A General and Facile Synthesis of Novel Polysubstituted Quinazolin-4(3*H*)-ones

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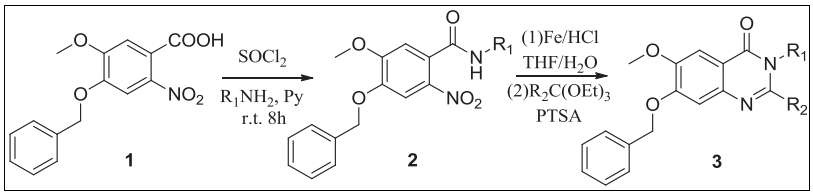

A simple and efficient approach to synthesize novel polysubstituted quinazolin-4(3*H*)-ones has been developed, and the key step is a sequential procedure involved iron-mediated reduction and acid-catalytic cyclization. The present method provides a convenient and practical strategy for the synthesis of quinazolin-4(3*H*)-one derivatives.

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INTRODUCTION

Quinazolin-4(3*H*)-ones have attracted much attention for their various biological activities and medicinal properties. For example, they act as the potent phosphoinositide 3-kinase inhibitors, *N*-methyl-D-aspartate receptor antagonists, histamine receptor agonists, 5-hydroxytryptamine receptor antagonists, and chemokine receptor antagonists [1]. Some of them show remarkable activities as antitumor, anti-neurodegenerative, anti-allergic, and anti-inflammatory agents. Moreover, therapeutic agents containing the quinazolin-4(3*H*)-one moiety have been on the market or are in clinical trials. For example, methaqualone is used as a sedative–hypnotic drug and piriqualone as an anticonvulsant. Ispinesib (SB-715992), a kinesin spindle protein targeting inhibitor, has recently warranted in phase II trial and is of potential therapeutic value in malignant melanoma. IC-87114 as a phosphoinositide 3-kinase inhibitor is now on phase I trial for relapsed or refractory chronic lymphocytic leukemia, acute myeloid leukemia, and selected B-cell non-Hodgkin's lymphoma (Figure 1) [2]. Because of their various applications, some synthetic strategies for quinazolin-4(3*H*)-ones have been reported in the literature. The most common method employed anthranilic acid as starting material, which condensed with aromatic amines and orthoesters under acidic conditions, such as perfluorinated resin-supported sulfonic acid (Nafion-H), $La(NO_3)_3$, $Bi(TFA)_3$–[nbp]$FeCl_4$, silica gel/$FeCl_3$, $ZrOCl_2$, $Yb(OTf)_3$, and $SnCl_2{\cdot}2H_2O$ [3]. Other method mainly focused on cyclization of 2-aminobenzamide or its derivatives or 2-aminobenzonitrile with some substrates such as arylamines, imidates, iminohalides, and isocyanides [4]. Moreover, a recent report revealed that quinazolin-4(3*H*)-one derivatives have also been synthesized using copper-catalystic *N*-arylation of quinazolin-4(3*H*)-ones with arylboronic acids [5]. Although these protocols for the synthesis of quinazolin-4(3*H*)-ones are useful, the development of flexible, efficient, economically competitive, and simple methodology is still needed for quinazolin-4(3*H*)-ones, especially for the complex polysubstituted quinazolin-4(3*H*)-one derivatives [1–7].

Recently, Shi *et al*. described a one-pot synthesis of quinazolin-4(3*H*)-ones by using $TiCl_4$/Zn-catalyzed cyclization of triethyl orthoformate with *o*-nitrobenzamides [6]. However, the procedure suffered from some difficulties such as inconvenient preparation of catalytic system, poor achievement of catalytic activity, harsh reaction condition, and disgusting smoking of Lewis acid $TiCl_4$. Considering the reaction mechanism and the reactive characteristics of Zn and $TiCl_4$, we elicited that we can employ a sequential procedure of iron-mediated reduction and acid-catalytic cyclization instead. In continuation of our studies on the diversity-oriented synthesis of novel quinazolin-4(3*H*)-one unit-containing compounds for a drug discovery program, herein we report a simple, efficient, and practical method for the synthesis of novel polysubstituted quinazolin-4(3*H*)-ones that involved acylation and a sequential reaction of iron-mediated reduction and acid-catalytic cyclization, and the acid-catalytic condition was also fully discussed (Scheme 1).

