

Q-Tube © assisted MCRs for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones

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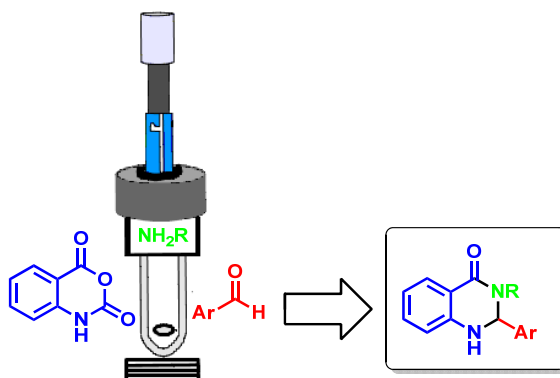
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Abstract

A Q-tube assisted, efficient method for the preparation of 2-phenylquinazolin-4-ones is here presented. The target structures were prepared through the one-pot, multicomponent reaction between isatoic anhydride, an aromatic aldehyde and a primary amine following a catalyst-free approach. The use of the commercially available Q-tube© apparatus allowed to perform reactions at external temperature higher to the solvent boiling point generating medium pressure conditions, shortening the reaction times and affording good yields in all the example herein reported.



Keywords: 2,3-Dihydroquinazolin-4(1H)-ones, 2-phenylquinazolin-4-ones, Q-tube, isatoic anhydride, chemoselectivity

Introduction

Quinazolinone scaffolds, either in the reduced (compound I, 2,3-dihydroquinazolin-4(1*H*)-one) or in the oxidized (compound II, quinazolin-4(3*H*)-one) form, are widely distributed in biologically relevant molecules (Figure 1).

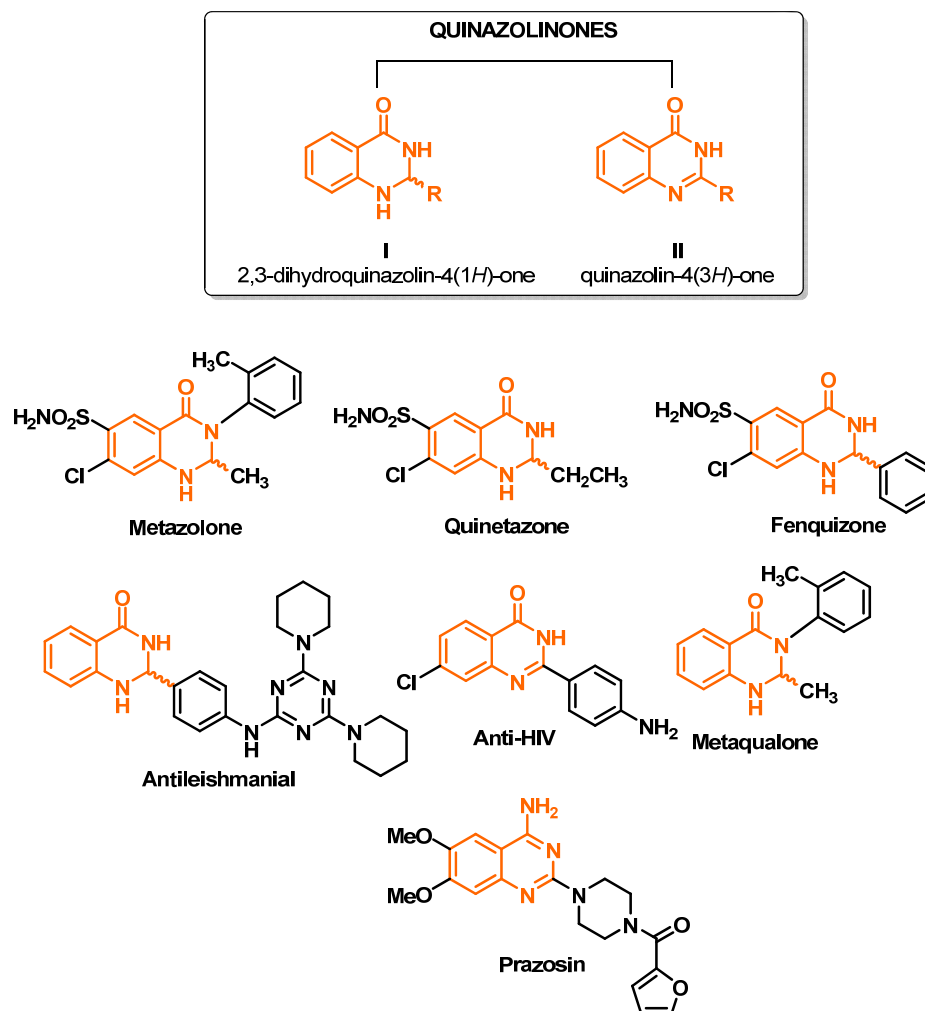
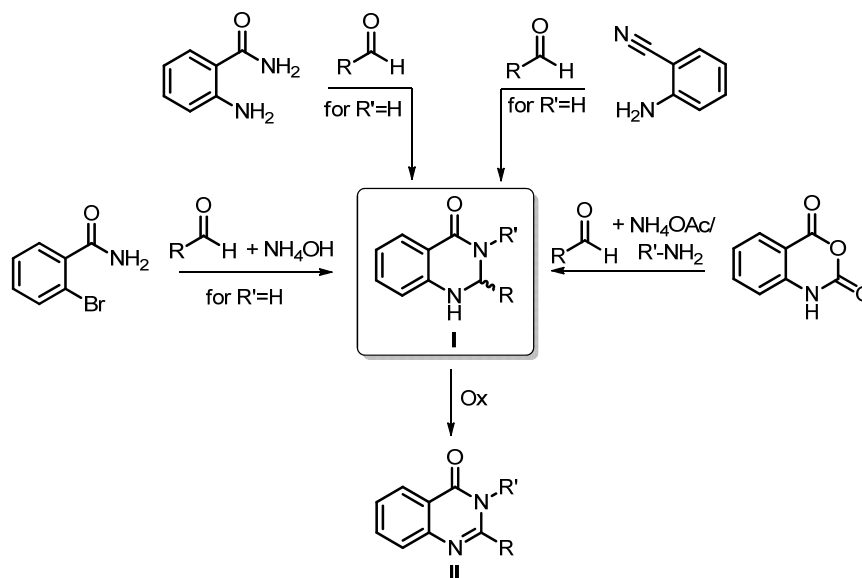


