Tetrahedron 68 (2012) 250–261

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 12-oxobenzo[*c*]phenanthridinones and 4-substituted 3-arylisoquinolones via Vilsmeier–Haack reaction

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ARTICLE INFO

Article history:
Received 30 August 2011
Received in revised form 13 October 2011
Accepted 14 October 2011
Available online 31 October 2011

Keywords:
12-Oxobenzo[*c*]phenanthridinone
4-Substituted 3-arylisoquinolone
Vilsmeier–Haack reaction
Mitsunobu reaction
Knoevenagel condensation

ABSTRACT

Vilsmeier–Haack reaction on 3-arylisoquinolones resulted in versatile 4-formylated 3-arylisoquinolones that were further derivatized into 12-oxobenzo[*c*]phenanthridinones, 4-alkoxymethyl-3-arylisoquinolones, 3-aryl-4-phenoxymethylisoquinolones, 4-aminomethyl-3-arylisquinolone, and 3-isoquinolinyl-2-phenyl-acrylonitrile by different synthetic strategies.

1. Introduction

Isoquinolones are an important class of compounds that comprise a large variety of natural products like dorianine[1] and ruprechstyril.[2] Isoquinolone is also the basic frame of different classes of alkaloids, such as protoberberines[3,4] and benzo[*c*]phenanthridines.[5] Natural and synthetic analogs of isoquinolones exhibit a wide spectrum of pharmacological properties. In addition, isoquinolones are useful intermediates for the synthesis of different types of chemical compounds. Due to these properties isoquinolones are widely used in medicinal and synthetic chemistry.

Isoquinolones with substituents at various positions exhibit different therapeutic activities (Fig. 1). 3-Aryl-1-isoquinolinamine **1**,[6] 2-substituted isoquinolone **3**,[7] and 3-arylisoquinolone **5**[8] have been reported to function as topoisomerase I (topo I) inhibitor, antiemetic, and antitumor agents, respectively. Tilisolol hydrochloride **6**,[9] a 4-substituted isoquinolone analog, is a non-selective β-adrenoceptor blocker used for treatment of hypertension and angina pectoris. In a similar fashion, 5-iodoisoquinolone **8**,[10] 6- and 7-substituted isoquinolones (**10** and **11**)[11,12] act as poly(ADP-ribose) polymerase (PARP), Rho-kinase, and thymidylate synthase (TS) inhibitors. Apart from the variance in biological activities brought about by functional groups at different positions, different functional groups at the same position also impart unique biological activities. Loss of topo I inhibitory activity by compound **2**,[6] tumor necrosis factor α (TNF α) inhibition by **4**,[13] antiallergic property of **7**,[14] and phosphoinositide-dependent kinase-1 (PDK-1) inhibition by **9**[15] show that chemical entities with different functional groups at the identical position can have novel pharmacological activities.

In addition to exhibiting potent biological properties, the isoquinolone moiety (more precisely 3-arylisoquinolone) is the chief precursor for synthesis of natural alkaloids like protoberberines,[16–18] benzo[*c*]phenanthridines,[19,20] and potent antitumor agents like indeno[1,2-*c*]isoquinoline, isoindolo[2,1-*b*]isoquinolines, 12-oxobenzo[*c*]phenanthridines, dibenzo[*c*,*h*][1,6]naphthyridines, and benz[*b*]oxepines.[21,22] The anticancer property of the aforementioned synthetic derivatives of 3-arylisoquinolines is primarily due to inhibition of topo I, which is essential for vital cellular processes, such as DNA replication, transcription, recombination, chromatin condensation, and chromosome partitioning during cell division.[23–25] Synthesis of 3-arylisoqinoline as topo I inhibitors involves conversion of the flexible 3-arylisoquinoline core into constrained, planar tetracyclic structures with increased ability to cease the activity of topo I.[21]

Based on the rationale that the isoquinolone skeleton with varied substitution at the same position can manifest clinically useful properties and that rigidification of 3-aryisoquinoline can improve topo I inhibition and cytotoxicity of non-flexible analogs, we herein describe methods for syntheses of a variety of 4-substituted 3-arylisoquinolones and newer 12-oxobenzophenanthridinones.

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0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.10.053

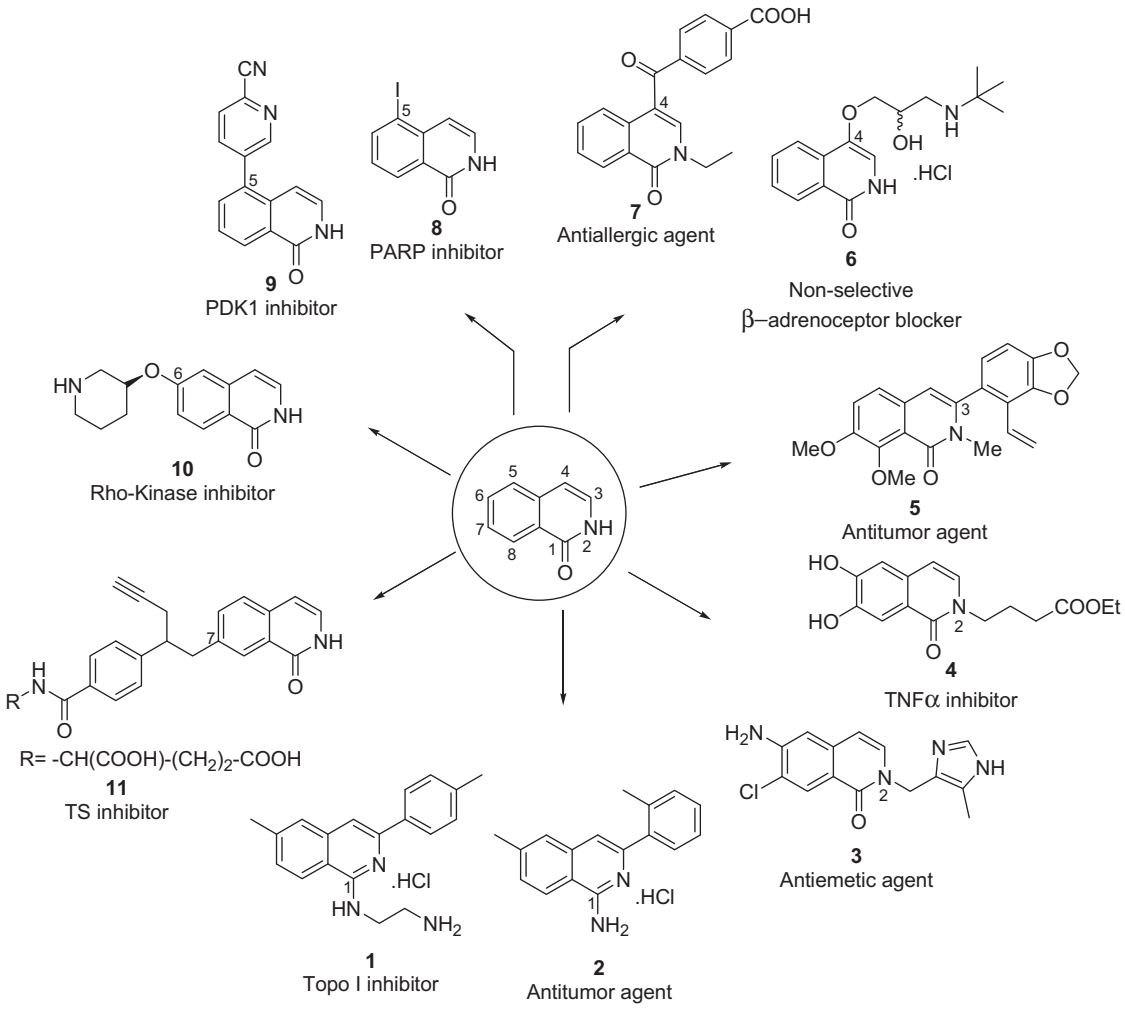


Fig. 1. Substituted isoquinolones and their pharmacological categories.

2. Results and discussion

2.1. Synthetic plan

A possible approach for the synthesis of 12-oxobenzophenanthridinones **12** and 4-substituted 3-arylisoquinolones is shown in Scheme 1. The synthetic strategy is principally centered in formation of 4-formylated isoquinolone by Vilsmeier–Haack reaction. Vilsmeier–Haack formylation is an efficient, economical, and mild reaction for formylation of a wide variety of reactive aromatic and heteroaromatic compounds.[26–28] The aldehyde, obtained as the end product of the Vilsmeier–Haack reaction, and the alcohol obtained after reduction of the aldehyde can be interconverted into various functional groups to generate a large array of derivatives.

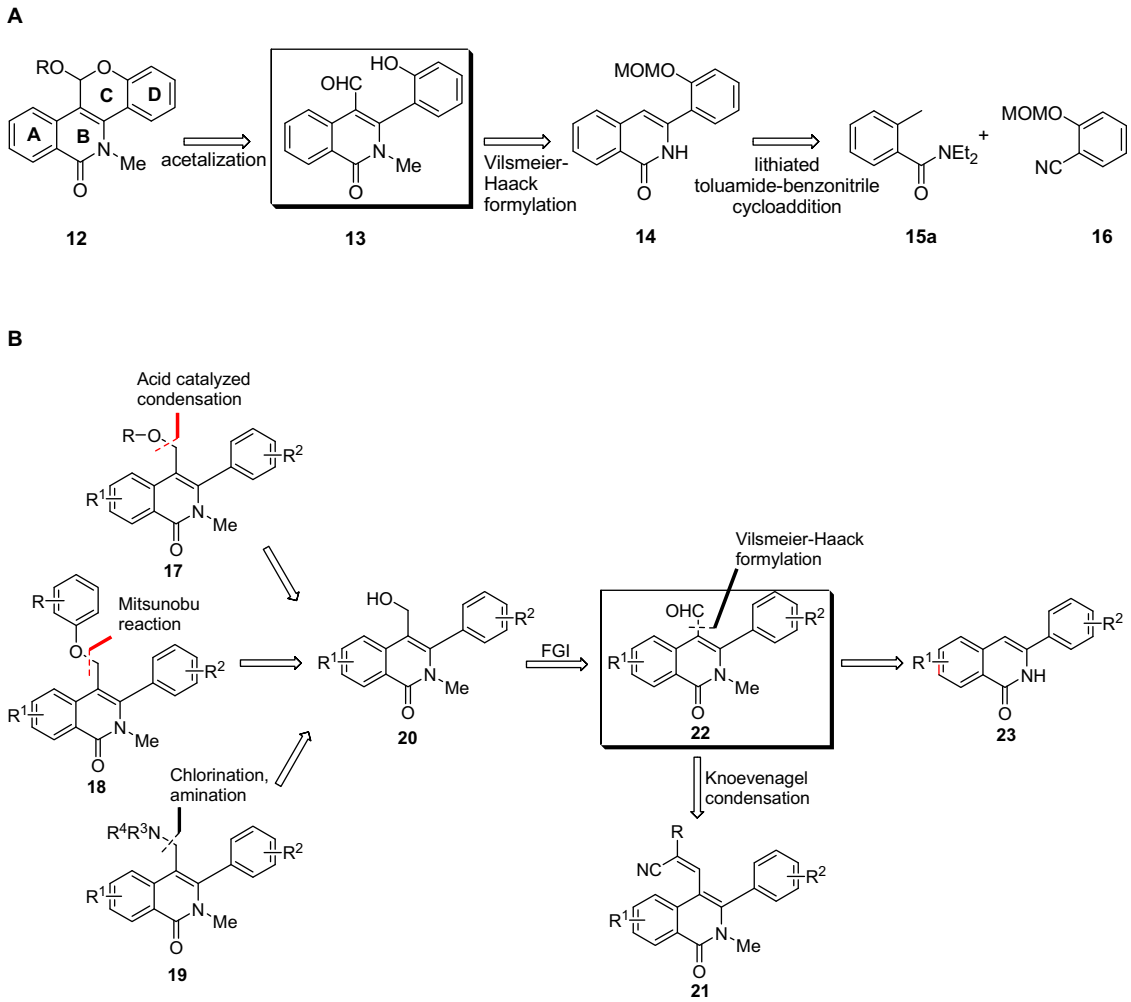
12-Oxobenzophenanthridinones **12** can be formed from 4-formylated isoquinolones **13** (Scheme 1A). The pyran ring C of 12-oxobenzophenanthridinones can be formed by acid-catalyzed acetalization of **13** in the presence of various aliphatic alcohols. The key 4-formylated precursor **13** can be obtained by Vilsmeier–Haack reaction of **14**, which in turn can be prepared by cycloaddition of lithiated toluamide **15a** and benzonitrile **16**.

