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DIRECT HALOGENATION REACTIONS IN 2,3-DIHYDRO-4(1*H*)-QUINAZOLINONES

Fanny A. Cabrera-Rivera,[a] Claudia Ortíz-Nava,[a] Perla Román-Bravo,[a] Marco A. Leyva,[b] and Jaime Escalante[a,*]

[a] Chemical Research Center, Morelos Autonomous State University, Av. Universidad No. 1001, Col. Chamilpa, C. P. 62209, Cuernavaca, Mor., Mexico
Tel: +52 (777) 3 29 70 00, Ext. 6040. [b] CINVESTAV-I.P.N, Chemistry Department, Av. Instituto Politécnico Nacional 2508, Col. San Pedro Zacatenco, C.P. 07000, México D.F., Mexico
E-mail: jaime@ciq.uaem.mx

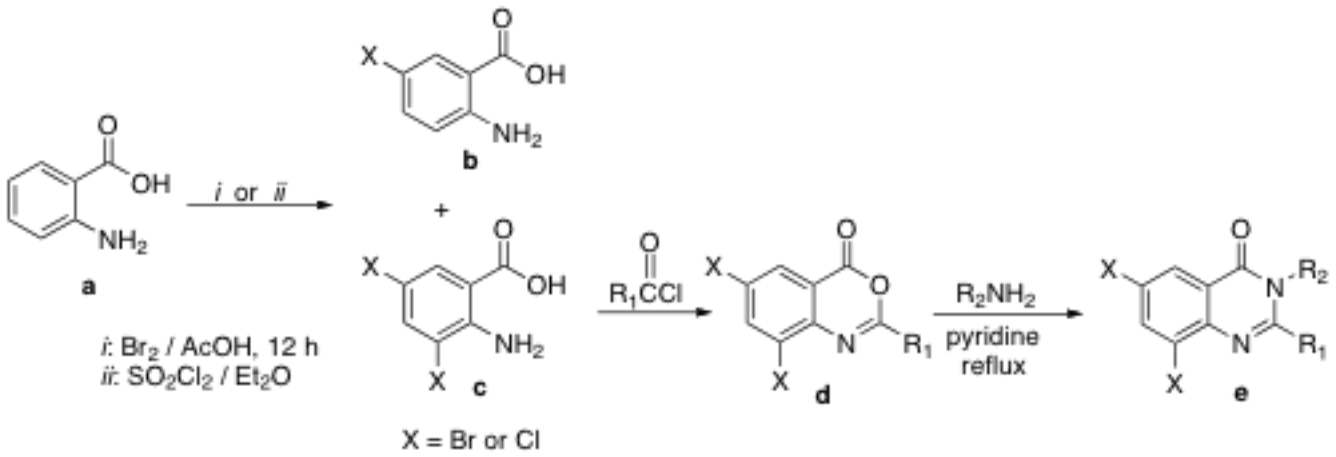
Abstract – Reaction of 2,3-dihydro-4(1*H*)-quinazolinones with NBS, Br_2/Et_3N and NCS yields 6,8-Br/Cl-2,3-dihydro-4(1*H*)-quinazolinones with moderate to good yield. The method does not require a catalyst and offers extremely short reaction time.

INTRODUCTION

2,3-Dihydro-4(1*H*)-quinazolinones form an important class of bioactive compounds and these can easily be oxidized to their quinazolin-4(3*H*)-one analogues.[1] In general, the derivatives of the quinazolinones are considered as an important building blocks[2] for a large number of diverse alkaloids[3] and present a wide range of biological and pharmaceutical activities.[4] In addition, numerous efforts of synthesis have been made to obtain halogenated quinazolinones for their pharmacophoric effect.[5] For example, the incorporation of a fluorine or chlorine atom into an active compound results in beneficial changes in molecular properties such as higher fat solubility giving different absorption and transport rate, altered electronic effects, improved stability, and equivalent steric size.[6] On the other hand, quinazolinones halogenated with bromine have shown their importance as building blocks in the synthesis of compounds with biological activity.[7]

In the literature, to obtain halogenated quinazolinones one first treats anthranilic acid (**a**) with bromine in presence of acetic acid or sulfuryl chloride to form the mono- and di-halogenated derivatives **b** and **c**,

respectively. The cyclocondensation of **c** with an anhydride or an acyl chloride affords benzoxazin-4-one **d**, which under condensation conditions with an amine gives 4(3*H*)-quinazolinone halogenated **e** with moderate to good yields (Scheme 1).[8]



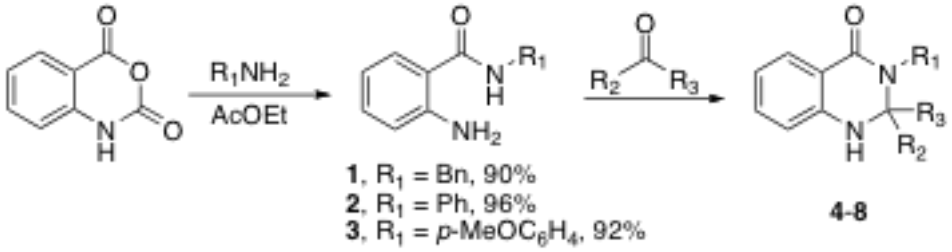
Scheme 1. Synthesis of halogenated quinazolinones from anthranilic acid

However, it is also reported that direct halogenation of 4(3*H*)-quinazolinones using iodine monochloride and bromine in acetic acid leads to 6-iodo/bromo-4(3*H*)-quinazolinones derivatives.[9]

In this work we describe the synthesis of 6,8-bromo/cloro-2,3-dihydro-4(1*H*)-quinazolinones through the direct halogenation.

RESULTS AND DISCUSSION

The synthesis of the derivatives of 2,3-dihydro-4(1*H*)-quinazolinones **4-8** and **10** was carried out according to the method previously reported by our research group;[10] the reaction of isatoic anhydride with different amines yields the aminobenzamides **1-3**. Direct cyclocondensation with the appropriate aldehyde in dichloromethane and *p*-TsOH as catalyst afford the quinazolinones **4-8** (Scheme 2, Table 1); it is important to mention that the reactions were carried out in the absence of light because of the sensitive of quinazolinones.[11]



Scheme 2. Synthesis of 2,3-dihydro-4(1*H*)-quinazolinones **4-8**

Relevant information on the conformation in the 4(1*H*)-quinazolinone **5** is shown in Figure 1. In all crystal structures, the N(1)-atom is shown to be only slightly or not at all pyramidalized (π-conjugation is stronger than n → σ* interaction).[12]

Table 1. Synthesis of 2,3-dihydro-4(1*H*)-quinazolinones **4-8**

Compound	R_1	R_2	R_3	Yield[a] (%)
4	Bn	*t*-Bu	H	86
5	Ph	*t*-Bu	H	97
6	*p*-$MeOC_6H_4$	*t*-Bu	H	94
7	Bn	Ph	H	83
8	Bn	Me	Me	68

a: Yield after flash chromatography.

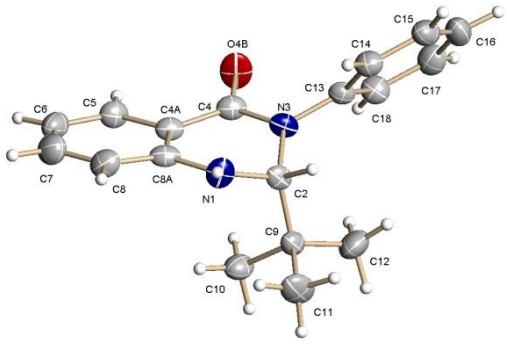
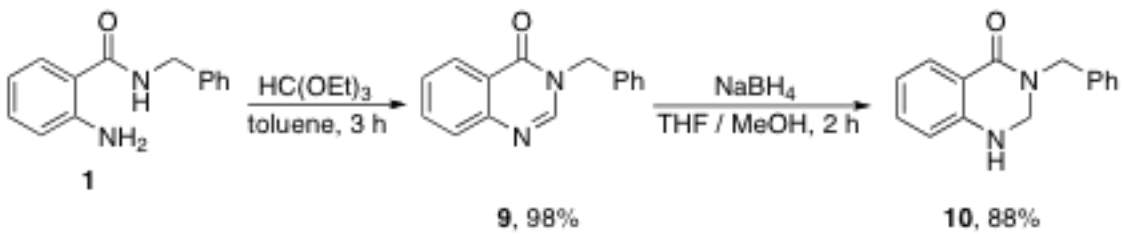


Figure 1. Crystal structure of 2-*tert*-butyl-3-phenyl-2,3-dihydro-4(1*H*)-quinazolinone (**5**)

3-Benzyl-2,3-dihydro-4(1*H*)-quinazolinone **10** was obtained by the cyclocondensation reaction of **1** with ethyl orthoformate in toluene followed by the direct reduction of **9** with 2 equiv of $NaBH_4$ in THF/MeOH in 88% yield (Scheme 3).[10]



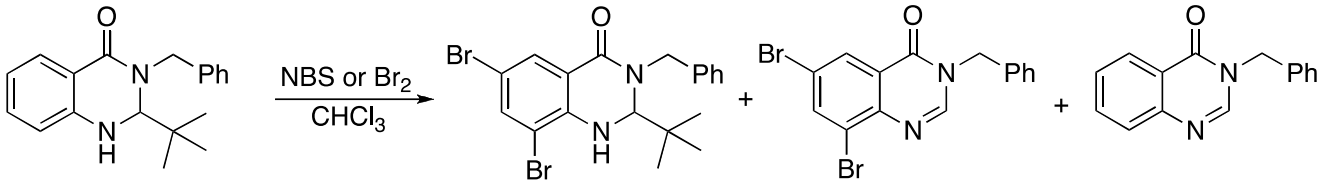
Scheme 3. Synthesis of quinazolinone **10**

Halogenation reactions

Bromination Reactions

The 3-benzyl-2-*tert*-butyl-2,3-dihydro-4(1*H*)-quinazolinone **4** was selected as a model substrate to perform the experimental conditions for the halogenation reactions (Table 2). Brominations reactions were carried out using NBS or Br_2/Et_3N in $CHCl_3$ at 68 mM. As shown in Table 2, with $h\nu$ and NBS in only 15 min afford a mixture of **4a** (59%) and **4b** (41%, entry 1). If the reaction is carried out under thermal conditions, we obtained 73% of **4a**, however, additional product was also detected (**4b** and **9**, entry 2). After considerable experimentation, we found that the best yield for **4a** (87%) is obtained when bromine and triethylamine at 50 ^{o}C (entry 3) were employed.

