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ARTICLE TYPE

Convenient synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones and 2-styryl-3-substituted quinazolin-4(3*H*)-ones: Applications towards the synthesis of drugs

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Simple, convenient, and green synthetic protocols have been developed for one pot synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones and 2-styryl-3-substituted quinazolin-4(3*H*)-ones under catalyst and solvent free condition. The multicomponent reaction (3-MCR) involving isatoic anhydride, an amine, and orthoester afforded the 2,3-disubstituted quinazolin-4(3*H*)-ones in excellent yields under classical heating at 120 °C for 5 h or under microwave irradiation at 140 °C for 20-30 min. The use of ammonium acetate instead of the amine provides the 2-substituted quinazolin-4(3*H*)-ones. The reactions are compatible with various substituted isatoic anhydrides, aryl/heteroaryl/alkyl/cycloalkyl amines, and orthoesters. The strategies are extended to the one pot tandem condensation involving isatoic anhydride, an amine, orthoester, and aldehyde to afford highly functionalized (*E*)-3-aryl/heteroaryl-2-styrylquinazolin/(2-(heteroaryl)vinyl)quinazolin-4(3*H*)-ones. The applications of the methodologies are demonstrated through the synthesis of various drugs acting on the central nervous system such as methaqualone, mebroqualone, mecloqualone, piriqualone, and diproqualone.

Introduction

Functionalised quinazolinones are highly sought for targets to synthetic medicinal/organic chemists due to the broad spectrum of biological activities exihibited by compounds bearing this scaffold (Fig 1).[1]

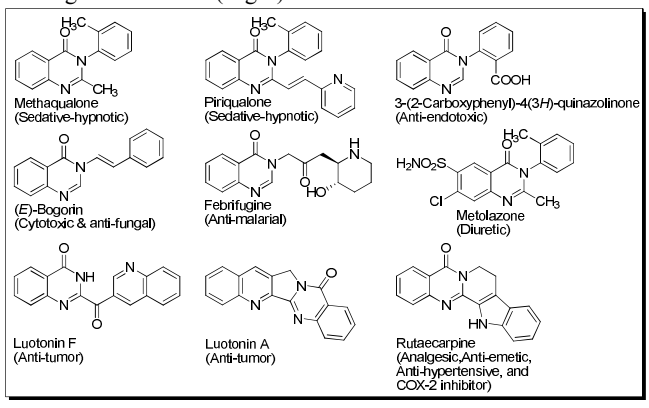
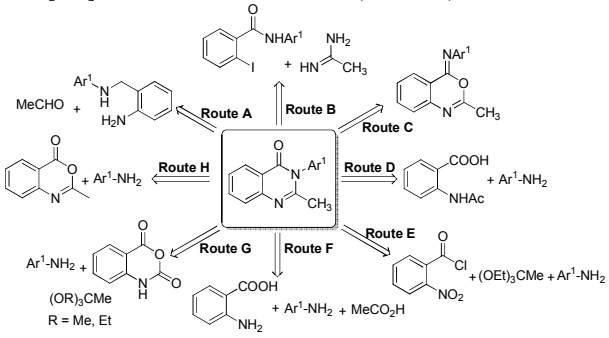


Figure 1. Some pharmaceutically important quinazolinones.

This spurred interest to develop synthetic methodologies for this privileged pharmacophore for generation of new therapeutic leads. The various synthetic strategies (Scheme 1) adopted for the generation of 2-methyl-3-substituted quinazolie-4(3*H*)-ones can be classified in the following routes: (i) reaction of *N*-(2-aminobenzyl)substituted amines with acetaldehyde followed by benzylic oxidation and oxidative dehydrogenation using potassium iodide-*tert*-butyl hydroperoxide[2] (Route A), (ii) domino coupling/condensation cyclization process involving 2-halo benzamide with amidine catalyzed by CuI[3] (Route B), (iii) acid catalyzed rearrangement of 4-imino-4*H*-3,1-benzoxazine[4] (Route C), (iv) reaction of *N*-acetyl anthranilic acid acetic anhydride followed by the acid catalysed reaction of the intermediate formed 4*H*-3,1-benzoxazine with amine[5] (Route D), (v) reaction of 2-nitro benzoyl chloride with amine followed by nitro reduction and its subsequent reaction with orthoester[1k] (Route E), (vi) reaction of anthranilic acid, amine and acetic acid[6] (Route F), (vii) reaction of isatoic anhydride, amine and orthoester[7] (Route G) and, (viii) reaction of 2-methyl-4*H*-benzo[1,3]oxazin-4-one with amine (Route H).[8]