RESULTS AND DISCUSSION

In the synthesis of target substituted quinazolin-4(3*H*)-ones, 2-nitro-4-benzyloxy-5-methoxy benzoic acid (**1**) was used as starting material, which was prepared according to the literature method in good yield [7]. Treatment of

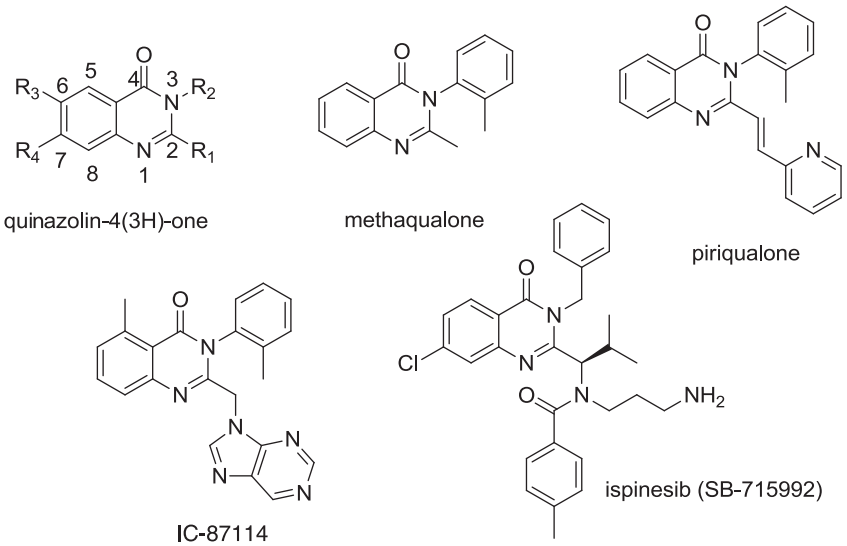
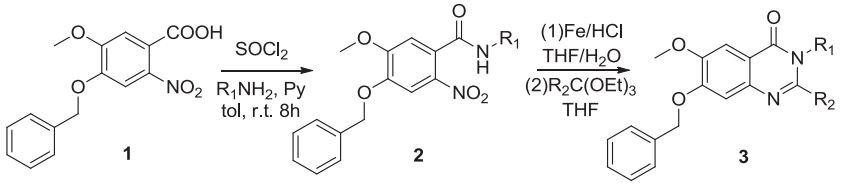


Figure 1. Some drugs and drug candidates containing the quinazolin-4(3*H*)-one unit.

Scheme 1. Synthetic route of polysubstituted quinazolin-4(3*H*)-one derivatives.

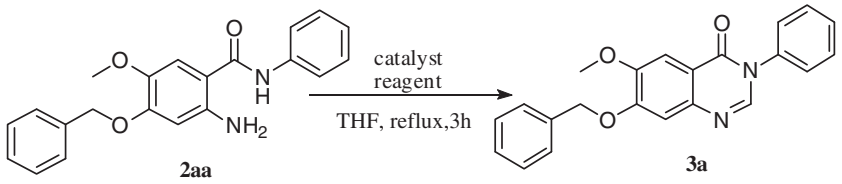


compound **1** with $SOCl_2$ to offer an acyl chloride, then with aromatic amines or alkyl amines at room temperature gave the precursors **2** in excellent yield, as illustrated in Scheme 1. Our investigation focused on the preparation of target quinazolin-4(3*H*)-ones. The iron-mediated reduction was easily carried out almost quantitatively. Then, we initially carried out a set of experiments using *N*-phenyl-2-amino-4-benzyloxy-5-methoxy benzamide (**2aa**) as model substrate for optimizing the acid-catalytic cyclization conditions, and the results are summarized in Table 1. The reagents formic acid and triethyl orthoformate and the acid catalysts including concentrated sulfuric acid, zinc chloride, and *p*-toluene sulfuric acid (PTSA) were investigated. To our delight, when acid catalysts were employed, the yield increased notably, and when PTSA was used, the excellent yield (98%) of the expected product **3a** was provided (Table 1, entries 1–6). Accordingly, acid catalyst facilitated the reaction. Next, the catalyst loading was optimized, and thus, several amounts of PTSA catalyst were investigated in a range of 100, 50, 20 and 10 mol% (Table 1, entries 6–9), and it was found that 20 mol% of PTSA loading is appropriate (Table 1, entry 8). No decline in the yield was observed on decreasing the catalyst loading from 100 to 20 mol% (Table 1, entries 6–8). Other different reaction parameters including solvent, temperature, time, and triethyl orthoformate amount were also performed. Finally, the optimum conditions for the ring closure of **3** were to conduct the reaction using triethyl orthoformate (10 equiv) and PTSA (20 mol%) in refluxing THF for **3** h.

