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FULL PAPER

Palladium Catalyzed *Cross*-Dehydrogenative Coupling/Annulation Reaction: A Practical and Efficient Approach to Hydroxyisoindolo[1,2-*b*]quinazolinone

Minoo Dabiri,*[a] Noushin Farajinia Lehi,[a] Siyavash Kazemi Movahed[a] and Hamid Reza Khavasi[a]

Abstract: The palladium-catalyzed cross-dehydrogenative coupling (CDC) followed by an intramolecular cyclization between arylquinazolinones and aldehydes has been described. This viable transformation provides a variety of novel substituted hydroxyisoindolo[1,2-*b*]quinazolinone compounds in moderate to good yields. Additionally, the reaction is performed with toluene in place of benzaldehyde by using an excess amount of *tert*-butyl hydroperoxide (TBHP) as the oxidant in good yield.

Introduction

Development of selective and efficient C-C bond-forming reactions is of paramount importance in organic chemistry since they provide reliable access to the key steps that are required for building complex molecules from simple precursors. Transition-metal-catalyzed cross-coupling reactions based on using two pre-functionalized substrates belong to one of the most effective processes that are used for C-C bond formation. Transition-metal-catalyzed C-H bond activation and subsequent C-C bond formation has attracted considerable interest in recent years as they prevent the needs for multi-step preparation of pre-activated starting materials and production of stoichiometric metallic waste.[1,2] However, in these cases, one coupling partner still has to be pre-functionalized.[3,4] As one of the most important C−H activation processes, cross dehydrogenative-coupling (CDC) reactions have emerged in recent years and provided a viable alternative to conventional methods of C–C bond-forming reactions. Regarding the atom economy, this synthetic method offers one of the ideal synthetic procedures for selective C-C bond-forming reactions. Compared with traditional cross-coupling reactions, which usually involve pre-functionalized starting materials (e.g., such as -Hal, -OTf, -BR_2, -SnR_3, -SiR_3, -ZnHal, -MgHal and, thus, lead to stoichiometric amounts of waste), the direct dehydrogenative functionalization of C-H bonds has been proven to be as a more eco-friendly option.[5–8]

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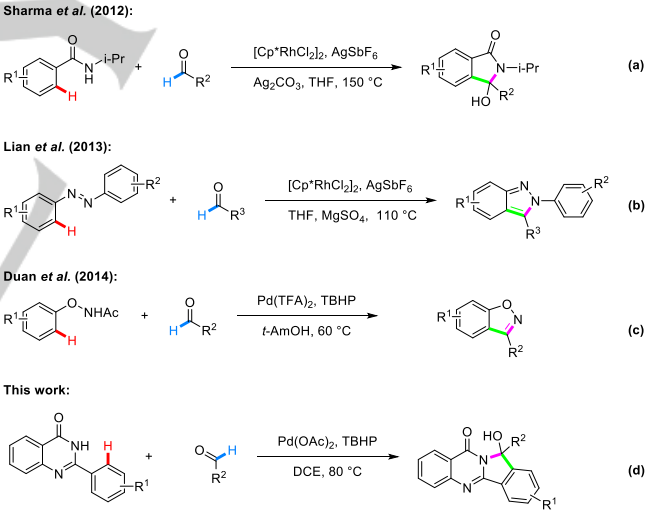
Several recent reports have utilized aldehydes in directed transition metal-catalyzed CDC/annulation reaction for the preparation of heterocyclic compounds. Sharma *et al.* have described the first efficient synthetic route to 3-hydroxyisoindolin-1-ones *via* tandem Rh-catalyzed CDC of secondary benzamides with aldehydes and intramolecular cyclization (Scheme 1a).[9] Lian *et al.* have shown an efficient, one-step, and highly functional group-compatible synthesis of substituted *N*-aryl-2*H*-indazoles *via* the Rh-catalyzed CDC reaction between azobenzenes and aldehydes with subsequent cyclization and aromatization (Scheme 1b).[10] Duan *et al.* have reported a Pd-catalyzed CDC/annulation pathway for *N*-phenoxyacetamides with aldehydes to form 1,2-benzisoxazoles (Scheme 1c).[11]



Scheme 1. Representative approaches for the CDC reaction of aldehyde and arenes and followed by intramolecular cyclization.

The pyrrolo[2,1-*b*]quinazolinone structural motif is gaining prominence in medicinal and organic chemistry.[12] They have been found in a broad spectrum of pharmacologically and biologically active compounds, such as luotonin A, cruciferane, vasicinone, tryptanthrin, nigellastrine, phaitanthrins, and peharmaline, while defined as a notable class of pharmacologically active compounds exhibiting anticancer, antiviral, anti-Alzheimer's disease, anti-inflammatory, and anti-allergic characteristics (Figure 1).[13–17] In spite of their biological importance, the number of studies on the synthesis of these fused heterocyclic structures have rarely been reported. Thus, the

development of effective and more economical approaches for the construction of these compounds is highly promising and can further develop their applications in organic and medicinal chemistry.

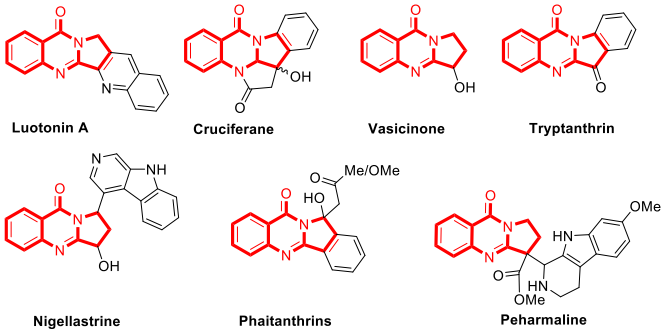


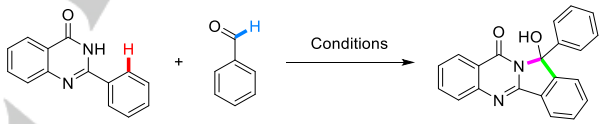
Figure 1 Biological active compounds with a pyrrolo[2,1-*b*]quinazolinone skeleton.

