A Practical, Ligand-Free, Palladium-Catalyzed Isocyanide Insertion Reaction for the Construction of Novel Ring-Fused Quinazolinones

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Abstract: A high-yielding, ligand-free, palladium-catalyzed isocyanide insertion reaction for the synthesis of phthalazino[1,2-*b*]quinazolinones from the readily obtainable quinazolinones has been developed. Easily handled and relatively low-cost palladium(II) acetate was used as the catalyst, without an additional ligand. Preparation of the quinazolinones involved the cascade reaction of isatoic anhydrides, phenylhydrazines and 2-bromobenzaldehyde catalyzed by *p*-toluenesulfonic acid in one pot. This novel protocol may be applicable for the synthesis of other important ring-fused heterocyclic compounds.

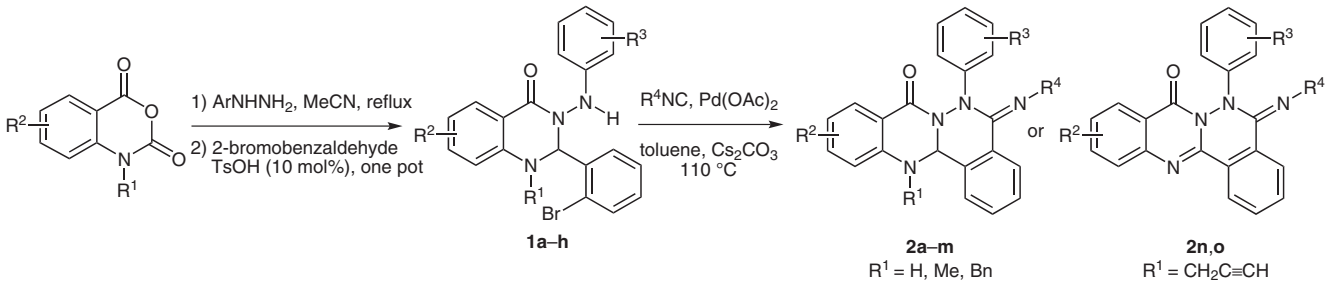
Key words: ligand-free, palladium catalysis, isocyanide insertion reaction, ring-fused quinazolinones, depropargylation

In recent years, isocyanides have emerged as powerful building blocks in the construction of medicinally important molecules and natural products.[1] Isocyanides have an isoelectronic relationship with carbon monoxide,[2] which enables their inclusion into organic synthesis with transition-metal-catalyzed protocols.[3] The use of isocyanides in place of carbon monoxide in transition-metal-catalyzed reactions has considerable advantages, such as simple handling, an extra diversity point and the possibilities of further elaboration of use of convertible isocyanides.[3,4] Moreover, the palladium-catalyzed reaction for the insertion of isocyanides is an efficient but relatively unexplored method that offers more possibilities for the synthesis of heterocyclic compounds. It is therefore not surprising that interest in this field has recently increased significantly.[2d,5]

Ring-fused quinazolinones as considered privileged heterocyclic motifs have been found in the core structural skeletons of many natural products including evodiamine[6a] and rutaecarpine[6b] isolated from *Evodia rutaecarpa*, luotonin A isolated from *Peganum nigellastrum*,[6c] tryptanthrin isolated from *Couroupita guianensis*[6d] and deoxyvasicinone isolated from *Adhatoda vasica*.[6e] These quinazolinone alkaloids exhibit a wide range of biological and medicinal activities.[6a,7] In addition, biological assays have shown that ring-fused quinazolinones containing the –CO–N–N– structural fragment have analgesic properties, and some derivatives exhibit anti-inflammatory activities.[8] These pharmacological records promoted us to develop an efficient method for the preparation of ring-fused quinazolinones. Some procedures for the synthesis of ring-fused quinazolinones are known;[8,9] however, previous reported pathways often suffer from the poor availability of starting materials, poor regioselectivity, low yields and low functional group diversity. Thus, it is still necessary to develop an efficient and simple pathway to synthesize ring-fused quinazolinones and their analogues.

Herein, we report the development of a novel, ligand-free, palladium-catalyzed isocyanide insertion reaction for the synthesis of phthalazino[1,2-*b*]quinazolinones from the readily obtainable quinazolinones. As shown in Scheme 1, the cascade reaction of isatoic anhydrides, phenylhydrazines and 2-bromobenzaldehyde catalyzed by *p*-toluenesulfonic acid could be used to prepare the quinazolinones,[10] which provided the starting materials for the palladium-catalyzed isocyanide insertion reaction.

In the initial phase of the investigation, several kinds of quinazolinones were synthesized via the cascade reaction of isatoic anhydrides, phenylhydrazines and 2-bromobenzaldehyde catalyzed by *p*-toluenesulfonic acid, in moderate to high yields (Table 1).



Scheme 1 General strategy for the synthesis of phthalazino[1,2-*b*]quinazolinones

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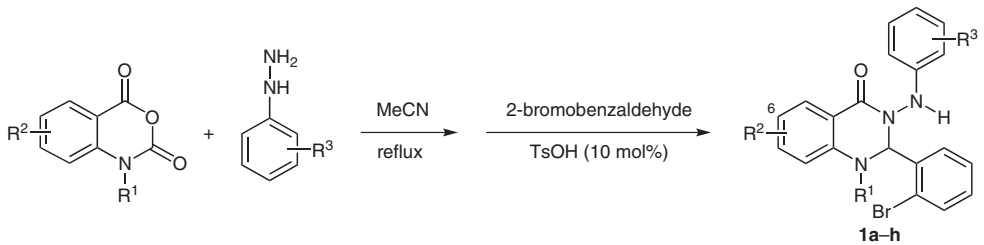
Table 1 Synthesis of Quinazolinones

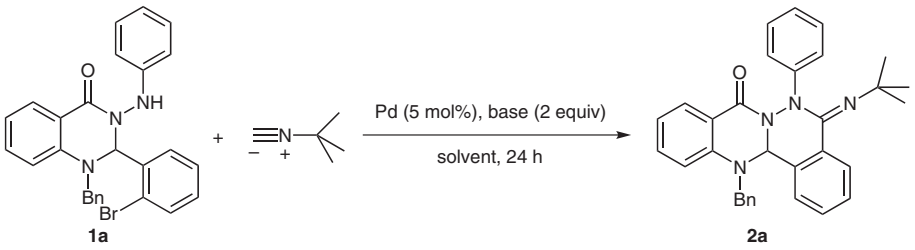


R^1	R^2	R^3	Product	Yield[a] (%)
Bn	H	H	**1a**	87
Me	H	H	**1b**	85
Bn	6-Cl	H	**1c**	82
Me	6-Cl	H	**1d**	84
Me	H	4-Cl	**1e**	75
Me	H	4-Me	**1f**	89
H	H	H	**1g**	75
$CH_2C{\equiv}CH$	H	H	**1h**	78

[a] Isolated yield.

