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Three-component one-pot metal-free synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones using Mukaiyama's reagent

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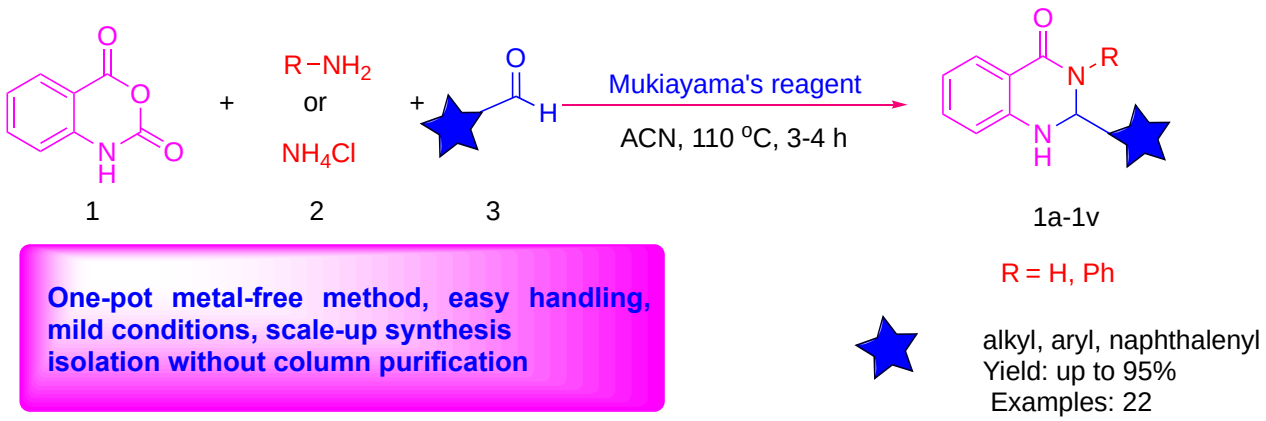
Abstract

A rapid, effective, without transition metal and column chromatography-free protocol for the synthesis of 2,3-dihydroquinazolinones (DHQ) derivatives via one-pot tri-component reaction using amine, aldehyde (aromatic or aliphatic) and isatoic anhydride in the existence of Mukaiyama's reagent (CMPI: 2-chloro-1-methylpyridinium iodide) has been developed with commendable isolated yields. The operation is a high atom economy experimental procedure, with good functional group tolerance, broad substrate scope, and gives high yields in a short period. The trace metal contamination in synthesized pharmaceuticals is a big issue, the metal-free conditions is the highlighted advantage in solving this issue.



Keywords: Mukaiyama's Reagent, dihydroquinazolin-4(1*H*)-ones, isatoic anhydride, aromatic aldehydes, coupling reaction

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Introduction

2,3-Dihydroquinazolin-4(1*H*)-ones occur in a family of pharmaceuticals which are used to treat cancer,[1] inflammation,[2] tumors,[3] bacterial infection,[4] malaria,[5] viral infection,[6,7] fungal infetion,[8] and convulsion.[9] Moreover, 2,3-dihydroquinazolin-4(1*H*)-ones can be oxidized to analogous quinazolin-4(3*H*)-one,[10] which occurs in alkaloids like lutonin and rutaecarpine.[11-12] The quinazolinones are main constituents of many drugs (Figure 1).

Due to the well-known pharmaceutical and physiological activity of DHQ derivatives, several synthetic protocols have been developed for quinazolinone-incorporated organic skeletons during the past decades,[13-16] various of them have demerits like unfavourable conditions,[13] long reaction times,[14] and the use of high-priced and hazardous acid catalysts.[15,16] Therefore, it seemed there is a need to develop simple, efficient, and easy methods to perform synthesis of quinazolinone derivatives under environmentally kind conditions. Eliminating a volatile organic component in organic synthesis is one of the many strategies to accomplish greenness in the processes.[17,18]

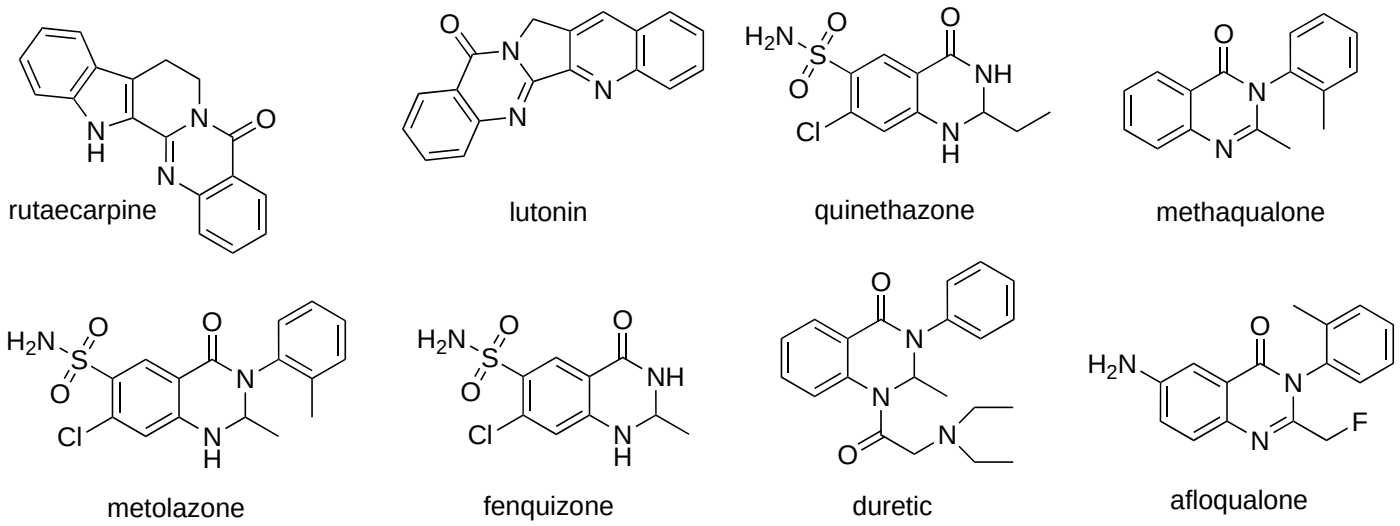


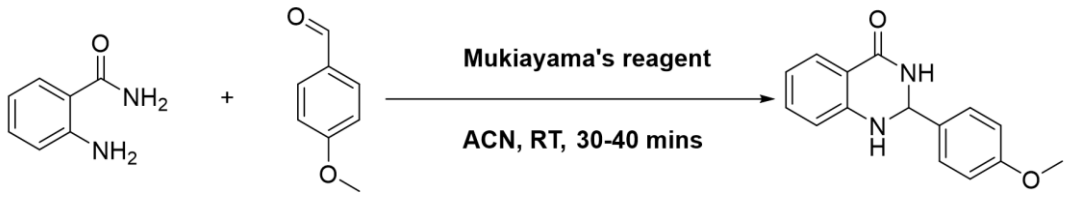
Figure 1. Structures of biologically important quinazolinones.