Table 2. Bromination reaction for **4**

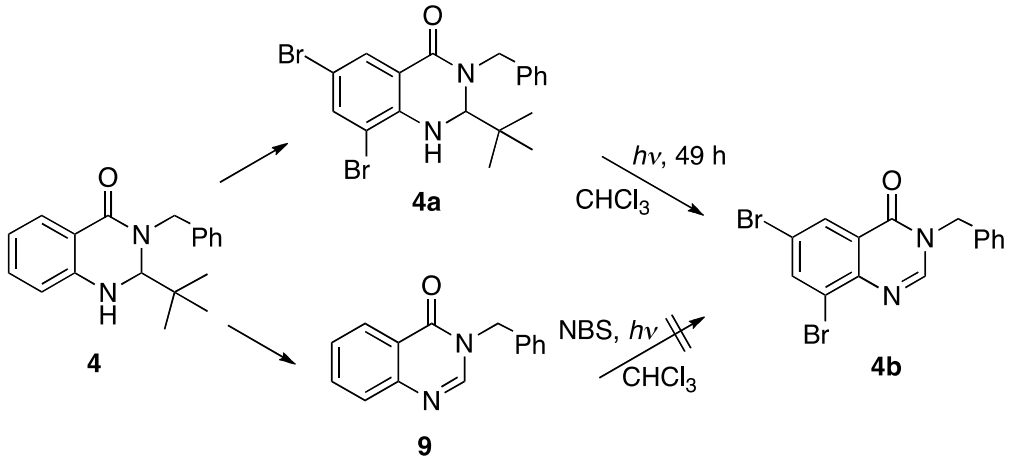


4 **4a** **4b** **9**

Entry	Condition	NBS (equiv)	Br_2 (equiv)	Et_3N (equiv)	Time (min)	Yield (%)[a]		
						4a	**4b**	**9**
1	$h\nu$	2.2	-	-	15	59	41	-
2	50 ^{o}C	2.2	-	-	30	73	11	14
3	50 ^{o}C	-	2.7	1.1	30	87	-	-

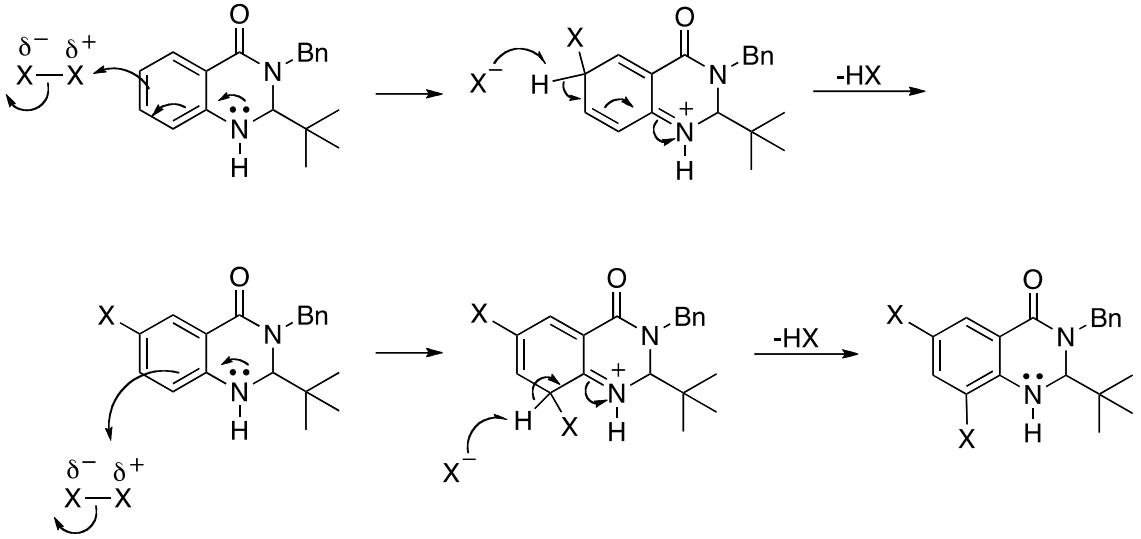
[a] Yield after column chromatographic purification.

In order to explain the formation of **4b**, the compound **4a** was irradiated with $h\nu$ and after 49 h, **4b** was isolated in 77% yield. However, when the compound **9** was treated with NBS and $h\nu$, the halogenation reaction did not proceed (Scheme 4). These experiments confirmed that compound **4b** was formed *via* **4a**. The elimination of *t*-Bu group of **4** and **4a** in presence of NBS and $h\nu$ is thought to occur through free radicals mechanism.[11]



Scheme 4

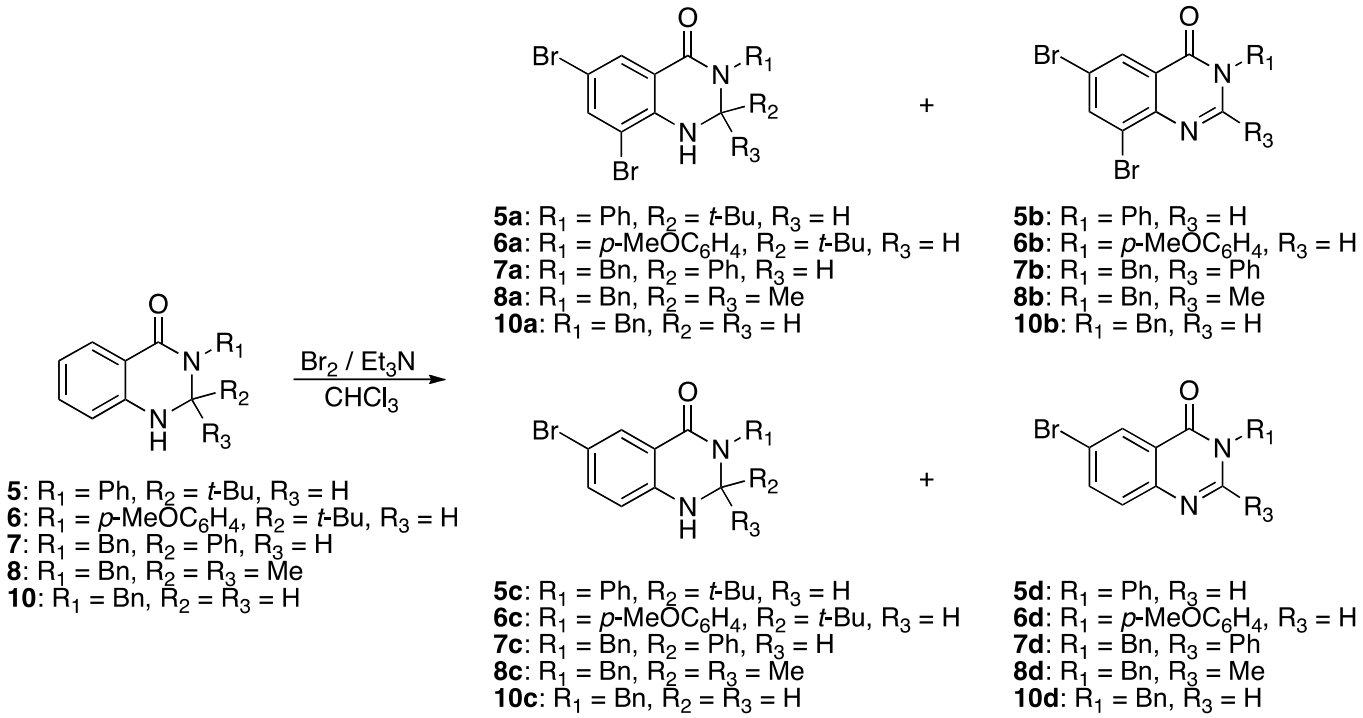
The halogenation of the aromatic ring at C-6 and C-8 occurs as a typical S_EAr reaction and the mechanism is shown in Scheme 5.



Scheme 5. Mechanism for the halogenation of 2,3-dihydroquinazolin-4(1*H*)-one **4**

We treated the compounds **5**–**8** and **10** with 2.7 equiv of Br_2, 1.1 equiv of Et_3N at 50 °C in the absence of light; the results are summarized in Scheme 6 and Table 3.

As shown in Table 3, quinazolinone **5** afforded **5a** in 91% yield (entry 1). Quinazolinone **6** afforded a mixture of **6a** (64% yield) and only traces of **6c** and **6d** (entry 2). However, when the reaction was carried out at 50 ^{o}C with the quinazolinone **7** the reaction time was very short (1 min, entry 3) and we did not observed **7a**; in this case compounds **7b** and **7d** were obtained in 60 and 38% yield respectively (entry 3).



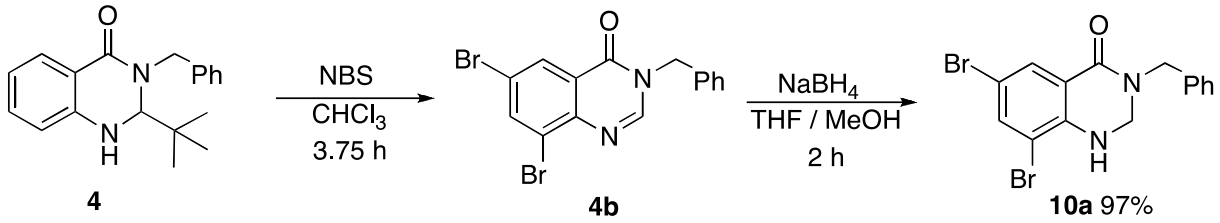
Scheme 6. Bromination reaction for **5**-**8** and **10**

Table 3. Bromination reactions for **5**–**8** and **10**

Entry	QNZ	R_1	R_2	Conditions	Time (min)	Yield (%)[a]			
1	**5**	Ph	*t*-Bu	50 ºC Br_2 /Et_3N	15	**5a**, 91	**5b**, -	**5c**, -	**5d**, -
2	**6**	*p*-$MeOC_6H_4$	*t*-Bu	50 ºC Br_2 /Et_3N	3	**6a**, 64	**6b**, -	**6c**[b]	**6d**[b]
3	**7**	Bn	Ph	50 °C Br_2 /Et_3N	1	**7a**, -	**7b**, 60	**7c**, -	**7d**, 38
4	**7**	Bn	Ph	r. t. Br_2 /Et_3N	1	**7a**, 39	**7b**, -	**7c**, 55	**7d**, -
5	**8**	Bn	Me	r. t. Br_2 /Et_3N	1	**8a**, 86	**8b**, -	**8c**[b]	**8d**, -
6	**10**	Bn	H	r. t. Br_2 /Et_3N	1	**10a**, -	**10b**, 11	**10c**, 11	**10d**, 57
7	**10**	Bn	H	0 ºC Br_2 /Et_3N	1	**10a**, -	**10b**, -	**10c**, 38	**10d**, -