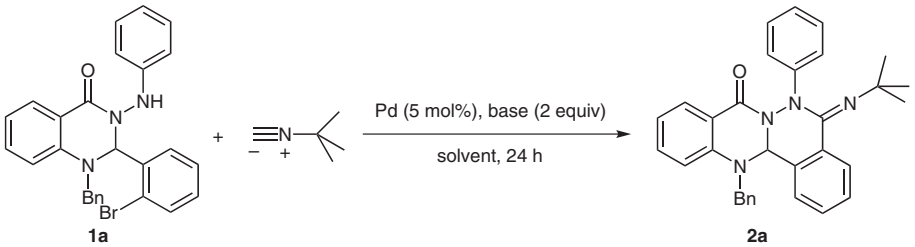
Next, the synthesized quinazolinone **1a** was chosen as a substrate for the optimization of the palladium-catalyzed isocyanide insertion reaction. The model reaction was carried out using different catalysts, bases, solvents and temperatures. The reaction failed to proceed when palladium catalyst was excluded (Table 2, entries 1 and 2). Among the three solvents (toluene, MeCN and DMF), toluene was found to be the best choice (Table 2, entries 3–5). A change of the palladium catalyst did not result in increased yield (Table 2, entries 3 and 6–10). With palladium(II) acetate as a catalyst and toluene as a solvent, bases were screened and cesium carbonate was found to be the most effective base (Table 2, entries 3 and 11–13). Meanwhile, decreasing the reaction temperature to 90 °C resulted in a significantly lower yield of **2a** (Table 2, entries 3, 14 and 15).

Table 2 Optimization of the Palladium-Catalyzed Isocyanide Insertion Reaction[a]



Entry	Catalyst	Base	Solvent	Temp (°C)	Yield[b] (%)
1	–	–	toluene	110	–
2	–	Cs_2CO_3	toluene	110	–
3	$Pd(OAc)_2$	Cs_2CO_3	toluene	110	85
4	$Pd(OAc)_2$	Cs_2CO_3	MeCN	80	75
5	$Pd(OAc)_2$	Cs_2CO_3	DMF	110	67
6	$PdCl_2$	Cs_2CO_3	toluene	110	72
7	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	toluene	110	83
8	$Pd(dppf)Cl_2$	Cs_2CO_3	toluene	110	76

Table 2 Optimization of the Palladium-Catalyzed Isocyanide Insertion Reaction[a] (continued)

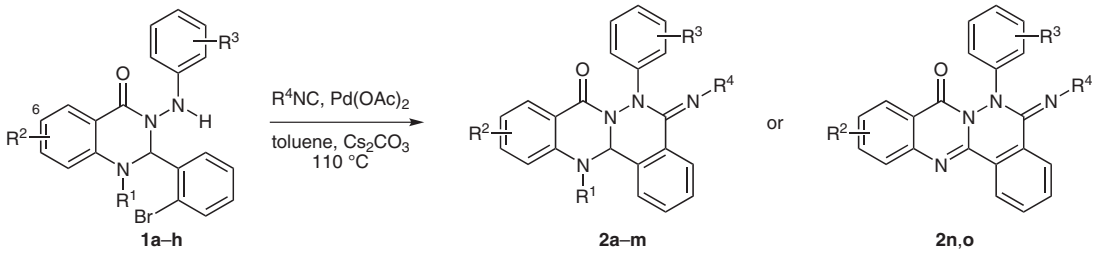


Entry	Catalyst	Base	Solvent	Temp (°C)	Yield[b] (%)
9	$Pd(PPh_3)_4$	Cs_2CO_3	toluene	110	81
10	$Pd(Amphos)_2Cl_2$	Cs_2CO_3	toluene	110	79
11	$Pd(OAc)_2$	K_2CO_3	toluene	110	53
12	$Pd(OAc)_2$	K_3PO_4	toluene	110	45
13	$Pd(OAc)_2$	DIPEA	toluene	110	78
14	$Pd(OAc)_2$	Cs_2CO_3	toluene	100	75
15	$Pd(OAc)_2$	Cs_2CO_3	toluene	90	63

[a] Reaction conditions: **1a** (0.5 mmol), catalyst (5 mol%), *tert*-butyl isocyanide (0.75 mmol), base (1 mmol), solvent (2 mL), 24 h, sealed tube.
[b] Isolated yield.

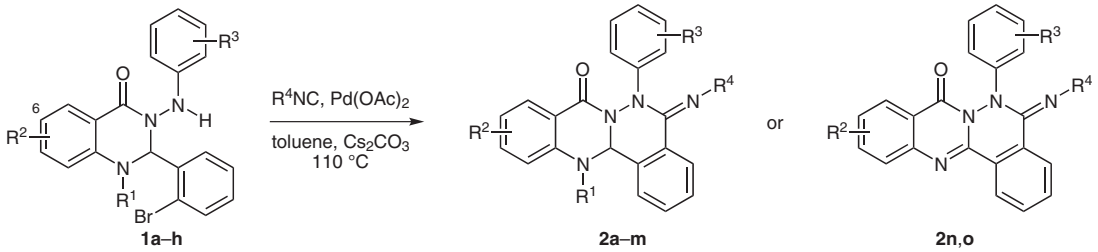
With this standard protocol in hand, we extended the method to the synthesis of various substituted phthalazino[1,2-*b*]quinazolinones (Table 3). Various substituted quinazolinones **1** could be employed in the isocyanide insertion reaction in high yields. Moreover, *tert*-butyl isocyanide and cyclohexyl isocyanide (R^4 = *t*-Bu, Cy) were found to effectively undergo the insertion reaction; however, when R^1 was a propargyl group ($R^1 = CH_2C{\equiv}CH$), the unexpected depropargylation products **2n** and **2o** were isolated. The resulting formation of the C=N double bond led to the further diversity expansion of phthalazino[1,2-*b*]quinazolinones.

