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Synthesis of Isoquinoline-Fused Quinazolinones through Ag(I)-Catalyzed Cascade Annulation of 2-Aminobenzamides and 2-Alkynylbenzaldehydes

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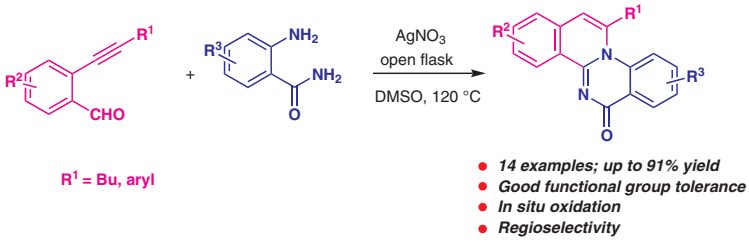

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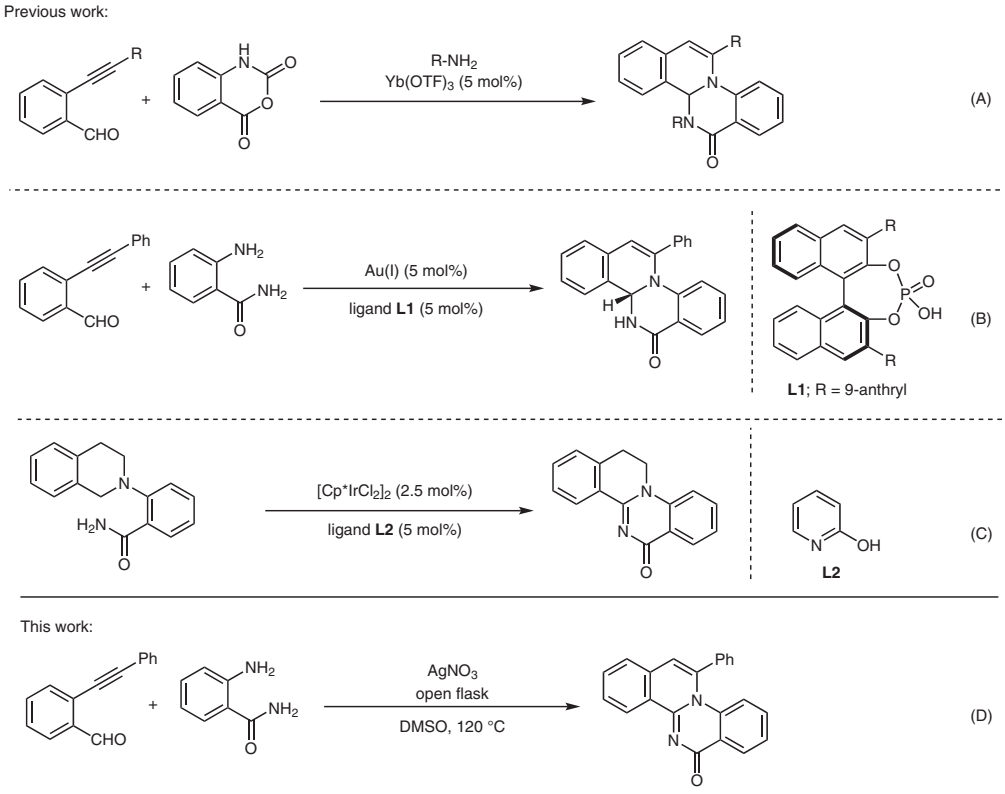
Abstract A new route for the expedient synthesis of a specific regioisomer of isoquinoline-fused quinazolinones is reported. Silver(I)-catalyzed cascade cyclization of 2-aminobenzamides and 2-alkynylbenzaldehydes followed by in situ oxidation gives 12-butyl- or 12-aryl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-ones in 69–91% yields. The structure of the isoquinoline-fused quinazolinone was confirmed by X-ray crystallography analysis.

Key words isoquinoline, quinazolinone, regioisomer, silver catalyst, cascade annulation