Figure 1. Drugs and pharmacologically relevant molecules characterized by the quinazoline scaffold.

The quinazolinone scaffold characterizes the marketed diuretic drugs Metazolone, Quinetazone and Fenquizone that are currently used to treat hypertension and related diseases or congestive heart failure.¹ In the antimicrobial research field, some anti leishmanial² and antiviral derivatives³ have been developed very recently, the latter through a fragment based drug discovery approach.⁴ Methaqualone, marketed using the brand name of Quaalude is a sedative and hypnotic medication widely used in US also, regrettably, as substance of abuse.⁵ The synthesis of the first in class, anti-hypertensive drug Prazosin and its congeners entails, as key step, the preparation of the quinazoline scaffold which is then converted into the 4-amino quinazoline core by a three-step procedure.⁶

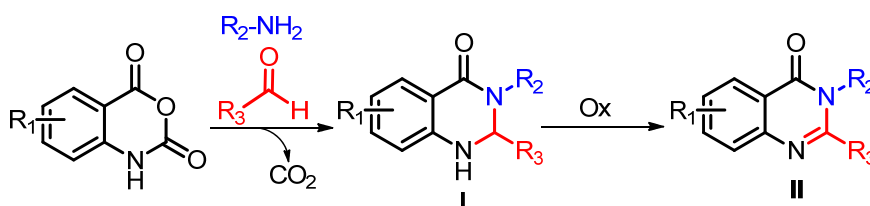
As a result of the pharmacological importance, a plethora of synthetic methodologies for the preparation of these privileged scaffolds have been reported and are summarized in Scheme 1.⁷⁻⁹



Scheme 1. General procedure for the preparation of Quinazolinones.