Based on above introduction and also as part of our ongoing research studies on the C-H activation reactions and organic synthesis,[18–23] herein we present the tandem palladium-catalyzed CDC reaction followed by an intramolecular cyclization between arylquinazolinones and aldehydes under *tert*-butyl hydroperoxide (TBHP) as a convenient oxidant to afford hydroxyisoindolo[1,2-*b*]quinazolinone. To the best of our knowledge, this is the first report of CDC/annulation reaction for the formation of hydroxyisoindolo[1,2-*b*]quinazolinone polyheterocyclic frameworks (Scheme 1d).

Results and Discussion

In our initial study, 2-phenylquinazolin-4(3*H*)-one (**1a**) and benzaldehyde (**2a**) were chosen as the model substrates for optimizing the reaction conditions. The results are summarized in Table 1. It is noteworthy that the combination of $Pd(OAc)_2$ (5 mol%) and two equivalents of TBHP as the oxidant in dichloroethane (DCE) under N_2 atmosphere at 80 °C for 16 h promoted the reaction of **1a** and **2a** to produce our target product **3aa** with 43% yield (Table 1, entry 1). Solvent screening has demonstrated that the choice of solvent is crucial for this transformation. When acetonitrile, dioxane, toluene and tetrahydrofuran (THF) were employed as the solvent, the product was formed in only trace amounts (Table 1, entries 2–5). It can be seen that the DCE was chosen as the best solvent. DCE would enhance the reactivity of catalytic species and stabilize activated complexes in the reaction.[24] Other oxidants such as $K_2S_2O_8$, H_2O_2, AgOAc and $Cu(OAc)_2$ did not promote the desired reaction (Table 1, entries 7–10). O_2, the ideal oxidant, was also tested under these conditions, but the chemical yield was not improved (Table 1, entry 11). Additionally, the increase in the mount of TBHP to four equivalents has resulted in a yield increase of up to 52% (Table 1, entry 12). In contrast, the further addition of TBHP equivalents failed to enhance the yield (Table 1, entry 13). It can be presumed that the increase in TBHP equivalents would lead to the further oxidation of the aldehydes and, therefore, reduce the reaction yield. In the absence of either $Pd(OAc)_2$ or TBHP, no product was observed, indicating that $Pd(OAc)_2$ and TBHP are indispensable ingredients for the CDC/annulation reaction (Table 1, entries 6 and 14). Other catalysts including $Cu(OAc)_2$, $PdCl_2$, Ru(*p*-cymene)Cl_2, Ru(COD)Cl_2, and $Co(OAc)_2$ were also ineffective under the present conditions (Table 1, entries 15-19). It was found that the yield could be remarkably improved by increasing the catalyst loading as an isolated yield of 71% for the product was obtained in the presence of 10 mol% of $Pd(OAc)_2$ (Table 1, entry 20). The increase in the loading of $Pd(OAc)_2$ to 15 mol% has not rendered any effect on the yield (Table 1, entry 21). Finally, the optimal reaction temperature was evaluated as it has a well-known and considerable influence on the reaction rate. Accordingly, the reduction of temperature could not improve the yield of the reaction (Table 1, entry 22). Also, There was no significant change in the yield when the temperature was increased to 100 °C (Table 1, entry 23). Thus, for all the subsequent reactions, we used the optimized reaction conditions, which were determined to be the combination of $Pd(OAc)_2$ (10 mol%), TBHP (4 eq.) in DCE solvent at 80 °C for 16 h under N_2 atmosphere, as shown in entry 20.

Table 1. Optimization of the reaction conditions[a]



1a 2a 3aa

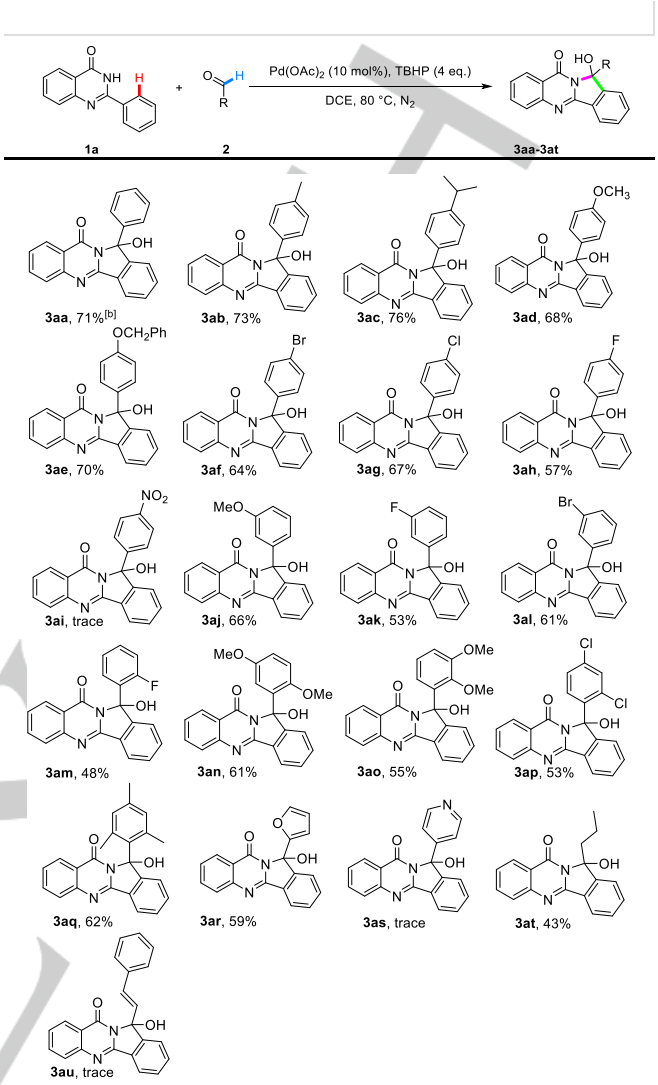
Entry	Cat. (mol %)	Solvent	Oxidant (equiv.)	Yield[b] (%)
1	$Pd(OAc)_2$ (5)	DCE	TBHP (2)	43
2	$Pd(OAc)_2$ (5)	Acetonitrile	TBHP (2)	36
3	$Pd(OAc)_2$ (5)	Dioxane	TBHP (2)	12
4	$Pd(OAc)_2$ (5)	Toluene	TBHP (2)	27
5	$Pd(OAc)_2$ (5)	THF	TBHP (2)	Trace
6	$Pd(OAc)_2$ (5)	DCE	-	Trace
7	$Pd(OAc)_2$ (5)	DCE	$K_2S_2O_8$ (2)	11
8	$Pd(OAc)_2$ (5)	DCE	H_2O_2 (2)	17
9	$Pd(OAc)_2$ (5)	DCE	AgOAc (2)	Trace
10	$Pd(OAc)_2$ (5)	DCE	$Cu(OAc)_2$ (2)	Trace
11	$Pd(OAc)_2$ (5)	DCE	O_2	13
12	$Pd(OAc)_2$ (5)	DCE	TBHP (4)	52
13	$Pd(OAc)_2$ (5)	DCE	TBHP (6)	49