Over the past few decades, transition-metal-catalyzed C–H bond functionalizations for C–C bond formation have proved to be a powerful method for the construction of complex chemical compounds[2] in an atom- and step-economic manner.[3] To date these transformations are widely used in the area of synthesis of both natural products and therapeutic agents. Among the transition-metal-catalyzed organic transformations, Ag-catalyzed C–H/C–C bond functionalization is one of the frontier areas in organic chemistry.[4] Compared with other transition metals such as gold or platinum, Ag(I) salts represent an inexpensive alternative for the electrophilic activation of alkynes under mild conditions.[4e,5] Thus, the development of new systems catalyzed by Ag(I) for C–H/C–C functionalization represents a central challenge for the construction of various types of fused N-heterocycles. Nitrogen-containing heterocycles are important molecular motifs in natural products, materials, and bioactive molecules.[6] In this regard, quinazolinone derivatives represent a class of privileged N-heterocyclic motifs present in a broad range of alkaloid natural products.[7] Furthermore, they also show a wide range of biological activities.[8,9] Much effort has focused on synthetic methods for ring-fused quinazolinone derivatives.[10] In particular, synthetic strategies for ring-fused quinazolinones, as the core structural skeletons in a variety of natural products and pharmaceutical molecules, have been intensely explored in recent years. Isoquinolines are ubiquitous structural motif present in a numerous biologically active natural products and pharmaceutically important compounds.[11] Molecular skeletons that integrate isoquinoline and quinazolinone moieties might possess the properties of both and enhance their activity.[12]

Several reports are available for the synthesis of isoquinoline-fused quinazolinones.[13] Pal and co-workers reported the synthesis of 4b,5-dihydro-6*H*-isoquinolino[2,1-*a*]quinazolin-6-ones via one-pot Yb(III)-mediated cascade reaction [Scheme 1 (A)].[14] Patil and co-workers reported Au(I)-catalyzed synthesis of optically pure 4b,5-dihydro-6*H*-isoquinolino[2,1-*a*]quinazolin-6-ones [Scheme 1 (B)][15] and Yan and co-workers used the Ir-catalyzed intramolecular acceptorless dehydrogenative cross-coupling of tertiary amines and amides for the synthesis of 12,13-dihydro-6*H*-isoquinolino[2,1-*a*]quinazolin-6-ones [Scheme 1 (C)].[13f] However, some of these procedures have significant drawbacks, such as low yield, long reaction times, harsh reaction conditions, and the use of expensive reagents. In an effort to synthesize N-fused heterocycles by a transition-metal-catalyzed C–C functionalization, herein we report, the synthesis of isoquinoline-fused quinazolinones via a $AgNO_3$-catalyzed one-pot cascade cyclization of 2-aminobenzamides and 2-alkynylbenzaldehydes through an oxidation process.

In the synthesis of isoquinoline-fused quinazolinones, the fusion of quinazolinone ring may occur in two different ways (linear and angular) for two different types of nitrogen atoms that would lead to the formation of two regioisomers. Both of the isomers should have certain unique pharmacological features. Therefore, a synthetic method that



Scheme 1 Approaches for the synthesis of quinazolinones

can exclusively provide a single regioisomer instead of a mixture is highly desirable. With this in mind, we initially began with reaction optimization conditions with 2-aminobenzamide (**1a**) and 2-(phenylethynyl)benzaldehyde (**2a**) as model substrates (Table 1). We initially subjected compounds **1a** and **2a** in an equimolar ratio to oxidative conditions using 30 mol% of AgOTf in DMSO solvent at 100 °C for 5 hours (Table 1, entry 1). To our delight, the reaction was very much regioselective and only a single regioisomer **4a** was formed (from TLC) as confirmed by NMR in low yield (29%).

Next, the yield of compound **4a** was increased to 54% by increasing the temperature to 120 °C (entry 2). However, the use of 10 mol% AgOTf in the reaction at this temperature resulted in a decrease in the product yield to 43% (entry 3). A significant improvement in the yield was observed when 20 mol% of AgOTf was used in the reaction and the desired product was isolated in 73% yield (entry 4). On the other hand, the use of Ag_2O and $AgPF_6$ catalysts in the reaction afforded desired product **4a** in 9% and 5% yields, respectively (entries 5 and 7); $AgClO_4$ yielded only 33% of product **4a** (entry 6). To improve the yield of the reaction, different solvents were screened with 20 mol% of $AgNO_3$ (entries 10, 12–14) and the best result was obtained when the reaction was carried out in DMSO solvent at 120 °C which provided required product **4a** in 89% yield (entry 10). Also, we carried out reaction of 2-aminobenzamide (**1a**) and 2-(phenylethynyl)benzaldehyde (**2a**) under a nitrogen atmosphere