Syntheses of 4-alkoxymethyl-3-arylisoquinolones **17**, 3-aryl-4-phenoxymethylisoquinolones **18**, and 4-aminomethyl-3-arylisoquinolones **19** were envisioned to be accomplished by acid-catalyzed condensation, Mitsunobu reaction, and chlorination followed by amination of alcohols **20** (Scheme 1B). The alcohols **20** in turn could be obtained by Functional Group Interconversion (FGI) of pivotal 4-formylated substrates **22**. Acrylonitrile derivatives **21** could also be obtained by Knoevenagel condensation of **22** with acetonitrile derivatives.

2.2. Synthesis of 12-oxobenzo[*c*]phenanthridines

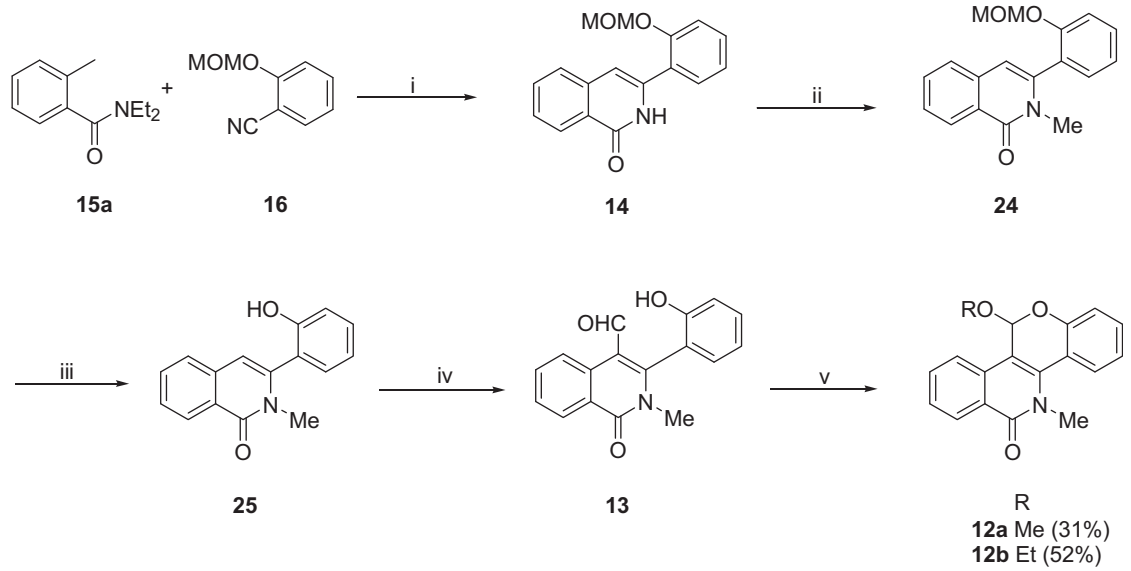
3-Arylisoquinolone **14**, the starting precursor for the synthesis of 12-oxobenzo[*c*]phenanthridinones **12** was synthesized by the one-pot, lithiated toluamide-benzonitrile cycloaddition method (Scheme 2).[29,30] *N*,*N*-Diethyl-*o*-toluamide **15a**, on treatment with 2 equiv of *n*-butyllithium, formed a dimetalated, orange-red reaction intermediate. The dilithiated toluamide species underwent intermolecular cyclization with benzonitrile **16** to yield 3-arylisoquinolone **14**. Treatment of **14** with methyl iodide in the presence of NaH provided the corresponding *N*-methylated compound **24**. Deprotection of the methoxymethyl group of **24** was achieved by treatment with 10% HCl in THF to give the phenol **25**. Phenolic compound **25** was in turn formylated at C4 by Vilsmeier–Haack reaction to afford isoquinoline-4-carbaldehyde **13**. Ultimately, 12-oxobenzo[*c*]phenanthridinones **12** were synthesized by acid-catalyzed acetalization of compound **13** in the presence of methyl and ethyl alcohols.

Synthesis of various 12-oxobenzophenanthridinones was unfortunately limited by Vilsmeier–Haack reaction of 3-(2-hydroxy-



Scheme 1. Retrosynthesis of (A) 12-oxobenzo[*c*]phenanthridinones **12**; (B) 4-substituted 3-arylisoquinolones.

phenyl)-substituted isoquinolone **25**. Extremely low solubility of desired formylated isoquinolone **13** and various by-products formed due to the presence of an electron-rich aromatic substituent at the C3 of the isoquinolone presented difficulties in the purification and isolation of the desired compounds. Considering this fact, Vilsmeier–Haack reaction was further adjusted with 3-arylisoquinolones lacking an electron-donating group in 3-phenyl ring to generate 4-substituted 3-arylisoquinolones.



Scheme 2. Synthesis of 12-oxobenzo[*c*]phenanthridinones **12**. Reagents and conditions: (i) *n*-BuLi, dry THF, −78 °C; (ii) MeI, NaH, dry THF, reflux; (iii) 10% HCl, THF, reflux; (iv) DMF–$POCl_3$, 60 °C; (v) *c*-HCl, R–OH, reflux.

2.3. Synthesis of 4-alkoxymethyl-3-arylisoquinolones

Synthesis of 4-alkoxymethyl-3-arylisoquinolones **17** was initiated by formation of isoquinolones **23** (Scheme 3). 3-Arylisoquinolones **23** were obtained by coupling of lithiated species of toluamides **15** and commercially available benzonitriles. N-Methylation of **23** was achieved with NaH and MeI under reflux conditions. Alkylation of the nitrogen of isoquinolone is essential, as the unprotected isoquinolone undergoes aromatization during Vilsmeier–Haack formylation with conversion of the lactam group into imine chloride. Vilsmeier–Haack reaction on **26** produced aldehydes **22**. Vilsmeier–Haack reaction on isoquinolones **26** resulted in selective formylation at C4 with high yields (92–69%). Reduction of the formylated products **22** by $NaBH_4$ resulted in alcohols **20**. Interestingly, when the 3-aryl-4-hydroxyisoquinolones **20** were reacted with various aliphatic alcohols in acidic conditions, the corresponding alkoxy compounds **17** were obtained in good yields (Table 1). The alkoxy derivatives were formed by acid-catalyzed dehydration and consecutive nucleophilic attack of aliphatic alcohols.

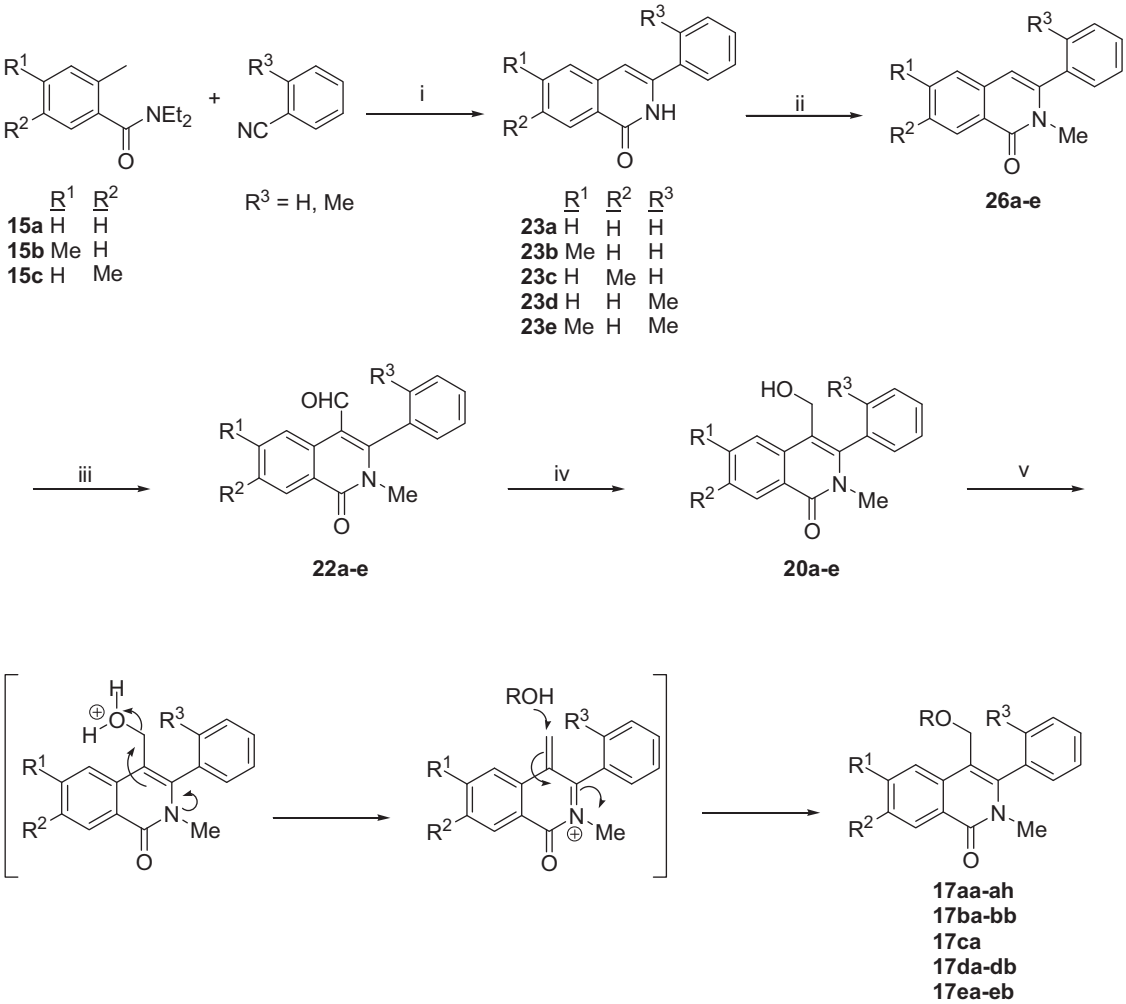
Despite the successful formylation of *N*-methylated isoquinolones, our further endeavors in the formylation of various *N*-alkylated isoquinolones (**27a**–**d**) with Vilsmeier–Haack reagents under similar reaction conditions as mentioned earlier was in vain (Scheme 4). The plausible reason for failure of Vilsmeier–Haack formylation on isoquinolones protected with bulky alkyl group can be the steric hindrance, which prevents the association of isoquinolonium and dichlorophosphate leading to destabilization of the transition state (Fig. 2).

Table 1
Synthesis of 4-alkoxymethyl-3-arylisoquinolones **17**

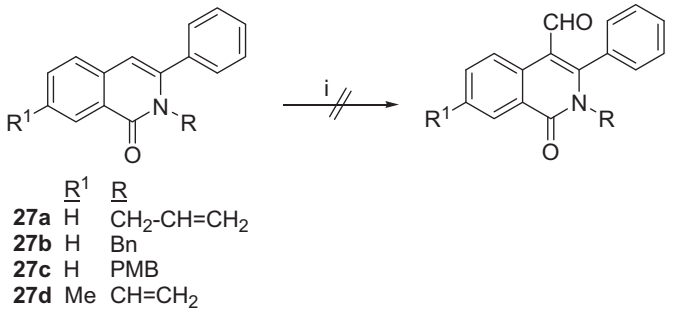
Entry	Compound	R^1	R^2	R^3	R	Yield[a] (%)
1	**17aa**	H	H	H	Me	92
2	**17ab**	H	H	H	Et	93
3	**17ac**	H	H	H	^{n}Pr	80
4	**17ad**	H	H	H	^{i}Pr	76
5	**17ae**	H	H	H	^{i}Bu	48
6	**17af**	H	H	H	EtOH	79
7	**17ag**	H	H	H	$(CH_2)_2OCH_3$	81
8	**17ah**	H	H	H	$(CH_2)_2$–Cl	52
9	**17ba**	Me	H	H	Et	90
10	**17bb**	Me	H	H	^{i}Bu	88
11	**17ca**	H	Me	H	^{i}Bu	90
12	**17da**	H	H	Me	Et	89
13	**17db**	H	H	Me	^{i}Bu	90
14	**17ea**	Me	H	Me	Et	91
15	**17eb**	Me	H	Me	^{i}Bu	82

[a] Isolated yield.

To our further disappointment, an attempt toward formylation of 3-(2-hydroxymethyl-phenyl)-isoquinolone **28** with Vilsmeier–Haack reagent under the identical conditions and procedures as above yielded chlorinated compound **29** instead of the expected 4-formylated derivative **30** (Scheme 5). Moreover, as



Scheme 3. Synthesis of 4-alkoxymethyl-3-arylisoquinolones **17**. Reagents and conditions: *n*-BuLi, dry THF, −78 °C; (ii) MeI, NaH, dry THF, reflux; (iii) DMF–$POCl_3$, 60 °C; (iv) $NaBH_4$, MeOH, rt; (v) *c*-HCl, R–OH, reflux.