Scheme 1. Strategies for synthesis of 2-methyl–substituted quinazolin-4(3*H*)-ones

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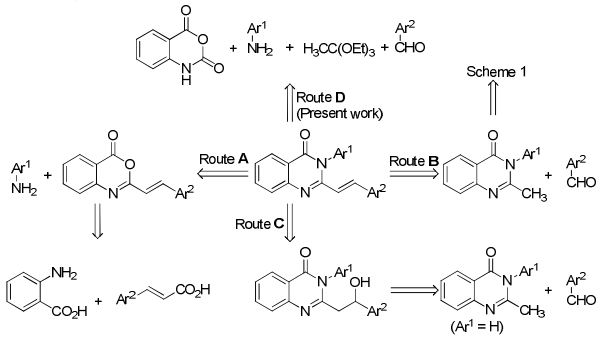
On the other hand, the available methodologies for the preparation of 2-styryl quinazolin-4(3*H*)-ones (Scheme 2) are limited to the: (i) reaction of anthranilic acid with styryl carboxylic acid followed by amine insertion[9] (Route A) and (ii) Knoevenagel condensation of 2-methyl-3-substituted quinazolin-4(3*H*)-one with aromatic aldehyde in the presence of LDA[1b] or in refluxing glacial acetic acid[10] (Route B), and (iii) reaction of double lithiated 2-methyl quinazolin-4(3*H*)-one with aldehyde followed by TFA mediated dehydration[11] (Route C).



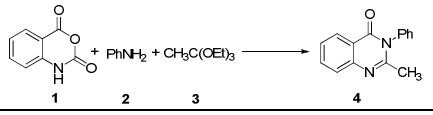
Scheme 2. General strategies for the synthesis of 2-styryl quinazolin-4(3*H*)-ones.

The adverse effect of the manufacturing processes of drugs and pharmaceuticals on the environment urges for sustainable development.[12] The major drive towards this initiative is the replacement of the use of volatile organic solvents (VOSs) by solvent free reaction condition as VOSs are major contributors to the environmental pollution due to their abundant use (more than 85% of the total mass utilization of a chemical process) and incomplete recovery efficiency (50 - 80%).[13] Further, the use of costly, explosive, toxic and carcinogenic chemicals (catalyst/reagents) do not qualify them under sustainability metrics as they augment the ecosystem toxicity resulting in socio-economic burden. Thus, the development of eco-friendly/green approaches to chemical synthesis is an ongoing demand. In view of the role of the *N*-based heterocycles as versatile pharmacophore there has been significant interest for the development of sustainable synthesis.[14] In this context, solvent-free and catalyst free protocol for organic synthesis is highly desirable to comply with the tripple bottomline philosophy of green chemistry,[15] to meet the demand of the timely supply of the designed molecules for biological evaluation,[16] and for enrichment of the medicinal chemists' tool box.[17]

Results and Discussions

In order to develop a convenient synthesis of 2-methylsubstituted quinazolinones, the model reaction involving equimolar mixture of isatoic anhydride **1**, aniline **2** and triethyl orthoacetate **3** was performed under solvent and catalyst free condition at different temperature (table 1) to form 2-methyl-3-phenylquinazolin-4(3*H*)-one **4**. No product formation was observed at rt (25-30 °C) (entry 1, table 1) after 6 h. However, the yield of **4** increased with the increase of the reaction temperature (entry 2-5, table 1). The optimal result was obtained at 120 °C (entry 6, table 1) with no further increase of yield at higher temperature (entry 7, table 1). The best result was obtained in performing the reaction at 120 °C for 4 h (entry 9, table 1) as lesser yield was obtained in lowering the reaction time to 2-3 h (entries 10 and 11, table 1). To evaluate any beneficial/detrimental effect of solvents on the formation of **4**, the reactions were performed in hydrocarbon, halogenated hydrocarbon, protic polar, and aprotic polar solvents under reflux but the yields were inferior compared to the solvent free condition. However, among the different solvents used, the best result was obtained in case of toluene (72%) followed by EtOH (56%).[†]

Table 1. The 3-MCR of **1**, **2**, and **3** under various conditions to form **4**.[a]



Entry	Temperature (°C)	Time (h)	Yield (%)[b]
1	rt (25-30)	6	nil
2	40	6	trace
3	60	6	22
4	80	6	56
5	100	6	68
6	120	6	85
7	150	6	85
8	120	5	85
9	120	4	85
10	120	3	66
11	120	2	54

[a]The mixture of **1** (1 mmol), **2** (1 mmol, 1 equiv), and **3** (1 mmol, 1 equiv) was treated under different condition. [b] Isolated yield of **4**.

