.; Tanaka, H.; Mouri, M.; Tokito, S.; Mori, T. Organic Electroluminescent Devices. JP2000156288 **2000**, Jun 6, 2000.

(4) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; Wiley-Blackwell: Oxford: 2010.

(5) For selected examples, see: (a) Chen, J.; Natte, K.; Spannenberg, A.; Neumann, H.; Langer, P.; Beller, M.; Wu, X. F. Base-controlled Selectivity in the Synthesis of Linear and Angular Fused Quinazolinones by a Palladium-catalyzed Carbonylation/Nucleophilic Aromatic Substitution

Sequence. *Angew. Chem. Int. Ed.* **2014**, *53*, 7579-7583. (b) Liu, X.; Fu, H.; Jiang, Y.; Zhao, J. A Simple and Efficient Approach to Quinazolinones under Mild Copper-catalyzed Conditions. *Angew. Chem. Int. Ed.* **2009**, *48*, 348-351; (c) Lee, J. B.; Kang, M. E.; Kim, J.; Lee, C. Y.; Kee, J. M.; Myung, K.; Park, J. U.; Hong, S. Y. Direct Diversification of Unmasked Quinazolin-4(3*H*)-ones through Orthogonal Reactivity Modulation. *Chem. Commun.* **2017**, *53*, 10394-10397; (d) Yang, Y.; Zhu, C.; Zhang, M.; Huang, S.; Lin, J.; Pan, X.; Su, W. Condensation of Anthranilic Acids with Pyridines to Furnish Pyridoquinazolones via Pyridine Dearomatization. *Chem. Commun.* **2016**, *52*, 12869-12872. (e) Servais, A.; Azzouz, M.; Lopes, D.; Courillon, C.; Malacria, M. Radical Cyclization of *N*-acylcyanamides: Total Synthesis of Luotonin A. *Angew. Chem. Int. Ed.* **2007**, *46*, 576-579.

(6) For a recent review, see: (a) Wang, D.; Gao, F. Quinazoline derivatives: synthesis and bioactivities. *Chem. Cent. J.* **2013**, *7*, 95 (b) Feng, Y.; Tian, N.; Li, Y.; Jia, C.; Li, X.; Wang, L.; Cui, X. Construction of Fused Polyheterocycles through Sequential [4 + 2] and [3 + 2] Cycloadditions. *Org. Lett.* **2017**, *19*, 1658-1661. (c) Lee, J. B.; Kang, M. E.; Kim, J.; Lee, C. Y.; Kee, J. M.; Myung, K.; Park, J. U.; Hong, S. Y. Direct diversification of unmasked quinazolin-4(3*H*)-ones through orthogonal reactivity modulation. *Chem. Commun.* **2017**, *53*, 10394-10397. (d) Banerji, B.; Bera, S.; Chatterjee, S.; Killi, S. K.; Adhikary, S. Regioselective Synthesis of Quinazolinone-/Phenanthridine-Fused Heteropolycycles by Pd-Catalyzed Direct Intramolecular Aerobic Oxidative C-H Amination from Aromatic Strained Amides. *Chem. Eur. J.* **2016**, *22*, 3506-3512. (e) Rao, D. N.; Rasheed, S.; Das, P. Palladium/Silver Synergistic Catalysis in Direct Aerobic Carbonylation of C(sp2)−H Bonds Using DMF as a Carbon Source: Synthesis of Pyrido-Fused Quinazolinones and Phenanthridinones. *Org. Lett.* **2016**, *18*, 3142-3145. (f) Gupta, P. K.; Yadav, N.; Jaiswal, S.; Asad, M.; Kant, R.; Hajela, K. Palladium-Catalyzed Synthesis of