Scheme 4. Unsuccessful attempt of Vilsmeier–Haack reaction. Reagents and conditions: (i) DMF–$POCl_3$, 60 °C.

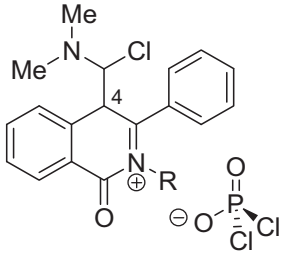
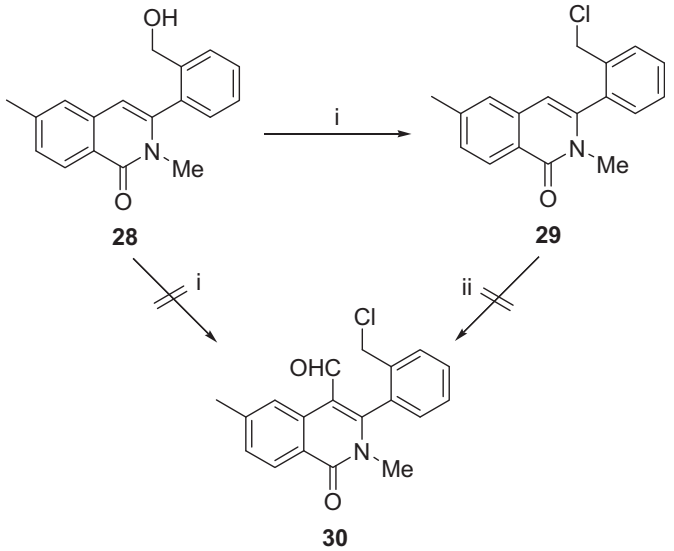


Fig. 2. Isoquinolonium dichlorophosphate transition state, attained after electrophilic attack of Vilsmeier–Haack reagent (Cl–CH=$N^+(Me)_2$) on electron-rich C4 of isoquinolone ring.

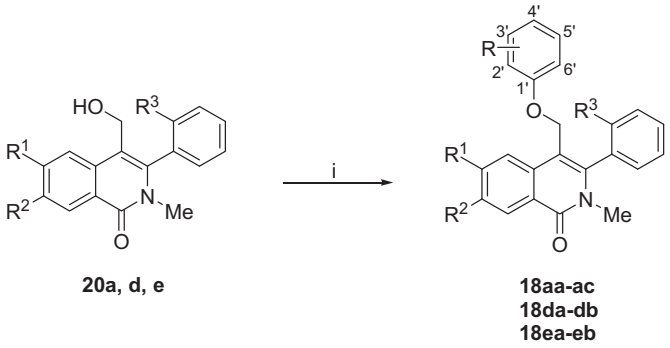


Scheme 5. Unsuccessful attempt of Vilsmeier–Haack formylation. Reagents and conditions: (i), (ii) DMF–$POCl_3$, 60 °C.

a continuation of the reaction sequence, the Vilsmeier–Haack reaction on **29** did not produce new product. This may be due to steric hindrance and the electronic effect of the electronegative chloromethyl group on C4 of the isoquinolone ring.

2.4. Synthesis of 3-aryl-4-phenoxymethylisoquinolones

The diversity of 4-substituted 3-arylisoquinolones was broadened by the application of Mitsunobu reaction to produce various novel 3-aryl-4-phenoxymethylisoquinolones **18**. 3-Aryl-4-hydroxymethylisoquinolones (**20a**,**d**, and **e**) were reacted with phenols under Mitsunobu reaction conditions to yield 3-aryl-4-phenoxymethylisoquinolones **18** (Scheme 6, Table 2).



Scheme 6. Synthesis of 3-aryl-4-phenoxymethylisoquinolones **18**. Reagents and conditions: (i) Substituted/unsubstituted phenol, PPh_3, DIAD, dry THF, rt.

Table 2
Synthesis of 3-aryl-4-phenoxymethylisoquinolones **18**

Entry	Compound	R^1	R^2	R^3	R	Yield[a] (%)
1	**18aa**	H	H	H	H	53
2	**18ab**	H	H	H	4′-Br	49
3	**18ac**	H	H	H	4′-^{i}Pr	19
4	**18da**	H	H	Me	2′-^{i}Pr	36
5	**18db**	H	H	Me	2′-OCH_3, 4′-Me	60
6	**18ea**	Me	H	Me	3′,5′-Me	17
7	**18eb**	Me	H	Me	2′-Me, 4′-Cl	36

[a] Isolated yield.

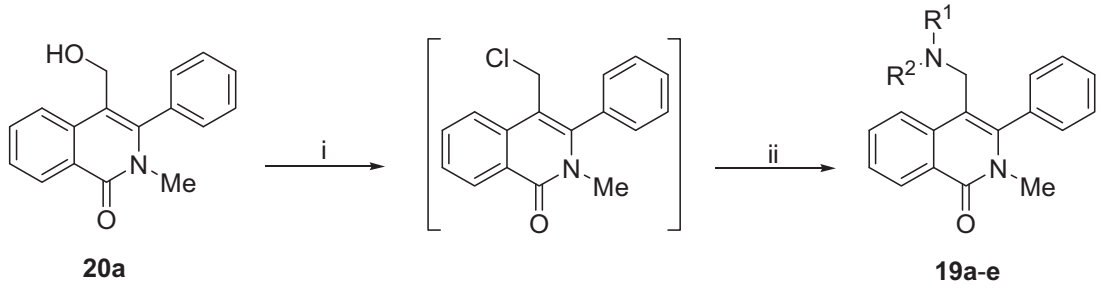
2.5. Synthesis of 4-aminomethyl-3-arylisoquinolones and 3-isoquinolinyl-2-phenyl-acrylonitrile

Besides 4-alkoxy-3-arylisoquinolones and 3-aryl-4-phenoxymehtylisoquinolones, 4-aminomethyl-3-arylisoquinolones **19** were also prepared from the same precursor **20a** (Scheme 7). Alcohol **20a** was chlorinated with thionyl chloride. The chloride reaction intermediate, thus obtained was subjected to amination with various primary and secondary amines to afford the desired 4-aminomethyl-3-arylisoquinolones **19** with average yield ranging from 41 to 85% (Table 3). Finally, 3-isoquinolinyl-2-phenyl-acrylonitrile **21** was synthesized by Knoevenagel condensation of **22a** and benzyl cyanide (Scheme 8).

3. Conclusion

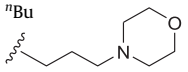
In summary, 12-oxobenzophenanthridinones were synthesized as constrained structures of 3-arylisoquinolones, whereas 4-alkoxymethyl-3-arylisoquinolones, 3-aryl-4-phenoxymethylisoquinolones, 4-aminomethyl-3-arylisoquinolones, and 3-isoquinolinyl-2-phenyl-acetonitrile were prepared as flexible forms of 3-arylisoquinolones. The pivotal 4-formylated precursors essential for preparation of the isoquinolone derivatives were obtained by Vilsmeier–Haack reaction. In doing so we have illustrated the limitations of the Vilsmeier–Haack reaction to formylate isoquinolone whose lactam *N* is protected by alkyl with more than one carbon unit. Also, the negative, steric and electronic effects of the electronegative chloromethyl group at the Vilsmeier–Haack formylation site have also been reported.

The synthesis of 4-substituted 2-methylisoquinolinone via Vilsmeier–Haack reaction is noteworthy because it allows a large array of substituted isoquinolones with novel and improved pharmacological activities to be designed and developed. The topo I inhibition and cell antiproliferative activities of the synthesized 12-oxobenzophenathridinones and 4-substituted 3-arylisoquinolones will duly be reported along with those of 3,4-diarylisoquinolinamines.

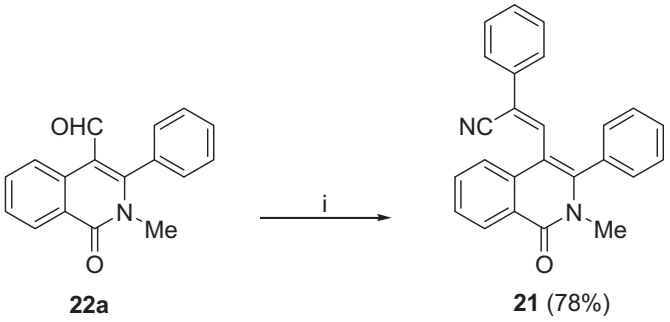


Scheme 7. Synthesis of 4-aminomethyl-3-arylisoquinolones **19**. Reagents and conditions: (i) $SOCl_2$, reflux; (ii) NHR^1R^2, CH_2Cl_2, rt.

Table 3
Synthesis of 4-aminomethyl-3-arylisoquinolones **19**

Entry	Compound	R^1	R^2	Yield[a] (%)
1	**19a**	H	^{n}Pr	85
2	**19b**	H	^{n}Bu	75
3	**19c**	H		47
4	**19d**	Et	Et	81
5	**19e**	^{i}Pr	^{i}Pr	41

[a] Isolated yield.



Scheme 8. Synthesis of 3-isoquinolinyl-2-phenyl-acrylonitrile **21**. Reagents and conditions: (i) BnCN, *t*-BuOK, EtOH, rt.

4. Experimental

4.1. General information

Melting points were determined by the capillary method with an Electrothermal IA9200 digital melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded with Varian 300 spectrometer at the Korea Basic Science Institute. The chemical shifts are reported in parts per million downfield to TMS (δ=0) for ^{1}H NMR. The coupling constants *J* are given in Hertz. The data are reported in the following order: chemical shift, multiplicity, coupling constant, and number of protons. Multiplicity of proton resonance signals are reported as—s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br s: broad singlet. IR spectra were recorded on a JASCO FT/IR 300E spectrometer using KBr pellets. Mass spectra were obtained on JEOL JNS-DX 303 using the electron-impact (EI) method. Column chromatography was performed on Merck silica gel 60 (70–230 mesh). TLC was performed using plates coated with silica gel 60 F_{254} (Merck). Chemical reagents were purchased from Aldrich Chemical Co. and Tokyo Chemical Industry and were used without further purification. Solvents were distilled prior to use; THF was distilled from sodium/benzophenone. All reactions were conducted under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring.

4.2. Chemistry

*4.2.1. N,N-Diethyl-2-methyl-benzamide (**15a**).* Thionyl chloride was added drop wise to *o*-toluic acid (5.0 g, 36.7 mmol) at 0 °C. The reaction mixture was refluxed overnight. Excess thionyl chloride and volatile reaction by-products like HCl and SO_2 were removed by vacuum distillation. The residue obtained was dissolved in CH_2Cl_2, and diethylamine (21.4 g, 0.29 mol) was added at 0 °C. After stirring overnight, the reaction mixture was diluted with water, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The organic layers were washed with water and brine, dried over anhydrous sodium sulfate, and then concentrated. The residue was purified using column chromatography with *n*-hexane–ethyl acetate 3:1 to obtain compound **15a** as yellowish oil (6.3 g, 89%). IR (cm^{-1}): 1631. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.23–7.13 (m, 4H), 3.80 (s, 1H), 3.40 (s, 1H), 3.09 (q, *J*=6.9 Hz, 2H), 2.27 (s, 3H), 1.24 (t, *J*=6.9 Hz, 3H), 0.99 (t, *J*=7.2 Hz, 3H). MS (ESI) *m*/*z* 192 $(M+H)^+$.

*4.2.2. 2-Methoxymethoxy-benzonitrile (**16**).* Diisopropylethylamine (DIPEA) (13.0 g, 0.10 mol) and chloromethyl methyl ether (8.11 g, 0.10 mol) were added to a solution of 2-hydroxy-benzonitrile (6.0 g, 50.4 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred at the same temperature for 1 h and at room temperature overnight. After the reaction was over, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layers were washed with water and brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane–ethyl acetate 3:1 to afford compound **16** as oil (8.0 g, 97%). IR (cm^{-1}): 2229. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59–7.49 (m, 2H), 7.24 (d, *J*=8.5 Hz, 1H), 7.06 (t, *J*=7.6 Hz, 1H), 5.29 (s, 2H), 3.52 (s, 3H). MS (ESI) *m*/*z* 164 $(M+H)^+$.