The requirement of longer time (4 h) led to search for an alternative mode in performing the reaction to minimise the reaction time. The microwave-assisted synthesis offers means towards green and rapid synthesis[18] and has been used in this laboratory for various organic reactions including the synthesis of heterocycles.[19] Therefore, the model reaction of **1**, **2** and **3** was performed under microwave heating with variation of the temperature and reaction time. The best reaction condition was found to be the use of 150 W input power at 140 °C for 20 min affording 4 in 90% yield[†].

Thus, two methods for solvent and catalyst-free synthesis of 2-methylsubstituted quinazolinones adopting the 3-MCR strategy are developed by the treatment of isatoic anhydride, amine, and orthoacetate under: (i) conventional heating at 120 °C (oil-bath) for 4 h (Method A) and (ii) microwave heating at 140 °C for 20 min (Method B).

The versatility of these two methodologies can be demonstrated through the reaction involving varieties of isatoic anhydrides, amines, and orthoesters under conventional (Method A, table 2) and microwave (Method B, table 2) heating. Various aryl/heteroaryl/alkyl amines react smoothly with isatoic anhydrides and orthoesters to form the corresponding 2,3-disubstituted quinazolin-4(3*H*)-ones in excellent yields. However, inferior yields were obtained from amines having electron withdrawing substituents (entry 17 & 18, table 2) compared to the amines bearing electron donating substituents (entry 10 & 11, table 2). The reaction conditions are compatible with heterocyclic (entry 19-21, table 2), arylalkyl (entry 22-25, table 2), alicyclic (entry 26, table 2),

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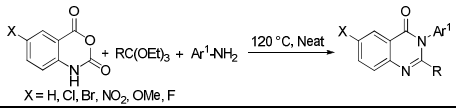
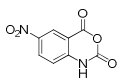
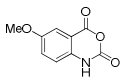
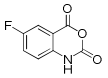
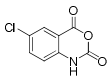
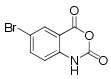
and allyl (entry 27, table 2) amines.

With respect to the orthoesters, the reactions were performed with commercially available orthoesters and excellent yields were obtained in each case. The reaction works well with substituted isatoic anhydrides (entries 28-34, table 2).

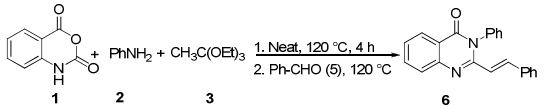
Table 2. The 3-MCR for one-pot synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones.[a]



Entry	Isatoic anhydride	R	Amine/ NH_4OAc	Yield (%)[b] Method A	Method B
1		H	NH_4OAc	91	92
2		Me	NH_4OAc	91	90
3		Et	NH_4OAc	90	91
4		^{n}Bu	NH_4OAc	83	90
5		Ph	NH_4OAc	78	86
6		H	 $R^1 = H$	90	92
7		Me	$R^1 = H$	85	88
8		H	$R^1 = 4$-Me	90	90
9		Me	$R^1 = 4$-Me	86	87
10		H	$R^1 = 4$-OMe	92	91
11		Me	$R^1 = 4$-OMe	88	90
12		H	$R^1 = 2$-Cl	85	86
13		H	$R^1 = 4$-Cl	85	88
14		Me	$R^1 = 4$-Cl	82	85
15		Me	$R^1 = 4$-Br	81	82
16		Me	$R^1 = 4$-F	82	81
17		H	$R^1 = 4$-CF_3	72	80
18		Me	$R^1 = 4$-CF_3	70	79
19		H		78	81
20		H		70	72
21		Me		68	71
22		H		72	75
23		Me		70	72
24		H		76	76
25		Me		72	75
26		H		70	73
27		Me		78	82
28		Me	$R^1 = H$	82	85
29		Me	$R^1 = H$	69	73
30		Me	$R^1 = 4$-CH_3	67	70
31		Me	$R^1 = H$	80	81
32		Me	$R^1 = 4$-SCH_3	74	77
33		Me	$R^1 = H$	80	82
34		Me	$R^1 = H$	78	84

[a]**Method A**: Isatoic anhydride (2.5 mmol) was treated with the amine/NH_4OAc (2.5 mmol, 1 equiv) and orthoester (2.5 mmol, 1 equiv) under neat condition at 120 °C for the 5 h. **Method B**: Isatoic anhydride (2.5 mmol) was treated with the amine/NH_4OAc (2.5 mmol, 1 equiv) and orthoester (2.5 mmol, 1 equiv) under neat condition at 140 °C (150 W) for 20-30 min. [b] Isolated yield of the desired quinazolinone.

