ACS Combinatorial Science

Research Article

pubs.acs.org/acscombsci

# Solid-Phase Synthesis of Quinolinone Library

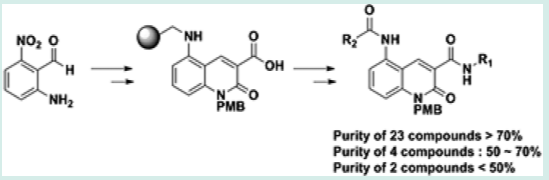
Seung-hwa Kwak,[†] Min jeong Kim,[†] So-Deok Lee,[†] Hyun You,[‡] Yong-Chul Kim,*[,†,‡] and Hyojin Ko*[,†]

[†]School of Life Sciences, Gwangju Institute of Science and Technology (GIST), Gwangju 500-712, Republic of Korea

[‡]Department of Medical System Engineering (DMSE), Gwangju Institute of Science and Technology, Gwangju 500-712, Republic of Korea

Supporting Information

**ABSTRACT:** Quinolinones have various biological activities, including antibacterial, anticancer, and antiviral properties. The 3-substituted amide quinolin-2(1*H*)-ones not only show antibacterial activity, but also act as immunomodulators, 5-HT$_4$ receptor agonists, cannabinoid receptor inverse agonists, and AchE and, BuchE inhibitors. To investigate the potent biological activity of 3-substituted amide quinolin-2(1*H*)-ones, a large number of 3,5-amide substituted-2-oxoquinolinones were prepared by parallel solid-phase synthesis. The compound 5-amino-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxylic acid was loaded onto 4-formyl-3,5-dimethoxyphenoxy (PL-FDMP) resin by reductive amination with high efficiency. Various building blocks were attached to the 3 and 5 positions to yield 3,5-disubstituted-2-oxoquinolinones with high purity and good yield. The ability some of these compound to inhibit the release of IL-1$\beta$, a cytokine involved in the immune response was measured, and they showed about 50% inhibition at 10 $\mu$M.




**KEYWORDS:** *quinolinone, solid-phase synthesis, IL-1β, immune response*

## INTRODUCTION

A large number of pharmacologically active molecules have been generated by synthesizing derivatives of quinolinone. Many of these compounds have potent and varied biological activities including antibacterial,[1,2] anticonvulsant,[3,4] and antithyroid[5−7] properties. In addition, amide derivatives of substituted 2-oxo-quinoline acids have shown anticancer[8−10] and antituberculosis[11−14] activities. Especially various 3-substituted amide quinolin-2(1*H*)-ones have shown potent activity, with compounds **1** acting as immunomodulators,[15] **2** as a 5-HT$_4$ receptor agonist,[16] **3** as cannabinoid receptor inverse agonists,[17] **4** as an AchE inhibitor, and **5** as a BuchE inhibitor[18] (Chart 1).

Roquinimex (**1a**, linomide) and laquinimod (**1b**) are synthetic immunomodulators developed by Active Biotech and Teva, respectively. Roquinimex has been shown effective against various types of cancer, including leukemia, and autoimmune disorders, including multiple sclerosis (MS),[19] rheumatoid arthritis, and type I diabetes,[20,21] as well as in MRL/l mice, (NZB_NZW) F1 hybrid mice, experimental autoimmune encephalomyelitis, and systemic lupus erythematosus. Compound **1a** can be categorized as both an immunostimulant and an immunosuppressant because it increases lymphocyte proliferation, interleukin-2 production and natural killer cell activity, and antagonizes the immunosuppressive effect of cyclosporine.[22] Laquinimod is a derivative of roquinimex, with less toxicity and greater efficacy than roquinimex in the MS model and in experimental autoimmune encephalomyelitis (EAE).[23−25] Although roquinimex and laquinimod have failed phase II and phase III clinical trials in patients with MS, they are useful for studies of related diseases. Tasquinimod (ABR215050, **1c**), which blocks the growth of new blood vessels to prostate cancers, has entered clinical trials for the treatment of prostate cancer.[26] Moreover, a phase III trial showed that tasquinimod delays disease progression compared with placebo. Compound **1d** inhibits proteinuria and anti-DNA antibody in chronic CVHD mice. It is comparable with prednisolone, a representative steroid used to treat nephritis.[27]

Optimization of established 5-HT$_4$ agonists, including renzapride, cisapride, and prucalopride, resulted in the synthesis of compound **2**, a selective, orally efficacious 5-HT$_4$ agonist for the potential treatment of gastrointestinal motility-related disorders.[28]

Compound **3a** (JTE-907) was found to be a selective inverse agonist for CB2 receptor in vitro and has anti-inflammatory properties in vivo.[17] Its fluorinated analogue **3b** showed increased potency, with a subnanomolar $K_i$. These compounds can be used to treat neuropathic pain, neuroinflammatory diseases, and immune disorders.[17]

Among the synthesized cholinesterase inhibitors, **4** was found to selectively inhibit AChE and **5** to selectively inhibit BuChE.[18]

To investigate the biological properties of molecules containing 2-oxo-quinoline-3-carboxamide, it is necessary to first synthesize these compounds. Few synthetic protocols for 3,5-carboxamide quinolin-2(1*H*)-one are available through combinatorial chemistry on solid support. In this study, we

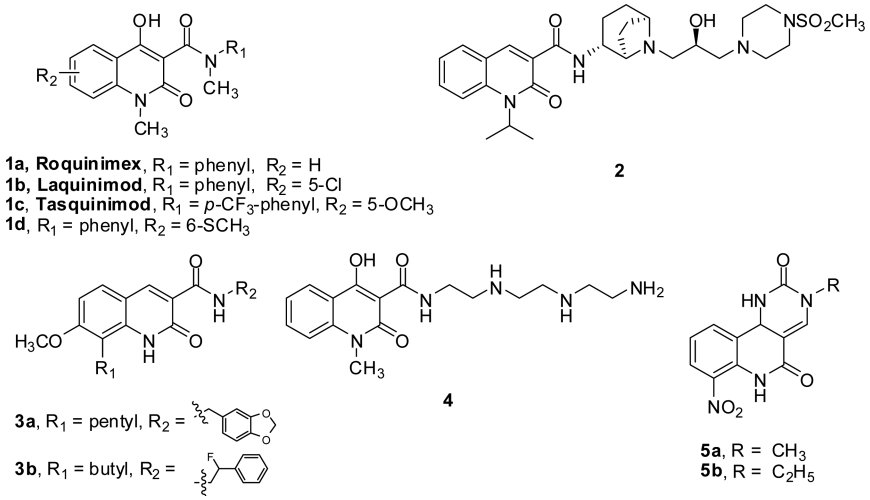
**Received:** October 10, 2014
**Revised:** November 11, 2014
**Published:** November 17, 2014



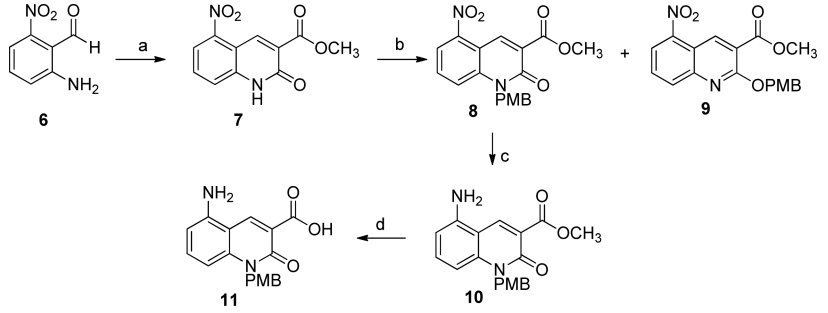


DOI: 10.1021/co5001585
*ACS Comb. Sci.* 2015, 17, 60−69

**Chart 1. Biologically Active 2-Oxo-quinoline-3-carboxamide**

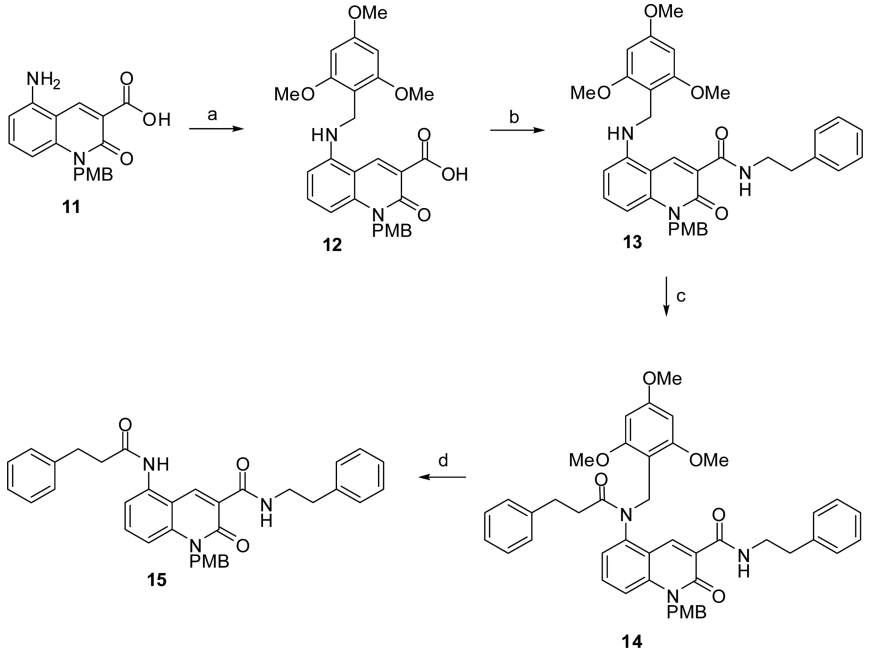



**Scheme 1**[a]




[a]Reagents and conditions: (a) $CH_3ONa$, dimethyl malonate, MeOH, 12 h; (b) PMBCl, $CS_2CO_3$, DMF, 12 h; (c) Pd/C, MeOH, $H_2$ gas, 1 h; (d) 10% KOH in DCM, 80 °C, 12 h.