*4.2.3. 3-(2-Methoxymethoxy-phenyl)-2H-isoquinolin-1-one (**14**).* A 100-mL oven-dried, three-necked flask was sealed with septa and evacuated/backfilled with N_2 three times before starting the reaction. A solution of *N,N*-diethyltoluamide **15a** (1.86 g, 9.75 mmol) and benzonitrile **16** (2.38 g, 14.6 mmol) in dry THF (5 mL) was added drop wise to a solution of *n*-BuLi (10 mL of 2.5 M in hexane, 24.4 mmol) in dry THF (25 mL) at −50 °C and the reaction mixture was stirred at −78 °C for 10 h. The reaction mixture was quenched with water, extracted with ethyl acetate. The organic layers were washed with water and brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane–ethyl acetate 3:1 to afford compound **14** as white solid (2.8 g, 100%). Mp: 138–140 °C. IR (cm^{-1}): 1638. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.60 (s, 1H), 8.40 (d, *J*=7.9 Hz, 1H), 7.64 (t, *J*=7.4 Hz, 1H), 7.58 (d, *J*=7.9 Hz, 2H), 7.48 (t, *J*=7.4 Hz, 1H), 7.41 (t, *J*=7.3 Hz, 1H), 7.27 (d, *J*=8.2 Hz, 1H), 7.14 (t, *J*=7.5 Hz, 1H), 6.71 (s, 1H), 5.28 (s, 2H), 3.47 (s, 3H). MS (ESI) *m*/*z* 282 $(M+H)^+$.

*4.2.4. 3-(2-Methoxtmethoxy-phenyl)-2-methyl-2H-isoquinolin-1-one (**24**).* 60% NaH dispersion (771 mg, 19.3 mmol) was added to

a solution of compound **14** (2.71 g, 9.63 mmol) in dry THF at 0 °C under nitrogen. The resulting mixture was stirred at the same temperature for 1 h. After the ice bath was removed, MeI (2.73 g, 19.3 mmol) was added to the reaction mixture and refluxed overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water and brine and dried over anhydrous sodium sulfate. After removing the solvent, the residue was purified by column chromatography on silica gel with *n*-hexane–ethyl acetate 2:1 to give the *N*-methylated product **24** as beige solid (2.5 g, 88%). Mp: 116.9–118 °C. IR (cm^{-1}): 1644. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.47 (d, J=8.1 Hz, 1H), 7.63 (m, 1H), 7.51–7.43 (m, 3H), 7.31 (dd, J=1.8, 7.4 Hz, 1H), 7.26–7.22 (m, 1H), 7.11 (t, J=7.5 Hz, 1H), 6.44 (s, 1H), 5.14 (m 2H), 3.40 (s, 3H), 3.37 (s, 3H). MS (ESI) m/z 296 $(M+H)^+$.

*4.2.5. 3-(2-Hydroxy-phenyl)-2-methyl-2H-isoquinolin-1-one (**25**).* 10% HCl (20 mL) was added to a solution of compound 2**4** (2.51 g, 8.93 mmol) in THF and was refluxed for 6 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water and brine, dried over anhydrous sodium sulfate, and then concentrated. The residue was recrystallized from methanol to give **25** as white solid (1.8 g, 82%). Mp: 300–310 °C (dec). ^1H NMR (300 MHz, DMSO-d_6) δ: 10.03 (s, 1H), 8.24 (d, J=7.5 Hz, 1H), 7.71–7.66 (m, 2H), 7.50 (t, J=8.1 Hz, 1H), 7.34 (t, J=8.1 Hz, 1H), 7.28 (d, J=7.5 Hz, 1H), 7.00–6.92 (m, 2H), 6.53 (s, 1H), 3.29 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 161.3, 154.8, 139.0, 136.1, 131.5, 131.0, 130.9, 127.1, 126.2, 124.5, 121.7, 119.7, 116.3, 113.2, 54.9, 32.8. MS (ESI) m/z 252 $(M+H)^+$.

*4.2.6. 3-(2-Hydroxy-phenyl)-2-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carbaldehyde (**13**).* Phosphorus oxychloride (2.44 g, 15.9 mmol) was added to dimethylformamide (10 mL) cooled in ice bath and the resulting mixture was stirred at the same temperature for 2 h. Ice-cold solution of 3-(2-hydroxy-phenyl)-2-methyl-2*H*-isoquinolin-1-one **25** (800 mg, 3.18 mmol) in DMF (10 mL) was added drop wise to the above mixture and after addition was complete, the temperature of the resulting mixture was slowly raised to 60 °C and maintained for 19 h. The reaction mixture was cooled in an ice bath, cautiously quenched with ice-cold water (50 mL), and basified with 35% NaOH solution. The solid formed was filtered off. The filtrate was extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water and brine, dried over anhydrous sodium sulfate, and then concentrated. The residue was recrystallized from methanol to give **13** as light brown solid (768 mg, 85%). Mp: 192–194 °C. IR (cm^{-1}): 3230, 1632, 1505. ^1H NMR (300 MHz, DMSO-d_6) δ: 10.28 (s, 1H), 9.39 (s, 1H), 9.08 (d, J=8.3 Hz, 1H), 8.36 (d, J=8.0 Hz, 1H), 7.86 (t, J=7.8 Hz, 1H), 7.64 (t, J=8.0 Hz, 1H), 7.46 (t, J=6.8 Hz, 1H), 7.35 (d, J=7.5 Hz, 1H), 7.07 (d, J=7.8 Hz, 1H), 7.03 (t, J=7.4 Hz, 1H), 3.25 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 190.6, 161.9, 156.5, 154.9, 133.7, 133.0, 131.9, 131.0, 127.6, 127.3, 124.4, 123.7, 119.5, 118.4, 116.1, 112.1, 32.6. MS (ESI) m/z 278 $(M-H)^-$.

*4.2.7. 11-Methoxy-5-methyl-5,11-dihydro-12-oxa-5-aza-chrysen-6-one (**12a**).* Concentrated HCl (5 mL) was added to a solution of compound **13** (64 mg, 0.23 mmol) in methanol (15 mL) and the resulting mixture was refluxed for 18 h. The solvent was removed in vacuo. Water was poured into the residue and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water and brine, dried over anhydrous sodium sulfate, and then concentrated. The residue was purified by column chromatography on silica gel with *n*-hexane–ethyl acetate 4:1 to give **12a** as off-white solid (21 mg, 31%). Mp: 168–170 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.49 (d, J=8.4 Hz, 1H), 7.75–7.69 (m, 2H), 7.58 (d, J=8.0 Hz, 1H), 7.52 (t, J=7.5 Hz, 1H), 7.37 (t, J=7.9 Hz, 1H), 7.26–7.22 (m, 1H), 7.16 (t, J=7.2 Hz, 1H), 6.30 (s, 1H), 3.85 (s, 3H), 3.58 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.8, 151.8, 133.0, 130.4, 127.6, 127.3, 126.4, 124.4, 124.1, 122.4, 122.1, 118.8, 118.2, 110.3, 96.1, 55.1, 37.0. MS (ESI) m/z 262 $(M-31)^+$, 294 $(M+H)^+$.

*4.2.8. 11-Ethoxy-5-methyl-5,11-dihydro-12-oxa-5-aza-chrysen-6-one (**12b**).* The procedure described for the preparation of compound **12a** was used with compound **13** (200 mg, 0.71 mmol) and concentrated HCl (746 mg, 7.16 mmol) in ethanol to give **12b** as transparent crystals (116 mg, 52%). Mp: 160–163 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.48 (d, J=7.6 Hz, 1H), 7.73–7.69 (m, 2H), 7.58 (d, J=8.1 Hz, 1H), 7.52 (t, J=7.5 Hz, 1H), 7.36 (t, J=7.9 Hz, 1H), 7.20 (d, J=8.1 Hz, 1H), 7.15 (t, J=7.3 Hz, 1H), 6.42 (s, 1H), 3.95 (q, J=7.1 Hz, 1H), 1.20 (t, J=7.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.1, 152.2, 134.4, 133.1, 132.7, 130.0, 128.4, 127.1, 126.1, 124.8, 121.9, 121.2, 118.8, 118.4, 110.8, 95.9, 64.0, 37.2, 15.0. MS (ESI) m/z 262 $(M-45)^+$, 308 $(M+H)^+$.

*4.2.9. N,N-Diethyl-2,4-dimethyl-benzamide (**15b**).* The procedure described for compound **15a** was used with 2,4-dimethyl-benzoic acid (6.0 g, 39.1 mmol), thionyl chloride (25 mL), and diethylamine (14.3 g, 0.19 mol) to give compound **15b** as hay colored liquid (7.9 g, 98%). IR (cm^{-1}): 1632. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.06–6.98 (m, 3H), 3.56 (br s, 2H), 3.12 (q, J=6.9 Hz, 2H), 2.31 (s, 3H), 2.24 (s, 3H), 1.25 (t, J=6.9 Hz, 3H), 1.02 (t, J=7.2 Hz, 3H). MS (ESI) m/z 228 $(M+Na)^+$, 269 $(M+Na+CH_3CN)^+$, 206 $(M+H)^+$.

*4.2.10. N,N-Diethyl-2,5-dimethyl-benzamide (**15c**).* The procedure described for compound **15a** was used with 2,5-dimethyl-benzoic acid (7.5 g, 50 mmol), thionyl chloride (50 mL), and diethylamine (6.94 g, 190 mmol) to give compound **15c** as bright yellow oil (9.6 g, 94%). IR (cm^{-1}): 1632. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.05 (s, 1H), 3.75 (s, 1H), 3.40 (s, 1H), 3.15–3.09 (m, 2H), 2.29–2.20 (m, 6H), 1.25 (t, J=7.1 Hz, 3H), 1.02 (t, J=7.1 Hz, 3H). MS (ESI) m/z 206 $(M+H)^+$.

*4.2.11. 3-Phenyl-2H-isoquinolin-1-one (**23a**).* The procedure described for compound **14** was used with *o*-toluamide **15a** (3.0 g, 15.7 mmol) and benzonitrile (2.42 g, 23.5 mmol) in the presence of *n*-BuLi (15.7 mL of 2.5 M in hexane, 39.2 mmol) in dry THF at −78 °C to afford compound **23a** as white floppy, needle shaped crystals (2.5 g, 74%). Mp: 198–200 °C. IR (cm^{-1}): 1635. ^1H NMR (300 MHz, $CDCl_3$) δ: 9.45 (s, 1H), 8.41 (d, J=8.1 Hz, 1H), 7.71–7.65 (m, 3H), 7.60 (d, J=6.9 Hz, 1H), 7.55–7.46 (m, 4H), 6.78 (s, 1H). HRMS (EI^+): calcd for $C_{15}H_{12}NO$, 222.0919; found, 222.0917.

*4.2.12. 6-Methyl-3-phenyl-2H-isoquinolin-1-one (**23b**).* The procedure described for compound **14** was used with *o*-toluamide **15b** (5.0 g, 24.3 mmol) and benzonitrile (3.76 g, 36.5 mmol) in the presence of *n*-BuLi (24.4 mL of 2.5 M in hexane, 60.9 mmol) in dry THF at −78 °C to afford compound **23b** as yellow solid (2.6 g, 44%). Mp: 209–217 °C. IR (cm^{-1}): 1635. ^1H NMR (300 MHz, $CDCl_3$) δ: 9.46 (s, 1H), 8.29 (d, J=7.8 Hz, 1H), 7.70–7.67 (m, 2H), 7.54–7.46 (m, 3H), 7.38 (s, 1H), 7.31 (d, J=8.1 Hz, 1H), 6.70 (s, 1H), 2.50 (s, 3H). MS (ESI) m/z 258 $(M+Na)^+$, 236 $(M+H)^+$.

*4.2.13. 7-Methyl-3-phenyl-2H-isoquinolin-1-one (**23c**).* The procedure described for compound **14** was used with *o*-toluamide **15c** (5.02 g, 24.5 mmol) and benzonitrile (3.78 g, 36.7 mmol) in the presence of *n*-BuLi (24.5 mL of 2.5 M in hexane, 61.2 mmol) in dry THF at −78 °C to afford compound **23c** as pink solid (2.3 g, 40%). Mp: 199–202 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 9.21 (s, 1H), 8.21 (s, 1H), 7.68–7.64 (m, 2H), 7.54–7.43 (m, 5H), 6.75 (s, 1H), 2.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.9, 138.6, 136.7, 135.9, 134.3, 129.2, 129.1, 126.9, 126.4, 126.0, 124.8, 104.2, 21.4. MS (ESI) m/z 258 $(M+Na)^+$, 236 $(M+H)^+$.

*4.2.14. 3-o-Tolyl-2H-isoquinolin-1-one (**23d**).* The procedure described for compound **14** was used with *o*-toluamide **15a** (956 mg, 4.99 mmol) and 2-methyl-benzonitrile (878 mg, 7.49 mmol) in the

presence of *n*-BuLi (5 mL of 2.5 M in hexane, 12.5 mmol) in dry THF at −78 °C to afford compound **23d** as off-white solid (920 mg, 78%). Mp: 179–181 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.42 (s, 1H), 8.20 (d, J=8.1 Hz, 1H), 7.37–7.65 (m, 2H), 7.51–7.46 (m, 1H), 7.39–7.25 (m, 4H), 6.48 (s, 1H), 2.30 (s, 3H). MS (ESI) m/z 236 $(M+H)^+$.

