Journal of Medicinal Chemistry

Article

pubs.acs.org/jmc

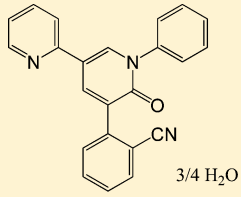
Discovery of 2-(2-Oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile (Perampanel): A Novel, Noncompetitive α-Amino-3-hydroxy-5-methyl-4-isoxazolepropanoic Acid (AMPA) Receptor Antagonist

Shigeki Hibi,*[,†] Koshi Ueno,[†] Satoshi Nagato,[†] Koki Kawano,[†] Koichi Ito,[†] Yoshihiko Norimine,[†] Osamu Takenaka,[§] Takahisa Hanada,[‡] and Masahiro Yonaga[†]

[†]Medicinal Chemistry, [‡]Biopharmacology, and [§]Drug Metabolism and Pharmacokinetics, Tsukuba Research Laboratories, Eisai Co., Ltd., 5-1-3 Tokodai, Tsukuba-shi, Ibaraki 300-2635, Japan

Supporting Information

ABSTRACT: Dysfunction of glutamatergic neurotransmission has been implicated in the pathogenesis of epilepsy and numerous other neurological diseases. Here we describe the discovery of a series of 1,3,5-triaryl-1*H*-pyridin-2-one derivatives as noncompetitive antagonists of AMPA-type ionotropic glutamate receptors. The structure−activity relationships for this series of compounds were investigated by manipulating individual aromatic rings located at positions 1, 3, and 5 of the pyridone ring. This culminated in the discovery of 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile (perampanel, **6**), a novel, noncompetitive AMPA receptor antagonist that showed potent activity in an in vitro AMPA-induced Ca^{2+} influx assay (IC_{50} = 60 nM) and in an in vivo AMPA-induced seizure model (minimum effective dose of 2 mg/kg po). Perampanel is currently in regulatory submission for partial-onset seizures associated with epilepsy.



Perampanel (**6**)

INTRODUCTION

The amino acid glutamate is the primary excitatory neurotransmitter in the human brain.[1] Glutamate exerts its physiologic effects via interaction with two major families of receptor proteins: metabotropic glutamate receptors (mGluRs) and ionotropic glutamate receptors (iGluRs). mGluRs allow glutamate to modulate cell excitability and synaptic transmission via second messenger signaling pathways, while iGluRs are ligand-gated tetrameric ion channels that mediate fast synaptic responses to glutamate.[2−4] Three classes of iGluRs have been identified and are named according to their selective agonists: AMPA, kainate, and NMDA.[3]

Dysfunction of glutamatergic neurotransmission has long been implicated in the pathogenesis of neurological diseases such as epilepsy, Parkinson's disease, neuropathic pain, and stroke.[1] In the case of epilepsy, it is more than 50 years since an increase of glutamate concentrations in the brain above a critical level was proposed to be the trigger for seizure activity.[5] Moreover, the discovery and characterization of mGluRs and iGluRs led to intensive efforts over the past 2 decades to generate novel drugs that inhibit the activity of these receptors. Nevertheless, no specific glutamate receptor antagonists have been approved for clinical use. Indeed, many putative NMDA receptor antagonists failed to reach the clinic because of the occurrence of severe psychotomimetic adverse events.[6] The first reported selective AMPA receptor antagonists were quinoxalinedione derivatives such as NBQX (**1**) (Figure 1) whose therapeutic usefulness was hampered by poor solubility and low blood−brain barrier penetration.[7] These quinoxalinedione derivatives competitively block glutamate gating. Other competitive AMPA receptor antagonists, including ZK-200775 (**2**) and tezampanel (**3**), have not yet reached the clinic (Figure 1).[8,9]

Meanwhile, noncompetitive AMPA receptor antagonists have actively been explored, driven by the belief that such drugs would exercise effectiveness independent of glutamate levels and the synaptic membrane polarization state, with minor influence on normal glutamatergic activity compared with competitive antagonists.[10]

Piriqualone (**4**) and talampanel (**5**) are categorized as noncompetitive AMPA receptor antagonists (Figure 1).[11,12] The latter compound was assessed in clinical trials against refractory epilepsy (last reported in 2002)[13] and is currently under investigation for the treatment of amyotrophic lateral sclerosis.[14] Overall, this early research suggested that AMPA receptor antagonists could be viable treatments for certain neurologic disorders without psychotomimetic adverse events.

Here we summarize our efforts to identify a selective, noncompetitive AMPA receptor antagonist that exhibits potent in vitro and in vivo efficacy with a pharmacokinetic profile compatible with oral administration. Systematic investigations of SARs for the series of 1,3,5-triaryl-1*H*-pyridin-2-one derivatives led to the discovery of 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile (perampanel, **6**) (Figure 1), a potent noncompetitive AMPA receptor antagonist currently in regulatory submission for partial-onset seizures associated with epilepsy.

Received: September 3, 2012
Published: November 26, 2012

dx.doi.org/10.1021/jm301268u | *J. Med. Chem.* 2012, 55, 10584−10600

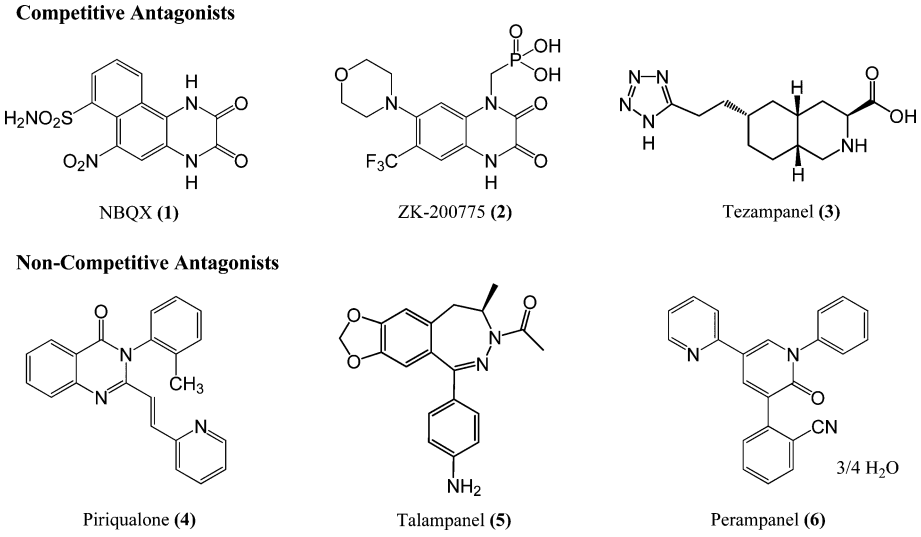
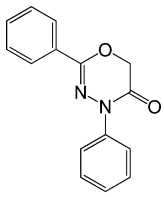


Figure 1. Known AMPA receptor antagonists including **6** (perampanel).

RESULTS AND DISCUSSION

Hit Identification by HTS. To identify a starting compound for our discovery efforts, we first screened our compound library using two HTS (high throughput screening) assays. The rat cortical neuron AMPA-induced cell-death assay identified compounds with AMPA antagonist activity, while the tritiated-AMPA binding assay allowed the detection and elimination of compounds acting as competitive AMPA receptor antagonists. Subsequently, a confirmatory AMPA-induced Ca^{2+} influx assay was used to characterize the potency of hit compounds and to enable identification of false-positive hits arising during HTS. After completion of these assays, commercially available 2,4-diphenyl-4*H*-[1,3,4]oxadiazin-5-one (**8a**) (AMPA-induced Ca^{2+} influx assay IC_{50} = 9.17 μM, Figure 2) was selected as a suitable starting compound with a novel structure versus other HTS hit compounds and known AMPA antagonists.



8a

Figure 2. Structure of the starting compound **8a**.

Discovery of 1,3,5-Triaryl-1*H*-pyridin-2-one Template. As our first effort to grasp the SARs for the oxadiazinone derivatives, introduction of an aliphatic substituent at either R^1 or R^2 (**8b**–**f**) was investigated in the AMPA-induced Ca^{2+} influx assay. The replacement with aliphatic substituent reduced activity, suggesting that conjugated aromaticity would be required to maintain AMPA antagonism in these oxadiazinone derivatives (Table 1).

Next, the oxadiazinone core structures were modified to improve both chemical and metabolic stability (Table 2). Replacement of the oxadiazinone (**8a**, IC_{50} = 9.17 μM) with the diazinone (**9**) (IC_{50} = 28.10 μM) or the pyridone derivatives (**13**) (IC_{50} = 69.54 μM) and (**16**) (IC_{50} = 57.72 μM) diminished but still maintained weak in vitro activity in the Ca^{2+} influx assay. From a comparison of metabolic stability between pyridone derivatives **13** and **16**, acidic hydrogen seemed to affect metabolic stability in human (H), mouse (M), and rat (R) liver microsomes. To mask the acidic hydrogen in **16**, another phenyl group was added to the pyridone template (**17**). Surprisingly, compound **17** showed both good Ca^{2+} influx activity (IC_{50} = 1.08 μM) and good metabolic stability and was chosen for further optimization.

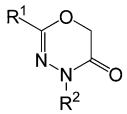
Optimization of 1,3,5-Triaryl-1*H*-pyridin-2-one Derivatives. Additional optimization of the 1,3,5-triaryl-1*H*-pyridin-2-one template was conducted by focusing on manipulation of the individual aromatic rings located at positions 1, 3, and 5 of the pyridone ring to yield a series of potent and selective noncompetitive AMPA receptor antagonists. First, the introduction of basicity via a 2-pyridine ring was assessed (Table 3). In comparison with **17** (IC_{50} = 1.08 μM), both **24a** (IC_{50} = 0.32 μM) and **28a** (IC_{50} = 0.44 μM) improved the activity to submicromolar level, resulting in the selection of a 2-pyridyl substituent at position 5 on the pyridone ring (Ar^1) for further optimization. Moreover, **28a** indicated the possibility of modifying the aromatic ring at position 1.

To investigate whether steric or electrical effects of the carbonyl group at position 2 on the pyridone ring affect in vitro activity, several substituents were introduced to the aromatic ring at position 3 on the pyridone ring (Ar^2). A cyano group was selected as a representative substituent because of its steric interactions with the carbonyl group and its electron-withdrawing force.

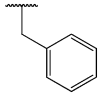
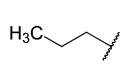
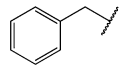
To clarify the substituent effect of the cyano group on the phenyl group, we synthesized ortho, meta, and para position substituted compounds **6**, **24b**, and **24c**, respectively (Table 4). The ortho substituent was shown to be the most appropriate from an activity aspect. Next, bulkiness and electron density were investigated. Among cyano, halogen, alkyl, and alkoxy substituents in the ortho position, the cyano group was most effective, suggesting that both electron-withdrawing properties and steric hindrance, which induces a certain twist angle between the pyridone core and 3-aryl ring, are essential to improve the activity. In addition, the possibility of pyridyl substituent at position 3 (**24h**, **24i**, and **24j**) was assessed, but the phenyl group was found to be stronger than the pyridine.

dx.doi.org/10.1021/jm301268u | *J. Med. Chem.* 2012, 55, 10584–10600

Table 1. SARs for the Oxadiazinone Derivatives (8a−f)[a]

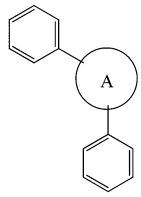


Inhibition Activity against AMPA Induced $[Ca^{2+}]_i$ Increase

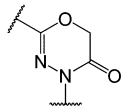
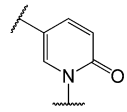
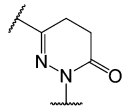
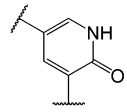
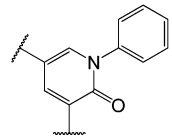
Compound No.	R^1	R^2	AMPA IC_{50} (μM)	Compound No.	R^1	R^2	AMPA IC_{50} (μM)
8a			9.17 ± 1.44	**8d**			>150
8b			33.70 ± 1.84	**8e**			>150
8c			>150	**8f**			>150

[a]All values are from three measurements and are expressed as the mean ± SEM.

Table 2. Effects on in Vitro Potency and Metabolic Stability of Replacement of 4*H*-[1,3,4]Oxadizin-5(6*H*)-one Ring with 4,5-Dihydro-3(2*H*)pyridinone or 1*H*-Pyridin-2-one Derivatives (8a vs 9, 13, 16, 17)



Inhibition Activity against AMPA Induced $[Ca^{2+}]_i$ Increase

Compound No.	A part	AMPA IC_{50} (μM)[a]	CLint (μL/min/mg pro)[b]	Compound No.	A part	AMPA IC_{50} (μM)[a]	CLint (μL/min/mg pro)[b]
8a		9.17 ± 1.44	H; 0.305 ± 0.003 M; 1.158 ± 0.075 R; 0.476 ± 0.010	**13**		69.54 ± 8.99	H; 0.114 ± 0.003 M; >1.535 R; 0.486 ± 0.031
9		28.10 ± 2.23	H; 0.172 ± 0.003 M; >1.535 R; 0.497 ± 0.018	**16**		57.72 ± 7.14	H; 0.371 ± 0.003 M; 1.230 ± 0.000 R; 0.822 ± 0.019
				17		1.08 ± 0.17	H; 0.045 ± 0.001 M; 0.148 ± 0.005 R; 0.052 ± 0.003

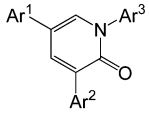
[a]All values are from three measurements and are expressed as the mean ± SEM. [b]Rate of human (H), mouse (M), and rat (R) intrisic clearance in vitro.

When the phenyl group was substituted with an ortho electron-withdrawing group, the cyano group in particular had a positive effect on the in vitro activity (Table 4). Similar SARs were observed in 1,5-dipyridylpyridone derivatives (Table 5). In the series, **28b** and **28e** exhibited promising activity.

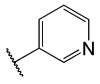
To confirm whether 2-pyridine at position 5 is optimized even in derivatives with a 2-cyanophenyl substituent at position 3 of the pyridone, several aryl rings were introduced at position 5 (Table 6). From a comparison of the substituent patterns of the pyridine rings, a 2-pyridyl derivative (**6**) showed greater in vitro activity than the other pyridine region isomers (**33a** and **33b**). Phenyl and thiophene (**33c**, **33e**, and **33h**) or ortho-substituted phenyl groups (**33d**, **33f**, and **33g**) decreased in vitro activity. In conclusion, the 2-pyridyl group was shown to confer the greatest in vitro potency. A final optimization at position 1 was executed by introduction of any substituted (methoxy, cyano, and fluorine) phenyl or pyridine ring, demonstrating that nonsubstituted phenyl (**6**) was best for in vitro activity (Table 7). Subsequently, some of the most potent compounds in Tables 4−7 were chosen to evaluate in vivo

dx.doi.org/10.1021/jm301268u | J. Med. Chem. 2012, 55, 10584−10600

Table 3. In Vitro Potency of Potential Template 1,3,5-Triaryl-1*H*-pyridin-2-ones (17, 24a, and 28a)[a]



Inhibition Activity against AMPA Induced $[Ca^{2+}]_i$ Increase

Compound No.	Ar^1	Ar^2	Ar^3	AMPA IC_{50} (μM)
17				1.08 ± 0.17
24a				0.32 ± 0.03
28a				0.44 ± 0.03

[a]All values are from three measurements and are expressed as the mean ± SEM.

effects using a mouse AMPA-induced seizure model: **6**, **24h**, **24j**, **28b**, **28d**, **28e**, **28g**, and **33c**.

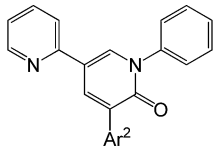
6, **28b**, **24h**, and **24j** showed strong effects in the mouse seizure model (as shown by the minimum effective dose) and sufficient stability in liver microsomes derived from three species (including human) (Table 8). The selected compounds were subjected to further preclinical pharmacokinetic studies. Data from the AMPA-induced seizure model (minimum effective dose of 2 mg/kg po) and the pharmacokinetic profile, which demonstrated good oral bioavailability, rapid absorption, and extensive distribution into body tissues (Tables 8 and 9), indicated that **6** was the most promising compound. Compound **6** was thus selected for advancement to clinical development.

The pharmacokinetic properties of **6** were evaluated in rats after iv (n = 3) and po (n = 3) administration at a dose of 1 mg/kg (Table 9). The results indicated a time to reach maximal plasma concentration of 0.50 h, a half-life of 2.37 h, a plasma clearance (CL) of 1.82 L h^{-1} kg^{-1}, and an oral bioavailability of 64.3%. The CL was investigated by in vitro metabolic stability (CLint) with in vitro−in vivo extrapolation (IVIVE), which indicated that the main elimination route of **6** is hepatic metabolism. As the CL_{int} of **6** in human liver microsomes was low (0.009 μL/min/mg protein), it was predicted by IVIVE to have good oral availability in humans.