Phenanthridine/Benzoxazine-Fused Quinazolinones by Intramolecular C-H Bond Activation. *Chem. Eur. J.* **2015**, *21*, 13210-13215. (g) Bairy, G.; Das, S.; Begam, H. M.; Jana, R. Exceedingly Fast, Direct Access to Dihydroisoquinolino[1,2‑b]quinazolinones through a Ruthenium(II)-Catalyzed Redox-Neutral C–H Allylation/Hydroamination Cascade. *Org. Lett.* **2018**, *20*, 7107-7112. (h) Lu, H.; Yang, Q.; Zhou, Y.; Guo, Y.; Deng, Z.; Ding, Q.; Peng. Y. Cross-coupling/annulations of quinazolones with alkynes for access to fused polycyclic heteroarenes under mild conditions. *Org. Biomol. Chem.* **2014**, *12*, 758-764. (i) Rohokale, R. S.; Kalshetti, R. G.; Ramana, C. V. Iridium(III)-Catalyzed Alkynylation of 2‑(Hetero)arylquinazolin-4-one Scaffolds via C–H Bond Activation. *J. Org. Chem.* **2019**, *84*, 2951-2961. (j) Liu, J.; Zou, J.; Yao, J.; Chen, G. Copper-Mediated Tandem C(sp2)-H Amination and Annulation of Arenes with 2-Aminopyridines: Synthesis of Pyrido-fused Quinazolinone Derivatives. *Adv. Synth. Catal.* **2018**, *360*, 659-663.

(7) For selected studies, see: (a) Nareddy, P.; Jordan, F.; Brenner-Moyer, S. E.; Szostak, M. Ruthenium(II)-Catalyzed Regioselective C-H Arylation of Cyclic and *N*,*N*-Dialkyl Benzamides with Boronic Acids by Weak Coordination. *ACS Catal.* **2016**, *6*, 4755-4759. (b) Nareddy, P.; Jordan, F.; Szostak, M. Highly Chemoselective Ruthenium(II)-catalyzed Direct Arylation of Cyclic and *N*, *N*-Dialkyl Benzamides with Aryl Silanes. *Chem. Sci.* **2017**, *8*, 3204-3210. (c) Zhang, J.; Zhuang, Y.; Ma, Y.; Yang, X. and Szostak, M. Palladium-Catalyzed Synthesis of Benzothiophenes via Cross-Dehydrogenative Coupling of 4-Arylthiocoumarins and Pyrones. *Adv. Synth. Catal.* **2019**, *361*, 5709-5714.

(8) For representative studies from our laboratory, see: (a) Zhang, J.; Hou, Y.; Ma, Y.; Szostak, M. Synthesis of Amides by Mild Palladium-Catalyzed Aminocarbonylation of Arylsilanes with Amines Enabled by Copper(II) Fluoride. *J. Org. Chem.* **2019**, *84*, 338-345. (b) Wang, X.; Zhang, J.;

Chen, D.; Wang, B.; Yang, X.; Ma, Y.; Szostak, M. Rh(III)-Catalyzed C-H Amidation of 2-Arylindoles with Dioxazolones: A Route to Indolo[1,2-*c*]quinazolines. *Org. Lett.* **2019**, *21*, 7038-7043. (c) Chen, P.; Nan, J.; Hu, Y.; Ma, Q.; Ma, Y. RuII-Catalyzed/NH_2-Assisted Selective Alkenyl C-H [5+1] Annulation of Alkenylanilines with Sulfoxonium Ylides to Quinolines. *Org. Lett.* **2019**, *21*, 4812-4815.