*4.2.15. 6-Methyl-3-o-tolyl-2H-isoquinolin-1-one (**23e**).* The procedure described for compound **14** was used with *o*-toluamide **15b** (6.4 g, 31.2 mmol) and 2-methyl-benzonitrile (5.48 g, 46.8 mmol) in the presence of *n*-BuLi (31 mL of 2.5 M in hexane, 77.9 mmol) in dry THF at −78 °C to afford compound **23e** as light yellow solid (5.9 g, 75%). Mp: 204–206 °C. IR (cm^{-1}): 1631. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.55 (s, 1H), 8.29 (d, J=8.1 Hz, 1H), 7.39–7.29 (m, 5H), 6.39 (s, 1H), 2.49 (s, 3H), 2.39 (s, 3H). MS (ESI) m/z 272 $(M+Na)^+$.

*4.2.16. 2-Methyl-3-phenyl-2H-isoquinolin-1-one (**26a**).* The procedure described for compound **24** was used with 3-aryl isoquinolinone **23a** (3.75 g, 16.9 mmol) and MeI (4.81 g, 33.9 mmol) in the presence of 60% NaH (1.35 g, 33.9 mmol) in dry THF to afford compound **26a** as white solid (3.3 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.45 (d, J=8.3 Hz, 1H), 7.64 (t, J=7.5 Hz, 1H), 7.51–7.39 (m, 7H), 6.46 (s, 1H), 3.43 (s, 3H). MS (ESI) m/z 236 $(M+H)^+$.

*4.2.17. 2,6-Dimethyl-3-phenyl-2H-isoquinolin-1-one (**26b**).* The procedure described for compound **24** was used with 3-aryl isoquinolinone **23b** (995 mg, 4.23 mmol) and MeI (1.20 g, 8.45 mmol) in the presence of 60% NaH (338 mg, 8.45 mmol) in dry THF to afford compound **26b** as white free flowing solid (708 mg, 67%). Mp: 143–145 °C. IR (cm^{-1}): 1644. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.33 (d, J=7.8 Hz, 1H), 7.48–7.45 (m, 3H), 7.41–7.38 (m, 2H), 7.31–7.27 (m, 2H), 6.38 (s, 1H), 3.41 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.3, 143.9, 142.7, 136.5, 136.3, 128.8, 128.7, 128.5, 128.2, 127.7, 125.4, 122.6, 107.3, 34.0, 21.7. MS (ESI) m/z 250 $(M+H)^+$.

*4.2.18. 2,7-Dimethyl-3-phenyl-2H-isoquinolin-1-one (**26c**).* The procedure described for compound **24** was used with 3-aryl isoquinolinone **23c** (1.29 g, 5.48 mmol) and MeI (1.55 g, 10.9 mmol) in the presence of 60% NaH (439 mg, 10.9 mmol) in dry THF to afford compound **26c** as orange solid (1.1 g, 77%). Mp: 93–95 °C. IR (cm^{-1}): 1644. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.25 (s, 1H), 7.48–7.38 (m, 7H), 6.43 (s, 1H), 3.42 (s, 3H), 2.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.3, 142.9, 136.6, 136.3, 134.0, 133.7, 128.8, 128.5, 127.3, 125.7, 124.7, 107.4, 34.1, 21.5. HRMS (EI^+): calcd for $C_{17}H_{16}NO$, 250.1232; found, 250.1291.

*4.2.19. 2-Methyl-3-o-tolyl-2H-isoquinolin-1-one (**26d**).* The procedure described for compound **24** was used with 3-aryl isoquinolinone **23d** (3.60 g, 15.3 mmol) and MeI (4.34 g, 30.6 mmol) in the presence of 60% NaH (1.2 g, 30.6 mmol) in dry THF to afford compound **26d** as transparent viscous liquid (2.9 g, 78%). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.25 (d, J=8.1 Hz, 1H), 7.74–7.64 (m, 2H), 7.55–7.49 (m, 1H), 7.45–7.37 (m, 2H), 7.34–7.33 (m, 2H), 6.52 (s, 1H), 3.15 (s, 3H), 2.15 (s, 3H). MS (ESI) m/z 250 $(M+H)^+$.

*4.2.20. 2,6-Dimethyl-3-o-tolyl-2H-isoquinolin-1-one (**26e**).* The procedure described for compound **24** was used with 3-aryl isoquinolinone **23e** (1.82 g, 7.32 mmol) and MeI (2.07 g, 14.6 mmol) in the presence of 60% NaH (586 mg, 14.6 mmol) in dry THF to afford compound **26e** as off-white solid (1.8 g, 92%). Mp: 110–111 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.13 (d, J=8.4 Hz, 1H), 7.43–7.31 (m, 6H), 6.42 (s, 1H), 3.12 (s, 3H), 2.43 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.1, 143.0, 142.6, 136.6, 136.5, 135.8, 130.2, 129.2, 129.1, 128.1, 127.7, 126.0, 125.4, 122.7, 106.5, 32.5, 21.7, 19.3. MS (ESI) m/z 286 $(M+Na)^+$.

*4.2.21. 2-Methyl-1-oxo-3-phenyl-1,2-dihydro-isoquinoline-4-carbaldehyde (**22a**).* The procedure described for compound **13** was used with *N*-methylated isoquinolinone **26a** (3.02 g, 12.8 mmol), dimethylformamide (30 mL), and phosphorus oxychloride (9.84 g, 64.2 mmol) to give compound **22a** as off-white floppy solid (3.1 g, 92%). Mp: 142–148 °C. IR (cm^{-1}): 1651, 1316. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.28 (br s, 1H), 9.39 (s, 1H), 9.08 (d, J=8.4 Hz, 1H), 8.36 (d, J=6.9 Hz, 1H), 7.86 (t, J=7.6 Hz, 1H), 7.68–7.53 (m, 6H), 3.18 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 191.2, 162.7, 157.2, 133.7, 133.1, 131.8, 130.1, 129.3, 129.2, 127.8, 127.7, 125.3, 124.3, 113.5, 33.9. HRMS (EI^+): calcd for $C_{17}H_{14}NO_2$, 264.1024; found, 264.1026.

*4.2.22. 2,6-Dimethyl-1-oxo-3-phenyl-1,2-dihydro-isoquinoline-4-carbaldehyde (**22b**).* The procedure described for compound **13** was used with *N*-methylated isoquinolinone **26b** (680 mg, 2.72 mmol), dimethylformamide (30 mL), and phosphorus oxychloride (2.09 g, 13.6 mmol) to give compound **22b** as white floppy solid (641 mg, 84%). Mp: 143–145 °C. IR (cm^{-1}): 1647, 1305. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.46 (s, 1H), 9.00 (s, 1H), 8.38 (d, J=8.4 Hz, 1H), 7.58–7.56 (m, 3H), 7.42–7.36 (m, 3H), 3.29 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 191.3, 162.7, 157.3, 144.6, 133.1, 131.9, 130.0, 129.3, 129.3, 129.1, 128.7, 128.5, 128.2, 127.7, 125.0, 113.4, 33.8, 22.3. HRMS (EI^+): calcd for $C_{18}H_{16}NO_2$, 278.1181; found, 278.1188.

*4.2.23. 2,7-Dimethyl-1-oxo-3-phenyl-1,2-dihydro-isoquinoline-4-carbaldehyde (**22c**).* The procedure described for compound **13** was used with *N*-methylated isoquinolinone **26c** (1.03 g, 4.16 mmol), dimethylformamide (15 mL), and phosphorus oxychloride (3.19 g, 20.8 mmol) to give compound **22c** as orange solid (974 mg, 84%). Mp: 162–167 °C. IR (cm^{-1}): 1642, 1316. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.46 (s, 1H), 9.07 (d, J=8.4 Hz, 1H), 8.29 (s, 1H), 7.62–7.55 (m, 4H), 7.39–7.36 (m, 2H), 3.30 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 191.3, 162.7, 156.3, 137.9, 135.1, 131.9, 130.7, 130.0, 129.4, 129.1, 127.2, 125.2, 124.3, 113.6, 33.9, 21.3. MS (ESI) m/z 278 $(M+H)^+$.

*4.2.24. 2-Methyl-1-oxo-3-o-tolyl-1,2-dihydro-isoquinoline-4-carbaldehyde (**22d**).* The procedure described for compound **13** was used with *N*-methylated isoquinolinone **26d** (2.74 g, 10.9 mmol), dimethylformamide (25 mL), and phosphorus oxychloride (8.42 g, 54.9 mmol) to give compound **22d** as reddish brown solid (2.1 g, 69%). Mp: 115–120 °C. IR (cm^{-1}): 1646, 1316. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.45 (s, 1H), 9.19 (d, J=7.8 Hz, 1H), 8.50 (d, J=8.1 Hz, 1H), 7.79 (t, J=7.8 Hz, 1H), 7.59 (t, J=7.6 Hz, 1H), 7.50–7.45 (m, 1H), 7.41–7.36 (m, 2H), 7.27–7.24 (m, 1H), 3.26 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 191.0, 162.9, 157.0, 136.4, 133.7, 133.1, 131.5, 130.8, 130.3, 129.3, 127.7, 126.7, 125.3, 124.2, 113.0, 32.9, 19.4. MS (ESI) m/z 278 $(M+H)^+$.

*4.2.25. 2,6-Dimethyl-1-oxo-3-o-tolyl-1,2-dihydro-isoquinoline-4-carbaldehyde (**22e**).* The procedure described for compound **13** was used with *N*-methylated isoquinolinone **26e** (1.71 g, 6.51 mmol), dimethylformamide (30 mL), and phosphorus oxychloride (4.99 g, 32.6 mmol) to give compound **22e** as off-white solid (1.5 g, 78%). Mp: 126–133 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.43 (s, 1H), 9.01 (s, 1H), 8.39 (d, J=8.1 Hz, 1H), 7.50–7.35 (m, 4H), 7.26–7.23 (m, 1H), 3.25 (s, 3H), 2.54 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 191.1, 162.8, 157.1, 144.6, 136.4, 133.2, 131.6, 130.8, 130.3, 129.2, 127.7, 126.6, 125.0, 122.0, 112.9, 32.8, 22.2, 19.4. MS (ESI) m/z 346 $(M+Na+CH_3OH)^+$.

*4.2.26. 4-Hydroxymethyl-2-methyl-3-phenyl-2H-isoquinolin-1-one (**20a**).* 98% $NaBH_4$ (343 mg, 8.87 mmol) was added portion wise to a solution of compound **22a** (1.55 g, 5.91 mmol) in methanol at 0 °C. The reaction mixture was then warmed to room temperature and stirred overnight. The solvent was removed in vacuo. Water was poured into the residue followed by saturated NH_4Cl solution (20 mL) and extracted with ethyl acetate. The combined ethyl

acetate extracts were washed with water and brine, dried over anhydrous sodium sulfate, and then concentrated. The residue was purified by column chromatography on silica gel with *n*-hexane–ethyl acetate 3:1 to give compound **20a** as free flowing shiny white crystals (1.4 g, 92%). Mp: 156–157 °C. IR (cm^{-1}): 3398, 1629. ^1H NMR (300 MHz, DMSO-d_6) δ: 8.32 (d, J=8.0 Hz, 1H), 7.99 (d, J=8.1 Hz, 1H), 7.79 (t, J=7.0 Hz, 1H), 7.58–7.53 (m, 4H), 7.46–7.43 (m, 2H), 4.80 (t, J=4.8 Hz, 1H), 4.22 (d, J=4.8 Hz, 2H), 3.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.7, 142.9, 135.8, 134.3, 132.4, 129.1, 128.9, 128.0, 126.7, 125.3, 123.5, 114.1, 59.2, 34.1. MS (ESI) m/z 266 $(M+H)^+$.

*4.2.27. 4-Hydroxymethyl-2,6-dimethyl-3-phenyl-2H-isoquinolin-1-one (**20b**).* The procedure described for compound **20a** was used with compound **22b** (623 mg, 2.24 mmol) and 98% $NaBH_4$ (130 mg, 3.36 mmol) to give compound **20b** as free flowing white solid (448 mg, 71%). Mp: 187–189 °C. ^1H NMR (300 MHz, DMSO-d_6) δ: 8.20 (d, J=8.1 Hz, 1H), 7.78 (s, 1H), 7.57–7.52 (m, 3H), 7.45–7.36 (m, 3H), 4.73 (t, J=5.1 Hz, 1H), 4.20 (d, J=4.8 Hz, 2H), 3.10 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 162.6, 143.1, 143.0, 135.9, 134.4, 129.0, 128.9, 128.3, 128.1, 123.2, 123.1, 113.8, 59.2, 34.0, 22.0. MS (ESI) m/z 280 $(M+H)^+$.