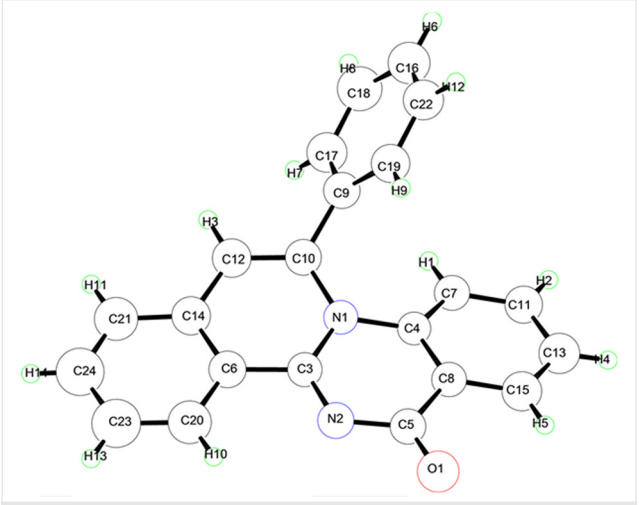
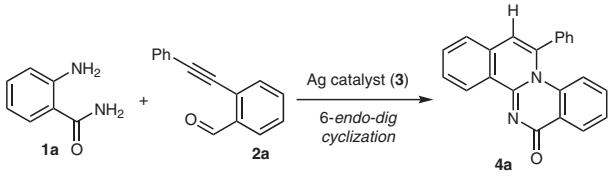


Figure 1 X-ray crystal structure of **4a** (ORTEP diagram); thermal ellipsoids are drawn at 50% probability level

Table 1 Optimization of the Synthesis of 12-Phenyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (**4a**)[a]



Entry	Ag catalyst **3** (mol%)	Solvent	Time (h)	Temp (°C)	Yield[b] (%)
1	AgOTf (30)	DMSO	5	100	29
2	AgOTf (30)	DMSO	4	120	54
3	AgOTf (10)	DMSO	8	120	43
4	AgOTf (20)	DMSO	4	120	73
5	Ag_2O (20)	DMSO	6	120	9
6	$AgClO_4$ (20)	DMSO	6	120	33
7	$AgPF_6$ (20)	DMSO	6	120	5
8	$AgNO_3$ (2)	DMSO	10	120	77
9	$AgNO_3$ (5)	DMSO	9	120	82
10	$AgNO_3$ (20)	DMSO	6	120	89
11	$AgNO_3$ (20)	DMSO	6	120	13[c]
12	$AgNO_3$ (20)	DMF	6	120	42
13	$AgNO_3$ (20)	DMA[d]	6	120	58
14	$AgNO_3$ (20)	toluene	6	110	34

[a] Reaction conditions: 2-aminobenzamide (**1a**; 0.242 mmol), 2-(phenylethynyl)benzaldehyde (**2a**; 0.242 mmol); solvent (4 mL), open flask.
[b] Isolated yield.
[c] Reaction was carried out under N_2 atmosphere. **4a** was obtained together with 12-phenyl-4b,5-dihydro-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (72%).
[d] DMA = dimethylacetamide.

(entry 11), interestingly we obtained unaromatized 12-phenyl-4b,5-dihydro-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one[15] in 72% yield and only 13% of the required product **4a**.

Next, to assess the substrate scope and generality of the newly developed $AgNO_3$-catalyzed cascade reaction, a variety of 2-alkynylbenzaldehydes **2** bearing different variously substituted alkynyl groups and/or substitution on the benzaldehyde ring and a range of 2-aminobenzamides **1** were employed under the optimized reaction conditions (Scheme 2). As shown in Scheme 2, 2-alkynylbenzaldehydes **2** with alkynyl groups bearing a variety of substituents, such as butyl, phenyl, 4-methoxyphenyl, and 4-fluoro-3-methylphenyl, and/or the benzaldehyde ring containing electron-withdrawing halide groups or electron-donating methoxy groups were well tolerated under the present reaction conditions and afforded the desired isoquinoline-fused quinazolinones **4a–n** in good to excellent yields (Scheme 2, 69–91%). Electron-donating groups on the benzaldehyde aromatic ring were also well tolerated. The presence of an electron-withdrawing halide group in the 2-aminobenzamide ring also did not make a significant difference to the yield. The synthesized compounds **4a–n** were characterized by IR, HRMS, ^1H and ^{13}C NMR spectral analysis.

Finally, the regioselectivity achieved through Ag(I)-catalyzed cascade annulation of 2-aminobenzamides and 2-alkynylbenzaldehydes in the synthesis of isoquinoline-fused quinazolinones **4** was confirmed by X-ray crystallography analysis. The crystal structure of the representative compound 12-phenyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (**4a**) was confirmed by the X-ray crystallography analysis (Figure 1).[16]

