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Copper-Catalyzed C-O Bond Cleavage and Cyclization: Synthesis of Indazolo[3,2-*b*]quinazolinones†

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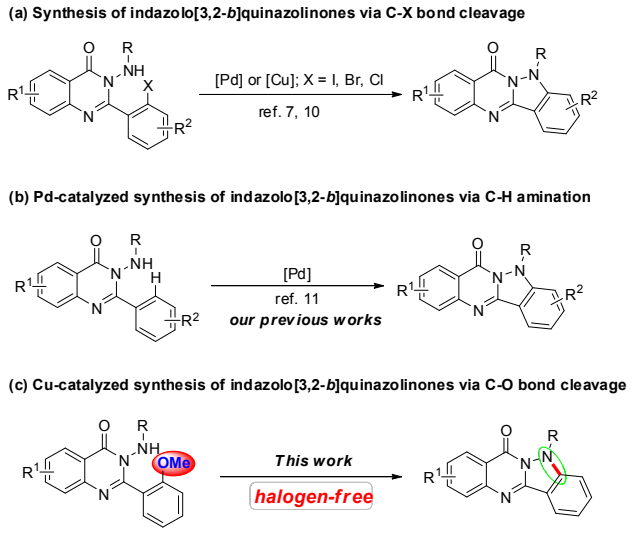
The first example of copper-catalyzed halogen-free protocol to construct indazolo[3,2-*b*]quinazolinones was developed through sequential inert C-O bond cleavage followed by an intramolecular C-N bond formation. This protocol represents an efficient synthetic tool for accessing a more diverse array of functionalized indazolo[3,2-*b*]quinazolinones. The structure of the newly synthesized indazolo[3,2-*b*]quinazolinones was unambiguously confirmed by X-ray crystal diffraction analysis.

Introduction

As an important class of nitrogen-containing heterocycles, fused quinazolinone polyheterocycles have been shown to be an important class of alkaloids, such as luotonin A,[1] cruciferane,[2] circumdatins,[3] rutaecarpine,[4] vasicinone,[5] and tryptanthrin,[6] *etc.* In particular, the combined molecules of indazole and quinazolinone skeletons, indazolo[3,2-*b*]quinazolinones, are important biological molecules and potent inhibitors of phosphodiesterase 4 (PDE4).[7] Furthermore, indazolo[3,2-*b*]quinazoline is a promising new class of small-molecule fluorophores.[8] Recently, we have demonstrated that indazolo[3,2-*b*]quinazolinones could act as anti-tumor agents in hepatocellular carcinoma cell line, probably through inhibiting the cytoprotective aspect of the Nrf_2/ARE signaling pathway and inducing apoptosis via inflicting injury to the mitochondria.[9] However, the synthesis of indazolo[3,2-*b*]quinazolinones are still rarely been investigated. To the best of our knowledge, only two different types of model reaction have been developed leading to indazolo[3,2-*b*]quinazolinones.[7,10-11] First, Pal,[7] Wang,[10a] and our group[10b] have independently reported the classic methods for the preparation of indazolo[3,2-*b*]quinazolinone derivatives by transition-metal-catalyzed cross-coupling reactions of halogenated substrates via the C-X (X = I, Br or Cl) bond cleavage (Scheme 1a). Second, we recently reported palladium-catalyzed synthesis of indazolo[3,2-*b*]quinazolinones involving intramolecular aerobic oxidative C-H amination of 2-aryl-3-(arylamino)quinazolinones (Scheme 1b).[11]

In recent years, the use of phenol derivates as aryl C(sp^2)–O electrophiles in cross-coupling reactions have attracted broad interest.[12] On the other hand, palladium catalyst is very expensive compared with the corresponding copper catalyst. This work forms part of the continuing efforts in our laboratory toward the development of new methods for copper-catalyzed chemistry[13] and the synthesis of quinazolinone derivatives.[14] we herein report a novel halogen-free copper-catalyzed intramolecular cross-coupling reactions of quinazolinone-based aromatic ethers by the cleavage of inert C–O bond and cyclization event to afford indazolo[3,2-*b*]quinazolinone derivatives (Scheme 1c). Facile access to such ring systems which possess diverse functional groups would be of high value to both synthetic and medicinal chemistry.



Scheme 1 Strategies for the Synthesis of Indazolo[3,2-*b*]quinazolinones.