*4.2.28. 4-Hydroxymethyl-2,7-dimethyl-3-phenyl-2H-isoquinolin-1-one (**20c**).* The procedure described for compound **20a** was used with compound **22c** (934 mg, 3.36 mmol) and 98% $NaBH_4$ (195 mg, 5.05 mmol) to give compound **20c** as free flowing white solid (778 mg, 82%). Mp: 173–174 °C. IR (cm^{-1}): 3385, 1617. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.32 (s, 1H), 7.84 (d, J=8.4 Hz, 1H), 7.57–7.49 (m, 4H), 7.34–7.30 (m, 2H), 4.46 (d, J=5.7 Hz, 2H), 3.24 (s, 3H), 2.52 (s, 3H), 1.39 (t, J=5.7 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 162.6, 142.0, 136.8, 134.3, 133.9, 133.5, 129.1, 129.0, 128.8, 127.6, 125.2, 123.5, 114.0, 59.2, 34.1, 21.3. MS (ESI) m/z 302 $(M+Na)^+$.

*4.2.29. 4-Hydroxymethyl-2-methyl-3-o-tolyl-2H-isoquinolin-1-one (**20d**).* The procedure described for compound **20a** was used with compound **22d** (2.05 g, 7.42 mmol) and 98% $NaBH_4$ (421 mg, 11.1 mmol) to give compound **20d** as free flowing white solid (1.2 g, 60%). Mp: 176–178 °C. IR (cm^{-1}): 3409, 1589. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.54 (d, J=8.1 Hz, 1H), 7.95 (d, J=7.9 Hz, 1H), 7.74 (t, J=7.5 Hz, 1H), 7.55 (t, J=7.5 Hz, 1H), 7.42–7.31 (m, 3H), 7.22–7.19 (m, 1H), 4.59–4.33 (m, 2H), 3.22 (s, 3H), 2.14 (s, 3H), 1.34 (t, J=5.7 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 162.8, 142.2, 136.5, 135.9, 133.9, 132.4, 130.5, 129.4, 129.1, 128.1, 126.7, 126.4, 125.3, 123.5, 113.6, 59.1, 33.0, 19.4. MS (ESI) m/z 302 $(M+Na)^+$.

*4.2.30. 4-Hydroxymethyl-2,6-dimethyl-3-o-tolyl-2H-isoquinolin-1-one (**20e**).* The procedure described for compound **20a** was used with compound **22e** (1.49 g, 5.13 mmol) and 98% $NaBH_4$ (297 mg, 7.69 mmol) to give compound **20e** as white solid (917 mg, 48%). Mp: 180–181 °C. IR (cm^{-1}): 3364, 1627. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.42 (d, J=8.1 Hz, 1H), 7.72 (s, 1H), 7.44–7.31 (m, 4H), 7.19 (d, J=7.5 Hz, 1H), 4.57–4.31 (m, 2H), 3.20 (s, 3H), 2.53 (s, 3H), 2.13 (s, 3H), 1.34 (t, J=5.5 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 162.8, 143.0, 142.3, 136.5, 135.9, 134.0, 130.5, 129.4, 129.1, 128.3, 128.1, 126.4, 123.1, 113.3, 59.2, 32.9, 22.0, 19.3. MS (ESI) m/z 316 $(M+Na)^+$.

*4.2.31. 4-Methoxymethyl-2-methyl-3-phenyl-2H-isoquinolin-1-one (**17aa**).* Concentrated HCl (791 mg, 7.59 mmol) was added to a solution of compound **20a** (200 mg, 0.76 mmol) in methanol (20 mL) and refluxed for 5 h. The reaction was diluted with water and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water and brine and dried over anhydrous sodium sulfate. After removing the solvent, the residue was purified by column chromatography on silica gel with *n*-hexane–ethyl acetate 1:1 to afford **17aa** as white crystals (196 mg, 92%). Mp: 129–131 °C. IR (cm^{-1}): 1644. ^1H NMR (300 MHz, DMSO-d_6) δ: 8.32 (d, J=8.1 Hz, 1H), 7.83 (d, J=7.5 Hz, 1H), 7.78 (t, J=7.5 Hz, 1H), 7.59–7.53 (m, 4H), 7.43–7.40 (m, 2H), 4.13 (s, 2H), 3.14 (s, 3H), 3.09 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 162.8, 143.6, 136.1, 134.4, 132.3, 129.2, 129.0, 128.7, 127.9, 126.7, 125.3, 123.6, 111.5, 68.7, 57.7, 34.2. MS (ESI) m/z 280 $(M+H)^+$, 248 $(M-31)^+$.

*4.2.32. 4-Ethoxymethyl-2-methyl-3-phenyl-2H-isoquinolin-1-one (**17ab**).* The same procedure as described in the preparation of compound **17aa** was used with compound **20a** (200 mg, 0.76 mmol) and concentrated HCl (791 mg, 7.59 mmol) in ethanol (20 mL) to give **17ab** as white crystals (208 mg, 93%). Mp: 118–120 °C. ^1H NMR (300 MHz, DMSO-d_6) δ: 8.32 (d, J=7.9 Hz, 1H), 7.87 (d, J=8.1 Hz, 1H), 7.78 (t, J=7.6 Hz, 1H), 7.58–7.53 (m, 4H), 7.44–7.40 (m, 2H), 4.16 (s, 2H), 3.28 (q, J=6.9 Hz, 2H), 3.14 (s, 3H), 0.98 (t, J=6.9 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 162.8, 143.4, 136.2, 134.4, 132.3, 129.3, 129.0, 128.7, 127.9, 126.6, 125.3, 123.7, 111.7, 66.7, 65.4, 34.2, 15.1. MS (ESI) m/z 294 $(M+H)^+$, 248 $(M-45)^+$.

*4.2.33. 2-Methyl-3-phenyl-4-propoxymethyl-2H-isoquinolin-1-one (**17ac**).* The same procedure as described in the preparation of compound **17aa** was used with compound **20a** (200 mg, 0.76 mmol) and concentrated HCl (791 mg, 7.59 mmol) in 1-propanol (15 mL) to give **17ac** as viscous liquid (187 mg, 80%). ^1H NMR (300 MHz, DMSO-d_6) δ: 8.32 (d, J=8.1 Hz, 1H), 7.86 (d, J=8.1 Hz, 1H), 7.78 (t, J=7.6 Hz, 1H), 7.58–7.53 (m, 4H), 7.44–7.40 (m, 2H), 4.16 (s, 2H), 3.18 (t, J=6.6 Hz, 2H), 3.14 (s, 3H), 1.43–1.31 (m, 2H), 0.77 (t, J=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.8, 143.4, 136.2, 134.4, 132.3, 129.3, 129.0, 128.6, 127.9, 126.6, 125.3, 123.8, 71.9, 66.9, 34.2, 22.7, 10.6. MS (ESI) m/z 308 $(M+H)^+$, 248 $(M-59)^+$.

*4.2.34. 4-Isopropoxymethyl-2-methyl-3-phenyl-2H-isoquinolin-1-one (**17ad**).* The same procedure as described in the preparation of compound **17aa** was used with compound **20a** (150 mg, 0.57 mmol) and concentrated HCl (594 mg, 5.69 mmol) in isopropyl alcohol (20 mL) to give **17ad** as white solid (134 mg, 76%). Mp: 81–84 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.50 (d, J=8.1 Hz, 1H), 7.86 (d, J=8.4 Hz, 1H), 7.70 (t, J=7.6 Hz, 1H), 7.54–7.48 (m, 4H), 7.37–7.34 (m, 2H), 4.21 (s, 2H), 3.49 (septet, J=6.0 Hz, 1H), 3.27 (s, 3H), 1.07 (d, J=6.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.8, 143.4, 136.3, 134.4, 132.2, 129.2, 129.0, 128.6, 127.9, 126.6, 125.4, 123.6, 111.8, 71.0, 64.4, 34.2, 21.9. MS (ESI) m/z 308 $(M+H)^+$, 248 $(M-59)^+$.

*4.2.35. 4-Isobutoxymethyl-2-methyl-3-phenyl-2H-isoquinolin-1-one (**17ae**).* The same procedure as described in the preparation of compound **17aa** was used with compound **20a** (150 mg, 0.57 mmol) and concentrated HCl (594 mg, 5.69 mmol) in isobutyl alcohol (20 mL) to give **17ae** as transparent liquid (89 mg, 48%). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.50 (d, J=8.1 Hz, 1H), 7.86 (d, J=8.4 Hz, 1H), 7.70 (t, J=7.6 Hz, 1H),7.54–7.48 (m, 4H), 7.37–7.33 (m, 2H), 4.20 (s, 2H), 3.27 (s, 3H), 3.07 (d, J=6.6 Hz, 2H), 1.84–1.70 (m, 1H), 0.85 (d, J=6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.9, 143.4, 136.3, 134.5, 132.3, 129.3, 129.0, 128.7, 127.9, 126.6, 125.4, 123.8, 111.8, 67.1, 34.2, 28.2, 19.4. MS (ESI) m/z 322 $(M+H)^+$, 248 $(M-73)^+$.

*4.2.36. 4-(2-Hydroxy-ethoxymethyl)-2-methyl-3-phenyl-2H-isoquinolin-1-one (**17af**).* The same procedure as described in the preparation of compound **17aa** was used with compound **20a** (200 mg, 0.76 mmol) and concentrated HCl (791 mg, 7.59 mmol) in ethylene glycol (15 mL) to give **17af** as white solid (186 mg, 79%). Mp: 122–126 °C. IR (cm^{-1}): 3445, 1633. ^1H NMR (300 MHz, DMSO-d_6) δ: 8.31 (d, J=7.9 Hz, 1H), 7.92 (d, J=8.1 Hz, 1H), 7.78 (t, J=7.6 Hz, 1H), 7.58–7.53 (m, 4H), 7.44–7.41 (m, 2H), 4.52 (t, J=5.4 Hz, 1H), 4.20 (s, 1H), 3.37 (q, J_1=5.4, 5.1 Hz, 2H), 3.25 (t, J=5.1 Hz, 2H), 3.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.7, 143.7, 136.0, 134.3, 132.4,

129.2, 128.8, 128.0, 126.7, 125.3, 123.5, 111.2, 70.9, 67.3, 61.6, 34.2. MS (ESI) m/z 310 $(M+H)^+$, 248 $(M-61)^+$.

*4.2.37. 4-(2-Methoxy-ethoxymethyl)-2-methyl-3-phenyl-2H-isoquinolin-1-one (**17ag**).* The same procedure as described in the preparation of compound **17aa** was used with compound **20a** (200 mg, 0.76 mmol) and concentrated HCl (594 mg, 5.69 mmol) in 2-methoxy ethanol (15 mL) to give **17ag** as viscous transparent liquid (204 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.50 (d, J=8.1 Hz, 1H), 7.92 (d, J=7.8 Hz, 1H), 7.70 (t, J=7.6 Hz, 1H), 7.54–7.50 (m, 4H), 7.35–7.32 (m, 2H), 4.33 (s, 2H), 3.45 (s, 4H), 3.31 (s, 3H), 3.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.8, 143.5, 136.1, 134.3, 132.3, 129.2, 129.0, 128.7, 127.8, 126.6, 125.3, 123.9, 111.3, 71.7, 68.8, 58.8, 34.1. MS (ESI) m/z 346 $(M+Na)^+$, 248 $(M-75)^+$.

*4.2.38. 4-(2-Chloro-ethoxymethyl)-2-methyl-3-phenyl-2H-isoquinolin-1-one (**17ah**).* The same procedure as described in the preparation of compound **17aa** was used with compound **20a** (200 mg, 0.76 mmol) and concentrated HCl (791 mg, 7.59 mmol) in 2-chloroethanol (10 mL) to give **17ah** as off-white solid (133 mg, 52%). Mp: 108–110 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.49 (d, J=7.9 Hz, 1H), 7.87 (d, J=8.1 Hz, 1H), 7.70 (t, J=7.5 Hz, 1H), 7.54–7.49 (m, 4H), 7.35–7.32 (m, 2H), 4.31 (s, 2H), 3.59–3.48 (m, 4H), 3.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.8, 143.9, 136.0, 134.2, 132.4, 129.2, 128.8, 127.9, 126.8, 125.3, 123.7, 110.9, 69.8, 67.3, 42.6, 34.2. MS (ESI) m/z 248 $(M-79)^+$.