**Scheme 2**[a]

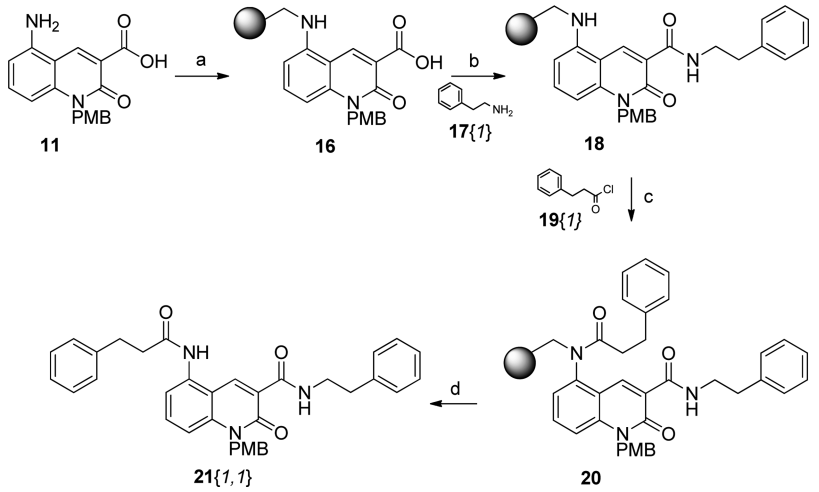



[a]Reagents and conditions: (a) 2,4,6-trimethoxy benzaldehyde, $NaBH(OAc)_3$, DCM, DCE, 12 h; (b) phenethylamine, PyBop, DIPEA, DCM, 3 h; (c) hydrocinnamoyl chloride, DIPEA, DCM, 15 min; (d) 10% TFA in DCM, 1 h.



DOI: 10.1021/co5001585
ACS Comb. Sci. 2015, 17, 60−69

**Scheme 3**[a]




[a]Reagents and conditions: (a) PL-FDMP resin, $NaBH(OAc)_3$, DCM, DCE, 12 h; (b) PyBop, DIPEA, DCM, 3 h; (c) DIPEA, DCM, 15 min; (d) 10% TFA in DCM, 1 h.

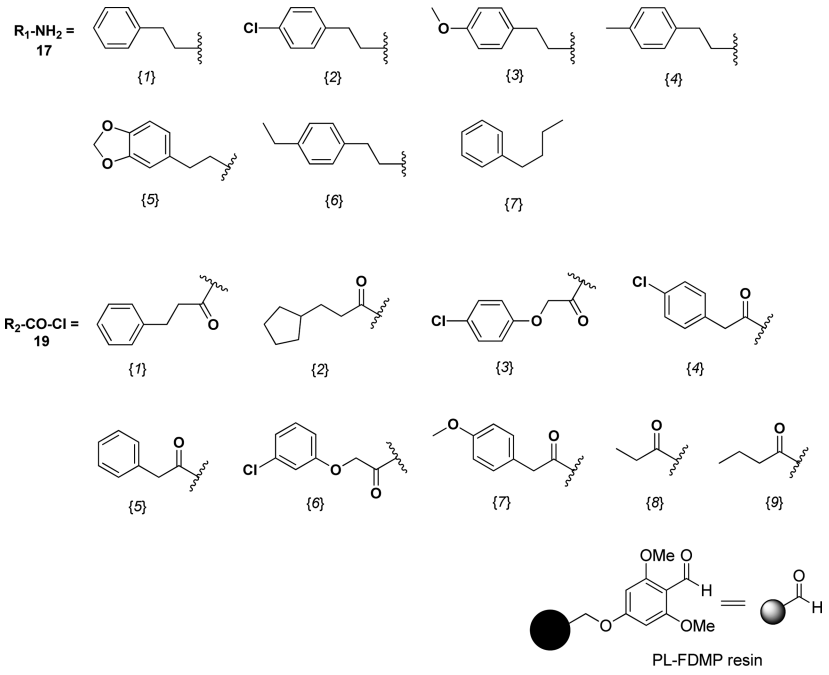



**Figure 1.** Building blocks and notation of final structures.

report the successful parallel solid-phase synthesis of various 3,5-carboxamide quinolin-2(1*H*)-ones, included those with two diversity points. Most of synthesized compounds showed high purity (>70%) after strong anion exchange (SAX) filtration. We also tested the ability of several of these compounds to inhibit IL-1$\beta$, an immune system cytokine.

## RESULTS AND DISCUSSION

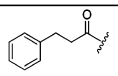
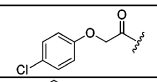
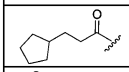
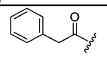
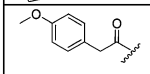
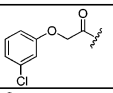
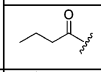
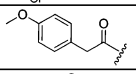
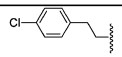
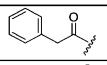
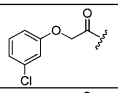
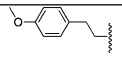
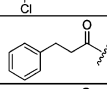
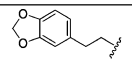
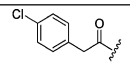
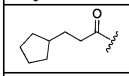
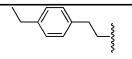
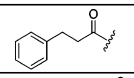
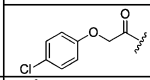
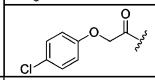
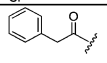
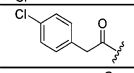
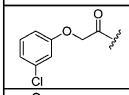
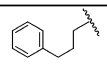
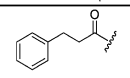
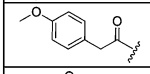
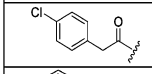
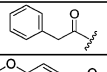
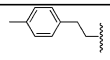
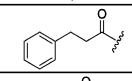
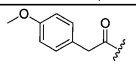
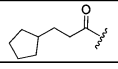
Parallel solid-phase synthesis was used to obtain various 3,5-carboxamide quinolin-2(1*H*)-one compounds. Prior to formulating a solid-phase method, a model study of solution-phase synthesis was performed, as shown in Schemes 1 and 2. Benzaldehyde **6** was prepared from anthranilic acids as described,[29] added to dimethyl malonate and condensed in the presence of sodium methoxide to form the quinolin-2(1*H*)-one ring of **7**. The nitro group at the 5-position of **7** was protected by a para-methoxybenzyl group (PMB) to produce a 1:1 mixture of compounds **8** and **9**. Although various agents, including potassium carbonate, sodium hydride and cesium carbonate, were tested for their ability to introduce the PMB group, cesium carbonate in DMF yielded the desired compound **8** and its regioisomer **9** as primary products without many side products. Compound **8** was converted to an amine using palladium activated on carbon. The methyl ester of **10** was hydrolyzed by treatment with 10% KOH in dichloromethane (DCM) to yield carboxylic acid **11**.

A mixture of **11** and sodium triacetoxyborohydride was added to 2,4,6-trimethoxy benzaldehyde in DCM and 1,2-dichloroethane (DCE) for reductive amination to produce **12** (Scheme 2). 2,4,6-Trimethoxy benzaldehyde was a substitute for PL-FDMP resin (4-formyl-3,5-dimethoxy phenoxy resin) as the solid-phase. Phenethylamine was coupled with 3-carboxylic



DOI: 10.1021/co5001585
*ACS Comb. Sci.* 2015, 17, 60−69

**Table 1. Summary of Prepared Products**

| Code of Structure | $R_1$ | $R_2$ | Purity[a] (%) | Yield[b] (%) | Code of Structure | $R_1$ | $R_2$ | Purity[a] (%) | Yield[b] (%) |
|---|---|---|---|---|---|---|---|---|---|
| **21**{*1,1*} |  |  | 52 | 86 | **21**{*4,3*} | |  | 90 | 76 |
| **21**{*1,2*} | |  | 85 | 59 | **21**{*4,5*} | |  | 39 | 41 |
| **21**{*1,7*} | |  | 75 | 85 | **21**{*4,6*} | |  | 80 | 53 |
| **21**{*1,9*} | |  | 38 | 22 | **21**{*4,7*} | |  | 77 | 44 |
| **21**{*2,5*} |  |  | 89 | 68 | **21**{*4,8*} | |  | 66 | 26 |
| **21**{*2,6*} | |  | 78 | 73 | **21**{*4,9*} | |  | 73 | 36 |
| **21**{*3,1*} |  |  | 79 | 55 | **21**{*5,4*} |  |  | 95 | 18 |
| **21**{*3,2*} | |  | 76 | 59 | **21**{*6,1*} |  |  | 72 | 74 |
| **21**{*3,3*} | |  | 90 | 76 | **21**{*6,3*} | |  | 73 | 76 |
| **21**{*3,5*} | |  | 69 | 64 | **21**{*6,4*} | |  | 90 | 76 |
| **21**{*3,6*} | |  | 79 | 53 | **21**{*7,1*} |  |  | 91 | 85 |
| **21**{*3,7*} | |  | 76 | 59 | **21**{*7,4*} | |  | 72 | 74 |
| **21**{*3,9*} | |  | 59 | 36 | **21**{*7,5*} | |  | 89 | 29 |
| **21**{*4,1*} |  |  | 72 | 74 | **21**{*7,7*} | |  | 94 | 54 |
| **21**{*4,2*} | |  | 91 | 51 | | | | | |

[a]All of the purified products were checked by HPLC after SAX purification. [b]Four-step overall yields from compound **11** (loading capacity of resin is 1.5 mmol/g).

acid **12** to produce **13** in the presence of DIPEA, PyBop, and DCM. However, we found that the chain length of $R_1$-$NH_2$ affected the reaction time. For example, the coupling reaction with benzylamine took 2−3 days, whereas the reaction with phenethylamine or an amine with a longer chain took around 3 h. Therefore, building blocks showing steric hindrance were excluded from parallel synthesis. PyBop was superior to EDC and HATU as a coupling agent in this step. However, when the amine was not protected by PMB or another group, only HATU was successful in forming amide compounds. The next step consisted of the reaction of hydrocinnamoyl acid chloride with **13** in the presence of DIPEA to yield compound **14**.