Thus, on the basis of optimized reaction conditions, we carried out the synthesis of a number of polysubstituted quinazolin-4(3*H*)-ones in good or excellent yields. The results are summarized in Table 2. In general, anilines carrying either electron-donating (Table 2, entries 2–5, 12) or electron-withdrawing groups (Table 2, entries 6–10, 13–15) all afford excellent yields (72–92%). Steric hindrance is appearing to have little effects on the efficiency of this one-pot continuous reaction. However, hydroxyl-substituted aniline gives the lowest yield (39%, Table 2, entry 11). Other different substituted functional groups are seemed to be tolerated, such as alkyl, halogen, ketone, methoxy, and ester in the anilines (Table 2, entries 2–15). Furthermore, this approach was extended to alkyl amines for preparation of their corresponding quinazolin-4(3*H*)-ones (Table 2, entries 16–17). Also, they were found to be also effective in the reaction system, and the yield is satisfactory (86% and 86%). In addition, 2-positon methyl substituted quinazolin-4(3*H*)-ones were synthesized via using triethyl orthoacetate instead of triethyl orthoformate

Table 1

Optimization of the cyclization conditions.



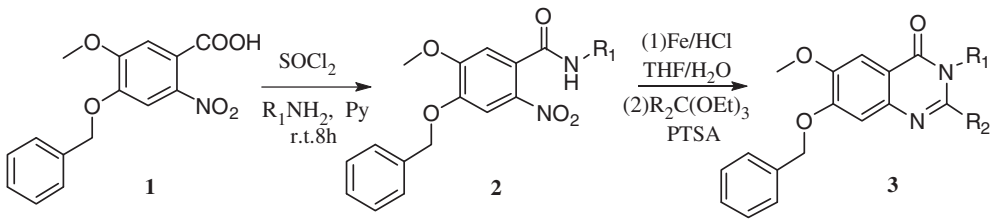
2aa **3a**

Entry	Reagent	Catalyst	Amount (mol%)[a]	Yield (%)[b]
1	HCOOH	—	—	19
2	HCOOH	H_2SO_4	1 drop	39
3	$HC(OEt)_3$	—	—	68
4	$HC(OEt)_3$	H_2SO_4	1 drop	94
5	$HC(OEt)_3$	$ZnCl_2$	100	96
6	$HC(OEt)_3$	PTSA	100	98
7	$HC(OEt)_3$	PTSA	50	97
8	$HC(OEt)_3$	PTSA	20	98
9	$HC(OEt)_3$	PTSA	10	92

[a]Reaction conditions of cyclization in the optimized experiments: compound **2aa** (100 mg, 0.29 mmol), catalyst (amount), reagent (2.9 mmol, 10 equiv) in refluxing THF (5 mL).
[b]Yield of isolated and purified product.

Table 2

Synthesis of this polysubstituted quinazolin-4(3*H*)-ones **3**.



1 **2** **3**

Entry	R_1	R_2	Product	Yield (%)[a]
1	Ph	H	**3a**	98
2	4-MePh	H	**3b**	90
3	3-MePh	H	**3c**	86
4	2-MePh	H	**3d**	72
5	2,4-Me_2Ph	H	**3e**	79
6	4-ClPh	H	**3f**	89
7	3-ClPh	H	**3g**	90
8	2-ClPh	H	**3h**	85
9	4-FPh	H	**3i**	80
10	4-(MeCO)Ph	H	**3j**	89
11	4-HOPh	H	**3k**	39
12	4-MeOPh	H	**3l**	80
13	2,4-F_2Ph	H	**3m**	80
14	2,4-Cl_2Ph	H	**3n**	84
15	2-Me-4-(MeOCO)Ph	H	**3o**	92
16	Cyclohexyl	H	**3p**	86
17	Benzyl	H	**3q**	86
18	4-FPh	Me	**3r**	84
19	4-MeOPh	Me	**3s**	87

[a]Yield of isolated and purified product.