Results and discussion

The study was initiated by examining the conversion of 2-(2-methoxyphenyl)-3-(phenylamino)quinazolinone (**1a**) into 5-

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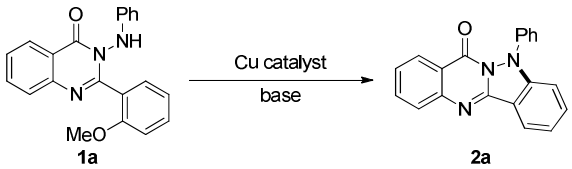
phenylindazolo[3,2-*b*]quinazolinone (**2a**) using copper catalysis (Table 1).

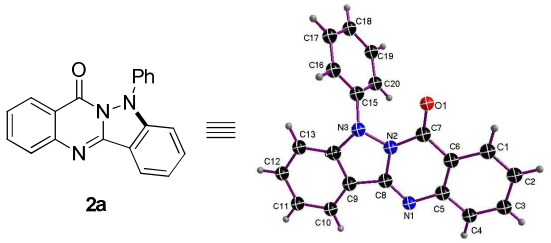
Table 1 Optimization of the reaction conditions[a]



Entry	Cu catalyst	Base	Solvent	Yield (%)[b]
1	$Cu(OAc)_2$	Cs_2CO_3	DMF	60 (43)[c]
2	$Cu(OAc)_2$	K_2CO_3	DMF	19
3	$Cu(OAc)_2$	$NaHCO_3$	DMF	trace
4	$Cu(OAc)_2$	DABCO	DMF	trace
5	$Cu(OAc)_2$	NaOH	DMF	0
6	$Cu(OAc)_2$	^{t}BuOK	DMF	79
7	**$Cu(OAc)_2$**	**^{t}BuOK**	**DMA**	**91**
8	$Cu(OAc)_2$	^{t}BuOK	DMSO	75
9	$Cu(OAc)_2$	^{t}BuOK	CH_3CN	33
10	$Cu(OTf)_2$	^{t}BuOK	DMA	62
11	$Cu(acac)_2$	^{t}BuOK	DMA	55
12	$CuCl_2$	^{t}BuOK	DMA	70
13	$CuBr_2$	^{t}BuOK	DMA	67
14	CuI	^{t}BuOK	DMA	48
15	$Cu(OAc)_2$	^{t}BuOK	DMA	31[d]
16	$Cu(OAc)_2$	^{t}BuOK	DMA	60[e]
17		^{t}BuOK	DMA	trace
18	$Cu(OAc)_2$		DMA	0

[a] Unless otherwise noted, the reaction conditions were as follows: **1a** (0.2 mmol), Cu catalyst (0.04 mmol), base (0.2 mmol), MS 4 Å (60 mg) and solvent (5 mL), air, 120 °C, 48 h. [b] Isolated yield. [c] without MS 4 Å. [d]Under O_2 atmosphere. [e]Under N_2 atmosphere.