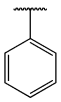
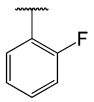
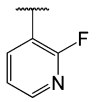
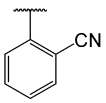
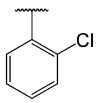
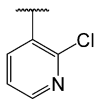
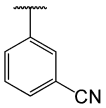
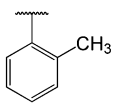
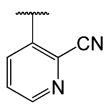
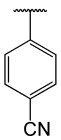
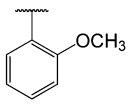
In order to assess CNS penetration of compound **6**, brain-to-plasma concentration ratios were evaluated in mice and rats. The ratios of **6** were 1.06 and 1.14 in mice and rats, respectively (Table 10). Furthermore, the cerebrospinal fluid (CSF) concentration of **6** was measured in mice, and the CSF concentration to unbound plasma concentration ratio was calculated to be 1.14. These results indicated a good CNS penetration of **6** in preclinical animal models, which is expected to be maintained in humans.

Chemistry. 2,4-Disubstituted-4*H*-1,3,4-oxadiazin-5(6*H*)-ones derivatives (**8a−f**) were synthesized by cyclization of intermediate **7** (Scheme 1).[15−17]

Table 4. SARs for the Aryl Group at Position 3 of the Pyridone Ring (i) (6, 24a−j)[a]



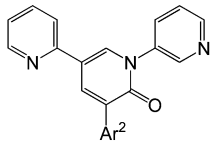
Inhibition Activity against AMPA Induced $[Ca^{2+}]_i$ Increase

Compound No.	Ar^2	AMPA IC_{50} (μM)	Compound No.	Ar^2	AMPA IC_{50} (μM)	Compound No.	Ar^2	AMPA IC_{50} (μM)
24a		0.32 ± 0.03	**24d**		0.20 ± 0.03	**24h**		0.37 ± 0.01
6		0.06 ± 0.01	**24e**		0.10 ± 0.01	**24i**		0.68 ± 0.02
24b		7.26 ± 2.26	**24f**		0.40 ± 0.01	**24j**		0.20 ± 0.01
24c		28.73 ± 1.28	**24g**		1.42 ± 0.24			

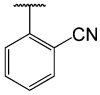
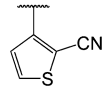
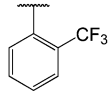
[a]All values are from three measurements and are expressed as the mean ± SEM.

dx.doi.org/10.1021/jm301268u | *J. Med. Chem.* 2012, 55, 10584−10600

Table 5. SARs for the Aryl Group at Position 3 of the Pyridone Ring (ii) (28a–g)[a]

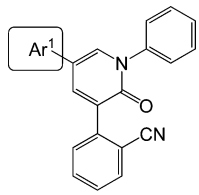


Inhibition Activity against AMPA Induced $[Ca^{2+}]_i$ Increase

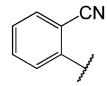
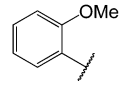
Compound No.	Ar^2	AMPA IC_{50} (μM)	Compound No.	Ar^2	AMPA IC_{50} (μM)	Compound No.	Ar^2	AMPA IC_{50} (μM)
28a		0.44 ± 0.03	**28d**		0.40 ± 0.02	**28g**		1.45 ± 0.03
28b		0.21 ± 0.02	**28e**		0.18 ± 0.02			
28c		0.78 ± 0.11	**28f**		2.10 ± 0.18			

[a]All values are from three measurements and are expressed as the mean ± SEM.

Table 6. SARs for the Aryl Group at Position 5 of the Pyridone Ring (6, 33a–h)[a]



Inhibition Activity against AMPA Induced $[Ca^{2+}]_i$ Increase

Compound No.	Ar^1	AMPA IC_{50} (μM)	Compound No.	Ar^1	AMPA IC_{50} (μM)	Compound No.	Ar^1	AMPA IC_{50} (μM)
6		0.06 ± 0.01	**33c**		0.33 ± 0.05	**33f**		8.43 ± 0.26
33a		4.02 ± 0.76	**33d**		0.20 ± 0.01	**33g**		0.74 ± 0.17
33b		5.53 ± 1.11	**33e**		0.10 ± 0.01	**33h**		0.14 ± 0.02

[a]All values are from three measurements and are expressed as the mean ± SEM.

The 4,5-dihydro-2,6-diphenyl-3(2*H*)pyridinone (**9**) was obtained by condensation of ethyl benzoylacetate and phenylhydrazine in EtOH.[18] The 1,5-diphenyl-1,2-dihydropyridin-2-one (**13**) was afforded by Ullmann-type reaction of a pyridone derivative (**12**), prepared from 2-methoxy-5-bromopyridine (**10**) in two steps in the usual manner with phenylboronic acid (Scheme 2).

The 3,5-diarylsubstituted-pyridone derivative (**16**) was produced by Suzuki–Miyaura coupling of 3,5-dibromo-2-methoxypyridine (**14**) and phenylboronic acid followed by acidic deprotection.

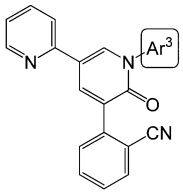
The preparation of trisubstituted derivatives is described in Schemes 3–7. 1,3,5-Triaryl-substituted-pyridone derivative **17** was synthesized by Ullmann-type reaction[19−21] of compound **16** using phenylboronic acid (Scheme 3).

1,3,5-Triaryl-2(1*H*)-pyridone derivatives **6**, **24a**, **24f**, **24h–j** were synthesized according to Scheme 4. 5-Ar-2(1*H*)-pyridone **21** was prepared by Suzuki–Miyaura coupling of **19**, followed by deprotection under acidic conditions. Modified Ullmann reaction of compound **21** with Ar^3-$B(OH)_2$ gave compound **22**, which was subjected to halogenation by NBS or NIS and then Suzuki–Miyaura coupling with the Ar^2 moiety to deliver the final compounds (**6**, **24a**, **24f**, **24h–j**) (Scheme 4).

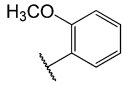
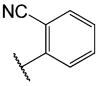
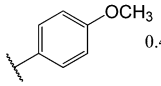
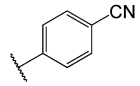
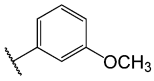
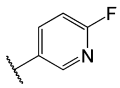
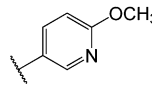
1-Aryl-5-(2-pyridyl)-3-aryl-2(1*H*)-pyridone derivatives **28a–g**, **38a**, **38c–g** were synthesized by bromination of intermediate

dx.doi.org/10.1021/jm301268u | J. Med. Chem. 2012, 55, 10584–10600

Table 7. SARs for the Aryl Group at Position 1 of the Pyridone Ring (6, 28b, 38a−g)[a]



Inhibition Activity against AMPA Induced $[Ca^{2+}]_i$ Increase

Compound No.	Ar^3	AMPA IC_{50} (μM)	Compound No.	Ar^3	AMPA IC_{50} (μM)	Compound No.	Ar^3	AMPA IC_{50} (μM)
6		0.06 ± 0.01	**38b**		0.15 ± 0.02	**38e**		>15
28b		0.21 ± 0.02	**38c**		0.44 ± 0.05	**38f**		0.52 ± 0.07
38a		0.25 ± 0.03	**38d**		0.50 ± 0.02	**38g**		0.62 ± 0.07

[a]All values are from three measurements and are expressed as the mean ± SEM.

21 followed by sequential couplings under modified Ullmann conditions and Suzuki−Miyaura/Stille conditions (Scheme 5).

The compounds **33a−h** and **24b−d** were afforded by selective arylation of 3-iodo-5-bromo-2(1*H*)-pyridone (**30**) as outlined in Scheme 6. Reaction of **30** with phenylboronic acid in the presence of copper acetate provided 5-bromo-3-iodo-1-phenyl-2(1*H*)-pyridone (**31**) in 52% yield. Coupling reaction of **31** with 2-aryl-1,3,2-dioxanorinate or arylboronic acid with tetrakis(triphenylphosphine)palladium as a catalyst in DMF furnished 5-bromo-3-aryl-1-phenyl-2(1*H*)-pyridone derivatives **32a−d** in 28−52% yield. These compound were reacted with various arylboronic acid derivatives or aryltributylstannane derivatives in the presence of a palladium catalyst to afford compounds **33a−h** and **24b−d** in 20−70% yields.

Finally, Scheme 7 demonstrated the introduction of a 1-aryl substitute on the pyridone ring (Ar^3) in the final step. Reaction of 5-bromo-2-methoxypyridine (**18**) with 2-pyridyltributylstannane in the presence of tetrakis(triphenylphosphine)palladium provided 2-methoxy-5-(2-pyridyl)pyridine (**34**). Then bromination of **34** was carried out by using stoichiometric amounts of silver acetate in acetic acid to afford 3-bromo-2-methoxy-5-(2-pyridyl)pyridine (**35**), which was coupled with phenyl[1,3,2]-dioxaborinate or arylboronic acid in the presence of palladium catalyst to give a 3,5-diaryl-2-methoxypyridine derivative (**36a−c**). **36** was treated with chlorotrimethylsilane and sodium iodide in acetonitrile to afford the 3,5-diaryl-2(1*H*)-pyridone derivative (**37a−c**). The coupling reaction of pyridine with various arylboronic acids in the presence of a copper(II) catalyst provided derivatives **24e**, **24g**, and **38b**.

CONCLUSIONS

We have described the entire discovery process from HTS to identification of our compound **6** by comprehensive manipulation of the three aromatic rings of a novel 1,3,5-triaryl-1*H*-pyridin-2-one template.

Pyridone derivative **6** exhibited extremely potent in vitro/in vivo effects (IC_{50} = 60 nM in the AMPA-induced Ca^{2+} influx assay; MED = 2 mg/kg po in the AMPA-induced seizure model) and had a preclinical pharmacokinetic profile favorable for clinical use due to its greater stability in humans (CL_{int} = 0.009 μL min^{-1} mg^{-1}) than in rats (CL_{int} = 0.108 μL min^{-1} mg^{-1}). The binding assay results[22] indicated that the binding site for **6** is similar to those of other known noncompetitive AMPA receptor antagonists. Moreover, pyridone derivative **6** was proven to be highly selective against the AMPA receptor using radioligand binding assays that included 63 physiologically relevant enzymes, ion channels, and neurotransmitter transporters (see Supporting Information).[23]

The potent in vivo activity of pyridone derivative **6** was confirmed in a number of preclinical seizure models, such as audiogenic seizures (ED_{50} = 0.47 mg/kg), maximal electroshock seizures (ED_{50} = 1.6 mg/kg), and pentylenetetrazole-induced seizures (ED_{50} = 0.94 mg/kg),[22] in addition to the mouse AMPA-induced seizure model.

In early clinical studies involving healthy subjects, **6** was well tolerated and displayed favorable pharmacokinetic characteristics, including good oral availability and a long half-life (approximately 70−100 h).[24]

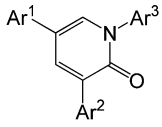
We believe that the discovery of pyridone derivative **6** and its passage through phases I−III of clinical development[25,26] have validated the clinical utility of an orally active, highly selective, and noncompetitive AMPA receptor antagonist.

EXPERIMENTAL SECTION

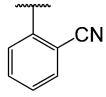
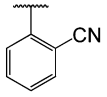
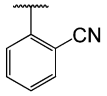
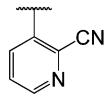
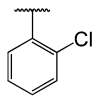
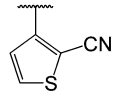
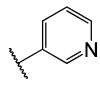
Chemistry. ^{1}H NMR spectra were recorded on a Bruker Avance spectrometer (600, 400, 300 MHz) or Varian Mercury 400 spectrometer (400 MHz). ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer (150 MHz) or JEOL JNM α400 spectrometer (100 MHz). Chemical shifts were expressed in ppm (δ) from the residual $CHCl_3$ signal at (δ_H) 7.26 ppm and (δ_C) 77.0 ppm in $CDCl_3$ and the residual C_5HD_4N signal at (δ_H) 8.71 ppm and (δ_C) 149.2 ppm in C_5D_5N. High-resolution mass spectra were recorded on a ThermoFisher LTQ-Orbitrap XL spectrometer (using ESI). The melting point of pyridone derivative **6** was determined by visual inspection according to the Japanese pharmacopeia. The elemental carbon, hydrogen, and nitrogen content was measured by

dx.doi.org/10.1021/jm301268u | J. Med. Chem. 2012, 55, 10584−10600

Table 8. In Vitro and in Vivo Efficacy of Selected 1,3,5-Triaryl-1*H*-pyridin-2-one Derivatives



Anticonvulsant Activity of below Compounds Against AMPA Induced Seizures

Compound No.	Ar^1	Ar^2	Ar^3	AMPA IC_{50} (μM)[a]	CL int (μL/min/mg pro)[b]	Minimum Effective Dose (*po*, mg/kg)
33c				0.33 ± 0.05	H; 0.022 ± 0.000 M; 0.059 ± 0.004 R; 0.226 ± 0.012	25
6				0.06 ± 0.01	H; 0.009 ± 0.000 M; 0.020 ± 0.000 R; 0.108 ± 0.003	2
28b				0.21 ± 0.02	H; 0.014 ± 0.001 M; 0.016 ± 0.001 R; 0.035 ± 0.002	10
24h				0.37 ± 0.01	H; 0.010 ± 0.000 M; 0.012 ± 0.000 R; 0.031 ± 0.001	5
28g				1.45 ± 0.03	H; 0.005 ± 0.000 M; 0.018 ± 0.000 R; 0.002 ± 0.000	10
24j				0.20 ± 0.01	H; 0.007 ± 0.000 M; 0.015 ± 0.000 R; 0.068 ± 0.002	5
28d				0.40 ± 0.02	H; 0.003 ± 0.000 M; 0.006 ± 0.000 R; 0.082 ± 0.002	25
28e				0.18 ± 0.02	H; 0.029 ± 0.001 M; 0.075 ± 0.001 R; 0.069 ± 0.001	25

[a]All values are from three measurements and are expressed as the mean ± SEM. [b]Rate of human (H), mouse (M), and rat (R) intrisic clearance in vitro.

Table 9. Pharmacokinetic Parameters for 6 (iv and po) in Male Rats[a]

iv (1 mg/kg)		po (1 mg/kg)	
parameter		parameter	
CL (L h^{-1} kg^{-1})	1.82	C_{max} (μg/mL)	0.17
V_{dss} (L/kg)	4.56	T_{max} (h)	0.50
AUC (μg mL^{-1} h^{-1})	0.56	AUC (μg mL^{-1} h^{-1})	0.36
$T_{1/2}$ (h)	2.37	*F* (%)	64.3

[a]Each parameter is calculated from the mean of plasma concentration of three animals. *F* is the ratio of AUC(0−inf) values after oral and intravenous administrations.

Table 10. Brain/Plasma or CSF/Unbound Plasma Concentration Ratios for 6 in Male Mice or Rats[a]

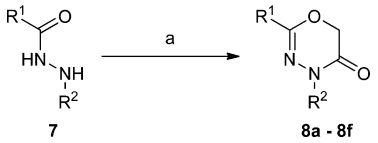
species	dose (mg/kg)	sampling time (min)	brain/plasma concn ratio	CSF/unbound plasma concn ratio
mice	3, po	60	1.06	NT
mice	0.5, ip	20	NT	1.14
rats	10, po	30	1.14	NT

[a]Each value represents the mean of two or three animals. NT: not tested.

a thermal-conductivity method using a CHN Corder MT5 analyzer (Yanaco, Japan). The purity of the biological tested compounds was determined by an analytical HPLC method and was found to be greater than or equal to 95% unless specified otherwise. The parameters of the HPLC method were as follows: Accucore RP-MS column (2.1 mm × 50 mm, 2.6 μm); mobile phase A = H_2O with 0.1% HCO_2H, B = acetonitrile with 0.1% HCO_2H; 0−1 min, 0% B; 1−4

dx.doi.org/10.1021/jm301268u | *J. Med. Chem.* 2012, 55, 10584−10600

Scheme 1[a]



[a]Reagents and conditions: (a) chloroacetyl chloride, base, solvent. For **8b**, (a) also requires BnBr, NaH, DMF.

min, 0% B → 100% B; 4−8 min, 100% B; 8−11 min, 0% B; flow rate of 0.4 mL/min; detector, UV 254 nm; run time of 11 min.

Reagents were purchased from commercial sources. Chromatography was performed on silica gel using the solvent systems indicated below. For mixed solvent systems, the volume ratios are given.

2,4-Diphenyl-4*H*-1,3,4-oxadiazin-5(6*H*)-one (8a). Benzoyl chloride (14.0 g, 100 mmol) was added dropwise at room temperature to a stirred solution of phenylhydrazine (10.8 g, 100 mmol) in pyridine (100 mL). After this addition, the reaction mixture was stirred at ambient temperature for 2 h. The mixture was then poured into ice−water (500 mL). The precipitates were collected by filtration and dissolved in EtOAc (500 mL). The organic layer was washed with 1 N HCl and brine and then dried over $MgSO_4$. After the drying agent was filtered off, the reaction solution was evaporated to give **7a** (10.1g, 47.6 mmol, 48%) without further purification.