All the reported procedures first entailed the preparation of the reduced quinazolinone **I** which is then converted into the corresponding oxidized form **II**. In many cases it is impossible to prevent the oxidation reaction thus the compounds having the C2 with a sp^3 hybridization represent *per se* a synthetic target. The literature survey revealed that the synthetic methodologies could be clustered into 4 groups. In the first one 2-aminobenzamide is cyclo-condensed with aromatic and aliphatic aldehydes,¹⁰ or rarely with substituted benzyl alcohols¹¹ or gem-dibromomethylarenes.¹² Recently, also 2-aminobenzonitrile was used as a starting point in a green procedure for the preparation of quinazolinones. The reactions took place in presence of aromatic aldehydes in water with K_3PO_4 as inorganic base leading to the preparation of various products.¹³

Among the MCRs, in 2014 Guo and co-workers reported the synthesis of the target compounds **I** starting from 2-bromobenzamide, which reacted with aldehydes and aqueous ammonia in DMSO for 24 h. In principle, this approach is suited for the modification of the N-3 position by replacing ammonium hydroxide with a different primary amine, nevertheless the authors reported just the use of the inorganic amine to selectively obtain compounds **II**.¹⁴ Isatoic anhydride is the elective starting material for a multicomponent approach because it gives the possibility to introduce 3 points of diversity in the desired final structures (R_1 , R_2 and R_3 in Scheme 2).



Scheme 2. Synthesis of quinazolinone starting from isatoic anhydride.

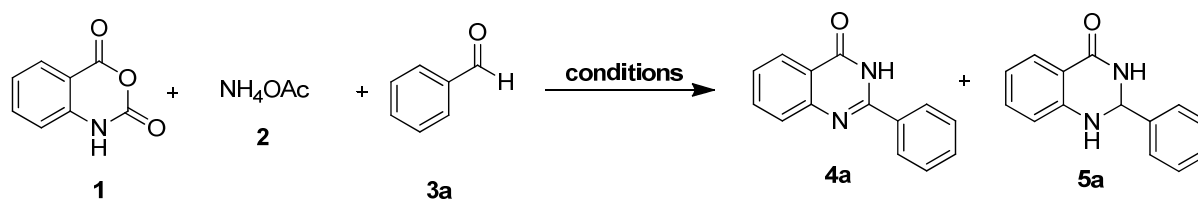
The commonly used methodology entails the treatment of isatoic anhydride with an aldehyde, a primary amine or an ammonium salt under basic conditions. In one case the Lewis acid gallium triflate was used to catalyse the reaction.¹⁵ As previously stated, the selective synthesis of type **I** compounds is not easy and often the reaction mixtures contain, beside the desired products also appreciable amounts of the oxidized derivatives **II**. For this reason, in most of the reported procedures a mild oxidant, such as iodine or DMSO, is used to force the reaction directly to the oxidated product **II** without even attempting to isolate the reduced intermediate **I**.

Here we report the Q-Tube mediated, *one pot*, multicomponent procedure for the selective preparation of compounds **I**, under mild conditions. The protocol is straightforward and affords the quantitative conversion of the starting material into the target products. The use of the Q-Tube technology permits to exceed the solvent boiling point thus shortening the reaction times.¹⁶

Result and Discussion

We started the investigations exploring the best combination solvent/temperature for the reaction between isatoic anhydride **1**, benzaldehyde **3a** and ammonium acetate **2** in a ratio 1:1:1.5 in the presence of a catalytic amount of the Lewis acid niobium oxide, as prosecution of our interest in exploring the reactivity of this scarcely studied catalyst.