(Table 2, entries 18 and 19). It was found that the reaction system was also efficient, and the products were afforded in excellent yields (84% and 87%).

In summary, we have developed a general facile, practical, and economically competitive method for the synthesis of this type of polysubstituted quinazolin-4(3*H*)-ones. This approach might provide a new access to the synthesis of novel quinazolinone derivatives as potential pharmaceutical interest.

EXPERIMENTAL

Melting points of compounds were measured on an RY-1 melting point apparatus (Tianjin, China) and were uncorrected. IR spectra were recorded on a Nicolet Impact-410 instrument (Thermo Nicolet, USA); samples were prepared as KBr (Beijing, China) plates. ^{1}H-NMR spectra were recorded on a Bruker AV-300 (300 MHz) spectrometer (Bruker, Germany). Samples were prepared in $CDCl_3$ or DMSO-d_6 with TMS ($\delta = 0$) (Beijing, China) as an internal standard unless noted otherwise. EIMS data were obtained on SHIMADZU GCMS-QP2010 system (Shimadzu, Japan). All chemicals were purchased from commercial sources and were used without further purification unless otherwise noted. The solvents (such as THF, EtOAc, CH_2Cl_2, and others) were CP grade purchased from Nanjing Chemical Co., Ltd. and used without further purification. Column chromatography was carried out on silica gel (200–300 mesh, Qindao Ocean Chemical Company, China). TLC analyses were carried out on silica gel GF254 (Qindao Ocean Chemical Company, China) glass plates (2.5 cm × 10 cm with 250-μm layer). Concentration and evaporation of the solvent after reaction or extraction were carried out on rotary evaporator operated at reduced pressure. The 2-nitro-4-benzoxyl-5-methoxy benzoic acid (compound **1**) was synthesized according to the literature procedures in good yield [7].

Intermediate substituted nitrobenzamides 2: general procedure. In a 50-mL reaction vial, a solution of 2-nitro-4-benzyloxy-5-methoxy benzoic acid (2 mmol) in thionyl chloride (15 mL) was heated at reflux for 1.5 h, allowed to cool to room temperature, and concentrated. The residue was diluted with toluene (20 mL), chilled in an ice bath, and then pyridine (4 mmol), and the appropriate amine (1.5 mmol) were added. The reaction mixture was removed from the bath and stirred at room temperature for 8 h. The separated solid was collected by filtration.

***N*-Phenyl-2-amino-4-benzyloxy-5-methoxy benzamide (2aa); compound 2aa provided for optimizing cyclization conditions.** In a 50-mL reaction vial, the water (10 mL), iron powder (20 mmol), and concentrated HCl (three drops) were added to a solution of *N*-phenyl-2-nitro-4-benzyloxy-5-methoxy benzamide (2 mmol) in THF (30 mL), and then the mixture was heated at reflux for 3 h. After allowed to cool to room temperature, the reaction mixture was diluted with saturated brine (50 mL) and filtrated. The filtrate was extracted with THF, and the organic layer was dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue was triturated to provide a solid. Yield: 99%; yellow solid; mp 176–179°C. ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 9.72$ (s, 1H, CONH), 7.66–7.64 (m, 2H, ArH), 7.47–7.29 (m, 7H, ArH), 7.26 (s, 1H, ArH), 7.08–7.04 (m, 1H, ArH), 6.48 (s, 1H, ArH), 5.07 (s, 2H, $PhCH_2O$), 3.75 (s, 3H, OCH_3) ppm. MS (EI, *m*/*z*): 348 $[M]^+$.

Substituted quinazolin-4(3*H*)-ones 3: general procedure using one-pot continuous reaction. In a 50-mL reaction vial, the water (10 mL), iron powder (20 mmol) and concentrated HCl (three drops) were added to a solution of 2-nitro-4-benzyloxy-5-methoxy benzamide compound (**2**, 2 mmol) in THF (30 mL), and then the mixture was heated at reflux for 3 h. After allowed to cool to room temperature, the reaction mixture was diluted with saturated brine (50 mL) and filtrated. The filtrate was extracted with THF and dried over sodium sulfate, and then the *p*-toluene sulfuric acid and orthoesters (20 mmol) were added. The mixture was heated at reflux for 3 h, allowed to cool to room temperature, and concentrated. The residue was purified by column chromatography, eluting with (petroleum ether/EtOAc) to give pure product.

