Synthesis R. P. Pandit et al. Paper

Mild and Efficient Silver(I) Triflate Catalyzed Synthesis of 2-Aryl-2,3-dihydroquinolin-4(1*H*)-ones, and Their Antioxidant Activities

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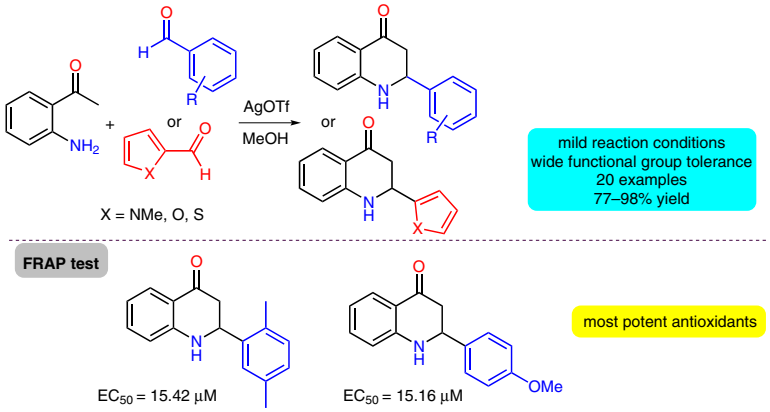


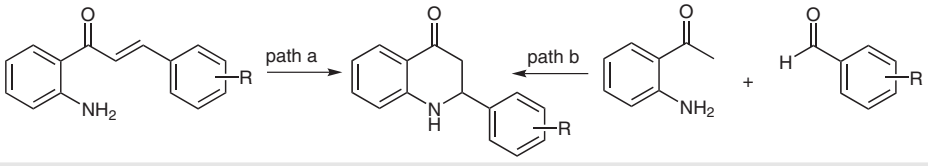
Received: 04.08.2015
Accepted after revision: 31.08.2015
Published online: 30.09.2015
DOI: 10.1055/s-0035-1560322; Art ID: ss-2015-f0468-op

Abstract Biologically interesting 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones were synthesized using a mild and efficient one-pot procedure starting from *o*-aminoacetophenones and aromatic aldehydes in the presence of silver(I) triflate. This synthetic protocol provides rapid access to a variety of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones. This technique has several advantages, such as the use of easily available starting materials, the efficiency of the catalyst, a simple operation, and tolerance of a wide range of functionality in the aldehydes. Screening of the synthesized compounds for their antioxidant properties revealed that two compounds (with EC_{50} = 15.42 μM and 15.16 μM) exhibit a potent free-radical scavenging ability towards TEAC free radicals compared to the standard, Trolox.

Key words *o*-aminoacetophenones, aldehydes, silver(I) triflate, condensation, quinolinones, antioxidants

Aza analogues of flavonoids are an important class of heterocycles that display a range of potent biological properties, such as antibacterial, antitumor, antifungal, anti-inflammatory, anthelmintic, antibiotic, and antihypertensive activities.[1,2] Among them, molecules bearing a dihydroquinolin-4(1*H*)-one moiety have been used as building blocks in the synthesis of medically important compounds[3] and natural products.[4–6] A number of synthetic approaches for the construction of 2,3-dihydroquinolin-4(1*H*)-ones based on intra- and intermolecular cyclization reactions have been developed.[7–25] Representative intramolecular approaches for 2,3-dihydroquinolin-4(1*H*)-ones include the cyclization of 2-aminochalcones under a range of reaction conditions, such as antimony(III) chloride,[7,8] ytterbium(III) triflate,[9] indium(III) chloride,[10] zinc chloride,[11] phosphorous acid,[12] phosphomolybdic acid–silica gel,[13] silica gel supported sodium bisulfite,[14] silica gel supported tantalum(V) bromide,[15] silica chloride with microwave irradiation,[16] PEG-400,[17] montmorillonite,[18] alumina-supported cerium(III) chloride heptahydrate–sodium iodide,[19] piperidine with potassium hydroxide,[20] sodium ethoxide,[21] and ionic liquids[22] (Scheme 1, path a). Several intermolecular approaches have also been reported for 2,3-dihydroquinolin-4(1*H*)-ones, which include the condensation of *o*-aminoacetophenones and aryl aldehydes in the presence of L-proline,[23] per-6-amino-β-cyclodextrin,[24] and amino acid derived sulfonamides[25] as organocatalysts (Scheme 1, path b).

Despite their merits, many of the methods reported thus far suffer from long reaction times, low yields, the need for expensive catalysts, and harsh reaction conditions. Therefore, more efficient and general methods are needed to overcome these limitations, which prompted this study into the development of a new approach using silver(I) triflate (AgOTf) as a mild and efficient catalyst. Recently, AgOTf has been widely used as a potential Lewis acid catalyst.[26] In this context, the use of AgOTf has attracted consid-



Scheme 1 General methods for the preparation of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones

Scheme 2 AgOTf-catalyzed synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones

erable attention because of its easy availability and ease of handling, and the enhanced reaction rates in organic reactions.[27]

This paper reports the synthesis of a variety of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones starting from commercially available *o*-aminoacetophenones and aryl aldehydes, using AgOTf as a mild and efficient catalyst (Scheme 2). In addition, we also report the antioxidant activities of the synthesized 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones. To the best of our knowledge, the antioxidant properties of these synthetic compounds have not been previously investigated.