14	-	DCE	TBHP (4)	n.r
15	$Cu(OAc)_2$ (5)	DCE	TBHP (4)	trace
16	$PdCl_2$ (5)	DCE	TBHP (4)	29
17	Ru(*p*-cymene)Cl_2	DCE	TBHP (4)	Trace
18	$Ru(COD)Cl_2$	DCE	TBHP (4)	9
19	$Co(OAc)_2$	DCE	TBHP (4)	trace
20	**$Pd(OAc)_2$ (10)**	**DCE**	**TBHP (4)**	**71**
21	$Pd(OAc)_2$ (15)	DCE	TBHP (4)	74
22[c]	$Pd(OAc)_2$ (10)	DCE	TBHP (4)	41
23[d]	$Pd(OAc)_2$ (10)	DCE	TBHP (4)	73

[a] 2-Phenylquinazolin-4(3*H*)-one (**1a**) (1 mmol), benzaldehyde (**2a**) (1.2 mmol), catalyst (X mol %), oxidant (X eq.), solvent (3 mL), temp. = 80 °C, time = 16 h, sealed tube, N_2 [b] Isolated yield. [c] Temp. = 50 °C. [d] Temp. = 100 °C.

The scope of the method was investigated by synthesizing a broad range of hydroxyisoindolo[1,2-*b*]quinazolinones by using a variety of aldehydes and 2-arylquinazolin-4(3*H*)-one derivatives under the optimized reaction conditions. First, we used 2-phenylquinazolin-4(3*H*)-one to react with different aldehydes, as shown in Table 2. A wide range of benzaldehydes with substituents on the benzene rings was investigated. In general, the reaction of **1a** with benzaldehydes derivatives bearing electron-releasing groups such as (*p*-Me, *p*-*i*-Pr, *p*-OMe, and *p*-OBn) gave good yields (**3ab-3ae**). In contrast, electron-deficient benzaldehydes were relatively less reactive under these reaction conditions. Halogen-substituted aldehydes (*p*-F, *p*-Cl, and *p*-Br) were moderately converted to the corresponding products (**3af-3ah**), respectively. However, the reaction was completely hampered in the presence of the strongly electron-withdrawing group (*p*-NO_2) (**3ai**). A slightly steric effect was observed when *meta*-substituted (*m*-OMe, *m*-Br, and *m*-F) and *ortho*-substituted (*o*-F) benzaldehyde reacted with **1a**, and inferior yields of the products (**3aj-3am**) were obtained. Polysubstituted benzaldehydes such as 2,5-dimethoxy, 2,3-dimethoxy, 2,4-dichloro and 2,4,6-trimethyl groups gave moderate yields of the corresponding products (**3an-3aq**), respectively. The moderate yield obtained in the case of the polysubstituted benzaldehydes could be, in part, because of the instability of intermediate acyl radical, a steric factor, or a combination of both.[25] Furfural as an electron-rich heteroaromatic aldehyde was used, and the desired product (**3ar**) was obtained in good yield (59%). The heteroaromatic aldehyde (4-pyridinecarboxaldehyde) was found to be unreactive and did not afford the corresponding product **3as**. The aliphatic aldehyde (*n*-butyraldehyde) was used, and the product **3at** was isolated in 43% yield. Additionally, the α-β unsaturated aldehyde (cinnamaldehyde) was used but failed to provide the desired product **3au**.

Table 2. Scope of aldehydes for Pd-catalyzed CDC/annulation reaction[a]

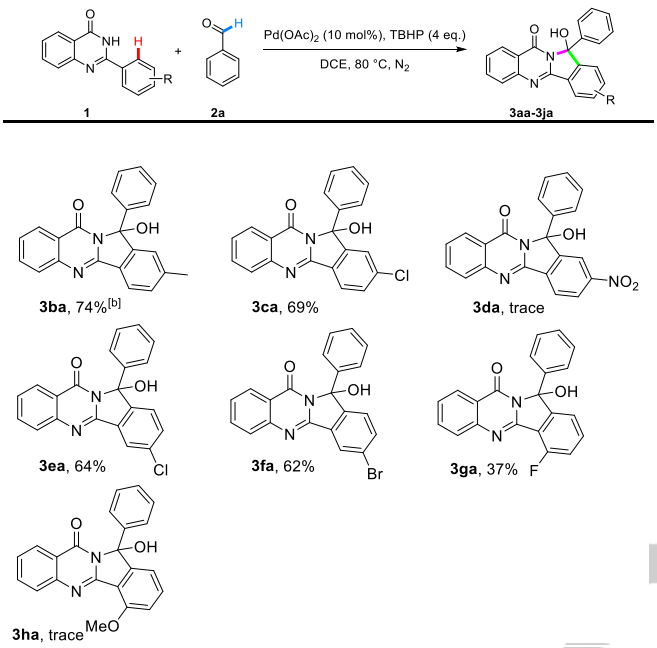


[a] 2-Phenylquinazolin-4(3*H*)-one (**1a**) (1 mmol), aldehyde (**2**) (1.2 mmol), $Pd(OAc)_2$ (10 mol%), TBHP (4 eq.), DCE (3 mL), temp. = 80 °C, time = 16 h, sealed tube, N_2, [b] Isolated yield.

Furthermore, the scope of 2-arylquinazolin-4(3*H*)-one substrate was also screened (Table 3). The *para*-substituted arylquinazolinones with the electron-releasing group (*p*-Me) on the benzene rings were favored in the reaction and able to form the desired product in good yield (**3ba**). By contrast, electron-withdrawing groups (*p*-Cl and *p*-NO_2) were relatively less reactive in these reaction conditions (**3ca** and **3da**). Notably, the reaction of *meta*-substituted arylquinazolinone derivatives preferentially occurred at the more sterically accessible position to give the corresponding products (**3ea** and **3fa**) since the steric effects would seemingly prevent either the formation of the cyclopalladated intermediate or the access of the aldehyde to the cyclopalladated intermediate. Nevertheless, the *ortho*-substituted arylquinazolinones showed relatively less reactivity since

coplanar conformation between the aromatic ring and the quinazolinone moiety was not accessible (**3ga** and **3ha**).