3-Phenyl-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3a). Yield: 98%; yellow solid; mp 178–181°C. IR (KBr): 3428, 2359, 1677 (C═O), 1608 (C═N), 1498, 1301, 1250, 869, 756 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.02$ (s, 1H, quinazolinone-2-H), 7.70 (s, 1H, quinazolinone-5-H), 7.57–7.48 (m, 5H, ArH), 7.42–7.31 (m, 5H, ArH), 7.20 (s, 1H, quinazolinone-8-H), 5.31 (s, 2H, $PhCH_2O$), 3.95 (s, 3H, OCH_3) ppm. MS (EI, *m*/*z*): 358 $[M]^+$. *Anal*. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.46; H, 5.29; N, 7.54.

3-(4-Methylphenyl)-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3b). Yield: 90%; yellow solid; mp 194–196°C. IR (KBr): 3477, 2955, 2359, 1674 (C═O), 1606 (C═N), 1501, 1245, 1144, 1057, 863, 746 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 8.19$ (s, 1H, quinazolinone-2-H), 7.52 (s, 1H, quinazolinone-5-H), 7.49 (d, $J = 6.9$ Hz, 2H, ArH), 7.43 (d, $J = 7.0$ Hz, 2H, ArH), 7.40–7.33 (m, 5H, ArH), 7.30 (s, 1H, quinazolinone-8-H), 5.30 (s, 2H, $PhCH_2O$), 3.90 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3) ppm. MS (EI, *m*/*z*): 372 $[M]^+$. *Anal*. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 73.87; H, 5.74; N, 7.22.

3-(3-Methylphenyl)-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3c). Yield: 86%; pale yellow solid; mp 156–159°C. IR (KBr): 3422, 2918, 1677 (C═O), 1608 (C═N), 1507, 1303, 1139, 1065, 869, 741, 699 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.01$ (s, 1H, quinazolinone-2-H), 7.70 (s, 1H, quinazolinone-5-H), 7.50–7.30 (m, 7H, ArH), 7.20 (s, 1H, quinazolinone-8-H), 7.18 (m, 2H, ArH), 5.30 (s, 2H, $PhCH_2O$), 4.01 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3) ppm. MS (EI, *m*/*z*): 372 $[M]^+$. *Anal*. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 73.98; H, 5.55; N, 7.52.

3-(2-Methylphenyl)-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3d). Yield: 72%; pale yellow solid; mp 198–199°C. IR (KBr): 3457, 2910, 1673 (C═O), 1609 (C═N), 1499, 1303, 1145, 868, 748 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.91$ (s, 1H, quinazolinone-2-H), 7.70 (s, 1H, quinazolinone-5-H), 7.51–7.48 (m, 2H, ArH), 7.42–7.34 (m, 5H, ArH), 7.24 (s, 1H, quinazolinone-8-H), 7.23–7.21 (m, 2H, ArH), 5.32 (s, 2H, $PhCH_2O$), 4.02 (s, 3H, OCH_3), 2.19 (s, 3H, CH_3) ppm. MS (EI, *m*/*z*): 372 $[M]^+$. *Anal*. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 73.81; H, 5.47; N, 7.39.

3-(2,4-Dimethylphenyl)-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3e). Yield: 79%; pale yellow solid; mp 99–102°C. IR (KBr): 3442, 2918, 2351, 1683 (C═O), 1608 (C═N), 1499, 1305, 1147, 1058, 876, 846, 757, 696 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 8.12$ (s, 1H, quinazolinone-2-H), 7.53 (s, 1H, quinazolinone-5-H), 7.52–7.23 (m, 8H, ArH), 7.19 (s, 1H, quinazolinone-8-H), 5.31 (s, 2H, $PhCH_2O$), 3.90 (s, 3H, OCH_3), 2.33 (s, 3H, CH_3), 2.03 (s, 3H, CH_3) ppm. MS (EI, *m*/*z*): 386 $[M]^+$. *Anal*. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.21; H, 5.84; N, 7.06.

