Synthesis, Structure−Activity Relationship, and Receptor Pharmacology of a New Series of Quinoline Derivatives Acting as Selective, Noncompetitive mGlu1 Antagonists

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We describe the discovery and the structure−activity relationship of a new series of quinoline derivatives acting as selective and highly potent noncompetitive mGlu1 antagonists. We first identified ***cis*-10** as a fairly potent mGlu1 antagonist (IC_{50} = 20 nM) in a cell-based signal transduction assay on the rat mGlu1 receptor expressed in CHO-K1 cells, and then we were able to design and synthesize highly potent compounds on both rat and human mGlu1 receptors as exemplified by compound ***cis*-64a**, which has an antagonist potency of 0.5 nM for the human mGlu1 receptor. We briefly present and discuss the in vitro metabolic stability of the compounds in human liver microsomes. We finally report the pharmacokinetic properties of our lead compound ***cis*-64a**.

Introduction

Glutamate (Glu) is the major excitatory neurotransmitter in the mammalian central nervous system (CNS) and plays an important role in a wide variety of CNS functions. The actions of Glu are mediated through membrane-bound Glu receptors.

Glu receptors are believed to exist as oligomers of ionotropic Glu (iGlu) receptor subunits[1] or as dimers of metabotropic Glu (mGlu) receptors.[2,3] Both receptor types can be divided into several families based on sequence identity and pharmacological, electrophysiological, and biochemical characteristics. iGlu receptors comprise *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA), and kainate (KA) receptors. Mammals express six NMDA receptor subunits (NR1, NR2A−D, NR3A), four AMPA receptor subunits (Glu1−4), and five KA receptor subunits (Glu5−7, KA1, KA2).[4,5] mGlu receptors are G-protein-coupled receptors characterized by a large extracellular amino-terminal domain that contains the Glu binding site. There are at least eight subtypes of mGlu (mGlu1−8) receptors, divided into three groups,[6,7] based on sequence homology, signal transduction, and pharmacology. Group I comprises mGlu1 and mGlu5, group II receptors comprises mGlu2 and mGlu3, and group III holds mGlu4, -6, -7, and -8.

The group I receptors are coupled to Gq/11, and activation of these receptors stimulates phospholipase C, which hydrolyses phosphatidyl inositol 4,5-bisphosphate into inositol trisphosphate (IP3) and diacylglycerol. IP3 in turn binds to the IP3 receptor on the endoplasmic reticulum, evoking a release of Ca^{2+} from these intracellular stores. Ca^{2+} and diacylglycerol activate protein kinase C. Group II and group III receptors are coupled to Gi, and activation of the receptors leads to an inhibition of adenylate cyclase, thereby inhibiting intracellular cAMP formation and protein kinase A activation.[7]

mGlu1 receptors are widely distributed in the CNS, where they modulate synaptic transmission, neuronal excitability, and brain plasticity. The physiological function of mGlu receptors[7−11] and the involvement of group I receptors in epilepsy, neurodegeneration,[10] pain,[12−14] anxiety,[15] and thalamic sensory processing[16] have been described in the literature.

The vast majority of known mGlu receptors antagonists are amino acid derivatives and therefore interact with the Glu binding site. These derivatives generally show poor pharmacokinetic properties and are seen as pharmacological tools rather than potential drugs.

The increasing use of recently available high-throughput functional assays has allowed the identification of ligands of the mGlu1 receptor with a novel mechanism of action. During the past decade, several noncompetitive mGlu1 antagonists have been described. These compounds belong to highly diverse chemical classes having high affinities at the mGlu1 receptor and very low affinities at other metabotropic and ionotropic Glu receptors.

CPCCOEt (**1**, Figure 1) is a low affinity, selective, noncompetitive antagonist interacting with the mGlu1 receptor transmembrane domain.[17] The same type of interaction has been shown for BAY 36-7620 (**2**), a lactone derivative, which is an antagonist at the mGlu1 receptor[18] (IC_{50} value of 160 nM). Thiazolo[3,2-*a*]benzimidazole-2-carboxamide[19] derivatives represented by **3** have been reported as low nanomolar mGlu1 antago-