(9) For selected reviews on C–H activation, see: (a) *Science of Synthesis: Catalytic Transformations via C–H Activation*, Yu, J. Q., Ed.; Thieme: Stuttgart, 2015. (b) Davies, H. M. L.; Morton, D. Recent Advances in C–H Functionalization. *J. Org. Chem.* **2016**, *81*, 343-350. (c) Rossi, R.; Bellina, F.; Lessi, M.; Manzini, C. Cross-Coupling of Heteroarenes by C-H Functionalization: Recent Progress towards Direct Arylation and Heteroarylation Reactions Involving Heteroarenes Containing One Heteroatom. *Adv. Synth. Catal.* **2014**, *356*, 17-117. (d) Rouquet, G.; Chatani, N. Catalytic functionalization of C(sp^2)-H and C(sp^3)-H bonds by using bidentate directing groups. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726-11743. (e) Yeung, C. S.; Dong, V. M. Catalytic Dehydrogenative Cross-Coupling: Forming Carbon–Carbon Bonds by Oxidizing Two Carbon–Hydrogen Bonds. *Chem. Rev.* **2011**, *111*, 1215-1292. (f) Lyons, T.; Sanford, M. Palladium-Catalyzed Ligand-Directed C–H Functionalization Reactions. *Chem. Rev.* **2010**, *110*, 1147-1169. (g) Ackermann, L.; Vicente, R.; Kapdi, A. R. Transition-metal-catalyzed direct arylation of (hetero)arenes by C-H bond cleavage. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826. (h) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition Metals for C–H Activation. *Chem. Rev.* **2019**, *119*, 2192-2452. (i) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Farooq Zia, M.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. A Comprehensive Overview of Directing Groups Applied in Metal-catalysed C–

H Functionalisation Chemistry. *Chem. Soc. Rev.* **2018**, *47*, 6603-6743.

(10) For a review on C–H alkylation reactions, see: Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. Transition-Metal-Catalyzed C-H Alkylation Using Alkenes. *Chem. Rev.* **2017**, *117*, 9333-9403.

(11) (a) Xu, Y.; Zhou, X.; Zheng, G.; Li, X. Sulfoxonium Ylides as a Carbene Precursor in Rh(III)-Catalyzed C-H Acylmethylation of Arenes. *Org. Lett.* **2017**, *19*, 5256-5259. (b) Xu, Y.; Zheng, G.; Yang, X.; Li, X. Rhodium(III)-catalyzed Chemodivergent Annulations between N-Methoxybenzamides and Sulfoxonium Ylides via C-H Activation. *Chem. Commun.* **2018**, *54*, 670-673. (c) Zheng, G.; Tian, M.; Xu, Y.; Chen, X.; Li, X. Rhodium(III)-catalyzed Annulative Coupling between Arenes and Sulfoxonium Ylides via C-H Activation. *Org. Chem. Front.* **2018**, *5*, 998-1002. (d) Barday, M.; Janot, C.; Halcovitch, N. R.; Muir, J.; Aissa, C. Cross-Coupling of α-Carbonyl Sulfoxonium Ylides with C-H Bonds. *Angew. Chem. Int. Ed.* **2017**, *56*, 13117-13121. For additional studies on Rh(III)-catalyzed C–H functionalization with sulfoxonium ylides, see: (e) Vaitla, J.; Bayer, A. Sulfoxonium Ylide Derived Metal Carbenoids in Organic Synthesis. *Synthesis* **2019** *51*, 612-628. (f) Wu, X.; Sun, S.; Yu, J. T.; Cheng, J. Recent Applications of α-Carbonyl Sulfoxonium Ylides in Rhodium- and Iridium-Catalyzed C–H Functionalizations. *Synlett* **2019**, *30*, 21-29. (g) Chen, G.; Zhang, X.; Jia, R.; Li, B.; Fan, X. Selective Synthesis of Benzo[*a*]Carbazoles and Indolo[2,1-*a*]-Isoquinolines via Rh(III)-Catalyzed C−H Functionalizations of 2-Arylindoles with Sulfoxonium Ylides. *Adv. Synth. Catal.* **2018**, *360*, 3781-3787. (h) Yang, R.; Wu, X.; Sun, S.; Yu, J. T.; Cheng, J. Rhodium-Catalyzed Annulation of 2-Arylimidazoles and α-Aroyl Sulfoxonium Ylides toward 5-Arylimidazo[2,1-a]isoquinolines. *Synthesis* **2018**, *50*, 3487-3492.