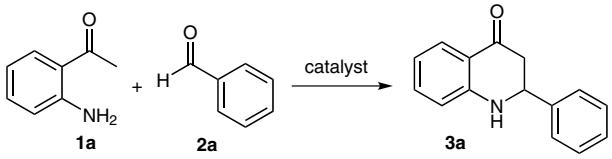
In order to identify the optimal reaction conditions, cyclization of *o*-aminoacetophenone (**1a**, 1.0 mmol) with benzaldehyde (**2a**, 1.2 mmol) was first examined in the presence of several silver catalysts and various solvents (Table 1). The reaction of **1a** with **2a** using silver(II) oxide (20 mol%) or silver(I) oxide (20 mol%) in refluxing methanol for 24 hours gave none of the desired product (Table 1, entries 1 and 2). With silver carbonate (20 mol%) and silver nitrate (20 mol%), product **3a** was produced in 51% and 72% yield, respectively (Table 1, entries 3 and 4). Importantly, the treatment of **1a** and **2a** in the presence of AgOTf in refluxing methanol for 24 hours provided **3a** in the best yield (88%; Table 1, entry 6). With other solvents (EtOH, toluene, DMF), the yield of **3a** was lower than that with methanol. When 20 mol% of copper(II) triflate as another catalyst was used, **3a** was produced in low yield (21%; Table 1, entry 10). The structure of **3a** was confirmed by an analysis of the spectroscopic data and by a comparison with the literature values.[28]

To explore the generality and scope of this methodology, additional reactions between *o*-aminoacetophenone (**1a**) and different aryl aldehydes **2b**–**m** were carried out under the optimized conditions (Table 2, entries 1–12). The reactions between **1a** and aryl aldehydes **2b**–**f** bearing electron-donating groups, such as methyl or methoxy groups, on the benzene ring in refluxing methanol for 12 hours produced **3b**–**f** in 86–98% yield. When aryl aldehydes **2g**–**k** bearing an electron-withdrawing group, such as a fluoro, chloro, bromo, or nitro group, on the benzene ring were used, the desired products **3g**–**k** were produced in 80–87% yield after longer reaction times (18–24 h). With 1-naphthaldehyde (**2l**) and 2-naphthaldehyde (**2m**), the desired products **3l** and **3m** were also formed, in 84% and 87% yield, respectively.

To further demonstrate the versatility of this protocol, additional reactions with several substituted *o*-aminoacetophenones bearing an additional electron-donating or electron-withdrawing group on the benzene ring were next explored (Table 2, entries 13–16). Reaction of **1b** or **1c** bearing an electron-donating group (4-Me and 3-OMe) with benzaldehyde (**2a**) provided the desired products **3n** (85%) and **3o** (77%), respectively, whereas those of **1d** or **1e** bearing an electron-withdrawing group (5-Cl and 5-Br) with **2a** gave compounds **3p** and **3q** in 92% and 90% yield, respectively. These reactions provided a rapid route to the preparation of a variety of 2-aryl-2,3-dihydroquinolin-4(*H*)-ones in a one-pot procedure.

Next, control experiments to identify the potential intermediate that allows the cyclization to product **3a** were carried out (Scheme 3). For example, the reaction of *o*-aminoacetophenone (**1a**) and benzaldehyde (**2a**) in the pres-

Table 1 Effect of Catalyst and Solvent in the Synthesis of **3a**[a]



Entry	Catalyst (mol%)	Conditions	Yield[b] (%)
1	AgO (20 mol%)	MeOH, reflux, 24 h	0
2	Ag_2O (20 mol%)	MeOH, reflux, 24 h	0
3	Ag_2CO_3 (20 mol%)	MeOH, reflux, 24 h	51
4	$AgNO_3$ (20 mol%)	MeOH, reflux, 24 h	72
5	AgOTf (20 mol%)	MeOH, reflux, 24 h	79
6	AgOTf (10 mol%)	MeOH, reflux, 24 h	88
7	AgOTf (10 mol%)	EtOH, reflux, 24 h	73
8	AgOTf (10 mol%)	toluene, reflux, 12 h	37
9	AgOTf (10 mol%)	DMF, 100 °C, 24 h	12
10	$Cu(OTf)_2$ (20 mol%)	MeOH, reflux, 24 h	21

[a] Reaction conditions: *o*-aminoacetophenone (1.0 mmol), benzaldehyde (1.2 mmol), solvent (5.0 mL).
[b] Isolated yield.

ence of silver catalyst in refluxing methanol for 3 hours provided products **3a** (8%) and **4a** (13%), together with the recovered starting material **1a** (77%). Importantly, treatment of **4a** with 10 mol% of silver catalyst in refluxing methanol for 20 hours afforded the desired product **3a** in 91% yield. The observation of intermediate **4a** shows that the cycloaddition for the product **3a** proceeds through an aldol reaction.

Table 2 Additional Syntheses of a Variety of 2-Aryl-2,3-dihydroquinolin-4(1*H*)-ones

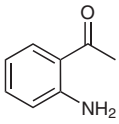
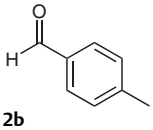
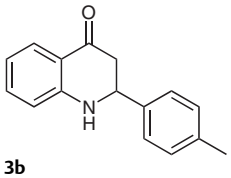
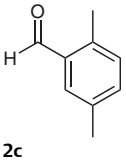
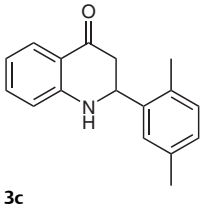
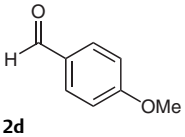
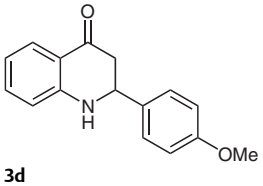
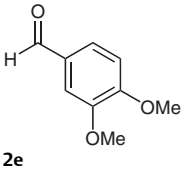
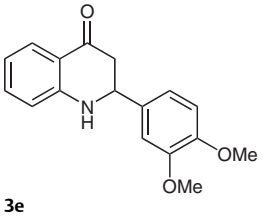
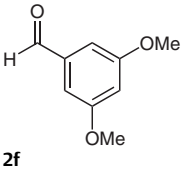
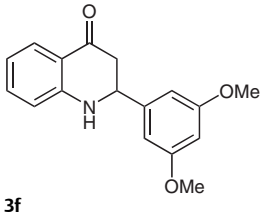
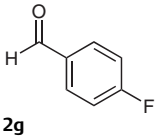
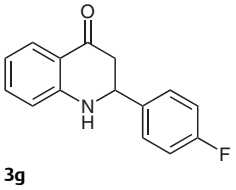
Entry	*o*-Aminoacetophenone	Aryl aldehyde	Time (h)	Product	Yield (%)
1	 **1a**	 **2b**	12	 **3b**	86
2	**1a**	 **2c**	12	 **3c**	90
3	**1a**	 **2d**	12	 **3d**	95
4	**1a**	 **2e**	12	 **3e**	98
5	**1a**	 **2f**	12	 **3f**	98
6	**1a**	 **2g**	18	 **3g**	85