Table 3 Synthesis of Phthalazino[1,2-*b*]quinazolinones



R^1	R^2	R^3	R^4	Product	Yield[a] (%)
Bn	H	H	*t*-Bu	**2a**	85
Bn	H	H	Cy	**2b**	83
Me	H	H	*t*-Bu	**2c**	86
Me	H	H	Cy	**2d**	81
Bn	6-Cl[b]	H	*t*-Bu	**2e**	78
Bn	6-Cl[b]	H	Cy	**2f**	80
Me	6-Cl[b]	H	*t*-Bu	**2g**	84
Me	6-Cl[b]	H	Cy	**2h**	87
H	H	H	*t*-Bu	**2i**	65
Me	H	4-Cl	*t*-Bu	**2j**	78

Table 3 Synthesis of Phthalazino[1,2-*b*]quinazolinones (continued)



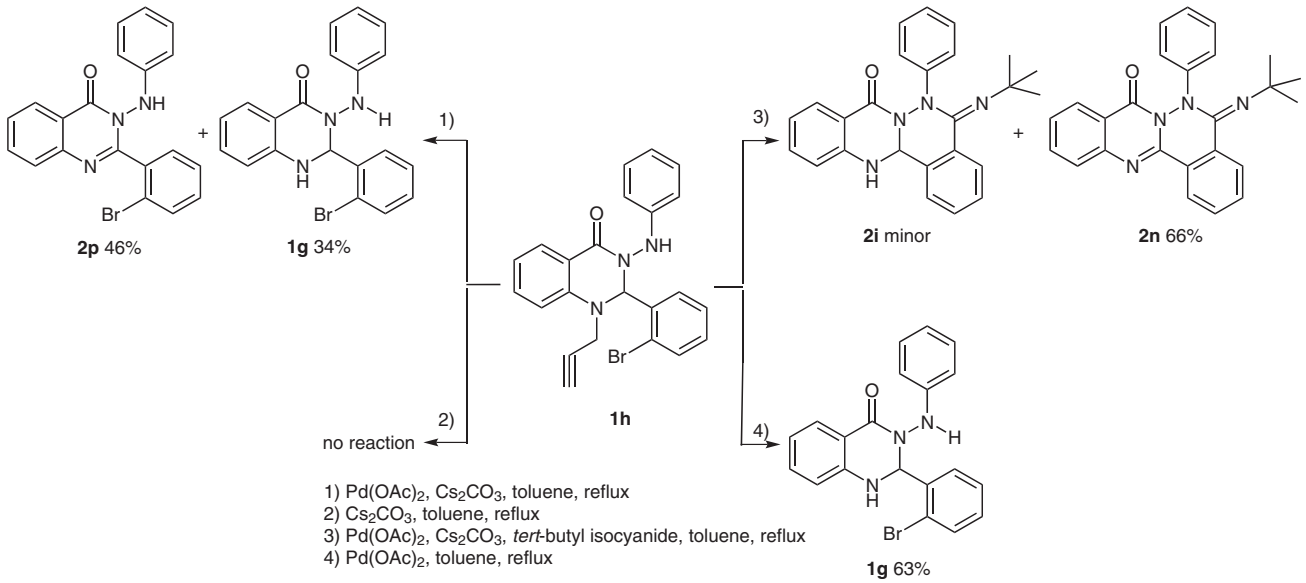
1a–h **2a–m** **2n,o**

R^1	R^2	R^3	R^4	Product	Yield[a] (%)
Me	H	4-Cl	Cy	**2k**	75
Me	H	4-Me	*t*-Bu	**2l**	83
Me	H	4-Me	Cy	**2m**	81
$CH_2C{\equiv}CH$	H	H	*t*-Bu	**2n**	66
$CH_2C{\equiv}CH$	H	H	Cy	**2o**	72

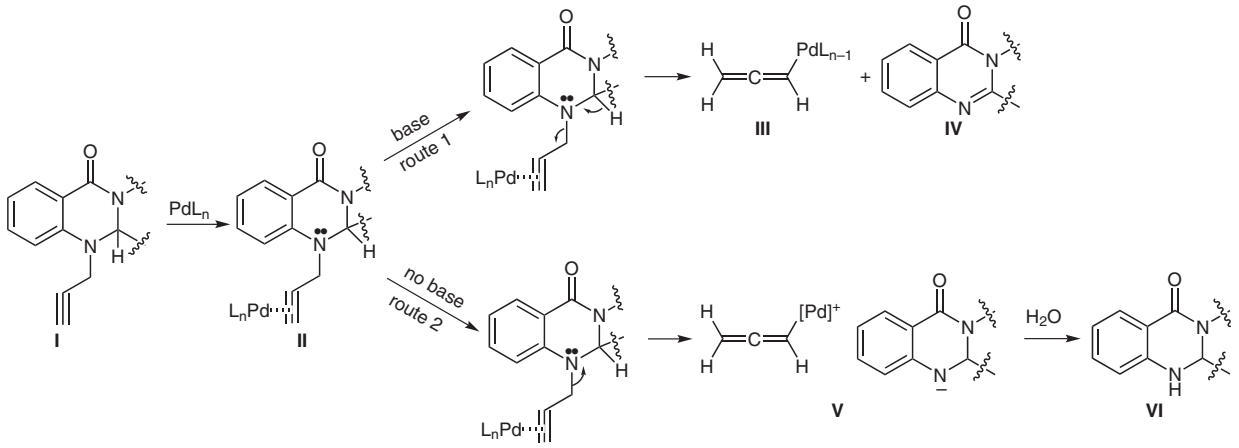
[a] Isolated yield.
[b] Numbering refers to the starting quinazolinone.

To understand the mechanism of the depropargylation reaction, control experiments for this reaction were executed (Scheme 2). It was found that the base plays a key role in the reaction, affecting the final product outcome. Furthermore, the presence of isocyanide is favorable for the formation of the C=N double bond. The presumed mechanism of the palladium-catalyzed depropargylation reaction is proposed as follows (Scheme 3):[11] Firstly, compound **I** reacts with the palladium catalyst, leading to the formation of palladium complex **II**. Under the base conditions, C–H bond cleavage triggers an elimination reaction, generating **III** and **IV** (Scheme 3, route 1). Without a base, C–N bond cleavage directly leads to the formation of an allenylpalladium intermediate **V** at high temperature. This allenylpalladium intermediate then undergoes nucleophilic attack at the central sp-hybridized carbon by a water molecule, thereby releasing the desired compound **VI** (Scheme 3, route 2). Further investigations on this depropargylation reaction are in progress.