Compound **7a** (10.1 g, 47.6 mmol) was dissolved in methyl ethyl ketone (250 mL). Chloroacetyl chloride (3.77 mL, 47.4 mmol) was added, followed by heating under reflux for 1 h. The solution was left and cooled to room temperature, after which potassium carbonate (39.4 g, 285.1 mmol) was added and the mixture was refluxed for 3 h under heating. The reaction solution was left and cooled to room temperature, evaporated, diluted with EtOAc, washed with water and brine, and then dried over $MgSO_4$. After the drying agent was filtered off, the product was evaporated and the resulting crystalline residues were recrystallized from *n*-hexane and EtOAc and then from methanol/hexane to give **8a** (6.80 g, 27.0 mmol, 56.6%) as a pinkish white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (s, 2H), 7.29−7.34 (m, 1H), 7.42−7.52 (m, 5H), 7.73−7.78 (m, 2H), 7.94−7.98 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 65.4, 123.5 2*C, 126.8 3*C, 128.5 2*C, 128.7 2*C, 129.4, 131.2, 139.6, 149.1, 158.7. HRMS calculated for ($C_{15}H_{12}N_2O_2$) $[M + H]^+$ 253.0972; found 253.0962.

2-Phenyl-4-benzyl-4*H*-1,3,4-oxadiazin-5(6*H*)-one (8b). Benzoylhydrazine (25 g, 0.18 mol) was dissolved in acetone (500 mL). Et_3N (21.8 g, 0.12 mol) was added to the solution. The resulting solution was cooled to 0 °C, and chloroacetyl chloride was added (17.2 mL, 0.216 mol). The mixture was stirred at room temperature overnight. H_2O was added to the reaction mixture, and then the mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and evaporated. A small amount of ether and heptane was added to the residue. The resulting precipitate was collected by filtration. The solid was dried at 50 °C and used for the next reaction without further purification. The solid was dissolved in DMF (190 mL), and K_2CO_3 (55 g, 0.401 mol) and NaI (4.2 g, 0.0268 mol) were added to the solution. The mixture was heated to 60 °C for 2 h.

The reaction mixture was filtered through Celite. The filtrate was evaporated, and EtOAc and H_2O were added to the residue. The mixture was acidified with 2 N aqueous HCl and then extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue solidified after the addition of toluene. The resulting precipitate was collected by filtration to give 2-phenyl-4*H*-1,3,4-oxadiazin-5(6*H*)-one (2.2 g). The filtrate was evaporated and the residue was purified by silica gel column chromatography (heptane/EtOAc = 20:1 to 2:1) to afford 2-phenyl-4*H*-1,3,4-oxadiazin-5(6*H*)-one (3.3 g). In total, 5.5 g (0.0312 mol) of 2-phenyl-4*H*-1,3,4-oxadiazin-5(6*H*)-one was obtained.

2-Phenyl-4*H*-1,3,4-oxadiazin-5(6*H*)-one (151.8 mg, 0.862 mmol) was dissolved in DMF (1 mL). The solution was cooled to 0 °C, and NaH (41.4 mg, 1.034 mmol) was added to the solution. The resulting solution was stirred at room temperature for 10 min. The solution was cooled to 0 °C, and benzyl bromide was added (0.113 mL, 0.948 mmol). The mixture was stirred at room temperature overnight. H_2O and EtOAc were added to the reaction mixture. The organic layer was separated, and the water layer was extracted with EtOAc. The combined organic layer was washed with H_2O and dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (heptane/EtOAc = 0:1 to 1:1) to afford **8b** (196 mg, 0.734 mmol, 85%) as white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (s, 2H), 4.96 (s, 2H), 7.29−7.33 (m, 1H), 7.34−7.42 (m, 4H), 7.43−7.48 (m, 3H), 7.80−7.91 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 51.5, 65.0, 126.6 2*C, 127.7, 128.3 2*C, 128.5 2*C, 128.6 2*C, 129.5, 130.9, 136.4, 148.5, 158.7. HRMS calculated for ($C_{16}H_{14}N_2O_2$) $[M + H]^+$ 267.1128; found 267.1119.

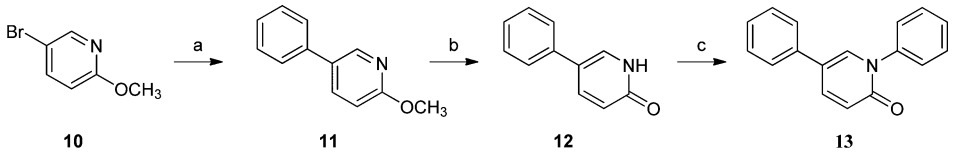
2-Phenyl-4-cyclohexyl-4*H*-1,3,4-oxadiazin-5(6*H*)-one (8c). Compound **8c** was prepared according to the procedure described for the synthesis of **8a** using *N*′-cyclohexylbenzohydrazide **7c** (1.0 g, 4.58 mmol). The product was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 10:1) to give **8c** (150 mg, 0.58 mmol, 13%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13−1.27 (m, 1H), 1.33−1.47 (m, 2H), 1.65−1.89 (m, 7H), 4.46−4.56 (m, 1H), 4.69 (s, 2H), 7.36−7.47 (m, 3H), 7.87 (dd, *J* = 1.6, 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 25.4 2*C, 29.9 2*C, 53.9, 65.0, 126.5 2*C, 128.3 2*C, 130.0, 130.7, 148.1, 158.1. HRMS calculated for ($C_{15}H_{18}N_2O_2$) $[M + H]^+$ 259.1441; found 259.1434.

2-Cyclohexyl-4-phenyl-4*H*-1,3,4-oxadiazin-5(6*H*)-one (8d). Compound **8d** was prepared according to the procedure described for the synthesis of **8a** using *N*′-phenylcyclohexanecarbohydrazide **7d** (1.0g, 4.58 mmol). The product was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 10:1) to give **8d** (962 mg, 3.72 mmol, 81%) as a pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.18−1.38 (m, 3H), 1.48 (dq, *J* = 3.4, 12.3 Hz, 2H), 1.67−1.74 (m, 1H), 1.82 (td, *J* = 3.3, 13.0 Hz, 2H), 1.96 (dd, *J* = 2.3, 13.6 Hz, 2H), 2.36 (tt, *J* = 3.4, 11.5 Hz, 1H), 4.67 (s, 2H), 7.24−7.27 (m, 1H), 7.38−7.44 (m, 2H), 7.65−7.69 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.6 2*C, 25.8, 29.5 2*C, 41.1, 65.0, 123.2 2*C, 126.5, 128.6 2*C, 139.6, 156.4, 158.5. HRMS calculated for ($C_{15}H_{18}N_2O_2$) $[M + H]^+$ 259.1441; found 259.1433.

2-*n*-Propyl-4-phenyl-4*H*-1,3,4-oxadiazin-5(6*H*)-one (8e). Compound **8e** was prepared according to the procedure described for the synthesis of **8a** using *N*′-phenylbutanehydrazide **7e** (500 mg, 2.81 mmol). The product was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 10:1) to give **8e** (60 mg, 0.27 mmol, 10%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 2H), 4.63 (s, 2H), 7.25−7.45 (m, 8H), 7.63 (m, 2H). HRMS calculated for ($C_{12}H_{14}N_2O_2$) $[M + H]^+$ 219.1128; found 219.1127.

2-Benzyl-4-phenyl-4*H*-1,3,4-oxadiazin-5(6*H*)-one (8f). Compound **8f** was prepared according to the procedure described for the synthesis of **8a** using *N*′,2-diphenylacetohydrazide **7f** (500 mg, 2.21

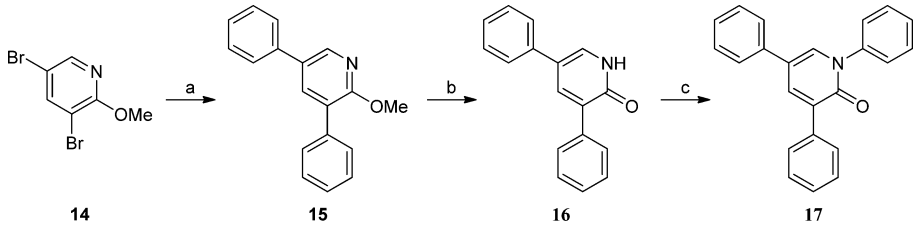
Scheme 2[a]



[a]Reagents and conditions: (a) phenylboronic acid, $Pd(PPh_3)_4$, sodium carbonate, xylene; (b) HBr, H_2O; (c) bromobenzene, KOAc, copper powder.

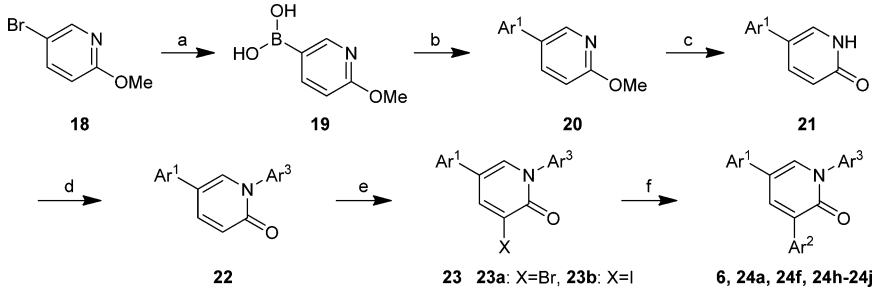
dx.doi.org/10.1021/jm301268u | *J. Med. Chem.* 2012, 55, 10584−10600

Scheme 3[a]



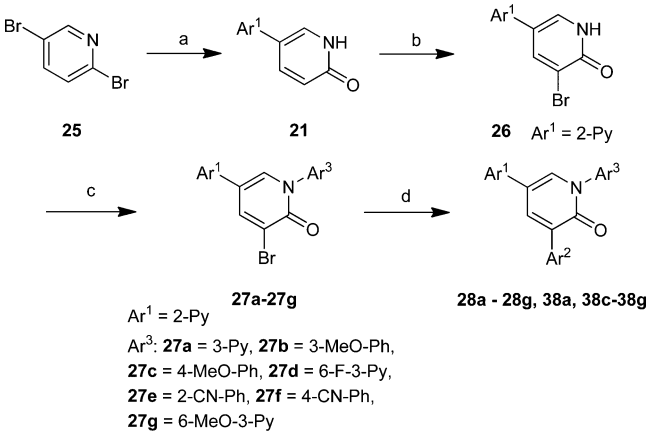
[a]Reagents and conditions: (a) phenylboronic acid, $Pd(PPh_3)_4$, potassium phosphate, toluene−water−EtOH; (b) HBr, H_2O; (c) phenylboronic acid, copper(II) acetate, pyridine, DMF.

Scheme 4[a]



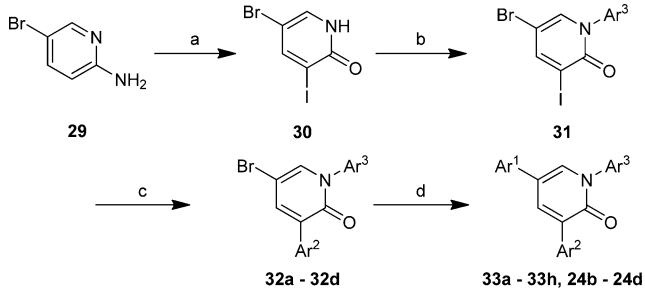
[a]Reagents and conditions: (a) *n*-BuLi, $B(OMe)_3$; (b) Ar^1-Br, $Pd(OAc)_2$, PPh_3, K_2CO_3, 1,2-dimethoxyethane−H_2O; (c) 4 N HCl; (d) Ar^3-$B(OH)_2$, $Cu(OAc)_2$, pyridine, DMF. (e) X = Br: NBS, DMF. X = I: NIS, DMF. (f) Ar^2[1,3,2]dioxaborinane, $PdCl_2$, PPh_3 polymer or Ar^2-$B(OH)_2$, $Pd(PPh_3)_4$, Cs_2CO_3, DMF . For **24j**, (f) $(SnBu_3)_2$, $Pd(PPh_3)_4$, xylene, then Ar^2Br, CuI, $Pd(PPh_3)_4$, xylene.

Scheme 5[a]



[a]Reagents and conditions: (a) (i) NaOMe, MeOH, (ii) Ar^1-$SnBu_3$, $Pd(PPh_3)_4$, DMF, (iii) 48% HBr; (b) NBS, DMF; (c) Ar^3-$B(OH)_2$, Cu(II) catalyst, base, solvent; (d) Ar^2-$B(OH)_2$ or Ar^2-$SnBu_3$ or Ar^2-1,3-dioxaborinane, $Pd(PPh_3)_4$, base, DMF.

Scheme 6[a]



[a]Reagents and conditions: (a) (i) HIO_4, I_2, AcOH, H_2O, (ii) $NaNO_2$, H_2SO_4; (b) Ar^3-$B(OH)_2$, $Cu(OAc)_2$, Et_3N, CH_2Cl_2; (c) Ar^2[1,3,2]-dioxaborinate or Ar^2-$B(OH)_2$, $Pd(PPh_3)_4$, Cs_2CO_3, DMF; (d) Ar^1-$B(OH)_2$, $Pd(PPh_3)_4$, Cs_2CO_3, DMF or Ar^1-$SnBu_3$, $Pd(PPh_3)_4$, DMF.

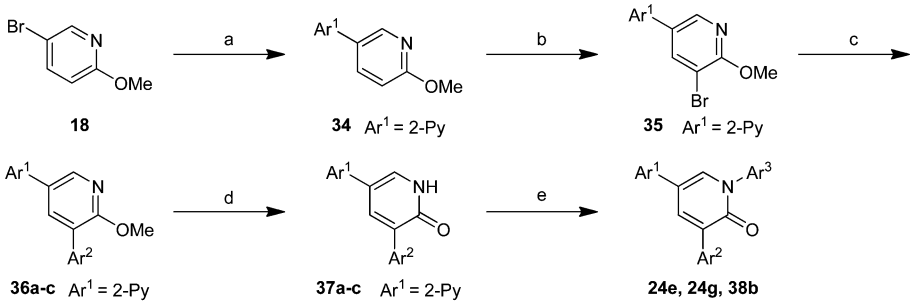
mmol). The product was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 10:1) to give **8f** (70 mg, 0.263 mmol, 12%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, J = 7.6 Hz, 3H), 1.71 (sxt, J = 7.6 Hz, 2H), 2.36 (t, J = 7.6 Hz, 2H), 4.70 (s, 2H), 7.25−7.31 (m, 1H), 7.43 (dd, J = 2.0, 7.6 Hz, 2H), 7.65 (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 19.3, 33.8, 64.8, 123.5 2*C, 126.7, 128.7 2*C, 139.4, 153.6, 158.4. HRMS calculated for ($C_{16}H_{14}N_2O_2$) $[M + H]^+$ 267.1128; found 267.1124. HPLC purity, 84.5%.

2-Methoxy-5-(pyridin-2-yl)pyridine (11). Phenylboronic acid (1.83 g, 15.0 mmol), 5-bromo-2-methoxypyridine **10** (1.90 g, 10.1 mmol), $Pd(PPh_3)_4$ (0.20 g, 0.17 mmol), 10% sodium carbonate solution (20 mL), and xylene (40 mL) were heated under reflux for 5 h with stirring. After the reaction solution was cooled, EtOAc (100 mL) was added to the extract. The organic layer was washed with 10% aqueous solution of ammonium chloride (60 mL), 10% aqueous ammonia (60 mL), and 10% saline (100 mL). The organic layer was dried over $MgSO_4$ and then evaporated to give **11** (1.86 g, 10.0 mmol, >99%) without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 6.81 (d, J = 8.4 Hz, 1H), 7.32−7.38 (m, 1H), 7.42−7.47 (m, 2H), 7.50−7.54 (m, 2H), 7.78 (dd, J = 2.4, 8.4 Hz, 1H), 8.39 (d, J = 2.4 Hz, 1H).

5-Phenyl-2(1*H*)-pyridone (12). A mixture of 2-methoxy-5-phenylpyridine **11** (1.86 g, 10.0 mmol) and 48% aqueous solution of HBr (10 mL) was heated at 130 °C for 1.5 h. After the reaction solution was cooled, EtOAc (100 mL) and water (50 mL) were added. The organic layer was separated and washed with saturated sodium bicarbonate solution (30 mL) and saturated sodium chloride solution. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (EtOA/cyclohexane = 1:1) to give **12** (1.14 g, 6.66 mmol, 67%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.43 (d, J = 9.6 Hz, 1H), 7.28 (dt, J = 1.2, 7.8 Hz, 1H), 7.37−7.43 (m, 2H), 7.53−7.57 (m, 2H), 7.69 (d, J = 2.8 Hz, 1H), 8.39 (dd, J = 2.8, 9.6 Hz, 1H), 11.78 (br s, 1H).

dx.doi.org/10.1021/jm301268u | J. Med. Chem. 2012, 55, 10584−10600

Scheme 7[a]



[a]Reagents and conditions: (a) Ar^1-$SnBu_3$, $Pd(PPh_3)_4$, DMF; (b) Br_2, CH_3CO_2Ag, AcOH, DMF; (c) phenyl[1,3,2]dioxaborinate or Ar^2-$B(OH)_2$, $Pd(PPh_3)_4$, Cs_2CO_3 or Et_3N, DMF; (d) for **37a** and **37b**, HBr; or for **37c**, chlorotrimethylsilane, NaI, CH_3CN; (e) Ar^3-$B(OH)_2$, $Cu(OAc)_2$, Et_3N, CH_2Cl_2.