The O-alkylated compound **9** was converted to its carboxylic acid form. Attempts to couple the latter with several amines, including phenethylamine, were unsuccessful, and we failed to synthesize 2-OPMB quinoline-3-carboxamide. The desired product **15** could be obtained by removing the trimethoxybenzyl group of **14** in the presence of 10% TFA in DCM.

On the basis of this model study, we formulated the solid-phase synthesis protocol shown in Scheme 3.

PL-FDMP resin and selected diverse building blocks are depicted in Figure 1. Compound **11** was added to a mixture of PL-FDMP resin and $NaBH(OAc)_3$ in DCM, and the tube shaken for 12 h. The reaction mixture was filtered and the solid was washed three times each with DMF, DCM, and MeOH. Substituted phenethylamine and 3-phenylpropanamine (**17**, Figure 1) were introduced at the 3-carboxylic acid of **16** by treatment with PyBOP and DIPEA to produce **18**.

Various acid chlorides (**19**, Figure 1) containing aromatic and alkyl groups were introduced at the 5 position of quinoline-2(1*H*)-one. When **19** was added, chemical hindrance of building blocks seemed to affect the reaction because of the resin. For example, isobutyryl chloride did not work at all whereas, *n*-butyryl chloride could yield the desired compounds. The final compounds **21** were obtained from the solid **20** after the resin was cleaved by 10% TFA in DCM. The residues were passed through SAX resins using a parallel silica gel column chromatography system. The 29 compounds synthesized as shown in Scheme 3 are listed in Table 1. Of these compounds, 23, 4, and 2 were 70−100%, 50−70%, and <50% pure, respectively, as measured by HPLC. The products were characterized by their LC/MS, and $^1$H NMR. Some of the products were measured HRMS and $^{13}$C NMR spectra to confirm their structures. The yields of the final compounds



DOI: 10.1021/co5001585
*ACS Comb. Sci.* 2015, 17, 60−69

came from compound **11** and they depended on various substituents. The presence of an alkyl group at the $R_2$ position resulted in lower yields than the presence of an aromatic group (Table 1).

Several products were biologically evaluated to determine the relationship between their potential activities and structures. All tested compounds were purified once again by column chromatography and their purities were checked by $^1$H NMR data (see Supporting Information). The ability of these 3,5-dicarboxamide-quinoline-2(1*H*)-one derivatives to inhibit IL-1$\beta$ release by differentiated THP-1 cells was assessed after receptor activation by 2′(3′)-*O*-(4-benzoylbenzoyl)-ATP (BzATP). Some of these compounds, at concentrations of 10 $\mu$M, reduced the secretion of IL-1$\beta$ by about 50%. IL-1$\beta$ is a proinflammatory cytokine, involved especially in stimulating immune system and brain glial cells. These results suggest that derivatives of 3,5-dicarboxamide-quinoline-2(1*H*)-one may have potent activities as immunomodulators, although other biological tests related to the immune system are required to assess the activity of these derivatives.

**Table 2. Compounds with IL-1$\beta$ Identified from Initial Screening of Compound Library**

| code of structure | % inhibition[a] (10 $\mu$M) |
|---|---|
| **21**{*1,7*} | 49 |
| **21**{*2,5*} | 45 |
| **21**{*4,3*} | 42 |
| **21**{*4,7*} | 42 |
| **21**{*7,1*} | 42 |
| **21**{*7,4*} | 45 |
| **21**{*7,5*} | 42 |

[a]% inhibition at concentration 10 $\mu$M and number of determination ≥ 2. All of the tested products were purified once again by column chromatography after SAX purification.

In conclusion, we have developed an efficient method to synthesize 3,5-dicarboxamide-quinoline-2(1*H*)-one derivatives using PL-FDMP resin. All reaction steps were completed with high purity and yield. This procedure may be useful tool in synthesizing various target molecules from a large number of commercially available building blocks.

## EXPERIMENTAL PROCEDURES

**Chemical and Instrument.** Starting materials, reagents, and solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI) and used as supplied without further purification. PL-FDMP resin was purchased from Polymer Laboratories. $^1$H NMR spectra were recorded on JEOL 400 MHz; chemical shifts ($\delta$) are reported in parts per million relative to TMS as the internal standard. All samples were dissolved in $CDCl_3$. LC/MS data were recorded on VG BIOTECH platform. Parallel solid-phase synthesis was performed on a MiniBlock from Mettler-Toledo Bohdan, Inc. (Vernon Hills, IL). The SPE tube, SAX, was purchased from Alltech Associates (Lot No. 2312; Deerfield, IL). Parallel purification was performed on Quad3, Parallel FLASH Purification System, Biotage, Inc. (Charlottesvile, VA).

**HPLC Analysis.** It was performed on a Shimadzu SCL-10A VP HPLC system using a Shimadzu Shim-pack C18 analytical column (250 mm × 4.6 mm, 5 $\mu$m, 100 A) in isocratic solvent systems. Solvent system was 0.1% TFA in $H_2O/CH_3CN$ = 2:8 over 30 min at a flow rate = 1 mL/min. Peaks were detected by UV absorption using a diode array detector (250 nm).

**Enzyme-Linked Immunosorbent Assay (ELISA).** Human monocytic leukemia THP-1 cells were plated onto 12-well plates to $1 \times 10^6$ cells/mL/well. To differentiate THP-1 cells into macrophages, 25 ng/mL LPS and 10 ng/mL IFN$\gamma$ were added to the cells for 3 h. Differentiated cells were incubated with derivatives for 30 min at 37 °C, and then with 1 mM BzATP for an additional 1 h at 37 °C. Next, the culture media were collected by centrifugation at 3000 rpm for 5 min, and the supernatants were stored in aliquots at −70 °C. The level of IL-1 in the media was determined by ELSIA using antihuman IL-1 antibody as a capture antibody and a biotinylated antihuman IL-1 antibody as a detection antibody (BD bioscience). Recombinant human IL-1 was used as a standard (BD bioscience). A basal level of IL-1$\beta$ was subtracted from the measurement.

*Methyl 5-Nitro-2-oxo-1,2-dihydroquinoline-3-carboxylate (**7**).* Compound **6** (10.0 g, 60.2 mmol) was dissolved in anhydrous MeOH (100 mL). Dimethyl malonate (20.7 mL, 180.6 mmol) and $CH_3ONa$ (13.0 g, 240.8 mmol) was added to the solution. The mixture was stirred at room temperature for 12 h and then filtered, and the filtrate residue was washed with MeOH to give **7** (9.7 g, 97%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.76 (s, 1H), 7.92 (dd, $J$ = 1.8 Hz, 1.2 Hz, 1H), 7.77 (t, $J$ = 8.2 Hz, 1H), 7.64 (d, $J$ = 8.9 Hz, 1H), 3.80 (s, 3H). MS (ESI) $m/z$: 247.14 ($[M - H]^-$).

*Methyl 1-(4-Methoxybenzyl)-5-nitro-2-oxo-1,2-dihydroquinoline-3-carboxylate (**8**).* Compound **7** (7.0 g, 28.2 mmol) was dissolved in DMF (230 mL). $CS_2CO_3$ (12.5 g, 38.4 mmol) and PMBCl (5.2 mL, 38.4 mmol) was added to the reaction mixture and then stirred for 22 h, followed by extraction with ethyl acetate and $H_2O$. The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. Purification by column chromatography ($CHCl_3$/MeOH = 50:1) gave **8** (2.4 g, 23%), product **10** (1.79 g, 82%) was prepared from the compound **8**. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.98 (s, 1H), 7.82 (t, $J$ = 4.0 Hz, 1H), 7.62−7.61 (m, 2H), 7.18 (d, $J$ = 8.0 Hz, 2H), 6.86 (d, $J$ = 8.0 Hz, 2H), 5.55 (s, 2H), 3.99 (s, 3H), 3.77 (s, 3H). MS (ESI) $m/z$: 368.93 ($[M + H]^+$). HRMS (ESI): calcd for $C_{19}H_{16}N_2O_6$ $[M + H]^+$ 368.1008, found 368.1006.

*Methyl 2-((4-Methoxybenzyl)oxy)-5-nitroquinoline-3-carboxylate (**9**).* Following the same procedure as outlined in the preparation of **8**. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.36 (s, 1H), 8.22 (dd, $J$ = 8.0 Hz, 4.0 Hz, 1H), 8.17−8.15 (m, 1H), 7.80−7.76 (m, 1H), 7.51−7.49 (m, 2H), 6.93−6.91 (m, 2H), 5.61 (s, 2H), 3.97 (s, 3H), 3.81 (s, 3H). MS (ESI) $m/z$: 369.16 ($[M + H]^+$).

*Methyl 5-Amino-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxylate (**10**).* Compound **8** (2.4 g, 6.52 mmol) was dissolved in MeOH (66 mL) and Pd/C (810 mg) was added. $H_2$ gas was exchanged and stirred for 1 h and filtered through Celite. The filtrate residue was washed with MeOH. Concentration in vacuo gave the solid product **10** (1.79 g, 81%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.68 (s, 1H), 7.29 (d, $J$ = 8.0 Hz, 1H), 7.18 (d, $J$ = 12.0 Hz, 2H), 6.80 (d, $J$ = 12.0 Hz, 2H), 6.67 (d, $J$ = 12.0 Hz, 1H), 6.47 (dd, $J$ = 1.2 Hz, $J$ = 1.2 Hz, 1H), 5.46 (s, 2H), 4.37 (s, 2H), 3.96 (s, 3H), 3.75 (s, 3H). MS (ESI) $m/z$: 339.17 ($[M + H]^+$). HRMS (ESI): calcd for $C_{19}H_{18}N_2O_4$ $[M + H]^+$ 338.1267, found 338.1267.