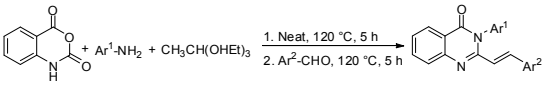
The 2-methyl-3-substituted quinazolinones serve as the starting materials for the preparation of 2-styryl-3-substituted quinazolinones during the condensation with aldehydes which however requires the use of strong base such as LDA[1b,11] or reflux in HOAc for prolonged period (12 h). The multicomponent reactions (MCRs)[20] have been recognised as new green synthetic tools to rapidly generate the synthetic targets in convergent and atom-economical fashion. Therefore, the tandem one pot reaction (Route D, Scheme 3)[21] of **1**, **2**, **3**, and benzaldehyde **5** to form the 2-styryl-3-phenyl quinazolinone **6** was planned that would involve a 3-MCR process involving **1**, **2**, **3** followed by condensation of **5** with the in situ generated **4** in tandem. The only report for the preparation of 2-styryl quinazolinones following this strategy requires the use of 50 mol% of the protic ionic liquid [Hmim]TFA as the promoter.[21a]



Scheme 3. The one-pot tandem synthesis of 3-phenyl-2-styrylquinazolin-4(3*H*)-one.

To test the feasibility, the model reaction was performed using optimized reaction conditions (conventional and microwave heating) for the condensation of **1**, **2**, **3**, to form **4** followed by the addition of benzaldehyde **5** (1 equiv) and stirring the reaction mixture for further 5 h. This one pot process proved to be effective under both conventional and microwave heating (entry 1, table 3). Thus, it was realized that these two steps can be effectively carried out in one-pot to afford varieties of 2-styryl quinazolinones. The different combinations of amines and aldehydes were opted to get diversified synthesis of 2-styryl-4(3*H*)-quinazolinones (table 3). The aromatic aldehydes having different functional groups as well as hetero-aromatic aldehydes worked adequately under the optimized condition giving highly functionlized 2-styryl-4(3*H*)-quinazolinones.

Table 3. One-pot synthesis of (*E*)-3-aryl/heteroaryl-2-styrylquinazolin-4(3*H*)-one.[a]



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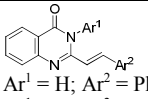
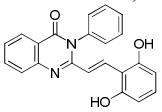
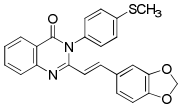
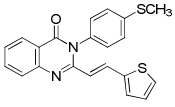
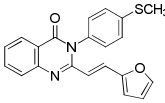
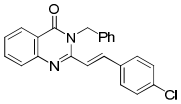
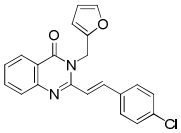
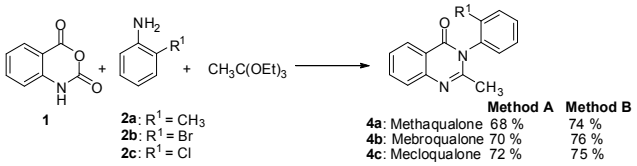
Entry	Product	Yield (%)[b] Method A	Method B
1	 Ar^1 = H; Ar^2 = Ph	79	81
2	Ar^1 = H; Ar^2 = 4-OMe-C_6H_4	75	76
3	Ar^1 = Ph; Ar^2 = Ph	74	78
4	Ar^1 = Ph; Ar^2 = 4-Me-C_6H_4	72	75
5	Ar^1 = Ph; Ar^2 = 4-Br-C_6H_4	75	74
6	Ar^1 = Ph; Ar^2 = 4-CF_3-C_6H_4	78	80
7	Ar^1 = Ph; Ar^2 = 4-OMe-C_6H_4	70	72
8	Ar^1 = Ph; Ar^2 = 4-OCH_2Ph-C_6H_4	70	75
9	Ar^1 = 4-Me-C_6H_4; Ar^2 = 4-Cl-C_6H_4	75	76
10	Ar^1 = 4-OMe-C_6H_4; Ar^2 = 4-OMe-C_6H_4	76	79
11	Ar^1 = 4-SMe-C_6H_4; Ar^2 = 4-OMe-C_6H_4	74	76
12	Ar^1 = 4-SMe-C_6H_4; Ar^2 = 4-NMe_2-C_6H_4	77	76
13	Ar^1 = 4-SMe-C_6H_4; Ar^2 = 4-Cl-C_6H_4	75	75
14	Ar^1 = 4-F-C_6H_4; Ar^2 = 4-Cl-C_6H_4	71	77
15		70	72
16		76	78
17		72	75
18		72	75
19		71	76
20		71	76