Table 3. Scope of 2-arylquinazolin-4(3*H*)-ones for Pd-catalyzed CDC/annulation reaction[a]



[a] 2-Arylquinazolin-4(3*H*)-one (**1**) (1 mmol), benzaldehyde (**2a**) (1.2 mmol), $Pd(OAc)_2$ (10 mol%), TBHP (4 eq.), DCE (3 mL), temp. = 80 °C, time = 16 h, sealed tube, N_2, [b] Isolated yield.

Finally, the structure of product **3ac** was confirmed unambiguously by single crystal X-ray analysis (Figure 2).

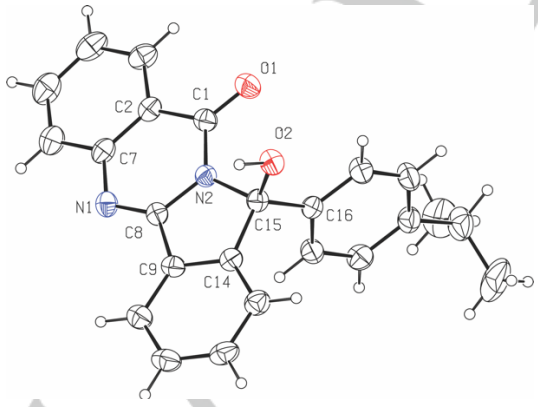
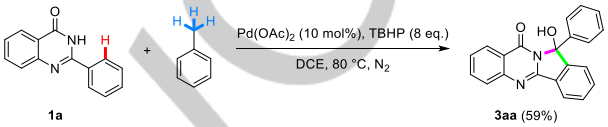


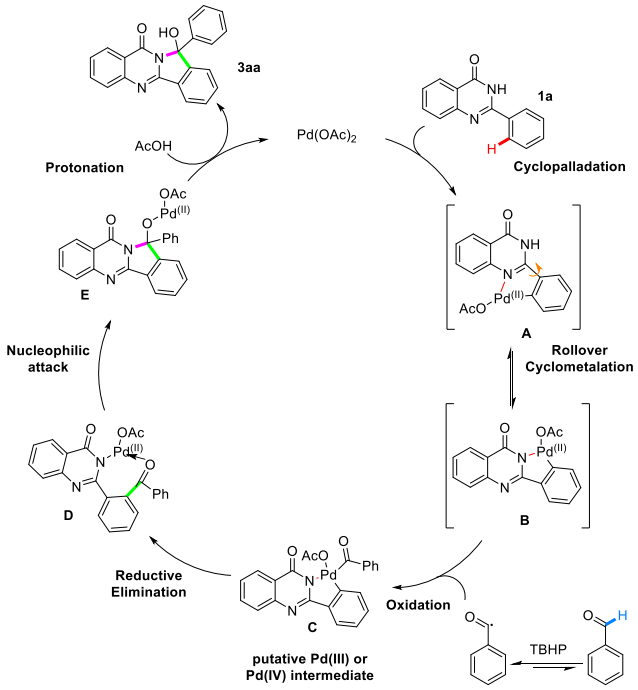
Figure 2. Single crystal X-ray structure of compound **3ac** (CCDC: 1875974)

Encouraged by the recent reports of C-H bond acylation with toluene derivatives,[26,27] we further explored the compatibility of this protocol with toluene instead of benzaldehyde. In this respect, we optimized the reaction conditions by varying only the concentration of TBHP to achieve better product yields. Accordingly, the best results were obtained when 2-phenylquinazolin-4(3*H*)-one (**1a**, 1 mmol) was treated with toluene (2 mmol) in the presence of $Pd(OAc)_2$ (10 mol%) and TBHP (8 eq.) at 80 °C for 16 h, which produced the target compound **3aa** with 59% yield (Scheme 2).



Scheme 2. Pd catalyzed CDC/annulation reaction between 2-phenylquinazolin-4(3*H*)-one and toluene

On the basis of the previous reports,[11,28,29] a plausible mechanism pathway is proposed and depicted in Scheme 3. The reaction is probably initiated by chelate-assisted *ortho*-selective cyclometalation of 2-phenylquinazolin-4(3*H*)-one (**1a**) by $Pd(OAc)_2$ and generates a five-membered cyclopalladated intermediate (**A**). Then, a "rollover" cyclometalation of intermediate (**A**) affords the intermediate (**B**).[30,31] The palladacycle (**B**) undergoes oxidation with acyl radical, generated in situ by hydrogen abstraction, to produce the highly active Pd(IV) species or dimeric Pd(III) (**C**) intermediates.[32] After reductive elimination, a new C-C bond can be formed with Pd attached to an amide nitrogen atom of phenylquinazolinone. The intramolecular nucleophilic attack occurs to form a palladium alkoxide (**E**), which is protonated by acetic acid to give our desired product (**3aa**).



Scheme 3. A plausible mechanism.

Conclusions

We have described a highly efficient method for palladium-catalyzed CDC/annulation reaction of arylquinazolinones with aldehydes. These transformations have been applied to a wide range of substrates, and typically proceeded with high levels of regio- and chemoselectivity. Additionally, the reaction is performed with toluene in place of benzaldehyde by using an excess amount of TBHP in good yield. This method provides an alternative approach for the synthesis of biologically important hydroxyisoindolo[1,2-*b*]quinazolinones. Further investigations into the biological properties, scopes, and synthetic of these hydroxyisoindolo[1,2-*b*]quinazolinone derivatives and the studies of the reaction mechanism are currently in progress.

Experimental Section

General Information. All solvents and starting materials were purchased from Merck and Sigma. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F254 plates. The products were purified by thin layer chromatography (MERCK Silica Gel 60). ^{1}H and ^{13}C-NMR Spectra: were recorded on Bruker DRX 300 and 75 MHz and INOVA 500 and 126 MHz, respectively. Mass spectra were recorded on an Agilent Technology (HP) 5973 Network Mass Selective Detector operating at an ionization potential of 70 eV. Elemental analysis of products was performed using an Elementar Analysensysteme GmbH VarioEL CHNS.