*5-Amino-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (**11**).* Compound **10** (1.7 g, 5.0 mmol)


DOI: 10.1021/co5001585
ACS Comb. Sci. 2015, 17, 60−69

was stirred in 10% KOH in MeOH (100 mL) at 80 °C for 12 h; the mixture was filtered, and the filtrate residue was washed with $H_2O$ to give **11** (1.5 g, 92%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 14.66 (s, 1H), 9.22 (s, 1H), 7.33 (t, $J$ = 8.0 Hz, 1H), 7.14 (d, $J$ = 8.0 Hz, 2H), 6.83 (d, $J$ = 8.0 Hz, 2H), 6.74 (s, 2H), 6.69 (d, $J$ = 8.0 Hz, 1H), 6.52 (d, $J$ = 8.0 Hz, 1H), 5.45 (s, 2H), 3.66 (s, 3H). MS (ESI) $m/z$: 325.14 ($[M + H]^+$). HRMS (ESI): calcd for $C_{18}H_{16}N_2O_4$ $[M + H]^+$ 324.1110, found 324.1111.

*1-(4-Methoxybenzyl)-2-oxo-5-(2,4,6-trimethoxybenzylamino)-1,2-dihydroquinoline-3-carboxylic acid (**12**).* Compound **11** (1.7 g, 5.2 mmol) was dissolved in DCE (50 mL) and DCM (50 mL). $NaBH(OAc)_3$ (2.2 g, 10.4 mmol) and 2,4,6-trimethoxybenzaldehyde (1.2 g, 6.2 mmol) was added in reaction mixtures. The mixture was stirred at room temperature for 12 h. The residue obtained was extracted with ethyl acetate and saturated $NH_4Cl$ aqueous solution. The organic layer was dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The product was purified by silica gel column chromatography (DCM/MeOH = 25:1) gave **13** (2.5 g, 95% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.63 (s, 1H), 7.33 (t, $J$ = 11.2 Hz, 1H), 7.16 (d, $J$ = 10.4 Hz, 2H), 6.79 (dd, $J$ = 2.8 Hz, 2.8 Hz, 2H), 6.63 (d, $J$ = 10.8 Hz, 1H), 6.55 (d, $J$ = 10.8 Hz, 1H), 6.16 (s, 2H), 5.43 (s, 2H), 5.02 (s, 1H), 4.36 (s, 2H), 3.95 (s, 3H), 3.85 (s, 6H), 3.82 (s, 3H). MS (ESI) $m/z$: 505.08 ($[M + H]^+$).

*1-(4-Methoxybenzyl)-2-oxo-N-phenethyl-5-(2,4,6-trimethoxybenzylamino)-1,2-dihydroquinoline-3-carboxamide (**13**).* Compound **12** (450 mg, 0.9 mmol) was dissolved in DMF (5 mL). DIPEA (0.5 mL, 2.7 mmol), phenethylamine (0.2 mL, 1.3 mmol), and PyBop (0.9 mg, 1.8 mmol) were added in reaction mixtures. The mixture was stirred at room temperature for 3 h. The residue obtained was extracted with ethyl acetate and water. The organic layer was dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The product was purified by silica gel column chromatography ($CHCl_3$:MeOH = 30:1) gave **13** (430 mg, 78%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.04 (s, 1H), 9.00 (s, 1H), 7.38−7.29 (m, 8H), 7.11−7.08 (m, 2H), 6.84−6.80 (m, 2H), 6.67 (d, $J$ = 10.8 Hz, 1H), 6.55 (d, $J$ = 11.6 Hz, 1H), 5.45 (s, 2H), 5.15 (s, 1H), 4.37 (d, $J$ = 6.8 Hz, 2H), 3.83 (d, $J$ = 8.8 Hz, 9H), 3.75 (s, 3H), 3.72−3.65 (m, 2H), 2.94 (t, $J$ = 10.2 Hz, 2H). MS (ESI) $m/z$: 608.07 ($[M + H]^+$). HRMS (ESI): calcd for $C_{36}H_{37}N_3O_6$ $[M + H]^+$ 607.2682, found 607.2679.

*1-(4-Methoxybenzyl)-2-oxo-N-phenethyl-5-(3-phenyl-N-(2,4,6 trimethoxybenzyl)propanamido)-1,2-dihydroquinoline-3-carboxamide (**14**).* Compound **13** (430 mg, 0.7 mmol), DIPEA (0.2 mL, 1.1 mmol), and hydrocinnamoyl chloride (0.1 mL, 0.8 mmol) was stirred in DCM (20 mL) for 15 min. The residue obtained was extracted with ethyl acetate and saturated $NaHCO_3$ aqueous solution. The organic layer was dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The product was purified by silica gel column chromatography ($CHCl_3$/MeOH = 40:1) gave **14** (403 mg, 71%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.79 (s, 1H), 8.76 (s, 1H), 7.36−7.28 (m, 6H), 7.25−7.09 (m, 6H), 7.05−6.99 (m, 4H), 6.84−6.82 (m, 2H), 6.78 (d, $J$ = 6.0 Hz, 1H), 5.72 (s, 2H), 3.71 (s, 3H), 3.68−3.66 (m, 2H), 3.64 (s, 3H), 3.44 (d, $J$ = 5.2 Hz, 6H), 2.99−2.90 (m, 4H), 2.22−2.17 (m, 4H). MS (ESI) $m/z$: 740.10 ($[M + H]^+$).

*1-(4-Methoxybenzyl)-2-oxo-N-phenethyl-5-(3-phenylpropanamido)-1,2-dihydroquinoline-3 carboxamide (**15**).* Compound **14** (403 mg, 0.5 mmol) was treated with 10% TFA/DCM (10 mL) for 1 h, and the product was filtered and washed well with DMF, DCM and MeOH gave **15** (270 mg, 96%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.99 (s, 1H), 9.08 (s, 1H), 7.96 (s, 1H), 7.72 (s, 1H), 7.52−7.50 (m, 2H), 7.31−7.27 (m, 5H), 7.23−7.15 (m, 4H), 7.09 (d, $J$ = 8.4 Hz, 2H), 6.84−6.82 (m, 2H), 5.52 (s, 2H), 3.75 (s, 3H), 3.70−3.65 (m, 2H), 3.10 (t, $J$ = 7.6 Hz, 2H), 2.91 (t, $J$ = 7.6 Hz, 2H), 2.83 (d, $J$ = 7.2 Hz, 2H). MS (ESI) $m/z$: 558.80 ($[M - H]^-$).

*General Procedure of Reductive Amination for the Preparation of Resin-Bound Quinolinone (**16**).* To the PL-FDMP resin (1.5 mmol/g, 2.3 g, 3.3 mmol) was added a solution of compound **11** (2.0 g, 6.2 mmol) and $NaBH(OAc)_3$ (1.5 g, 6.6 mmol) in DCE (100 mL) and DCM (100 mL). The mixture was gently stirred for 12 h at room temperature and filtered, and the resin was sequentially washed with DMF (3 × 30 mL), DCM (3 × 30 mL), and MeOH (3 × 30 mL). The resin was dried in vacuo to a constant weight (yield 95%).

*General Procedure of Coupling (**18**).* Resin-bound quinolinone **16** (364 mg, 1.1 mmol) was dissolved in DCM (12 mL). Amine (340 mg, 1.7 mmol), DIPEA (0.5 mL, 3.3 mmol), and PyBop (1.1 g, 2.2 mmol) was added to each reaction tube. The reaction mixtures were shaken for 3 h, the mixture was filtered, and the resin was washed with DMF (3 × 30 mL), DCM (3 × 30 mL) and MeOH (3 × 30 mL).

*General Procedure of Acylation (**20**).* Resin bound 3-coupled quinolinone **18** (418 mg, 1.2 mmol) was suspended in DCM (12 mL). Acid chloride (0.2 mL, 1.5 mmol) and DIPEA (0.3 mL, 1.9 mmol) was added to each reaction tube. After the reaction tube was shaken for 15 min, the mixture was filtered, and the resin was sequentially washed with DMF (3 × 30 mL), DCM (3 × 30 mL) and MeOH (3 × 30 mL).

*General Procedure of Cleavage and Purification (**21**).* Each resin was treated with 10% TFA/DCM (3 mL) for 1 h, and the resin was filtered and washed well with DMF (3 × 30 mL), DCM (3 × 30 mL) and MeOH (3 × 30 mL). The cleavage step was repeated twice. The combined filtrate was evaporated in parallel under reduced pressure using a Genevac DD-4 system, and the products were dissolved in chloroform and eluted through SAX resin to convert the free base form. The eluent was evaporated, and all final products were purified by a Quad3 parallel purification system with an appropriate mixture of hexane/EtOAc. Homogeneous fractions were combined and evaporated in vacuo, and the weight of residue was determined to calculate the yield. The structures of all final products were determined by $^1$H NMR and LC/MS mass.

*1-(4-Methoxybenzyl)-2-oxo-N-phenethyl-5-(3-phenylpropanamido)-1,2-dihydroquinoline-3 carboxamide (**21**{1,1}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.99 (s, 1H), 9.08 (s, 1H), 7.96 (s, 1H), 7.72 (s, 1H), 7.52−7.50 (m, 2H), 7.31−7.27 (m, 5H), 7.23−7.15 (m, 4H), 7.09 (d, $J$ = 8.4 Hz, 2H), 6.83 (d, $J$ = 8.8 Hz, 2H), 5.52 (s, 2H), 3.75 (s, 3H), 3.70−3.65 (m, 2H), 3.10 (t, $J$ = 7.6 Hz, 2H), 2.91 (t, $J$ = 7.6 Hz, 2H), 2.83 (d, $J$ = 7.2 Hz, 2H). MS (ESI) $m/z$: 558.80 ($[M - H]^-$). HRMS (ESI): calcd for $C_{35}H_{33}N_3O_4$ $[M + H]^+$ 559.2471, found 559.2467.