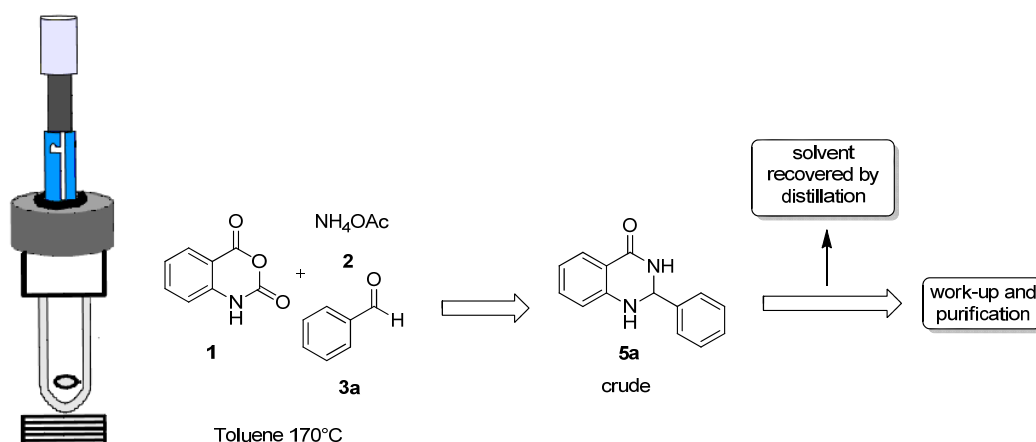
Table 1



Entry	Solvent	T (°C)	1:2:3a	Cat (mol %)	Conv. (Yield) % ^a	4a : 5a	Time (h)
1	EtOH	reflux	1:1.5:1	Nb ₂ O ₅ (10%)	--		2.5
2	DMSO	25))))	1:1.5:1	Nb ₂ O ₅ (10%)	--		2.5
3	DMSO	50	1:1.5:1	Nb ₂ O ₅ (10%)	traces		2.5
4	DMSO	50))))	1:1.5:1	Nb ₂ O ₅ (10%)	100 (79)	1 : 99	2.5
5	DMSO	100	1:1.5:1	Nb ₂ O ₅ (10%)	100 (89)	1 : 99	2.5
6	DMSO	170	1:1.5:1	Nb ₂ O ₅ (10%)	100 (91)	23 : 77	1.5
7	DMSO	170	1:1.5:1	--	100 (86)	30 : 70	1.5
8	DMF	170 (Q-tube) ^c	1:1.5:1	Nb ₂ O ₅ (10%)	--		1.5
9	H ₂ O	170 (Q-tube) ^c	1:1.5:1	--	--		1.5
10	H ₂ O	170 (Q-tube) ^c	1:1.5:1	Nb ₂ O ₅ (10%)	--		1.5
11	toluene	170 (Q-tube) ^c	1:1.5:1	--	100 (90)	8 : 92	1.5
12 ^b	toluene	reflux	1:1.2:1	PFPAT (10%) ^d	90		3

^aConversions were determined by ¹H-NMR based on the consumption of the aldehyde. Yields are referred to the amount of **4b+5b** recovered as pure mixture after workup without further purification ^b see reference 15. ^c Temperature of the oil bath. ^d PFPAT= Pentafluorophenylammonium Triflate.

The reaction in refluxing EtOH (entry 1) as well as in DMSO at room temperature under sonication (entry 2) did not produce the desired product. Nevertheless, the reactivity in DMSO resulted nicely controlled by temperature since at 50°C, 100°C, and 170°C the formation of **4a/5a** was obtained in traces, 89% and 91%, respectively (entries 3, 5 and 6) allowing, in the latter case, to reduce the reaction time at 1.5 h. The chemoselectivity resulted to be dependent on the temperature, as well. The almost complete formation of **5a** was observed at 100°C whereas at 170° the oxidized form **4a** was detected in a **4a/5a** ratio of 23:77. We also investigated the possibility to use ultrasounds for the activation of the reaction at lower temperature without appreciable improvements (entry 4). We proved that at 170°C the catalysis of niobium oxide is minimal, discouraging its use for a better atom economy of the entire process (see entry 6 vs entry 7). Several different solvents were also tested and, at the same time, a Q-Tube® device was used to perform reactions at external temperatures higher than those of the solvents boiling point and under medium pressure conditions. DMF and water did not afford desired product whereas using toluene in Q-Tube® in an oil bath at 170°C 2-phenylquinazolin-4-one **5a** was obtained in 90% yield (entry 11). In toluene, Q-tube® allowed to avoid the use of catalysts, reducing reaction time, yielding the target compound in 1.5 hours rather than 3 hours, as reported in literature for refluxing conditions (entry 11 and 12).¹⁷ In addition the solvent can be recovered by distillation in its pure form (confirmed by ¹H-NMR analysis) and reused for subsequent reactions, reducing waste production and the issues connected with the toxicity and environmental risks.



Scheme 3. General reaction setup.