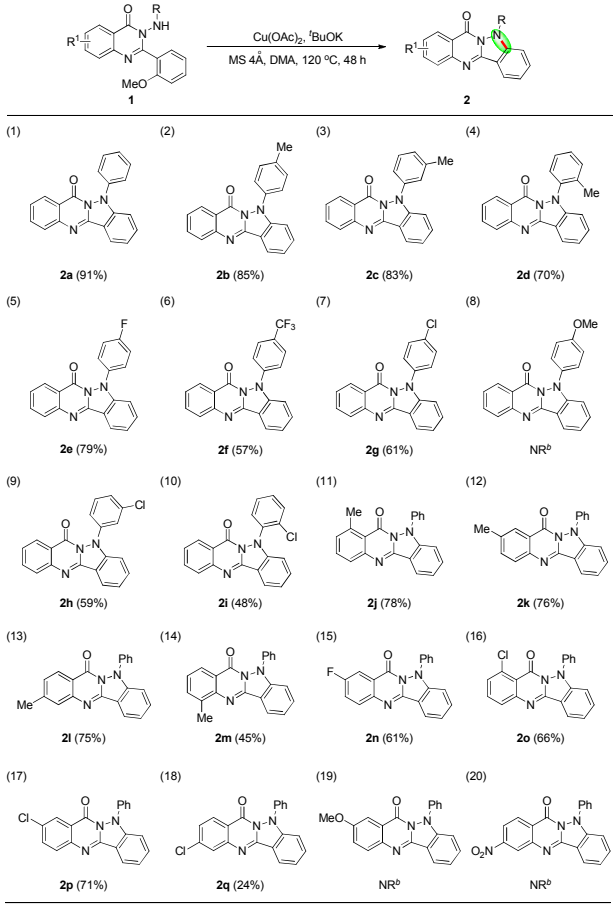
After an initial screen using $Cu(OAc)_2$ as a catalysts with different bases and solvents, we were delighted to find that the desired product 5-phenylindazolo[3,2-*b*]quinazolinone (**2a**) was isolated in 43% yield when $Cu(OAc)_2$ was used in combination with cesium carbonate in DMF (Table 1, entry 1). It is noteworthy that the structure of **2a** was unambiguously confirmed by an X-ray single-crystal diffraction analysis (Scheme 2).[15] The yield of **2a** was increased to 60% with 4 Å molecular sieves as an additive. Encouraged by this promising result, we further evaluated other reaction parameters in order to obtain more satisfactory results. First, we evaluated various bases and found a promising result that the yield of **2a** was increased to 79% when employing $Cu(OAc)_2$ and potassium *tert*-butanolate as base in DMF (Table 1, entry 4). Other bases, including Cs_2CO_3, K_2CO_3, $NaHCO_3$, DABCO and NaOH, were less efficient (Table 1, entries 1–5). An investigation of the effect of solvent (Table 1, entries 6-9) revealed that the use of dimethylacetamide (DMA) as solvent achieved the best result (91%, Table 1, entry 7). Among the copper sources evaluated, $Cu(OAc)_2$ exhibited the highest catalytic reactivity with 91% yield (Table 1, entries 5 and 10-14). In addition, the reaction failed to improve the yield under nitrogen or oxygen atmosphere (Table 1, entries 15-16). Trace or no desired product was observed if either copper catalyst or base was absent (Table 1, entries 17-18).



Scheme 2 X-ray crystal structure of 5-phenylindazolo[3,2-*b*]quinazolinone (**2a**).

Having the optimized reaction conditions in hand, we next examined a series of 2-(2-methoxyphenyl)-3-(phenylamino) quinazolinone derivatives containing inert C-O bonds to explore the scope of the cross-coupling reaction (Table 2).

Table 2 Synthesis of indazolo[3,2-*b*]quinazolinone derivatives[a]



[a] Unless otherwise noted, the reaction conditions were as follows: **1** (0.2 mmol), $Cu(OAc)_2$ (0.04 mmol), ^{t}BuOK (0.2 mmol), MS 4 Å (60 mg), and DMA (5 mL), air, 120 °C, 48 h. Isolated yield. [b] NR = no reaction.

First, the influence of substitutions on the *N*-aryl ring moiety of the 2-(2-methoxyphenyl)-3-(phenylamino)quinazolinone was