General procedure for the Synthesis of substituted quinazolin-4(3*H*)-one substrates:

Anthranilamide (15 mmol) and an aldehyde (18 mmol) were dissolved in DMSO (40 mL). Then, the reaction mixture was stirred at 100 °C in an open flask and monitored by TLC. After complete consumption of the starting materials, the reaction mixture was cooled to room temperature. When water (100 mL) was added to the reaction mixture, the precipitate was formed and collected by filtration. Recrystallization in ethanol afforded quinazolinone.[33]

General procedure for the Synthesis of hydroxyisoindolo[1,2-*b*]quinazolinone compounds:

A sealed tube (10 mL) that contained 2-arylquinazolinone 1 (1.0 mmol), aldehyde (1.2 mmol), $Pd(OAc)_2$ (10 mol%), TBHP (4 mmol) and DCE as a solvent (3.0 mL) was purged with nitrogen gas and the reaction was stirred at 80 ℃ for 16h. At the end of the reaction, the reaction mixture was cooled to room temperature, concentrated under reduced pressure, water was added, and then extracted with EtOAc (2 x 15 mL). The organic layer was further washed with brine solution. Afterward, the organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure using a rotary evaporator. Finally, purification was accomplished by thin layer chromatography to afford the desired pure product.

2-phenylquinazolin-4(3*H*)-one: White solid, Yield: 84%, mp: 234-236 °C (lit.[34] mp: 237-238 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.56 (br s, 1H), 8.20 – 8.15 (m, 3H), 7.88 – 7.74 (m, 2H), 7.63 – 7.50 (m, 4H).

2-(*p*-tolyl)quinazolin-4(3*H*)-one: White solid, Yield: 78%, mp: 239-241 °C (lit.[35] mp: 245-247 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.47 (br s, 1H), 8.16 – 8.09 (m, 3H), 7.83 (t, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 2H), 2.39 (s, 3H).

2-(4-chlorophenyl)quinazolin-4(3*H*)-one: White solid, Yield: 65%, mp: 304-306°C (lit.[34] mp: 300-308 °C);^{1}H NMR (300 MHz, DMSO-d_6) δ 12.61 (br s, 1H), 8.22– 8.14 (m, 3H), 7.87 – 7.73 (m, 2H), 7.64 – 7.51 (m, 3H).

2-(4-nitrophenyl)quinazolin-4(3*H*)-one: White solid, Yield: 52%, mp: 359-361 °C (lit. [34] mp: 362-364 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.78 (br s, 1H), 8.48 – 8.35 (m, 4H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.90 – 7.73 (m, 2H), 7.58 (t, *J* = 7.7 Hz, 1H).

2-(3-chlorophenyl)quinazolin-4(3*H*)-one: White solid, Yield: 56%, mp: 292-294 °C (lit. [34] mp: 296-298 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.53 (br s, 1H), 8.24 (s, 1H), 8.18 – 8.15 (m, 2H), 7.88 – 7.75 (m, 2H), 7.66 – 7.58 (m, 2H), 7.54 – 7.51 (m, 1H).

2-(3-bromophenyl)quinazolin-4(3*H*)-one: White solid, Yield: 52%, mp: 293-291 °C (lit.[35] mp: 300 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.63 (br s, 1H), 8.38 (s, 1H), 8.17 (t, *J* = 8.3 Hz, 2H), 7.92 – 7.75 (m, 3H), 7.53 (q, *J* = 7.8 Hz, 2H).

2-(2-fluorophenyl)quinazolin-4(3*H*)-one: White solid, Yield: 52%, mp: 160-162 °C (lit.[36] mp: 162-163 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.61 (br s, 1H), 8.19 – 8.16 (m, 1H), 7.89 – 7.72 (m, 3H), 7.66 – 7.55 (m, 2H), 7.46 – 7.35 (m, 2H).

2-(2-methoxyphenyl)quinazolin-4(3*H*)-one: White solid, Yield: 52%, mp: 199-201 °C (lit.[35] mp: 201-203 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.12 (br s, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 7.83 (t, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 2H), 7.56 – 7.50 (m, 2H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 3.86 (s, 3H).

12-hydroxy-12-phenylisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3aa): White solid, Yield: 71%, mp: 269-270°C, IR (KBr) (ν_{max} /cm^{-1}): 3422, 1690, 1579, 1424; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 – 8.15 (m, 2H), 7.96 (s, 2H), 7.86 – 7.73 (m, 2H), 7.61 – 7.49 (m, 4H), 7.38 – 7.34 (m, 4H);); ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.0, 156.2, 149.1, 145.6, 142.6, 134.7, 133.9, 129.2, 128.7, 126.6, 125.9, 125.1, 120.9; MS (m/z): 326 (M$^+$); Anal. Calcd for $C_{21}H_{14}N_2O_2$: C, 77.29; H, 4.32; N, 8.58. Found: C, 77.36; H, 4.41; N, 8.64.

12-hydroxy-12-(p-tolyl)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3ab): White solid, Yield: 73%, mp: 246-248 °C; IR (KBr) (ν_{max} /cm^{-1}): 3448, 1698, 1619, 1468;^{1}H NMR (300 MHz, DMSO-d_6) δ 8.09 – 8.06 (m, 2H), 7.86 – 7.76 (m, 3H), 7.65 – 7.59 (m, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.36 – 7.28 (m, 3H), 7.12 (d, *J* = 7.9 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.2, 159.5, 148.4, 139.2, 136.9, 134.8, 133.1, 130.5, 129.3, 127.1, 126.6, 126.3, 125.8, 122.5, 21.1; MS (m/z): 340 (M$^+$); Anal. Calcd for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23. Found: C, 77.82; H, 4.80; N, 8.14.