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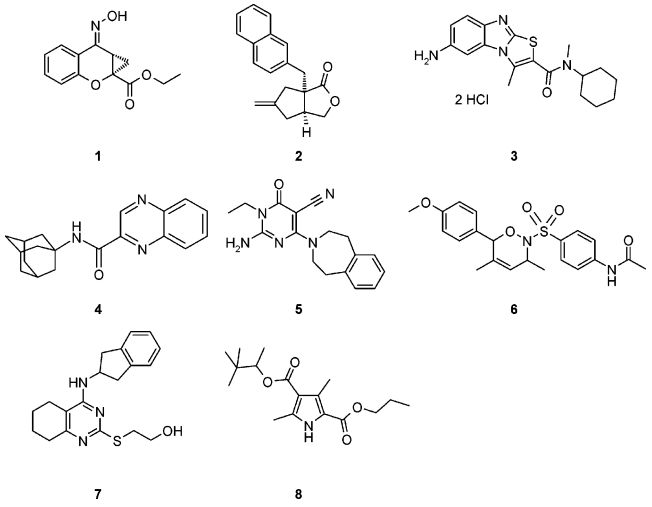


Figure 1. Structures of known noncompetitive mGlu1 antagonists.

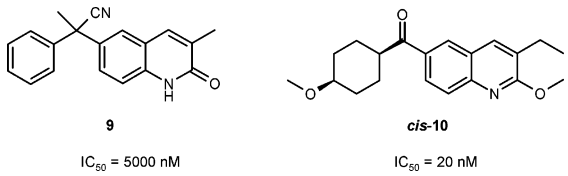


Figure 2. Hit compounds.

nists, whereas NPS-2390 (**4**), a quinoxaline derivative,[20] showed noncompetitive antagonist activity on both mGlu1 and mGlu5 receptors. Azepinyl derivatives[21] such as **5** had a functional IC_{50} value in the low nanomolar range. Other types of chemical entities such as oxazine derivatives[22] **6** or the 4-amino-5,6,7,8-tetrahydroquinazoline derivative[23] **7** have also been claimed as mGlu1 noncompetitive antagonists. Finally, PPP-1 (**8**) has been described as a potent and selective noncompetitive mGlu1 antagonist endowed with excellent in vitro activity[24] and showing a clear "opiate-like" antinociceptive profile in different animal models of pain.

We now report on the identification of a novel class of selective and highly potent noncompetitive mGlu1 antagonists. These compounds belong to a family of quinoline derivatives. Primary screening of our compound library has been executed as a cell-based signal transduction assay on the rat mGlu1 receptor expressed in CHO-K1 cells. Compound **9** (Figure 2) was first identified as a weak (IC_{50} = 5000 nM) mGlu1 receptor antagonist. Chemical modifications were made around the structure of **9** without gain of activity. In the meantime, analogues of **9** were searched and compound ***cis*-10** was detected with a substantially improved activity (IC_{50} = 20 nM).

***cis*-10** was devoid of any activity on rat mGlu5 up to 10 μM and on human mGlu2 up to 100 μM, as measured in signal transduction assays, and on NMDA ([^{3}H]MK801 and [^{3}H]L-689,560 binding) and AMPA ([^{3}H]AMPA binding) receptors up to 10 μM, as measured in radioligand binding on a membrane fraction derived from rat forebrain.