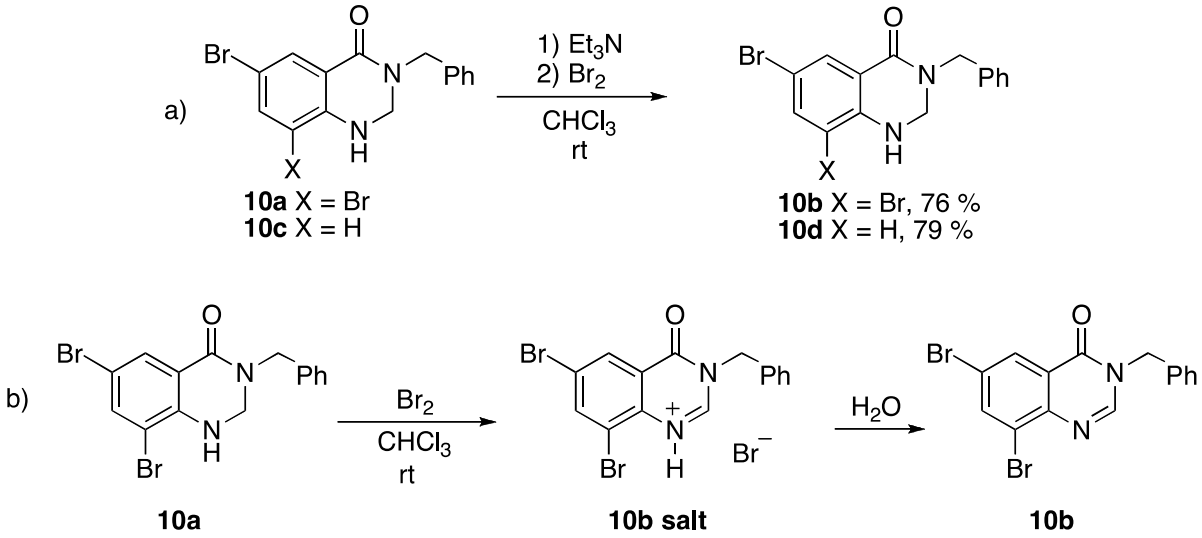
[a] Yield after column chromatographic purification. [b] This product was observed in traces

When the reaction was carried out at room temperature, however the compound **7a** was obtained only with moderate yield (39%) and **7c** (55%, entry 4). The bromination reaction of **8** was also very fast and heating was not necessary; compound **8a** was obtained in 86% yield with traces of **8c** (entry 5). Quinazolinone **10** behaved very similar to **7**, and unfortunately **10a** was not obtained under these conditions. Furthermore, compound **10a** was readily converted in excellent yield (97%) by the halogenations-elimination reaction of **4** to **4b**, which was reduced with $NaBH_4$ in THF/MeOH to give **10a** (Scheme 7).



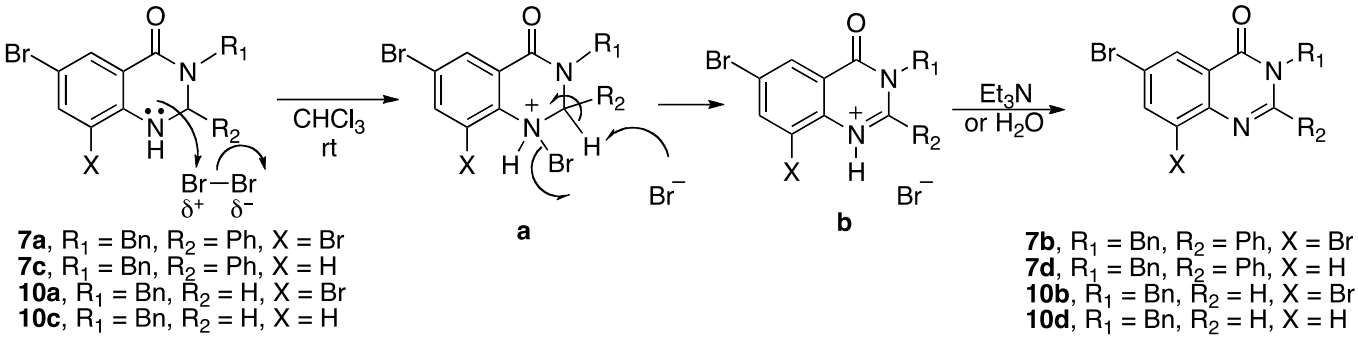
Scheme 7. Halogenation-elimination and reduction reactions of **4** to obtain **10a**

In order to explain the stability of **10a** and **10c**, these quinazolinones were treated with 1.1 equiv of Et_3N at room temperature, and after 30 min TLC showed only starting materials. However, when 2.7 equiv of Br_2 was added, the reaction instantaneously gave **10b** and **10d**, respectively (Scheme 8a). On the other hand, when we added only Br_2 to the compound **10a**, immediate preciptiation of the salt of **10b** and in presence of water gave the quinazolinone **10b** (Scheme 8b). These experiments confirmed that **10a** and **10c** are sensitive to Br_2.



Scheme 8. Stability of **10a** and **10c**

On the basis of the above results and by referring to the literature[13] we propose that the elimination of hydrogen on the position 2 of the compounds **7a**, **7c**, **10a**, and **10c** would be carried out through heterolytic process, according to the mechanism shown in Scheme 9.



Scheme 9. Mechanism reaction for the elimination for **7a**, **7c**, **10a**, and **10c** in C(2)

Recrystallization of quinazolinones **5a**, **6a**, and **7c** yielded a suitable crystals for X-ray diffraction analysis. The observed structures and solid-state conformations are presented in Figures 2-4. Salient feature in these crystallographic structures is the pyramidalized of N(1)-atom.

Chlorination Reactions

Chlorination reactions of **4**-**8** and **10** were carried out using NCS at 68 mM in chloroform (Scheme 10 and Table 4).

In these reactions we observed the formation of mono-halogenated compounds in the position 8 in addition to mono-halogenation in position 6, as observed in the bromination reaction above.

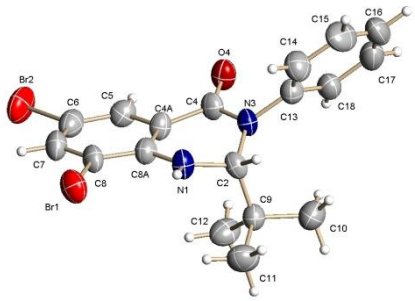


Figure 2. Crystal structure of 6,8-dibromo-2-*tert*-butyl-3-phenyl-2,3-dihydro-4(1*H*)-quinazolinone (**5a**)

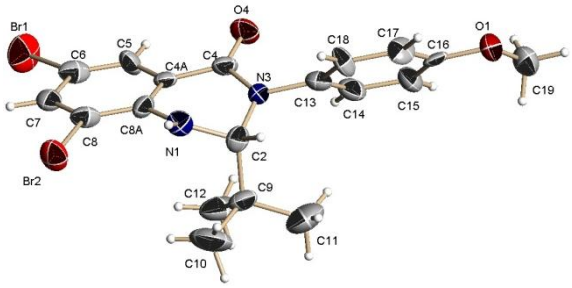


Figure 3. Crystal structure of 6,8-dibromo-2-*tert*-butyl-3-(4-methoxyphenyl)-2,3-dihydro-4-(1*H*)-quinazolinone (**6a**)

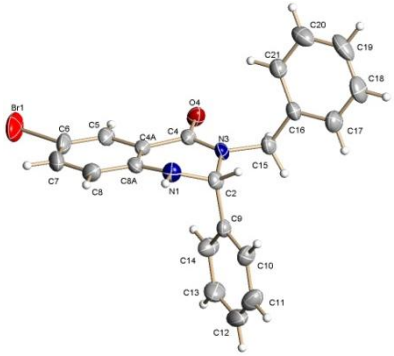
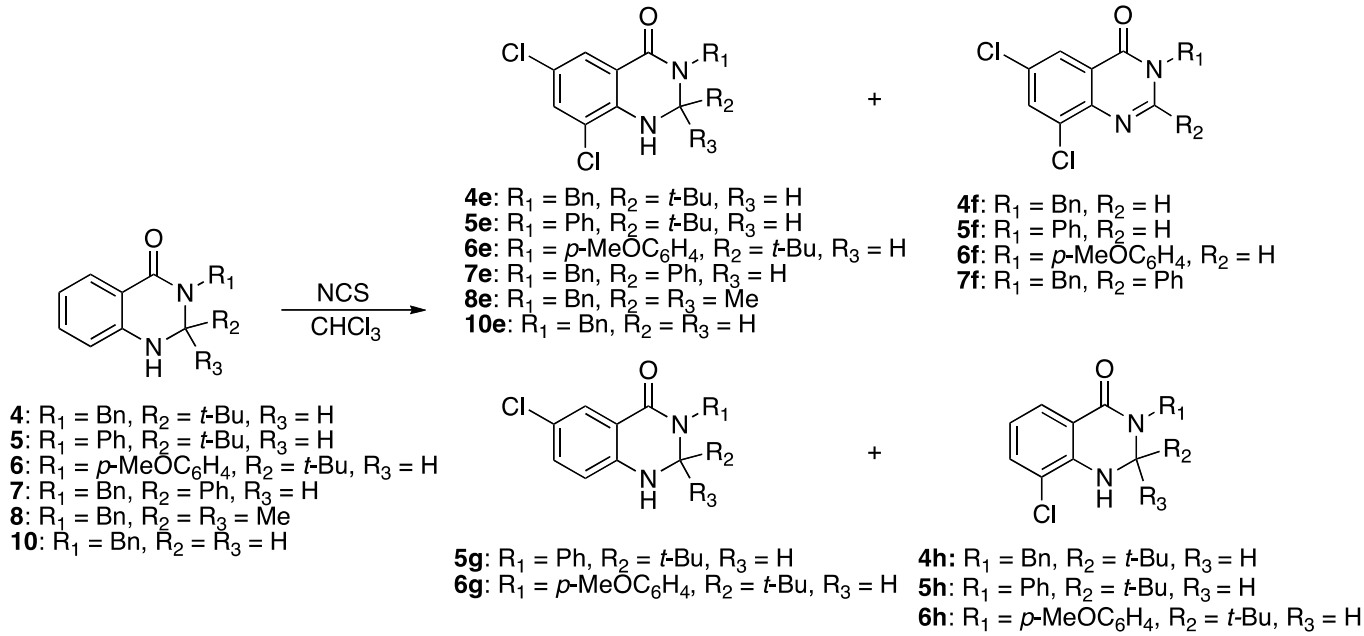


Figure 4. Crystal structure of 3-benzyl-6-bromo-2-phenyl-2,3-dihydro-4(1*H*)-quinazolinone (**7c**)



Scheme 10. Chlorination reactions of **4**-**8** and **10**

Table 4. Chlorination reactions for **4**–**8** and **10**

Entry	QNZ	R_1	R_2	Conditions	Time (h)	Yield (%)			
1	**4**	Bn	*t*-Bu	50 ºC NCS (4.2 Eq)	3.0	**4e**, 90	**4f**, 4	**4g**, -	**4h**, 2
2	**5**	Ph	*t*-Bu	50 ºC NCS (2.2 Eq)	0.5	**5e**, 44	**5f**, -	**5g**, 21[a]	**5h**, 37[a]
3	**6**	*p*-MeOC$_6$H$_4$	*t*-Bu	50 ºC NCS (2.2 Eq)	1.0	**6e**, 52	**6f**, 12	**6g**, -	**6h**, -
4	**7**	Bn	Ph	hv NCS (2.2 Eq)	0.5	**7e**, 60[b]	**7f**, 29	**7g**, -	**7h**, -
5	**8**	Bn	Me	hv NCS (2.2 Eq)	2.0	**8e**, 48[c]	**8f**, -	**8g**, -	**8h**, -
6	**10**	Bn	H	50 ºC NCS (2.2 Eq)	0.25	**10e**, 62	**10f**, -	**10g**, -	**10h**, -

[a] The products **5g** and **5h** were isolated from a second reaction carried out at 15 min. [b] When the reaction was carried out at 50 ºC, the product **7e** was isolated at 43%. [c] When the reaction was carried out at 50 ºC any product was isolated.