*5-(3-Cyclopentylpropanamido)-1-(4-methoxybenzyl)-2-oxo-N-phenethyl-1,2-dihydroquinoline-3-carboxamide (**21**{1,2}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.02 (s, 1H), 9.17 (s, 1H), 8.17 (t, $J$ = 10 Hz, 1H), 8.03 (s, 1H), 7.84 (s, 1H), 7.61−7.49 (m, 1H), 7.34−7.22 (m, 4H), 7.21−7.04 (m, 4H), 6.83 (d, $J$ = 8.0 Hz, 1H), 5.53 (s, 2H), 3.76 (s, 3H), 3.74−3.63 (m. 2H), 3.58−3.44 (m, 2H), 2.97−2.87 (m, 2H), 2.51 (t, $J$ = 9.4 Hz, 2H), 2.59−2.44 (m, 2H), 1.76−1.32 (m, 9H). MS (ESI) $m/z$: 552.28 ($[M + H]^+$).



DOI: 10.1021/co5001585
ACS Comb. Sci. 2015, 17, 60−69

*1-(4-Methoxybenzyl)-5-(2-(4-methoxyphenyl)acetamido)-2-oxo-N-phenethyl-1,2-dihydroquinoline-3-carboxamide (**21**{1,7}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.97 (s, 1H), 9.07 (s, 1H), 8.52 (s, 1H), 7.77 (d, $J$ = 8.0 Hz, 1H), 7.54 (t, $J$ = 8.0 Hz, 1H), 7.36 (d, $J$ = 8.0 Hz, 2H), 7.29−7.25 (m, 2H), 7.22−7.17 (m, 1H), 7.15 (d, $J$ = 8.0 Hz, 2H), 7.08 (d, $J$ = 8.0 Hz, 2H), 6.96 (d, $J$ = 8.0 Hz, 2H), 6.82−6.80 (m, 2H), 5.50 (s, 2H), 3.81−3.80 (m, 5H), 3.75 (s, 3H), 3.65−3.60 (m, 2H), 2.89 (t, $J$ = 8.0 Hz, 2H). $^{13}$C NMR (500 MHz, $CDCl_3$): $\delta$ 170.59, 163.45, 161.66, 159.14, 158.97, 140.88, 138.98, 137.55, 136.20, 133.21, 130.53, 128.67, 128.51, 127.66, 127.43, 126.39, 126.14, 120.45, 118.29, 114.82, 114.35, 113.28, 112.10, 55.30, 55.28, 46.27, 43.56, 41.37, 35.80. MS (ESI) $m/z$: 546.78 ($[M + H]^+$). HRMS (ESI): calcd for $C_{35}H_{33}N_3O_5$ $[M + H]^+$ 575.2420, found 575.2417.

*5-Butyramido-1-(4-methoxybenzyl)-2-oxo-N-phenethyl-1,2-dihydroquinoline-3-carboxamide (**21**{1,9}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.30 (s, 1H), 9.78 (m, 1H), 7.59 (t, $J$ = 8.0 Hz, 1H), 7.38−7.31 (m, 3H), 7.25−7.11 (m, 5H), 6.84−6.78 (m, 3H), 5.51 (s, 2H), 3.66 (s, 6H), 3.56 (t, $J$ = 8.0 Hz, 2H), 2.83 (t, $J$ = 8.0 Hz, 2H), 2.53 (t, $J$ = 8.0 Hz, 2H), 2.39 (t, $J$ = 8.0 Hz, 2H). MS (ESI) $m/z$: 496.21 ($[M - H]^-$).

*N-(4-Chlorophenethyl)-1-(4-methoxybenzyl)-2-oxo-5-(2-phenylacetamido)-1,2-dihydroquinoline-3-carboxamide (**21**{2,5}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.97 (s, 1H), 9.04 (s, 1H), 8.21 (s, 1H), 7.73 (d, $J$ = 8.0 Hz, 1H), 7.54 (t, $J$ = 8.0 Hz, 1H), 7.45−7.44 (m, 4H), 7.25−7.23 (m, 2H), 7.18−7.12 (m, 3H), 7.09−7.06 (m, 2H), 6.84−6.81 (m, 2H), 5.51 (s, 2H), 3.88 (s, 2H), 3.76 (s, 3H), 3.67−3.62 (m, 2H), 2.89 (t, $J$ = 8.0 Hz, 2H). $^{13}$C NMR (600 MHz, $CDCl_3$): $\delta$ 163.44, 161.64, 159.01, 140.90, 137.46, 137.41, 137.37, 135.99, 134.16, 133.50, 133.23, 132.18, 130.08, 129.45, 129.42, 128.62, 127.84, 127.67, 127.35, 118.55, 114.37, 112.37, 55.28, 46.31, 44.50, 41.09, 35.10. MS (ESI) $m/z$: 577.58 ($[M - H]^-$). HRMS (ESI): calcd for $C_{34}H_{30}ClN_3O_4$ $[M + H]^+$ 579.1925, found 579.1923.

*N-(4-Chlorophenethyl)-5-(2-(3-chlorophenoxy)-acetamido)-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide (**21**{2,6}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.91 (s, 1H), 9.12 (s, 1H), 8.78 (s, 1H), 7.74 (d, $J$ = 8.0 Hz, 1H), 7.57 (t, $J$ = 8.0 Hz, 1H), 7.31 (t, $J$ = 8.0 Hz, 1H), 7.20−7.16 (m, 2H), 7.12−7.04 (m, 5H), 7.02−6.98 (m, 2H), 6.84 (d, $J$ = 12.0 Hz, 2H), 5.54 (s, 2H), 4.72 (s, 1H), 3.76 (s, 3H), 3.71−3.66 (m, 2H), 2.95−2.85 (m, 2H), 1.32−1.23 (m, 2H). MS (ESI) $m/z$: 629.66 ($[M + H]^+$).

*1-(4-Methoxybenzyl)-N-(4-methoxyphenethyl)-2-oxo-5-(3-phenylpropanamido)-1,2-dihydroquinoline-3-carboxamide (**21**{3,1}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.02 (s, 1H), 9.28 (s, 1H), 7.74 (s, 1H), 7.52 (t, $J$ = 8.0 Hz, 1H), 7.30−7.11 (m, 9H), 7.09 (d, $J$ = 8.0 Hz, 1H), 7.02 (d, $J$ = 8.0 Hz, 1H), 6.86−6.74 (m, 3H), 5.50 (s, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 3.58−3.49 (m, 2H), 3.09 (t, $J$ = 8.0 Hz, 2H), 2.94 (t, $J$ = 8.0 Hz, 2H), 2.61−2.53 (m, 2H). MS (ESI) $m/z$: 590.16 ($[M + H]^+$).

*5-(3-Cyclopentylpropanamido)-1-(4-methoxybenzyl)-N-(4-methoxyphenethyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide (**21**{3,2}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.11 (s, 1H), 9.30 (s, 1H), 8.47 (s, 1H), 7.89 (s, 1H), 7.54 (t, $J$ = 8.2 Hz, 1H), 7.18−7.06 (m, 4H), 6.83 (d, $J$ = 8.0 Hz, 4H), 5.51 (s, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 3.70−3.60 (m, 2H), 2.87 (t, $J$ = 7.6 Hz, 2H), 2.55 (t, $J$ = 7.4 Hz, 2H), 2.36 (t, $J$ = 4.2 Hz, 2H), 1.28−1.03 (m, 9H). MS (ESI) $m/z$: 580.18 ($[M - H]^-$).

*5-(2-(4-Chlorophenoxy)acetamido)-1-(4-methoxybenzyl)-N-(4-methoxyphenethyl)-2-oxo-1,2 dihydroquinoline-3-carboxamide (**21**{3,3}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.92 (s, 1H), 9.15 (s, 1H), 8.90 (s, 1H), 7.77 (d, $J$ = 7.6 Hz, 1H), 7.56 (t, $J$ = 8.4 Hz, 1H), 7.33 (d, $J$ = 12.0 Hz, 2H), 7.16 (d, $J$ = 8.0 Hz, 2H), 7.10 (d, $J$ = 8.0 Hz, 2H), 7.02 (d, $J$ = 8.0 Hz, 2H), 6.87−6.80 (m, 4H), 5.53 (s, 2H), 4.68 (s, 2H), 3.77 (s, 3H), 3.70 (s, 3H), 3.69−3.60 (m, 2H), 2.87 (t, $J$ = 7.4 Hz, 2H). MS (ESI) $m/z$: 624.09 ($[M - H]^-$). HRMS (ESI): calcd for $C_{35}H_{32}ClN_3O_6$ $[M + H]^+$ 625.1980, found 625.1978.

*1-(4-Methoxybenzyl)-N-(4-methoxyphenethyl)-2-oxo-5-(2-phenylacetamido)-1,2-dihydroquinoline-3-carboxamide (**21**{3,5}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.00 (s, 1H), 9.28 (s, 1H), 7.74 (s, 1H), 7.54 (t, $J$ = 8.0 Hz, 1H), 7.30−7.13 (m, 9H), 7.11 (d, $J$ = 8.0 Hz, 1H), 7.02 (d, $J$ = 8.0 Hz, 1H), 6.86−6.73 (m, 3H), 5.50 (s, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.58−3.49 (m, 2H), 3.09 (t, $J$ = 8.0 Hz, 2H), 2.94 (t, $J$ = 8.0 Hz, 2H). MS (ESI) $m/z$: 573.86 ($[M - H]^-$).

*5-(2-(3-Chlorophenoxy)acetamido)-1-(4-methoxybenzyl)-N-(4-methoxyphenethyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide (**21**{3,6}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.98 (s, 1H), 9.15 (s, 1H), 8.99 (s, 1H), 7.77 (d, $J$ = 7.6 Hz, 1H), 7.56 (t, $J$ = 8.4 Hz, 1H), 7.33 (d, $J$ = 12.0 Hz, 2H), 7.16 (d, $J$ = 8.0 Hz, 2H), 7.13 (d, $J$ = 8.0 Hz, 2H), 6.89 (d, $J$ = 8.0 Hz, 2H), 6.87−6.80 (m, 4H), 5.53 (s, 2H), 4.68 (s, 2H), 3.75 (s, 3H), 3.71 (s, 3H), 3.69−3.60 (m, 2H), 2.87 (t, $J$ = 7.4 Hz, 2H). MS (ESI) $m/z$: 623.68 ($[M - H]^-$).