3-(4-Chlorophenyl)-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3f). Yield: 89%; yellow solid; mp 240–241°C. IR (KBr):

3436, 2926, 2363, 1666 (C=O), 1607 (C=N), 1502, 1285, 1244, 735 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.00 (s, 1H, quinazolinone-2-H), 7.68 (s, 1H, quinazolinone-5-H), 7.53–7.48 (m, 4H, ArH), 7.42–7.35 (m, 5H, ArH), 7.21 (s, 1H, quinazolinone-8-H), 5.31 (s, 2H, $PhCH_2O$), 4.01 (s, 3H, OCH_3) ppm. MS (EI, *m/z*): 392/394 $[M]^+$. *Anal*. Calcd for $C_{22}H_{17}ClN_2O_3 \cdot 0.5H_2O$: C, 65.76; H, 4.51; N, 6.97. Found: C, 66.04; H, 4.39; N, 6.87.

3-(3-Chlorophenyl)-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3g). Yield: 90%; pale yellow solid; mp 221–223°C. IR (KBr): 3438, 3065, 1676 (C=O), 1609 (C=N), 1503, 1299, 1143, 867, 783, 735, 688 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.24 (s, 1H, quinazolinone-2-H), 7.70 (s, 1H, quinazolinone-5-H), 7.58–7.53 (m, 2H, ArH), 7.51–7.49 (m, 4H, ArH), 7.45–7.38 (m, 3H, ArH), 7.32 (s, 1H, quinazolinone-8-H), 5.31 (s, 2H, $PhCH_2O$), 3.90 (s, 3H, OCH_3) ppm. MS (EI, *m/z*): 392/394 $[M]^+$. *Anal*. Calcd for $C_{22}H_{17}ClN_2O_3$: C, 67.26; H, 4.36; N, 7.13. Found: C, 66.93; H, 4.59; N, 6.92.

3-(2-Chlorophenyl)-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3h). Yield: 85%; pale yellow solid; mp 176–179°C. IR (KBr): 3424, 2914, 1681 (C=O), 1608 (C=N), 1501, 1309, 1145, 1047, 758, 733 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.17 (s, 1H, quinazolinone-2-H), 7.75–7.71 (m, 1H, ArH), 7.69–7.66 (m, 1H, ArH), 7.61–7.52 (m, 4H, ArH), 7.50 (s, 1H, quinazolinone-5-H), 7.45–7.36 (m, 4H, ArH), 7.34 (s, 1H, quinazolinone-8-H), 5.32 (s, 2H, $PhCH_2O$), 3.91 (s, 3H, OCH_3) ppm. MS (EI, *m/z*): 392/394 $[M]^+$. *Anal*. Calcd for $C_{22}H_{17}ClN_2O_3 \cdot 0.5H_2O$: C, 65.76; H, 4.51; N, 6.97. Found: C, 65.85; H, 4.21; N, 6.80.

3-(4-Fluorophenyl)-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3i). Yield: 80%; pale yellow solid; mp 207–209°C. IR (KBr): 3420, 3066, 1677 (C=O), 1609 (C=N), 1497, 1310, 1144, 1057, 866, 845, 749, 699 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.21 (s, 1H, quinazolinone-2-H), 7.60–7.58 (m, 2H, ArH), 7.56 (s, 1H, quinazolinone-5-H), 7.55–7.49 (m, 2H, ArH), 7.45–7.36 (m, 5H, ArH), 7.31 (s, 1H, quinazolinone-8-H), 5.31 (s, 2H, $PhCH_2O$), 3.90 (s, 3H, OCH_3) ppm. MS (EI, *m/z*): 376 $[M]^+$. *Anal*. Calcd for $C_{22}H_{17}FN_2O_3 \cdot 0.2H_2O$: C, 69.54; H, 4.62; N, 7.37. Found: C, 69.60; H, 4.77; N, 6.99.

3-(4-Acetylphenyl)-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3j). Yield: 89%; pale yellow solid; mp 236–237°C. IR (KBr): 3439, 1681 (C=O), 1665 (C=O), 1607 (C=N), 1499, 1287, 1249, 1142, 1056, 865, 780, 696 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.1 Hz, 2H, ArH), 8.08 (s, 1H, quinazolinone-2-H), 7.69 (s, 1H, quinazolinone-5-H), 7.55 (d, *J* = 8.1 Hz, 2H, ArH), 7.51–7.48 (m, 2H, ArH), 7.43–7.35 (m, 3H, ArH), 7.26 (s, 1H, quinazolinone-8-H), 5.32 (s, 2H, $PhCH_2O$), 4.02 (s, 3H, OCH_3), 2.67 (s, 3H, CH_3) ppm. MS (EI, *m/z*): 400 $[M]^+$. *Anal.* Calcd for $C_{24}H_{20}N_2O_4$: C, 71.99; H, 5.03; N, 7.00. Found: C, 72.29; H, 5.18; N, 6.86.