Recrystallization of quinazolinones **4e**, **4h**, **6e,** and **6h** afforded a suitable crystals for X-ray diffraction analysis shown in Figures 5-8 respectively.

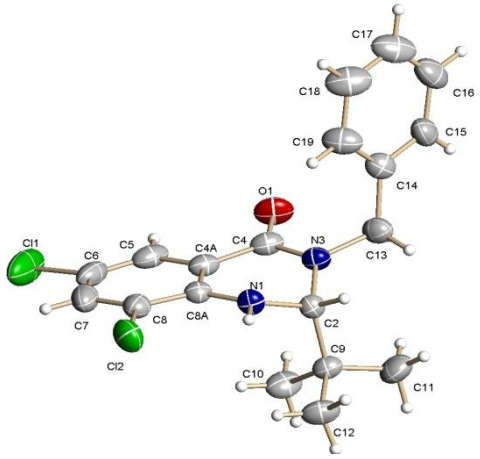


Figure 5. Crystal structure of 3-benzyl-2-*tert*-butyl-6,8-dichloro-2,3-dihydro-4(1*H*)-quinazolinone (**4e**)

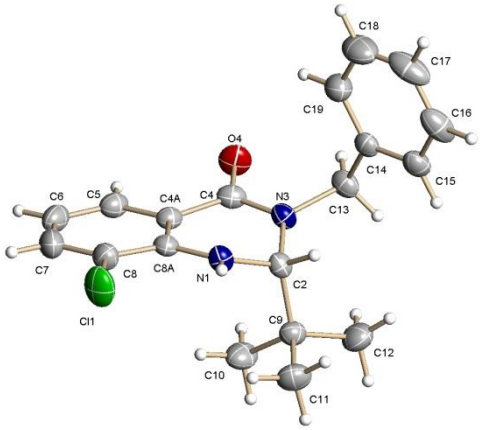


Figure 6. Crystal structure of 3-benzyl-2-*tert*-butyl-8-chloro-2,3-dihydro-4(1*H*)-quinazolinone (**4h**)

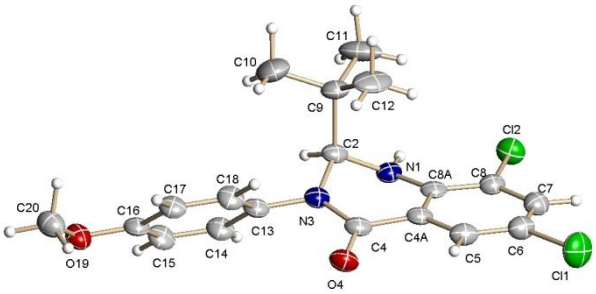


Figure 7. Crystal structure of 2-*tert*-butyl-6,8-dichloro-3-(4-methoxyphenyl)-2,3-dihydro-4-(1*H*)-quinazolinone (**6e**)

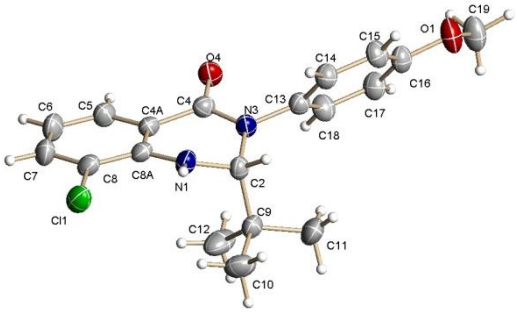
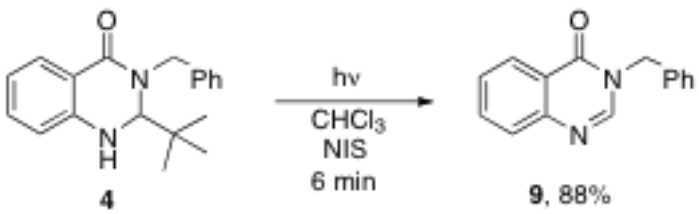


Figure 8. Crystal structure of 2-*tert*-butyl-8-chloro-3-(4-methoxyphenyl)-2,3-dihydro-4(1*H*)-quinazolinone (**6h**)

Iodination reaction

Finally, the reaction of **4** with 2.2 equiv of NIS did not yield any halogenated product, and quinazolinone **9** was isolated in good yield (88%) in only 6 min (Scheme 11). It is important to mention that the elimination reaction with *hν* conditions takes place in approximately 6 h.[11]



Scheme 11

In conclusion, we have reported the synthesis of halo-2,3-dihydro-4(1*H*)-quinazolinones derivatives through direct halogenations, without catalyst, with faster reaction time and with moderate to good yields.

EXPERIMENTAL

All chemicals were obtained commercially (Aldrich) and were used without purification. Solvents were dried using standard techniques. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (60 F_{254}). Separations by chromatography were performed on silica gel (70-230 and 230-400 mesh). The reactions with microwaves were carried out in Discover CEM equipment. The photochemical reactions were carried out in a Rayonet equipment RPR-100 (UV light 254nm). Melting points were measured in open capillary tubes using a Melt-temp Electrothermal apparatus, and are uncorrected. Elemental analyses were obtained on a Elementar Vario EL III. High resolution MS measurements were obtained on a MStation JMS-700 JEOL apparatus. The structures of X-ray were obtained using APEX-Brucker apparatus. NMR spectra were taken with a Varian Gemini and Varian Oxford at 200 and 400 MHz (^{1}H) and 100 and 50 MHz (^{13}C) using $CDCl_3$ as the solvent with TMS as internal standard.

General procedure for the synthesis of aminobenzamides (*GP-1*).

A suspension of isatoic anhydride and 1.1 equiv of aryl- or benzylamine in EtOAc was stirred and heated at 40 ºC or irradiated in microwave for the appropriate time. After completion of the reaction, which was indicated by TLC (eluent hexane:EtOAc 6:4), the brown solution was filtered in a Büchner funnel packed with a layer of celite and activated charcoal, then the colorless solution was concentrated under reduced pressure.

2-Amino-*N*-benzylbenzamide (1)

A suspension of isatoic anhydride (10 g, 62 mmol) and 1.1 equiv of benzylamine in 50 mL of EtOAc was stirred and heated according to *GP-1* for 1.3 h. The reaction was purified by flash chromatography giving 12.7 g (90%) of **1** as white crystals; mp 121–123 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 4.55 (d, J = 5.6 Hz, 2H, CH_2), 5.26 (br s, 2H, NH_2), 6.50 (br, 1H, NH), 6.59 (t, J_{ortho} = 7.4 Hz, 1H, C5-H), 6.65 (d, J_{ortho} = 8.4 Hz, 1H, C3-H), 7.18 (t, J_{ortho} = 7.8 Hz, 1H, C4-H), 7.24–7.35 (m, 6H, C6-H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 43.8, 115.8, 116.7, 117.4, 127.2, 127.5, 128.8, 132.4, 138.3, 148.8, 169.2. Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.29; H, 6.24; N, 12.38. Found: C, 74.28; H, 6.21; N, 12.38.

2-Amino-*N*-phenylbenzamide (2)

A suspension of isatoic anhydride (5 g, 30.6 mmol) and 1.1 equiv of aniline in 20 mL of EtOAc were irradiated in the microwave in open system with 65-80 Watts at 90 ºC, for 4 h. The reaction was purified

by flash chromatography yielding 6.25 g (96%) of **2** as cream solid; mp 124–126 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 5.30 (br s, 2H, NH_2), 6.62-6.70 (m, 2H, C5-H, C3-H), 7.08-7.56 (m, 7H, C4-H, C6-H and Ph), 7.85 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 116.4, 116.9, 117.6, 120.7, 124.6, 127.3, 129.1, 132.8, 137.9, 148.9, 167.7. Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.40; H, 5.63; N, 13.11.

2-Amino-*N*-(4-methoxyphenyl)benzamide (3)

A suspension of isatoic anhydride (1.63 g, 10 mmol) and 1 equiv of 4-methoxyaniline (1.23 g) in 20 mL of EtOAc were irradiated in the microwave in open system with 65-80 Watts at 90 ºC, for 2.5 h. The reaction was purified by flash chromatography yielded 2.22 g (92%) of **3** as cream solid; mp 118–121 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 3.77 (s, 3H, -OCH_3), 5.46 (br s, 1H, NH_2), 6.61-6.69 (m, 2H, C3-H, C5-H), 6.86 (d, 2H, J_{ortho} 9.2 Hz, C3′-H), 7.21 (td, J_{ortho} = 7.9 Hz, J_{meta} = 1.6 Hz, 1H, C4-H), 7.36-7.45 (m, 3H, C6-H, C2′-H), 7.79 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 55.7, 114.3, 116.4, 116.9, 117.5, 122.8, 127.3, 130.9, 132.6, 148.9, 156.7, 167.7. Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.23; H, 5.71; N, 11.87.

General procedure for the synthesis of 2,3-dihydro-4(1*H*)-quinazolinones (*GP-2*).

A solution of aminobenzamide in CH_2Cl_2 was added 1.2 equiv of appropriate aldehyde and then was added 2-5% by weight of *p*-TsOH; the reactions were carried out in the absence of light because the quinazolinones are sensitive.[11] Colorless solution was refluxed for the appropriate time. The reaction was monitored by TLC (hexane:EtOAc 6:4). The straw yellow solution was concentrated and the crude of reaction was purified by flash chromatography eluting with hexane:EtOAc 9:1 - 6:4.