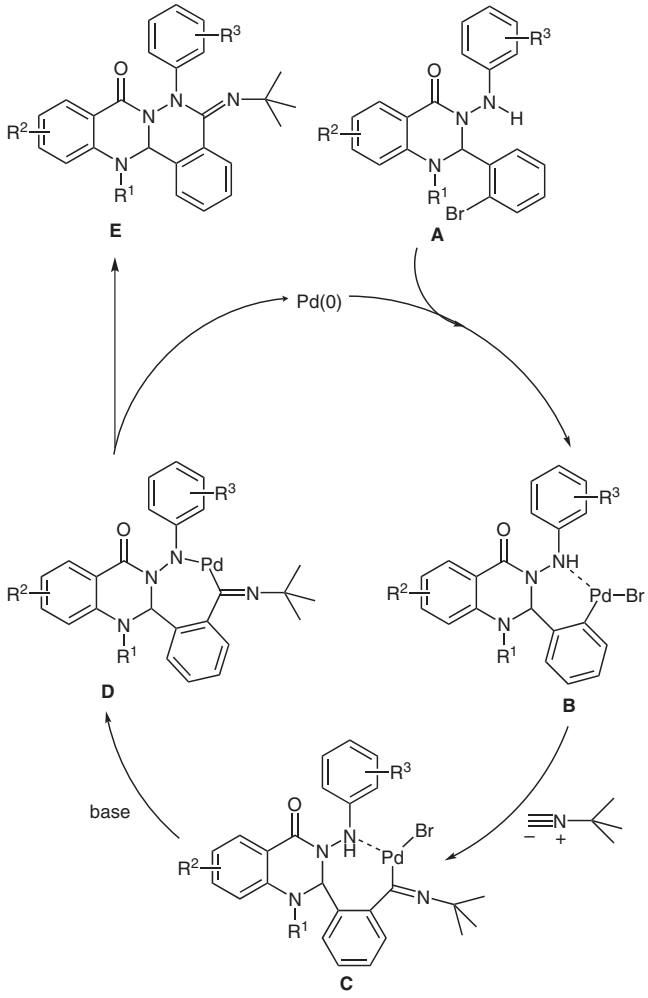
The possible mechanism of the isocyanide insertion reaction is also depicted (Scheme 4).[5k,12] The proposed mechanism involves oxidative addition of **A** and coordination of the palladium to the intramolecular nitrogen atom to give species **B**. This could then undergo an isocyanide insertion process to give the intermediate **C**. Next, with the aid of the base, hydrogen bromide is extruded out of **C** to generate the seven-membered-ring product **D**. Finally, reductive elimination affords **E**, regenerating the palladium(0) catalyst.



Scheme 2 Control experiments for the depropargylation reaction



Scheme 3 Possible mechanism of the depropargylation reaction



Scheme 4 Possible mechanism of the isocyanide insertion reaction

The structures of the novel phthalazino[1,2-*b*]quinazolinones were fully characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The structure of **2a** was also confirmed by single-crystal X-ray analysis (Figure 1).

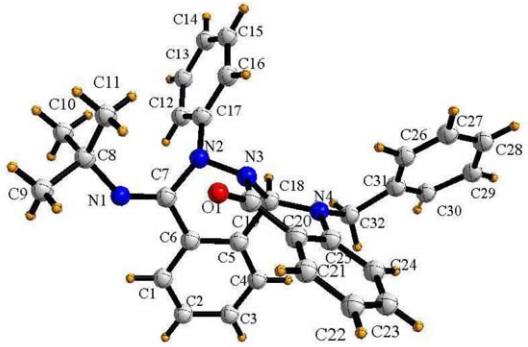


Figure 1 Single-crystal X-ray analysis of **2a**

In conclusion, we have described a palladium-catalyzed isocyanide insertion reaction for the synthesis of phthalazino[1,2-*b*]quinazolinones from the readily obtainable quinazolinones. Easily handled and relatively low-cost palladium(II) acetate was used as the catalyst, without an additional ligand. This methodology has several advantages, such as good yields, accessible materials and high functional group diversity. Meanwhile, a depropargylation phenomenon was found and the resulting formation of the C=N double bond led to the further diversity expansion of phthalazino[1,2-*b*]quinazolinones. The possible mechanism of the depropargylation reaction has also been proposed and further research on this aspect is in progress.

Materials were obtained from commercial suppliers and used without further purification. All melting points are uncorrected. Mass spectra were recorded on a Shimadzu LCMS-2020 system. ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, in $CDCl_3$ or DMSO-d_6, and chemical shifts are reported in ppm from internal TMS (δ). Elemental analyses were performed on a Yanagimoto MT3CHN recorder. Infrared spectra were recorded as thin films on a Thermo Scientific Nicolet IS-10 FT-IR spectrometer.

Quinazolinones 1 via the Cascade Reaction; General Procedure
To a soln of an isatoic anhydride (2 mmol) in MeCN (3 mL) was added a phenylhydrazine (2 mmol) and the mixture was stirred under reflux (progress of the reaction was monitored by TLC). After the reaction was finished, 2-bromobenzaldehyde (2 mmol) and TsOH (10 mol%) were added, and the mixture was stirred at 81 °C overnight. Upon completion of this cascade reaction, the mixture was concentrated under reduced pressure and the resulting residue was purified by column chromatography.

1-Benzyl-2-(2-bromophenyl)-3-(phenylamino)-2,3-dihydroquinazolin-4(1*H*)-one (1a)
White solid; yield: 0.840 g (87%); mp 192–194 °C.

IR: 3244, 3044, 2940, 1653, 1601, 1493, 1385, 1341, 1225, 1153, 1099 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.38 (d, *J* = 16.5 Hz, 1 H), 4.70 (d, *J* = 16.0 Hz, 1 H), 6.52 (s, 1 H), 6.69 (d, *J* = 8.5 Hz, 1 H), 6.90 (m, 4 H), 7.22 (m, 4 H), 7.36 (m, 6 H), 7.56 (m, 2 H), 8.07 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 50.57, 76.46, 111.70, 112.77, 114.30, 117.66, 118.84, 122.08, 126.58, 127.02, 127.65, 128.20, 128.34, 130.54, 132.63, 133.96, 136.34, 137.84, 145.33, 146.66, 160.76.

MS (ESI): *m*/*z* = 484 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{22}BrN_3O$: C, 66.95; H, 4.58; N, 8.67. Found: C, 66.77; H, 4.55; N, 8.75.

2-(2-Bromophenyl)-1-methyl-3-(phenylamino)-2,3-dihydroquinazolin-4(1*H*)-one (1b)
White solid; yield: 0.692 g (85%); mp 162–164 °C.

IR: 3244, 3012, 2940, 1663, 1601, 1493, 1403, 1333, 1261, 1197, 1099 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.94 (s, 3 H), 6.37 (s, 1 H), 6.47 (s, 1 H), 6.64 (d, *J* = 8.0 Hz, 1 H), 6.91 (m, 1 H), 6.99 (m, 3 H), 7.20 (m, 2 H), 7.29 (m, 2 H), 7.44 (m, 2 H), 7.58 (m, 1 H), 8.03 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.41, 77.69, 110.89, 113.09, 113.59, 117.36, 120.73, 122.46, 126.03, 127.49, 127.93, 128.34, 129.79, 132.39, 133.72, 136.16, 145.39, 145.77, 161.80.

MS (ESI): *m*/*z* = 408 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{18}BrN_3O$: C, 61.78; H, 4.44; N, 10.29. Found: C, 61.97; H, 4.51; N, 10.25.

1-Benzyl-2-(2-bromophenyl)-6-chloro-3-(phenylamino)-2,3-dihydroquinazolin-4(1*H*)-one (1c)
White solid; yield: 0.848 g (82%); mp >230 °C.