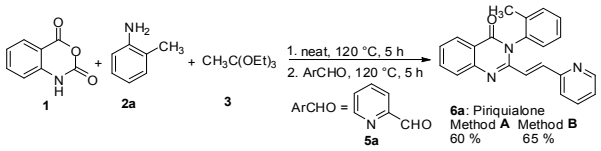
[a]**Method A**: The mixture of isatoic anhydride (2.5 mmol), amine/NH_4OAc (2.5 mmol) and triethyl orthoacetate (2.5 mmol) was heated under neat condition at 120 ºC for 5 h followed by addition of aldehyde (2.5 mmol, 1 equiv) and continued stirring for further 5 h. **Method B**: The mixture of isatoic anhydride (2.5 mmol), amine/NH_4OAc (2.5 mmol) and triethyl orthoacetate (2.5 mmol) was heated under neat condition at 140 °C (150 W) for 20 min followed by addition of aldehyde (2.5 mmol, 1 equiv) and continued for further 20-30 min. [b] Isolated yield of the corresponding 2-styrylquinazolinone.

The ultimate utility of any synthetic potocol is judged on the basis of its use for the synthesis of target molecules. The wide applications of 4(3*H*)-quinazolinones and its 2-styryl derivatives as CNS depressant prompted us to test these new methodologies for the synthesis of a few CNS depressants. Thus the sedative and hypnotic drugs methaqualone **4a**, mebroqualone **4b**, and mecloqualone **4c** were synthesized through the 3-MCR process involving isatoic anhydride, appropriate amine and triethyl orthoacetate following the Method A and Method B in very good yields (Scheme 4).



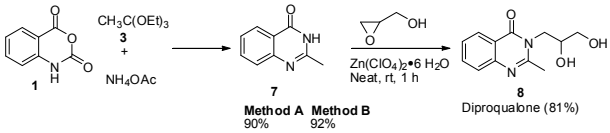
Scheme 4. Synthesis of the sedative and hypnotic drugs **4a-c** following the 3-MCR procedures.

The tandem one pot procedure for the synthesis of 2-styrylquinazolinone was extended for the preparation of piriquialone **6a** following the sequential addition of **1**, *o*-toludine **2a**, **3** and pyridine-2-carboxaldehyde **5a** (Scheme 5).



Scheme 5. The tandem process for the synthesis of the sedative and hypnotic drug **6a**.

The synthesis of the sedative and hypnotic drug diproqualone **8** would involve the epoxide aminolysis[22] of glycidol with the 2-methylquinazolinone **7**. The requisite starting material **7** was synthesesd in 90-92% yields by the newly developed 3-MCR of **1**, **3**, and NH_4OAc. The treatment of **7** with glycidol in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ (2 mol%)[22b] at room temperature under neat condition afforded **8** in 81% yield (Scheme 6).



Scheme 6. Synthesis of the sedative and hypnotic drug **8**.

Conclusions

The present work reports a simple and convenient synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones under catalyst and solvent free conditions following 3MCR strategies. The reactions are performed under classical heating at 120 °C for 5 h or under microwave dielectric heating under controlled input power, temperature, and pressure for 20-30 min. The reactions were compatible with different variations of isatoic anhydride, amine and orthoester to generate functionalized 2,3-disubstituted quinazolin-4(3*H*)-ones. This has been further extended for the one-pot synthesis of functionalized (*E*)-3-aryl/heteroaryl-2-styrylquinazolin/(2-(heteroaryl)vinyl)quinazolin-4(3*H*)-ones without the necessity of acid/base in the final condensation step. The catalyst and solvent free condition along with operational simplicity (recrystllisation using EtOH) offers a green process for the synthesis of quinazolin-4(3*H*)-ones. The synthetic utility was demonstared through the synthesis of several CNS depressants such as methaqualone, mebroqualone, mecloqualone, piriquialone, and diproqualone in good to excellent yields.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Typical experimental procedure, spectral data of all compounds, scanned spectra of unknown compounds. See DOI: 10.1039/b000000x/