3-Benzyl-2-*tert*-butyl-2,3-dihydro-4(1*H*)-quinazolinone (4)

A solution of aminobenzamide **1** (6 g, 26.5 mmol) in 100 mL of CH_2Cl_2 was added 3.26 mL (1.2 equiv) of pivalaldehyde and then was added 0.12 g (2% by weight) of *p*-TsOH. The colorless solution was refluxed for 5 h according to *GP-2*. The crude of reaction was purified by flash chromatography yielding 6.7 g (86%) of **4** as white solid; mp 140–143 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 0.87 (s, 9H, *t*-Bu), 3.92 (d, *J* = 15.6 Hz, 1H, CH_2), 4.24 (d, *J* = 3.2 Hz, 1H, C2-H), 4.40 (br d, *J* = 3.2 Hz, 1H, NH-1), 5.81 (d, *J* = 15.2 Hz, 1H, CH_2), 6.49 (d, J_{ortho} = 8 Hz, 1H, C8-H), 6.73 (t, J_{ortho} = 7.5 Hz, 1H, C6-H), 7.20-7.34 (m, 6H, C7-H y Ph), 7.85 (dd, J_{ortho} = 7.8 Hz, J_{meta} = 1.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 26.6, 42.0, 51.4, 75.7, 113.3, 116.6, 118.1, 127.3, 127.4, 128.5, 128.7, 133.6, 137.4, 146.6, 163.8. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.61; H, 7.46; N, 9.30.

2-*tert*-Butyl-3-phenyl-2,3-dihydro-4(1*H*)-quinazolinone (5)

A solution of aminobenzamide **2** (6.25 g, 29.5 mmol) in 100 mL of CH_2Cl_2 was added 3.84 mL (1.2 equiv) of pivalaldehyde and then was added 0.31 g (5% by weight) of *p*-TsOH. The colorless solution was refluxed for 6 h according to *GP-2*. The crude of reaction was purified by flash chromatography affording 8 g (97%) of **5** as colorless needless; mp 149–151 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 0.82 (s, 9H, *t*-Bu), 4.94 (br s, 1H, NH), 5.01 (d, J = 1.6 Hz, 1H, C2-H), 6.60 (d, J_{ortho} = 8 Hz, 1H, C8-H), 6.76 (t, J_{ortho} = 7.4 Hz, 1H, C6-H), 7.19-7.27 (m, 2H, C7-H, CH), 7.37 (t, J_{ortho} = 7.6 Hz, 2H, 2CH), 7.49 (d, J_{ortho} = 8.2 Hz, 2H, CH), 7.89 (d, J_{ortho} = 7 Hz, 1H, C5-H; ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm): 26.9, 42.4, 80.0, 113.4, 116.8, 118.4, 126.2, 127.5, 128.7, 128.9, 133.8, 143.7, 146.8, 162.5. Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.82; H, 7.12; N, 10.14. X-Ray crystallographic structure in Figure 1.[14]

2-*tert*-Butyl-3-(4-methoxyphenyl)-2,3-dihydro-4(1*H*)-quinazolinone (6)

A solution of aminobenzamide **3** (1.45 g, 5.98 mmol) in 50 mL of CH_2Cl_2 was added 0.78 mL (1.2 equiv) of pivalaldehyde and then was added 0.04 g (3% by weight) of *p*-TsOH. The colorless solution was refluxed for 5 h according to *GP-2*. The crude of reaction was purified by flash chromatography yielding 1.73 g (94%) of **6** as white solid; mp 165–168 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.82 (s, 9H, *t*-Bu), 3.78 (s, 3H, -OCH_3), 4.92 (s, 1H, C2-H), 4.94 (br s, 1H, N-H), 6.56 (d, J_{ortho} = 8 Hz, 1H, C8-H), 6.74 (td, J_{ortho} = 7.5 Hz, J_{meta} = 1 Hz, 1H, C6-H), 6.88 (d, J_{ortho} = 9.2 Hz, 2H, C3′-H), 7.23 (td, J_{ortho} = 7.7 Hz, J_{meta} = 1.4 Hz, 1H, C7-H), 7.38 (d, J_{ortho} = 8.8 Hz, 2H, C2′-H), 7.87 (dd, J_{ortho} = 7.8 Hz, J_{meta} = 1.5 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 26.87 (CH_3 of *t*-Bu), 42.3, 55.6, 80.1, 113.4, 113.9, 116.7, 118.2, 128.6, 128.8, 133.7, 136.6, 146.9, 157.5, 162.8. Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 74.09; H, 7.27; N, 9.10.

3-Benzyl-2-phenyl-2,3-dihydro-4(1*H*)-quinazolinone (7)

A solution of aminobenzamide **1** (1 g, 4.42 mmol) in 50 mL of CH_2Cl_2 was added 0.53 mL (1.2 equiv) of benzaldehyde and then was added 0.03 g (3% by weight) of *p*-TsOH. The colorless solution was refluxed for 4 h according to *GP-2*. The crude of reaction was purified by flash chromatography yielding 1.55 g (83%) of **7** as white solid; mp 145–148 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 3.64 (d, J = 15.4 Hz, 1H, CH_2), 4.63 (br, 1H, NH), 5.57 (d, J = 15.4 Hz, 1H, CH_2), 5.59 (s, 1H, C2-H), 6.48 (d, J_{ortho} = 8.2 Hz, 1H, C8-H), 6.82 (t, J_{ortho} = 7.6 Hz, 1H, C6-H), 7.17-7.30 (m, 11H, C7-H, CH of Ph), 7.99 (d, J_{ortho} = 7.6 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 47.1, 71.2, 114.4, 115.7, 119.2, 126.6, 127.5, 128.1, 128.7, 128.8, 129.0, 129.3, 133.7, 136.8, 139.4, 145.2, 163.3. Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.21; H, 5.78; N, 8.86.

3-Benzyl-2,2-dimethyl-2,3-dihydro-4(1*H*)-quinazolinone (8)

A solution of aminobenzamide **1** (1.5 g, 6.62 mmol) in 50 mL of CH_2Cl_2 was added 0.58 mL (1.2 equiv) of anhydrous acetone and then was added 0.045 g (3% by weight) of *p*-TsOH. The colorless solution was refluxed for 4 h according to *GP-2*. The crude of reaction was purified by flash chromatography yielding 1.20 g (68%) of **8** as white solid; mp 199-200 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.45 (s, 6H, CH_3), 4.27 (br, 1H, NH), 4.79 (s, *2*H, CH_2), 6.60 (d, J_{ortho} = 8.2 Hz, 1H, C8-H), 6.84 (t, J_{ortho} = 7.5 Hz, 1H, C6-H), 7.19-7.33 (m, 6H, C7-H, Ph), 7.96 (d, J_{ortho} = 7.6 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 27.7, 45.2, 72.1, 114.4, 115.9, 119.1, 126.9, 127.2, 128.6, 129.0, 133.6, 139.4, 145.1, 164.0. HRMS: Calcd for $C_{17}H_{18}N_2O$: 266.1419, found: $[M+H]^+$ $C_{17}H_{19}N_2O$, 267.1418.

3-Benzyl-4(3*H*)-quinazolinone (9)

A solution of aminobenzamide **1** (2.8 g, 12 mmol) in 50 mL of toluene was added 1.99 mL (1 equiv) of triethyl orthoformate and then was added 0.12 g (3% by weight) of *p*-TsOH. The colorless solution was refluxed for 6 h according to *GP-2*. The crude of reaction was recrystallzed with methanol, yielding 2.7 g (98%) of **9** as white solid. The compound **9** also can be obtained from the compound **4**: a solution of **4** (0.34 mmol) in $CHCl_3$ was stirred and irradiated with UV light in the Rayonet equipment RPR-100 for 6 hours. The reaction mixture was monitored by flash chromatography (Hex:AcOEt, 80:20) until disappearance of starting material; the reaction mixture was concentrated under reduced pressure and the crude of reaction was purified by flash chromatograpy, yielding 98% of **9**.[11] mp 118-119 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 5.14 (s, *2*H, CH_2), 7.22–7.29 (m, 5H, C6-H, 4CH), 7.43–7.47 (m, 1H, C8-H), 7.64–7.72 (m, 2H, C7-H, CH), 8.08 (s, 1H, C2-H), 8.26 (ddd, J_{ortho} = 8.0 Hz, J_{meta} = 1.6 Hz, J_{ortho} = 0.8 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 49.7, 122.3, 126.9, 127.4, 127.6, 128.1, 128.4, 129.1, 134.4, 135.8, 146.4, 148.1, 161.1. HRMS: Calcd for $C_{15}H_{12}N_2O$: 236.0949, found: 236.0954.

3-Benzyl-2,3-dihydro-4(1*H*)-quinazolinone (10)

4(3*H*)-Quinazolinone **9** (1.73 g, 7.3 mmol) was dissolved in anhydrous THF (24 mL), the solution was cooled at 0 ºC and then 0.55 g (2 equiv) of sodium borohydride was slowly added, finally was added 6 mL of MeOH. The reaction mixture was stirred at rt under nitrogen atmosphere for 2 h. The solvent was concentrated and the residue was suspended in water, which was extracted with EtOAc. The organic extracts were dried with anhydrous sodium sulfate and concentrated. After flash chromatography yielded 1.5 g (88%) of **10** as white solid; mp 66–68 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 4.49 (s, 2H, CH_2), 4.50 (br s, 1H, NH), 4.71 (s, 2H, C2-H_2), 6.65 (d, J_{ortho} = 8.2 Hz, 1H, C8-H), 6.67 (td, J_{ortho} = 7.5 Hz, J_{meta} = 0.6 Hz, 1H, C6-H), 7.22-7.30 (m, 6H, C7-H and Ph), 7.97 (dd, J_{ortho} = 7.7 Hz, J_{meta} = 1.1 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 48.5, 59.0, 115.0, 117.4, 119.7, 127.7, 127.9, 128.8, 129.0, 133.3,

136.7, 147.7, 163.8. HRMS: Calcd for $C_{15}H_{14}N_2O$: 238.1106, found: $[M+H]^+$ $C_{15}H_{15}N_2O$, 239.1203.

General procedure for the halogenation reactions with *N*-halosuccinimides (*GP-3*).

A solution of 2,3-dihydro-4(1*H*)-quinazolinone (0.34 mmol) in $CHCl_3$ (5 mL) was added 2.2–4.2 equiv of NBS or NCS. The solution was stirred and irradiated with $h\nu$ (254 nm) in Rayonet equipment RPR-100 or heated at 50 °C. After this, colored solution was monitored by TLC (hexane:EtOAc 6:4) until disappearance of starting material. The reaction mixture was concentrated under reduced pressure and the crude of reaction was purified by flash chromatography eluting with hexane:EtOAc (9:1–6:4).