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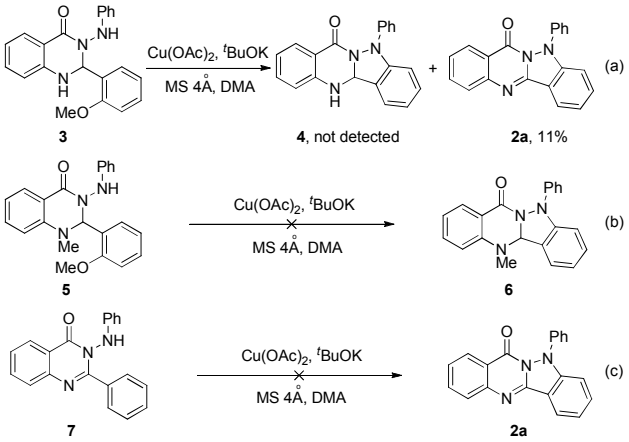
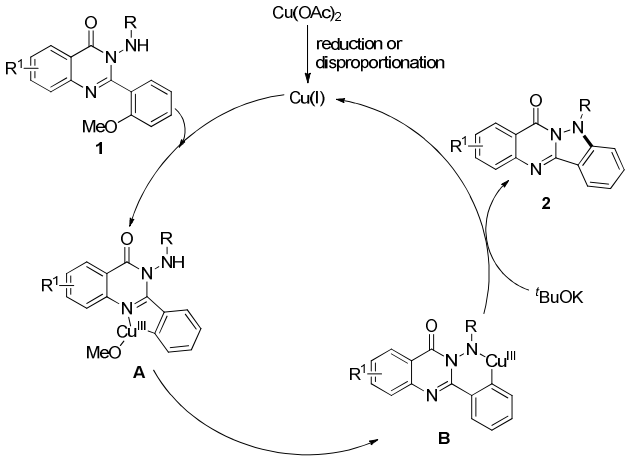
investigated. The monosubstituent positions at the *N*-aryl ring moiety were evaluated, and the results demonstrated that steric effects of substituents had little effects on the reaction. For example, when substrates bearing a *para*-, *meta*-, and *ortho*-methyl group were examined, the corresponding desired indazolo[3,2-*b*]quinazolinones **2b**, **2c** and **2d** were obtained in 85%, 83% and 70% yield respectively (Table 2, entries 2-4). The same phenomena were observed using substrates bearing a *para*-, *meta*-, and *ortho*-chloro group (Table 2, entries 7 and 9-10). The electronic properties of the substituents on the *N*-aryl ring moiety affected the yields to some extent. In general, the *N*-aryl ring moiety bearing an electron-donating substituent (e.g., −Me) generally produced a higher yield than those analogues bearing an electron-withdrawing substituent (e.g., −F, −Cl, and $-CF_3$) (Table 2, entries 2 and 5-7). However, the reaction failed to deliver the desired product under the same reaction conditions when 2-(2-methoxyphenyl)-3-((4-methoxyphenyl)amino)quinazolin-4(3*H*)-one was used (Table 2, entry 8).

Next, we turned our attention to study the effect of the various groups (e.g., R^1 = Me, F, Cl, OMe and NO_2) of substrates (Table 2, entries 11-20). First, the steric effects of substituents had an obvious impact on the efficiency of this transformation. For example, when substrates bearing a methyl group were examined, corresponding desired indazolo[3,2-*b*]quinazolinones **2j**, **2k**, and **2l** were obtained in 78%, 76% and 75% yield respectively (Table 2, entries 11-13), while the yield of **2m** possessing an *ortho*-methyl group was decreased to 45% (Table 2, entry 14). The electronic properties of groups R^1 on the phenyl ring had some effects on the reaction. Both electron-donating (e.g., −Me) and electron-withdrawing (e.g., −F and −Cl) substituents were tolerated in the reaction. Generally, substrates with an electron-donating substituent on the aryl group gave a slightly higher yield of addition products than those analogues bearing an electron-withdrawing substituent (Table 2, entries 15-18). The reaction worked well with the substrates containing the chloro group (commonly used for cross-coupling reactions) and to afford the corresponding products, leading to a useful handle for further cross-coupling reactions (Table 2, entries 7, 9-11 and 16-18). However, the reaction did not work under the same reaction conditions when substrates bearing methoxy or nitro group was used (Table 2, entries 19-20).



Scheme 3 Control experiments.

To elucidate the reaction mechanism of the formation of indazolo[3,2-*b*]quinazolinones, some control experiments were performed under the standard conditions as shown in Scheme 3. The reaction of 2-(2-methoxyphenyl)-3-(phenylamino)-2,3-dihydroquinazolin-4(1*H*)-one (**3**) failed to deliver 5-phenyl-12,12a-dihydroindazolo[3,2-*b*]quinazolin-7(5*H*)-one (**4**) along with product **2a** in 11% yield (Scheme 3a). However, the product **6** could not be detected when 2-(2-methoxyphenyl)-1-methyl-3-(phenylamino)-2,3-dihydroquinazolin-4(1*H*)-one (**5**) was used as the substrate under the standard conditions; almost 90% of **5** was recovered (Scheme 3b). The reaction failed to deliver the desired product **2a** under the same reaction conditions when 2-phenyl-3-(phenylamino)quinazolin-4(3*H*)-one (**7**) was used (Scheme 3c).



Scheme 4 Possible mechanism for the formation of Indazolo[3,2-*b*]quinazolinones.