Table 2 (continued)

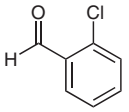
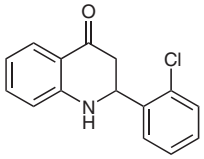
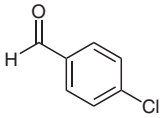
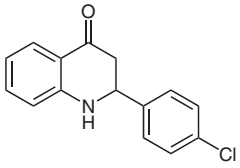
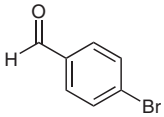
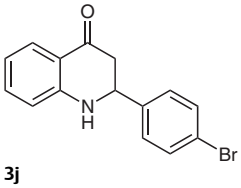
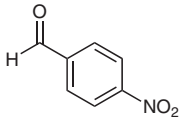
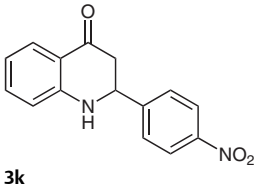
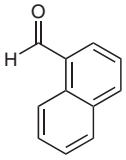
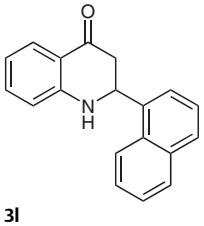
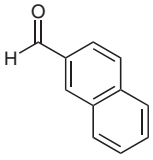
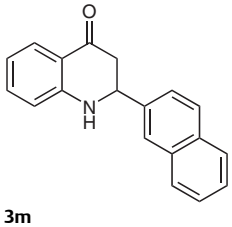
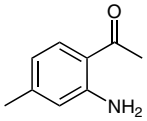
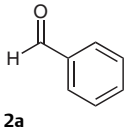
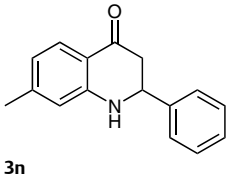
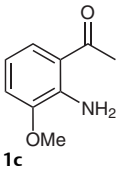
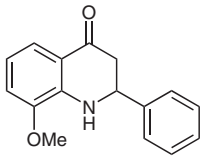
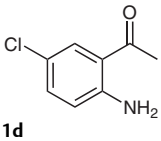
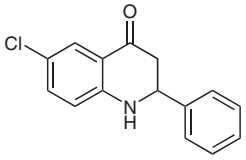
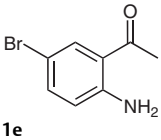
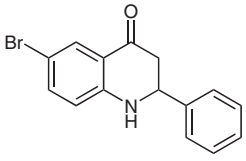
Entry	*o*-Aminoacetophenone	Aryl aldehyde	Time (h)	Product	Yield (%)
7	**1a**	 **2h**	18	 **3h**	87
8	**1a**	 **2i**	18	 **3i**	84
9	**1a**	 **2j**	18	 **3j**	81
10	**1a**	 **2k**	24	 **3k**	80
11	**1a**	 **2l**	20	 **3l**	84
12	**1a**	 **2m**	20	 **3m**	87
13	 **1b**	 **2a**	18	 **3n**	85

Table 2 (continued)

Entry	*o*-Aminoacetophenone	Aryl aldehyde	Time (h)	Product	Yield (%)
14	 **1c**	**2a**	24	 **3o**	77
15	 **1d**	**2a**	12	 **3p**	92
16	 **1e**	**2a**	12	 **3q**	90

Based on the results of the control experiments, the formation of **3a** can be explained by the mechanism shown in Scheme 4. In the presence of AgOTf catalyst, benzaldehyde (**2a**) initially forms an activated complex **2a′**, which is attacked by enolizable **1a** to afford the intermediate **4a** through the protonation of aldol adduct **4** with methanol or a proton (path a). The AgOTf-catalyzed elimination of water from **4a** produces another intermediate **5**, which undergoes intramolecular cyclization to yield final product **3a** via **5a**. Although intermediate **4a** was isolated, it may be possible to proceed through another mechanistic pathway, via tautomerization of **4** followed by E1cB reaction of **4b** to give **5** (path b).

To explore the applications of this methodology, further reactions with heteroaryl aldehydes for the synthesis of dihydroquinolin-4(1*H*)-ones bearing heteroaromatics were attempted (Scheme 5). Reaction of **1a** with *N*-methylpyrrole-2-carboxaldehyde in the presence of 10 mol% of AgOTf in refluxing methanol for 20 hours provided the desired