*1-(4-Methoxybenzyl)-N-(4-methoxyphenethyl)-5-(2-(4-methoxyphenyl)acetamido)-2-oxo-1,2-dihydroquinoline-3-carboxamide (**21**{3,7}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.92 (s, 1H), 9.15 (s, 1H), 8.90 (s, 1H), 7.72 (d, $J$ = 7.6 Hz, 1H), 7.55 (t, $J$ = 8.4 Hz, 1H), 7.33 (d, $J$ = 12.0 Hz, 2H), 7.15 (d, $J$ = 8.0 Hz, 2H), 7.10 (d, $J$ = 8.2 Hz, 2H), 7.06 (d, $J$ = 8.0 Hz, 2H), 6.87−6.80 (m, 4H), 5.53 (s, 2H), 4.68 (s, 2H), 3.77 (s, 3H), 3.74 (m, 6H), 3.69−3.60 (m, 2H), 2.87 (t, $J$ = 7.4 Hz, 2H). MS (ESI) $m/z$: 603.78 ($[M - H]^-$).

*5-Butyramido-1-(4-methoxybenzyl)-N-(4-methoxyphenethyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide (**21**{3,9}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.99 (s, 1H), 9.15 (s, 1H), 7.88−7.78 (m, 2H), 7.59−7.50 (m, 1H), 7.18 (d, $J$ = 8.0 Hz, 3H), 7.15 (d, $J$ = 12.0 Hz, 2H), 6.85 (d, $J$ = 8.0 Hz, 3H), 5.53 (s, 2H), 5.34 (s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.72−3.67 (m, 2H), 2.53−2.48 (m, 2H), 2.22 (t, $J$ = 8.0 Hz, 2H), 1.87−1.80 (m, 2H), 1.07 (s, 3H). MS (ESI) $m/z$: 525.88 ($[M - H]^-$).

*1-(4-Methoxybenzyl)-N-(4-methylphenethyl)-2-oxo-5-(3-phenylpropanamido)-1,2-dihydroquinoline-3-carboxamide (**21**{4,1}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.26 (s, 1H), 9.76 (s, 1H), 8.98 (s, 1H), 7.58 (t, $J$ = 8.0 Hz, 1H), 7.39−7.30 (m, 3H), 7.27 (d, $J$ = 4.0 Hz, 3H), 7.18−7.07 (m, 6H), 6.83 (d, $J$ = 8.0 Hz, 1H), 5.52 (s, 2H), 3.66 (s, 3H), 3.59−3.51 (m, 2H), 2.94 (t, $J$ = 4.0 Hz, 2H), 2.84−2.72 (m, 2H), 2.56−2.49 (m, 2H), 2.05 (s, 3H). MS (ESI) $m/z$: 572.22 ($[M - H]^-$).

*5-(3-Cyclopentylpropanamido)-1-(4-methoxybenzyl)-N-(4-methylphenethyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide (**21**{4,2}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.98 (s, 1H), 9.11 (s, 1H), 7.87−7.76 (m, 2H), 7.53 (t, $J$ = 8.0 Hz, 1H), 7.17−7.06 (m, 6H), 6.83 (d, $J$ = 8.0 Hz, 2H), 5.53 (s, 2H), 5.33 (s, 1H), 3.75 (s, 3H), 2.90 (t, $J$ = 8.0 Hz, 2H), 2.61 (s, 3H), 2.54−2.47 (m, 2H), 2.24−2.19 (m, 2H), 2.04−1.95 (m, 2H), 1.68−1.59 (m, 9H). MS (ESI) $m/z$: 566.27 ($[M + H]^+$). HRMS (ESI): calcd for $C_{35}H_{39}N_3O_4$ $[M + H]^+$ 565.2941, found 566.2939.

*5-(2-(4-Chlorophenoxy)acetamido)-1-(4-methoxybenzyl)-N-(4-methylphenethyl)-2-oxo-1,2 dihydroquinoline-3-carboxamide (**21**{4,3}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ $^1$H



DOI: 10.1021/co5001585
ACS Comb. Sci. 2015, 17, 60−69

NMR (400 MHz, $CDCl_3$) $\delta$ 9.98 (s, 1H), 9.11 (s, 1H), 8.20 (s, 1H), 7.70−7.61 (m, 5H), 7.50 (t, $J$ = 8.0 Hz, 1H), 7.47−7.30 (m, 2H), 7.17−7.06 (m, 5H), 6.72 (d, $J$ = 8.0 Hz, 2H), 5.53 (s, 2H), 3.80 (s, 1H), 3.75 (s, 3H), 3.62 (t, $J$ = 8.0 Hz, 2H), 2.89 (m, 2H), 2.52 (s, 2H). MS (ESI) $m/z$: 610.13 ($[M + H]^+$).

*1-(4-Methoxybenzyl)-N-(4-methylphenethyl)-2-oxo-5-(2-phenylacetamido)-1,2-dihydroquinoline-3-carboxamide (**21**{4,5}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.72 (s, 1H), 9.28 (s, 1H), 7.88 (s, 1H), 7.54 (t, $J$ = 8.0 Hz, 1H), 7.30−7.10 (m, 9H), 7.06 (d, $J$ = 8.0 Hz, 1H), 7.02 (d, $J$ = 8.0 Hz, 1H), 6.86−6.71 (m, 3H), 5.42 (s, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.58−3.49 (m, 2H), 3.09 (t, $J$ = 8.0 Hz, 2H), 2.94 (t, $J$ = 8.0 Hz, 2H). MS (ESI) $m/z$: 557.87 ($[M - H]^-$).

*5-(2-(3-Chlorophenoxy)acetamido)-1-(4-methoxybenzyl)-N-(4-methylphenethyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide (**21**{4,6}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.02 (s, 1H), 9.15 (s, 1H), 8.99 (s, 1H), 7.42 (d, $J$ = 7.6 Hz, 1H), 7.40 (t, $J$ = 8.4 Hz, 1H), 7.33 (d, $J$ = 12.0 Hz, 2H), 7.16 (d, $J$ = 8.0 Hz, 2H), 7.13 (d, $J$ = 8.0 Hz, 2H), 6.89 (d, $J$ = 8.0 Hz, 2H), 6.87−6.80 (m, 4H), 5.53 (s, 2H), 4.68 (s, 2H), 3.75 (s, 3H), 3.64 (s, 3H), 3.62−3.60 (m, 2H), 2.87 (t, $J$ = 7.4 Hz, 2H). MS (ESI) $m/z$: 610.13 ($[M + H]^+$).

*1-(4-Methoxybenzyl)-5-(2-(4-methoxyphenyl)acetamido)-N-(4-methylphenethyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide (**21**{4,7}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.70 (s, 1H), 9.18 (s, 1H), 7.88 (s, 1H), 7.54 (t, $J$ = 8.0 Hz, 1H), 7.30−7.13 (m, 9H), 7.00 (d, $J$ = 8.0 Hz, 1H), 6.90 (d, $J$ = 8.0 Hz, 1H), 6.86−6.71 (m, 2H), 5.42 (s, 2H), 3.77 (s, 1H), 3.74 (s, 3H), 3.58−3.49 (m, 5H), 3.09 (t, $J$ = 8.0 Hz, 2H), 2.94 (t, $J$ = 8.0 Hz, 2H). MS (ESI) $m/z$: 587.84 ($[M - H]^-$). HRMS (ESI): calcd for $C_{36}H_{35}N_3O_5$ $[M + H]^+$ 589.2577, found 589.2573.

*1-(4-Methoxybenzyl)-N-(4-methylphenethyl)-2-oxo-5-propionamido-1,2-dihydroquinoline-3-carboxamide (**21**{4,8}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.87 (s, 1H), 9.32 (s, 1H), 8.97 (s, 1H), 7.56 (t, $J$ = 8.0 Hz, 1H), 7.17 (d, $J$ = 8.0 Hz, 1H), 7.12−7.04 (m, 7H), 6.83 (d, $J$ = 8.0 Hz, 2H), 5.53 (s, 2H), 3.77 (s, 3H), 3.63−3.52 (m, 2H), 2.80 (t, $J$ = 8.0 Hz, 2H), 2.62 (s, 3H), 2.51 (t, $J$ = 8.0 Hz, 2H), 2.33 (s, 3H). MS (ESI) $m/z$: 496.56 ($[M - H]^-$).

*5-Butyramido-1-(4-methoxybenzyl)-N-(4-methylphenethyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide (**21**{4,9}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.05 (s, 1H), 9.32 (s, 1H), 8.77 (s, 1H), 7.56 (t, $J$ = 8.0 Hz, 1H), 7.17 (d, $J$ = 8.0 Hz, 1H), 7.12−7.04 (m, 7H), 6.83 (d, $J$ = 8.0 Hz, 2H), 5.53 (s, 2H), 3.77 (s, 3H), 3.63−3.58 (m, 2H), 2.83 (t, $J$ = 8.0 Hz, 2H), 2.62 (s, 3H), 2.51 (t, $J$ = 8.0 Hz, 2H), 2.31 (s, 3H), 1.86−1.81 (m, 2H). MS (ESI) $m/z$: 509.82 ($[M - H]^-$).

*N-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-5-(2-(4-chlorophenyl)acetamido)-1-(4 methoxybenzyl)-2-oxo-1,2 dihydroquinoline-3-carboxamide (**21**{5,4}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.49 (s, 1H), 9.73 (s, 1H), 9.03 (s, 1H), 7.40−7.31 (m, 4H), 7.12 (d, $J$ = 8.0 Hz, 3H), 6.85−6.77 (m, 4H), 6.68 (d, $J$ = 8.0 Hz, 2H), 5.93 (s, 2H), 5.50 (s, 1H), 3.78 (s, 3H), 3.59−3.52 (m, 2H), 2.80−2.73 (m, 2H), 2.65−2.61 (m, 2H), 2.50 (s, 2H). MS (ESI) $m/z$: 622.11 ($[M - H]^-$). HRMS (ESI): calcd for $C_{35}H_{30}ClN_3O_6$ $[M + H]^+$ 623.1823, found 623.1821.