(12) For reviews, see: (a) Kaiser, D.; Klose, I.; Oost, R.; Neuhaus, J.; Maulide, N. Bond-Forming

and -Breaking Reactions at Sulfur(IV): Sulfoxides, Sulfonium Salts, Sulfur Ylides, and Sulfinate Salts. *Chem. Rev.* **2019**, *119*, 8701-8780. (b) Neuhaus, J. D.; Oost, R.; Merad, J.; Maulide, N. Sulfur-Based Ylides in Transition-Metal-Catalysed Processes. *Top. Curr. Chem.* **2018**, *376*, 15.

(13) For additional representative examples, see: (a) Ji, S.; Yan, K.; Li, B.; Wang, B. Cp*Co(III)-Catalyzed C-H Acylmethylation of Arenes by Employing Sulfoxonium Ylides as Carbene Precursors. *Org. Lett.* **2018**, *20*, 5981-5984. (b) Halskov, K. S.; Witten, M. R.; Hoang, G. L.; Mercado, B. Q.; Ellman, J. A. Rhodium(III)-Catalyzed Imidoyl C-H Activation for Annulations to Azolopyrimidines. *Org. Lett.* **2018**, *20*, 2464-2467. (c) Wu, X.; Xiong, H.; Sun, S.; Cheng, J. Rhodium-Catalyzed Relay Carbenoid Functionalization of Aromatic C-H Bonds toward Fused Heteroarenes. *Org. Lett.* **2018**, *20*, 1396-1399. (d) Neuhaus, J. D.; Bauer, A.; Pinto, A.; Maulide, N. A Catalytic Cross-Olefination of Diazo Compounds with Sulfoxonium Ylides. *Angew. Chem. Int. Ed.* **2018**, *57*, 16215-16218. (e) Li, C.; Li, M.; Zhong, W.; Jin, Y.; Li, J.; Wu, W.; Jiang, H. Palladium-Catalyzed Oxidative Allylation of Sulfoxonium Ylides: Regioselective Synthesis of Conjugated Dienones. *Org. Lett.* **2019**, *21*, 872-875. (f) Talero, A. G.; Martins, B. S.; Burtoloso, A. C. B. Coupling of Sulfoxonium Ylides with Arynes: A Direct Synthesis of Prochiral Aryl Ketosulfoxonium Ylides and Its Application in the Preparation of α-Aryl Ketones. *Org. Lett.* **2018**, *20*, 7206-7211. For further examples, see: (g) Lou, J.; Wang, Q.; Zhou, Y. G.; Yu, Z. Rhodium(III)-Catalyzed Annulative Coupling of Sulfoxonium Ylides and Allenoates: An Arene C–H Activation/Cyclopropanation Cascade. *Org. Lett.* **2019**, *21*, 9217-9222. (h) Hanchate, V.; Kumar, A.; Prabhu, K. R. Synthesis of Naphthols by Rh(III)-Catalyzed Domino C–H Activation, Annulation, and Lactonization Using Sulfoxonium Ylide as a Traceless Directing Group. *Org. Lett.* **2019**, *21*, 8424-8428. (i) Lv, N.; Chen, Z.; Liu, Z.; Zhang, Y. Redox-Neutral Rhodium(III)-Catalyzed Annulation of Arylhydrazines with

Sulfoxonium Ylides To Synthesize 2-Arylindoles. *J. Org. Chem.* **2019**, *84*, 13013-13021. (j) Li, H.; Wu, C.; Liu, H.; Wang, J. Ruthenium(II)-Catalyzed C–H Acylmethylation between (Hetero)arenes and α-Cl Ketones/Sulfoxonium Ylides. *J. Org. Chem.* **2019**, *84*, 13262-13275. (k) Xie, H.; Lan, J.; Gui, J.; Chen, F.; Jiang, H.; Zeng, W. Ru(II)-Catalyzed Coupling-Cyclization of Sulfoximines with alpha-Carbonyl Sulfoxonium Ylides as an Approach to 1,2-Benzothiazines. *Adv. Synth. Catal.* **2018**, *360*, 3534-3543.