1,5-Diphenyl-1,2-dihydropyridin-2-one (13). A mixture of 5-phenyl-1,2-dihydropyridin-2-one **12** (500 mg, 2.92 mmol), copper powder (560 mg, 8.8 mmol), potassium acetate (800 mg, 8.2 mmol), and bromobenzene (5.0 mL, 47.6 mmol) was stirred at 160 °C overnight. After the reaction mixture was cooled to room temperature, it was directly purified by silica gel column chromatography (EtOA/cyclohexane = 1:1). The solvent was evaporated in vacuo to give **13** (140 mg, 0.566 mmol, 19%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.57 (dd, J = 1.8, 8.4 Hz, 1H), 7.23−7.30 (m, 1H), 7.31−7.55 (m, 7H), 7.60 (dd, J = 2.0, 7.2 Hz, 2H), 7.85−7.95 (m, 1H), 7.92 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.8, 121.1, 126.0 2*C, 127.4 2*C, 127.5, 128.7, 129.4 2*C, 129.5 2*C, 136.2, 136.5, 140.3, 141.3, 161.0. HRMS calculated for ($C_{17}H_{13}NO$) [M + H]$^+$ 248.107; found 248.1071.

3,5-Dibromo-2-methoxypyridine (14). Sodium methoxide methanol solution (28%, 80 mL) was incorporated with 2,3,5-tribromopyridine (30 g, 95.0 mmol) under ice-cooling, followed by stirring at 50 °C for 2 h. The reaction solution was diluted with water and extracted with diethyl ether. The organic layer was washed with brine and then dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by silica gel chromatography (*n*-hexane/EtOAc = 20:1) to give **14** (18.5g, 69.3 mmol, 73%) as a greyish solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.88 (s, 3H), 8.27 (d, J = 2.4 Hz, 1H), 8.30 (d, J = 2.1 Hz, 1H).

3,5-Diphenyl-2-methoxypyridine (15). A mixture of 3,5-dibromo-2-methoxypyridine **14** (780 mg, 2.92 mmol) and phenylboronic acid (712 mg, 5.84 mmol) was incorporated with $Pd(PPh_3)_4$ (1.0 g, 0.87 mmol) and potassium phosphate in toluene−water−EtOH. This was heated with stirring under reflux overnight in a nitrogen atmosphere. After the mixture was cooled to room temperature, the solvent was evaporated and the residue was extracted with EtOAc. The organic layer was washed with water and brine and then dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel chromatography (*n*-hexane/EtOAc = 3:1) to give **15** (680 mg, 2.60 mmol, 89%) as a an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.94 (s, 3H), 7.37−7.41 (m, 2H), 7.45−7.50 (m, 4H), 7.66 (br d, J = 5.4 Hz, 1H), 7.76 (br d, J = 5.4 Hz, 1H), 8.01 (d, J = 1.8 Hz, 1H), 8.50 (d, J = 1.8 Hz, 1H).

3,5-Diphenyl-1,2-dihydropyridin-2-one (16). A mixture of 3,5-diphenyl-2-methoxypyridine **15** (680 mg, 2.60 mmol) and a 48% aqueous solution of HBr in EtOH was heated under reflux for 3 h. After the reaction solution was cooled, it was washed with *tert*-butyl methyl ether. An 8 mol/L aqueous solution of NaOH was added to the aqueous layer under cooling with ice−water, and then the mixture was washed twice with *tert*-butyl methyl ether. Then it was adjusted to pH 8 with concentrated HCl and an 8 mol/L aqueous solution of NaOH, followed by partitioning between EtOAc and brine. The aqueous layer was extracted again with EtOAc, and the combined organic layer was evaporated. *tert*-Butyl methyl ether was added to the resulting residue. The resulting precipitate was collected by filtration under reduced pressure and air-dried at 60 °C to give **16** (500 mg, 2.02 mmol, 78%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28−7.37 (m, 2H), 7.38−7.45 (m, 4H), 7.65 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 2.4 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.97 (d, J = 2.4 Hz, 1H), 11.95−12.22 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.8, 126.0 2*C, 127.2, 127.9, 128.4 2*C, 128.9 2*C, 129.4 2*C, 130.4, 132.2, 136.7, 137.1, 138.1, 161.1. HRMS calculated for ($C_{17}H_{13}NO$) [M + H]$^+$ 248.107; found 248.1065.

1,3,5-Triphenyl-1,2-dihydropyridin-2-one (17). A mixture of 3,5-diphenyl-1,2-dihydropyridin-2-one **16** (400 mg, 1.62 mmol), phenylboronic acid (260 mg, 2.13 mmol), copper(II) acetate (42 mg, 0.23 mmol), pyridine (0.37 mL), and DMF (5 mL) was stirred at room temperature overnight under an oxygen atmosphere. The reaction solution was poured into ice-cooled 10% aqueous ammonia and extracted with EtOAc. The organic layer was washed with water and brine. The organic layer was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give **17** (170 mg, 0.525 mmol, 32%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.55 (m, 13H), 7.62 (d, J = 2.8 Hz, 1H), 7.81 (d, J = 7.6 Hz, 2H), 7.90 (d, J = 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.1, 125.9 2*C, 126.8 2*C, 127.5, 128.0, 128.2 2*C, 128.6, 128.8 2*C, 129.1 2*C, 129.4 2*C, 132.4, 134.3, 136.5, 136.6, 137.9, 141.4, 160.8. HRMS calculated for ($C_{23}H_{17}NO$) [M + H]$^+$ 324.1383; found 324.1368.

5-Bromo-2-methoxypyridine (18). 2,5-Dibromopyridine (200 g, 0.84 mol) and 28% NaOMe methanol solution (1535 g) were heated under reflux for 30 min followed by cooling to room temperature. The mixture was partitioned between water (1.6 L) and *tert*-butyl methyl ether (1.6 L). The resulting organic layer was washed with brine (1 L) three times and then dried over $MgSO_4$ overnight. The dried organic layer was evaporated at 65 °C to give **18** (159 g, 0.84 mol, >99%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 6.66 (d, J = 8.8 Hz, 1H), 7.64 (dd, J = 2.2, 8.8 Hz, 1H), 8.20 (d, J = 2.2 Hz, 1H).

2-Methoxy-5-pyridylboronic Acid (19). 5-Bromo-2-methoxypyridine **18** (152 g, 0.81 mol) was dissolved in THF (1520 mL) under a nitrogen atmosphere, followed by cooling to −75.1 °C. Under cooling and stirring, a 2.46 mol/L *n*-butyl lithium solution (380 mL, 0.935 mol) was added dropwise, followed by the dropwise addition of trimethoxyborane (192 mL, 1.718 mol). The cooling bath was removed 30 min after completion of the dropwise addition, and the mixture was stirred at room temperature overnight. A 2 mol/L aqueous solution of HCl (1.5 L) was then added, followed by stirring for 1.5 h. The mixture was neutralized with a 5 mol/L aqueous solution of NaOH (460 mL) and then extracted with EtOAc (1 L × 2). The combined organic layer was washed twice with 10% saline water (1 L), dried over $MgSO_4$, and evaporated to give **19** (105 g, 85%, 0.69 mol) as a slightly yellowish white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.74 (d, J = 8.4 Hz, 1H), 7.98 (dd, J = 2.0, 8.4 Hz, 1H), 8.10 (s, 2H), 8.50 (d, J = 2.0 Hz, 1H).

dx.doi.org/10.1021/jm301268u | J. Med. Chem. 2012, 55, 10584−10600

2-Methoxy-5-(pyridin-2-yl)pyridine (20). 2-Methoxy-5-pyridylboronic acid **19** (105 g, 0.69 mol), 2-bromopyridine (90 g, 0.57 mol), palladium(II) acetate (3.21 g, 0.014 mol), triphenylphosphine (15 g, 0.057 mol), potassium carbonate (237 g, 1.72 mol), 1,2-dimethoxyethane (900 mL), and water (900 mL) were heated under reflux for 5 h and under stirring for 40 min. After the reaction solution was cooled, EtOAc (1 L) was added. The organic layer was washed with 10% aqueous solution of ammonium chloride (1 L), 10% aqueous ammonia (1 L), and 10% saline (1 L) and then evaporated to give **20** (126 g, 0.68 mol, 98%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.86 (s, 3H), 6.87 (dd, J = 0.6, 8.1 Hz, 1H), 7.25−7.30 (m, 1H), 7.77−7.90 (m, 2H), 8.31 (dd, J = 2.4, 8.7 Hz, 1H), 8.59−8.61 (m, 1H), 8.78−8.85 (m, 1H).

5-(Pyridin-2-yl)-2(1*H*)-pyridone (21). A mixture of 2-methoxy-5-(pyridin-2-yl)pyridine **20** (308 g, 1.65 mol) and a 4 mol/L aqueous solution of HCl (2.4 L) was heated under reflux for 3 h. After the reaction solution was cooled, it was washed with *tert*-butyl methyl ether (2.2 L). An 8 mol/L aqueous solution of NaOH (1.1 L) was added to the aqueous layer under cooling with ice−water, and then the mixture was washed twice with *tert*-butyl methyl ether (2.2 L). Then it was adjusted to pH 8 with concentrated HCl (310 mL) and an 8 mol/L aqueous solution of NaOH (100 mL), followed by partitioning between 1-butanol (4.5 L) and brine (1.8 L). The aqueous layer was extracted again with 1-butanol (4.5 L), and the combined organic layer was evaporated at 45−50 °C. *tert*-Butyl methyl ether (2.2 L) was added to the resulting residue. The resulting precipitate was collected by filtration. Water (1.6 L) was then added to dissolve the residue under heating. The mixture was water-cooled, recrystallized, and the resulting precipitate was collected by filtration to give **21** (188 g, 1.09 mol, 66%) as a grayish white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.42 (d, J = 9.6 Hz, 1H), 7.19−7.26 (m, 1H). 7.74−7.81 (m, 2H), 8.11 (d, J = 2.8 Hz, 1H), 8.17 (dd, J = 2.8, 9.6 Hz, 1H), 8.52−8.55 (m, 1H).

1-Phenyl-5-(pyridin-2-yl)-2(1*H*)-pyridone (22). While 5-(pyridin-2-yl)-2(1*H*)-pyridone **21** (185 g, 1.07 mol), phenylboronic acid (261 g, 2.14 mol), copper(II) acetate (19.4 g, 0.107 mol), pyridine (173 mL), and DMF (1480 mL) were stirred at room temperature, air was blown in at 2.0 L/min to initiate the reaction. Since 26% of the reactant remained unreacted 7 h after the initiation of the reaction, the flow of air was stopped to suspend the reactions. On the next day, air was blown into the solution to restart the reaction, and the reactant was consumed to 0.57% of the initial weight in 5.5 h. The reaction solution was poured into ice-cooled 10% aqueous ammonia (7.5 L). The resulting precipitate was collected by filtration under reduced pressure and washed with water (3 L). The resulting crystals were suspended into 10% aqueous ammonia (3.6 L) under stirring at room temperature for 1 h. Then the crystals were collected by filtration under reduced pressure and washed with water (2 L). The resulting crystals were air-dried overnight to give **22** (187 g, 70%, 0.753 mol) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, J = 9.5 Hz, 1H), 7.19 (dd, J = 4.9, 7.3 Hz, 1H), 7.42−7.48 (m, 3H), 7.49−7.55 (m, 3H), 7.72 (dt, J = 1.7, 7.8 Hz, 1H), 8.04 (dd, J = 2.7, 9.5 Hz, 1H), 8.21 (d, J = 2.7 Hz, 1H), 8.57−8.59 (m, 1H).

3-Bromo-1-phenyl-5-(pyridin-2-yl)-2(1*H*)-pyridone (23a). 1-Phenyl-5-(pyridin-2-yl)-2(1*H*)-pyridone **22** (186 g, 0.749 mol), NBS (141.7 g, 0.796 mol), and DMF (900 mL) were stirred at room temperature. After 2.5 h, NBS (6.45 g, 0.036 mol) was added. After depletion of the reactant was confirmed, the reaction solution was poured into water (4.5 L) under ice cooling, followed by stirring in a cold room (approximately 4 °C) overnight. The resulting crystals were collected by filtration under reduced pressure, followed by dissolving in IPA (3.25 L) and H_2O (650 mL) under heating. After complete dissolution was confirmed, the solution was left to cool gradually and then ice cooled. Then the mixture was stirred in a cold room overnight. The resulting solid was collected by filtration to give **23a** (191 g, 0.583 mol, 78%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29−7.34 (m,1H), 7.50−7.60 (m, 6H), 7.81−7.88 (m, 1H), 8.46 (d, J = 1.8 Hz, 1H), 8.55−8.62 (m, 1H), 8.77−8.80 (m, 1H).

2-(2-Oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)-benzonitrile (6). A mixture of 3-bromo-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one **23a** (50 mg, 0.152 mmol), 2-(1,3,2-dioxaborinan-2-yl)benzonitrile (40 mg, 0.213 mmol), palladium chloride (2.7 mg, 0.015 mmol), triphenylphosphine polymer (20 mg), Cs_2CO_3 (100 mg, 0.307 mmol), and DMF (1.5 mL) was stirred at 80 °C under a nitrogen atmosphere for 6 h. Subsequently, EtOAc (50 mL) was added to the reaction mixture and the mixture was filtered and washed with 12.5% aqueous ammonia, water, and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Acetone (4 mL) was added, followed by concentration under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/*n*-hexane = 1:2) to give **6** (39 mg, 0.111 mmol, 73%) as a yellowish white solid (mp 180 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 (dd, J = 4.8, 7.6 Hz, 1H), 7.48−7.63 (m, 6H), 7.73 (dd, J = 8.4 Hz, 1H), 7.79 (ddd, J = 1.2, 6.4, 8.0 Hz, 1H), 7.85 (ddd, J = 2.0, 6.4, 8.0 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 8.48 (d, J = 2.8 Hz, 1H), 8.54 (d, J = 2.8 Hz, 1H), 8.59 (ddd, J = 0.8, 1.2, 4.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 112.5, 118.3, 118.6, 118.8, 122.1, 126.7 2*C, 128.2, 128.8, 129.0, 129.4 2*C, 131.1, 132.3, 133.2, 137.1, 138.0, 138.9, 140.3, 140.9, 149.8, 153.1, 160.5. HRMS calculated for ($C_{23}H_{15}N_3O$) $[M + H]^+$ 350.1288; found 350.1276.

3-Phenyl-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (24a). Compound **24a** was prepared according to the procedure described for the synthesis of **6** using **23a** (1.6 g, 4.9 mmol) and phenylboronic acid to give **24a** (440 mg, 1.36 mmol, 28%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 (ddd, J = 0.8, 4.8, 8.4 Hz, 1H), 7.35−7.40 (m, 1H), 7.41−7.47 (m, 2H), 7.49−7.54 (m, 2H), 7.56−7.60 (m, 3H), 7.83 (ddd, J = 1.6, 6.0, 8.4 Hz, 3H), 8.02 (dd, J = 0.8, 8.4 Hz, 1H), 8.42 (d, J = 2.8 Hz, 1H), 8.44 (d, J = 2.8 Hz, 1H), 8.59 (ddd, J = 0.8, 1.6, 4.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 118.4, 118.5, 121.9, 126.8 2*C, 128.0, 128.1 2*C, 128.6, 128.9 2*C, 129.3 2*C, 132.0, 136.3 2*C, 136.6, 137.0, 141.3, 149.8, 153.5, 161.1. HRMS calculated for ($C_{22}H_{16}N_2O$) $[M + H]^+$ 325.1336; found 325.1347.

3-(3-Cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (24b). Compound **24b** was prepared according to the procedure described for the synthesis of **33c** using **32** (114 mg, 0.32 mmol) and 2-(tributylstannyl)pyridine to give **24b** (42 mg, 0.12 mmol, 38%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (ddd, J = 0.8, 4.8, 7.6 Hz, 1H), 7.46−7.66 (m, 8H), 7.78 (td, J = 1.6, 7.6 Hz, 1H), 8.10 (dt, J = 1.2, 8.0 Hz, 1H), 8.16 (t, J = 8.0 Hz, 1H), 8.25 (d, J = 2.4 Hz, 1H), 8.31 (d, J = 2.4 Hz, 1H), 8.61−8.63 (m,1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 111.6, 117.9, 119.3, 119.7, 122.6 2*C, 127.5, 128.4, 129.1 2*C, 129.6, 129.7, 131.7, 132.7, 133.8, 137.7, 137.7, 138.1, 138.3, 141.5, 149.8, 152.9, 160.3. HRMS calculated for ($C_{23}H_{15}N_3O$) $[M + H]^+$ 350.1288; found 350.1301.