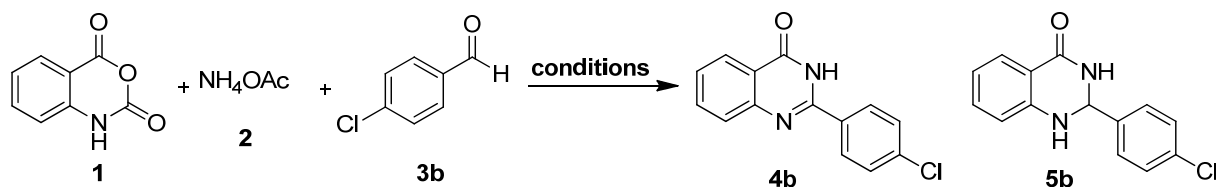
A similar comparison of the different reaction conditions has been performed starting from *p*-chlorobenzaldehyde **3b** and the results are summarized in Table 2.

In this case, the catalytic effect of Nb₂O₅ is slightly evident in DMSO at 170 °C (entry 1 vs entry 2). The use of the Q-tube © continues to be superior affording in 1.5 hours **5b** in 98 % yield without catalyst (Table 2, entry 4) affording better results in comparison with the refluxing conditions in the presence of pentafluorophenylammonium triflate as catalyst.

Having elected as the best conditions those depicted in Table 1 entry 12, we explored the scope of the reaction. As reported in Table 3 entries 1-6, aldehydes bearing both electron donating and withdrawing groups were tested indicating that the nature of substituent did not influence the yield that, in all the cases, are very good. On the contrary, the chemoselectivity appear to be influenced by the electronic properties of substituents: the electron-withdrawing effect of halogens facilitates the exclusive formation of compound **5b**,

5e while the methoxy group favours the oxidation reaction leading to a mixture of **4c:5c** in both toluene and DMSO (Table 3, entry 5 and 6).

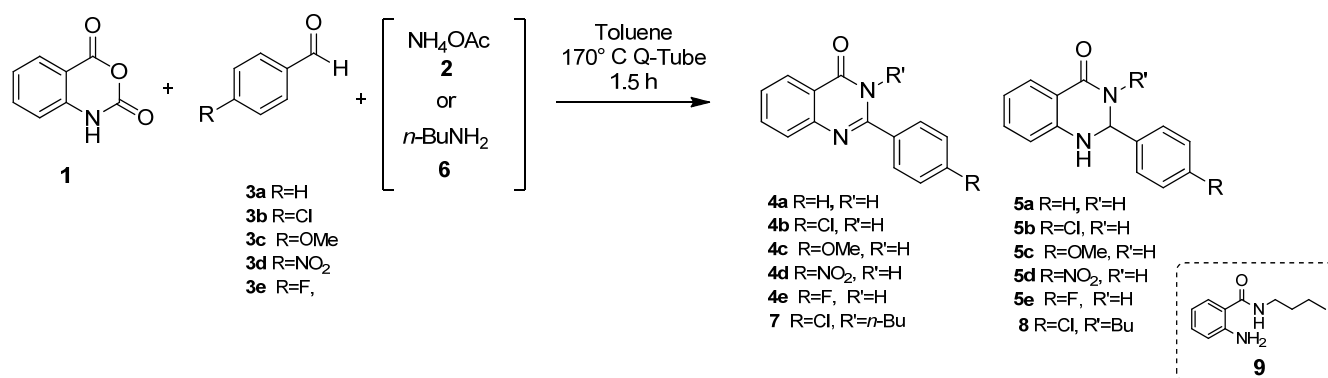
Table 2



Entry	Solvent	T(°C)	1:2:3b	Cat (mol %)	Yield (%) ^a	4b:5b	Time (h)
1	DMSO	170	1:1.5:1	Nb ₂ O ₅ (10%)	91	25 : 75	1.5
2	DMSO	170	1:1.5:1	--	78	23 : 77	1.5
3	THF	170 (Q-tube) ^e	1:1.5:1	--	73	1 : 99	1.5
4	Toluene	170 (Q-Tube) ^e	1:1.5:1	--	98	1 : 99	1.5
5 ^b	Toluene	reflux	1:1.2:1	PFPAT (10%) ^c	95	n.r. ^d	3

^aConversions, determined by ¹H-NMR based on the consumption of the aldehyde, were in all the cases quantitative. Yields are referred to the amount of **4b+5b** recovered as pure mixture after workup without further purification. ^bReference 15 ^cPFPAT: Pentafluorophenylammonium Triflate. ^dNot reported. ^eTemperature of the oil bath.