On the basis of the above experimental results and relevant reports in the literature,[12,16] a possible mechanism for the formation of indazolo[3,2-*b*]quinazolinones is proposed in Scheme 4. First, the active Cu(I) species can be initially formed through either the reduction of Cu(II) by the nucleophile or the disproportionation of Cu(II). Then, the oxidative addition of the 2-(2-methoxyphenyl)-3-(phenylamino)quinazolinones (**1**) to the Cu(I) salt would generate the key C-O insertion Cu(III) intermediate **A** that can undergo a "rollover" cyclometalation[17] with increasing temperature to afford six-membered intermediate **B** by intramolecular ligand exchange with H-N(Ph)-quinazolinone. Finally, the reductive elimination of intermediate **B** along with the C–N bond formation affords the indazolo[3,2-*b*]quinazolinones (**2**) and regenerates the Cu(I) catalyst. However, a detailed mechanism of the formation of the indazolo[3,2-*b*]quinazolinones remain unclear at the current stage.

Conclusions

In summary, we have developed an alternative synthetic pathway to access indazolo[3,2-*b*]quinazolinones by copper-catalyzed the inert C-O bond cleavage and intramolecular C-N bond formation reaction of 2-(2-methoxyphenyl)-3-(arylamino)quinazolinones. Further efforts to explore the detailed mechanism and extend the applications of quinazolinone as a directing group are now being undertaken in our laboratory.

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Experimental section

General Methods

All commercial reagents were used without further purification unless otherwise noted. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured on a 500 MHz spectrometer using DMSO-d_6 or $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, and the coupling constants J are given in hertz. High-resolution mass spectrometry (HRMS) was performed with a TOF MS instrument with an EI or ESI source. 2-(2-Methoxyphenyl)-3-(arylamino)quinazolinones were synthesized according to the literature procedures.[18] Other commercially obtained reagents were used without further purification. Column chromatography was performed using EM silica gel 60 (300–400 mesh).

General procedure for copper-catalyzed synthesis of indazolo[3,2-*b*]quinazolinones (2a-2q)

In a 25 mL sealed tube, 2-(2-methoxyphenyl)-3-(phenylamino)-quinazolinones (0.2 mmol, 1.0 equiv), $Cu(OAc)_2$ (0.04 mmol, 20 mol %), ^{t}BuOK (0.2 mmol, 1.0 equiv) and MS 4Å (60 mg), were dissolved in DMA (5 mL). The reaction mixture was then tightly capped and stirred for 10 minutes at room temperature for proper mixing of the reactants, and then heated at 120 °C with vigorous stirring for 48 hours. The reaction mixture was then cooled to room temperature, diluted with dichloromethane and filtered through a small pad of Celite. The filtrate was concentrated in vacuo and purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate as the eluent to afford the desired products.

5-Phenylindazolo[3,2-*b*]quinazolin-7(5*H*)-one (2a). White solid, mp 203-204 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34-8.28 (m, 2H),7.91 (d, *J* = 8.0Hz 1H), 7.83-7.80 (m, 1H), 7.64-7.60 (m, 1H), 7.49-7.39 (m, 5H), 7.37-7.35 (m, 2H), 7.21(d, *J* = 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 148.2, 147.8, 147.4, 141.0, 133.1, 132.5, 128.6, 127.6, 126.1, 125.8, 124.5, 123.6, 123.4, 122.3, 118.9, 117.9, 111.5.

5-(*p*-Tolyl)indazolo[3,2-*b*]quinazolin-7(5*H*)-one (2b). White solid, mp 184-185 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.24 (d, *J* = 7.5 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.89 (s, 2H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.54-7.48 (m, 2H), 7.35-7.26 (m, 5H), 3.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 149.4, 148.4, 147.3, 141.4, 140.4, 132.4, 132.2, 128.6, 127.4, 127.2, 124.4, 124.2, 123.4, 122.4, 118.0, 117.5, 111.5, 22.4; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 148.4, 147.7, 147.2, 138.3, 137.8, 133.0, 132.4, 129.2, 126.0, 125.8, 124.4, 123.7, 123.2, 122.3, 118.9, 117.8, 111.4, 20.4.

5-(*m*-Tolyl)indazolo[3,2-*b*]quinazolin-7(5*H*)-one (2c). White solid, mp 245-246 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34-8.28 (m, 2H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.84-7.80 (m, 1H), 7.64-7.60 (m, 1H), 7.48-7.34 (m, 3H), 7.22-7.14 (m, 4H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 148.4, 147.8, 144.5, 138.8, 137.6, 133.0, 132.4, 128.6, 128.4, 126.1, 125.8, 124.4, 124.1, 123.4, 122.3, 120.8, 119.0, 118.1, 111.6, 20.5.