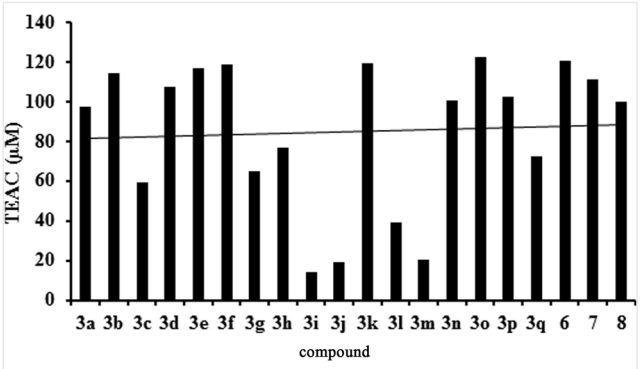
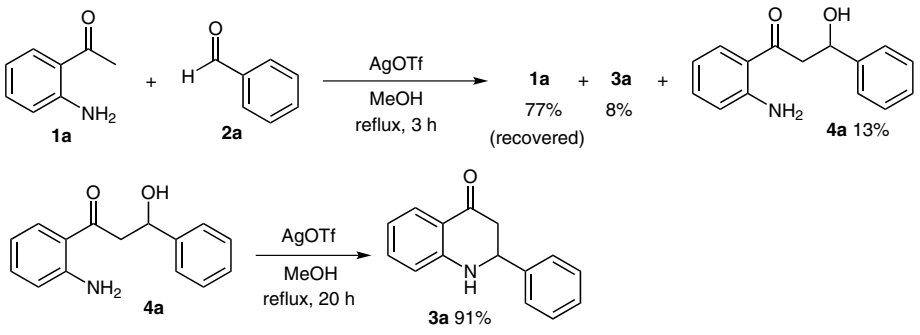
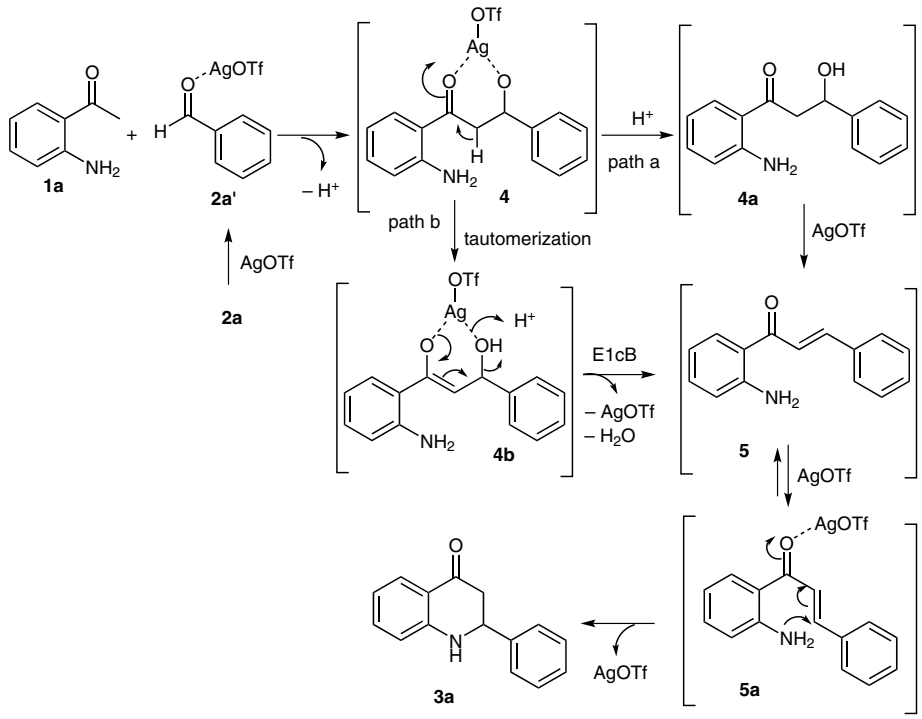


Figure 1 FRAP test results of the synthesized compounds **3a–q** and **6–8** as TEAC values



Scheme 3 Control experiments

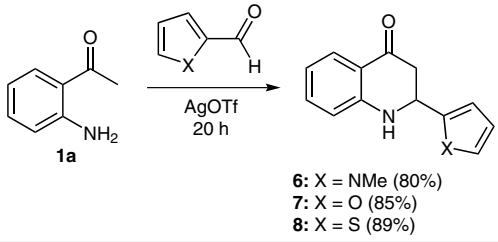


Scheme 4 Proposed mechanism for the formation of **3a**

product **6** in 80% yield, whereas treatment with furan-2-carboxaldehyde and thiofuran-2-carboxaldehyde for 20 hours afforded **7** and **8** in 85% and 89% yield, respectively.

The antioxidant activity of organic compounds seems to be related to their molecular structure, more precisely to the presence of hydroxy groups, double bond conjugation, and resonance effects.[29] The synthesized 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones contain C=O and NH groups, and aromatic substitution at C2. Results of FRAP (ferric reducing antioxidant power) assays are given in Figure 1 as TEAC (Trolox equivalent antioxidant capacity) values, which were obtained from the calibration graph prepared with Trolox. The Trolox concentration giving the same absorbance values as the test sample and the higher value of TEAC means higher antioxidant capacity. All the compounds were active in the FRAP test and the EC_{50} values are presented in Figure 2. The starting material *o*-aminoacetophenone showed slightly lower activity as compared to the synthesized compounds.

The regression line drawn with Microsoft Excel for synthesized compounds **3a**–**q** and **6**–**8** is in agreement with the FRAP test results. The haloaryl derivatives **3i** and **3j** and naphthyl-substituted 2,3-dihydroquinolin-4(1*H*)-ones **3l** and **3m** exhibited lower activity as compared to aryl- and heteroaryl-substituted 2,3-dihydroquinolin-4(1*H*)-ones **3a**–**h**,**k**,**n**–**q**, and **6**–**8**. The antioxidant activities of the compounds are well correlated with their EC_{50} values.



Scheme 5 Synthesis of dihydroquinolin-4(1*H*)-ones bearing heteroaromatics

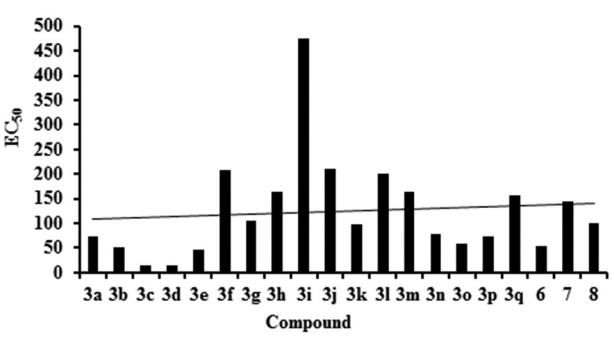


Figure 2 EC_{50} (μg/mL) values of the synthesized compounds **3a**–**q** and **6**–**8**

In conclusion, a novel and efficient methodology was developed for the synthesis of a variety of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones by the silver(I) triflate catalyzed reaction of *o*-aminoacetophenones with aryl aldehydes. The advantage of this protocol over existing methods lies in the simplicity of the procedure, milder reaction conditions, easily available catalyst, and improved substrate scope, as well as eliminating the need for preparation of any chalcones. Compounds **3c** and **3d** (with EC_{50} = 15.42 μM and 15.16 μM, respectively) showed potent antioxidant activities towards TEAC free radicals compared to the standard, Trolox. These bioactive compounds can potentially be utilized as antioxidants in the future.