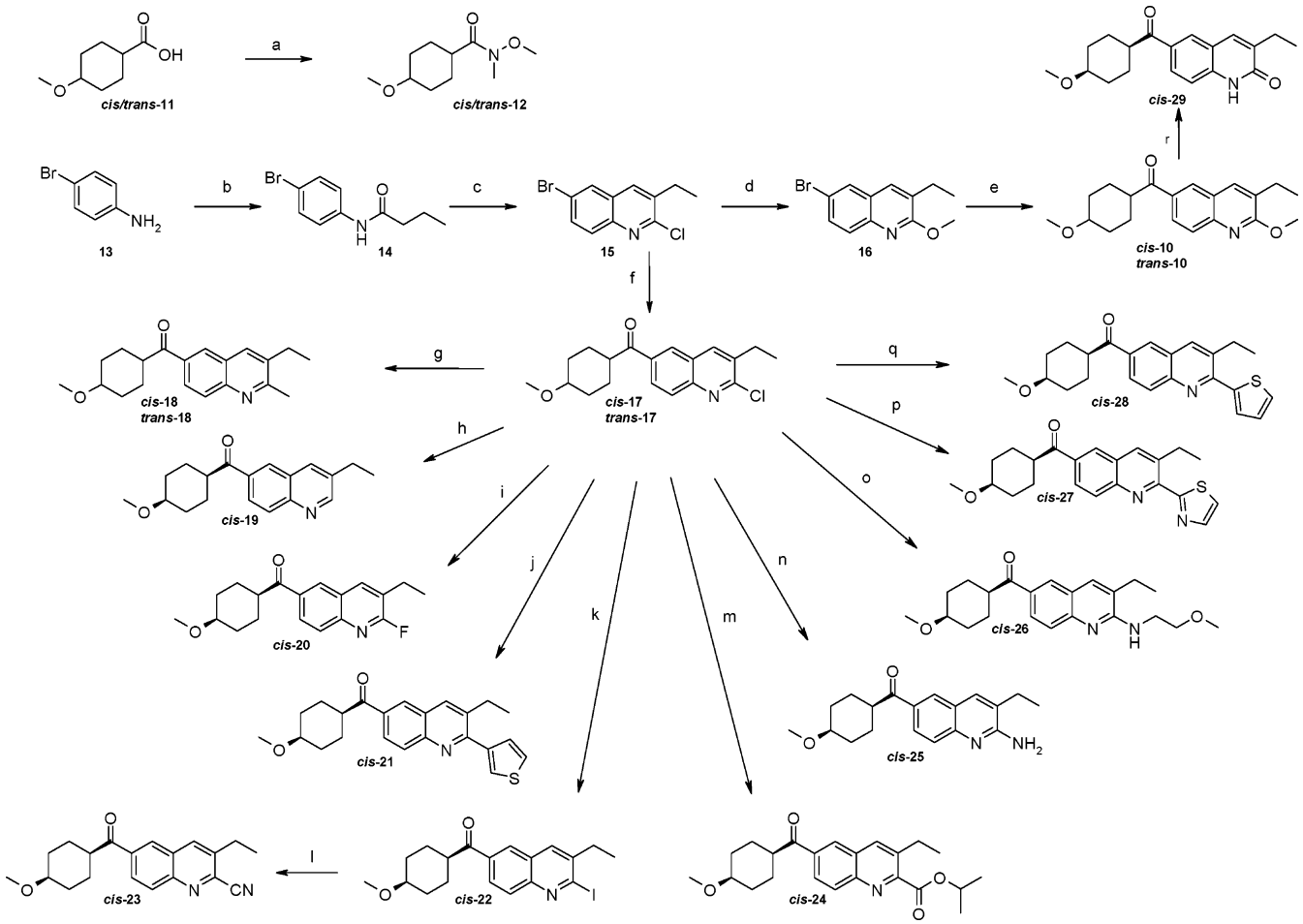
These results prompted us to further investigate the structure activity relationship (SAR) within this new chemical series with the aim of improving the primary activity on the mGlu1 receptor and the metabolic stability of the compounds and eventually developing an orally active mGlu1 antagonist. We present our results in the end of this investigation.

Chemistry

We first investigated the effect of the substitution at position 2 of the quinoline moiety in the lead compound ***cis*-10**. Most of the compounds were prepared from a common intermediate, the 2-chloroquinoline derivative ***cis*-17**, for which the synthesis is described in Scheme 1. 4-Bromoaniline **13** was acylated and the resulting anilide **14** was subjected to a Vilsmeier−Haack reaction to give the quinoline **15**. Selective lithium−bromo exchange of **15** with butyllithium at low temperature followed by the addition of the Weinreb amide ***cis*/*trans*-12**, prepared from the commercially available 4-methoxycyclohexylcarboxylic acid ***cis*/*trans*-11** (Scheme 1), afforded key intermediates ***cis*-17** and ***trans*-17**. The lead compound ***cis*-10** was also prepared from **15**. Nucleophile substitution with sodium methoxide followed by lithium−halogen exchange with butyllithium and subsequent addition of ***cis*/*trans*-12** afforded ***cis*-10** and its isomer ***trans*-10**. The intermediates ***cis*-17** and ***trans*-17** where submitted to a battery of experimental conditions to deliver a large variety of compounds. For instance, ***cis*-17** was methylated under Stille conditions using tetramethyl tin to give the 2-methylquinoline ***cis*-18**. Dehalogenation of ***cis*-17** with zinc in AcOH gave compound ***cis*-19**. Compounds ***cis*-17** and ***trans*-17** were submitted to nucleophilic substitution at quite high temperature either with potassium fluoride or methoxyethylamine to provide ***cis*-20** and ***cis*-26**, respectively. Compound ***cis*-17** was also a suitable substrate for a Suzuki coupling and as such was reacted with 3-thienyl boronic acid to give ***cis*-21**. Other oxidative aryl−aryl couplings were performed under Stille conditions with 2-tributylstannylthiazole and 2-tributylstannylthiophene to provide ***cis*-27** and ***cis*-28**, respectively. Chloroquinoline ***cis*-17** could be converted to the more reactive iodo derivative ***cis*-22** by treatment with sodium iodide in the presence of acetyl chloride.[25] Subsequently, ***cis*-22** was coupled with trimethylsilylcyanide[26] to afford the cyano quinoline ***cis*-23**. Carbon monoxide insertion on ***cis*-17** in 2-propanol gave the isopropyl ester ***cis*-24**. Compound ***cis*-25** was obtained by thermal condensation of ***trans*-17** with acetamide. Finally, acidic cleavage of methyl ether ***cis*-10** gave the quinolone ***cis*-29**.