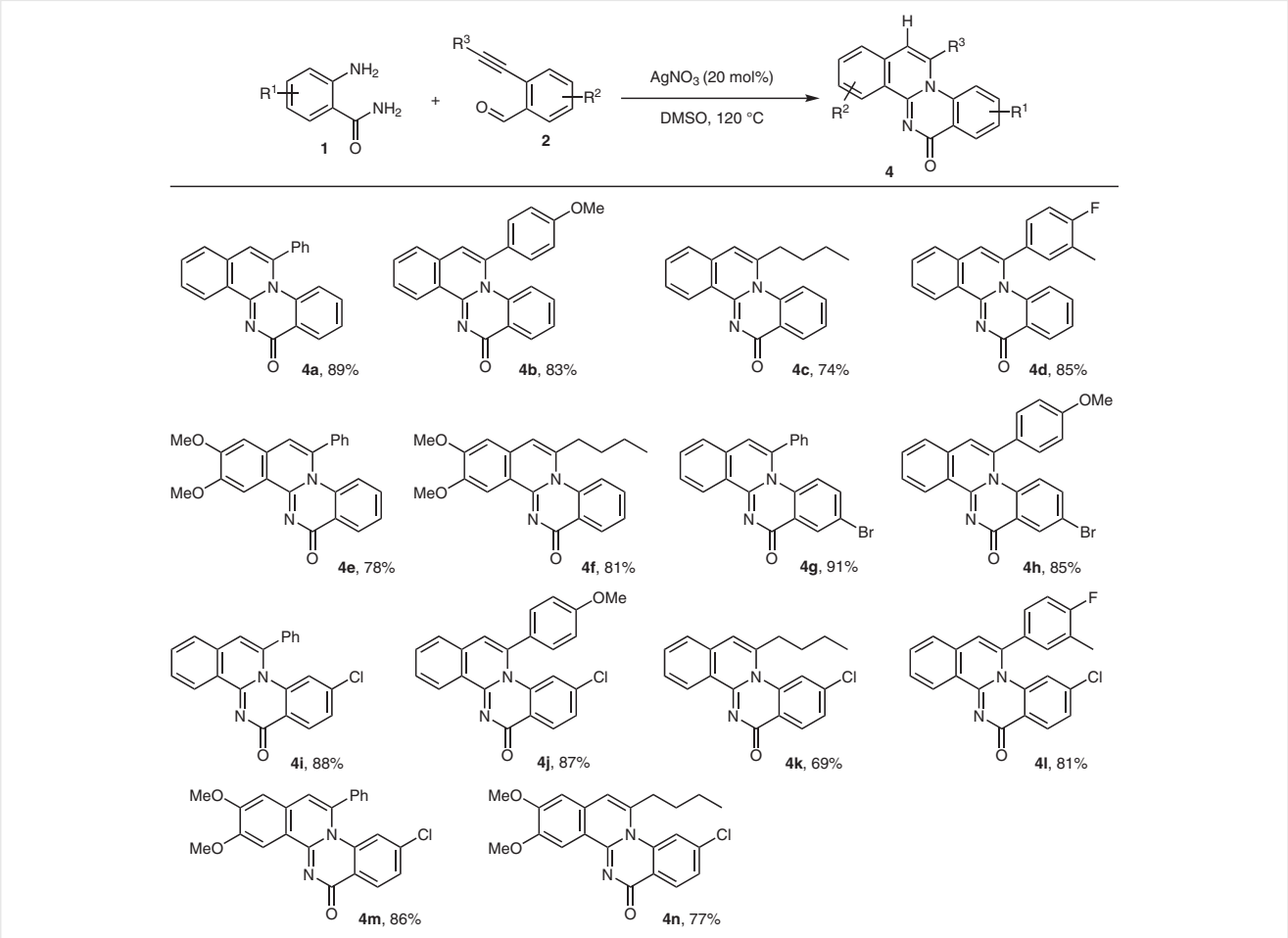
A plausible mechanism for the formation of isoquinoline-fused quinazolinones **4** is presented in Scheme 3. The reaction of 2-aminobenzamide **1** and 2-alkynylbenzaldehyde **2** gives an imine in which the C≡C bond coordinates to the Ag catalyst to give intermediate **I**. Intermediate **I** on 6-*endo-dig* cyclization via protodemetalation delivers intermediate **II**. Finally, in situ oxidation of intermediate **II** delivers the desired isoquinoline-fused quinazolinone derivative **4** and regenerates the silver catalyst for a new catalytic cycle.

In summary, we developed a novel $AgNO_3$-catalyzed cascade cyclization of 2-aminobenzamides and 2-alkynylbenzaldehydes which underwent in situ oxidation to deliver isoquinoline-fused quinazolinone derivatives in good to excellent yields. This novel synthetic approach is amenable to the generation of a library of isoquinoline-fused quinazolinone analogues. Further expansion of the current strategies and evaluation of biological activities are in progress.