The cheap and commercially available Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide: CMPI) is used for triggering between carboxylic acids and alcohols.[19] It is extensively utilized in organic chemistry.[20-24] Recently Mukaiyama's reagent has also been employed in C-N bond formation as in formation of 3-alkylquinazolin-4-ones.[25]

Multi-component reactions (MCRs) are considered a noteworthy tool in synthetic chemistry and have been used in synthetic transformations where traditional techniques involve several steps. The MCR comes within reach of offering a high yield at a low price in a short time. MCR is eco-friendly and acts as an amenable tool for the creation of carbon-carbon and carbon-heteroatom bonds in pharmaceutically significant chemical entities.

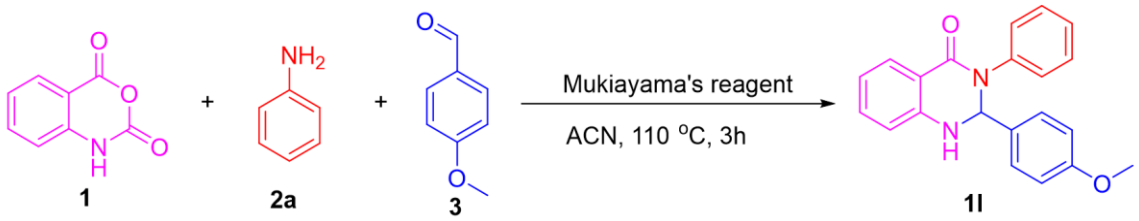
Results and Discussion

In continuation of our research on the use of Mukaiyama's reagent-mediated mild protocols for metal-free one-pot production of 2,3-dihydroquinazolin-4(1*H*)-ones via cyclocondensation of anthranilamide with a variety of aldehydes or ketones (Scheme 1),[26] we developed an innovative tactic for the synthesis of a DHQ derivative.



Scheme 1. Mukaiyama's reagent promoted mild protocol for one pot metal-free synthesis of dihydroquinazolinones.[26]

Herein, we wish to report a novel, transition metal, and column chromatography-free milder one-pot three-component reaction of isatoic anhydride, aniline or ammonium chloride or benzyl amine, and an aldehyde (aliphatic or aromatic) in the presence of Mukaiyama's reagent to produce an important class of heterocycles, 2,3-dihydroquinazolin-4(1*H*)-ones (Scheme 2).



Scheme 2. Effective approach for Mukaiyama's reagent mediated one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-one.

To determine the best conditions, isatoic anhydride, 4-methoxybenzaldehyde, and aniline were used as a model substrate. Optimization was focused on the best-suited solvent and amount of catalyst to afford a good yield of product in a minimum time period.

In the process of optimization, the model reaction was conducted with isatoic anhydride with aniline and 4-methoxybenzaldehyde in the presence of different equivalents (0, 0.25, 0.5, 0.75 and 1.0) of Mukaiyama's reagent (CMPI) in the solvent MeCN at 110 °C. Without the reagent reaction was very slow and low yielding (Table-1: entry 1), 0.25 equivalent of CMPI is an adequate amount for completion of reaction with 55% isolated yield in 24 h, while with 0.5 equivalent the product was obtaianed in 85% in 18 h, though with 0.75 equivalent the product was obtained with 89% yield in 9 h, further increase of CMPI up to 1.0 equivalent resulted in 91% isolated yield of product in 3 h (Table 1).

Table 1. Reaction optimization study

Entry[a]	CMPI (equiv.)	Solvent	Temperature (°C)	Yield[b] (%)	Time (h)
1	0	MeCN	110	10	48
2	0.25	MeCN	110	55	24
3	0.50	MeCN	110	85	18
4	0.75	MeCN	110	89	9
5	1.0	MeCN	110	91	3
6	1.0	tetrahydrofuran	110	24	24
7	1.0	1,4-dioxane	110	47	24
8	1.0	1,2-dimethoxyethane	110	33	24
9	1.0	ethanol	110	53	16
10	1.0	acetic acid	110	28	10
11	1.0	dimethylformamide	110	35	9
12	1.0	water	110	35	24

[a] Molar ratio: isatoic anhydride (5.0 mmol), ammonium salt or aniline or benzyl amine (5.0 mmol), aromatic/aliphatic aldehydes (5.0 mmol), [b]Yields reported after recrystallization.

To find the best solvent, we screened a range of non-polar to polar solvents (Table-1). In THF, 1,4-dioxane and dimethoxyethane isolated yields were moderately low, as the intermediate was not consumed even after 24 h (Table-1: entry 6, 7 and 8); in the case of ethanol, acetic acid, and dimethylformamide product isolated was lower (entry 9, 10 and 11). In water, poor solubility of reactants results in an isolated yield of up to 35% in 24 h (entry 12). In the case of MeCN, all reactants and reagents were soluble even at room temperature, and as the reaction progressed product started to precipitate out as solid, which made isolation easy by filtration. From the results obtained it was certain that MeCN is a better solvent to get a product with a higher yield in a short time period using 1.0 equivalent of Mukaiyama's reagent (CMPI).

Furthermore, we applied an optimized synthetic procedure on a wide range of aldehydes (aliphatic or aromatic) having substituents with different electronic effects and primary amine with isatoic anhydride for preparation of derivatives of 2,3-dihydroquinazolin-4(1*H*)-one and study the scope of the three-component reaction method.