*N-(4-Ethylphenethyl)-1-(4-methoxybenzyl)-2-oxo-5-(3-phenylpropanamido)-1,2-dihydroquinoline-3-carboxamide (**21**{6,1}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.02 (s, 1H), 9.22 (s, 1H), 8.50 (s, 1H), 7.58−7.46 (m, 1H), 7.22−7.05 (m, 12H), 6.88−6.77 (m, 2H), 5.49 (s, 2H), 3.76 (s, 3H), 3.64−3.54 (m, 2H), 3.15−3.04 (m, 2H), 3.00−2.75 (m, 6H), 1.62 (s, 3H). MS (ESI) $m/z$: 586.17 ($[M - H]^-$).

*5-(2-(4-Chlorophenoxy)acetamido)-N-(4-ethylphenethyl)-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide (**21**{6,3}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.47 (s, 1H), 9.75 (s, 1H), 8.97 (s, 1H), 7.62 (t, $J$ = 8.0 Hz, 1H), 7.40−7.35 (m, 4H), 7.16−7.05 (m, 7H), 6.84 (d, $J$ = 12.0 Hz, 2H), 6.72 (d, $J$ = 8.0 Hz, 1H), 5.52 (s, 2H), 4.84 (s, 1H), 3.58−3.53 (m, 2H), 2.87 (s, 3H), 2.80 (t, $J$ = 12.0 Hz, 2H), 2.53 (t, $J$ = 12.0 Hz, 2H), 1.12−1.09 (m, 5H). MS (ESI) $m/z$: 624.56 ($[M + H]^+$). HRMS (ESI): calcd for $C_{36}H_{34}ClN_3O_5$ $[M + H]^+$ 623.2187, found 623.2185.

*5-(2-(4-Chlorophenyl)acetamido)-N-(4-ethylphenethyl)-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide (**21**{6,4}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.97 (s, 1H), 9.10 (s, 1H), 8.21 (s, 1H), 7.70 (s, 1H), 7.52 (t, $J$ = 10.0 Hz, 1H), 7.37 (s, 4H), 7.17 (d, $J$ = 8.0 Hz, 1H), 7.11 (s, 4H), 7.08 (d, $J$ = 8.0 Hz, 2H), 6.81 (d, $J$ = 8.0 Hz, 2H), 5.55 (s, 2H), 5.34 (s, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 3.70−3.58 (m, 2H), 2.86 (t, $J$ = 8.0 Hz, 2H), 2.60 (s, 2H), 1.24−1.19 (m, 2H). MS (ESI) $m/z$: 606.08 ($[M - H]^-$). HRMS (ESI): calcd for $C_{36}H_{34}ClN_3O_4$ $[M + H]^+$ 607.2238, found 607.2240.

*1-(4-Methoxybenzyl)-2-oxo-5-(3-phenylpropanamido)-N-(3-phenylpropyl)-1,2-dihydroquinoline-3-carboxamide (**21**{7,1}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.00 (s, 1H), 9.10 (s, 1H), 8.97 (s, 1H), 7.50−7.48 (m, 1H), 7.38−7.31 (m, 3H), 7.28−7.11 (m, 8H), 6.83 (d, $J$ = 8.0 Hz, 4H), 5.53 (s, 2H), 3.66 (s, 3H), 3.00 (s, 2H), 2.74−2.68 (m, 2H), 2.62 (s, 4H). MS (ESI) $m/z$: 574.23 ($[M + H]^+$). HRMS (ESI): calcd for $C_{36}H_{35}N_3O_4$ $[M + H]^+$ 573.2628, found 573.2625.

*5-(2-(4-Chlorophenyl)acetamido)-1-(4-methoxybenzyl)-2-oxo-N-(3-phenylpropyl)-1,2-dihydroquinoline-3-carboxamide (**21**{7,4}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.51 (s, 1H), 9.75 (s, 1H), 9.03 (s, 1H), 7.59 (t, $J$ = 8.2 Hz, 1H), 7.43−7.30 (m, 6H), 7.29−7.18 (m, 5H), 7.17−7.08 (m, 2H), 6.87−6.80 (m, 1H), 5.55 (s, 2H), 4.11−4.01 (m, 2H), 3.14 (s, 3H), 3.12 (s, 3H), 2.67−2.59 (m, 2H), 1.90−1.80 (m, 2H). MS (ESI) $m/z$: 594.16 ($[M + H]^+$).

*1-(4-Methoxybenzyl)-2-oxo-5-(2-phenylacetamido)-N-(3-phenylpropyl)-1,2-dihydroquinoline-3-carboxamide (**21**{7,5}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.96 (s, 1H), 9.13 (s, 1H), 8.56 (s, 1H), 7.77 (d, $J$ = 8.0 Hz, 1H), 7.54 (t, $J$ = 8.0 Hz, 1H), 7.46−7.41 (m, 4H), 7.35−7.31 (m, 1H), 7.25−7.23 (m, 2H), 7.18−7.14 (m, 4H), 7.09 (d, $J$ = 8.0 Hz, 2H), 6.83−6.81 (m, 2H), 5.51 (s, 2H), 3.88 (s, 2H), 3.75 (s, 3H), 3.44 (m, 2H), 2.66 (t, $J$ = 8.0 Hz, 2H), 1.93−1.86 (m, 2H). $^{13}$C NMR (600 MHz, $CDCl_3$): $\delta$ 170.17, 163.46, 161.72, 158.96, 141.36, 140.86, 137.58, 136.11, 134.29, 133.19, 129.43, 129.31, 128.36, 127.61, 127.35, 125.88, 118.55, 114.36, 113.44, 112.24, 55.27, 46.31, 44.44, 39.33, 33.27, 30.96. MS (ESI) $m/z$: 560.22 ($[M + H]^+$). HRMS (ESI): calcd for $C_{35}H_{33}N_3O_4$ $[M + H]^+$: 559.2471, found 559.2467.

*1-(4-Methoxybenzyl)-5-(2-(4-methoxyphenyl)acetamido)-2-oxo-N-(3-phenylpropyl)-1,2-dihydroquinoline-3-carboxamide (**21**{7,7}).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.95 (s, 1H), 9.01 (s, 1H), 8.07 (s, 1H), 7.72 (d, $J$ = 7.6 Hz, 1H), 7.53 (t, $J$ = 10.0 Hz, 1H), 7.49−7.38 (m, 3H), 7.34−7.26 (m, 1H), 7.25−7.23 (m, 2H), 7.20−7.13 (m, 3H), 7.07 (d, $J$ = 8.0 Hz, 2H), 6.81 (d, $J$ = 8.0 Hz, 2H), 5.51 (s, 2H), 3.87 (s, 1H), 3.70 (m, 6H), 3.51−3.43 (m, 2H), 2.69 (t, $J$ = 8.0 Hz, 2H), 2.01−1.88 (m, 4H). MS (ESI) $m/z$: 590.34($[M + H]^+$).



DOI: 10.1021/co5001585
ACS Comb. Sci. 2015, 17, 60−69

## ■ ASSOCIATED CONTENT

### Supporting Information

Spectral data and HRMS data. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


### Corresponding Authors

*Tel: +82-62-715-3238. Fax: +82-62-715-2484. E-mail: yongchul@gist.ac.kr.

*E-mail: kohyojin@gist.ac.kr.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This research was supported by a Basic Science Research Program of the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (Grant NRF-2012R1A1A3013563).

## ■ ABBREVIATIONS

AchE, acetylcholinesterase; BuchE, pseudocholinesterase; IL, interleukin; $K_i$, inhibition constant; ELISA, enzyme-linked immunosorbent assay; DMF, dimethylformamide; KOH, potassium hydroxide;; DIPEA, *N*,*N*-diisopropylethylamine;; PyBop, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate;; EDC, 1-ethyl-3-(3-(dimethylamino)propyl)-carbodiimide;; HATU, (dimethylamino)-*N*,*N*-dimethyl(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methaniminium hexafluorophosphate; TFA, trifluoroacetic acid; ESI, electrospray ionization; NMR, nuclear magnetic resonance

## ■ REFERENCES


(1) Muhammad, A.; Munawar, A. M.; Hamaid, L. S. Antimicrobial activity and synthesis of quinoline-based chalcones. *J. Applied Sci.* **2007**, *7* (17), 2485−2489.

(2) Yeh-Long, C.; Chao-Ho, C.; I. -Li, C.; Po-Hsu, C.; Haw-Yaun, J. Synthesis and cytotoxic activity evaluation of indolo-, pyrrolo-, and benzofuro-quinoline-2(1*H*)-ones and 6 anilinoindoloquinoline derivatives. *Bioorg. Med. Chem.* **2002**, *10* (8), 2705−2712.

(3) Li-Ping, G.; Qing-Hao, J.; Guan-Rong, T.; Kyn-Yun, C.; Zhe-Shan, Q. Synthesis of some quinoline-2-(1*H*)-one and 1,2,4-triazolo-[4,3-a] quinoline derivatives as potent anticonvulsants. *J. Pharm. Pharm. Sci.* **2007**, *10* (3), 254−262.

(4) Michael, R.; Paul, D. L.; Graeme, I. S.; Angela, M. M.; Ian, S.; Lesley, R.; Raymond, B.; John, A. K.; George, R. M.; Alan, C. F.; Sarah, G.; Mark, D. T.; Kay, L. S. 3-Acyl-4-hydroxyquinolin-2(1*H*)-ones. Systemically active anticonvulsants acting by antagonism at the glycine site of the *N*-methyl-$_D$-aspartate receptor complex. *J. Med. Chem.* **1993**, *36* (22), 3386−3396.

(5) Ukrainets, I. V.; Taran, S. G.; Kodolova, O. L.; Gorokhova, O. V.; Kravchenko, V. N. 4-Hydroxy-2-quinolines. 35. Synthesis and study of antithyroid properties of 1*H*-2-oxo-3-(coumarin-3-yl)-4-hydroxyquinolines. *Chem. Heterocycl. Compd.* **1997**, *33* (8), 959−963.