12-hydroxy-12-(4-isopropylphenyl)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3ac): White solid, Yield: 76%, mp: 236-238 °C; IR (KBr) (ν_{max} /cm^{-1}): 3214, 1696, 1622, 1422; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.12 – 8.07 (m, 2H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.62 – 7.59 (m, 2H), 7.51 (t, *J* = 7.1 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 3H), 7.18 (d, *J* = 7.7 Hz, 2H), 2.88 – 2.78 (m, 1H), 1.16 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.1, 149.0, 148.7, 137.2, 134.9, 133.7, 130.5, 130.1, 127.6, 127.2, 126.7, 126.6, 125.8, 124.3, 123.4, 122.5, 33.5, 24.2; MS (m/z): 368 (M$^+$); Anal. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 78.41; H, 5.55; N, 7.71. CCDC: 1875974

12-hydroxy-12-(4-methoxyphenyl)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3ad): White solid, Yield: 68%, mp: 177-180 °C; IR (KBr) (ν_{max} /cm^{-1}): 3394, 1677, 1604, 1466; ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.25 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.75 – 7.61 (m, 2H), 7.52 – 7.42 (m, 2H), 7.35 – 7.21 (m, 3H), 7.02 - 6.84 (m, 3H), 3.71 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.4, 157.5, 148.4, 139.3, 135.0, 134.2, 133.1, 129.1, 127.5, 127.1, 126.8, 126.5, 126.1, 121.8, 114.7, 114.1, 55.6; MS (m/z): 356 (M$^+$); Anal. Calcd for $C_{22}H_{16}N_2O_3$: C, 74.15; H, 4.53; N, 7.86. Found: C, 74.30; H, 4.63; N, 7.80.

12-(4-(benzyloxy)phenyl)-12-hydroxyisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3ae): White solid, Yield: 70%, mp: 198-200 °C; IR (KBr) (ν_{max} /cm^{-1}): 3414, 1644, 1572, 1415; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.09 – 8.04 (m, 2H), 7.83 – 7.79 (m, 2H), 7.64 – 7.61 (m, 2H), 7.53 – 7.30 (m, 10H), 6.96 – 6.93 (m, 2H), 5.06 (s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.6, 157.4, 156.1, 147.5, 146.8, 138.6, 137.4, 134.9, 134.4, 134.1, 130.5, 128.9, 128.3, 128.1, 127.7, 127.6, 126.6, 118.1, 115.7, 114.9, 69.7; MS (m/z): 313 (M$^+$ - 119); Anal. Calcd for $C_{28}H_{20}N_2O_3$: C, 77.76; H, 4.66; N, 6.48. Found: C, 78.01; H, 4.89; N, 6.23.

12-(4-bromophenyl)-12-hydroxyisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3af): White solid, Yield: 64%, mp: 281-283 °C; IR (KBr) (ν_{max} /cm^{-1}): 3428, 1696, 1568, 1416; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.13 -8.02 (m, 2H), 7.77 – 7.61 (m, 5H), 7.52 – 7.49 (m, 2H), 7.40 – 7.32 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.1, 139.4, 134.9, 133.7, 131.6, 130.7, 128.3, 127.6, 127.1, 126.6, 124.3, 123.6, 122.4, 121.9. MS (m/z): 404 (M$^+$); Anal. Calcd for $C_{21}H_{13}BrN_2O_2$: C, 62.24; H, 3.23; N, 6.91. Found: C, 62.47; H, 3.32; N, 6.88.

12-(4-chlorophenyl)-12-hydroxyisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3ag): White solid, Yield: 67%, mp: 265-268 °C; IR (KBr) (ν_{max} /cm^{-1}): 3429, 1693, 1561, 1435; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.11 – 8.03 (m, 2H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.70 (s, 1H), 7.63 – 7.61 (m, 2H), 7.46 – 7.44 (m, 3H), 7.37 – 7.32 (m, 4H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.3, 159.2, 149.2, 146.4, 141.0, 139.0, 134.0, 133.4, 130.6, 130.6, 130.2, 128.7, 128.7, 128.6, 128.6, 128.1, 126.7, 122.4; MS (m/z): 360 (M$^+$); Anal. Calcd for $C_{21}H_{13}ClN_2O_2$: C, 69.91; H, 3.63; N, 7.76. Found: C, 70.06; H, 3.69; N, 7.67.

12-(4-fluorophenyl)-12-hydroxyisoindolo[1,2-*b*]quinazolin-10(12H)-one (3ah): White solid, Yield: 57%, mp: 228-231 °C; IR (KBr) (ν_{max} /cm^{-1}): 3450, 1693, 1565, 1416; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.16 – 8.04 (m, 2H), 7.82 – 7.68 (m, 2H), 7.63 – 7.61 (m, 2H), 7.49 – 7.45 (m, 3H), 7.35 – 7.32 (m, 1H), 7.15 – 7.10 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.8, 152.8, 149.1, 148.5, 147.9, 135.1, 133.2, 131.8, 129.1, 128.2, 128.0, 127.0, 126.3, 121.4; MS (m/z): 344 (M$^+$); Anal. Calcd for $C_{21}H_{13}FN_2O_2$: C, 73.25; H, 3.81; N, 8.14. Found: C, 73.46; H, 3.85; N, 8.11.

12-hydroxy-12-(3-methoxyphenyl)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3aj): White solid, Yield: 72%, mp: 217-219 °C; IR (KBr) (ν_{max} /cm^{-1}): 3437, 1690, 1608, 1500; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.09 (d, *J* = 7.6 Hz, 2H), 7.91 – 7.75 (m, 2H), 7.63 (d, *J* = 4.7 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.39 – 7.36 (m, 1H), 7.21 – 7.14 (m, 2H), 6.88 – 6.85 (m, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.7, 141.5, 134.9, 133.7, 133.4, 130.6, 130.0, 127.7, 127.2, 126.6, 124.2, 122.5, 117.7, 115.7, 113.6, 112.1, 55.6; MS (m/z): 356 (M$^+$); Anal. Calcd for $C_{22}H_{16}N_2O_2$: C, 74.15; H, 4.53; N, 7.86. Found: C, 74.33; H, 4.47; N, 7.71.

12-(3-fluorophenyl)-12-hydroxyisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3ak): White solid, Yield: 53%, mp: 274-276 °C; IR (KBr) (ν_{max} /cm^{-1}): 3435, 1672, 1565, 1415;^{1}H NMR (300 MHz, DMSO-d_6) δ 8.08 (d, *J* = 6.9 Hz, 1H), 7.87 – 7.75 (m, 2H), 7.63- 7.58 (m, 2H), 7.53 – 7.27 (m, 5H), 7.20 – 7.07 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.9, (d, *J* = 242.2 Hz), 149.0, 147.8, 135.0, 133.9, 130.8, 127.7, 127.3, 126.6, 124.1, 123.3, 122.4, 121.7, 115.3 (d, *J*= 20.3 Hz), 113.1 (d, *J* = 23.3 Hz). MS (m/z): 344 (M$^+$); Anal. Calcd for $C_{21}H_{13}FN_2O_2$: C, 73.25; H, 3.81; N, 8.14. Found: C, 73.42; H, 3.90; N, 8.12.