*4.2.39. 4-Ethoxymethyl-2,6-dimethyl-3-phenyl-2H-isoquinolin-1-one (**17ba**).* The same procedure as described in the preparation of compound **17aa** was used with compound **20b** (200 mg, 0.71 mmol) and concentrated HCl (766 mg, 7.15 mmol) in ethanol (20 mL) to give **17ba** as off-white solid (199 mg, 90%). Mp: 101–103 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.39 (d, J=8.1 Hz, 1H), 7.64 (s, 1H), 7.52–7.50 (m, 3H), 7.35–7.32 (m, 3H), 4.23 (m, 2H), 3.38 (q, J=6.9 Hz, 2H), 3.26 (s, 3H), 3.53 (s, 3H), 1.14 (d, J=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.8, 143.5, 142.7, 136.3, 134.6, 129.3, 128.9, 128.6, 128.2, 127.9, 123.4, 123.1, 111.4, 66.6, 65.3, 34.1, 22.1, 15.1. MS (ESI) m/z 308 $(M+H)^+$.

*4.2.40. 4-Isobutoxymethyl-2,6-dimethyl-3-phenyl-2H-isoquinolin-1-one (**17bb**).* The same procedure as described in the preparation of compound **17aa** was used with compound **20b** (210 mg, 0.75 mmol) and concentrated HCl (783 mg, 7.51 mmol) in 2-methyl-1-propanol (15 mL) to give **17bb** as white solid (223 mg, 88%). Mp: 71–74 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.39 (d, J=8.1 Hz, 1H), 7.64 (s, 1H), 7.53–7.48 (m, 3H), 7.35–7.32 (m, 3H), 4.20 (s, 2H), 3.26 (s, 3H), 3.80 (d, J=6.6 Hz, 2H), 2.52 (s, 3H), 1.79 (m, 1H), 0.86 (d, J=6.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.8, 143.4, 142.6, 136.3, 134.6, 129.3, 128.9, 128.6, 128.2, 127.9, 123.6, 123.2, 111.6, 67.2, 34.1, 28.1, 22.1, 19.3. MS (ESI) m/z 358 $(M+Na)^+$.

*4.2.41. 4-Isobutoxymethyl-2,7-dimethyl-3-phenyl-2H-isoquinolin-1-one (**17ca**).* The same procedure as described in the preparation of compound **17aa** was used with compound **20c** (200 mg, 0.71 mmol) and concentrated HCl (746 mg, 7.16 mmol) in 2-methyl-1-propanol (10 mL) to give **17ca** as yellowish brown viscous liquid (217 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.30 (s, 1H), 7.75 (d, J=8.4 Hz, 1H), 7.54–7.47 (m, 4H), 7.35–7.32 (m, 2H), 4.19 (s, 2H), 3.26 (s, 3H), 3.06 (d, J=6.6 Hz, 2H), 2.51 (s, 3H), 1.76 (m, 1H), 0.84 (d, J=6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.8, 142.4, 136.6, 134.5, 133.9, 133.7, 129.4, 128.9, 128.8, 128.6, 127.4, 125.3, 123.8, 111.8, 77.1, 67.2, 34.2, 28.2, 21.3, 19.3. HRMS (EI^+): calcd for $C_{22}H_{26}NO_2$, 336.1964; found, 336.1965.

*4.2.42. 4-Ethoxymethyl-2-methyl-3-o-tolyl-2H-isoquinolin-1-one (**17da**).* The same procedure as described in the preparation of compound **17aa** was used with compound **20d** (200 mg, 0.71 mmol) and concentrated HCl (746 mg, 7.15 mmol) in ethanol (10 mL) to give **17da** as transparent crystals (198 mg, 89%). Mp: 103–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.51 (d, J=8.1 Hz, 1H), 7.87 (d, J=8.1 Hz, 1H), 7.71 (t, J=7.6 Hz, 1H), 7.52 (t, J=7.6 Hz, 1H), 7.43–7.30 (m, 3H), 7.23–7.21 (m, 1H), 4.33–4.08 (m, 2H), 3.35 (q, J=7.2 Hz, 2H), 3.22 (s, 3H), 2.13 (s, 3H), 1.10 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.9, 142.6, 136.7, 136.2, 134.1, 132.3, 130.3, 129.4, 129.3, 127.9, 126.6, 126.2, 125.3, 123.7, 111.4, 66.6, 65.5, 33.1, 19.3, 15.0. MS (ESI) m/z 330 $(M+Na)^+$, 308 $(M+H)^+$.

*4.2.43. 4-Isobutoxymethyl-2-methyl-3-o-tolyl-2H-isoquinolin-1-one (**17db**).* The same procedure as described in the preparation of compound **17aa** was used with compound **20d** (200 mg, 0.71 mmol) and concentrated HCl (746 mg, 7.15 mmol) in 2-methyl-1-propanol (15 mL) to give **17db** as transparent viscous liquid (218 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.51 (d, J=8.1 Hz, 1H), 7.86 (d, J=7.8 Hz, 1H), 7.70 (t, J=7.8 Hz, 1H), 7.52 (t, J=7.8 Hz, 1H), 7.43–7.29 (m, 3H), 7.23–7.20 (m, 1H), 4.31–4.05 (m, 2H), 3.22 (s, 3H), 3.05 (d, J=6.6 Hz, 2H), 2.13 (s, 3H), 1.74 (m, 1H), 0.82 (d, J=6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.0, 142.5, 136.7, 136.3, 134.1, 132.2, 130.3, 129.5, 129.3, 127.9, 126.6, 126.2, 125.3, 123.9, 111.6, 77.3, 67.1, 33.1, 28.1, 19.4. MS (ESI) m/z 358 $(M+Na)^+$, 336 $(M+H)^+$.

*4.2.44. 4-Ethoxymethyl-2,6-dimethyl-3-o-tolyl-2H-isoquinolin-1-one (**17ea**).* The same procedure as described in the preparation of compound **17aa** was used with compound **20e** (200 mg, 0.68 mmol) and concentrated HCl (710 mg, 6.81 mmol) in ethanol (10 mL) to give **17ea** as transparent viscous liquid (200 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.39 (d, J=8.1 Hz, 1H), 7.64 (s, 1H), 7.42–7.29 (m, 4H), 7.21 (d, J=7.8 Hz, 1H), 4.31–4.08 (m, 2H), 3.34 (q, J=6.9 Hz, 2H), 3.20 (s, 3H), 2.52 (s, 3H), 2.12 (s, 3H), 1.10 (t, J=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.9, 142.8, 136.8, 136.3, 134.2, 130.3, 129.4, 129.2, 128.2, 127.9, 126.1, 123.4, 111.2, 66.6, 65.5, 33.0, 22.1, 19.3, 15.0. MS (ESI) m/z 344 $(M+Na)^+$, 385 $(M+Na+CH_3CN)^+$.

*4.2.45. 4-Isobutoxymethyl-2,6-dimethyl-3-o-tolyl-2H-isoquinolin-1-one (**17eb**).* The same procedure as described in the preparation of compound **17aa** was used with compound **20e** (200 mg, 0.68 mmol) and concentrated HCl (710 mg, 6.81 mmol) in 2-methyl-1-propanol (15 mL) to give **17eb** as viscous liquid (197 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.40 (d, J=8.4 Hz, 1H), 7.64 (s, 1H), 7.42–7.28 (m, 4H), 7.21 (d, J=7.5 Hz, 1H), 4.29–4.04 (m, 2H), 3.20 (s, 2H), 3.05 (d, J=6.3 Hz, 2H), 2.51 (s, 3H), 2.12 (s, 3H), 1.75 (septet, J=6.9 Hz, 1H), 0.83 (d, J=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.9, 142.6, 142.5, 136.7, 136.4, 134.2, 130.3, 129.4, 129.2, 128.2, 127.9, 126.1, 123.7, 123.1, 111.3, 67.1, 32.9, 28.1, 22.1, 19.3. MS (ESI) m/z 372 $(M+Na)^+$, 413 $(M+Na+CH_3CN)^+$, 350 $(M+H)^+$.

*4.2.46. 2-Methyl-4-phenoxymethyl-3-phenyl-2H-isoquinolin-1-one (**18aa**).* Phenol (72 mg, 0.76 mmol), PPh_3 (249 mg, 0.95 mmol), and **20a** were dissolved in anhydrous tetrahydrofuran (10 mL) and stirred at 0 °C. 95% DIAD (275 mg, 1.29 mmol) was slowly added and stirred at room temperature. The reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated in vacuo to obtain yellowish oil. Excess phenol was neutralized into water soluble sodium salt with saturated $NaHCO_3$ solution. The reaction mixture was extracted with $CHCl_3$. The organic extract was dried over anhydrous sodium sulfate and evaporated in vacuo. The residue thus obtained was purified by column chromatography with n-hexane–ethyl acetate 5:1 on silica gel to afford **18aa** as white solid (139 mg, 53%). Mp: 124–126 °C. IR (cm^{-1}): 1643. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.36 (d, J=8.1 Hz, 1H), 7.81–7.72 (m, 2H), 7.58 (t, J=7.0 Hz, 1H), 7.51–7.42 (m, 5H), 7.23 (t, J=7.5 Hz, 2H), 6.91 (t, J=7.2 Hz, 1H), 6.84 (d, J=8.1 Hz, 2H), 4.74 (s, 2H), 3.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.9, 158.5, 144.4, 136.0, 134.0, 132.5,

129.4, 129.2, 128.9, 128.1, 126.9, 125.4, 123.4, 121.1, 114.9, 110.2, 65.0, 34.3. MS (ESI) *m*/*z* 364 $(M+Na)^+$.

*4.2.47. 4-(4-Bromo-phenoxymethyl)-2-methyl-3-phenyl-2H-isoquinolin-1-one (**18ab**).* The same procedure as described for the preparation of compound **18aa** was used with 4-bromophenol (132 mg, 0.76 mmol), PPh_3− (249 mg, 0.95 mmol), **20a** (260 mg, 0.98 mmol), 95% DIAD (275 mg, 1.29 mmol), and anhydrous THF to give **18ab** as white solid (157 mg, 49%). Mp: 187–190 °C. IR (cm^{-1}): 1651. ^1H NMR (300 MHz, DMSO-d_6) δ: 8.35 (d, *J*=7.8 Hz, 1H), 7.81–7.72 (m, 2H), 7.58 (t, *J*=7.2 Hz, 1H), 7.52–7.50 (m, 3H), 7.45–7.37 (m, 4H), 6.82 (d, *J*=8.7 Hz, 2H), 4.74 (s, 2H), 3.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.8, 157.5, 144.6, 135.9, 133.9, 132.6, 132.2, 129.3, 129.1, 128.9, 128.1, 126.9, 125.3, 123.2, 116.7, 113.3, 109.8, 65.4, 34.3. HRMS (EI^+): calcd for $C_{23}H_{19}^{79}BrNO_2$ and $C_{23}H_{19}^{81}BrNO_2$, 420.0599 and 422.0582; found, 420.0596 and 422.0688.

*4.2.48. 4-(4-Isopropyl-phenoxymethyl)-2-methyl-3-phenyl-2H-isoquinolin-1-one (**18ac**).* The same procedure as described for the preparation of compound **18aa** was used with 4-isopropylphenol (106 mg, 0.76 mmol), PPh_3− (249 mg, 0.95 mmol), **20a** (260 mg, 0.98 mmol), 95% DIAD (275 mg, 1.29 mmol), and anhydrous THF to give **18ac** as white solid (58 mg, 19%). Mp: 154–156 °C. ^1H NMR (300 MHz, DMSO-d_6) δ: 8.35 (d, *J*=8.5 Hz, 1H), 7.81–7.72 (m, 2H), 7.61–7.50 (m, 4H), 7.46–7.41 (m, 2H), 7.09 (d, *J*=8.7 Hz, 2H), 6.75 (d, *J*=8.7 Hz, 2H), 4.71 (s, 2H), 3.17 (s, 3H), 2.79 (septet, *J*=6.9 Hz, 1H), 1.14 (d, *J*=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.9, 156.5, 144.3, 141.6, 136.1, 134.0, 132.5, 129.2, 128.9, 128.1, 127.2, 126.8, 125.4, 123.5, 114.8, 110.3, 65.1, 34.3, 33.2. MS (ESI) *m*/*z* 406 $(M+Na)^+$, 447 $(M+Na+CH_3CN)^+$.