‡ **General Information:** The glasswares were thoroughly washed and dried in an oven. Chemicals and all solvents were commercially available (Aldrich Chemical, Merck AG, Fluka and S-D Fine Chemicals) and used without further purification. The $^1H/^{13}C$ NMR spectra were recorded on a Bruker Avance 400/100 MHz NMR spectrometer in $CDCl_3$ with residual undeuterated solvent ($CDCl_3$: 7.26/77.0) using TMS as an internal standard. Chemical shifts (δ) are given in ppm and *J* values are given in Hz. ^{13}C NMR spectra were fully decoupled and were referenced to the middle peak of the solvent $CDCl_3$ at 77.0 ppm. Splitting pattern were designated as s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet. Mass spectra were recorded on a Finnigan MAT-LCQ [for APCI] mass spectrometer. Infra-red (IR) spectra were recorded on Perkin Elmer FT-IR spectrometer in the range 4000-600 cm^{-1} either as neat samples for liquids or using KBr for preparing pellets for solid samples. Compounds were routinely checked for their purity on the silica gel GF-254 and visualized under UV at wavelength 254 nm. Melting points were measured with Gupta scientific melting point apparatus and were uncorrected. The microwave-assisted reactions were performed using CEM Discover model no 908010 equipment. Evaporation of solvents was performed at reduced pressure, using a rotary evaporator.

Typical experimental procedure for the synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones (Entry 7, Table 3):

Method A: The equimolar mixture of isatoic anhydride **1** (0.41 g, 2.5 mmol), aniline **2** (0.23 g, 2.5 mmol) and triethyl orthoacetate **3** (0.41 g, 2.5 mmol) was stirred magnetically at 120 °C (oil bath temp). After completion of the reaction (TLC, 4 h), the crude reaction mixture was recrystallized from EtOH to obtain analytically pure **4** (0.50 g, 85 %) as white solid; mp = 144-145 °C (lit[18c] 144-146 °C); IR (KBr) ν_{max} : 2968, 1648, 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = 7.2 Hz 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.51 (m, 4H), 7.27 (d, *J* = 6.0 Hz, 2 H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 154.2, 147.5, 137.8, 134.6, 130.0, 129.3, 128.0, 127.0, 126.8, 126.6, 120.8, 24.4; MS(APCI) *m/z*: 237.33 $(M+H)^+$.

Method B: The equimolar mixture of isatoic anhydride **1** (0.41 g, 2.5 mmol), aniline **2** (0.23 g, 2.5 mmol) and triethyl orthoacetate **3** (0.41g, 2.5 mmol) was subjected to microwave irradition (150W/140 °C) for 20 min. After completion of reaction, the crude reaction mixture was recrystallized from EtOH to obtain analytically pure **4** (0.52 g, 88 %) as white solid.

Typical experimental procedure for the synthesis of 2-styryl quinazolin-4(3*H*)-ones (Entry 3, Table 4)

Method A: The equimolar mixture of isatoic anhydride **1** (0.41 g, 2.5 mmol), aniline **2** (0.23 g, 2.5 mmol) and triethyl orthoacetate **3** (0.41 g, 2.5 mmol) was stirred magnetically at 120 °C (oil bath temp) for 4 h followed by addition of benzaldehyde **5** (0.26 g, 2.5 mmol) and the stirring was continued for another 4 h (TLC). The crude reaction mixture was recrystallized from EtOH to obtain analytically pure **6** (0.64 g, 79%) as white solid; mp = 196-197 °C (lit[21] 196 °C); IR (KBr) ν_{max} : 3442, 1676, 1545, 1472, 1258, 1132 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.30 (d, *J* = 7.9 Hz, 1H), 7.97 (d, *J* = 15.5 Hz, 1H), 7.79 (d, *J* = 3.4 Hz, 2H) 7.53- 7.61 (m, 3H), 7.47-7.50 (m, 1H), 7.28-7.34 (m, 7H), 6.39 (d, *J* = 15.5 Hz, 1H); MS (APCI) m/z: 325.21 $(M + H)^+$.