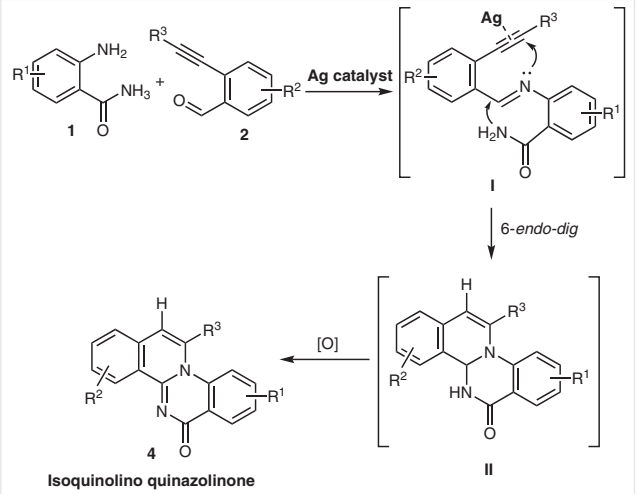
All solvents and reagents were purchased from the suppliers and used without further purification. IR spectra were recorded on a JASCO FT/IR-460 Plus spectrophotometer. Reactions were monitored by TLC on silica plates using UV-light or I_2 chamber for visualization. Evaporation and condensation were carried out in vacuo. NMR spectra were recorded with JEOL JNM-ECS 400 spectrometers with TMS as an internal standard. The data of all known compounds data are consistent with the literature reports. Scale up reactions also performed as per the given general procedure without any deviation. Melting points were measured by a Yanaco micro melting point apparatus.

2-(Phenylethynyl)benzaldehyde (2a); Typical Procedure[17]

To a solution of 2-bromobenzaldehyde (500 mg, 2.7 mmol, 1 equiv) in THF (10 mL) were added $PdCl_2(PPh_3)_2$ (95 mg, 5 mol%) and Et_3N (820 mg, 8.1 mmol, 3 equiv); the resulting mixture was stirred and purged with N_2 gas for 10 min. Then phenylacetylene (414 mg, 4.054 mmol, 1.5 equiv) and CuI (26 mg, 5 mol%) were added. The mixture was further stirred under N_2 gas at r.t. for 24 h. After completion, the reaction was quenched with sat. NH_4Cl and extracted with EtOAc. Organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The crude residue was purified by chromatography (silica gel, EtOAc/*n*-hexane 3:97) to afford **2a** (347 mg, 62%) as a brown oil. Spectroscopic data are consistent with those previously reported.[17]



Scheme 2 Synthesis of 12-substituted 6*H*-isoquinolino[2,1-*a*]quinazolin-6-one derivatives **4** via $AgNO_3$ catalyst. *Reagents and conditions*: 2-aminobenzamide **1** (0.24 mmol), 2-alkynylbenzaldehyde **2** (0.24 mmol), $AgNO_3$ (20 mol%), DMSO, 120 °C; isolated yields are given.



Scheme 3 Plausible mechanism for the formation of isoquinoline-fused quinazolinones

12-Butyl- or 12-Aryl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-ones 4; General Procedure

To a solution of 2-aminobenzamide **1** (0.24 mmol, 1 equiv) and 2-alkynylbenzaldehyde **2** (0.24 mmol, 1 equiv) in DMSO (4 mL) was added $AgNO_3$ (8 mg, 20 mol%). The resulting mixture was then heated at 120 °C for 4 h. After completion of the reaction, the mixture was extracted with EtOAc. The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated. The crude product was purified by chromatography (silica gel, acetone/hexane 20:80) to afford the product.

12-Phenyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4a)

White solid; yield: 70 mg (89%); mp 211–213 °C.

IR (neat): 2999, 1655, 1630, 1599, 1586, 1561, 1479, 1467, 1254, 1179, 1136, 1066, 858, 832, 752, 676, 580, 542 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.69 (d, *J* = 8.1 Hz, 1 H), 8.08 (d, *J* = 6.7 Hz, 1 H), 7.87 (d, *J* = 4.0 Hz, 2 H), 7.71 (q, *J* = 3.9 Hz, 1 H), 7.50 (d, *J* = 3.6 Hz, 2 H), 7.40–7.46 (m, 5 H), 7.31 (t, *J* = 7.2 Hz, 1 H), 6.97 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.44, 153.40, 138.49, 138.23, 136.86, 133.54, 130.44, 129.10, 128.91, 128.70, 127.48, 127.02, 126.79, 126.70, 126.49, 125.30, 122.28, 122.19, 117.16.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{15}N_2O$: 323.1184; found: 323.1155.

12-(4-Methoxyphenyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4b)

Yellow solid; yield: 62 mg (83%); mp 235–236 °C.