Table 3



Entry	R	R'	yield (%) ^a	4 : 5
1	H	H	90	8 : 92
2	Cl	H	98	1 : 99
3	F	H	96	1 : 99
4	NO ₂	H	96 ^b	1 : 99 ^b
5	OMe	H	82	30 : 70
6 ^c	OMe	H	88	20 : 80
7	Cl	nBu	52 ^e	0 : 100 ^d

^aConversions, determined by ¹H-NMR based on the consumption of the aldehyde, were in all the cases quantitative. Yields are referred to the amount of **4b+5b** recovered as pure mixture after workup without further purification excepted where otherwise indicated ^b Some other impurities (<10%) are present and cannot be removed due to the instability of **5d**. ^c Reaction was performed in DMSO at 170°C and 10 mol% Nb₂O₅ was used. ^d 40 % of the amide **9** was recovered. ^e Isolated yield by chromatography

In the case of the nitro aldehyde **3d** the corresponding **5d** was obtained almost quantitatively as proved by the ¹H-NMR analysis of the crude, but it was impossible to isolate in pure form due to its instability. In one example, ammonium acetate was replaced with *n*-butylamine **6**, giving the target compound **8** in moderate yield but in mixture with the butyl-substituted anthranilamide **9**. The isolation of this intermediate gives some information about a plausible reaction mechanism and can be supposed that, in this case, after isatoic anhydride decomposition and the formation of **9**, the butyl substituent exerts a steric hindrance that disfavours the successive condensation reaction with the aldehyde.

Conclusions

In conclusion we described the possibility to use the Q-tube © apparatus to promote the chemoselective synthesis of 2,3-dihydroquinazolin-4(1H)-ones skeletons starting from isatoic anhydride without any catalyst or additive. The organic solvent used for the synthesis can be recovered and reused reducing the environmental issues correlated to the use of toluene.

Experimental Section

General. Reactions were conducted in Q-tube® and were stirred with Teflon-coated magnetic stirring bar. Solvents and reagents were used as received unless otherwise noted. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 pre-coated aluminium foil sheets and visualized by UV irradiation or by use of a KMnO₄ stain. Silica gel Kieselgel 60 (70–230 mesh) was used for column chromatography. NMR experiments were obtained at 25 °C on a Bruker DPX 200 spectrometer operating at 200 MHz for ¹H and 50.31 MHz for ¹³C experiments or in a Bruker DRX spectrometer operating at 400 MHz for ¹H and 50.31 MHz for ¹³C experiments. ¹H and ¹³C chemical shifts (δ) are reported in parts per million (ppm) and they are relative to TMS 0.0 ppm and the residual solvent peak of DMSO-d₆ at δ 2.54 and δ 40.45 in ¹H and ¹³C NMR, respectively. Data are reported as follows: chemical shift (multiplicity, number of hydrogens, coupling constants where applicable, and assignment where possible). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), tt (triplet of triplet), m (multiplet), bs (broad signal). Coupling constant (J) quoted in Hertz (Hz) to the nearest 0.1 Hz. All the starting material are commercially available.

General procedure for synthesis of 2H-quinazolin-4-one 5a-e and 8. Q-tube is charged with isatoic anhydride **1** (150 mg, 0.919 mmol), ammonium acetate **2** (106 mg, 1.378 mmol) to obtain compounds **5a-e**, or *n*-butylamine **6** (137 μL, 1.378 mmol) to obtain compound **8**, aldehyde **3a, 3b, 3c, 3d, 3e** (0.919 mmol) with 0.8 mL of toluene. The reaction mixture is then vigorously stirred at 170 °C for 1.5 hour. After cooling at room

temperature, the solvent was recovered by distillation and the crude residue was diluted with water (15 ml) and extracted three times with EtOAc (3 X 15 ml). The organic layers were dried using Na₂SO₄ and then evaporated under reduced pressure. Crude products starting from **3c** were purified by chromatographic column affording **5c** and **8**, in all the other cases the target compounds were obtained after workup as a pure mixture of **4** and **5** in the ratios reported in the Tables. Spectral data for all the compounds agree with those reported in literature and for the major products, ¹H NMR and selected examples of ¹³C and ¹⁹F NMR spectra, extrapolated from the mixture, are reported below.