Method B: (Entry 3, Table 4): The equimolar mixture of isatoic anhydride **1** (0.41 g, 2.5 mmol), aniline **2** (0.23 g, 2.5 mmol) and triethyl orthoacetate **3** (0.41g, 2.5 mmol) was subjected to microwave irradition (150W/140 °C) for 20 min followed by addition of benzaldehyde **5** (0.26 g, 2.5 mmol) and continued the reaction for another 20 min. The crude reaction mixture was recrystallized using EtOH to obtain analytically pure **6** (0.66 g, 81%) as white solid.

Typical experimental procedure for the synthesis of methaqualone 4a (Scheme 3):

2-Methyl-3-*o*-tolylquinazolin-4(3*H*)-one 4a: The equimolar mixture of isatoic anhydride **1** (0.41 g, 2.5 mmol), triethyl orthoacetate **3** (0.41 g, 2.5 mmol) and 2-methyl aniline (0.21 g, 2.5 mmol) was stirred magnetically at 120 °C (oil bath temp). After completion of reaction (TLC, 4 h), the crude reaction mixture was recrystallized from EtOH to obtain analytically pure **4a** (0.43 g, 68 %) as white solid; mp = 118-119 °C (lit[1b] 114-115 °C); IR (KBr) ν_{max} = 3008, 1683, 1600, 1471, 1274 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.29 (d, *J* = 7.9 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.41-7.36 (m, 3H), 7.16 (d, *J* = 7.3 Hz, 1H), 2.19 (s, 3H), 2.13 (s, 3H); MS(APCI) *m/z* 251.41 $(M+H)^+$.

Typical experimental procedure for the synthesis of mebroqualone 4b (Scheme 3):

Synthesis of 3-(2-Bromophenyl)-2-methylquinazolin-4(3*H*)-one 4b: The equimolar mixture of isatoic anhydride **1** (0.41 g, 2.5 mmol), triethyl orthoacetate **3** (0.41 g, 2.5 mmol) and 2-bromo aniline (0.28 g, 2.5 mmol) was stirred magnetically at 120 °C (oil bath temp). After completion of reaction (TLC, 4 h), the crude reaction mixture was recrystallized from EtOH to obtain analytically pure **4b** (0.54 g, 70 %) as white solid; mp = 143-145 °C (lit[1b] 143-144 °C); IR (KBr) ν_{max} = 2923, 1687, 1607, 1471, 1281 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 7.9 Hz, 1H), 7.79-7.76 (m, 2H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.51-7.47 (m, 2H), 7.50-7.46 (m, 3H), 7.40-7.36 (m, 2H), 2.22 (s, 3H); MS(APCI) *m/z* 271.24 $(M+H)^+$

Typical experimental procedure for the synthesis of mecloqualone 4c (Scheme 3):

Synthesis of 3-(2-chlorophenyl)-2-methylquinazolin-4(3*H*)-one 4c: The equimolar mixture of isatoic anhydride **1** (0.41 g, 2.5 mmol), triethyl orthoacetate **3** (0.41 g, 2.5 mmol) and 2-Chloro aniline (0.32 g, 2.5 mmol) was stirred magnetically at 120 °C (oil bath temp). After completion of reaction (TLC, 4 h), the crude reaction mixture was recrystallized from EtOH to obtain analytically pure **4c** (0.48 g, 72 %) as brown solid; mp = 126-128 °C (lit[1b] 126-127 °C); IR (KBr) ν_{max} = 2925, 1688, 1608, 1471, 1281 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 6.8 Hz, 1H), 7.78 (t, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.62-7.60 (m, 1H), 7.50-7.46 (m, 3H), 7.36-7.33 (m, 1H), 2.23 (s, 3H); MS(APCI) *m/z* 271.24 $(M+H)^+$

Typical experimental procedure for the synthesis of piriquilone 6a (Scheme 4):