3-(4-Cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (24c). Compound **24c** was prepared according to the procedure described for the synthesis of **33c** using **32** (55 mg, 0.16 mmol) and 2-(tributylstannyl)pyridine to give **24c** (23 mg, 0.066 mmol, 41%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.26 (m, 1H), 7.47−7.60 (m, 6H), 7.70−7.78 (m, 3H), 7.95−7.98 (m, 2H), 8.26 (d, J = 2.4 Hz, 1H), 8.33 (d, J = 2.4 Hz,1H), 8.61−8.63 (m,1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.4, 118.5, 118.6, 119.0, 122.2*C, 126.7, 129.0*C, 129.4, 129.5*C, 129.8, 131.9*C, 137.1, 137.4, 137.4, 140.9, 141.2, 149.8, 152.9, 160.6. HRMS calculated for ($C_{23}H_{15}N_3O$) $[M + H]^+$ 350.1288; found 350.1282.

3-(2-Fluorophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (24d). Compound **24d** was prepared according to the procedure described for the synthesis of **33c** using **32** (75 mg, 0.22 mmol) and 2-(tributylstannyl)pyridine to give **24d** (19 mg, 0.006 mmol, 27%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13−7.22 (m, 3H), 7.31−7.59 (m, 7H), 7.66 (td, J = 1.6, 7.6 Hz, 1H), 7.74 (td, J = 1.6, 7.6 Hz, 1H), 8.22 (dd, J = 1.2, 2.8 Hz, 1H), 8.29 (d, J = 2.8 Hz, 1H), 8.58−8.60 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 115.7(d, J(c,f) = 22.4 Hz), 118.1, 118.6, 121.9, 123.8 (d, J(c,f) = 3.4 Hz), 124.3 (d, J(c,f) = 14.4 Hz), 126.8, 127.1, 128.6, 129.3, 129.7 (d, J(c,f) = 8.5 Hz), 131.7 (d, J(c,f) = 2.7 Hz), 137.0, 136.7*2, 138.5 (d, J(c,f) = 3 Hz), 141.2, 149.7, 153.4, 160.2 (d, J(c,f) = 246 Hz), 160.5. HRMS calculated for ($C_{22}H_{15}N_2O$) $[M + H]^+$ 343.1241; found 343.1257.

3-(2-Chlorophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (24e). A suspension of 3-(2-chlorophenyl)-5-(2-pyridyl)-2(1*H*)-pyridone **37a** (430 mg, 1.52 mmol), phenylboronic acid (570 mg, 4.67 mmol), copper(II) acetate (840 mg, 4.62 mmol), and Et_3N (0.8 mL, 5.74 mmol) in methylene chloride (15 mL) was stirred at room temperature overnight. Concentrated aqueous ammonia (10 mL), water (20 mL), and EtOAc (100 mL) were added, and the organic layer was separated, washed with water and a saturated saline solution, and dried over $MgSO_4$. The solvent was concentrated in vacuo and the residue was purified by a silica gel column chromatography (*n*-hexane/EtOAc = 2:1) to give **24e** (120 mg, 0.33 mmol, 22%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76–6.81 (m, 2H), 6.86–6.91 (m, 1H), 7.17–7.22 (m, 2H), 7.26–7.75 (m, 5H), 7.61 (d, J = 8.0 Hz, 1H), 7.78–7.86 (m, 1H), 8.11 (d, J = 2.0 Hz, 1H), 8.41 (br s, 1H), 8.62 (d, J = 5.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.9, 118.6, 121.9, 126.5, 126.7 2*C, 128.6, 129.2 2*C, 129.3, 129.7, 130.9, 131.8, 133.7, 135.6, 137.0, 137.1, 138.4, 141.1, 149.7, 153.4, 160.4. HRMS calculated for ($C_{22}H_{15}ClN_2O$) [M + H]$^+$ 359.0946; found 359.0936.

3-(2-Tolyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (24f). Compound **24f** was prepared according to the procedure described for the synthesis of **6** using **23a** (108 mg, 0.33 mmol) and 2-tolylboronic acid to give **24f** (76 mg, 0.225 mmol, 68%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.24 (s, 3H), 7.22–7.34 (m, 5H), 7.47–7.60 (m, 5H), 7.78–7.84 (td, J = 2.4, 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 3.2 Hz, 1H), 8.45 (d, J = 3.2 Hz, 1H), 8.56 (d, J = 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 117.5, 119.5, 122.4, 126.0, 127.5 2*C, 128.3, 128.9, 129.6 2*C, 130.1, 130.5, 133.0, 137.1, 137.4, 137.6, 137.7, 138.0, 141.7, 149.8, 153.1, 160.1. HRMS calculated for ($C_{23}H_{18}N_2O$) [M + H]$^+$ 339.1492; found 339.1506.

3-(2-Methoxyphenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (24g). A suspension of 3-(2-methoxyphenyl)-5-(2-pyridyl)-2(1*H*)-pyridone **37b** (150 mg, 0.54 mmol), phenylboronic acid (120 mg, 0.98 mmol), copper(II) acetate (160 mg, 0.88 mmol), and Et_3N (0.5 mL, 3.59 mmol) in methylene chloride (5 mL) was stirred at room temperature overnight. Concentrated aqueous ammonia (5 mL), water (10 mL), and EtOAc (50 mL) were added to this, and the organic layer was separated, washed with water and a saturated saline solution, and dried over $MgSO_4$. The solvent was concentrated in vacuo and the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2:1) to give compound **24g** (45 mg, 0.127 mmol, 23.6%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.76 (s, 3H), 7.00 (td, J = 0.8, 7.6 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.27 (ddd, J = 0.8, 4.8, 7.2 Hz, 1H), 7.30–7.40 (m, 1H), 7.46–7.52 (m, 1H), 7.53–7.59 (m, 3H), 7.76–7.84 (m, 3H), 7.94 (d, J = 8.0 Hz, 1H), 8.23 (d, J = 2.8 Hz, 1H), 8.38 (d, J = 2.8 Hz, 1H), 8.55–8.58 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.9, 111.2, 117.9, 118.5, 120.4, 121.7, 125.9, 126.8 2*C, 128.4, 129.2 2*C, 129.4, 130.3, 131.3, 136.4, 136.9, 137.9, 141.5, 149.7, 153.8, 157.3, 160.8. HRMS calculated for ($C_{23}H_{18}N_2O_2$) [M + H]$^+$ 355.1441; found 355.1432.

3-(2-Fluoro-3-pyridyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (24h). Compound **24h** was prepared according to the procedure described for the synthesis of **6** using **23a** (66 mg, 0.20 mmol) and 2-fluoro-3-pyridylboronic acid to give **24h** (40 mg, 0.116 mmol, 58%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.28 (m, 2H), 7.44–7.56 (m, 5H), 7.56–7.60 (m, 1H), 7.75 (td, J = 1.6, 7.8 Hz, 1H), 8.19–8.21 (m, 1H), 8.26 (ddd, J = 0.9, 7.4, 9.4 Hz, 1H), 8.30 (d, J = 2.8 Hz, 1H), 8.34 (t, J = 2.2 Hz, 1H), 8.59–8.61 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 118.3, 118.6, 119.0 (d, J(c,f) = 28.0 Hz), 121.1 (d, J(c,f) = 4.1 Hz), 122.1, 124.5 (d, J(c,f) = 4.1 Hz), 126.7, 128.9, 129.4, 137.1, 137.6, 139.0 (d, J(c,f) = 4.6 Hz), 140.9, 142.3 (d, J(c,f) = 3.8 Hz), 146.9 (d, J(c,f) = 4.7 Hz), 149.8, 153.0, 160.5, 160.6 (d, J(c,f) = 239.3 Hz). HRMS calculated for ($C_{21}H_{14}FN_3O$) [M + H]$^+$ 344.1194; found 344.1184.

3-(2-Chloro-3-pyridyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydronyridin-2-one (24i). 3-Iodo-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one **23b** (200 mg, 0.53 mmol) was synthesized by the same method as for the bromo derivative (**23a**). 2-Chloro-3-pyridylboronic acid (130 mg, 0.826 mmol) and Cs_2CO_3 (250 mg, 0.767 mmol) were suspended in DMF (10 mL). $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) was added, and the mixture was stirred at 100 °C in a nitrogen atmosphere for 3 h. After it had cooled, the reaction solution was poured into water, the mixture was extracted with EtOAc, the extract was dried over $MgSO_4$, the solvent was evaporated in vacuo, and the residue was purified by a silica gel column chromatography (*n*-hexane/EtOAc = 1:1) to give **24i** (143 mg, 0.397 mmol, 75%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.24 (m, 1H), 7.31 (dd, J = 4.7, 7.6 Hz, 1H), 7.44–7.59 (m, 6H), 7.75 (dt, J = 1.6, 7.9 Hz, 1H), 7.91 (dd, J = 1.6, 7.9 Hz, 1H), 8.25 (d, J = 3.2 Hz, 1H), 8.33 (d, J = 3.2 Hz, 1H), 8.41 (dd, J = 1.6, 4.7 Hz, 1H), 8.59–9.62 (m, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 118.1, 118.6, 122.1, 122.2, 126.7 2*C, 128.5, 128.9, 129.4 2*C, 132.0, 137.1, 137.7, 139.1, 140.6, 140.8, 149.0, 149.8, 150.4, 153.0, 160.3. HRMS calculated for ($C_{21}H_{14}ClN_3O$) [M + H]$^+$ 360.0898; found 360.0883.

3-(2-Cyano-3-pyridyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (24j). 3-Bromo-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one **23a** (2.9 g, 8.86 mmol) was dissolved in xylene (200 mL). Bis(tributyltin) (5 mL, 0.01 mmol) and $Pd(PPh_3)_4$ (400 mg, 0.346 mmol) were added, and the mixture was stirred at 140 °C for 2 h. 3-Bromo-2-cyanopyridine (3.2 g, 17.4 mmol) and $Pd(PPh_3)_4$ (100 mg, 0.087 mmol) were added, and the mixture was stirred at 140 °C for 2 h. $Pd(PPh_3)_4$ (1.0 g, 0.865 mmol) and copper iodide (800 mg) were divided into four and added every 1 h. Then 3-bromo-2-cyanopyridine (2.0 g, 10.92 mmol) was added and the mixture was stirred at 140 °C overnight. The reaction solution was cooled to room temperature, water and EtOAc were added, the organic layer was partitioned, washed with water, and dried over anhydrous sodium sulfate, the drying agent was filtered off, the filtrate was concentrated in vacuo, and the residue was purified by a silica gel column chromatography (*n*-hexane/EtOAc system) to give **24j** (1.5 g, 4.28 mmol, 48%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (ddd, J = 0.8, 4.8, 7.4 Hz, 1H), 7.47–7.57 (m, 6H), 7.63 (d, J = 8.0 Hz, 1H), 7.77 (td, J = 1.6, 6.0 Hz, 1H), 8.22 (dd, J = 1.6, 8.4 Hz, 1H), 8.37 (d, J = 2.6 Hz, 1H), 8.43 (d, J = 2.6 Hz, 1H), 8.59–8.61 (m, 1H), 8.69 (dd, J = 1.6, 4.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 117.0, 118.5, 118.9, 122.3, 125.8, 125.9, 126.6 2*C, 129.1, 129.5 2*C, 132.9, 137.3, 137.4, 138.8, 138.9, 139.5, 140.7, 149.8, 149.9, 152.7, 160.4. HRMS calculated for ($C_{22}H_{14}N_4O$) [M + H]$^+$ 351.1241; found 351.1229.

3-Bromo-5-(2-pyridyl)-1,2-dihydropyridin-2-one (26). 5-(2-Pyridyl)-1,2-dihydropyridin-2-one (**21**) (201.5 g, 1.17 mol) was dissolved in DMF (1300 mL). NBS (208.3 g, 1.17 mol) was added, and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into 4 L of ice–water and the precipitate was filtered and dried with warm air at 50 °C for 2 days and nights to give **26** (230 g, 0.916 mL, 78%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.26 (m, 1H), 7.52 (d, J = 7.2 Hz, 1H), 7.75 (dt, J = 2.0, 7.8 Hz, 1H), 8.21 (d, J = 2.4 Hz, 1H), 8.61–8.64 (m, 1H), 8.67 (d, J = 2.4 Hz, 1H).

3-Bromo-5-(2-pyridyl)-1-(3-pyridyl)-1,2-dihydropyridin-2-one (27a). Dichloromethane (300 mL) was added to 3-bromo-5-(2-pyridyl)-1,2-dihydropyridin-2-one **26** (18.75 g, 74.7 mmol) and (pyridin-3-yl)boronic acid (18.36 g, 0.15 mol). Then di-μ-hydroxo-bis[(*N*,*N*,*N*′,*N*′-tetramethylethylenediamine)copper(II)] chloride (3.47 g, 7.47 mmol) was added, and the mixture was stirred in an oxygen atmosphere for 4 days and nights. The reaction solution was purified by an NH silica gel short column (eluted by EtOAc), the solvent was evaporated in vacuo, and the resulting crude crystals were washed with diethyl ether to give **27a** (24.3 g, 74.09 mmol, 99%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.26 (m,1H), 7.47–7.51 (m,1H), 7.52–7.56 (m,1H), 7.77 (dt, J = 2.0, 7.8 Hz, 1H), 7.87–7.91 (m, 1H), 8.19 (d, J = 2.4 Hz, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.59–8.62 (m, 1H), 8.71–8.75 (m, 2H).

3-Phenyl-5-(2-pyridyl)-1-(3-pyridyl)-1,2-dihydropyridin-2-one (28a). Compound **28a** was prepared according to the procedure described for the synthesis of **28b** using **27a** (58 mg, 0.177 mmol) and phenylboronic acid to give **28a** (29 mg, 0.089 mmol, 50%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (ddd, J = 1.0, 4.8, 7.4 Hz,

1H), 7.36−7.50 (m, 4H), 7.60 (td, J = 1.0, 8.0 Hz, 1H), 7.75 (dd, J = 2.0, 7.6 Hz, 1H), 7.76−7.80 (m, 2H), 7.94 (ddd, J = 1.6, 2.6, 8.2 Hz, 1H), 8.22 (d, J = 2.8 Hz, 1H), 8.24 (d, J = 2.8 Hz, 1H), 8.62 (ddd, J = 0.8, 2.0, 4.8 Hz, 1H), 8.71 (dd, J = 1.4, 4.6 Hz, 1H), 8.75−8.79 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 118.6, 119.1, 122.2, 123.6, 128.3 2*C, 128.8, 132.3, 134.7, 135.4, 136.2, 136.7, 137.1, 137.9, 147.5, 149.7, 149.8, 153.1, 161.0. HRMS calculated for ($C_{21}H_{15}N_3O$) [M + H]$^+$ 326.1288; found 326.1287.

3-(2-Cyanophenyl)-5-(2-pyridyl)-1-(3-pyridyl)-1,2-dihydropyridin-2-one (28b). 3-Bromo-5-(2-pyridyl)-1-(3-pyridyl)-1,2-dihydropyridin-2-one **27a** (5.39 g, 16.4 mmol) was dissolved in DMF (200 mL). Cs_2CO_3 (6.42 g, 19.70 mmol), 2-(1,3,2-dioxaborinan-2-yl)-benzonitrile (3.69 g, 19.7 mmol), and $Pd(PPh_3)_4$ (949 mg, 0.82 mmol) were added, and the mixture was stirred at 120 °C for 1 h. The reaction solution was cooled to room temperature, water and EtOAc were added, the organic layer was partitioned, washed with water, and dried over $MgSO_4$, the drying agent was filtered off, the filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography (n-hexane/EtOAc system) to give **28b** (4.8 g, 13.7 mmol, 84%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.26 (m, 1H), 7.46−7.52 (m, 2H), 7.62 (dt, J = 1.0, 8.2 Hz, 1H), 7.66 (dt, J = 1.4, 7.7 Hz, 1H), 7.74−7.81 (m, 3H), 7.97 (ddd, J = 1.6, 2.5, 8.2 Hz, 1H), 8.32 (s, 2H), 8.61 (ddd, J = 1.0, 1.8, 4.8 Hz, 1H), 8.72 (dd, J = 1.5, 4.8 Hz, 1H), 8.80−8.81 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 112.6, 118.5, 118.8, 118.9, 122.4, 123.7, 128.5, 129.3, 131.0, 132.5, 133.3, 134.7, 137.2, 137.2, 137.6, 139.3, 139.9, 147.3, 149.8, 149.9, 152.6, 160.3. HRMS calculated for ($C_{22}H_{14}N_4O$) [M + H]$^+$ 351.1241; found 351.1232.