General procedure for the halogenation reactions with Br_2/Et_3N (*GP-4*).

A solution of 2,3-dihydro-4(1*H*)-quinazolinone (0.34 mmol) in $CHCl_3$ (5 mL) was added 1.1–2.1 equiv of Et_3N and 2.0-2.27 equiv of Br_2. The solution was stirred and heated at 50 ºC or at rt or at 0 °C. After this, colored solution was monitored by TLC (hexane:EtOAc 6:4) until disappearance of starting material. The reaction mixture was concentrated under reduced pressure and the crude of reaction was suspended in water (5 mL), which was extracted with EtOAc (3 x 5 mL). The organic layer was dried with anhydrous sodium sulfate and concentrated. The residue was purified by flash chromatography eluting with Hex:EtOAc (9:1–6:4).

3-Benzyl-6,8-dibromo-2-*tert*-butyl-2,3-dihydro-4(1*H*)-quinazolinone (4a)

This compound was obtained from *GP-3* and *4* with hν and at 50 °C. Yield 87%, white solid; mp 116–118 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.94 (s, *t*-Bu, 9H), 4.00 (d, J = 15.4 Hz, 1H, CH_2), 4.42 (d, J = 3.2 Hz, 1H, C2-H), 5.00 (br d, J = 2.6 Hz, 1H, NH), 5.81 (d, J = 15.4 Hz, 1H, CH_2), 7.27-7.31 (m, 5H, Ph), 7.59 (d, J_{meta} = 2.2 Hz, 1H, C7-H), 7.96 (d, J_{meta} = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 26.5, 42.0, 51.6, 75.7, 107.8, 109.5, 118.8, 127.5, 127.7, 128.9, 130.6, 136.8, 137.9, 143.1, 161.8. Anal. Calcd for $C_{19}H_{20}Br_2N_2O$: C, 50.47; H, 4.46; N, 6.20. Found: C, 50.32; H, 4.31; N, 6.39.

3-Benzyl-6,8-dibromo-4(3*H*)-quinazolinone (4b)

This compound was obtained from *GP-3* at 50 °C. Yield 41% (UV light), white solid; mp 176.5–178.5 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.19 (s, 2H, CH_2), 7.34-7.35 (m, 5H, Ph), 8.13 (d, J_{meta} = 2.2 Hz, 1H, C7-H), 8.22 (s, 1H, C2-H), 8.41 (d, J_{meta} = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 50.3, 120.9, 123.5, 124.5, 128.3, 128.8, 129.3, 135.0, 140.4, 144.9, 147.3, 159.4. Anal. Calcd for $C_{15}H_{10}Br_2N_2O$: C, 45.72; H, 2.56; N, 7.11. Found: C, 45.97; H, 2.57; N, 7.35.

3-Benzyl-2-*tert*-butyl-6,8-dichloro-2,3-dihydro-4(1*H*)-quinazolinone (4e)

This compound was obtained from *GP-3* with UV light and at 50 °C. Yield 90% (at 50 °C), white solid; mp 130–132 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.94 (s, *t*-Bu, 9H), 4.01 (d, J = 15.8 Hz, 1H, CH_2), 4.43 (d, J = 3.4 Hz, 1H, C2-H), 4.96 (br d, J = 2.6 Hz, 1H, NH), 5.82 (d, J = 15.8 Hz, 1H, CH_2), 7.26-7.33 (m, 6H, C7-H, Ph), 7.78 (d, J_{meta} = 2.6 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 26.5, 42.0, 51.6, 75.7, 117.9, 118.4, 122.6, 127.1, 127.5, 127.8, 128.9, 132.5, 136.8, 141.7, 161.9. Anal. Calcd for $C_{19}H_{20}Cl_2N_2O$: C, 62.82; H, 5.55; N, 7.71. Found: C, 62.34; H, 5.37; N, 8.35. X-Ray crystallographic structure in Figure 5.[14]

3-Benzyl-6,8-dichloro-4(3*H*)-quinazolinone (4f)

This compound was obtained from GP-3 at 50 °C. Yield 16% (UV light), white solid; mp 177–179 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 5.19 (s, 2H, CH_2), 7.35 (m, 5H, Ph), 7.81 (d, J_{meta} = 2.2 Hz, 1H, C7-H), 8.20-8.21 (m, 2H, C2-H and C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 50.3, 124.4, 125.4, 128.3, 128.8, 129.3, 133.1, 134.8, 135.0, 147.1, 159.4. Anal. Calcd for $C_{15}H_{10}Cl_2N_2O$: C, 59.04; H, 3.30; N, 9.18. Found: C, 58.77; H, 3.36; N, 9.22.

3-Benzyl-2-*tert*-butyl-6-chloro-2,3-dihydro-4(1*H*)-quinazolinone (4g)

This compound was obtained from *GP-3* at 50 °C (4 h). Yield 16%, white solid; mp 86–89 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.93 (s, *t*-Bu, 9H), 3.99 (d, J = 15.8 Hz, 1H, CH_2), 4.31 (d, J = 3.2 Hz, 1H, C2-H), 4.53 (br s, 1H, NH), 5.85 (d, J = 15.8 Hz, 1H, CH_2), 6.51 (d, J_{ortho} = 8.4 Hz, 1H, C8-H), 7.18 (dd, J_{ortho} = 8.7 Hz, J_{meta} = 2.6 Hz, 1H, C7-H), 7.26-7.34 (m, 5H, Ph), 7.84 (d, J_{meta} = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 26.7, 42.1, 51.5, 75.7, 114.8, 117.9, 123.4, 127.5, 127.6, 128.3, 128.9, 133.5, 137.3, 145.0, 162.8. HRMS: Calcd for $C_{19}H_{21}ClN_2O$, 328.1342; found: $[M+H]^+$ $C_{19}H_{22}ClN_2O$, 329.1391.

3-Benzyl-2-*tert*-butyl-8-chloro-2,3-dihydro-4(1*H*)-quinazolinone (4h)

This compound was obtained from *GP-4* (4 h). Yield 30%, white solid; mp 123–126 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.98 (s, *t*-Bu, 9H), 4.01 (d, J = 15.8 Hz, 1H, CH_2), 4.42 (d, J = 3 Hz, 1H, C2-H), 4.99 (br s, 1H, NH), 5.86 (d, J = 15.8 Hz, 1H, CH_2), 6.70 (t, J_{ortho} = 7.9 Hz, 1H, C6-H), 7.24-7.36 (m, 6H, C7-H, Ph), 7.80 (dd, J_{ortho} = 7.8 Hz, J_{meta} = 1.4 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 26.6, 41.9, 51.5, 75.8, 117.3, 117.9, 118.1, 127.2, 127.5, 127.6, 128.9, 132.9, 137.4, 143.1, 163.0. HRMS: Calcd for $C_{19}H_{21}ClN_2O$: 328.1342 Found: $[M+H]^+$ $C_{19}H_{22}ClN_2O$, 329.1396. X-Ray crystallographic structure in Figure 6.[14]

6,8-Dibromo-2-*tert*-butyl-3-phenyl-2,3-dihydro-4(1*H*)-quinazolinone (5a)

This compound was obtained by the *GP-3* and *4* at 50 °C. Yield 91% (*GP-4* at 50 °C), white solid; mp 155–156 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.84 (s, *t*-Bu, 9H), 5.14 (d, *J* = 3.4 Hz, 1H, C2-H), 5.24 (br s, 1H, NH), 7.20-7.54 (m, 5H, Ph), 7.63 (d, J_{meta} = 2.2 Hz, 1H, C7-H), 7.98 (d, J_{meta} = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm): 26.7, 42.3, 80.2, 107.8, 109.7, 118.9, 126.8, 127.3, 129.0, 130.9, 138.2, 143.0, 143.3, 160.4. HRMS: Calcd for $C_{18}H_{18}Br_2N_2O$, 435.9785; found: $[M+H]^+$ $C_{18}H_{19}Br_2N_2O$, 436.9897.

6,8-Dibromo-3-phenyl-4(3*H*)-quinazolinone (5b)

This compound was obtained by the *GP-3* with UV light. Yield 13%, white solid; mp 213–215 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7.38-7.62 (m, 5H, Ph), 8.18 (d, J_{meta} = 1.8 Hz, 1H, C7-H), 8.23 (s, 1H, C2-H), 8.44 (d, J_{meta} = 1.6 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm): 121.2, 123.6, 124.8, 126.9, 129.5, 129.7, 130.0, 136.9, 140.7, 147.1, 159.0 HRMS: Calcd for $C_{14}H_8Br_2N_2O$, 379.8983; found: $[M+H]^+$ $C_{14}H_9Br_2N_2O$, 380.9134.

6-Bromo-3-phenyl-4(3*H*)-quinazolinone (5d)

This compound was obtained from *GP-3* at 50 °C. Yield 32% as white solid; mp 172–174 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7.38-7.56 (m, 5H, Ph), 7.63 (d, J_{ortho} = 8.4 Hz, 1H, C8-H), 7.87 (dd, J_{ortho} = 8.0 Hz, *J* 2.8 Hz, 1H, C7-H), 8.21 (s, 1H, C2-H), 8.47 (d, J_{meta} = 2.6 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm): 121.4, 123.8, 127.0, 127.0, 129.4, 129.5, 129.8, 137.2, 137.8, 146.5, 146.7, 159.6. HRMS: Calcd for $C_{14}H_9BrN_2O$, 299.9898; found: $[M+H]^+$ $C_{14}H_{10}BrN_2O$, 300.9949.

6,8-Dichloro-2-*tert*-butyl-3-phenyl-2,3-dihydro-4(1*H*)-quinazolinone (5e)

This compound was obtained from *GP-3* with UV light and at 50 °C. Yield 44% (at 50 °C), white solid; mp 204–206 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.83 (s, *t*-Bu, 9H), 5.14 (d, *J* = 3.8 Hz, 1H, C2-H), 5.24 (br d, *J* = 3 Hz, 1H, NH), 7.23 (tt, J_{ortho} = 7 Hz, J_{meta} 1.8 = Hz, 1H, C4′), 7.35-7.50 (m, 5H, C7-H, Ph), 7.81 (d, J_{meta} = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm): 26.7, 42.3, 80.1, 118.0, 118.5, 122.8, 126.7, 127.3, 128.9, 132.7, 141.8, 143.0, 160.6. HRMS: Calcd for $C_{18}H_{18}Cl_2N_2O$, 348.0796; found: $[M+H]^+$ $C_{18}H_{19}Cl_2N_2O$, 349.0872.