Synthesis of (*E*)-2-(2-(pyridin-2-yl)vinyl)-3-(o-tolyl)quinazolin-4(3*H*)-one (piriquialone) 6a: The equimolar mixture of isatoic anhydride **1** (0.41 g, 2.5 mmol), triethyl orthoacetate **3** (0.41g, 2.5 mmol) and NH_4OAc (0.23 g, 3 mmol) was stirred magnetically at 120 °C (oil bath temp) for 5 h followed by addition of pyridine-2-carboxaldehyde **5a** (0.27 g, 2.5 mmol) and the stirring was continued for another 4 h (TLC). The crude reaction mixture was recrystallized from EtOH to obtain analytically pure **6a** (0.50 g, 60%) as white solid; mp = 195-196 °C (lit[21] 195 °C); IR (KBr) ν_{max} = 3326, 1645, 1525, 1126, 1023 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.50 (d, *J* = 3.9 Hz, 1 H), 8.31-8.34 (m, 1 H), 8.00 (d, *J* = 15.0 Hz, 1 H), 7.80-7.82 (m, 2 H), 7.61-7.63 (m, 1 H), 7.48-7.52 (m, 1 H), 7.40-7.46 (m, 3 H), 7.30 (d, *J* = 7.8 Hz, 1 H), 7.22 (d, *J* = 7.6 Hz, 1 H), 7.14-7.18 (m, 1 H), 6.92 (d, *J* = 15.0 Hz, 1 H); MS (APCI) m/z: 340.42 $(M + H)^+$.

Typical experimental procedure for the synthesis of diproqualone 8 (Scheme 5):

Step-1 Synthesis of 2-methylquinazolin-4(1*H*)-one 7: The mixture of isatoic anhydride **1** (0.41 g, 2.5 mmol), triethyl orthoacetate **3** (0.41 g, 2.5 mmol) and NH_4OAc (0.23 g, 3 mmol, 1.2 equiv) was stirred magnetically at 120 °C (oil bath temp). After completion of the reaction (TLC, 4 h), the crude reaction mixture was recrystallized from EtOH to obtain analytically pure 2-methylquinazolin-4(3*H*)-one **7** (0.36 g, 90 %) as white solid; mp = 230-232 °C (lit[7c] 229-230 °C); IR (KBr) ν_{max} : 1675, 1462, 1258, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 12.07 (s, 1 H), 8.29 (d, *J* = 7.9 Hz, 1H), 7.77 (t, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.47 (t, *J* = 7.1 Hz, 1H), 2.60 (s, 3 H); MS(APCI) m/z: 161.28 $(M+H)^+$.

Step-2 Ring opening of glycidol with 2-methylquinazolin-4(1*H*)-one: To a magentiaclly stirred mixture of 2-methylquinazolin-4(3*H*)-one **7** (0.16 g, 1 mmol) and oxiran-2-ylmethanol (0.07 g, 1 mmol) was added $Zn(ClO_4)_2{\cdot}6H_2O$ (2 mol%) under neat condition at rt and the stirring was continued for 30 min. The crude reaction mixture was purified by flash column chromatography to obtain analytically pure **8** (0.18 g, 78 %) as

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white solid; mp = 142-145 °C (lit[34] 142-145 °C); IR (KBr) ν_{max} : 3132, 1632, 1613, 1543, 1390 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, *J* = 8.0 Hz & 1.2 Hz, 1H),7.76-7.80 (m, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.45-7.49 (m, 1H), 5.08 (d, *J* = 4.6 Hz, 1H), 4.79 (t, *J* = 5.7 Hz, 1H), 4.27-4.30 (m, 1H), 3.82-3.87 (m, 2H), 2.65 (s, 3H); MS(APCI) m/z: 235.32 $(M+H)^+$.

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Convenient synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones and 2-styryl-3-substituted quinazolin-4(3*H*)-ones: Applications towards the synthesis of drugs.

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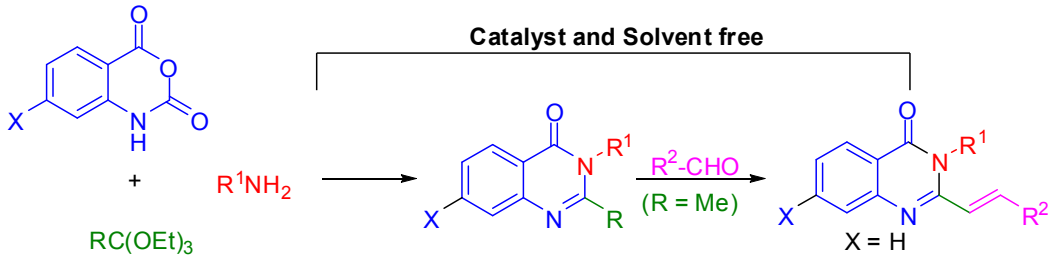

X = H, NO_2, Cl, Br; R = H, Me, Et, *n*-Bu; R^1 = Aryl or Hetroaryl or alkyl; R^2 = Aryl or Hetroaryl