3-(Thiophen-3-yl)-5-(2-pyridyl)-1-(3-pyridyl)-1,2-dihydropyridin-2-one (28c). Compound **28c** was prepared according to the procedure described for the synthesis of **28b** using **27a** (56 mg, 0.17 mmol) and thiophen-3-boronic acid to give **28c** (36 mg, 0.109 mmol, 64%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (ddd, J = 0.8, 4.8, 7.4 Hz, 1H), 7.39 (dd, J = 2.8, 5.2 Hz, 1H), 7.50 (dd, J = 4.8. 8.0 Hz, 1H), 7.60−7.63 (m, 1H), 7.65 (dd, J = 1.2, 5.2 Hz, 1H), 7.77 (td, J = 2.0, 7.8 Hz, 1H), 7.93 (ddd, J = 1.6, 2.6, 8.4 Hz, 1H), 8.15 (d, J = 2.8 Hz, 1H), 8.32 (dd, J = 1.2, 3.2 Hz, 1H), 8.44 (d, J = 2.4 Hz, 1H), 8.62−8.64 (m, 1H), 8.72−7.73 (m, 1H), 8.77 (d, J = 2.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 118.7, 119.0, 122.2, 123.7, 125.1, 125.4, 126.6, 126.7, 134.4, 134.5, 134.7, 135.9, 137.1, 138.0, 147.5, 149.8, 149.8, 153.1, 160.59. HRMS calculated for ($C_{19}H_{13}N_3OS$) [M + H]$^+$ 332.0852; found 332.0843.

3-(2-Chlorophenyl)-5-(2-pyridyl)-1-(3-pyridyl)-1,2-dihydropyridin-2-one (28d). Compound **28d** was prepared according to the procedure described for the synthesis of **28b** using **27a** (58 mg, 0.158 mmol) and 2-chlorophenylboronic acid to give **28d** (26 mg, 0.072 mmol, 46%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (ddd, J = 1.2, 4.6, 7.4 Hz, 1H), 7.31−7.36 (m, 2H), 7.41−7.51 (m, 3H), 7.56−7.59 (m, 1H), 7.75 (td, J = 2.0, 8.0 Hz, 1H), 7.95 (ddd, J = 1.6, 2.6, 8.2 Hz, 1H), 8.15 (d, J = 2.8 Hz, 1H), 8.30 (d, J = 2.4 Hz, 1H), 8.60−8.62 (m, 1H), 8.69 (dd, J = 1.6, 4.8 Hz, 1H), 8.80 (d, J = 2.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 118.6 2*C, 122.2, 123.5, 126.7, 129.5, 129.8, 131.2, 131.6, 133.7, 134.6, 135.2, 136.3, 137.1, 137.7, 138.9, 147.3, 149.7, 149.8, 152.9, 160.2. HRMS calculated for ($C_{21}H_{14}ClN_3O$) [M + H]$^+$ 360.0898; found 360.0889.

3-(2-Cyanothiophen-3-yl)-5-(2-pyridyl)-1-(3-pyridyl)-1,2-dihydropyridin-2-one (28e). Compound **28e** was prepared according to the procedure described for the synthesis of **28b** using **27a** (58 mg, 0.177 mmol) and 2-formyl-3-thienylboronic acid to give the 2-formyl-3-thienyl derivative (42 mg, 38%). This formyl derivative (20 mg) was treated with hydroxylamine hydrochloride in NaOAc and EtOH at 80 °C and then 1,1′-carbonyldiimidazole with Et_3N in DMF at 60 °C to give **28e** (20 mg, 0.056 mmol, 67% in two steps) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.26 (m, 1H), 7.50 (dd, J = 4.8, 8.0 Hz, 1H), 7.61−7.74 (m, 3H), 7.79 (td, J = 2.0, 7.6 Hz, 1H), 7.91−7.94 (m, 1H), 8.36 (d, J = 2.8 Hz, 1H), 8.57 (d, J = 2.4 H, 1H), 8.60−8.61 (m, 1H), 8.74 (dd, J = 1.4, 5.0 Hz, 1H), 8.79 (d, J = 2.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 106.72, 114.79, 118.96, 119.09, 122.49, 123.72, 124.39, 129.79, 131.19, 134.51, 137.39, 137.41, 137.44, 138.60, 146.36, 147.37, 149.84, 150.05, 152.43, 159.95. HRMS calculated for ($C_{20}H_{12}N_4OS$) [M + H]$^+$ 357.0805; found 357.0818.

3-(2-Trifluoromethylphenyl)-5-(2-pyridyl)-1-(3-pyridyl)-1,2-dihydropyridin-2-one (28f). Compound **28f** was prepared according to the procedure described for the synthesis of **28b** using **27a** (58 mg, 0.158 mmol) and 2-trifluoromethylphenylboronic acid to give **28f** (24 mg, 0.061 mmol, 39%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (ddd, J = 0.8, 4.8, 7.2 Hz, 1H), 7.44−7.56 (m, 4H), 7.59−7.63 (m, 2H), 7.72−7.78 (m, 1H), 7.94 (ddd, J = 1.6, 2.4, 8.0 Hz, 1H), 8.04 (d, J = 2.0 Hz, 1H), 8.30 (d, J = 2.4 Hz, 1H), 8.59−8.61 (m, 1H), 8.69 (dd, J = 1.2, 4.8 Hz, 1H), 8.78−8.79 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.5, 118.7, 122.3, 122.8, 123.6, 125.6, 126,4 (q, J(c,f) = 50 Hz), 128.4, 129.3 (q, J(c,f) = 298 Hz), 131.4, 131.6, 132.1, 134.6, 135.0, 136.3, 137.2, 138.1, 147,3, 149.7, 149.8, 152.8, 160.8. HRMS calculated for ($C_{22}H_{14}F_3N_3O$) [M + H]$^+$ 394.1162; found 394.1155.

3-(2-Fluoro-3-pyridyl)-5-(2-pyridyl)-1-(3-pyridyl)-1,2-dihydropyridin-2-one (28g). Compound **28g** was prepared according to the procedure described for the synthesis of **28g** using **27a** (100 mg, 0.30 mmol) and 2-fluoro-3-pyridylboronic acid to give **28g** (52 mg, 0.151 mmol, 50%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.29 (m, 2H), 7.45−7.52 (m, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.78 (dt, J = 2.1, 8.1 Hz, 1H), 7.91−7.95 (m, 1H), 8.19−8.25 (m, 2H), 8.30 (d, J = 2.6 Hz, 1H), 8.35 (t, J = 2.1 Hz, 1H), 8.60−8.63 (m, 1H), 8.70−8.73 (m, 1H), 8.79 (d, J = 2.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 118.6, 118.6 (d, J(c,f) = 28.6 Hz), 118.9, 121.2 (d, J(c,f) = 4.2 Hz), 122.4, 123.7, 124.9 (d, J(c,f) = 5.2 Hz), 134.6, 136.7, 137.2, 137.5, 139.4 (d, J(c,f) = 4.4 Hz), 142.2 (d, J(c,f) = 3.4 Hz), 147.1 (d, J(c,f) = 14.9 Hz), 147.3, 149.9, 149.9, 152.5, 160.3, 160.3 (d, J(c,f) = 239.7 Hz). HRMS calculated for ($C_{20}H_{13}FN_4O$) [M + H]$^+$ 345.1146; found 345.1136.

5-Bromo-3-iodo-1,2-dihydropyridin-2-one (30). 2-Amino-5-bromopyridine **30** (300 g, 1.73 mol) was dissolved in a mixed solvent consisting of acetic acid (1000 mL) and water (200 mL). Concentrated H_2SO_4 (30 mL) was gradually dropped in under stirring. Then acid hydrate (79.1 g, 0.347 mol) and iodine (176 g, 0.693 mol) were added periodically, followed by stirring at 80 °C for 4 h. Acid hydrate (40 g, 0.175 mol) and iodine (22 g, 0.086 mol) were added periodically to the reaction mixture followed by further stirring at 80 °C for 2 h. After cooling to room temperature, the reaction mixture was poured onto ice (3 L) and neutralized to pH 7.0 with 5 N aqueous NaOH. The resulting precipitate was collected by filtration, dissolved in a mixed solvent of EtOAc/diethyl ether, successively washed with aqueous sodium thiosulfate, water, 1 N aqueous NaOH, and brine, and dried over $MgSO_4$. The solvent was evaporated to give 2-amino-5-bromo-3-iodopyridine (392 g, 1.31 mol, 76%).

2-Amino-5-bromo-3-iodopyridine (100 g, 0.34 mol) was gradually added to concentrated sulfuric acid (300 mL) under ice cooling. After the reaction mixture was stirred at room temperature for 2 h, it was ice cooled again. Sodium nitrite (35 g, 0.51 mol) was gradually added, followed by stirring at room temperature for 3 days and nights. The reaction solution was poured onto ice (3 L) and neutralized to pH 4.0 with NaOH. The resulting precipitate was collected by filtration, washed with water, and warm-air-dried at 60 °C for 1 day and night to give **30** (102 g, 0.34 mol, >99%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 2.4 Hz, 1H), 8.14 (d, J = 2.4 Hz, 1H).

5-Bromo-1-phenyl-3-iodo-1,2-dihydropyridin-2-one (31). 5-Bromo-3-iodo-1,2-dihydropyridin-2-one **30** (10.0 g, 33.3 mmol), phenylboronic acid (10.0 g, 82.0 mmol), and copper acetate (8.1 g, 44.6 mmol) were suspended in dichloromethane (500 mL). Et_3N (15 mL, 107.6 mmol) was added, followed by stirring at room temperature for 5 days and nights. Water (200 mL) and aqueous ammonia (50 mL) were added to the reaction solution, and it was stirred vigorously. Then the insoluble matter was filtered off through Celite, the filtrate was extracted with dichloromethane, and the extract was dried over $MgSO_4$. The solvent was evaporated, and the residue was recrystallized from EtOAc and n-hexane to give **31** (6.54 g, 17.4 mmol, 52%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.38 (m, 2H), 7.44−7.52 (m, 3H), 7.53 (d, J = 2.6 Hz, 1H), 8.10 (d, J = 2.6 Hz, 1H).

5-Bromo-3-(2-cyanophenyl)-1-phenyl-1,2-dihydropyridin-2-one (32a). 5-Bromo-1-phenyl-3-iodo-1,2-dihydropyridin-2-one **31** (11.69 g, 31.1 mmol), 2-(1,3,2-dioxaborinan-2-yl)benzonitrile (8.0 g, 42.8 mmol), and Cs_2CO_3 (16.0 g, 49.1 mmol) were suspended in DMF (150 mL). $Pd(PPh_3)_4$ (3.0 g, 2.6 mmol) was added, followed by stirring at 80 °C in a nitrogen atmosphere for 2 h. The reaction solution was poured into water. The mixture was extracted with EtOAc. The extract was successively washed with water and brine and dried over $MgSO_4$. Then the solvent was evaporated, and the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc system) followed by recrystallizing from EtOAc and *n*-hexane to give **32a** (5.67 g, 16.1 mmol, 52%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.54 (m, 6H), 7.61−7.65 (m, 3H), 7.66 (d, J = 2.8 Hz, 1H), 7.74−7.77 (m, 1H).

5-Bromo-3-(3-cyanophenyl)-1-phenyl-1,2-dihydropyridin-2-one (32b). Compound **32b** was prepared according to the procedure described for the synthesis of **32a** using **31** (52 mg, 0.14 mmol) and 3-cyanophenylboronic acid to give **32b** (15 mg, 0.04 mmol, 28%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.38 (m, 1H), 7.39−7.42 (m, 2H), 7.46−7.53 (m, 3H), 7.58 (d, J = 2.8 Hz, 1H), 7.62−7.65 (m, 1H), 7.65 (d, J = 2.8 Hz, 1H), 7.94−7.98 (m, 1H), 8.06−8.08 (m, 1H).

5-Bromo-3-(4-cyanophenyl)-1-phenyl-1,2-dihydropyridin-2-one (32c). Compound **32c** was prepared according to the procedure described for the synthesis of **32a** using **31** (150 mg, 0.40 mmol) and 3-cyanophenylboronic acid to give **32c** (55 mg, 0.16 mmol, 40%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 2H), 7.39−7.42 (m, 2H), 7.47−7.56 (m, 2H), 7.60 (d, J = 2.8 Hz, 1H), 7.67(d, J = 2.8 Hz, 1H), 7.68−7.71 (m, 1H), 7.84−7.87 (m, 2H).

5-Bromo-3-(2-fluorophenyl)-1-phenyl-1,2-dihydropyridin-2-one (32d). Compound **32d** was prepared according to the procedure described for the synthesis of **32a** using **31** (300 mg, 0.80 mmol) and 3-cyanophenylboronic acid to give **32d** (150 mg, 44 mmol, 55%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11−7.25 (m, 4H), 7.26−7.37 (m, 2H), 7.41−7.63 (m, 5H).

3-(2-Cyanophenyl)-5-(3-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (33a). Compound **33a** was prepared according to the procedure described for the synthesis of **33c** using **32a** (90 mg, 0.256 mmol) and 3-pyridylboronic acid to give **33a** (89 mg, 0.255 mmol, 99%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (dd, J = 4.7, 8.1 Hz, 1H), 7.46−7.51 (m, 2H), 7.52−7.60 (m, 4H), 7.66 (dt, J = 1.3, 7.7 Hz, 1H), 7.74 (d, J = 2.6 Hz, 1H), 7.78−7.88 (m, 3H), 7.96 (d, J = 2.6 Hz, 1H), 8.62 (dd, J = 1.3, 4.7 Hz, 1H), 8.80 (d, J = 2.3 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 112.4, 116.7, 118.6, 123.8, 126.6 2*C, 128.5, 129.0, 129.5, 129.8 2*C, 131.1, 131.9, 132.3, 133.3, 133.5, 136.4, 139.9 2*C, 140.7, 147.1, 148.9, 160.1. HRMS calculated for ($C_{23}H_{15}N_3O$) [M + H]$^+$ 350.1288; found 350.1277.

3-(2-Cyanophenyl)-5-(4-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (33b). Compound **33b** was prepared according to the procedure described for the synthesis of **33c** using **32a** (90 mg, 0.256 mmol) and 4-pyridyllboronic acid to give **33b** (89 mg, 0.255 mmol, 99%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43−7.46 (m, 2H), 7.47−7.54 (m, 4H), 7.55−7.59 (m, 2H), 7.66 (dt, J = 1.1, 7.7 Hz, 1H), 7.82 (dd, J = 1.7, 7.7 Hz, 2H), 7.84 (d, J = 2.6 Hz, 1H), 8.02 (d, J = 2.6 Hz, 1H), 8.65−8.70 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 112.4, 116.8, 118.6, 120.1 2*C, 126.6 2*C, 128.5, 129.1, 129.6 2*C, 129.8, 131.0, 132.4, 133.3, 137.1, 139.2, 139.8, 140.6, 143.4, 150.7 2*C, 160.2. HRMS calculated for ($C_{23}H_{15}N_3O$) [M + H]$^+$ 350.1288; found 350.1277.

3-(2-Cyanophenyl)-1,5-diphenyl-1,2-dihydropyridin-2-one (33c). A mixture of compound **32a** (280 mg, 0.797 mmol), phenylboronic acid (194 mg, 1.59 mmol), $Pd(PPh_3)_4$ (80 mg, 0.069 mmol), and Cs_2CO_3 (775 mg, 2.38 mmol) in DMF (8 mL) was stirred at 110−120 °C under a nitrogen atmosphere for 6 h. The mixture was diluted with water (50 mL) and then extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5:1) to give **33c** (90 mg, 0.258 mmol, 32%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.37 (m, 1H), 7.41−7.56 (m, 10H), 7.63 (td, J = 1.6, 7.8 Hz, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.77−7.82 (m, 2H), 7.98 (d, J = 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.4, 118.7, 120.1, 126.1 2*C, 126.7 2*C, 127.7, 128.3, 128.8, 129.2 2*C, 129.2, 129.5 2*C, 131.1, 132.3, 133.3, 136.0, 136.1, 140.3, 140.6, 141.0, 160.2. HRMS calculated for ($C_{24}H_{16}N_2O$) [M + H]$^+$ 349.1335; found 349.1336.