5-(*o*-Tolyl)indazolo[3,2-*b*]quinazolin-7(5*H*)-one (2d). White solid, mp 228-229 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32-8.29 (m, 2H), 7.91 (d, *J* = 8.0 Hz, 1H) 7.82-7.79 (m, 1H), 7.63-7.60 (m, 1H), 7.46-7.34 (m, 4H), 7.20 (t, *J* = 7.0 Hz, 1H), 6.94 (t, *J* = 8.5 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 157.0, 147.6, 144.0, 134.8, 131.4, 130.5, 129.7, 128.2, 127.8, 127.2, 127.1, 126.9, 124.2, 123.6, 121.8, 121.6, 120.9, 120.1, 110.6, 22.0.

5-(4-Fluorophenyl)indazolo[3,2-*b*]quinazolin-7(5*H*)-one (2e). White solid, mp 194-195 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32-8.28 (m, 2H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.84-7.80 (m, 1H), 7.64 (t, *J* = 7.0 Hz, 1H), 7.48-7.42 (m, 2H), 7.38-7.35 (m, 2H), 7.18-7.13 (m, 3H); ^{13}C NMR (125 MHz, $DCCl_3$) δ 156.6, 149.4, 148.8, 148.2, 138.0, 134.2, 133.6, 128.8, 127.2, 126.8, 125.6, 124.6, 123.4, 120.0, 119.0, 116.7, 116.6, 112.5.

5-(4-(Trifluoromethyl)phenyl)indazolo[3,2-*b*]quinazolin-7(5*H*)-one (2f). White solid, mp 215-216 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34-8.30 (m, 2H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.86-7.83 (m, 1H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.67-7.64 (m, 1H), 7.52-7.45 (m, 4H), 7.24 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.3, 148.2, 147.7, 147.4, 144.9, 134.2, 134.0, 128.0, 127.0, 126.4, 126.0, 125.5, 125.1, 124.3, 124.0, 123.1, 119.4, 118.7, 112.2 .

5-(4-Chlorophenyl)indazolo[3,2-*b*]quinazolin-7(5*H*)-one (2g). White solid, 233.8-234 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33-8.28 (m, 2H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.82 (t, *J* = 7.5 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 2H), 7.50-7.44 (m, 4H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 147.9, 147.2, 146.6, 139.2, 133.6, 133.3, 132.6, 128.9, 126.2, 125.8, 125.3, 124.7,123.7, 122.5, 119.0, 118.1, 111.4.

5-(3-Chlorophenyl)indazolo[3,2-*b*]quinazolin-7(5*H*)-one (2h). White solid, mp 249-250 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34-8.30 (m, 2H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.84 (t, *J* =7.0 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.50-7.40 (m, 4H), 7.34 (s, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 147.8, 147.7, 147.2, 142.2, 134.3, 133.3, 132.6, 129.6, 128.0, 126.2, 125.8, 124.8, 123.9, 123.8, 122.5, 121.9, 118.8, 118.2, 111.4.

5-(2-Chlorophenyl)indazolo[3,2-*b*]quinazolin-7(5*H*)-one (2i). White solid, mp 203-204 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.82-7.80(m, 1H), 7.64(t, *J* =7.0 Hz, 1H), 7.53 -7.52 (m, 1H), 7.48 -7.40 (m, 5H), 7.07 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 147.8, 146.6, 137.2, 133.0, 132.6, 131.4, 130.0, 129.6, 127.8, 127.0, 126.2, 125.7, 124.4, 123.2, 122.4, 118.7, 117.9, 110.7, 99.2. IR (KBr): 3435, 3061, 2367, 1678, 1602, 1470 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{13}ClN_3O^+$ $[M + H]^+$ 346.0742, found 346.0744.

8-Methyl-5-phenylindazolo[3,2-*b*]quinazolin-7(5*H*)-one (2j). White solid, mp 210-211 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.0 Hz 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.66-7.59 (m, 2H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.41-7.34 (m, 4H), 7.20 (d, *J* = 8.5 Hz, 2H), 2.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 149.4, 148.4, 147.3, 141.4, 140.4, 132.4, 132.2, 128.6, 127.4, 127.2, 124.4, 124.2, 123.4, 122.4, 118.0, 117.5, 111.5, 22.4.