2-*tert*-Butyl-6-chloro-3-phenyl-2,3-dihydro-4(1*H*)-quinazolinone (5g)

This compound was obtained from *GP-3* at 50 °C. Yield 21% as white solid; mp 159–161 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.82 (s, *t*-Bu, 9H), 5.01 (br s, *2*H, C2-H, NH), 6.55 (d, J_{ortho} = 8.8 Hz, 1H, C8-H), 7.21 (dt, J_{ortho} = 9.1 Hz, *J* = 2.5 Hz, 1H, C7-H), 7.34-7.57 (m, 5H, Ph), 7.84 (d, J_{meta} = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm): 26.8, 42.5, 80.0, 114.9, 117.8, 123.3, 126.5, 127.4, 128.4,

128.9, 133.7, 143.4, 145.3, 161.4. HRMS: Calcd for $C_{18}H_{19}ClN_2O$, 314.1185; found: $[M+H]^+$ $C_{18}H_{20}ClN_2O$, 315.1272.

2-*tert*-Butyl-8-chloro-3-phenyl-2,3-dihydro-4(1*H*)-quinazolinone (5h)

This compound was obtained from *GP-3* at 50 °C. Yield 37% as white solid; mp 145–148 ºC. ^{1}H NMR ($CDCl_3$, 200 MHZ): δ (ppm) 0.84 (s, *t*-Bu, 9H), 5.15 (d, J = 3.4 Hz, 1H, C2-H), 5.24 (br s, 1H, NH), 6.72 (t, J_{ortho} = 7.8 Hz, 1H, C6-H), 7.22 (tt, J_{ortho} = 7.2 Hz, J_{meta} = 1.4 Hz, 1H, C4′-H) 7.33-7.52 (m, 5H, C7-H, Ph), 7.82 (dd, J_{ortho} = 8.0 Hz, J_{meta} = 1.1 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm): 26.7, 42.2, 80.1, 117.4, 117.8, 118.3, 126.6, 127.5, 127.5, 128.9, 133.1, 143.2, 143.3, 161.8. HRMS: Calcd for $C_{18}H_{19}ClN_2O$, 314.1185; found: $[M+H]^+$ $C_{18}H_{20}ClN_2O$, 315.1280.

6,8-Dibromo-2-*tert*-butyl-3-(4-methoxyphenyl)-2,3-dihydro-4(1*H*)-quinazolinone (6a)

This compound was obtained from *GP-3* and *4*. Yield 64% (*GP-4* 5 at 50 °C), white solid; mp 154–155 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.84 (s, 9H, *t*-Bu), 3.80 (s, 3H, -OCH_3), 5.06 (d, J = 3 Hz, 1H, C2-H), 5.22 (br d, J = 2.6 Hz, 1H, N-H), 6.91 (d, J_{ortho} = 8.8 Hz, 2H, C3′-H), 7.37 (d, J_{ortho} = 9.2 Hz, 2H, C2′-H), 7.62 (d, J_{meta} = 2.2 Hz, 1H, C7-H), 7.96 (d, J_{meta} = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 26.7, 42.2, 55.6, 80.3, 107.7, 109.6, 114.20, 118.9, 128.4, 130.8, 135.8, 138.1, 143.3, 157.9, 160.7. HRMS: Calcd for $C_{19}H_{20}Br_2N_2O_2$, 467.9871; found: $[M+H]^+$ $C_{19}H_{21}Br_2N_2O_2$, 467.0004. X-Ray crystallographic structure in Figure 3.[14]

6-Bromo-3-(4-methoxyphenyl)-4(3*H*)-quinazolinone (6d)

This compound was obtained from *GP-3* and *4* with UV light and at rt. Yield 40% (*GP-3* with UV light), white solid; mp 197-199 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 3.87 (s, 3H, -OCH_3), 7.04 (d, J_{ortho} = 8.8 Hz, 2H, C3′-H), 7.32 (d, J_{ortho} = 8.8 Hz, 2H, C2′-H), 7.63 (d, J_{ortho} = 8.4 Hz, 1H, C8-H), 7.87 (dd, J_{ortho} = 8.6 Hz, J_{meta} = 2.6 Hz, 1H, C7-H), 8.11 (s, 1H, C2-H), 8.47 (d, J_{meta} = 2.6 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 55.8, 115.1, 121.4, 123.9, 128.2, 129.5, 129.8, 129.9, 137.8, 146.9, 159.9, 160.1. HRMS: Calcd for $C_{15}H_{12}BrN_2O_2$, 330.0004; found: $[M+H]^+$ $C_{15}H_{13}BrN_2O_2$, 331.0085.

2-*tert*-Butyl-6,8-dichloro-3-(4-methoxyphenyl)-2,3-dihydro-4(1*H*)-quinazolinone (6e)

This compound was obtained from *GP-3* with UV light and at 50 °C. Yield 52% (at 50 °C), white solid; mp 200–203 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.84 (s, 9H, *t*-Bu), 3.80 (s, 3H, -OCH_3), 5.06 (d, J = 3.4 Hz, 1H, C2-H), 5.20 (br d, J = 2.4 Hz, 1H, N-H), 6.91 (d, J_{ortho} = 8.8 Hz, 2H, C3′-H), 7.37 (d, J_{ortho} = 8.8 Hz, 3H, C2′-H, C7-H), 7.77 (d, J_{meta} = 2.6 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 26.7, 42.1, 55.6, 80.3, 114.2, 117.9, 118.5, 122.7, 127.2, 128.4, 132.6, 135.8, 141.9, 157.9, 160.8. HRMS:

Calcd for $C_{19}H_{20}Cl_2N_2O_2$, 378.0901; found: $[M+H]^+$ $C_{19}H_{21}Cl_2N_2O_2$, 379.0973. X-Ray crystallographic structure in Figure 7.[14]

6,8-Dichloro-3-(4-methoxyphenyl)-4(3*H*)-quinazolinone (6f)

This compound was obtained from *GP-3* at 50 °C. Yield 12%, white solid; mp 195–196 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 3.87 (s, 3H, -OCH_3), 7.04 (d, J_{ortho} = 8.8 Hz, 2H, C3′-H), 7.32 (d, J_{ortho} = 8.8 Hz, 2H, C2′-H), 7.71 (d, J_{meta} = 2.2 Hz, 1H, C7-H), 7.71 (d, J_{meta} = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 55.8, 115.1, 126.7, 128.2, 129.4, 129.9, 133.6, 135.0, 146.5, 146.8, 160.2. HRMS: Calcd for $C_{15}H_{10}Cl_2N_2O_2$, 320.0119; found: $[M+H]^+$ $C_{15}H_{11}Cl_2N_2O_2$, 321.0201.

2-*tert*-Butyl-6-chloro-3-(4-methoxyphenyl)-2,3-dihydro-4(1*H*)-quinazolinone (6g)

This compound was obtained from GP-4 with UV light. Yield 16%, white solid; mp 189–191 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 0.81 (s, 9H, *t*-Bu), 3.79 (s, 3H, -OCH_3), 4.91 (br, 1H, C2-H), 5.09 (br d, 1H, N-H), 6.51 (d, J_{ortho} = 8.8 Hz, 1H, C8-H), 6.89 (d, J_{ortho} = 8.8 Hz, 2H, C3′-H), 7.15 (dd, J_{ortho} = 8.8 Hz, J_{meta} = 2.6 Hz, 1H, C7-H), 7.36 (d, J_{ortho} = 8.8 Hz, 2H, C2′-H), 8.29 (d, J_{meta} =3 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 26.8, 42.3, 55.6, 80.1, 114.0, 114.9, 117.7, 122.4, 127.6, 128.1, 130.2, 134.6, 147.9, 157.6, 161.0. HRMS: Calcd for $C_{19}H_{21}ClN_2O_2$, 344.1291; found: $[M+H]^+$ $C_{19}H_{22}ClN_2O_2$, 345.1337.

2-*tert*-Butyl-8-chloro-3-(4-methoxyphenyl)-2,3-dihydro-4(1*H*)-quinazolinone (6h)

This compound was obtained from *GP-3* with UV light. Yield 24%, white solid; mp 223–225 ºC. ^{1}H NMR ($CDCl_3$, 200 MHZ): δ (ppm) 0.84 (s, *t*-Bu, 9H), 3.80 (s, 3H, -OCH_3), 5.07 (d, J = 3 Hz, 1H, C2-H), 5.21 (br d, 1H, NH), 6.71 (t, J_{ortho} = 7.9 Hz, 1H, C6-H), 6.90 (d, J_{ortho} = 9.2 Hz, 2H, C3′-H), 7.32-7.43 (m, 3H, C7-H, C-H), 7.81 (dd, J_{ortho} = 7.7 Hz, J_{meta} = 1.1 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 26.7, 42.1, 55.6, 80.3, 114.1, 117.3, 117.9, 118.2, 127.5, 128.5, 133.0, 136.2, 143.2, 157.8, 161.9. HRMS: Calcd for $C_{19}H_{21}ClN_2O_2$, 344.1291; found: $[M+H]^+$ $C_{19}H_{22}ClN_2O_2$, 345.1368. X-Ray crystallographic structure in Figure 8.[14]

3-Benzyl-6,8-dibromo-2-phenyl-2,3-dihydro-4(1*H*)-quinazolinone (7a)

This compound was obtained from *GP-3* and *4* at rt. Yield 39% (*GP-4*), white solid; mp 161–163 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 3.68 (d, J = 15.4 Hz, 1H, CH_2), 5.03 (br, 1H, NH), 5.59 (d, J = 15.4 Hz, 1H, CH_2), 5.69 (d, 1H, C2-H), 7.19-7.42 (m, 10H, Ph), 7.60 (d, J_{meta} = 2.2 Hz, 1H, C7-H), 8.11 (d, J_{meta} = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 47.4, 70.6, 108.8, 110.5, 117.7, 126.5, 127.8, 128.1, 128.8, 129.3, 129.7, 130.9, 136.1, 138.2, 138.7, 141.8, 161.2. HRMS: Calcd for $C_{21}H_{16}Br_2N_2O$, 469.9629; found: $[M+H]^+$ $C_{21}H_{17}Br_2N_2O$, 470.9644.

3-Benzyl-6,8-dibromo-2-phenyl-4(3*H*)-quinazolinone (7b)

This compound was obtained from *GP-3* at rt. Yield 24%, white solid; mp 144.5–146 ºC. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 5.28 (s, 2H, CH_2), 6.90-6.91 (m, 2H, CH), 7.20-7.21 (m, 3H, CH), 7.40-7.42 (m, 5H, CH), 8.14 (d, J = 2.2 Hz, 1H, C7-H), 8.43 (d, J = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 49.57 (CH_2), 120.30, 123.1, 123.9, 127.1, 127.8, 128.5, 128.7, 128.7, 129.4, 130.4, 134.9, 136.1, 140.6, 144.3, 157.3, 161.14. HRMS: Calcd for $C_{21}H_{14}Br_2N_2O$, 467.9472; found: $[M+H]^+$ $C_{21}H_{14}Br_2N_2O$, 468.9551.