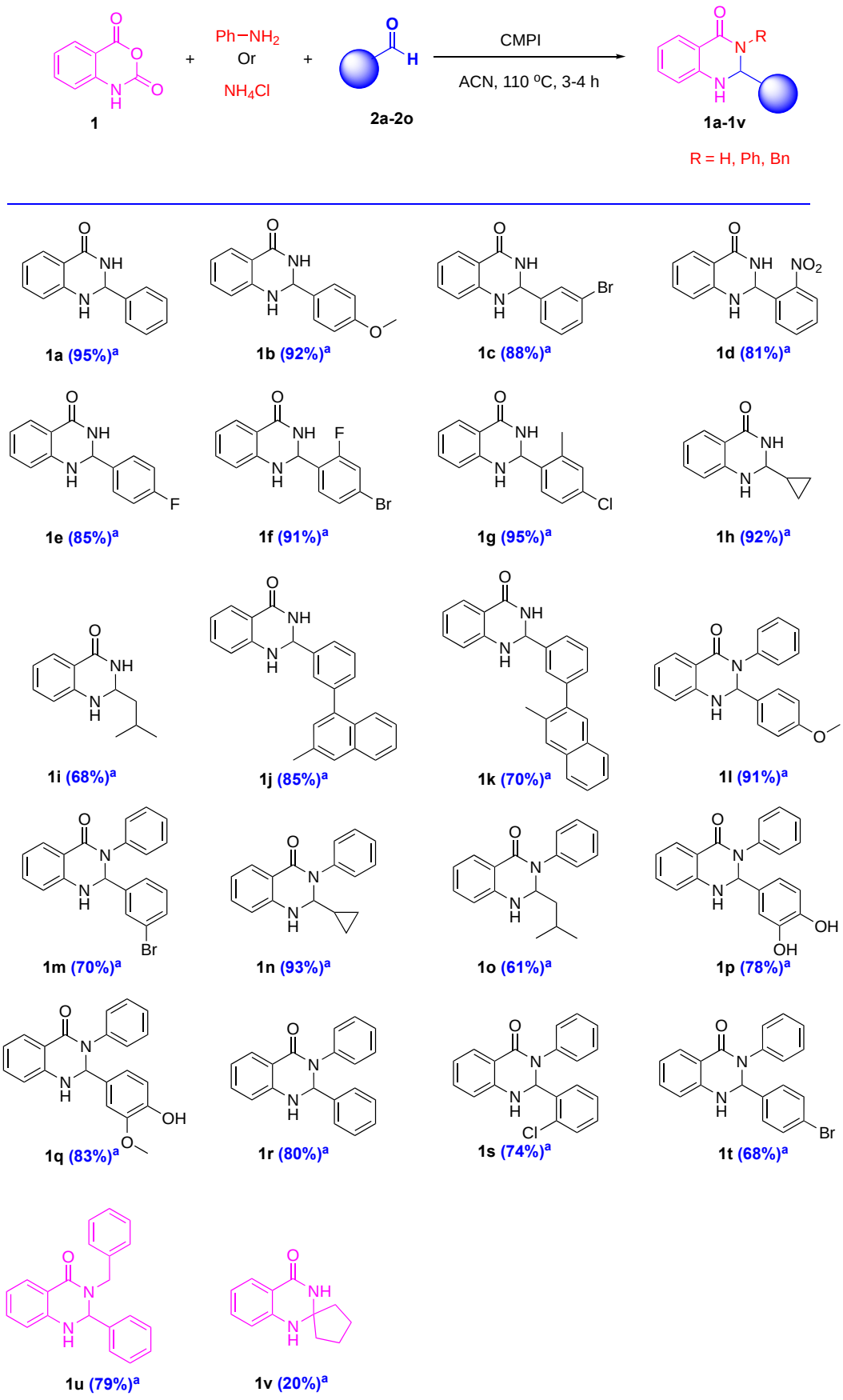
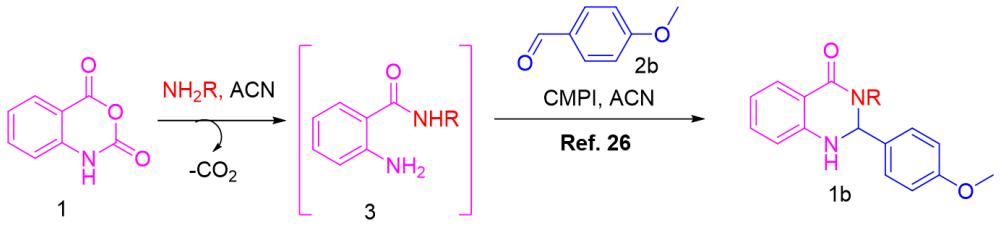


Figure 2. Molar ratio: isatoic anhydride (5.0 mmol), ammonium salt or aniline or benzyl amine (5.0 mmol), aromatic/aliphatic aldehydes (5.0 mmol), ACN. [a]isolated yield.

Employment of ammonium chloride as a source of ammonia produced 2-substituted-2,3-dihydro-4(1*H*)-quinazolinones (**1a**-**1k**). By using optimized synthetic protocol, along with functionally variable aryl aldehyde including those having electron withdrawing fluoro (**1e**, **1f**), chloro (**1g**, **1s**), bromo (**1c**, **1f**, **1m**, **1t**), nitro (**1d**)] and electron-releasing groups methoxy (**1b**, **1l**, **1q**), methyl (**1g**); naphthalene-1-yl-benzaldehyde and naphthalene-2-yl-benzaldehyde were also successfully incorporated into the 2-position of dihydroquinazolinones to obtain (**1j**) and (**1k**) with good to excellent yields. There was no significant impact of electronic effect on reaction rate and yield. Aromatic aldehydes having bulky substituens like nitro at the *ortho* position (**1d**) had a moderately sluggish rate of reaction. Further, in an attempt to introduce a heterocyclic aldehyde in the 2-position of dihydroquinazolinones, use of furfural was employed, but this led to multiple byproduct formation. Aliphatic aldehydes such as cyclopropanecarboxaldehyde and 3-methylbutanal successfully led to the synthesis of corresponding DHQ derivatives (**1h**, **1i**, **1n** and **1o**). However, in the case of 3-methylbutanal, isolated yield of the product was comparatively low (**1i**, **1o**), which might be due to the poor stability of aliphatic aldehyde in the reaction mixture. In order to check the scope of primary amine, use of benzyl amine effectively leads to the desired product (**1u**) formation. In addition, the use of cyclopentanone to synthesize spiro compound (**1v**) was low-yielding. So there is further scope for optimization in reaction conditions to improve better conversion for some other spiro compounds.