3-(4-Hydroxyphenyl)-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3k). Yield: 39%; white solid; mp 243–244°C. IR (KBr): 3432, 3212, 2930, 1651 (C=O), 1609 (C=N), 1500, 1288, 1145, 1056, 865, 751 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.02 (s, 1H, quinazolinone-2-H), 7.70 (s, 1H, quinazolinone-5-H), 7.50–7.48 (m, 2H, ArH), 7.42–7.34 (m, 3H, ArH), 7.20 (d, *J* = 6.3 Hz, 2H, ArH), 7.16 (s, 1H, quinazolinone-8-H), 6.85 (d, *J* = 8.7 Hz, 2H, ArH), 6.42 (brs, 1H, PhOH), 5.31 (s, 2H, $PhCH_2O$), 3.99 (s, 3H, OCH_3) ppm. MS (EI, *m/z*): 374 $[M]^+$. *Anal*. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.26; H, 4.92; N, 7.36.

3-(4-Methoxyphenyl)-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3l). Yield: 80%; pale yellow solid; mp 190–191°C. IR (KBr): 3436, 3053, 2930, 2840, 1673 (C=O), 1611 (C=N), 1497, 1251, 1177, 1023, 864, 843, 749, 699 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.18 (s, 1H, quinazolinone-2-H), 7.53 (s, 1H, quinazolinone-5-H), 7.49 (d, *J* = 9.0 Hz, 2H, ArH), 7.47–7.36 (m, 5H, ArH), 7.30 (s, 1H, quinazolinone-8-H), 7.10 (d, *J* = 9.0 Hz, 2H, ArH), 5.30 (s, 2H, $PhCH_2O$), 3.90 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3) ppm. MS (EI, *m/z*): 388 $[M]^+$. *Anal*. Calcd for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 70.91; H, 5.25; N, 6.83.

3-(2,4-Difluorophenyl)-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3m). Yield: 80%; pale yellow solid; mp 155–156°C. IR (KBr): 3447, 3065, 1677 (C=O), 1607 (C=N), 1500, 1297, 1143, 1054, 867, 840, 752, 700 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.68 (s, 1H, quinazolinone-2-H), 7.50 (s, 1H, quinazolinone-5-H), 7.48–7.43 (m, 2H, ArH), 7.41–7.31 (m, 4H, ArH), 7.26 (s, 1H, quinazolinone-8-H), 7.07 (t, 2H, ArH), 5.31 (s, 2H, $PhCH_2O$), 4.01 (s, 3H, OCH_3) ppm. MS (EI, *m/z*): 394 $[M]^+$. *Anal*. Calcd for $C_{22}H_{16}F_2N_2O_3$: C, 67.00; H, 4.09; N, 7.10. Found: C, 66.92; H, 4.34; N, 6.99.

3-(2,4-Dichlorophenyl)-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3n). Yield: 84%; pale yellow solid; mp 84–87°C. IR (KBr): 3448, 3085, 2938, 1680 (C=O), 1607 (C=N), 1500, 1289, 1146, 1045, 867, 747, 698, 597 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.82 (s, 1H, quinazolinone-2-H), 7.69 (s, 1H, quinazolinone-5-H), 7.56–7.31 (m, 8H, ArH), 7.22 (s, 1H, quinazolinone-8-H), 5.31 (s, 2H, $PhCH_2O$), 4.01 (s, 3H, OCH_3) ppm. MS (EI, *m/z*): 427/429 $[M]^+$. *Anal*. Calcd for $C_{22}H_{16}Cl_2N_2O_3$: C, 61.84; H, 3.77; N, 6.56. Found: C, 61.42; H, 4.11; N, 6.18.