(14) Szostak, M.; Aubé, J. Corey-Chaykovsky Epoxidation of Twisted Amides: Synthesis and Reactivity of Bridged Spiro-epoxyamines. *J. Am. Chem. Soc.* **2009**, *131*, 13246-13247.

(15) Candeias, N. R.; Paterna, R.; Gois, P. M. P. Homologation Reaction of Ketones with Diazo Compounds. *Chem. Rev.* **2016**, *116*, 2937-2981, and references cited therein.

(16) For a recent representative synthesis, see: Yuan, Y.; Wu, X. F. Direct Access to 1,1-Dicarbonyl Sulfoxonium Ylides from Aryl Halides or Triflates: Palladium-Catalyzed Carbonylation. *Org. Lett.* **2019**, *21*, 5310-5314.

(17) Barr, J. T.; Jones, J. P. Inhibition of Human Liver Aldehyde Oxidase: Implications for Potential Drug-Drug Interactions. *Drug. Metab. Dispos.* **2011**, *39*, 2381-2386.

(18) (a) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. Rhodium-Catalyzed Oxidative Coupling/Cyclization of 2-Phenylindoles with Alkynes via C-H and N-H Bond Cleavages with Air as the Oxidant. *Org. Lett.* **2010**, *12*, 2068-2071. (b) Yamauchi, D.; Nishimura, T.; Yorimitsu, H. Asymmetric Hydroarylation of Vinyl Ethers Catalyzed by a Hydroxoiridium Complex: Azoles as Effective Directing Groups. *Chem. Commun.* **2017**, *53*, 2760-2763.

(19) For a review on Lewis acid accelerated amidations, see: Marcia de Figueiredo, R.; Suppo, J. S.; Campagne, J. M. Nonclassical Routes for Amide Bond Formation. *Chem. Rev.* **2016**, *116*,

12029-12122.

(20) (a) Szostak, R.; Szostak, M. Chemistry of Bridged Lactams: Recent Developments. *Molecules* **2019**, *24*, 274. (b) Szostak, R.; Aubé, J.; Szostak, M. An Efficient Computational Model to Predict Protonation at the Amide Nitrogen and Reactivity along the C–N Rotational Pathway. *Chem. Commun.* **2015**, *51*, 6395-6398.

(21) (a) Dadashpour, S.; Emami, S. Indole in the target-based design of Anticancer Agents: A Versatile Scaffold with Diverse Mechanisms. *Eur. J. Med. Chem.* **2018**, *150*, 9-29. (b) Ouyang, B.; Knauf, J. A.; Smith, E. P.; Zhang, L.; Ramsey, T.; Yusuff, N.; Batt, D.; Fagin, J. A. Inhibitors of Raf Kinase Activity Block Growth of Thyroid Cancer Cells with RET/PTC or BRAF Mutations In vitro and In vivo. *Clin. Cancer Res.* **2006**, *12*, 1785-1793. (c) Casni, A.; Scozzafava, A.; Mastrolorenzo, A.; Supuran, C. T. Sulfonamides and Sulfonylated Derivatives as Anticancer Agents. *Curr. Cancer Drug Targets* **2002**, *2*, 55-75.

(22) Jafari, E.; Khajouei, M. R.; Hassanzadeh, F.; Hakimelahi, G. H.; Khodarahmi, G. A. Quinazolinone and Quinazoline Derivatives: Recent Structures with Potent Antimicrobial and Cytotoxic Activities. *Res. Pharm. Sci.* **2016**, *11*, 1-14.

(23) Kim, N. Y.; Cheon, C. H. Synthesis of Quinazolinones from Anthranilamides and Aldehydes via Metal-free Aerobic Oxidation in DMSO. *Tetrahedron Lett.* **2014**, *55*, 2340-2344.