All experiments were carried out under a nitrogen atmosphere. Merck silica gel plates (Art. 5554) precoated with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using Merck silica gel 9385. Melting points are uncorrected and were determined on a Fisher-Johns melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian VNS spectrometer (600 and 150 MHz, or 300 and 75 MHz, respectively), using δ = 7.24 and 77.0 ppm as the solvent chemical shift. Multiplicities are abbreviated as s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, and dt = doublet of triplets. IR spectra were recorded on a Bio-Rad FTIR or PerkinElmer Spectrum 2 ATR spectrophotometer. HRMS was carried out at the Korea Basic Science Institute.

2-Aryl-2,3-dihydroquinolin-4(1*H*)-ones 3 and 6–8; General Procedure

AgOTf (26 mg, 10 mol%) was added to a solution of an *o*-aminoacetophenone (1.0 mmol) and an aryl aldehyde (1.2 mmol) in MeOH (5 mL) at r.t. The reaction mixture was stirred under reflux for 12–24 h. After the reaction was complete, as indicated by TLC, the excess solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (hexanes–EtOAc, 20:1) to yield the desired product.

2-Phenyl-2,3-dihydroquinolin-4(1*H*)-one (3a)

Off-white solid; yield: 196 mg (88%); mp 155–157 °C.

IR (KBr): 3321, 2978, 1666, 1591, 1233 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.83 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.42 (d, *J* = 7.2 Hz, 2 H), 7.38–7.35 (m, 2 H), 7.33–7.30 (m, 2 H), 6.75 (t, *J* = 7.2 Hz, 1 H), 6.70 (d, *J* = 8.4 Hz, 1 H), 4.69 (dd, *J* = 13.8, 3.6 Hz, 1 H), 4.64 (s, 1 H, NH), 2.82 (dd, *J* = 16.2, 14.4 Hz, 1 H), 2.70 (dd, *J* = 16.8, 3.6 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 193.2, 151.5, 140.9, 135.3, 128.8, 128.3, 127.4, 126.5, 118.8, 118.2, 115.8, 58.3, 46.2.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{15}H_{13}NO$: 223.0997; found: 223.0994.

2-(*p*-Tolyl)-2,3-dihydroquinolin-4(1*H*)-one (3b)

Pale yellow solid; yield: 203 mg (86%); mp 145–147 °C.

IR (KBr): 3340, 2965, 1660, 1555, 1230, 910 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.8 Hz, 1 H), 7.33–7.28 (m, 3 H), 7.21–7.15 (m, 2 H), 6.76 (t, *J* = 7.5 Hz, 1 H), 6.67 (d, *J* = 8.4 Hz, 1 H), 4.69 (dd, *J* = 13.8, 3.6 Hz, 1 H), 4.44 (s, 1 H, NH), 2.91–2.71 (m, 2 H), 2.35 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.6, 151.8, 138.3, 138.1, 135.5, 129.7, 129.6, 127.7, 126.6, 119.1, 118.4, 116.0, 58.3, 46.6, 21.3.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{16}H_{15}NO$: 237.1154; found: 237.1154.

2-(2,5-Dimethylphenyl)-2,3-dihydroquinolin-4(1*H*)-one (3c)

Yellow solid; yield: 225 mg (90%); mp 95–97 °C.

IR (KBr): 3311, 2927, 1602, 1492, 1315, 1244, 752 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.87 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.46 (s, 1 H), 7.32 (td, *J* = 8.4, 1.2 Hz, 1 H), 7.07–7.03 (m, 2 H), 6.77 (t, *J* = 7.2 Hz, 1 H), 6.70 (d, *J* = 8.4 Hz, 1 H), 4.97 (dd, *J* = 14.4, 3.6 Hz, 1 H), 4.37 (s, 1 H, NH), 2.78 (dd, *J* = 16.8, 14.4 Hz, 1 H), 2.72–2.69 (m, 1 H), 2.36 (s, 3 H), 2.30 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.6, 152.2, 138.9, 136.3, 135.4, 131.9, 130.9, 128.8, 127.7, 126.6, 119.0, 118.4, 116.1, 54.6, 45.4, 21.2, 18.7.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{17}NO$: 251.1310; found: 251.1308.

2-(4-Methoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one (3d)

Brown solid; yield: 240 mg (95%); mp 145–147 °C.

IR (KBr): 3330, 2978, 1663, 1585, 1305, 1224 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 7.8, 1.5 Hz, 1 H), 7.37–7.33 (m, 2 H), 7.31–7.28 (m, 1 H), 6.93–6.88 (m, 2 H), 6.79–6.74 (m, 1 H), 6.68 (d, *J* = 8.1 Hz, 1 H), 4.68 (dd, *J* = 13.5, 3.6 Hz, 1 H), 4.41 (s, 1 H, NH), 3.80 (s, 3 H), 2.90–2.69 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.5, 159.8, 151.8, 135.5, 133.2, 127.9, 127.7, 119.1, 118.4, 116.0, 114.1, 58.0, 55.5, 46.6.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{16}H_{15}NO_2$: 253.1103; found: 253.1102.

2-(3,4-Dimethoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one (3e)

Off-white semisolid; yield: 277 mg (98%).

IR (neat): 3329, 2971, 1665, 1594, 1313, 1235 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 7.8, 0.9 Hz, 1 H), 7.35–7.29 (m, 1 H), 6.98–6.94 (m, 2 H), 6.85 (d, *J* = 8.1 Hz, 1 H), 6.79–6.75 (m, 1 H), 6.69 (d, *J* = 8.1 Hz, 1 H), 4.67 (dd, *J* = 13.8, 3.9 Hz, 1 H), 4.47 (s, 1 H, NH), 3.88 (s, 3 H), 3.87 (s, 3 H), 2.91–2.70 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.6, 151.7, 149.3, 149.0, 135.5, 133.6, 127.6, 119.0, 118.5, 116.1, 111.3, 109.4, 58.4, 56.1, 56.0, 46.8.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{17}NO_3$: 283.1208; found: 283.1209.

2-(3,5-Dimethoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one (3f)

Off-white semisolid; yield: 277 mg (98%).