12-(3-bromophenyl)-12-hydroxyisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3al): White solid, Yield: 61%, mp: 234-236 °C; IR (KBr) (ν_{max} /cm^{-1}): 3426, 1702, 1567, 1417; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.08 (d, *J* = 7.0 Hz, 2H), 7.90 – 7.79 (m, 3H), 7.63 (s, 2H), 7.51 – 7.49 (m, 2H), 7.36 (s, 2H), 7.24 – 7.18 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.7, 149.0, 142.6, 135.0, 133.9, 131.3, 131.0, 130.8, 128.7, 127.7, 127.3, 126.6, 124.8, 124.1, 123.4, 122.4, 122.1. MS (m/z): 249 (M$^+$ - 155); Anal. Calcd for $C_{21}H_{13}BrN_2O_2$: C, 62.24; H, 3.23; N, 6.91. Found: C, 62.41; H, 3.32; N, 6.82.

12-(2-fluorophenyl)-12-hydroxyisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3am): White solid, Yield: 48%, mp: 256-258 °C; IR (KBr) (ν_{max} /cm^{-1}): 3445, 1688, 1571, 1411; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.17 (s, 1H), 8.07 – 7.99 (m, 2H), 7.87 – 7.74 (m, 2H), 7.63 – 7.49 (m, 3H), 7.37 – 7. 24 (m, 3H), 6.97 – 6.90 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.7, 161.9 (d, *J*= 256.5 Hz), 158.6, 148.9, 146.9, 135.1, 133.8, 131.0, 130.8, 129.6, 127.7, 127.3, 126.9, 126.6, 125.5, 124.9, 123.0, 116.0 (d, *J*= 23.2 Hz); MS (m/z): 344 (M$^+$); Anal. Calcd for $C_{21}H_{13}FN_2O_2$: C, 73.25; H, 3.81; N, 8.14. Found: C, 73.42; H, 3.89; N, 8.09.

12-(2,5-dimethoxyphenyl)-12-hydroxyisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3an): White solid, Yield: 61%, mp: 272-274 °C; IR (KBr) (ν_{max} /cm^{-1}): 3410, 1690, 1600, 1467; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.07 – 8.00 (m, 2H), 7.81 (d, *J* = 7.3 Hz, 2H), 7.69 (d, *J* = 3.2 Hz, 1H), 7.64 – 7.43 (m, 4H), 7.27 – 7.25 (m, 1H), 6.88 – 6.84 (m, 1H), 6.72 (d, *J* = 9.0 Hz, 1H), 3.81 (s, 3H), 2.95 (s, 3H);. ^{13}C NMR (75 MHz, DMSO-d_6 + 1% CF_3COOH) δ 161.2, 158.1, 142.6, 135.9, 129.3, 129.1, 128.3, 126.8, 123.1, 122.2, 121.1, 120.4, 118.6, 117.3, 115.8, 114.2, 113.5, 109.7, 56.4,

55.6; MS (m/z): 356 (M^+ - 30); Anal. Calcd for $C_{23}H_{18}N_2O_4$: C, 71.49; H, 4.70; N, 7.25. Found: C, 71.64; H, 4.76; N, 7.15.

12-(2,3-dimethoxyphenyl)-12-hydroxyisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3ao): White solid, Yield: 55%, mp: 230-233 °C; IR (KBr) (ν_{max} /cm^{-1}): 3196, 1693, 1626, 1473; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.11 – 8.04 (m, 2H), 7.86 – 7.74 (m, 4H), 7.65 – 7.60 (m, 2H), 7.51 – 7.49 (m, 1H), 7.27 – 7.18 (m, 2H), 7.04 (d, *J* = 7.9 Hz, 1H), 3.66 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.5, 152.5, 148.2, 145.1, 134.8, 133.3, 132.8, 131.5, 130.3, 127.7, 127.0, 126.5, 123.6, 123.4, 122.8, 122.6, 120.5, 115.7, 113.7, 59.0, 56.0; MS (m/z): 386 (M^+); Anal. Calcd for $C_{23}H_{18}N_2O_4$: C, 71.49; H, 4.70; N, 7.25. Found: C, 71.69; H, 4.75; N, 7.16.

12-(2,4-dichlorophenyl)-12-hydroxyisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3ap): White solid, Yield: 53%, mp: 251-253 °C; IR (KBr) (ν_{max} /cm^{-1}): 3439, 1693, 1577, 1430; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 – 8.38 (m, 1H), 8.06 (d, *J* = 7.7 Hz, 2H), 7.88 – 7.90 (m, , 2H), 7.67 – 7.63 (m, 2H), 7.55 – 7.39 (m, 3H), 7.24 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.1, 158.7, 145.7, 143.2, 138.4, 135.4, 135.1, 134.3, 133.8, 132.0, 130.9, 130.2, 128.8, 127.9, 127.4, 126.7, 123.6, 121.9, 106.5; MS (m/z): 394 (M^+); Anal. Calcd for $C_{21}H_{12}Cl_2N_2O_2$: C, 63.82; H, 3.06; N, 7.09. Found: C, 63.99; H, 3.10; N, 7.07.

12-hydroxy-12-mesitylisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3aq): White solid, Yield: 62%, mp: 236-238 °C; IR (KBr) (ν_{max} /cm^{-1}): 3422, 1676, 1609, 1416; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.73 – 7.48 (m, 6H), 6.69 – 6.64 (m, 3H), 2.10 (s, 3H), 2.06 (s, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.0, 155.3, 151.6, 142.2, 139.1, 138.6, 136.4, 135.4, 134.3, 132.7, 130.6, 130.3, 127.4, 126.5, 126.1, 121.4; MS (m/z): 368 (M^+); Anal. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 78.30; H, 5.56; N, 7.51.