Study of the reaction mechanism was the next subject of investigation (Scheme 3). First, isatoic anhydride **1** is converted into 2-amino-N-substituted benzamide **3** by nucleophilic attack by the amine, with the loss of carbon dioxide. CMPI having a pyridinium nucleus (electron deficient) shows good electron affinity towards O-atom of carbonyl compound, which further promotes attack of NH_2 group on the carbonyl carbon to form an imine intermediate (Schiff base) with the generation of halogen acid and N-methylpyridin-2-one. The halogen acid might be helpful in intramolecular cyclisation of Schiff base to afford 2,3-dihydroquinazolin-4(1*H*)-one as we have already reported (Scheme 1).[26] To demonstrate the utility of the developed method, a variety of 2,3-disubstituted quinazolinones (**1a**-**1v**) were synthesized using aliphatic and aromatic aldehydes.



Scheme 3. Plausible reaction mechanism for the formation of dihydroquinazolinone.

To verify the utility and simplicity of this method, we illustrate (Fig. 3) the physical changes in the reaction mass and pure compound after filtration and washing with diethyl ether. A small-scale reaction was set into a vial with solid isatoic anhydride as starting material, then we added the solvent (ACN) and stirred for a minute followed by the addition of CMPI, ammonium salt or aniline or benzyl amine, aromatic/aliphatic aldehydes. The reaction mixture was heated at 110 °C for 3 to 4 h. The reaction mass was cooled to room temperature, and a solid precipitate was collected by filtration (Figure 3, image I). The solid was washed with cold diethyl ether and then dried under a high vacuum to yield a pure compound. (Figure 3, image II).

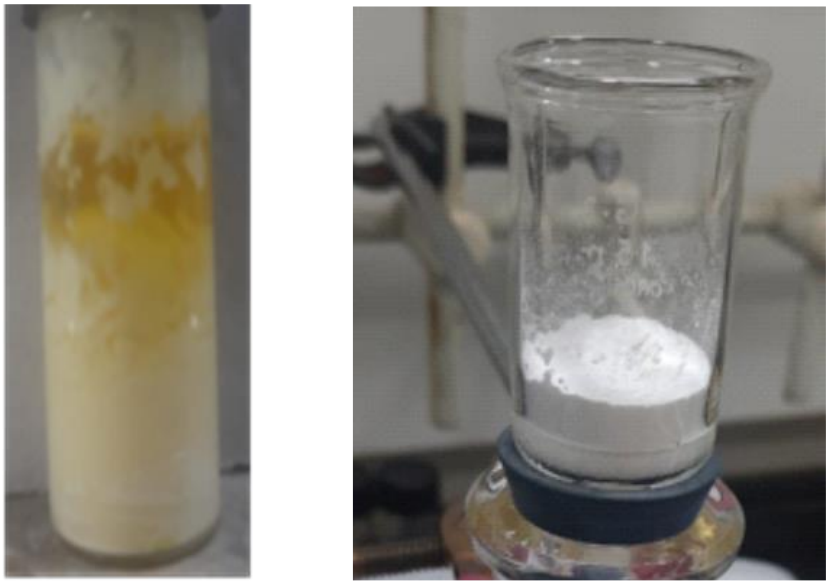


Figure 3. Physical changes in reaction mixture and pure compound after filtration.

Conclusions

In conclusion, Mukaiyama's reagent has been demonstrated to be an efficient reagent for the one-pot three-component reaction of isatoic anhydride, aromatic/aliphatic aldehyde, and ammonium salt or aniline or benzyl amine, in MeCN under mild reaction condition. This reaction methodology allows the synthesis of both mono- and di-substituted 2,3-dihydroquinazolin-4(1*H*)-ones in high yield. This method offers several advantages including a nontoxic, clean, and mild reaction conditions, a wide range of substrates, a simple work-up procedure, and isolation without column chromatography. Moreover, the absence of metal, any co-catalyst, and a nonvolatile byproduct make this an environment friendly method.

Experimental Section

General. All chemicals and reagents were purchased from Sigma Aldrich India and Spectrochem Chemical companies in high purity which was used without further purification. All reactions were run in an oven-dried round bottom flask containing a Teflon-coated stir bar and sealed with a septum. ^{1}H NMR and ^{13}C spectra were recorded on Brukar Avance II 400 MHz FT-NMR spectrometer (400 and ed in units δ (ppm) relative to tetramethylsilane (Me4Si) as an internal standard. Abbreviations used for NMR signals are s =singlet, d = doublet, t = triplet, and m = multiplet. Melting points were determined in open capillaries using an electrothermal Mk3 apparatus. The progress of the reactions was monitored by TLC (thin layer chromatography) on Merck Kieselgel 60F254 aluminum-backed plates, visualized by UV fluorescence (254 nm), and with $KMnO_4$ and ninhydrin stains.

General procedure for the synthesis of substituted 2,3-dihydroquinazolin-4(1*H*)-ones (1a-1t). To a solution of isatoic anhydride (5.0 mmol), ammonium salt or aniline (5.0 mmol), aromatic/aliphatic aldehydes (5.0 mmol) in

MeCN (8 mL) was added Mukaiyama's reagent CMPI (5 mmol) under inert atmosphere. The reaction mixture was heated at 110 °C for 3 to 4 h. The progress of the reaction was monitored by TLC (EtOAc-n-hexane, 1:3). The reaction mixture was cooled to room temperature, and a solid precipitate was collected by filtration. The solid was washed with cold Et_2O (5mL) and then dried under a high vacuum to afford substituted 2,3-dihydroquinazolin-4(1*H*)-ones in 61-95% yield. All the compounds (**1a**-**1t**) were synthesized according to the general method. The compounds were confirmed by ^{1}H-NMR, ^{13}C-NMR, and mass analysis.