2-Phenyl-2,3-Dihydroquinazolin-4(1H)one (5a). ¹H-NMR (DMSO-d₆, 400 MHz): δ 8.31 (s, 1 H), 7.63 (d, 1 H, J 7.2 Hz), 7.50 (d, 2 H, J 6.9 Hz), 7.38-7.42 (m, 3 H), 7.24-7.26 (m, 1 H), 7.13 (s, 1 H), 6.75 (d, 1 H, J 8.0 Hz), 6.68 (t, 1 H, J 7.3 Hz), 5.76 (s, 1 H) ppm. Physical data agree with those reported in literature.¹³

2-(4-chlorophenyl)-dihydroquinazolin-4(1H)one (5b). ¹H-NMR (DMSO-d₆, 200 MHz): δ 8.39 (s, 1 H), 7.63 (dd, 2 H, J 1.6, 7.7 Hz), 7.54 (m, 3 H), 7.29 (t, 1H), 7.19 (s, 1 H), 6.68-6.79 (m, 2 H), 5.80 (s, 1 H) ppm. Physical data agree with those reported in literature.¹³

2-(4-Methoxyphenyl)-dihydroquinazolin-4(1H)one (5c). 30% yield after chromatographic purification using as eluent Ethyl acetate/petroleum ether (8:2). ¹H-NMR (DMSO-d₆, 400 MHz): δ 8.15 (s, 1 H), 7.59 (d, 1 H, J 7.7 Hz), 7.40 (d, 2 H, J 8.6 Hz), 7.21 (t, 1 H, J 13.9 Hz), 7.00 (s, 1 H), 6.93 (d, 2 H, J 8.6 Hz), 6.72 (d, 1 H, J 8.0 Hz), 6.66 (t, 1 H, J 14.8), 5.69 (s, 1H) ppm. Physical data agree with those reported in literature.¹³

2-(4-Nitrophenyl)-dihydroquinazolin-4(1H)one (5d). ¹H-NMR (DMSO-d₆, 400 MHz): δ 8.62 (s, 1H) ; 8.30-8.25 (m, 2H) ; 7.80-7.75 (m,2H) ; 7.65 (dd, 1H, J 1.5 and 9.9 Hz) ; 7.30 (s, 1H) ; 7.25 dt, 1H, J 1.7 and 8.2Hz) ; 6.61-6.39 (m, 2H ; 6.05 (t, 1H, J 2.2Hz) Physical data agree with those reported in literature.¹⁵

2-(4-Fluorophenyl)-dihydroquinazolin-4(1H)one (5e). ¹H-NMR (DMSO-d₆, 400 MHz): δ 8.29 (s, 1 H), 7.58 (d, 1 H, J 7.3 Hz), 7.50-7.54 (m, 2 H, J 8.4 Hz), 7.21-7.25 (m, 3 H), 7.09 (s, 1 H), 6.72 (d, 1 H, J 7.8 Hz), 6.67 (t, 1 H, J 14.9 Hz), 5.75 (s, 1 H) ppm.¹³C-NMR (DMSO-d₆ 50.31 MHz) : 65.93, 114.68 (d, J 22.64 Hz), 114.91, 115.34, 117.28, 127.38, 129.07 (d, J 8.55 Hz), 133.39, 137.83, 147.86, 162.17 (d, J 244.00 Hz), 163.58 ¹⁹F-NMR (DMSO-d₆, 376 MHz): 114.29 ppm. Physical data agree with those reported in literature.¹⁸

3-Butyl-2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1H)one(8). Purified eluting with petroleum ether/ethyl acetate (7:3). ¹H-NMR (DMSO-d₆, 400 MHz): δ 7.64 (d, 1 H, J 7.8 Hz), 7.33-7.43 (m, 5 H), 7.19-7.22 (m, 1 H), 6.62-6.68 (m, 2 H), 5.87 (s, 1 H), 3.87-3.94 (m, 1 H), 2.71-2.77 (m, 1 H), 1.43-1.57 (m, 2 H), 1.24-1.31 (m, 3 H), 0.84-0.98 (m, 3H) ppm. Physical data agree with those reported in literature.¹⁴

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