*4.2.49. 4-(2-Isopropyl-phenoxymethyl)-2-methyl-3-o-tolyl-2H-isoquinolin-1-one (**18da**).* The same procedure as described for the preparation of compound **18aa** was used with 2-isopropylphenol (100 mg, 0.71 mmol), PPh_3− (338 mg, 1.28 mmol), **20d** (260 mg, 0.93 mmol), 95% DIAD (274 mg, 1.28 mmol), and anhydrous THF to give **18da** as white solid (107 mg, 36%). Mp: 97–100 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.51 (d, *J*=7.6 Hz, 1H), 7.74–7.65 (m, 2H), 7.57–7.52 (m, 1H), 7.41–7.26 (m, 3H), 7.20–7.17 (m, 2H), 7.08 (t, *J*=7.8 Hz, 1H), 6.92 (t, *J*=6.6 Hz, 1H), 6.71 (d, *J*=7.2 Hz, 1H), 4.82–4.68 (m, 2H), 3.24 (s, 3H), 3.12 (m, 1H), 2.16 (s, 3H), 1.07 (t, *J*=5.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.0, 155.6, 143.3, 137.5, 136.7, 136.3, 133.7, 132.3, 130.6, 129.5, 129.3, 128.0, 126.8, 126.4, 126.1, 125.3, 123.7, 120.9, 111.5, 110.3, 64.9, 33.2, 26.4, 22.8, 22.7, 19.3. MS (ESI) *m*/*z* 398 $(M+H)^+$.

*4.2.50. 4-(2-Methoxy-4-methyl-phenoxymethyl)-2-methyl-3-o-tolyl-2H-isoquinolin-1-one (**18db**).* The same procedure as described for the preparation of compound **18aa** was used with 2-methoxy-4-methylphenol (99 mg, 0.71 mmol), PPh_3− (338 mg, 1.28 mmol), **20d** (260 mg, 0.93 mmol), 95% DIAD (274 mg, 1.28 mmol), and anhydrous THF to give **18db** as transparent viscous gel (173 mg, 60%). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.53 (d, *J*=7.9 Hz, 1H), 8.05 (d, *J*=7.8 Hz, 1H), 7.73 (t, *J*=7.6 Hz, 1H), 7.54 (t, *J*=7.6 Hz, 1H), 7.39–7.22 (m, 4H), 7.07 (d, *J*=6.3 Hz, 1H), 6.66 (s, 1H), 6.56 (s, 1H), 4.86–4.62 (m, 2H), 3.70 (s, 3H), 3.21 (m, 3H), 2.18 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.0, 150.8, 145.4, 143.5, 136.8, 136.3, 133.8, 132.6, 132.4, 130.3, 129.4, 129.3, 127.9, 126.7, 126.2, 125.3, 124.0, 120.8, 117.8, 113.1, 110.6, 67.4, 55.5, 33.1, 21.0, 19.3. MS (ESI) *m*/*z* 422 $(M+Na)^+$.

*4.2.51. 4-(3,5-Dimethyl-phenoxymethyl)-2,6-dimethyl-3-o-tolyl-2H-isoquinolin-1-one (**18ea**).* The same procedure as described for the preparation of compound **18aa** was used with 98% 3,5-dimethylphenol (60 mg, 0.71 mmol), PPh_3− (228 mg, 0.86 mmol), **20d** (184 mg, 0.62 mmol), 95% DIAD (185 mg, 0.86 mmol), and anhydrous THF to give **18ea** as viscous liquid (33 mg, 17%). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.43 (d, *J*=8.1 Hz, 1H), 7.50 (s, 1H), 7.40–7.18 (m, 6H), 6.60 (s, 1H), 6.43 (s, 1H), 4.68 (q, *J*=9.9 Hz, 2H), 3.22 (s, 3H), 2.47 (s, 3H), 2.25 (s, 6H), 2.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.9, 158.7, 143.6, 143.1, 139.1, 136.7, 136.2, 133.8, 130.5, 129.4, 129.3, 128.4, 128.1, 126.3, 123.2, 123.1, 122.7, 112.6, 109.9, 64.7, 33.0, 22.1, 21.3, 19.3. MS (ESI) *m*/*z* 420 $(M+Na)^+$.

*4.2.52. 4-(4-Chloro-2-methyl-phenoxymethyl)-2,6-dimethyl-3-o-tolyl-2H-isoquinolin-1-one (**18eb**).* The same procedure as described for the preparation of compound **18aa** was used with 97% 4-chloro2-methylphenol (100 mg, 0.68 mmol), PPh_3− (322 mg, 1.22 mmol), **20d** (260 mg, 0.88 mmol), 95% DIAD (261 mg, 1.22 mmol), and anhydrous THF to give **18eb** as transparent viscous gel (107 mg, 36%). ^1H NMR (300 MHz, DMSO-d_6) δ: 8.25 (d, *J*=8.1 Hz, 1H), 7.55 (s, 1H), 7.43–7.25 (m, 5H), 7.17 (s, 1H), 7.11–7.08 (m, 1H), 6.78 (d, *J*=8.7 Hz, 1H), 4.79–4.61 (m, 2H), 3.07 (s, 3H), 2.43 (s, 3H), 2.10 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.9, 155.3, 143.6, 142.9, 136.7, 136.3, 133.7, 130.5, 130.4, 129.5, 129.3, 129.2, 128.4, 128.1, 126.4, 126.2, 125.4, 123.1, 112.9, 109.7, 65.5, 33.1, 22.1, 19.3, 16.1. MS (ESI) *m*/*z* 440 $(M+Na)^+$.

*4.2.53. 2-Methyl-3-phenyl-4-propylaminomethyl-2H-isoquinolin-1-one (**19a**).* Thionyl chloride (10 mL) was added to compound **20a** (200 mg, 0.95 mmol) cooled in an ice bath. The reaction mixture was refluxed overnight. Excess thionyl chloride and volatile reaction by-products like HCl and SO_2 were removed by vacuum distillation. The residue was dissolved in CH_2Cl_2 and propylamine (5 mL) was added at 0 °C. After stirring overnight, the reaction mixture was diluted with water, and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2. The organic layers were washed with water and brine, dried over anhydrous sodium sulfate, and then concentrated. The residue was purified using column chromatography with *n*-hexane–ethyl acetate 3:1 to obtain compound **19a** as light yellow colored viscous liquid (254 mg, 85%). Mp: 63–74 °C. IR (cm^{-1}): 1649. ^1H NMR (300 MHz, DMSO-d_6) δ: 8.29 (d, *J*=7.9 Hz, 1H), 7.99 (d, *J*=8.1 Hz, 1H), 7.75 (t, *J*=7.6 Hz, 1H), 7.55–7.46 (m, 6H), 3.37 (s, 2H), 3.12 (s, 3H), 2.32 (t, *J*=6.9 Hz, 2H), 1.52 (br s, 1H), 1.31–1.19 (m, 2H), 0.76 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.6, 142.3, 136.2, 134.8, 132.3, 129.0, 128.9, 128.1, 126.6, 125.4, 123.5, 113.2, 51.5, 46.8, 34.1, 22.5, 11.5. MS (ESI) *m*/*z* 248 $(M-58)^+$.

*4.2.54. 4-Butylaminomethyl-2-methyl-3-phenyl-2H-isoquinolin-1-one (**19b**).* The same procedure as described for the preparation of compound **19a** was applied with compound **20a** (200 mg, 0.76 mmol), excess thionyl chloride, and *n*-butylamine (5 mL) to obtain **19b** as yellow solid (185 mg, 75%). Mp: 122–126 °C. IR (cm^{-1}): 1644. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.52 (d, *J*=7.9 Hz, 1H), 7.87 (d, *J*=8.4 Hz, 1H), 7.71 (t, *J*=7.8 Hz, 1H), 7.53–7.44 (m, 4H), 7.33–7.29 (m, 2H), 3.51 (s, 2H), 3.25 (s, 3H), 2.47 (t, *J*=6.9 Hz, 2H), 1.36–1.19 (m, 4H), 0.84 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.8, 141.8, 136.6, 134.9, 131.3, 129.6, 129.0, 128.9, 128.7, 128.1, 127.4, 126.4, 125.6, 125.3, 112.2, 51.9, 50.5, 34.2, 27.9, 20.6, 13.9. MS (ESI) *m*/*z* 248 $(M-72)^+$.

*4.2.55. 2-Methyl-4-[(3-morpholin-4-yl-propylamino)-methyl]-3-phenyl-2H-isoquinolin-1-one (**19c**).* The same procedure as described for the preparation of compound **19a** was used with compound **20a** (200 mg, 0.76 mmol), excess thionyl chloride, and 4-(3-aminopropyl morpholine) (5 mL) to obtain compound **19c** as transparent light yellow viscous liquid (142 mg, 47%). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.51 (d, *J*=8.7 Hz, 1H), 7.86 (d, *J*=7.8 Hz, 1H), 7.69 (t, *J*=7.6 Hz, 1H), 7.53–7.45 (m, 2H), 7.33–7.28 (m, 2H), 3.67–3.64 (m, 5H), 3.51 (s, 2H), 3.24 (s, 3H), 2.52 (t, *J*=6.9 Hz, 2H), 2.37–2.34 (m, 4H), 2.28 (t, *J*=7.5 Hz, 2H), 1.54 (pentet, *J*=7.5 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.6, 142.5, 135.9, 134.6, 132.4, 129.1, 128.9, 128.3, 126.7, 125.5, 123.3, 112.4, 66.7, 57.1, 53.6, 48.1, 46.8, 34.2, 25.7. MS (ESI) m/z 248 $(M-143)^+$, 392 $(M+H)^+$.

*4.2.56. 4-Diethylaminomethyl-2-methyl-3-phenyl-2H-isoquinolin-1-one (**19d**).* The same procedure as described for the preparation of compound **19a** was used with compound **20a** (200 mg, 0.76 mmol), excess thionyl chloride, and diethylamine (5 mL) to obtain compound **19d** as transparent light yellow viscous liquid (198 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.50 (d, J=8.1 Hz, 1H), 8.23 (d, J=8.1 Hz, 1H), 7.66 (t, J=7.6 Hz, 1H), 7.52–7.47 (m, 4H), 7.26–7.23 (m, 2H), 3.39 (s, 2H), 3.22 (s, 3H), 2.37 (q, J=7.2 Hz, 4H), 0.84 (t, J=7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.8, 142.1, 136.9, 135.0, 131.6, 129.8, 128.7, 127.5, 126.4, 125.3, 112.4, 51.6, 45.6, 34.1, 11.4. MS (ESI) m/z 248 $(M-72)^+$.

*4.2.57. 4-[(Diisopropylamino)-methyl]-2-methyl-3-phenyl-2H-isoquinolin-1-one (**19e**).* The same procedure as described for the preparation of compound **19a** was used with compound **20a** (200 mg, 0.76 mmol), excess thionyl chloride, and diisopropylamine (5 mL) to obtain compound **19e** as white solid (109 mg, 41%). Mp: 103–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.19 (d, J=8.7 Hz, 1H), 7.64–7.57 (m, 2H), 7.51–7.45 (m, 4H), 7.25–7.22 (m, 2H), 3.54 (s, 2H), 3.21 (s, 3H), 2.97 (septet, J=6.9 Hz, 2H), 0.83 (d, J=6.9 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.8, 142.2, 136.9, 135.02, 133.7, 131.1, 130.1, 129.7, 129.3, 129.1, 128.7, 128.6, 127.7, 127.3, 126.3, 125.5, 125.3, 112.6, 45.7, 43.0, 34.1, 20.4. MS (ESI) m/z 349 $(M+H)^+$.

*4.2.58. 3-(2-Methyl-1-oxo-3-phenyl-1,2-dihydro-isoquinolin-4-yl)-2-phenyl-acrylonitrile (**21**).* Benzyl cyanide (178 mg, 1.51 mmol) and **22a** (200 mg, 0.76 mmol) were added into a 100-mL oven-dried, three-necked flask and was sealed with septa. The flask was then evacuated/backfilled with N_2 three times before starting the reaction. Ethanol (10 mL) was injected and the mixture was stirred for 30 min. Solution of 95% *t*-BuOK (80 mg, 0.9 mmol) in 5 mL ethanol was injected drop wise and stirred at room temperature. The reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with water and extracted with ethyl acetate. The organic extract was dried with brine and over anhydrous sodium sulfate, and then concentrated in vacuo. The residue obtained was purified by MPLC with *n*-hexane–ethyl acetate (5:1) to obtain **21** as light yellow solid (217 mg, 78%). Mp: 178–182 °C. IR (cm^{-1}): 1645. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.56 (d, J=8.1 Hz, 1H), 7.73–7.67 (m, 1H), 7.59–7.54 (m, 2H), 7.51–7.43 (m, 3H), 7.39–7.34 (m, 7H), 7.21 (s, 1H), 3.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.5, 142.7, 139.4, 138.7, 134.4, 134.2, 133.0, 132.6, 132.5, 129.4, 129.3, 128.9, 128.6, 128.5, 128.4, 128.0, 127.2, 125.7, 124.9, 123.9, 120.4, 116.6, 111.3, 34.1. MS (ESI) m/z 385 $(M+Na)^+$.

Acknowledgements

This work was supported by Korea Research Foundation grant (NRF-2011-0015551).

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