2-Phenyl-2,3-dihydroquinazolin-4(1*H*)-one (1a). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), ammonium chloride (1.0 eq), benzaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve 1a, as white solid, mp180-182 °C (218-219 °C)[28] ; yield : 1.06 g (95%); R_f = 0.5 (50% EtOAc/n-hexane); IR (cm^{-1}): 3302, 3167, 1654, 1610, 1509, 1481. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.28 (s, 1H), 7.61-7.59 (d, *J* 7.5 Hz, 1H), 7.49-7.47 (d, *J* 7.0 Hz, 2H), 7.40-7.34 (m, 3H), 7.23 (t, *J* 7.7 Hz, 1H), 7.10 (s,1H), 6.73 (d, *J* 8.0 Hz, 1H), 6.66 (t, *J* 7.4 Hz, 1H), 5.74 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 163.6, 147.8, 141.6, 133.3, 128.5, 128.3, 127.4, 126.8, 117.1, 114.9, 114.4, 66.6. MS (ESI/Q-Da) *m/z*: calculated for [$C_{14}H_{12}N_2O$+H$^+$] 225.0950, found 225.0959.

2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (1b). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), ammonium chloride (1.0 eq), 4-methoxybenzaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve 1b as white crystalline solid, mp177-178 °C (187–189 °C)[27]; yield: 1.16 g (92%); R_f = 0.5 (50% EtOAc/n-hexane); IR (cm^{-1}): 3296, 3175, 1652, 1610, 1506, 1486. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.17 (s, 1H), 7.60 (d, *J* 7.6 Hz, 1H), 7.41 (d, *J* 8.4 Hz, 2H), 7.24 (t, *J* 4.0 Hz, 1H), 7.00 (s, 1H), 6.94 (d, *J* 8.8 Hz, 2H), 6.73 (d, *J* 8.0 Hz, 1H), 6.66 (t, *J* 7.2 Hz, 1H), 5.69 (s, 1H), 3.74 (s, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 163.7, 159.4, 148.0, 133.4, 133.2, 128.2, 127.3, 117.0, 115.0, 114.4, 113.6, 66.3, and 55.1. MS (ESI/Q-Da) *m/z*: calculated for [$C_{15}H_{14}N_2O_2$+H$^+$] 255.1055, found 255.0936.

2-(3-Bromophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (1c). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), ammonium chloride (1.0 eq), 3-bromobenzaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve **1c** as an off white solid. mp185-188 °C (188-189 °C)[28]; yield: 1.32 g (88%); R_f = 0.5 (50% EtOAc/n-hexane); IR (cm^{-1}): 3274, 2920, 2851, 1678, 1645, 1609, 1509. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.38 (s, 1H), 7.66 (s, 1H), 7.59 (d, *J* 7.6 Hz, 1H), 7.53 (d, *J* 8.0 Hz, 1H), 7.48 (d, *J* 7.6 Hz, 1H), 7.35 (t, *J* 8.0 Hz, 1H), 7.25 (t, *J* 7.6 Hz, 1H), 7.21 (s, 1H), 6.75 (d, *J* 8.0 Hz, 1H), 6.68 (t, *J* 7.2 Hz, 1H), 5.76 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 163.8, 147.9, 145.1, 133.9, 131.6, 131.0, 130.1, 127.8, 126.2, 122.0, 117.8, 115.3, 114.9, 65.9. MS (ESI/Q-DA) *m/z*: calculated for [$C_{14}H_{11}BrN_2O$+H$^+$] 303.0055, found 303.0034.

2-(2-Nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (1d). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), ammonium chloride (1.0 eq), 2-nirobenzaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve **1d** as a yellow solid. mp197-198 °C (190-193 °C)[29]; yield: 1.09 g (81%); R_f = 0.55 (50% EtOAc/n-hexane); IR (cm^{-1}): 3408, 3071, 1654, 1605, 1505, 1346. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.21 (s, 1H), 8.06 (dd, *J* 0.8 Hz, 8.0 Hz, 1H), 7.85 (dd, *J* 1.2 Hz, 7.6 Hz, 1H), 7.79 (t, *J* 7.2 Hz, 1H), 7.65-7.60 (m, 2H), 7.25 (t, *J* 8.4 Hz, 1H), 7.00 (s, 1H), 6.77-6.70 (m, 2H), 6.32 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 163.3, 147.6, 147.1, 135.9, 133.9, 133.5, 129.8, 128.9, 127.3, 124.7, 117.6, 114.9, 114.5 and 62.2. MS (ESI/Q-DA) *m/z*: calculated for [$C_{14}H_{11}N_3O_3$+H$^+$] 270.0800, found 270.0779.

2-(4-Fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (1e). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), ammonium chloride (1.0 eq), 4-fluorobenzaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve **1e** as a white solid. m.p.194-195 °C (198-200 °C)[30]; yield: 1.02 g (85%); R_f = 0.5 (50% EtOAc/n-hexane); IR (cm^{-1}): 3298, 3179, 1651, 1602, 1503, 1479. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.29 (s, 1H), 7.61-7.59 (d, *J* 6.8 Hz, 1H), 7.55-7.51 (m, 2H), 7.28-7.20 (m, 3H), 7.10 (s,

1H), 6.75-6.73 (d, *J* 8.0 Hz, 1H), 6.68 (t, *J* 7.6 Hz, 1H), 5.77 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 163.5, 147.7, 137.8, 137.7, 133.3, 129.1, 128.9, 127.3, 117.2, 115.2, 115.0, 114.9, 114.4 and 65.9. MS (ESI/Q-DA) *m/z*: calculated for [$C_{14}H_{11}FN_2O$+H^+] 243.0855, found 243.0839.

2-(4-Bromo-2-fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (1f). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), ammonium chloride (1.0 eq), 4-bromo-2-fluorobenzaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve **1f** as an off white solid. mp197-198 °C; yield: 1.45 g (91%); R_f = 0.5 (50% EtOAc/n-hexane); IR (cm^{-1}): 3275, 3168, 1639, 1606, 1504, 1482. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.27 (s, 1H), 7.64-7.59 (m, 2H), 7.49-7.44 (m, 2H), 7.25 (t, *J* 8.8 Hz, 1H), 7.06 (s, 1H), 6.74-6.68 (m, 2H), 6.01 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 163.5, 148.3, 133.5, 133.0, 127.2, 116.8, 114.8, 114.3, 69.3, 16.2. MS (ESI/Q-DA) *m/z*: calculated for [$C_{14}H_{10}BrFN_2O$+H^+] 321.0039, found 321.0127.