IR (neat): 3335, 2839, 1674, 1602, 1320, 1138, 752 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.83 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.31 (td, *J* = 9.0, 1.8 Hz, 1 H), 6.76 (t, *J* = 6.6 Hz, 1 H), 6.70 (d, *J* = 8.4 Hz, 1 H), 6.57 (d, *J* = 2.4 Hz, 2 H), 6.39 (t, *J* = 2.4 Hz, 1 H), 4.63 (dd, *J* = 13.8, 3.6 Hz, 1 H), 4.57 (s, 1 H, NH), 3.77 (s, 6 H), 2.82 (dd, *J* = 15.6, 13.2 Hz, 1 H), 2.73 (dd, *J* = 16.2, 3.6 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 193.2, 161.1, 151.4, 143.4, 135.3, 127.5, 118.9, 118.4, 115.9, 104.4, 99.9, 58.5, 55.3, 46.3.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{17}NO_3$: 283.1208; found: 283.1210.

2-(4-Fluorophenyl)-2,3-dihydroquinolin-4(1*H*)-one (3g)

Off-white solid; yield: 204 mg (85%); mp 135–137 °C.

IR (KBr): 3339, 2966, 1662, 1553, 1228, 911 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.83 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.42–7.39 (m, 2 H), 7.32 (dd, *J* = 7.2, 1.8 Hz, 1 H), 7.07–7.03 (m, 2 H), 6.77 (t, *J* = 7.8 Hz, 1 H), 6.72 (d, *J* = 8.4 Hz, 1 H), 4.70 (dd, *J* = 13.8, 3.6 Hz, 1 H), 4.54 (s, 1 H, NH), 2.80 (dd, *J* = 15.6, 13.2 Hz, 1 H), 2.71 (dd, *J* = 16.8, 3.6 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 192.9, 162.5 (J_{C-F} = 246.0 Hz), 151.3, 136.7, 135.4, 128.3 (J_{C-F} = 8.1 Hz), 127.5, 119.0, 118.6, 115.9 (J_{C-F} = 5.8 Hz), 115.7, 57.8, 46.4.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{15}H_{12}FNO$: 241.0903; found: 241.0902.

2-(2-Chlorophenyl)-2,3-dihydroquinolin-4(1*H*)-one (3h)

Yellow solid; yield: 223 mg (87%); mp 146–147 °C.

IR (KBr): 3340, 2970, 1664, 1586, 1222, 758 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.86 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.65 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.38 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.34–7.31 (m, 1 H), 7.29 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.27–7.24 (m, 1 H), 6.79 (t, *J* = 7.2 Hz, 1 H), 6.72 (d, *J* = 7.8 Hz, 1 H), 5.24 (dd, *J* = 13.2, 4.2 Hz, 1 H), 4.51 (s, 1 H, NH), 2.93 (dd, *J* = 16.2, 4.2 Hz, 1 H), 2.75 (dd, *J* = 16.2, 12.0 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 192.7, 151.4, 138.2, 135.4, 132.7, 130.0, 129.3, 127.6, 127.5, 127.4, 119.1, 118.6, 116.0, 54.2, 44.0.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{15}H_{12}ClNO$: 257.0607; found: 257.0604.

2-(4-Chlorophenyl)-2,3-dihydroquinolin-4(1*H*)-one (3i)

Orange solid; yield: 215 mg (84%); mp 168–170 °C.

IR (KBr): 3343, 2971, 1666, 1585, 1221, 750 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.83 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.38–7.31 (m, 5 H), 6.78 (t, *J* = 7.2 Hz, 1 H), 6.71 (d, *J* = 7.8 Hz, 1 H), 4.69 (dd, *J* = 13.8, 4.2 Hz, 1 H), 4.54 (s, 1 H, NH), 2.79 (dd, *J* = 16.8, 13.8 Hz, 1 H), 2.71 (dd, *J* = 16.8, 4.2 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 192.8, 151.3, 139.5, 135.4, 134.1, 129.1, 127.9, 127.5, 119.0, 118.6, 115.9, 57.8, 46.3.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{15}H_{12}ClNO$: 257.0607; found: 257.0605.

2-(4-Bromophenyl)-2,3-dihydroquinolin-4(1*H*)-one (3j)

Brown solid; yield: 244 mg (81%); mp 165–167 °C.

IR (KBr): 3324, 3053, 1654, 1492, 1325, 754 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 7.8, 1.5 Hz, 1 H), 7.53–7.48 (m, 2 H), 7.36–7.30 (m, 3 H), 6.81–6.76 (m, 1 H), 6.70 (d, *J* = 8.2 Hz, 1 H), 4.71 (dd, *J* = 17.4, 4.8 Hz, 1 H), 4.44 (s, 1 H, NH), 2.87–2.77 (m, 1 H), 2.77–2.70 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.9, 151.5, 140.3, 135.6, 132.3, 128.5, 127.7, 122.4, 119.2, 118.8, 116.1, 58.1, 46.5.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{15}H_{12}BrNO$: 301.0102; found: 301.0102.

2-(4-Nitrophenyl)-2,3-dihydroquinolin-4(1*H*)-one (3k)

Pale yellow solid; yield: 214 mg (80%); mp 198–200 °C.

IR (KBr): 3357, 2911, 1670, 1466, 1187, 761 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.4 Hz, 2 H), 7.86 (d, *J* = 8.1 Hz, 1 H), 7.63 (d, *J* = 8.1 Hz, 2 H), 7.38–7.33 (m, 1 H), 6.84 (m, 1 H), 6.75 (d, *J* = 8.1 Hz, 1 H), 4.90–4.84 (m, 1 H), 4.55 (s, 1 H, NH), 2.82–2.79 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.0, 151.1, 148.4, 135.9, 127.8, 127.7, 124.5, 119.3, 116.2, 58.1, 46.3.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{15}H_{12}N_2O_3$: 268.0848; found: 268.0846.

2-(Naphthalen-1-yl)-2,3-dihydroquinolin-4(1*H*)-one (3l)

Yellow solid; yield: 230 mg (84%); mp 176–177 °C.

IR (KBr): 3332, 3056, 1647, 1490, 1318, 765, 630 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.12–8.09 (m, 1 H), 7.93–7.88 (m, 2 H), 7.83 (d, *J* = 8.1 Hz, 1 H), 7.78 (d, *J* = 7.2 Hz, 1 H), 7.56–7.47 (m, 3 H), 7.38–7.32 (m, 1 H), 6.83–6.78 (m, 1 H), 6.75 (d, *J* = 8.1 Hz, 1 H), 5.56 (dd, *J* = 11.4, 6.0 Hz, 1 H), 4.60 (s, 1 H, NH), 3.08–2.91 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.5, 152.0, 136.6, 134.2, 130.5, 129.4, 129.0, 127.9, 126.8, 126.2, 125.7, 123.9, 122.5, 119.3, 118.7, 116.3, 54.6, 45.5.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{19}H_{15}NO$: 273.1154; found: 273.1154.