IR (neat): 3067, 2905, 1651, 1626, 1602, 1523, 1510, 1337, 1258, 1023, 831, 822, 772, 762, 544 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.65 (d, *J* = 8.1 Hz, 1 H), 8.05 (d, *J* = 6.3 Hz, 1 H), 7.82 (d, *J* = 5.4 Hz, 2 H), 7.63–7.67 (m, 1 H), 7.39–7.45 (m, 3 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 7.27 (s, 1 H), 6.97 (dd, *J* = 14.8, 8.5 Hz, 3 H), 3.77 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.43, 159.57, 153.43, 138.40, 138.36, 133.71, 133.44, 130.35, 129.16, 128.90, 128.31, 126.73, 126.60, 126.43, 125.09, 122.20, 122.13, 116.15, 114.44, 55.28.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{16}N_2O_2Na$: 375.1109; found: 375.1133.

12-Butyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4c)

Brown solid; yield: 60 mg (74%); mp 95–96 °C.

IR (neat): 2931, 2872, 1647, 1634, 1603, 1592, 1516, 1456, 1343, 1271, 1189, 1114, 1066, 787, 759, 710, 544 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.58 (d, *J* = 8.1 Hz, 1 H), 8.14 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.96 (d, *J* = 8.5 Hz, 1 H), 7.74–7.83 (m, 3 H), 7.60–7.66 (m, 2 H), 7.27 (s, 1 H), 3.12 (t, *J* = 7.6 Hz, 2 H), 1.37–1.44 (m, 2 H), 1.08–1.16 (m, 2 H), 0.72 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.22, 153.40, 140.10, 137.75, 133.76, 133.34, 131.57, 127.89, 127.42, 126.60, 126.53, 126.03, 124.60, 122.32, 121.39, 114.50, 33.67, 30.98, 21.50, 13.48.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}N_2O$: 303.1497; found: 303.1469.

12-(4-Fluoro-3-methylphenyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4d)

Brown solid; yield: 63 mg (85%); mp 86–87 °C.

IR (neat): 3015, 1651, 1646, 1629, 1519, 1362, 1215, 1157, 1033, 824, 754, 666, 645, 537 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.95 (d, *J* = 8.1 Hz, 1 H), 8.33 (d, *J* = 8.1 Hz, 1 H), 7.75 (t, *J* = 7.0 Hz, 1 H), 7.61 (dd, *J* = 13.0, 7.6 Hz, 2 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 7.22–7.29 (m, 2 H), 7.10 (s, 1 H), 6.97–7.03 (m, 3 H), 2.27 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.03, 162.79, 160.26, 154.24, 138.50, 137.89, 133.57, 132.80, 130.65, 130.32, 130.26, 128.75, 128.20, 127.72, 126.88, 126.54, 126.46, 126.40, 125.99, 122.45, 122.03, 117.53, 116.23, 116.00, 14.76, 14.72.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{15}N_2OFNa$: 377.1066; found: 377.1096.

2,3-Dimethoxy-12-phenyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4e)

Yellow solid; yield: 56 mg (78%); mp 209–211 °C.

IR (neat): 3061, 1644, 1621, 1602, 1495, 1416, 1368, 1195, 1131, 991, 752, 698, 641, 529, 501 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 12.1 Hz, 2 H), 7.37 (d, *J* = 8.1 Hz, 6 H), 7.20 (t, *J* = 7.9 Hz, 1 H), 7.01 (q, *J* = 8.7 Hz, 3 H), 4.09 (s, 3 H), 4.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.13, 154.63, 153.62, 150.59, 138.61, 137.68, 137.25, 130.43, 129.52, 129.43, 128.96, 127.70, 127.21, 126.68, 122.50, 122.31, 120.11, 117.53, 108.19, 106.56, 56.80, 56.41.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{18}N_2O_3Na$: 405.1215; found: 405.1226.

12-Butyl-2,3-dimethoxy-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4f)

Brown sticky liquid; yield: 60 mg (81%).

IR (neat): 2934, 2961, 1719, 1630, 1604, 1592, 1439, 1398, 1340, 1267, 1226, 1166, 1064, 1032, 998, 878, 862, 771, 755, 664, 644 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 7.6 Hz, 1 H), 8.28 (s, 1 H), 7.66 (d, *J* = 3.6 Hz, 2 H), 7.55–7.60 (m, 1 H), 6.94 (d, *J* = 5.8 Hz, 2 H), 4.06 (s, 3 H), 4.04 (s, 3 H), 3.13 (t, *J* = 7.6 Hz, 2 H), 1.47–1.54 (m, 2 H), 1.17–1.25 (m, 2 H), 0.82 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.03, 154.56, 153.76, 150.11, 138.66, 138.30, 131.03, 129.78, 128.10, 127.24, 123.04, 120.72, 119.50, 115.18, 107.99, 105.88, 56.77, 56.37, 34.71, 32.31, 22.23, 13.78.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{23}N_2O_3$: 363.1709; found: 363.1679.