2-(4-Chloro-2-methylphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (1g). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), ammonium chloride (1.0 eq), 4-chloro-2-methylbenzaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve **1g** as a white solid. m.p.166-167 °C; yield: 1.29 g (95%); R_f = 0.5 (50% EtOAc/n-hexane); **IR** (cm^{-1}): 3275, 3170, 1643, 1608, 1499, 1481. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.09 (s, 1H), 7.64 (d, *J* 7.2 Hz, 1H), 7.55 (d, *J* 8.0 Hz, 1H), 7.32 (s, 1H), 7.30-7.23 (m, 2H), 6.87 (s, 1H), 6.74-6.69 (m, 2H), 5.98 (s, 1H), 2.32 (s, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 163.9, 148.4, 138.7, 137.1, 133.3, 132.8, 130.0, 129.3, 127.4, 125.8, 117.4, 114.9, 114.5, 64.0 and 18.4. MS (ESI/Q-DA) *m/z*: calculated for [$C_{15}H_{13}ClN_2O$+H^+] 273.0795, found 273.0827.

2-Cyclopropyl-2,3-dihydroquinazolin-4(1*H*)-one (1h). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), ammonium chloride (1.0 eq), Cyclopropanecarbaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve **1h** as a white solid. m.p.150-152 °C (150-152)[26]; yield: 0.86 g (92%); R_f = 0.6 (50% EtOAc/n-hexane); IR (cm^{-1}): 3277, 3175, 1652, 1608, 1507, 1476. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.03 (s, 1H), 7.58-7.56 (dd, *J* 1.2 Hz, 7.6 Hz, 1H), 7.23-7.19 (m, 1H), 6.74 (d, *J* 8.0 Hz, 1H), 6.72 (s, 1H), 6.64 (t, *J* 7.6 Hz, 1H), 3.93 (d, *J* 8.0 Hz, 1H), 1.17-1.10 (m, 1H), 0.49-0.44 (m, 2H), 0.33-0.32 (m, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 163.6, 148.3, 133.0, 127.3, 116.8, 114.8, 114.3, 69.3, 16.3, 1.97, and 1.88. MS (ESI/Q-DA) *m/z*: calculated for [$C_{11}H_{12}N_2O$+H^+] 189.0950, found 189.0611.

2-Isobutyl-2,3-dihydroquinazolin-4(1*H*)-one (1i). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), ammonium chloride (1.0 eq), 3-methylbutanal (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve **1i** as a white solid. m.p.168-169 °C (171-172 °C)[31]; yield: 0.69 g (68%); R_f = 0.6 (50% EtOAc/n-hexane); IR (cm^{-1}): 3288, 2957, 1644, 1610, 1519, 1469. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.89 (s, 1H), 7.56 (d, *J* 7.6 Hz, 1H), 7.24-7.20 (m, 1H), 6.73 (d, *J* 8.4 Hz, 1H), 6.65 (t, *J* 7.2 Hz, 1H), 6.55 (s, 1H), 4.68 (m, 1H), 1.89-1.80 (m, 1H), 1.56-1.45 (m, 2H), 0.88 (d, *J* 4.0 Hz, 6H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 163.8, 148.3, 133.0, 127.3, 116.9, 115.2, 114.5, 69.7, 44.3, 22.8, 22.7 and 22. MS (ESI/Q-DA) *m/z*: calculated for [$C_{12}H_{16}N_2O$+H^+] 205.1263, found 205.1014.

2-(3-(3-Methylnaphthalen-1-yl)phenyl)-2,3-dihydroquinazolin-4(1*H*)-one (1j). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), ammonium chloride (1.0 eq), (3-methylnaphthalen-1-yl) benzaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve **1j** as a white solid. mp272-273 °C (>250)[26]; yield: 1.54 g (85%); R_f = 0.55 (50% EtOAc/n-hexane); IR (cm^{-1}): 3287, 3055, 1649, 1611, 1508, 1487. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.42 (s, 1H), 7.89 (m, 2H), 7.59 (m, 3H), 7.45 (m, 2H), 7.35-7.20 (m, 6H), 6.76 (brs, 1H), 6.67 (brs, 1H), 5.83 (s, 1H), 2.14 (s, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 163.6, 147.9, 147.8, 141.9, 138.8, 137.2, 133.3, 132.7, 132.1, 131.6, 129.8, 128.5, 128.4, 128.3, 127.8, 127.2, 125.9, 125.6, 125.4, 124.8, 117.1, 115.1, 114.4, 66.3, 20.4. MS (ESI/Q-DA) *m/z*: calculated for [$C_{25}H_{20}N_2O$+H^+] 365.1664, found 365.1983.

2-(3-(3-Methylnaphthalen-2-yl)phenyl)-2,3-dihydroquinazolin-4(1*H*)-one (1k). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), ammonium chloride (1.0 eq), 3-(3-methylnaphthalen-2-yl)benzaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve 1k as a grey solid. mp188-189 °C (198-200 °C)[26]; yield: 1.27 g (70%); R_f = 0.5 (50% EtOAc/n-hexane); IR (cm^{-1}): 3312, 1636, 1608, 1507, 1482. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.40 (s, 1H), 7.89-7.84 (m, 3H), 7.76 (s, 1H), 7.61 (d, *J* 7.2 Hz, 1H), 7.54-7.40 (m, 6H), 7.27-7.21 (m, 2H), 6.77 (d, *J* 8.4 Hz, 1H), 6.67 (t, *J* 8.0 Hz, 1H), 5.84 (s, 1H), 2.32 (s, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 163.6, 147.8, 141.7, 140.9, 140.1, 133.3, 133.2, 132.4, 131.6, 129.1, 128.3, 128.2,128.1, 127.7, 127.5, 127.3, 126.8, 126.1, 125.6, 125.5, 117.1, 115.0, 114.4, 66.3, 20.8. MS (ESI/Q-DA) *m/z*: calculated for [$C_{25}H_{20}N_2O$+H^+] 365.1654, found 365.1759.