(6) Ukrainets, I. V.; Taran, S. G.; Gorokhova, O. V.; Marusenko, N. A.; Turov, A. V. 4-Hydroxy-2-quinolones. 32. Synthesis and antithyroid activity of thio analogs of 1*H*-2-oxo-3-(2-benzimidazolyl)-4-hydroxyquinoline. *Chem. Heterocycl. Compd.* **1997**, *33* (5), 600−604.

(7) Ukrainets, I. V.; Taran, S. G.; Gorokhova, O. V.; Taran, E. A.; Jaradat, N. A.; Petukhova, I. Y. 4-Hydroxy-2-quinolines. 40. Synthesis and biological properties of anilides of 1H-2-oxo-4-hydroxyquinoline-3-carboxylic acid. *Chem. Heterocycl. Compd.* **2007**, *36* (2), 166−169.

(8) Gisela, C. M.; Mariela, B.; Ana, M. B.; Silvia, E. A. Evaluation of antiparasitic, antituberculosis and antiangiogenic activities of 3-aminoquinolin-2-one derivatives. *J. Chil. Chem. Soc.* **2006**, *51* (2), 859−863.

(9) Jasminka, V.; Antonino, P.; Takahiko, H.; Richard, J. T.; Beryl, H. A.; John, T. I. Antiangiogenic effects of the quinoline-3-carboxamide linomide. *Cancer Res.* **1993**, *53* (8), 1833−1837.

(10) John, T. I.; Roberto, P.; David, Z. Q.; Susan, L. D.; Jason, B. G.; Natasha, K.; Anders, B.; Anders, O.; Tomas, L. Identification of ABR-215050 as lead second generation quinoline-3-carboxamide anti-anti-angiogenic agent for the treatment of prostate cancer. *Prostate.* **2006**, *66* (16), 1768−1778.

(11) Ukrainets, I. V.; Amer, M.; Bezuglyi, P. A.; Gorokhova, O. V.; Sidrenko, L. V.; Turov, A. V. 4-Hydroxy-2-quinolines. 56. 4-(Adamant-1-yl) thiazolyl-2-amides of 1-*R*-4-hydroxy-2-oxoquinoline-3-carboxylic acids as potential antitubercular agents. *Chem. Heterocycl. Compd.* **2002**, *38* (5), 571−575.

(12) Ukrainets, I. V.; Kolesnik, E. V.; Sidrenko, L. V.; Gorokhova, O. V.; Turov, A. V. 4-Hydroxy-2-quinolines 113. Synthesis and antitubercular activity of *N*-*R*-amides of 4-hydroxy-6-methyl-2-oxo-1-propyl-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic acid. *Chem. Heterocycl. Compd.* **2007**, *43* (3), 326−333.

(13) Ukrainets, I. V.; Kolesnik, E. V.; Sidrenko, L. V.; Gorokhova, O. V.; Turov, A. V. 4-hydroxy-2-quinolones. 95. Synthesis, structure, and antitubercular properties of hetarylamides of 4-hydroxy-2-oxo-1,2,5,6,7,8,-hexahydroquinoline-3-carboxylic acid. *Chem. Heterocycl. Compd.* **2006**, *42* (6), 765−775.

(14) Ukrainets, I. V.; Mospanova, E. V.; Bereznyakova, N. L.; Naboka, O. L. 4-Hydroxy-2-quinolones 138. Synthesis and study of structure−biological activity relationships in a series of 1-hydroxy-3-oxo-5,6-dihydro-3*H*-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid anilides. *Chem. Heterocycl. Compd.* **2007**, *43* (12), 1532−1539.

(15) (a) Kieseier; Bernd, C.; Wiendl; Heinz. Oral disease-modifying treatments for multiple sclerosis. *CNS Drugs* **2007**, *21* (6), 483−502. (b) Takashi, T.; Glen, W. S.; Kiyoshi, T.; Hiroaki, N.; Takashi, O.; Nobuo, S.; Aiko, S.; Masaaki, M. Quinoline-3-carbothioamides and related compounds as novel immunomodulating agents. *Bioorg. Med. Chem. Lett.* **2002**, *12* (17), 2427−2430.

(16) Gary, M.; Christian, H.; Michel, A.; Colombe, D.; Olivier, D.; Caroline, C.; Eric, G.; Genevieve, D.; Philip, J.; Anne-Marie, G.; Monque, D.; Frederique, G.; Stephen, O. Synthesis and SAR of 3- and 4-substituted quinolin-2-ones: Discovery of mixed 5-$HT_{1B}$/5-$HT_{2A}$ receptor antagonists. *Bioorg. Med. Chem.* **2001**, *9* (8), 2129−2137.

(17) (a) Nashaat, T.; Aleksander, S.; Roman, A. I.; Brian, R. Fluorinated cannabinoid CB2 receptors ligands: Synthesis and in vitro binding characteristics of 2-oxoquinoline derivatives. *Bioorg. Med. Chem.* **2011**, *19* (18), 5698−5707. (b) Katri, H. R.; Juha, R. S.; Jouko, V.; Jarmo, T. L.; Antti; Tomi, J.; Tapio, N. Synthesis and SAR studies of 2-oxoquinoline derivatives as CB2 receptor inverse agonists. *J. Med. Chem.* **2006**, *49* (6), 2022−2027.

(18) Tomassoli, I.; Ismaili, L.; Pudlo, M.; de Los Ríos, C.; Soriano, E.; Colmena, I.; Gandía, L.; Rivas, L.; Samadi, A.; Marco-Contelles, J.; Refouvelet, B. Synthesis, biological assessment and molecular modeling of new dihydroquinoline-3-carboxamides and dihydroquinoline-3-carbohydrazide derivatives as cholinesterase inhibitors, and Ca channel antagonists. *Eur. J. Med. Chem.* **2011**, *46* (1), 1−10.

(19) Noseworthy, J. H.; Wolinsky, J. S.; Lublin, F. D.; Whitaker, J. N.; Linde, A.; Gjorstrup, P.; Sullivan, H. C. North American linomide investigators: Linomide in relapsing and secondary progressive MS Part I: Trial design and clinical results. *Neurology* **2000**, *54* (9), 1726−1733.

(20) Nived, O.; Sturfelt, G.; Nilsson, B.; Termander, B.; Gunnarsson, P. O.; Strandgarden, K.; Wollheim, F. 1994: Clinical pilot study of roquinimex in patients with autoimmune disease. *Int. J. Immunotherapy* **1994**, *10* (2), 49−59.

(21) David, J. G.; Lola, W.; Israel, R.; Gunnar, H.; Eva, D.; Micha, J. R.; Shimon, S. The immunomodulator linomide: Role in treatment and prevention of autoimmune diabetes mellitus. *Int. Immunopharmacol.* **2001**, *1* (6), 1131−1139.

(22) Feurer, C.; Chow, C.; Borel, J. F. Preventive and therapeutic effects of cyclosporine and valine$^2$-dihydro-cyclosporin in chronic




DOI: 10.1021/co5001585
*ACS Comb. Sci.* 2015, 17, 60−69

relapsing experimental allergic encephalomyelitis in the Lewis rat. *Immunology* **1988**, *63* (2), 219−223.
(23) Karussis, D. M.; Lehmann, D.; Slavin, S.; Vourka-Karussis, U.; Mizrachi-Koll, R.; Ovadia, H.; Kalland, T.; Abramsky, O. Treatment of chronic-relapsing experimental autoimmune encephalomyelitis with the synthetic immunomodulator linomide (quinoline-3-carboxamide). *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90* (14), 6400−6404.
(24) Pekarski, O.; Björk, J.; Hedlund, G.; Andersson, G. The inhibitory effect in experimental autoimmune encephalomyelitis by the immunomodulatory drug linomide (PNU-212616) is not mediated via release of endogenous glucocorticoids. *Autoimmunity* **1998**, *28* (4), 235−241.
(25) Charlott, B.; Anna, R.; Lennart, O.; Birgitta, S.; Thomas, B.; Mikaennar, H. The new orally active immunoregulator laquinimod (ABR-215062) effectively inhibits development and relapses of experimental autoimmune encephalomyelitis. *J. Neuroimmunol.* **2002**, *130* (1−2), 163−172.
(26) Pili, R.; Haggman, M.; Stadler, W.; Gingrich, J. R.; Assikis, V. J.; Bjork, A. A randomized multicenter international phase II study of tasquinimod in chemotherapy-naive patients with metastatic castration-resistant prostate cancer. *J. Clin. Oncol.* **2010**, *28* (15), 75.
(27) Kiyoshi, T.; Glen, W. S.; Katsuya, N.; Takashi, T.; Nobuo, S. Synthesis and antinephritic activities of quinoline-3-carboxamides and related compounds. *Bioorg. Med. Chem. Lett.* **2000**, *12* (1), 85−88.
(28) McKinnell, R. M.; Armstrong, S. R; Beattie, D. T; Choi, S.-K.; Fatheree, P. R; Gendron, R. A. L; Goldblum, A.; Humphrey, P. P; Long, D. D; Marquess, D. G; Shaw, J. P.; Smith, J. A. M; Turner, S. D.; Vickery, R. G. A multivalent approach to the design and discovery of orally efficacious 5-$HT_4$ receptor agonists. *J. Med. Chem.* **2009**, *52* (17), 5330−5343.
(29) Wall, M. E.; Wani, M. C.; Nicholas, A. W.; Manikumar, G.; Tele, C.; Moore, L.; Truesdale, A.; Leitner, P.; Besterman, J. M. Plant antitumor agents. 30. Synthesis and structure activity of novel camptothecin analogs. *J. Med. Chem.* **1993**, *36* (18), 2689−2700.

## NOTE ADDED AFTER ASAP PUBLICATION

This article was published ASAP on December 1, 2014. The following sentence has been removed from the first paragraph of the Results and Discussion section, as there is no amino group present in compound 8 of Scheme 1: "NMR using deuterium oxide ($D_2O$) confirmed that the PMB group was not attached to the 5-amine group of 8." The correct version was published on December 18, 2014.


DOI: 10.1021/co5001585
*ACS Comb. Sci.* 2015, 17, 60−69