3-Benzyl-6-bromo-2-phenyl-2,3-dihydro-4(1*H*)-quinazolinone (7c)

This compound was obtained from *GP-4* at rt. Yield 55%, white solid; mp 112–115 ºC. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 3.65 (d, J = 15.3 Hz, 1H, CH_2), 4.76 (br, 1H, NH), 5.53 (d, J = 15.3 Hz, 1H, CH_2), 5.59 (s, 1H, C2-H), 6.40 (d, J_{ortho} = 8.5, 1H, C8-H), 7.19-7.32 (m, 11H, C7-H, Ph), 8.11 (d, J_{meta} = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 47.1, 71.1, 111.1, 116.2, 117.2, 126.6, 127.6 128.1, 128.7, 129.1, 129.5, 131.3, 136.3, 136.5, 139.1, 144.2, 162.1. HRMS: Calcd for $C_{21}H_{17}BrN_2O$, 392.0524; found: $[M+H]^+$ $C_{21}H_{18}BrN_2O$, 393.0482. X-Ray crystallographic structure in Figure 4.[14]

3-Benzyl-6-bromo-2-phenyl-4(3*H*)-quinazolinone (7d)

This compound was obtained from *GP-3* and *4* at rt. Yield 37% (*GP-4*), white solid; mp 115–117 ºC. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 5.26 (s, 2H, CH_2), 6.89-6.91 (m, 2H, CH), 7.20-7.21 (m, 3H, CH), 7.32-7.34 (m, 2H, CH), 7.39-7.42 (m, 2H, CH), 7.47 (tt, J_{ortho} = 7.6 Hz, J_{meta} = 1.3 Hz, 1H, CH), 7.63 (d, J_{ortho} = 8.7 Hz, 1H, C8-H), 7.85 (dd, J_{ortho} = 8.7 Hz, J_{meta} = 2.3 Hz, 1H, C7-H), 8.49 (d, J_{meta} = 2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 47.1, 71.1, 111.1, 116.2, 117.2, 126.6, 127.6, 128.1, 128.7, 129.1, 129.5, 131.3, 136.3, 136.5, 139.1, 144.2, 162.1. HRMS: Calcd for $C_{21}H_{15}BrN_2O$, 390.0368; found: $[M+H]^+$ $C_{21}H_{16}BrN_2O$, 391.0444.

3-Benzyl-6,8-dichloro-2-phenyl-2,3-dihydro-4(1*H*)-quinazolinone (7e)

This compound was obtained from *GP-3* with UV light and at 50 °C. Yield 60% (UV light), white solid; mp 157–160 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 3.67 (d, J = 15.4 Hz, 1H, CH_2), 5.04 (br, 1H, NH), 5.57 (d, J = 15.4 Hz, 1H, CH_2), 5.70 (d, 1H, C2-H), 7.17-7.36 (m, 11H, C7-H, Ph), 7.93 (d, J_{meta} = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 47.4, 70.7, 117.3, 119.1, 123.5, 126.5, 127.4, 127.8, 128.1, 128.8, 129.3, 129.8, 132.8, 136.1, 138.8, 140.4, 161.3. HRMS: Calcd for $C_{21}H_{16}Cl_2N_2O$, 382.0640; found: $[M+H]^+$ $C_{21}H_{17}Cl_2N_2O$, 383.0733.

3-Benzyl-6,8-dichloro-2-phenyl-4(3*H*)-quinazolinone (7f)

This compound was obtained from *GP-3* with UV light and at 50 °C. Yield 32% (at 50 °C), white solid; mp 145–147 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 5.26 (s, 2H, CH_2), 6.86-6.91 (m, 2H, CH), 7.17-7.20 (m, 3H, CH), 7.39-7.47 (m, 5H, CH), 7.78 (d, J = 2.2 Hz, 1H, C7-H), 8.20 (d, J = 2.6 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 49.4, 122.9, 125.4, 127.0, 127.7, 128.4, 128.6, 130.3, 132.4, 133.2, 134.8, 136.0, 142.8, 157.1, 161.1. Anal. Calcd for $C_{21}H_{14}Cl_2N_2O$: C, 66.16; H, 3.70; N, 7.35. Found: C, 66.20; H, 3.66; N, 7.35.

3-Benzyl-6,8-dibromo-2,2-dimethyl-2,3-dihydro-4(1*H*)-quinazolinone (8a)

This compound was obtained from *GP-3* and *4* at rt and 6 equiv of Br_2 and Et_3N. Yield 86% (method 5 at rt) white solid; mp 177–177.8 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 1.50 (s, 6H, CH_3), 4.62 (br s, 1H, NH), 4.78 (s, 2H, CH_2), 7.21-7.30 (m, 5H, Ph), 7.65 (d, J_{meta} = 2.2 Hz, 1H, C7-H), 8.07 (d, J_{meta} = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 27.9, 45.6, 72.3, 109.1, 110.4, 117.8, 127.2, 128.7, 131.1, 138.1, 138.7, 141.6, 153.5, 161.9. HRMS: Calcd for $C_{17}H_{16}Br_2N_2O$, 423.9609; found: $[M+H]^+$ $C_{17}H_{17}Br_2N_2O$, 424.9716.

3-Benzyl-6-bromo-2,2-dimethyl-2,3-dihydro-4(1*H*)-quinazolinone (8c)

This compound was obtained from *GP-4* at rt and 4 Eq of Br_2 and Et_3N. Yield 55% white solid; mp 167–169 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 1.45 (s, 6H, CH_3), 4.26 (br s, 1H, NH), 4.78 (s, 2H, CH_2), 6.51 (d, J_{ortho} = 8.4 Hz, 1H, C8-H), 7.19 - 7.30 (m, 5H, Ph), 7.36 (dd, J_{meta} = 2.2 Hz, J_{ortho} = 8.7 Hz, 1H, C7-H), 8.08 (d, J_{meta} = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 27.7, 45.4, 72.2, 111.2, 116.5, 117.5, 127.1, 127.2, 128.7, 131.6, 136.2, 139.1, 143.9, 162.8. HRMS: Calcd for $C_{17}H_{17}BrN_2O$, 344.0524; found: $[M+H]^+$ $C_{17}H_{18}BrN_2O$, 345.0600.

3-Benzyl-6,8-dibromo-2,3-dihydro-4(1*H*)-quinazolinone (10a)

The compound **4b** (0.68 mmol) was dissolved in anhydrous THF (16 mL), the solution was cooled at 0 ºC and then 2 equiv of sodium borohydride was slowly added, finally was added 4 mL of MeOH. The reaction mixture was stirred at rt under nitrogen atmosphere for 2 h. The solvent was concentrated, and the residue was suspended in water, which was extracted with EtOAc. The extracts were dried with anhydrous sodium sulfate and concentrated, and the residue was recrystallized with CH_2Cl_2 and hexane. Yield 97%, white solid; mp 148–150 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 4.58 (d, 2H, C2-H_2), 4.71 (s, 2H, CH_2), 4.79 (br s, 1H, NH), 7.23-7.35 (m, 5H, Ph), 7.63 (d, J_{meta} = 2.2 Hz, 1H, C7-H), 8.07 (d, J_{meta} = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 48.7, 58.5, 109.2, 111.0, 119.1, 128.1, 128.9, 131.8, 131.3, 136.0, 137.9, 144.1, 161.6. HRMS: Calcd for $C_{15}H_{12}Br_2N_2O$, 393.9316; found: $[M+H]^+$ $C_{15}H_{13}Br_2N_2O$, 394.9379.

3-Benzyl-6-bromo-2,3-dihydro-4(1*H*)-quinazolinone (10c)

This compound was obtained from *GP-4* at 0 °C. Yield 38%, white solid; mp 119–121 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.4 (br s, 1H, NH), 4.51 (s, 2H, C2-H_2), 4.71 (s, 2H, CH_2), 6.56 (d, J_{ortho}= 8.6 Hz, 1H, C8-H), 7.28-7.33 (m, 5H, Ph), 7.35 (dd, J_{ortho} = 8.6 Hz, J_{meta} = 2.2 Hz, 1H, C7-H), 8.09 (d, J_{meta} = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 48.5, 58.7, 111.9, 116.8, 118.9, 127.8, 128.0, 128.9, 131.6, 135.9, 136.4, 146.4, 162.6. HRMS: Calcd for $C_{15}H_{13}BrN_2O$, 316.0211; found: $[M+H]^+$ $C_{15}H_{14}BrN_2O$, 317.0256.

3-Benzyl-6-bromo-4(3*H*)-quinazolinone (10d)

This compound was obtained from *GP-4* at rt. Yield 79%, white solid; mp 124–126 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.33–7.38 (br s, 5H, Ph), 7.55 (d, J_{ortho} = 8.8 Hz, 1H, C8-H), 7.79 (dd, J_{ortho} = 8.8 Hz, J_{meta} = 2.2 Hz, 1H, C7-H), 8.10 (s, 1H, C2-H), 8.42 (d, J_{meta} = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 49.9, 121.1, 123.6, 128.1, 128.5, 129.2, 129.4, 129.5, 135.5, 135.5, 146.7, 146.9, 159.9. HRMS: Calcd for $C_{15}H_{11}BrN_2O$, 314.0055; found: $[M+H]^+$ $C_{15}H_{12}BrN_2O$, 315.0117.

3-Benzyl-6,8-dichloro-2,3-dihydro-4(*1H*)-quinazolinone (10e)

This compound was obtained from *GP-3* with UV light and at 50 °C. Yield 62% (at 50 °C), white solid; mp 122–124 ºC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 4.57 (d, 2H, C2-H_2), 4.69 (s, 2H, CH_2), 4.88 (br s, 1H, NH), 7.26-7.43 (m, 5H, Ph), 7.86 (d, J_{meta} = 2.2 Hz, 1H, C7-H), 8.18 (d, J_{meta} = 2.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 48.6, 58.4, 118.6, 119.4, 123.8, 127.4, 127.9, 127.9, 128.8, 132.4, 135.9, 142.6, 161.7. HRMS: Calcd for $C_{15}H_{12}Cl_2N_2O$, 306.0327; found: $[M+H]^+$ $C_{15}H_{13}Cl_2N_2O$, 307.0362.

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14. Crystallographic data are deposited at Cambridge Crystallographic Data Center (CCDC 871448, 871449, 871450, 871451, 871452, 871453, 871454, 871455).