3-(2-Cyanophenyl)-5-(2-fluorophenyl)-1-phenyl-1,2-dihydropyridin-2-one (33d). Compound **33d** was prepared according to the procedure described for the synthesis of **33c** using **32a** (50 mg, 0.142 mmol) and 2-fluorophenyllboronic acid to give **33d** (32 mg, 0.087 mmol, 62%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (ddd, J = 1.4, 8.1, 11.1 Hz, 1H), 7.23 (dt, J = 1.4, 7.5 Hz, 1H), 7.29−7.36 (m, 1H), 7.42−7.54 (m, 6H), 7.60−7.67 (m, 2H), 7.74−7.81 (m, 3H), 7.92 (dd, J = 1.3, 3.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 112.4, 114.1, 116.3 (d, J(c,f) = 21.7 Hz), 118.6, 123.7 (d, J(c,f) = 13.0 Hz), 124.9 (d, J(c,f) = 3.5 Hz), 126.6 2*C, 128.2, 128.8, 129.2, 129.4 2*C, 129.4 (d, J(c,f) = 12.7 Hz), 129.5, 131.1, 132.3, 133.3, 138.3 (d, J(c,f) = 4.6 Hz), 140.2, 140.9, 141.4, 159.6 (d, J(c,f) = 247.4 Hz), 160.0. HRMS calculated for ($C_{24}H_{15}FN_2O$) [M + H]$^+$ 367.1241; found 367.1231. HPLC purity; 83.8%.

3-(2-Cyanophenyl)-5-(thiophen-2-yl)-1-phenyl-1,2-dihydropyridin-2-one (33e). Compound **33e** was prepared according to the procedure described for the synthesis of **33c** using **32a** (50 mg, 0.142 mmol) and 2-thienylboronic acid to give **33e** (14 mg, 0.040 mmol, 28%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (dd, J = 3.6, 5.1 Hz, 1H), 7.17 (dd, J = 1.3, 3.6 Hz, 1H), 7.25−7.28 (m, 1H), 7.43−7.56 (m, 6H), 7.64 (dt, J = 1.3, 7.6 Hz, 1H), 7.72 (d, J = 2.6 Hz, 1H), 7.74−7.80 (m, 2H), 7.93 (d, J = 2.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 112.6, 114.3, 118.4, 123.4, 124.6, 126.7 2*C, 128.2, 128.4, 128.9, 129.5 2*C, 129.6, 131.0, 132.3, 133.2, 135.0, 138.7, 139.7, 139.9, 140.7, 159.9. HRMS calculated for ($C_{22}H_{14}N_2OS$) [M + H]$^+$ 355.0900; found 355.0888.

3-(2-Cyanophenyl)-5-(2-cyanophenyl)-1-phenyl-1,2-dihydropyridin-2-one (33f). A mixture of **31** (376 mg, 1.00 mmol), 2-(1,3,2-dioxaborolan-2-yl)benzonitrile (573 mg, 3.06 mmol), $Pd(PPh_3)_4$ (80 mg, 0.069 mmol), and Cs_2CO_3 (652 mg, 2.00 mmol) in DMF (8 mL) was stirred at 110−120 °C under a nitrogen atmosphere for 4 h. The mixture was diluted with water and then extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc = 5:1) to give crude product, which was triturated with PE/MTBE (5:1, 40 mL) to give **33f** (110 mg, 0.295 mmol 30%) as light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.59 (m, 7H), 7.62−7.72 (m, 3H), 7.76−7.80 (m, 2H), 7.82−7.84 (m, 1H), 7.86−7.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.6, 112.2, 116.3, 118.6, 118.7, 126.6, 126.6, 128.2, 128.5, 128.9, 129.5, 129.5 2*C, 129.5, 131.2, 132.4, 133.2, 133.6, 133.8, 138.7, 139.8, 140.0, 140.5, 141.0, 160.0. HRMS calculated for ($C_{25}H_{15}N_3O$) [M + H]$^+$ 374.1288; found 374.1297.

3-(2-Cyanophenyl)-5-(2-methoxyphenyl)-1-phenyl-1,2-dihydropyridin-2-one (33g). Compound **33g** was prepared according to the procedure described for the synthesis of **33c** using **32a** (268 mg, 0.763 mmol) and 2-methoxyphenylboronic acid to give **33g** (279 mg, 0.737 mmol, 97%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 6.95−7.04 (m, 3H), 7.29−7.54 (m, 7H), 7.58−7.64 (m, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.74−7.79 (m, 2H), 7.95 (d, J = 2.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.6, 111.2, 112.4, 117.0, 118.6, 121.1, 124.9, 126.7 2*C, 128.0, 128.2, 128.6, 129.3,129.3 2*C, 129.7, 131.3, 132.1, 133.3, 138.2, 140.5, 141.1, 142.9, 156.5, 160.1. HRMS calculated for ($C_{25}H_{18}N_2O_2$) [M + H]$^+$ 379.1441; found 379.1430.

3-(2-Cyanophenyl)-5-(thiophen-3-yl)-1-phenyl-1,2-dihydropyridin-2-one (33h). Compound **33h** was prepared according to the procedure described for the synthesis of **33c** using **32a** (50 mg, 0.142 mmol) and 3-thienylboronic acid to give **33h** (20 mg, 0.056 mmol, 40%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, J = 1.4, 6.0 Hz, 1H), 7.35 (dd, J = 1.4, 3.0 Hz, 1H), 7.41 (dd, J = 2.8, 5.2 Hz, 1H), 7.43−7.56 (m, 6H), 7.63 (dt, J = 1.4, 7.8 Hz, 1H), 7.70 (d, J = 2.8 Hz, 1H), 7.76−7.81 (m, 2H), 7.96 (d, J = 2.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 112.4, 115.5, 118.6, 119.9, 125.2, 126.7 2*C,

127.2, 128.3, 128.8, 129.4, 129.4 2*C, 131.1, 132.3, 133.3, 135.3, 136.9, 140.1 2*C, 140.9, 160.0. HRMS calculated for ($C_{22}H_{14}N_2OS$) $[M + H]^+$ 355.0900; found 355.0891.

3-(2-Cyanophenyl)-5-(2-pyridyl)-2-methoxypyridine (36c). $Pd(PPh_3)_4$ (0.15 g) was added to a mixed solution of 5-(2-pyridyl)-3-bromo-2-methoxypyridine **35** (500 mg, 1.89 mmol), 2-(1,3,2-dioxaborinan-2-yl)benzonitrile (0.42 g, 2.24 mmol), Cs_2CO_3 (0.82 g, 2.52 mmol), and DMF (20 mL), and the mixture was stirred at 140 °C in a nitrogen atmosphere for 5 h. After the mixture was cooled to room temperature, EtOAc was added, the mixture was washed with water and a saturated saline solution, and it was dried over $MgSO_4$. The solvent was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/*n*-hexane = 1:3) to give **36** (0.36 g, 1.25 mmol, 66%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (s, 3H), 7.24−7.28 (m, 1H), 7.46−7.51 (td, J = 1.6, 8.0 Hz, 1H), 7.57 (dd, J = 1.2, 8.0 Hz, 1H), 7.65−7.69 (td, J = 1.6, 8.0 Hz, 1H), 7.72−7.82 (m, 3H), 8.31 (d, J = 2.8 Hz, 1H), 8.66−8.69 (m, 1H), 8.83 (d, J = 2.8 Hz, 1H).

3-(2-Chlorophenyl)-5-(2-pyridyl)-2(1*H*)-pyridone (37a). $Pd(PPh_3)_4$ (150 mg) was added to a mixed solution of 5-(2-pyridyl)-3-bromo-2-methoxypyridine (**35**) (170 mg, 0.64 mmol), 2-chlorophenylboronic acid (150 g, 0.96 mmol), Et_3N (1 mL), and DMF (5 mL), and the mixture was stirred at 140 °C in a nitrogen atmosphere overnight. After the mixture was cooled to room temperature, EtOAc was added and the mixture was washed with water and a saturated saline solution and dried over $MgSO_4$. The solvent was concentrated in vacuo and the residue was passed through silica gel column chromatography (EtOAc/*n*-hexane = 1:3) to give crude 3-(2-chlorophenyl)-5-(2-pyridyl)-2-methoxypyridine **36a** (170 mg) without further purification.

A mixture of 3-(2-cyanophenyl)-5-(2-pyridyl)-2-methoxypyridine (170 mg, 0.70 mmol) and 48% HBr (2 mL) was stirred at 80 °C for 4 h. A saturated sodium bicarbonate solution was added to the mixture followed by extraction with EtOAc. The EtOAc layer was washed with water and a saturated saline solution and dried over $MgSO_4$. The solvent was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc:*n*-hexane = 1:1) to give **37a** (105 mg, 0.37 mmol, 58% in two steps) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 (t, J = 7.2 Hz, 1H), 7.32−7.45 (m, 3H), 7.50−7.57 (m, 1H), 7.80 (t, J = 7.5 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.96 (s, 1H), 8.02 (s, 1H), 8.55 (d, J = 5.0 Hz, 1H), 12.10−12.25 (br s, 1H).

3-(2-Methoxyphenyl)-5-(2-pyridyl)-2(1*H*)-pyridone (37b). $Pd(PPh_3)_4$ (0.3 g) was added to a mixed solution of 5-(2-pyridyl)-3-bromo-2-methoxypyridine (**35**) (1.19 g, 4.49 mmol), 2-methoxyphenylboronic acid (1.0 g, 6.58 mmol), Et_3N (1.5 g), and DMF (15 mL), and the mixture was stirred at 140 °C in a nitrogen atmosphere overnight. After the mixture was cooled to room temperature, EtOAc was added and the mixture was washed with water and a saturated saline solution and dried over $MgSO_4$. The solvent was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/*n*-hexane = 1:3) to give 3-(2-chlorophenyl)-5-(2-pyridyl)-2-methoxypyridine **36b** (1.06 g, 3.63 mmol, 81%). A mixture of **36b** (1.0 g, 0.70 mmol) and 48% HBr (8 mL) was stirred at 70 °C for 2 h. After the mixture was cooled to room temperature, potassium carbonate was added to neutralize it, followed by extraction with EtOAc. The EtOAc layer was washed with water and a saturated saline solution and dried over $MgSO_4$. The solvent was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/*n*-hexane = 1:1) to give **37a** (105 mg, 0.40 mmol, 58%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.73 (s, 3H), 6.96−7.03 (td, J = 1.2, 7.2 Hz, 1H), 7.06−7.09 (dd, J = 0.8, 8.0 Hz, 1H), 7.22−7.26 (ddd, J = 1.2, 4.8, 7.2 Hz, 1H), 7.27−7.30 (dd, J = 1.6, 8.0 Hz, 1H), 7.32−7.37 (ddd, J =1.6, 7.2, 8.0 Hz, 1H), 7.76−7.81 (ddd, J = 1.6, 7.2, 8.0 Hz, 1H), 7.82−7.84 (dt, J = 1.2, 8.0 Hz, 1H), 8.13 (s, 2H), 8.53−8.56 (ddd, J = 0.8, 1.6, 4.8 Hz, 1H), 11.96 (br s, 1H).

3-(2-Cyanophenyl)-5-(2-pyridyl)-2-(1*H*)-pyridone (37c). Chlorotrimethylsilane (0.1 mL, 7.88 mmol) was added to a suspension of 3-(2-cyanophenyl)-5-(2-pyridyl)-2-methoxypyridine **36c** (200 mg, 0.70 mmol) and sodium iodide (0.12 g, 0.80 mmol) in acetonitrile (10 mL), and the mixture was stirred at room temperature for 3 h. A saturated sodium bicarbonate solution was added to the mixture followed by extraction with EtOAc. The EtOAc layer was washed with water and a saturated saline solution and dried over $MgSO_4$. The solvent was concentrated in vacuo and the residue was purified by a silica gel column chromatography (EtOAc/*n*-hexane =1:1) to give **37c** (110 mg, 0.40 mmol, 58%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.26−7.30 (ddd, J = 0.8, 4.8, 8.0 Hz, 1H), 7.55−7.60 (td, J = 1.4, 8.0 Hz, 1H), 7.66 (dd, J = 0.8, 8.0 Hz, 1H), 7.74−7.79 (td, J = 1.4, 8.0 Hz, 1H), 7.80−7.86 (td, J = 1.4, 8.0 Hz, 1H), 7.89−7.94 (d, J = 8.0 Hz, 2H), 8.28 (d, J = 2.7 Hz, 1H), 8.37 (d, J = 2.7 Hz, 1H), 8.56−8.5.9 (m, 1H).

3-(2-Cyanophenyl)-5-(2-pyridyl)-1-(3-methoxyphenyl)-1,2-dihydropyridin-2-one (38a). Compound **27b** was prepared according to the procedure described for the synthesis of **22** using **26** (500 mg, 2.0 mmol) and 3-methoxyphenylboronic acid to give **27b** (122 mg, 0.3 mmol, 15%).

Compound **38a** was prepared according to the procedure described for the synthesis of **38f** using **27b** (100 mg, 0.28 mmol) and 2-(1,3,2-dioxaborinan-2-yl)benzonitrile to give **38a** (33 mg, 0.087 mmol, 31%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.95−7.03 (m, 1H), 7.06−7.10 (m, 2H), 7.20−7.22 (m, 1H), 7.41−7.81 (m, 7H), 8.31 (s, 2H), 8.59−8.61 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.6, 112.3, 112.5, 115.2, 118.2, 118.6, 118.8 2*C, 122.1, 128.2, 128.9, 130.2, 131.1, 132.3, 133.2, 137.1, 138.0, 138.9, 140.3, 142.0, 149.8, 153.1, 160.3, 160.4. HRMS calculated for ($C_{24}H_{17}N_3O_2$) $[M + H]^+$ 380.1394; found 380.1406.

3-(2-Cyanophenyl)-5-(2-pyridyl)-1-(2-methoxyphenyl)-1,2-dihydropyridin-2-one (38b). A suspension of 3-(2-cyanophenyl)-5-(2-pyridyl)-2(1*H*)-pyridone **37c** (250 mg, 0.914 mmol), 2-methoxyphenylboronic acid (250 mg, 1.65 mmol), copper(II) acetate (300 mg, 1.65 mmol), and Et_3N (1 mL, 7.17 mmol) in methylene chloride (10 mL) was stirred at room temperature overnight. Concentrated aqueous ammonia (5 mL), water (10 mL), and EtOAc (80 mL) were added, and the organic layer was separated, washed with water and a saturated saline solution, and dried over $MgSO_4$. The solvent was concentrated in vacuo and the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2:1) to give **38b** (45 mg, 0.12 mmol, 13%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.80 (s, 3H), 7.12 (t, J = 7.2 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.30 (dd, J = 4.8, 7.2 Hz, 1H), 7.44 (dd, J = 1.6, 8.0 Hz, 1H), 7.51 (ddd, J = 1.6, 7.2, 8.0 Hz, 1H), 7.59 (td, J = 1.2, 7.6 Hz, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.78 (dd, J = 1.2, 7.6 Hz, 1H), 7.83 (td, J = 1.6, 8.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 8.42 (d, J = 2.8 Hz, 1H), 8.47 (d, J = 2.8 Hz, 1H), 8.57 (br d, J = 4.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 56.0, 112.3, 112.5, 117.9, 118.6, 118.8, 120.9, 121.9, 128.1, 128.5, 128.7, 129.7, 130.6, 131.2, 132.2, 133.2, 137.1, 138.9, 140.0, 140.4, 149.7, 153.3, 154.4, 160.3. HRMS calculated for ($C_{24}H_{17}N_3O_2$) $[M + H]^+$ 380.1394; found 380.1382.

3-(2-Cyanophenyl)-5-(2-pyridyl)-1-(4-methoxyphenyl)-1,2-dihydropyridin-2-one (38c). Compound **27c** was prepared according to the procedure described for the synthesis of **22** using **26** (500 mg, 2.0 mmol) and 4-methoxyphenylboronic acid to give **27c** (137 mg, 0.4 mmol, 20%).

Compound **38c** was prepared according to the procedure described for the synthesis of **38f** using **27c** (100 mg, 0.28 mmol) and 2-(1,3,2-dioxaborinan-2-yl)benzonitrile to give **38c** (33 mg, 0.087 mmol, 31%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 7.02 (d, J = 8.8 Hz, 2H), 7.21 (ddd, J = 1.2, 4.8, 7.6 Hz, 1H), 7.42−7.80 (m, 8H), 8.29 (d, J = 8.0 Hz, 1H), 8.31 (d, J = 2.8 Hz, 1H), 8.58−8.60 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.6, 112.5, 114.6 2*C, 118.2, 118.6, 118.8, 122.0, 127.8 2*C, 128.2, 128.8, 131.1, 132.3, 133.2, 133.8, 137.1, 138.3, 138.8, 140.4, 149.7, 153.1, 159.7, 160.7. HRMS calculated for ($C_{24}H_{17}N_3O_2$) $[M + H]^+$ 380.1394; found 380.1406.