IR: 3272, 3226, 2926, 1645, 1601, 1493, 1395, 1341, 1251, 1179, 1019 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.39 (d, *J* = 16.5 Hz, 1 H), 4.64 (d, *J* = 16.5 Hz, 1 H), 6.35 (s, 1 H), 6.50 (s, 1 H), 6.62 (d, *J* = 8.5 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 2 H), 6.94 (m, 1 H), 7.23 (m, 4 H), 7.29 (m, 1 H), 7.34 (m, 5 H), 7.51 (m, 1 H), 7.57 (m, 1 H), 8.02 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 50.69, 76.44, 111.68, 114.94, 115.47, 118.95, 121.46, 122.03, 126.58, 126.66, 127.13, 128.26, 128.37, 130.69, 132.68, 133.54, 135.92, 137.46, 144.14, 146.37, 159.66.

MS (ESI): *m*/*z* = 518 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{21}BrClN_3O$: C, 62.50; H, 4.08; N, 8.10. Found: C, 62.67; H, 4.05; N, 8.15.

2-(2-Bromophenyl)-6-chloro-1-methyl-3-(phenylamino)-2,3-dihydroquinazolin-4(1*H*)-one (1d)
White solid; yield: 0.741 g (84%); mp 190–192 °C.

IR: 3262, 2986, 2896, 1645, 1601, 1493, 1439, 1385, 1333, 1207, 1179, 1099 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.93 (s, 3 H), 6.44 (s, 1 H), 6.58 (d, *J* = 9.0 Hz, 1 H), 6.97 (m, 3 H), 7.22 (m, 2 H), 7.29 (m, 2 H), 7.39 (m, 2 H), 7.59 (m, 1 H), 7.98 (d, *J* = 2.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.57, 77.64, 112.40, 113.08, 114.73, 120.88, 122.47, 122.66, 125.88, 127.44, 127.54, 128.37, 129.98, 132.51, 133.41, 135.80, 144.27, 145.04, 160.71.

MS (ESI): *m*/*z* = 442 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{17}BrClN_3O$: C, 56.97; H, 3.87; N, 9.49. Found: C, 56.79; H, 3.85; N, 9.55.

2-(2-Bromophenyl)-3-[(4-chlorophenyl)amino]-1-methyl-2,3-dihydroquinazolin-4(1*H*)-one (1e)
White solid; yield: 0.662 g (75%); mp 160–162 °C.

IR: 3272, 2986, 2888, 1646, 1601, 1493, 1385, 1341, 1261, 1207, 1163, 1091 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.92 (s, 3 H), 6.33 (s, 1 H), 6.43 (s, 1 H), 6.64 (d, *J* = 8.5 Hz, 1 H), 6.91 (m, 3 H), 7.21 (m, 4 H), 7.42 (m, 2 H), 7.58 (m, 1 H), 8.01 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.29, 77.67, 110.81, 113.26, 114.36, 117.42, 122.50, 125.52, 125.97, 127.54, 127.97, 128.28, 129.89, 132.41, 133.90, 135.93, 144.02, 145.80, 161.83.

MS (ESI): *m*/*z* = 442 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{17}BrClN_3O$: C, 56.97; H, 3.87; N, 9.49. Found: C, 56.74; H, 3.95; N, 9.45.

2-(2-Bromophenyl)-1-methyl-3-(*p*-tolylamino)-2,3-dihydroquinazolin-4(1*H*)-one (1f)
White solid; yield: 0.749 g (89%); mp 178–180 °C.

IR: 3226, 2986, 2888, 1645, 1609, 1485, 1395, 1349, 1261, 1207, 1163, 1099 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 2.94 (s, 3 H), 6.32 (s, 1 H), 6.46 (s, 1 H), 6.63 (d, *J* = 8.5 Hz, 1 H), 6.92 (m, 3 H), 7.09 (d, *J* = 8.5 Hz, 2 H), 7.20 (m, 2 H), 7.44 (m, 2 H), 7.58 (m, 1 H), 8.03 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.70, 34.38, 77.63, 110.86, 113.49, 113.64, 117.32, 122.45, 126.02, 127.48, 127.89, 128.85, 129.75, 130.21, 132.36, 133.64, 136.24, 142.97, 145.73, 161.72.

MS (ESI): *m*/*z* = 422 $[M + H]^+$.

Anal. Calcd for $C_{22}H_{20}BrN_3O$: C, 62.57; H, 4.77; N, 9.95. Found: C, 62.44; H, 4.85; N, 9.98.

2-(2-Bromophenyl)-3-(phenylamino)-2,3-dihydroquinazolin-4(1*H*)-one (1g)
White solid; yield: 0.590 g (75%); mp 184–186 °C.

IR: 3216, 2986, 2881, 1645, 1605, 1481, 1385, 1301, 1256, 1157, 1085 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.36 (s, 1 H), 6.26 (s, 1 H), 6.63 (d, *J* = 8.0 Hz, 1 H), 6.87 (m, 1 H), 6.98 (m, 1 H), 7.04 (d, *J* = 7.5 Hz, 2 H), 7.22 (m, 1 H), 7.29 (m, 5 H), 7.61 (d, *J* = 7.5 Hz, 1 H), 7.98 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 72.55, 113.01, 113.59, 113.89, 118.46, 120.91, 121.17, 126.03, 126.96, 127.66, 128.39, 129.44, 132.71, 133.35, 136.57, 143.88, 145.38, 163.23.

MS (ESI): *m*/*z* = 394 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{16}BrN_3O$: C, 60.93; H, 4.09; N, 10.66. Found: C, 60.84; H, 4.15; N, 10.78.

2-(2-Bromophenyl)-3-(phenylamino)-1-(prop-2-ynyl)-2,3-dihydroquinazolin-4(1*H*)-one (1h)
White solid; yield: 0.672 g (78%); mp 165–167 °C.

IR: 3272, 2986, 2896, 1653, 1601, 1493, 1395, 1323, 1243, 1163, 1099 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.11 (m, 1 H), 4.22 (m, 2 H), 6.34 (s, 1 H), 6.55 (s, 1 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 6.99 (m, 4 H), 7.19 (m, 2 H), 7.27 (m, 2 H), 7.42 (m, 1 H), 7.49 (m, 1 H), 7.58 (m, 1 H), 8.08 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.02, 72.36, 77.15, 112.64, 113.20, 114.97, 118.69, 120.78, 122.76, 126.50, 127.19, 128.03, 128.28, 129.78, 132.32, 133.53, 136.30, 143.83, 145.31, 161.90.

MS (ESI): *m*/*z* = 432 $[M + H]^+$.

Anal. Calcd for $C_{23}H_{18}BrN_3O$: C, 63.90; H, 4.20; N, 9.72. Found: C, 63.74; H, 4.15; N, 9.75.

Phthalazino[1,2-*b*]quinazolinones 2 via the Isocyanide Insertion Reaction; General Procedure

To a soln of a quinazolinone **1** (0.5 mmol) in toluene (2 mL) was successively added an isocyanide (0.75 mmol), $Pd(OAc)_2$ (5 mol%) and Cs_2CO_3 (1 mmol). The mixture was stirred in a sealed tube at 110 °C for 24 h. Upon completion of the reaction, the mixture was concentrated under reduced pressure and the resulting residue was purified by column chromatography.