2-(Naphthalen-2-yl)-2,3-dihydroquinolin-4(1*H*)-one (3m)

Pale yellow solid; yield: 238 mg (87%); mp 160–162 °C.

IR (KBr): 3333, 3053, 1654, 1492, 1325, 754 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.89–7.82 (m, 5 H), 7.56 (d, *J* = 8.7 Hz, 1 H), 7.53–7.47 (m, 2 H), 7.37–7.32 (m, 1 H), 6.82–6.77 (m, 1 H), 6.73 (d, *J* = 8.4 Hz, 1 H), 4.90 (dd, *J* = 13.5, 3.6 Hz, 1 H), 4.60 (s, 1 H, NH), 3.02–2.91 (m, 1 H), 2.86–2.79 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.6, 151.9, 138.6, 135.8, 133.6, 133.5, 129.2, 128.2, 128.1, 127.9, 126.8, 126.7, 125.9, 124.6, 119.3, 118.8, 116.3, 58.9, 46.7.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{19}H_{15}NO$: 273.1154; found: 273.1151.

7-Methyl-2-phenyl-2,3-dihydroquinolin-4(1*H*)-one (3n)

Yellow solid; yield: 201 mg (85%); mp 140–142 °C.

IR (ATR): 3337, 2840, 1609, 1464, 1302, 624 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.1 Hz, 1 H), 7.42–7.29 (m, 5 H), 6.58 (d, *J* = 8.1 Hz, 1 H), 6.50 (s, 1 H), 4.67 (dd, *J* = 13.2, 3.9 Hz, 1 H), 4.42 (s, 1 H, NH), 2.79 (dd, *J* = 16.2, 15.0 Hz, 1 H), 2.71–2.64 (m, 1 H), 2.27 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.8, 151.6, 146.8, 141.1, 128.8, 128.2, 127.4, 126.5, 119.9, 116.8, 115.8, 58.3, 46.3, 21.8.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{15}NO$: 237.1154; found: 237.1152.

8-Methoxy-2-phenyl-2,3-dihydroquinolin-4(1*H*)-one (3o)

Yellow solid; yield: 195 mg (77%); mp 151–153 °C.

IR (ATR): 3373, 2924, 1674, 1486, 1231, 1030, 616 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.49–7.46 (m, 3 H), 7.39 (t, *J* = 6.6 Hz, 2 H), 7.34 (t, *J* = 6.0 Hz, 1 H), 6.87 (d, *J* = 7.8 Hz, 1 H), 6.70 (t, *J* = 7.2 Hz, 1 H), 5.07 (s, 1 H, NH), 4.71 (dd, *J* = 13.8, 4.2 Hz, 1 H), 3.84 (s, 3 H), 2.88 (dd, *J* = 16.2, 14.4 Hz, 1 H), 2.76 (dd, *J* = 16.2, 3.6 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 193.2, 147.0, 142.6, 141.1, 128.9, 128.3, 126.6, 118.9, 118.7, 116.9, 113.8, 58.4, 55.6, 46.3.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{15}NO_2$: 253.1103; found: 253.1103.

6-Chloro-2-phenyl-2,3-dihydroquinolin-4(1*H*)-one (3p)

Yellow solid; yield: 236 mg (92%); mp 155–157 °C.

IR (ATR): 3336, 1657, 1490, 1197, 701, 612, 490 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 1.8 Hz, 1 H), 7.35–7.25 (m, 5 H), 7.17 (dd, *J* = 8.7, 1.8 Hz, 1 H), 6.57 (d, *J* = 8.7 Hz, 1 H), 4.63 (dd, *J* = 13.2, 4.5 Hz, 1 H), 4.48 (s, 1 H, NH), 2.76 (dd, *J* = 16.5, 13.2 Hz, 1 H), 2.67 (dd, *J* = 16.2, 4.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.1, 149.8, 140.5, 135.2, 129.0, 128.6, 126.5, 123.7, 119.6, 117.4, 58.3, 45.9.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{15}H_{12}ClNO$: 257.0607; found: 257.0605.

6-Bromo-2-phenyl-2,3-dihydroquinolin-4(1*H*)-one (3q)

Yellow solid; yield: 272 mg (90%); mp 165–167 °C.

IR (ATR): 3333, 3045, 1656, 1493, 1285, 595 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 2.1 Hz, 1 H), 7.42–7.33 (m, 6 H), 6.60 (d, *J* = 8.7 Hz, 1 H), 4.70 (dd, *J* = 12.9, 4.5 Hz, 1 H), 4.59 (s, 1 H, NH), 2.83 (dd, *J* = 16.5, 13.5 Hz, 1 H), 2.73 (dd, *J* = 16.2, 4.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.9, 150.2, 140.4, 137.9, 129.9, 129.0, 128.6, 126.5, 120.1, 117.7, 110.6, 58.2, 45.8.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{15}H_{12}BrNO$: 301.0102; found: 301.0100.

2-(1-Methyl-1*H*-pyrrol-2-yl)-2,3-dihydroquinolin-4(1*H*)-one (6)

Off-white solid; yield: 180 mg (80%); mp 160–162 °C.

IR (KBr): 3325, 1646, 1488, 1320, 733 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.84 (dd, *J* = 8.1, 1.2 Hz, 1 H), 7.31 (dt, *J* = 8.4, 1.5 Hz, 1 H), 6.76 (t, *J* = 7.5 Hz, 1 H), 6.69 (d, *J* = 8.4 Hz, 1 H), 6.59 (s, 1 H), 6.20–6.19 (m, 1 H), 6.11–6.09 (m, 1 H), 4.80 (dd, *J* = 13.2, 3.9 Hz, 1 H), 4.58 (s, 1 H, NH), 3.64 (s, 3 H), 2.95–2.73 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.2, 151.2, 135.2, 131.3, 127.5, 123.2, 118.9, 118.3, 115.8, 107.2, 107.0, 50.3, 44.5, 34.0.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{14}H_{14}N_2O$: 226.1106; found: 226.1105.