9-Methyl-5-phenylindazolo[3,2-*b*]quinazolin-7(5*H*)-one (2k). White solid, mp232-233 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27

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(d, *J* = 8.0 Hz, 1H), 8.11 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.65-7.58 (m, 2H), 7.48-7.34 (m, 6H), 7.21 (t, *J* = 8.0 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 148.2, 146.8, 145.8, 141.2, 134.8, 134.7, 132.2, 128.6, 127.6, 126.0, 125.1, 123.6, 123.4, 122.2, 118.8, 118.2, 111.5, 20.4.

10-Methyl-5-phenylindazolo[3,2-*b*]quinazolin-7(5*H*)-one (2l). White solid, mp 216-217 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.0 Hz 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 7.70 (s, 1H), 7.62-7.59 (m, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.42-7.34 (m, 4H), 7.29-7.27 (m, 1H), 7.20 (d, *J* = 8.5 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 148.2, 148.0, 147.4, 144.0, 141.1, 132.4, 128.6, 127.6, 126.3, 125.8, 125.6, 123.6, 123.4, 122.4, 118.1, 116.6, 111.4, 21.1. IR (KBr): 3434, 2359, 1671, 1601, 1460, 1270 cm^{-1}. HRMS (ESI): m/z calcd for $C_{21}H_{16}N_3O^+$ $[M + H]^+$ 326.1288, found 326.1294.

11-Methyl-5-phenylindazolo[3,2-*b*]quinazolin-7(5*H*)-one (2m). White solid, mp 169.8-170 °C.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.0 Hz 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.67-7.58 (m, 2H), 7.48-7.33 (m, 7H), 7.20 (d, *J* = 8.5 Hz, 1H), 2.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 157.2, 146.5, 146.2, 136.8, 136.5, 132.8, 131.3, 130.2, 129.1, 126.8, 124.8, 121.8, 120.8, 117.4, 114.0, 110.7, 100.1, 55.7, 21.4.

9-Fluoro-5-phenyl-12,12a-dihydroindazolo[3,2-*b*]quinazolin-7(5*H*)-one (2n). White solid, mp 239-239.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.0 Hz 1H), 7.95-7.90 (m, 2H), 7.64-7.61 (m, 1H), 7.57-7.52 (m, 1H), 7.50-7.47 (m, 2H), 7.44-7.40 (m, 2H), 7.36-7.34 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 148.2, 146.8, 140.8, 132.6, 128.7, 128.5, 128.4, 127.8, 123.8, 123.6, 122.3, 121.9, 117.8, 112.6, 111.6, 111.3, 110.4. IR (KBr):3439, 2923, 1673, 1624, 1482, 1273 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{13}FN_3O^+$ $[M + H]^+$ 330.1037, found 330.1041.

8-Chloro-5-phenylindazolo[3,2-*b*]quinazolin-7(5*H*)-one (2o). White solid, mp 224-225 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.5 Hz, 1H), 7.80-7.78 (m, 1H), 7.65-7.60 (m, 2H), 7.48-7.35 (m, 7H), 7.18 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 151.3, 149.5, 148.8, 141.7, 134.9, 134.2, 133.8, 133.2, 129.8, 129.7, 128.7, 126.4, 124.6, 124.5, 123.4, 119.4, 118.4, 117.0, 112.5. IR (KBr): 3437, 2359, 1683, 1632, 1589, 1461 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{13}N_3OCl^+$ $[M+H]^+$ 346.0742, found 346.0744.

9-Chloro-5-phenyl-12,12a-dihydroindazolo[3,2-*b*]quinazolin-7(5*H*)-one (2p). White solid, mp 256-257 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 2H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 7.48-7.42 (m, 4H), 7.35 (d, *J* = 6.5 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 151.3, 149.5, 148.8, 141.7, 134.9, 134.2, 133.8, 133.2, 129.8, 129.7, 128.7, 126.4, 124.6, 124.5, 123.4, 119.4, 118.4, 117.0, 112.5.

10-Chloro-5-phenylindazolo[3,2-*b*]quinazolin-7(5*H*)-one (2q). Pale-yellow solid, mp 204-205 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28-8.23 (m, 2H), 7.90-7.89 (m, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.50-7.34 (m, 7H), 7.20 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.8, 149.3, 148.9, 148.4, 141.3, 138.6, 134.2, 129.3, 128.0, 127.9, 125.8, 125.4, 124.7, 123.9, 123.1, 118.2, 118.0, 112.3.

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