13-Benzyl-5-(*tert*-butylimino)-6-phenyl-5,6,13,13a-tetrahydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one (2a)

White solid; yield: 0.206 g (85%); mp 188–190 °C.

IR: 2965, 2899, 1681, 1645, 1601, 1493, 1454, 1349, 1261, 1233, 1073, 1019 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 1.28 (s, 9 H), 4.74 (d, *J* = 16.0 Hz, 1 H), 5.06 (d, *J* = 16.0 Hz, 1 H), 5.87 (s, 1 H), 6.77 (m, 1 H), 7.07 (m, 4 H), 7.28 (m, 11 H), 7.67 (d, *J* = 6.5 Hz, 1 H), 8.18 (d, *J* = 6.5 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 29.56, 53.82, 56.41, 69.27, 115.50, 115.60, 118.57, 119.57, 122.86, 123.41, 126.81, 127.64, 127.81, 127.99, 128.85, 129.81, 130.55, 134.19, 136.82, 138.26, 140.33, 143.35, 145.00, 163.96.

MS (ESI): *m*/*z* = 487 $[M + H]^+$.

Anal. Calcd for $C_{32}H_{30}N_4O$: C, 78.98; H, 6.21; N, 11.51. Found: C, 78.87; H, 6.15; N, 11.65.

13-Benzyl-5-(cyclohexylimino)-6-phenyl-5,6,13,13a-tetrahydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one (2b)

White solid; yield: 0.212 g (83%); mp >230 °C.

IR: 2958, 2904, 1681, 1645, 1609, 1493, 1449, 1377, 1269, 1225, 1073, 1019 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.25 (m, 1 H), 1.42 (m, 2 H), 1.52 (m, 3 H), 1.71 (m, 3 H), 2.04 (m, 1 H), 3.58 (m, 1 H), 4.49 (d, *J* = 15.0 Hz, 1 H), 4.87 (d, *J* = 15.0 Hz, 1 H), 5.73 (s, 1 H), 6.88 (m, 1 H), 7.00 (d, *J* = 8.0 Hz, 1 H), 7.06 (m, 1 H), 7.23 (m, 12 H), 7.38 (m, 1 H), 7.93 (m, 1 H), 8.34 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.39, 23.61, 24.97, 31.65, 32.47, 56.54, 56.97, 69.74, 116.53, 117.62, 118.73, 119.81, 122.03, 122.75, 126.90, 127.33, 127.50, 127.78, 128.42, 129.13, 129.84, 133.45, 135.47, 137.06, 141.88, 143.58, 145.34, 164.42.

MS (ESI): *m*/*z* = 513 $[M + H]^+$.

Anal. Calcd for $C_{34}H_{32}N_4O$: C, 79.66; H, 6.29; N, 10.93. Found: C, 79.57; H, 6.45; N, 10.85.

5-(*tert*-Butylimino)-13-methyl-6-phenyl-5,6,13,13a-tetrahydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one (2c)

White solid; yield: 0.176 g (86%); mp 188–190 °C.

IR: 2958, 2904, 1689, 1645, 1601, 1493, 1449, 1377, 1287, 1225, 1197, 1163, 1091, 1055 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.36 (s, 9 H), 3.25 (s, 3 H), 5.70 (s, 1 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 6.82 (m, 1 H), 7.09 (m, 2 H), 7.15 (d, *J* = 7.5 Hz, 2 H), 7.27 (m, 1 H), 7.32 (m, 3 H), 7.38 (m, 1 H), 7.91 (m, 1 H), 8.33 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.33, 39.44, 56.49, 71.24, 113.33, 115.64, 118.26, 120.13, 121.77, 123.14, 127.40, 128.10, 128.25, 128.33, 128.95, 130.95, 133.44, 137.71, 140.27, 143.70, 145.50, 163.77.

MS (ESI): *m*/*z* = 411 $[M + H]^+$.

Anal. Calcd for $C_{26}H_{26}N_4O$: C, 76.07; H, 6.38; N, 13.65. Found: C, 76.31; H, 6.35; N, 13.77.

5-(Cyclohexylimino)-13-methyl-6-phenyl-5,6,13,13a-tetrahydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one (2d)

White solid; yield: 0.177 g (81%); mp 189–190 °C.

IR: 2922, 2852, 1689, 1637, 1601, 1493, 1449, 1367, 1297, 1225, 1163, 1091, 1027 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.05 (m, 1 H), 1.24 (m, 2 H), 1.52 (m, 3 H), 1.72 (m, 3 H), 2.04 (m, 1 H), 3.33 (s, 3 H), 3.58 (m, 1 H), 5.80 (s, 1 H), 6.79 (m, 2 H), 7.06 (d, *J* = 7.5 Hz, 1 H), 7.10 (m, 1 H), 7.17 (m, 2 H), 7.30 (m, 4 H), 7.39 (m, 1 H), 7.89 (m, 1 H), 8.37 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.41, 23.61, 24.97, 31.70, 32.49, 39.29, 56.99, 72.50, 112.93, 115.12, 118.04, 118.99, 121.69, 122.91, 127.51, 128.24, 128.47, 129.15, 129.93, 133.63, 137.47, 142.03, 143.35, 145.47, 164.51.

MS (ESI): *m*/*z* = 437 $[M + H]^+$.

Anal. Calcd for $C_{28}H_{28}N_4O$: C, 77.04; H, 6.46; N, 12.83. Found: C, 76.91; H, 6.55; N, 12.81.

13-Benzyl-5-(*tert*-butylimino)-10-chloro-6-phenyl-5,6,13,13a-tetrahydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one (2e)

White solid; yield: 0.203 g (78%); mp 196–198 °C.

IR: 2968, 2852, 1671, 1637, 1601, 1493, 1439, 1359, 1251, 1189, 1091, 1019 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.38 (s, 9 H), 4.45 (d, *J* = 15.0 Hz, 1 H), 4.80 (d, *J* = 15.0 Hz, 1 H), 5.68 (s, 1 H), 6.96 (d, *J* = 8.5 Hz, 1 H), 7.13 (m, 5 H), 7.28 (m, 9 H), 7.96 (m, 1 H), 8.32 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.33, 56.52, 56.64, 68.54, 118.13, 119.11, 120.16, 121.86, 123.24, 125.31, 126.93, 127.01, 127.46, 127.82, 128.22, 129.01, 130.77, 133.19, 135.02, 136.96, 140.08, 143.38, 143.64, 162.73.

MS (ESI): *m*/*z* = 521 $[M + H]^+$.

Anal. Calcd for $C_{32}H_{29}ClN_4O$: C, 73.76; H, 5.61; N, 10.75. Found: C, 73.51; H, 5.76; N, 10.87.