8-Bromo-12-phenyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4g)

Yellow solid; yield: 21 mg (91%); mp 218–219 °C.

IR (neat): 3027, 1772, 1630, 1508, 1482, 1491, 1317, 1250, 1183, 1168, 895, 814, 712, 638, 529 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.69 (d, *J* = 8.1 Hz, 1 H), 8.14 (d, *J* = 2.2 Hz, 1 H), 7.88 (q, *J* = 1.8 Hz, 2 H), 7.69–7.74 (m, 1 H), 7.49–7.55 (m, 3 H), 7.42–7.45 (m, 4 H), 6.91 (d, *J* = 9.4 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.22, 153.56, 138.32, 137.40, 136.57, 133.75, 133.60, 133.02, 129.22, 129.07, 128.82, 128.55, 127.52, 127.07, 126.91, 125.16, 124.64, 123.84, 119.46, 117.40.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{14}N_2OBr$: 401.0289; found: 401.0300.

8-Bromo-12-(4-methoxyphenyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4h)

Yellow solid; yield: 23 mg (85%); mp 254–256 °C.

IR (neat): 1648, 1628, 1603, 1506, 1478, 1317, 1277, 1248, 1163, 1122, 1026, 890, 833, 813, 793, 618, 540 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.66 (d, *J* = 8.1 Hz, 1 H), 8.12 (d, *J* = 2.2 Hz, 1 H), 7.86 (dd, *J* = 14.6, 8.3 Hz, 2 H), 7.66–7.70 (m, 1 H), 7.53 (dd, *J* = 9.2, 2.5 Hz, 1 H), 7.46 (d, *J* = 9.0 Hz, 2 H), 7.33 (d, *J* = 7.2 Hz, 1 H), 6.94–7.00 (m, 3 H), 3.79 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.25, 159.70, 153.62, 138.30, 137.56, 133.79, 133.69, 132.99, 129.03, 128.91, 128.50, 126.87, 124.98, 124.54, 123.89, 119.41, 116.43, 114.58, 55.31.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{16}N_2O_2Br$: 431.0395; found: 431.0394.

9-Chloro-12-phenyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4i)

Yellow solid; yield: 76 mg (88%); mp 268–270 °C.

IR (neat): 3170, 3040, 1707, 1646, 1629, 1586, 1509, 1474, 1302, 1067, 869, 843, 832, 756, 705, 681, 547 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.99 (d, *J* = 7.6 Hz, 1 H), 8.29 (d, *J* = 8.5 Hz, 1 H), 7.77–7.81 (m, 1 H), 7.66 (t, *J* = 7.2 Hz, 2 H), 7.46 (t, *J* = 3.4 Hz, 3 H), 7.36–7.39 (m, 3 H), 7.12 (s, 1 H), 6.96 (d, *J* = 1.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.24, 154.53, 139.20, 138.44, 137.04, 136.31, 133.79, 133.53, 129.61, 129.51, 129.19, 128.96, 128.35, 127.37, 127.21, 126.47, 125.87, 122.12, 120.72, 117.88.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{14}N_2OCl$: 357.0795; found: 357.0770.

9-Chloro-12-(4-methoxyphenyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4j)

Yellow solid; yield: 71 mg (87%); mp 177–178 °C.

IR (neat): 3066, 3000, 1655, 1630, 1599, 1586, 1479, 1467, 1316, 1254, 1136, 1098, 833, 788, 754, 663, 453 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.93 (d, *J* = 7.6 Hz, 1 H), 8.25 (d, *J* = 8.5 Hz, 1 H), 7.75 (t, *J* = 7.4 Hz, 1 H), 7.60 (t, *J* = 8.8 Hz, 2 H), 7.35 (d, *J* = 8.5 Hz, 1 H), 7.26 (d, *J* = 8.5 Hz, 2 H), 7.00 (d, *J* = 9.0 Hz, 2 H), 6.94 (d, *J* = 8.5 Hz, 2 H), 3.86 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.25, 160.48, 154.63, 139.36, 138.34, 136.93, 133.72, 129.13, 128.61, 128.28, 127.29, 126.29, 125.69, 122.09, 120.76, 116.99, 114.96, 55.53.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{15}N_2O_2ClNa$: 409.0720; found: 409.0749.