3-(2-Methyl-4-methoxycarbonylphenyl)-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3o). Yield: 92%; pale yellow solid; mp 209–210°C. IR (KBr): 3434, 2946, 1724 (C=O), 1678 (C=O), 1606 (C=N), 1500, 1297, 1267, 1193, 1150, 750 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.09 (s, 1H, quinazolinone-2-H), 8.03 (d, *J* = 8.2 Hz, 1H, ArH), 7.87 (s, 1H, ArH), 7.69 (s, 1H, quinazolinone-5-H), 7.51–7.48 (m, 2H, ArH), 7.43–7.31 (m, 4H, ArH), 7.23 (s, 1H, quinazolinone-8-H), 5.32 (s, 2H, $PhCH_2O$), 4.02 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3) ppm. MS (EI, *m/z*): 430 $[M]^+$. *Anal.* Calcd for $C_{25}H_{22}N_2O_5$: C, 69.76; H, 5.15; N, 6.51. Found: C, 69.36; H, 5.22; N, 6.15.

3-Cyclohexyl-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3p). Yield: 86%; yellow solid; mp 194–196°C. IR (KBr): 3441, 2934, 1655 (C=O), 1607 (C=N), 1505, 1287, 1104, 1001, 866, 784, 757, 738, 704 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.04 (s, 1H, quinazolinone-2-H), 7.64 (s, 1H, quinazolinone-5-H), 7.48–7.46 (m, 2H, ArH), 7.41–7.29 (m, 3H, ArH), 7.15 (s, 1H, quinazolinone-8-H), 5.28 (s, 2H, $PhCH_2O$), 4.81 (m, 1H, cyclohexyl), 4.01 (s, 3H, OCH_3), 2.02–1.92 (m, 4H, cyclohexyl), 1.81–1.77 (m, 1H, cyclohexyl), 1.69–1.50 (m, 4H, cyclohexyl), 1.28–1.24 (m, 1H, cyclohexyl) ppm. MS (EI, *m/z*): 364 $[M]^+$. *Anal*. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.12; H, 6.92; N, 7.55.

3-Benzyl-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3q). Yield: 86%; pale yellow solid; mp 154–157°C. IR (KBr): 3444, 2930, 1663 (C=O), 1606 (C=N), 1501, 1219, 1193, 1013, 867, 745, 699 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.04 (s, 1H, quinazolinone-2-H), 7.66 (s, 1H, quinazolinone-5-H), 7.48–7.45 (m, 2H, ArH), 7.40–7.31 (m, 8H, ArH), 7.15 (s, 1H, quinazolinone-8-H), 5.27 (s, 2H, $PhCH_2O$), 5.19 (s, 2H, $PhCH_2N$), 3.99 (s, 3H, OCH_3) ppm. MS (EI, *m/z*): 372 $[M]^+$. *Anal*. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 73.91; H, 5.41; N, 7.15.

2-Methyl-3-(4-fluorophenyl)-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3r). Yield: 84%; pale yellow solid; mp 197–198°C. IR (KBr): 3433, 3077, 1687 (C═O), 1608 (C═N), 1499, 1391, 1282, 1027, 855, 756, 700, 593 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.58 (s, 1H, quinazolinone-5-H), 7.50–7.42 (m, 2H, ArH), 7.40–7.31 (m, 3H, ArH), 7.24 (s, 1H, quinazolinone-8-H), 7.24–7.00 (m, 4H, ArH), 5.30 (s, 2H, $PhCH_2O$), 4.01 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3) ppm. MS (EI, *m/z*): 390 $[M]^+$. *Anal*. Calcd for $C_{23}H_{19}FN_2O_3$: C, 70.76; H, 4.91; N, 7.18. Found: C, 70.46; H, 5.08; N, 6.97.

2-Methyl-3-(4-methoxyphenyl)-6-methoxy-7-benzyloxyquinazolin-4(3*H*)-one (3s). Yield: 87%; white solid; mp 162–163°C. IR (KBr): 3432, 3057, 2930, 2828, 1688 (C═O), 1609 (C═N), 1499, 1392, 1247, 1026, 841, 752, 740, 567 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.60 (s, 1H, quinazolinone-5-H), 7.49–7.42 (m, 2H, ArH), 7.40–7.31 (m, 3H, ArH), 7.17 (d, *J* = 8.8 Hz, 2H, ArH), 7.14 (s, 1H, quinazolinone-8-H), 7.06 (d, *J* = 8.8 Hz, 2H, ArH), 5.29 (s, 2H, $PhCH_2O$), 3.98 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 2.22 (s, 3H, CH_3) ppm. MS (EI, *m/z*): 402 $[M]^+$. *Anal*. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.59; H, 5.65; N, 6.91.

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