2-(4-Methoxyphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (1l). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), aniline (1.0 eq), 4-methoxybenzaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve **1l** as a white solid. mp204-206 °C (202-205 °C)[32]; yield: 1.50 g (91%); R_f = 0.5 (50% EtOAc/n-hexane); IR (cm^{-1}): 3293, 1632, 1610, 1507, 1486. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.70 (d, *J* 7.6 Hz, 1H), 7.55 (s, 1H), 7.34-7.22 (m, 7H), 7.17 (t, *J* 6.8 Hz, 1H), 6.84 (d, *J* 8.8 Hz, 2H), 6.75-6.69 (m, 2H), 6.21 (s, 1H), 3.68 (s, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 162.8, 159.6, 147.1, 141.3, 134.1, 133.1, 129.0, 128.3, 128.4, 126.8, 126.4, 117.9, 115.8, 115.3, 114.1, 72.8, and 55.5. MS (ESI/Q-DA) *m/z*: calculated for [$C_{21}H_{18}N_2O_2$+H^+] 331.1447, found 331.1594.

2-(3-Bromophenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (1m). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), aniline (1.0 eq), 3-bromobenzaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve **1m** as a white solid. m.p.192-194 °C (188-190 °C)[33]; yield: 1.32 g (70%); R_f = 0.5 (50% EtOAc/n-hexane); IR (cm^{-1}): 3301, 1633, 1612, 1509, 1485. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.73-7.71 (m, 2H), 7.56 (s, 1H), 7.46 (d, *J* 8.0 Hz, 1H), 7.40-7.35 (m, 3H), 7.33-7.27 (m, 4H), 7.25-7.18 (m, 1H), 6.78-6.71 (m, 2H), 6.34 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 162.1, 146.3, 143.4, 140.6, 133.9, 131.1, 130.6, 129.5, 128.7, 128.0, 126.1, 126.0, 125.5, 121.7, 117.8, 115.3, 114.9, 71.7. MS (ESI/Q-DA) *m/z*: calculated for [$C_{20}H_{15}BrN_2O$+H^+] 379.0446, found 379.0532.

2-Cyclopropyl-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (1n). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), aniline (1.0 eq), Cyclopropanecarbaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve **1n** as light brown solid. m.p.119-120 °C; yield: 1.22 g (93%); R_f = 0.6 (50% EtOAc/n-hexane); IR (cm^{-1}): 3306, 1632, 1609, 1518, 1414. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.68 (d, *J* 8.0 Hz, 1H), 7.44-7.40 (m, 2H), 7.40-7.38 (m, 2H), 7.30 (t, *J* 7.6 Hz, 2H), 7.11 (s, 1H), 6.84 (d, *J* 8.0 Hz, 1H), 6.71 (t, *J* 7.6 Hz, 1H), 4.41 (d, *J* 8.0 Hz, 1H), 1.30-1.28 (m, 1H), 0.34 (m, 1H), 0.25-0.21 (m, 2H), -0.15 to -0.17 (m, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 161.8, 147.5, 140.9, 133.5, 128.7, 128.3, 127.9, 126.7, 120.5, 117.1, 114.8, 114.5, 75.8, 15.4, 3.7, and 1.5. MS (ESI/Q-DA) *m/z*: calculated for [$C_{17}H_{16}N_2O$+H^+] 265.1263, found 265.1291.

2-Isobutyl-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (1o). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), aniline (1.0 eq), 3-methylbutanal (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve **1o** as a white solid. M.p.163-165 °C (165-167 °C)[34]; yield: 0.85 g (61%); R_f = 0.6 (50% EtOAc/n-hexane); IR (cm^{-1}): 3292, 2962, 1626, 1611, 1508, 1448. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.69 (d, *J* 7.6 Hz, 1H), 7.45-7.36 (m, 4H), 7.33-7.25 (m, 2H), 7.15 (d, *J* 2.8 Hz, 1H), 6.83 (d, *J* 8.0 Hz, 1H), 6.72 (t, *J* 7.6 Hz, 1H), 5.14-5.10 (m, 1H), 1.84-1.80 (m, 1H), 1.71-1.60 (m, 1H), 1.42-1.36 (m, 1H), 0.77 (d, *J* 6.8 Hz, 3H), 0.72 (d, *J* 6.4 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 161.3, 146.4, 140.9, 133.6, 128.9, 127.9, 126.8, 126.2, 117.2, 115.4, 115.0, 69.9, 41.5, 23.4, 23.1, and 21.3. MS (ESI/Q-DA) *m/z*: calculated for [$C_{18}H_{20}N_2O$+H^+] 281.1654, found 281.1666.

2-(3,4-Dihydroxyphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (1p). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), aniline (1.0 eq), 3,4-dihydroxybenzaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve **1p** as an off white solid. mp204-206 °C; yield: 1.29 g (78%); R_f = 0.45 (50% EtOAc/n-hexane); IR (cm^{-1}): 3520, 3318, 1603, 1566, 1507, 1453. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.92 (s, 2H), 7.70 (d, *J* 7.6 Hz, 1H), 7.46 (s, 1H), 7.34-7.31 (m, 2H), 7.28-7.22 (m, 3H), 7.18 (t *J* 7.2 Hz, 1H), 6.79 (s, 1H), 6.74-6.67 (m, 2H), 6.59 (s, 2H), 6.04 (d, *J* 2.0 Hz, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 162.3, 146.7, 145.3, 145.0, 140.9, 133.6, 131.7, 128.5, 127.9, 126.3, 125.9, 117.8, 117.2, 115.2, 115.1, 114.7, 114.0 and 72.7. MS (ESI/Q-DA) *m/z*: calculated for [$C_{20}H_{16}N_2O_3$+H^+] 333.1239, found 333.1308.

2-(4-Hydroxy-3-methoxyphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (1q). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), aniline (1.0 eq), 4-hydroxy-3-methoxybenzaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve **1q** as an off white solid. mp211-212 °C (209-211 °C)[35]; yield: 1.43 g (83%); R_f = 0.5 (50% EtOAc/n-hexane); IR (cm^{-1}): 3291, 1605, 1507, 1448. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 9.034 (s, 1H), 7.71-7.69 (d, *J* 7.6 Hz, 1H), 7.48 (s, 1H), 7.33-7.23 (m, 5H), 7.17 (t, *J* 7.2 Hz, 1H), 6.94 (s, 1H), 6.77-6.69 (m, 3H), 6.63-6.61 (d, *J* 8.0 Hz, 1H), 6.15 (s, 1H), 3.65 (s, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 162.3, 147.9, 147.4, 147.1, 141.3, 134.1, 131.7, 128.9, 128.3, 127.1, 126.4, 119.9, 117.9, 115.8, 115.3, 115.2, 111.6, 73.2 and 56.0. MS (ESI/Q-DA) *m/z*: calculated for [$C_{21}H_{18}N_2O_3$+H^+] 347.1396, found 347.1391.