13-Benzyl-10-chloro-5-(cyclohexylimino)-6-phenyl-5,6,13,13a-tetrahydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one (2f)

White solid; yield: 0.218 g (80%); mp >230 °C.

IR: 2922, 2842, 1689, 1645, 1601, 1475, 1431, 1367, 1251, 1189, 1127, 1081, 1027 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.05 (m, 1 H), 1.28 (m, 2 H), 1.55 (m, 3 H), 1.72 (m, 3 H), 2.05 (m, 1 H), 3.58 (m, 1 H), 4.50 (d, *J* = 15.0 Hz, 1 H), 4.88 (d, *J* = 15.0 Hz, 1 H), 5.76 (s, 1 H), 6.96 (d, *J* = 8.5 Hz, 1 H), 7.09 (m, 1 H), 7.27 (m, 13 H), 7.93 (m, 1 H), 8.38 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.34, 23.54, 24.95, 31.60, 32.49, 56.56, 56.99, 69.84, 117.90, 118.72, 121.90, 122.87, 125.23, 126.83, 127.07, 127.55, 127.62, 127.87, 127.98, 129.22, 129.76, 133.34, 135.01, 136.62, 141.65, 143.28, 143.71, 161.32.

MS (ESI): *m*/*z* = 547 $[M + H]^+$.

Anal. Calcd for $C_{34}H_{31}ClN_4O$: C, 74.64; H, 5.71; N, 10.24. Found: C, 74.41; H, 5.76; N, 10.17.

5-(*tert*-Butylimino)-10-chloro-13-methyl-6-phenyl-5,6,13,13a-tetrahydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one (2g)
White solid; yield: 0.186 g (84%); mp >230 °C.

IR: 2968, 2896, 1682, 1645, 1609, 1493, 1421, 1359, 1305, 1215, 1117, 1099, 1037 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.38 (s, 9 H), 3.28 (s, 3 H), 5.72 (s, 1 H), 6.73 (d, *J* = 8.5 Hz, 1 H), 7.07 (m, 1 H), 7.16 (m, 3 H), 7.28 (m, 1 H), 7.35 (m, 4 H), 7.90 (s, 1 H), 8.37 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.30, 39.52, 56.57, 71.22, 114.75, 116.77, 120.07, 121.61, 123.29, 123.67, 127.59, 127.87, 128.22, 128.32, 129.02, 130.85, 133.25, 137.24, 139.93, 143.46, 143.97, 162.70.

MS (ESI): *m*/*z* = 445 $[M + H]^+$.

Anal. Calcd for $C_{26}H_{25}ClN_4O$: C, 70.18; H, 5.66; N, 12.59. Found: C, 70.42; H, 5.71; N, 12.47.

10-Chloro-5-(cyclohexylimino)-13-methyl-6-phenyl-5,6,13,13a-tetrahydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one (2h)
White solid; yield: 0.204 g (87%); mp 140–142 °C.

IR: 2986, 2904, 1717, 1671, 1601, 1457, 1359, 1323, 1287, 1243, 1189, 1145, 1027 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.05 (m, 1 H), 1.28 (m, 3 H), 1.55 (m, 2 H), 1.72 (m, 3 H), 2.05 (m, 1 H), 3.34 (s, 3 H), 3.58 (m, 1 H), 5.82 (s, 1 H), 6.74 (d, *J* = 8.5 Hz, 1 H), 7.05 (d, *J* = 7.5 Hz, 1 H), 7.17 (m, 3 H), 7.34 (m, 5 H), 7.89 (d, *J* = 2.5 Hz, 1 H), 8.41 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.36, 23.56, 24.95, 31.64, 32.50, 39.37, 57.01, 72.44, 114.42, 116.26, 118.88, 121.56, 123.05, 123.51, 127.65, 127.96, 128.32, 129.23, 129.84, 133.45, 137.00, 141.80, 143.09, 143.97, 163.43.

MS (ESI): *m*/*z* = 471 $[M + H]^+$.

Anal. Calcd for $C_{28}H_{27}ClN_4O$: C, 71.40; H, 5.78; N, 11.90. Found: C, 71.21; H, 5.66; N, 12.01.

5-(*tert*-Butylimino)-6-phenyl-5,6,13,13a-tetrahydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one (2i)
White solid; yield: 0.129 g (65%); mp 185–186 °C.

IR: 2988, 2845, 1674, 1632, 1601, 1456, 1356, 1245, 1135, 1091, 1025 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.34 (s, 9 H), 5.89 (s, 1 H), 6.81 (d, *J* = 7.5 Hz, 2 H), 6.88 (m, 1 H), 7.14 (m, 3 H), 7.46 (m, 3 H), 7.79 (m, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 8.33 (m, 1 H), 8.45 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.40, 50.34, 72.59, 116.62, 121.20, 122.06, 124.72, 125.51, 125.63, 126.15, 126.52, 126.66, 127.78, 128.39, 131.38, 133.22, 136.25, 144.92, 146.05, 148.11, 158.35.

MS (ESI): *m*/*z* = 397 $[M + H]^+$.

Anal. Calcd for $C_{25}H_{24}N_4O$: C, 75.73; H, 6.10; N, 14.13. Found: C, 75.81; H, 6.15; N, 14.01.

5-(*tert*-Butylimino)-6-(4-chlorophenyl)-13-methyl-5,6,13,13a-tetrahydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one (2j)
White solid; yield: 0.173 g (78%); mp 164–166 °C.

IR: 2976, 2914, 1689, 1653, 1609, 1475, 1349, 1269, 1225, 1163, 1091, 1037 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.39 (s, 9 H), 3.30 (s, 3 H), 5.69 (s, 1 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 6.85 (m, 1 H), 7.11 (d, *J* = 9.0 Hz, 3 H), 7.34 (m, 4 H), 7.42 (m, 1 H), 7.93 (m, 1 H), 8.34 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.32, 39.47, 56.63, 71.35, 113.40, 115.49, 118.37, 121.17, 121.84, 127.51, 128.14, 128.36, 129.13, 130.64, 133.59, 137.51, 139.69, 142.43, 145.47, 163.76.

MS (ESI): *m*/*z* = 445 $[M + H]^+$.

Anal. Calcd for $C_{26}H_{25}ClN_4O$: C, 70.18; H, 5.66; N, 12.59. Found: C, 70.31; H, 5.56; N, 12.67.

6-(4-Chlorophenyl)-5-(cyclohexylimino)-13-methyl-5,6,13,13a-tetrahydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one (2k)
White solid; yield: 0.176 g (75%); mp 151–153 °C.