12-Butyl-9-chloro-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4k)

Brownish sticky liquid; yield: 63 mg (69%).

IR (neat): 2960, 2873, 1719, 1561, 1479, 1466, 1450, 1423, 1340, 1316, 1266, 1155, 913, 876, 780, 564, 515 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.86 (d, *J* = 8.1 Hz, 1 H), 8.34 (d, *J* = 8.5 Hz, 1 H), 7.74 (t, *J* = 7.6 Hz, 1 H), 7.67 (s, 1 H), 7.54–7.60 (m, 3 H), 7.00 (s, 1 H), 3.10 (t, *J* = 7.9 Hz, 2 H), 1.50–1.58 (m, 2 H), 1.27 (d, *J* = 7.2 Hz, 2 H), 0.83–0.90 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.10, 154.62, 139.18, 138.87, 137.60, 133.68, 133.57, 129.63, 128.28, 128.01, 127.78, 125.67, 125.36, 121.21, 120.34, 115.85, 34.34, 32.02, 22.07, 13.64.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{18}N_2OCl$: 337.1108; found: 337.1097.

9-Chloro-12-(4-fluoro-3-methylphenyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4l)

Brown solid; yield: 66 mg (81%); mp 252–254 °C.

IR (neat): 3139, 3033, 1637, 1597, 1583, 1511, 1501, 1481, 1444, 1318, 1128, 1120, 833, 809, 772, 754, 611 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.97 (d, *J* = 7.6 Hz, 1 H), 8.28 (d, *J* = 8.5 Hz, 1 H), 7.77–7.81 (m, 1 H), 7.65 (t, *J* = 7.2 Hz, 2 H), 7.39 (dd, *J* = 8.3, 1.6 Hz, 1 H), 7.24 (d, *J* = 7.2 Hz, 1 H), 7.14 (q, *J* = 2.4 Hz, 1 H), 7.05–7.10 (m, 2 H), 6.99 (d, *J* = 1.7 Hz, 1 H), 2.30 (d, *J* = 1.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.23, 162.94, 160.40, 154.50, 139.14, 137.56, 137.05, 133.83, 133.46, 132.17, 132.13, 130.26, 130.21, 129.24, 128.96, 128.31, 127.44, 126.82, 126.63, 126.49, 126.42, 125.80, 121.96, 120.71, 117.73, 116.41, 116.19, 14.73, 14.70.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{15}N_2OClF$: 389.0857; found: 389.0827.

9-Chloro-2,3-dimethoxy-12-phenyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4m)

Yellow solid; yield: 67 mg (86%); mp 256–258 °C.

IR (neat): 3061, 3004, 1619, 1584, 1495, 1454, 1393, 1270, 1220, 1195, 1072, 998, 880, 771, 701, 646, 532 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 1 H), 8.28 (d, *J* = 8.5 Hz, 1 H), 7.43–7.45 (m, 3 H), 7.34–7.37 (m, 3 H), 7.05 (d, *J* = 14.8 Hz, 2 H), 6.97 (d, *J* = 1.3 Hz, 1 H), 4.09 (s, 3 H), 4.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.38, 154.92, 153.91, 150.77, 139.32, 137.47, 136.91, 136.62, 129.69, 129.56, 129.38, 129.24, 127.30, 127.25, 122.37, 120.83, 119.95, 117.73, 108.29, 106.66, 56.84, 56.46.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{18}N_2O_3Cl$: 417.1006; found: 417.0987.

12-Butyl-9-chloro-2,3-dimethoxy-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4n)

Yellow solid; yield: 62 mg (77%); mp 96–97 °C.

IR (neat): 2959, 2931, 1634, 1603, 1592, 1516, 1481, 1343, 1271, 1155, 962, 935, 760, 710, 622, 473 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 8.1 Hz, 1 H), 8.25 (s, 1 H), 7.67 (d, *J* = 1.8 Hz, 1 H), 7.54 (dd, *J* = 8.5, 1.8 Hz, 1 H), 6.94 (d, *J* = 6.7 Hz, 2 H), 4.06 (s, 3 H), 4.04 (s, 3 H), 3.10 (t, *J* = 7.9 Hz, 2 H), 1.51–1.58 (m, 2 H), 1.26 (td, *J* = 14.7, 7.5 Hz, 2 H), 0.85 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.26, 154.80, 154.05, 150.26, 139.04, 138.22, 137.44, 129.77, 129.73, 127.72, 121.36, 120.57, 119.34, 115.66, 108.05, 105.99, 56.78, 56.41, 34.49, 32.29, 22.19, 13.77.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{21}N_2O_3ClNa$: 419.1138; found: 419.1145.

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Supporting Information

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