3-(2-Cyanophenyl)-5-(2-pyridyl)-1-(2-fluoropyridin-5-yl)-1,2-dihydropyridin-2-one (38d). Compound **27d** was prepared according to the procedure described for the synthesis of **27f** using **26** (108 mg, 0.430 mmol) and 4-fluoro-3-pyridylboronic acid to give **27d** (69 mg, 0.200 mmol, 46%). Compound **38d** was prepared

according to the procedure described for the synthesis of **38f** using **27d** (11 mg, 0.032 mmol) and 2-(1,3,2-dioxaborinan-2-yl)benzonitrile to give **38d** (5 mg, 0.014 mmol, 42%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (dd, J = 3.2, 8.8 Hz, 1H), 7.25 (m, 1H), 7.42−7.84 (m, 6H), 8.08 (ddd, J = 2.7, 6.8, 8.7 Hz, 1H), 8.30 (t, J = 2.8 Hz, 2H), 8.41 (m, 1H), 8.61 (ddd, J = 1.0, 1.6, 5.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 110.1 (d, J(c,f) = 39.6 Hz), 112.6, 118.4, 118.8, 119.1, 122.5, 128.6, 129.4, 130.9, 132.5, 133.3, 135.4 (d, J(c,f) = 4.6 Hz), 137.0, 137.3, 139.4, 139.8, 140.1 (d, J(c,f) = 8.9 Hz), 145.1 (d, J(c,f) = 16.1 Hz), 149.9, 152.5, 160.3, 162.7 (d, J(c,f) = 242.8 Hz). HRMS calculated for ($C_{22}H_{13}FN_4O$) [M + H]$^+$ 369.1146; found 369.1137.

3-(2-Cyanophenyl)-5-(2-pyridyl)-1-(2-cyanophenyl)-1,2-dihydropyridin-2-one (38e). Compound **38e** was prepared according to the procedure described for the synthesis of **38f** using **27e** (110 mg, 0.312 mmol) and 2-(1,3,2-dioxaborinan-2-yl)benzonitrile to give **38e** (85 mg, 0.227 mmol, 73%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.35 (m, 2H), 7.52−7.58 (m, 2H), 7.64−7.71 (m, 2H), 7.72−7.84 (m, 5H), 8.51 (d, J = 2.0 Hz, 1H), 8.68−8.72 (m, 1H), 8.77 (d, J = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.1, 112.8, 115.8, 118.3, 120.3, 122.2, 122.8, 123.4, 125.5, 128.7, 131.4, 131.6, 133.0, 133.1, 133.4, 134.3, 137.1, 139.3, 139.7, 146.0, 150.1, 153.6, 155.4, 159.6. HRMS calculated for ($C_{24}H_{14}N_4O$) [M + H]$^+$ 375.1240; found 375.1232.

3-(2-Cyanophenyl)-5-(2-pyridyl)-1-(4-cyanophenyl)-1,2-dihydropyridin-2-one (38f). Pyridine (568 mg, 7.20 mmol) was added to a solution of **26** (600 mg, 2.40 mmol), 4-cyanophenylboronic acid (423 mg, 2.88 mmol), and $Cu(OAc)_2$ (1.31 g, 7.20 mmol) in anhydrous DMSO (8 mL). The resulting mixture was stirred under an oxygen balloon at 40−50 °C for 4 days. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layer was filtered through a pad of Celite. The filtrate was washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column (*n*-hexane/EtOAc = 1:1) to give **27f** (600 mg, 1.71 mmol, 72%) as an off-white solid.

DMF (10 mL) was added under a nitrogen atmosphere to a mixture of **27f** (350 mg, 1.00 mmol), Cs_2CO_3 (386 mg, 2.00 mmol), 2-(1,3,2-dioxaborinan-2-yl)benzonitrile (275 mg, 1.47 mmol), and $Pd(PPh_3)_4$ (55 mg, 0.050 mmol, 5 mol %). The resulting mixture was degassed and purged with nitrogen three times and stirred at 110−120 °C for 24 h. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 1:1) to give **38f** (60 mg, 0.160 mmol, 16%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.26 (m, 1H), 7.49 (dt, J = 1.2, 7.6 Hz, 1H), 7.61−7.86 (m, 9H), 7.28−7.30 (m, 2H), 8.60−8.62 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 111.8, 112.4, 118.1, 118.7, 118.7, 119.7, 122.8, 128.7 2*C, 129.2, 129.2, 131.4, 133.4, 133.5, 133.8 2*C, 137.8, 138.2, 139.5, 140.6, 144.9, 149.9, 152.6, 159.7. HRMS calculated for ($C_{24}H_{14}N_4O$) [M + H]$^+$ 375.1240; found 375.1231.

3-(2-Cyanophenyl)-5-(2-pyridyl)-1-(2-methoxypyridyn-5-yl)-1,2-dihydropyridin-2-one (38g). Compound **27g** was prepared according to the procedure described for the synthesis of **27f** using **26** (563 mg, 2.24 mmol) and 4-methoxy-3-pyridylboronic acid to give **27g** (417 mg, 52%).

Compound **38g** was prepared according to the procedure described for the synthesis of **38f** using **27g** (185 mg, 0.516 mmol) and 2-(1,3,2-dioxaborinan-2-yl)benzonitrile to give **38g** (148 mg, 0.389 mmol, 75%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (s, 3H), 6.88 (d, J = 9.0 Hz, 1H), 7.23 (ddd, J = 0.8, 4.8, 7.4 Hz, 1H), 7.47 (td, J = 1.2, 7.8 Hz, 1H), 7.59−7.62 (m, 1H), 7.65 (td, J = 1.2, 7.8 Hz, 1H), 7.73−7.82 (m, 4H), 8.28−8.31 (m, 3H), 8.60 (ddd, J = 0.8, 1.6, 4.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 54.0, 111.2, 112.5, 118.5, 118.6, 118.8, 122.2, 128.4, 129.0, 131.0, 131.7, 132.4, 133.3, 137.2, 137.4, 137.8, 139.2, 140.1, 144.1, 149.8, 152.8, 160.6, 163.8. HRMS calculated for ($C_{23}H_{16}N_4O_2$) [M + H]$^+$ 381.1346; found 381.1337.

Biology. AMPA-Induced Ca^{2+} Influx Assays. E18 rat cerebral cortical neurons were used for experiments on DIV 9. Changes in intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$) were measured using the fluorescent Ca^{2+} indicator dye fura-2 acetoxymethyl (AM), as previously described.[27] Cells were incubated with fura-2 AM (10 μM) in a 5% CO_2/95% air incubator at 37 °C for 2 h and washed with Ca^{2+} assay buffer (140 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 3 mM $CaCl_2$, 24 mM D-(+)-glucose, 10 mM HEPES, 1 μM MK801; pH 7.4 adjusted with NaOH). Changes in $[Ca^{2+}]_i$ were determined by fluorimetry (fluorescence drug screening system, Hamamatsu Photonics, Shizuoka, Japan) by measuring changes in the fluorescence emission ratio of fura-2 after consecutive excitations at 340 and 380 nm wavelengths. The inhibitory effects of compounds on the $[Ca^{2+}]_i$ response induced by 1 μM AMPA were assessed. IC_{50} values of test compounds were calculated from the concentration−response curves. Data are presented as the mean ± standard deviation and are the result of three experiments.

Mouse AMPA-Induced Seizure Model. Male 5-week-old ddY mice were used. Test compounds were suspended in 0.5% MC and were orally administered 1 h before each test. Clonic seizures were elicited by intracerebral-ventricle infusion of AMPA at a constant speed of 2 nmol/5 μL/min. The latency to occurrence of a clonic seizure was measured, and the lowest dose providing statistically significant prolongation of latency was defined as the MED.

DMPK. In Vitro Metabolism Study in Liver Microsomes. Hepatic intrinsic clearance (CL_{int}) was calculated from the substrate disappearance rate in liver microsomes. Each compound (0.1 μmol/L) was incubated with a reaction mixture (150 μL) consisting of mouse, rat, or human liver microsomal protein (0.2 mg/mL) in 100 mM potassium phosphate buffer (pH 7.4) and 0.1 mM EDTA. After preincubation for 5 min at 37 °C, the enzyme reaction was initiated by adding an NADPH-generating system (0.33 mmol/L β-NADP$^+$, 8 mmol/L glucose 6-phosphate, 6 mmol/L $MgCl_2$, and 0.1 unit/mL glucose 6-phosphate dehydrogenase). After incubation of the microsomal matrix for 15 min at 37 °C, 150 μL of internal standard (1 μmol/L propanolol in methanol/acetonitrile [3/7, v/v]) was added to the reaction mixture and mixed vigorously. After centrifugation, the supernatant was subjected to LC/MS/MS analyses in positive ion mode with multiple reaction monitoring.

Preclinical Pharmacokinetic Studies. For pharmacokinetic experiments, compound **6** was administered intravenously or orally to fasted male Sprague−Dawley rats at a dose of 1 mg/kg. Blood samples were collected at designated time points. Plasma was obtained by centrifugation and deproteinized using methanol/60% perchloric solution (500:1 v/v). Plasma concentrations were determined by HPLC with fluorescence. Pharmacokinetic parameters were calculated by model-independent analysis. For assessment of brain penetration of **6**, brain samples were obtained from male ddY mice and male Sprague−Dawley rats after oral administration. Cerebrospinal fluid (CSF) samples were collected from mice by cisternal puncture after intraperitoneal administration. Brain was homogenized in two volumes of water, and the brain homogenates and CSF samples were processed and analyzed in a manner similar to that for plasma samples.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

HPLC purity data and data from radioligand binding assays. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Address: Shigeki Hibi Product Creation Headquarters, Eisai Product Creation Systems, Eisai Co., Ltd., Koishikawa 4-6-10, Bunkyo-ku, Tokyo 112-8088, Japan. Phone: +81-3-3817-3656. Fax: +81-3-3815-6702. E-mail: s-hibi@hhc.eisai.co.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Editorial support was provided by Rick Flemming, Ph.D., and Sian-Marie Lucas, Ph.D., of Complete Medical Communications and was funded by Eisai Inc. We thank Mami Gomibuchi, Masaharu Gotoda, Satoko Naito, Yumi Yokoyama, and Eri Ena for HRMS, HPLC, and NMR analyses. The work described in this article was funded by Eisai Co., Ltd.

■ ABBREVIATIONS USED

AMPA, (*S*)-2-amino-3-hydroxy-5-methyl-4-isoxazolepropanoic acid; kainate, (2*S*,3*S*,4*S*)-3-carboxymethyl-4-isopropenylpyrrolidine-2-carboxylic acid; NMDA, *N*-methyl-D-aspartic acid; NIS, *N*-iodosuccinimide; CL, plasma clearance; CL_{int}, intrinsic clearance in liver microsomes; IVIVE, in vitro−in vivo extrapolation

■ REFERENCES

(1) Meldrum, B. S. Glutamate as a neurotransmitter in the brain: review of physiology and pathology. *J. Nutr.* **2000**, *130*, 1007S−1015S.
(2) Mayer, M. L.; Armstrong, N. Structure and function of glutamate receptor ion channels. *Annu. Rev. Physiol.* **2004**, *66*, 161−181.
(3) Watkins, J. C.; Jane, D. E. The glutamate story. *Br. J. Pharmacol.* **2006**, *147* (Suppl. 1), S100−S108.
(4) Niswender, C. M.; Conn, P. J. Metabotropic glutamate receptors: physiology, pharmacology, and disease. *Annu. Rev. Pharmacol. Toxicol.* **2010**, *50*, 295−322.
(5) Takagaki, G. The dawn of excitatory amino acid research in Japan. The pioneering work by Professor Takashi Hayashi. *Neurochem. Int.* **1996**, *29*, 225−229.
(6) Le, D. A.; Lipton, S. A. Potential and current use of *N*-methyl-D-aspartate (NMDA) receptor antagonists in diseases of aging. *Drugs Aging* **2001**, *18*, 717−724.
(7) Meldrum, B. S.; Rogawski, M. A. Molecular targets for antiepileptic drug development. *Neurotherapeutics* **2007**, *4*, 18−61.
(8) Ornstein, P. L.; Arnold, M. B.; Augenstein, N. K.; Lodge, D.; Leander, J. D.; Schoepp, D. D. (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-[2-(1*H*-Tetrazol-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid: a structurally novel, systemically active, competitive AMPA receptor antagonist. *J. Med. Chem.* **1993**, *36*, 2046−2048.
(9) Turski, L.; Huth, A.; Sheardown, M.; McDonald, F.; Neuhaus, R.; Schneider, H. H.; Dirnagl, U.; Wiegand, F.; Jacobsen, P.; Ottow, E. ZK200775: a phosphonate quinoxalinedione AMPA antagonist for neuroprotection in stroke and trauma. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 10960−10965.
(10) De Sarro, G.; Gitto, R.; Russo, E.; Ibbadu, G. F.; Barreca, M. L.; De Luca, L.; Chimirri, A. AMPA receptor antagonists as potential anticonvulsant drugs. *Curr. Top. Med. Chem.* **2005**, *5*, 31−42.
(11) Donevan, S. D.; Yamaguchi, S.; Rogawski, M. A. Non-*N*-methyl-D-aspartate receptor antagonism by 3-N-substituted-2,3-benzodiazepines: relationship to anticonvulsant activity. *J. Pharmacol. Exp. Ther.* **1994**, *271*, 25−29.
(12) Welch, W. M.; Ewing, F. E.; Huang, J.; Menniti, F. S.; Pagnozzi, M. J.; Kelly, K.; Seymour, P. A.; Guanowsky, V.; Guhan, S.; Guinn, M. R.; Critchett, D.; Lazzaro, J.; Ganong, A. H.; DeVries, K. M.; Staigers, T. L.; Chenard, B. L. Atropisomeric quinazolin-4-one derivatives are potent noncompetitive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 177−181.
(13) Chappell, A. S.; Sander, J. W.; Brodie, M. J.; Chadwick, D.; Lledo, A.; Zhang, D.; Bjerke, J.; Kiesler, G. M.; Arroyo, S. A crossover, add-on trial of talampanel in patients with refractory partial seizures. *Neurology* **2002**, *58*, 1680−1682.
(14) Bialer, M.; White, H. S. Key factors in the discovery and development of new antiepileptic drugs. *Nat. Rev. Drug Discovery* **2010**, *9*, 68−82.
(15) Justoni, R. New method of synthesis of pyrazole derivatives. II. The behavior of malonic derivatives in experiments on the pyrazole synthesis. *Gazz. Chim. Ital.* **1938**, *68*, 49−59.
(16) Hoppenbrouwers, W. J. 1,3,4-Oxadiazines. *Recl. Trav. Chim. Pays-Bas Belg.* **1934**, *53*, 325−354.
(17) Van Alphen, J. 1,3,4-Oxadiazines. II. *Recl. Trav. Chim. Pays-Bas Belg.* **1928**, *47*, 909−919.
(18) Nitta, Y.; Yoneda, F.; Ohtaka, T.; Kato, T.; Pyridazines., V. Derivatives of 6-phenyl-3(2*H*)-pyridazinones. *Chem. Pharm. Bull.* **1964**, *12* (1), 69−73.
(19) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. New N- and O-arylations with phenylboronic acids and cupric acetate. *Tetrahedron Lett.* **1998**, *39*, 2933−2936.
(20) Evans, D. A.; Katz, J. L.; West, T. R. Synthesis of diaryl ethers through the copper-promoted arylation of phenols with arylboronic acids. An expedient synthesis of thyroxine. *Tetrahedron Lett.* **1998**, *39*, 2937−2940.
(21) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. New aryl/heteroaryl C−N bond cross-coupling reactions via arylboronic acid/cupric acetate arylation. *Tetrahedron Lett.* **1998**, *39*, 2941−2944.
(22) Hanada, T.; Hashizume, Y.; Tokuhara, N.; Takenaka, O.; Kohmura, N.; Ogasawara, A.; Hatakeyama, S.; Ohgoh, M.; Ueno, M.; Nishizawa, Y. Perampanel: a novel, orally active, non-competitive AMPA-receptor antagonist that reduces seizure activity in rodent models of epilepsy. *Epilepsia* **2011**, *52*, 1331−1340.
(23) Tokuhara, N.; Hatakeyama, S.; Amino, H.; Hanada, T.; Nishizawa, Y. Pharmacological Profile of Perampanel: A Novel, Non-Competitive Selective AMPA Receptor Antagonist. Presented at the 60th Annual Meeting of the American Academy of Neurology, Chicago, IL, U.S., April 12−19, 2008; Abstract P02.112.
(24) Templeton, D. Pharmacokinetics of perampanel, a highly selective AMPA-type glutamate receptor antagonist. *Epilepsia* **2009**, *50* (Suppl. 11), 98−99.
(25) Krauss, G. L.; Bar, M.; Biton, V.; Klapper, J. A.; Rektor, I.; Vaiciene-Magistris, N.; Squillacote, D.; Kumar, D. Tolerability and safety of perampanel: two randomized dose-escalation studies. *Acta. Neurol. Scand.* **2012**, *125*, 8−15.
(26) Krauss, G. L.; Serratosa, J. M.; Villanueva, V. E.; Endziniene, M.; Hong, Z.; French, J.; Yang, H.; Squillacote, D.; Edwards, H. B.; Zhu, J.; Laurenza, A. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. *Neurology* **2012**, *78*, 1408−1415.
(27) Fischer, W.; Allgaier, C.; Illes, P. Inhibition by chloral hydrate and trichloroethanol of AMPA-induced Ca(2+) influx in rat cultured cortical neurones. *Eur. J. Pharmacol.* **2000**, *394*, 41−45.