2-(Furan-2-yl)-2,3-dihydroquinolin-4(1*H*)-one (7)

Brown solid; yield: 181 mg (85%); mp 95–97 °C.

IR (KBr): 3341, 1657, 1609, 1503, 1305, 1114, 767 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.1 Hz, 1 H), 7.35–7.27 (m, 2 H), 6.74 (t, *J* = 7.8 Hz, 1 H), 6.68 (d, *J* = 8.4 Hz, 1 H), 6.31–6.29 (m, 1 H), 6.23 (d, *J* = 2.7 Hz, 1 H), 4.79 (dd, *J* = 9.3, 5.8 Hz, 1 H), 4.74 (s, 1 H, NH), 3.02–2.87 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.5, 153.0, 150.4, 142.4, 135.3, 127.3, 119.1, 118.5, 115.9, 110.3, 106.7, 50.7, 41.9.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{13}H_{11}NO_2$: 213.0790; found: 213.0790.

2-(Thiophen-2-yl)-2,3-dihydroquinolin-4(1*H*)-one (8)

Brown solid; yield: 203 mg (89%); mp 135–136 °C.

IR (KBr): 3343, 2985, 1659, 1577, 1313, 1225 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.87 (dd, *J* = 8.1, 1.2 Hz, 1 H), 7.38–7.33 (m, 1 H), 7.28 (d, *J* = 5.1 Hz, 1 H), 7.07 (d, *J* = 3.0 Hz, 1 H), 7.01–6.98 (m, 1 H), 6.81 (t, *J* = 7.8 Hz, 1 H), 6.74 (d, *J* = 8.1 Hz, 1 H), 5.03 (dd, *J* = 10.5, 6.0 Hz, 1 H), 4.77 (s, 1 H, NH), 2.99–2.86 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.5, 150.7, 144.4, 135.3, 127.4, 126.7, 125.0, 124.9, 119.1, 118.6, 115.9, 53.5, 46.8.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{13}H_{11}NOS$: 229.0561; found: 229.0560.

Control Experiment for the Formation of 4a

AgOTf (26 mg, 10 mol%) was added to a solution of *o*-aminoacetophenone (**1a**; 135 mg, 1.0 mmol) and benzaldehyde (**2a**; 127 mg, 1.2 mmol) in MeOH (5 mL) at r.t. The reaction mixture was stirred under reflux for 3 h only. The excess solvent was removed under reduced pressure and the residue was purified by silica gel gradient column chromatography (hexanes–EtOAc, 20:1–5:1) to yield **1a** (104 mg, 77%, recovered), **3a** (17 mg, 8%), and **4a** (31 mg, 13%).

1-(2-Aminophenyl)-3-hydroxy-3-phenylpropan-1-one (4a)

Yellow liquid; yield: 31 mg (13%).

IR (ATR): 3471, 3349, 1755, 1619, 1210, 754 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 7.8 Hz, 1 H), 7.42 (d, *J* = 7.8 Hz, 2 H), 7.35 (t, *J* = 7.8 Hz, 2 H), 7.29–7.24 (m, 2 H), 6.64 (d, *J* = 8.4 Hz, 1 H), 6.59 (t, *J* = 7.2 Hz, 1 H), 6.29 (s, 2 H, NH_2), 5.29 (dd, *J* = 9.6, 3.0 Hz, 1 H), 3.73 (s, 1 H, OH), 3.34 (dd, *J* = 17.4, 3.0 Hz, 1 H), 3.29 (dd, *J* = 18.0, 9.6 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 202.0, 150.6, 143.1, 134.8, 131.1, 128.5, 127.5, 125.8, 117.6, 117.4, 115.9, 70.3, 47.6.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{15}H_{15}NO_2$: 241.1103; found: 241.1105.

Control Experiment for the Conversion of 4a into 3a

AgOTf (7 mg, 10 mol%) was added to a solution of 1-(2-aminophenyl)-3-hydroxy-3-phenylpropan-1-one (**4a**; 60 mg, 0.25 mmol) in MeOH (5 mL), and the mixture was stirred under reflux for 20 h. The excess solvent was removed under reduced pressure and the residue was purified by column chromatography (hexanes–EtOAc, 10:1) to afford **3a** (51 mg, 91%).

Antioxidant Activity Test

FRAP assays were performed as described by Benzie and Strain,[30] and were carried out using an Optizen 3220 UV spectrophotometer. Experiments were conducted at 37 °C under low pH (3.6) with a blank sample in parallel. At low pH, a complex of Fe^{3+}–TPTZ (2,4,6-tripyridyl-*s*-triazine) is reduced to the Fe^{2+}–TPTZ form, with development of an intense blue color at a wavelength maximum of 593 nm. The FRAP working reagent was freshly prepared by mixing 300 mM acetate buffer (pH 3.6), 10 mM TPTZ in 40 mM HCl, and 20 mM $FeCl_3 \cdot H_2O$ in the ratio of 10:1:1. For each assay, FRAP reagent (2.9 mL) and synthetic compound in MeOH (1 mg/mL, 100 µL) were mixed. Absorbance of the reaction (incubated at 37 °C) was measured at 593 nm after 30 min. The standard curve was linear between 125 and 2000 µM Trolox. All results are expressed in terms of TEAC (µM). In order to calculate the EC_{50} value, the synthesized compound in MeOH was further diluted and tested in the FRAP assay to establish 50% inhibition. The EC_{50} value was calculated by the graph method. Data were analyzed statistically by using OriginPro 8.1 software (OriginLab, Northampton, MA, USA).

Acknowledgment

This research was supported by the Nano Material Technology Development Program of the Korean National Research Foundation (NRF) funded by the Korean Ministry of Education, Science, and Technology (Grant no. 2012-049675). This work was also supported by the Korean National Research Foundation (NRF) grant funded by the Korean government (MSIP) (NRF-2014R1A2A1A11052391) and Priority Research Centers Program (2014R1A6A1031189).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560322.

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