IR: 2967, 2921, 1678, 1645, 1602, 1453, 1365, 1245, 1162, 1087, 1026 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.05 (m, 1 H), 1.27 (m, 2 H), 1.45 (m, 1 H), 1.54 (m, 2 H), 1.72 (m, 3 H), 2.04 (m, 1 H), 3.36 (s, 3 H), 3.56 (m, 1 H), 5.77 (s, 1 H), 6.81 (m, 2 H), 7.10 (m, 3 H), 7.30 (m, 4 H), 7.42 (m, 1 H), 7.90 (m, 1 H), 8.37 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.40, 23.58, 24.92, 31.63, 32.50, 39.33, 57.12, 72.58, 113.00, 114.93, 118.16, 121.77, 127.58, 127.88, 128.31, 128.48, 129.35, 129.62, 133.81, 137.30, 140.71, 142.92, 145.43, 164.52.

MS (ESI): *m*/*z* = 471 $[M + H]^+$.

Anal. Calcd for $C_{28}H_{27}ClN_4O$: C, 71.40; H, 5.78; N, 11.90. Found: C, 71.21; H, 5.76; N, 11.97.

5-(*tert*-Butylimino)-13-methyl-6-*p*-tolyl-5,6,13,13a-tetrahydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one (2l)
White solid; yield: 0.176 g (83%); mp 198–200 °C.

IR: 2976, 2914, 1681, 1642, 1609, 1493, 1449, 1367, 1269, 1215, 1163, 1081, 1037 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.38 (s, 9 H), 2.35 (s, 3 H), 3.28 (s, 3 H), 5.74 (s, 1 H), 6.77 (d, *J* = 8.5 Hz, 1 H), 6.83 (m, 1 H), 7.08 (m, 3 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.29 (m, 2 H), 7.41 (m, 1 H), 7.93 (m, 1 H), 8.35 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.89, 29.39, 39.34, 56.29, 70.93, 113.08, 115.52, 118.11, 120.67, 121.67, 127.37, 128.09, 128.32, 128.82, 128.90, 130.97, 133.06, 133.41, 137.82, 140.90, 141.16, 145.42, 163.72.

MS (ESI): *m*/*z* = 425 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{28}N_4O$: C, 76.39; H, 6.65; N, 13.20. Found: C, 76.21; H, 6.56; N, 13.27.

5-(Cyclohexylimino)-13-methyl-6-*p*-tolyl-5,6,13,13a-tetrahydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one (2m)
White solid; yield: 0.182 g (81%); mp 188–190 °C.

IR: 2922, 2852, 1681, 1637, 1609, 1493, 1449, 1377, 1297, 1225, 1163, 1099, 1037 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.05 (m, 1 H), 1.27 (m, 2 H), 1.54 (m, 3 H), 1.75 (m, 3 H), 2.07 (m, 1 H), 2.37 (s, 3 H), 3.34 (s, 3 H), 3.58 (m, 1 H), 5.83 (s, 1 H), 6.80 (m, 2 H), 7.12 (m, 5 H), 7.29 (m, 2 H), 7.42 (m, 1 H), 7.92 (m, 1 H), 8.39 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.85, 23.46, 23.63, 25.01, 31.83, 32.39, 39.18, 56.75, 72.26, 112.80, 115.11, 117.96, 119.46, 121.61, 127.43, 127.52, 128.46, 128.81, 129.08, 130.03, 132.76, 133.59, 137.52, 139.58, 143.78, 145.44, 164.45.

MS (ESI): *m*/*z* = 451 $[M + H]^+$.

Anal. Calcd for $C_{29}H_{30}N_4O$: C, 77.30; H, 6.71; N, 12.43. Found: C, 77.11; H, 6.66; N, 12.57.

5-(*tert*-Butylimino)-6-phenyl-5,6-dihydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one (2n)
White solid; yield: 0.130 g (66%); mp 154–156 °C.

IR: 2987, 2887, 1675, 1632, 1601, 1445, 1375, 1245, 1176, 1095, 1025 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.59 (s, 9 H), 6.72 (d, *J* = 8.0 Hz, 2 H), 6.92 (m, 1 H), 7.15 (m, 2 H), 7.58 (m, 3 H), 7.84 (m, 2 H), 7.96 (d, *J* = 8.0 Hz, 1 H), 8.34 (d, *J* = 8.5 Hz, 1 H), 8.45 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.66, 57.29, 114.87, 120.79, 121.99, 125.63, 126.05, 126.34, 126.77, 127.04, 127.65, 128.12, 129.81, 131.49, 133.66, 133.84, 143.18, 143.92, 145.82, 147.73, 158.44.

MS (ESI): *m*/*z* = 395 $[M + H]^+$.

Anal. Calcd for $C_{25}H_{22}N_4O$: C, 76.12; H, 5.62; N, 14.20. Found: C, 76.21; H, 5.66; N, 14.07.

5-(Cyclohexylimino)-6-phenyl-5,6-dihydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one (2o)
White solid; yield: 0.151 g (72%); mp 210–211 °C.

IR: 2985, 2892, 1685, 1632, 1613, 1435, 1356, 1243, 1125, 1099 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (m, 1 H), 1.43 (m, 1 H), 1.55 (m, 2 H), 1.69 (m, 1 H), 1.78 (m, 3 H), 1.87 (m, 1 H), 1.95 (m, 1 H), 4.42 (m, 1 H), 6.67 (d, *J* = 8.5 Hz, 2 H), 6.97 (m, 1 H), 7.20 (m, 2 H), 7.59 (m, 3 H), 7.85 (d, *J* = 4.0 Hz, 2 H), 8.04 (m, 1 H), 8.44 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.22, 23.56, 24.69, 28.71, 32.21, 33.32, 58.38, 113.68, 120.58, 122.23, 125.71, 125.82, 126.31, 126.75, 127.02, 127.77, 128.62, 130.29, 131.51, 133.80, 142.65, 145.69, 147.53, 158.09.

MS (ESI): *m*/*z* = 421 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{24}N_4O$: C, 77.12; H, 5.75; N, 13.32. Found: C, 77.31; H, 5.86; N, 13.17.

2-(2-Bromophenyl)-3-(phenylamino)quinazolin-4(3*H*)-one (2p)
White solid; yield: 0.090 g (46%); mp 190–191 °C.

IR: 3201, 2976, 2865, 1657, 1605, 1465, 1375, 1254, 1089, 1032 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.0 Hz, 1 H), 7.39 (m, 2 H), 7.43 (m, 2 H), 7.48 (m, 3 H), 7.65 (m, 1 H), 7.85 (m, 1 H), 7.95 (m, 1 H), 8.34 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 111.35, 117.64, 118.71, 122.34, 123.39, 124.46, 125.73, 125.84, 127.62, 128.55, 132.50, 133.08, 140.74, 147.16, 147.42, 148.08, 155.32.

MS (ESI): *m*/*z* = 392 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{14}BrN_3O$: C, 61.24; H, 3.60; N, 10.71. Found: C, 61.41; H, 3.56; N, 10.77.

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