2,3-Diphenyl-2,3-dihydroquinazolin-4(1*H*)-one (1r). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), aniline (1.0 eq), benzaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve **1r** as a light brown solid. mp210-212 °C (212-214 °C)[38]; yield: 1.20 g (80%); R_f = 0.5 (50% EtOAc/n-hexane); IR (cm^{-1}): 3292, 1634, 1611, 1509, 1388. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.71 (d, *J* 8.4 Hz, 1H), 7.64 (brs, 1H), 7.38-7.24 (m, 10H), 7.18 (t *J* 7.6 Hz, 1H), 6.76-6.71 (m, 2H), 6.28 (d, *J* 2.4 Hz, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 162.7, 147.1, 141.3, 141.2, 134.2, 129.1, 128.8, 128.7, 128.4, 127.1, 126.7, 126.5, 118.0, 115.8, 115.3, and 73.1. MS (ESI/Q-DA) *m/z*: calculated for [$C_{20}H_{16}N_2O$+H^+] 301.1263, found 301.1194.

2-(2-Chlorophenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (1s). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), aniline (1.0 eq), 2-chlorobenzaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve **1s** as a light brown solid. mp218-219 °C (217-218 °C)[36]; yield: 1.23 g (74%); R_f = 0.5 (50% EtOAc/n-hexane); IR (cm^{-1}): 3308, 1634, 1605, 1489, 1412. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.76 (d, *J* 6.8 Hz, 1H), 7.60-7.57 (m, 1H), 7.47 (d, *J* 2.4 Hz, 1H), 7.41-7.38 (m, 1H), 7.32-7.27 (m, 5H), 7.22-7.17 (m, 3H), 6.79-6.73(m 2H), 6.60 (d *J* 2.8 Hz, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 162.3, 146.1, 140.2, 137.0, 133.9, 131.4, 130.3, 129.9, 128.7, 128.2, 127.9, 127.5, 126.9, 126.6, 117.7, 114.8, 114.6 and 70.2. MS (ESI/Q-DA) *m/z*: calculated for [$C_{20}H_{15}ClN_2O$+H^+] 335.0873, found 335.0751.

2-(4-Bromophenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (1t). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), aniline (1.0 eq), 4-bromobenzaldehyde (1.0 eq) and CMPI (1.0 eq) were reacted in MeCN to achieve **1t** as a white solid. mp221-222 °C (222-224 °C)[37]; yield: 1.36 g (72%); R_f = 0.5 (50% EtOAc/n-hexane); IR (cm^{-1}): 3322, 3060, 1632, 1612, 1592, 1506, 1485. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.71 (d, *J* 6.6 Hz, 1H), 7.65 (brs, 1H), 7.51 (d, *J* 8.4 Hz, 2H), 7.38-7.27 (m, 4H), 7.26 (t *J* 7.6 Hz, 3H), 7.20 (t, *J* 7.2 Hz, 1H), 6.76-6.70 (m, 2H), 6.30 (d, *J* 2.4 Hz, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 162.1, 146.3, 140.6, 140.1, 133.8, 131.3, 128.8, 128.6, 127.9, 126.2, 126.0, 121.5, 117.7, 115.3, 114.8, 71.9. MS (ESI/Q-DA) *m/z*: calculated for [$C_{20}H_{15}BrN_2O$+H^+] 379.0446, found 379.0581.

3-Benzyl-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (1u). The title compound was prepared according to general procedure. Isatoic anhydride (0.815 g ; 5.0 mmol), benzylamine (1.0 eq), benzaldehyde (1.0 eq), and

CMPI (1.0 eq) were reacted in MeCN to achieve **1u** as a white solid. mp121-23 °C (125-127 °C)[38]; yield: 1.24 g (79%); R_f = 0.45 (40% EtOAc/n-hexane); IR (cm-1): 3403, 3059, 3033, 1676, 1634 1604, 1585, 1568. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.69 (d, *J* 7.6 Hz, 1H), 7.37-7.19 (m, 12H), 6.68 (t, *J* 7.6 Hz, 1H), 6.63 (d, *J* 8.0 Hz, 1H), 5.73 (d, *J* 2.4 Hz, 1H), 5.34-5.29 (d, *J* 15.2 Hz, 1H), 3.83-3.80 (d, *J* 15.2 Hz, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 162.8, 146.8, 141.1, 137.9, 133.9, 129.0, 128.9, 128.1, 127.9, 127.6, 126.6, 117.7, 115.1, 114.8, 70.3, 47.6. MS (ESI/Q-DA) *m/z*: calculated for [$C_{21}H_{18}N_2O$+ H^+] 315.1497, found 315.0781.

1'H-spiro[cyclopentane-1,2'-quinazolin]-4'(3'*H*)-one (1v). The title compound was prepared according to general procedure. Isatoic anhydride (0.2 g ; 1.0 mmol), ammonium chloride (1.0 eq), cyclopentanone (1.0 eq), and CMPI (1.0 eq) were reacted in MeCN to achieve **1v** as a white solid. mp282-283 °C (284-285 °C)[39]; yield: 0.024 g (10%); R_f = 0.50 (40% EtOAc/n-hexane); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.08 (br, 1H), 7.57-7.55 (d, *J* = 8.0 Hz 1H), 7.20 (t, *J* = 6.8 Hz, 1H), 6.73 (br, 1H), 6.70-6.67 (d, *J* = 8.8 Hz, 1H), 6.62 (t, *J* = 7.2 Hz, 1H), 1.78 (m, 4H), 1.67-1.65 (m, 4H); MS (ESI/Q-DA) *m/z*: calculated for [$C_{12}H_{14}N_2O$+ H^+] 202.2570, found 203.0751.

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Supplementary Material

Characterization data (for all the developed dihydroquinazolin-4(1H)-one) including copies of ^{1}H and ^{13}C NMR spectra associated with this paper can be found in the online version.

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