12-(furan-2-yl)-12-hydroxyisoindolo[1,2-b]quinazolin-10(12*H*)-one (3ar): White solid, Yield: 59%, mp: 175-177 °C; IR (KBr) (ν_{max} /cm^{-1}): 3140, 1691, 1566, 1468; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.16 – 8.05 (m, 3H), 7.87 – 7.80 (m, 2H), 7.72 – 7.67 (m, 2H), 7.58 – 7.44 (m, 3H), 6.81 (m, 1H), 6.48 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.7, 159.6, 148.7, 146.5, 135.0, 133.7, 130.7, 129.0, 128.2, 126.7, 123.4, 122.3, 96.6; MS (m/z): 316 (M^+); Anal. Calcd for $C_{19}H_{12}N_2O_3$: C, 72.15; H, 3.82; N, 8.86. Found: C, 72.40; H, 3.88; N, 8.82.

12-hydroxy-12-propylisoindolo[1,2-b]quinazolin-10(12*H*)-one (3at): White solid, Yield: 43%, mp: 151-153 °C; IR (KBr) (ν_{max} /cm^{-1}): 3076, 1682, 1565, 1489; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20 (t, *J* = 7.1 Hz, 2H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.75 – 7.70 (m, 2H), 7.58 – 7.51 (m, 2H), 7.30 (s, 1H), 3.07 – 2.95 (m, 1H), 2.34 – 2.26 (m, 1H), 0.90 – 0.73 (m, 2H), 0.71 – 0.64 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.7, 159.6, 149.0, 146.5, 135.0, 133.7, 130.7, 129.0, 128.2, 126.7, 123.4, 122.3, 96.6, 38.0, 17.3, 14.0; MS (m/z): 292 (M^+); Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 73.95; H, 5.52; N, 9.58. Found: C, 74.10; H, 5.62; N, 9.52.

12-hydroxy-2-methyl-12-phenylisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3ba): White solid, Yield: 74%, mp: 248-250 °C; IR (KBr) (ν_{max} /cm^{-1}): 3423, 1696, 1567, 1415; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.06 – 7.95 (m, 2H), 7.83 – 7.72 (m, 2H), 7.49 – 7.29 (m, 8H), 7.14 (s, 1H), 2.36 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.0, 148.6, 145.2, 144.3, 139.9, 135.0, 131.5, 128.8, 128.4, 127.0, 126.6, 125.7, 122.3, 21.8; MS (m/z): 340 (M^+); Anal. Calcd for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23. Found: C, 77.86; H, 4.76; N, 8.22.

2-chloro-12-hydroxy-12-phenylisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3ca): White solid, Yield: 69%, mp: 229-232 °C; IR (KBr) (ν_{max} /cm^{-1}): 3421, 1677, 1560, 1432; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.11 – 8.05 (m, 2H), 7.85 – 7.73 (m, 4H), 7.52 – 7.39 (m, 4H), 7.33 - 7.31 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.1, 149.8, 148.9, 143.9, 139.2, 130.1, 128.9, 128.4, 127.9, 127.6, 127.3, 126.7, 125.9, 124.3, 122.4; MS (m/z): 360 (M^+); Anal. Calcd for $C_{21}H_{13}ClN_2O_2$: C, 69.91; H, 3.63; N, 7.76. Found: C, 70.14; H, 3.70; N, 7.83.

3-chloro-12-hydroxy-12-phenylisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3ea): White solid, Yield: 64%, mp: 231-233 °C, IR (KBr) (ν_{max} /cm^{-1}): 3463, 1670, 1580, 1421;^{1}H NMR (300 MHz, DMSO-d_6) δ 8.11 – 8.04 (m, 2H), 7.81 – 7.62 (m, 4H), 7.50 – 7.43 (m, 4H), 7.36 – 7.30 (m, 5H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.3, 158.5, 150.3, 144.0, 141.1, 135.1, 133.4, 131.1, 130.3, 129.7, 128.7, 128.0, 126.9, 126.8, 126.2, 118.7; MS (m/z): 360; Anal. Calcd for $C_{21}H_{13}ClN_2O_2$: C, 69.91; H, 3.63; N, 7.76. Found: C, 70.02; H, 3.67; N, 7.72.

3-bromo-12-hydroxy-12-phenylisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3fa): White solid, Yield: 62%, mp: 245-247 °C; IR (KBr) (ν_{max} /cm^{-1}): 3448, 1689, 1562, 1464;^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (s, 1H), 8.08 (s, 1H), 7.83 – 7.82 (m, 2H), 7.73 – 7.65 (m 3H), 7.47 (s, 2H), 7.34 (s, 4H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 152.4, 149.0, 144.4, 142.7, 139.3, 134.8, 133.0, 130.7, 127.8, 127.6, 127.2, 126.6, 126.0, 123.5; MS (m/z): 404 (M^+); Anal. Calcd for $C_{21}H_{13}BrN_2O_2$: C, 62.24; H, 3.23; N, 6.91. Found: C, 62.35; H, 3.28; N, 6.87.

4-fluoro-12-hydroxy-12-phenylisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3ga): White solid, Yield: 37%, mp: 201-203 °C; IR (KBr) (ν_{max} /cm^{-1}): 3440, 1689, 1588, 1413; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.72 – 7.68 (m, 4H), 7.61 – 7.53 (m, 4H), 7.41 (s, 2H), 7.35 – 7.33 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.2, 158.2 (d, *J*= 248.2 Hz), 149.1, 147.6, 142.8, 134.3, 133.3, 133.0, 132.7, 129.4, 127.5, 127.1, 126.0, 125.6, 122.6, 121.7, 119.4 (d, *J*= 26.46 Hz), 113.7 (d, *J*= 32.76 Hz); MS (m/z): 344 (M^+); Anal. Calcd for $C_{21}H_{13}FN_2O_2$: C, 73.25; H, 3.81; N, 8.14. Found: C, 73.43; H, 3.86; N, 8.17

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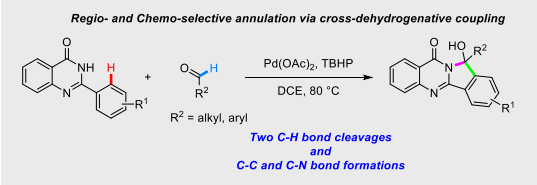

The palladium-catalyzed *cross*-dehydrogenative coupling followed by an intramolecular cyclization between arylquinazolinones and aldehydes is reported. This viable transformation provides a variety of novel substituted hydroxyisoindolo[1,2-b]quinazolinone compounds in moderate to good yields.

CDC Annulation

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Palladium Catalyzed Oxidative Cross-Dehydrogenative Coupling/Annulation Reactions: A Practical and Efficient Approach to hydroxyisoindolo[1,2-*b*]quinazolinone