The replacement of the 4-methoxycyclohexyl moiety was explored using two methods, with either 2-chloro-6-bromoquinoline **15** (method A) or 2-methyl-6-bromoquinoline **35** (method B) as intermediates (Scheme 2). Compound **35** was obtained by the condensation of 4-bromoaniline with the β-chlorovinyl aldehyde **34** in AcOH.[27,28] Both compounds **15** and **35** could be lithiated at position 6 on the quinoline ring by treatment with butyllithium and reaction with an electrophile such as a Weinreb amide or a nitrile to gain access to the 6-ylquinoline ketone derivatives of type **32** and **33f**−**h**. In method A, subsequent palladium-catalyzed methylation of compounds **32** with tetramethyltin afforded the expected 2-methyl-3-ethylquinolines derivatives **33a**−**e,i**. In method B, lithium−bromo exchange at position 6 of the quinoline ring **35** competed with proton abstraction on the methyl group at position 2, and yields of the reaction were low. Structures of compounds **33**

Scheme 1. Synthesis of 4-Methoxycyclohexylcarbonylquinolines: Variation at the 2-Position[a]



[a] Reagents and reaction conditions: (a) CDI, $H_3CNHOCH_3$·HCl, CH_2Cl_2, rt (99%); (b) $CH_3(CH_2)_2COCl$, Et_3N, CH_2Cl_2, rt (100%); (c) $POCl_3$, DMF, 80 °C (73%); (d) NaOMe, MeOH, reflux (74%); (e) *n*-BuLi, THF, −78 °C, ***cis/trans*-12**, −78 to 0 °C (***cis*-10** 38%, ***trans*-10** 28%); (f) *n*-BuLi, THF, −70 °C, ***cis/trans*-12**, −78 to −20 °C (***cis*-17** 29%, ***trans*-17** 3%); (g) $SnMe_4$, $Pd(PPh_3)_4$, toluene, reflux (***cis*-18**, 56% from ***cis*-17**; ***trans*-18**, 25% from ***trans*-17**); (h) from ***cis*-17**, Zn, AcOH, 60 °C (28%); (i) from ***cis*-17**, KF, DMSO, 140 °C (11%); (j) from ***cis*-17**, 3-thienylboronic acid, $Pd(PPh_3)_4$, dioxane, reflux (68%); (k) from ***cis*-17**, AcCl, NaI, CH_3CN, reflux (18%); (l) $(CH_3)_3SiCN$, $Pd(PPh_3)_4$, Et_3N (15%); (m) from ***cis*-17**, i-PrOH, $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, CO (5 bar), 90 °C (6%); (n) from ***trans*-17**, CH_3CONH_2, K_2CO_3, 200 °C (4%); (o) from ***trans*-17**, $NH_2(CH_2)_2OCH_3$, K_2CO_3, DMF, 140 °C (17%); (p) from ***cis*-17**, 2-tributylstannylthiazole, $Pd(PPh_3)_4$, dioxane, 80 °C (21%); (q) from ***cis*-17**, 2-tributylstannylthiophene, $Pd(PPh_3)_4$, dioxane, 80 °C (61%); (r) from ***cis*-10**, HCl 3N, THF, reflux (52%).

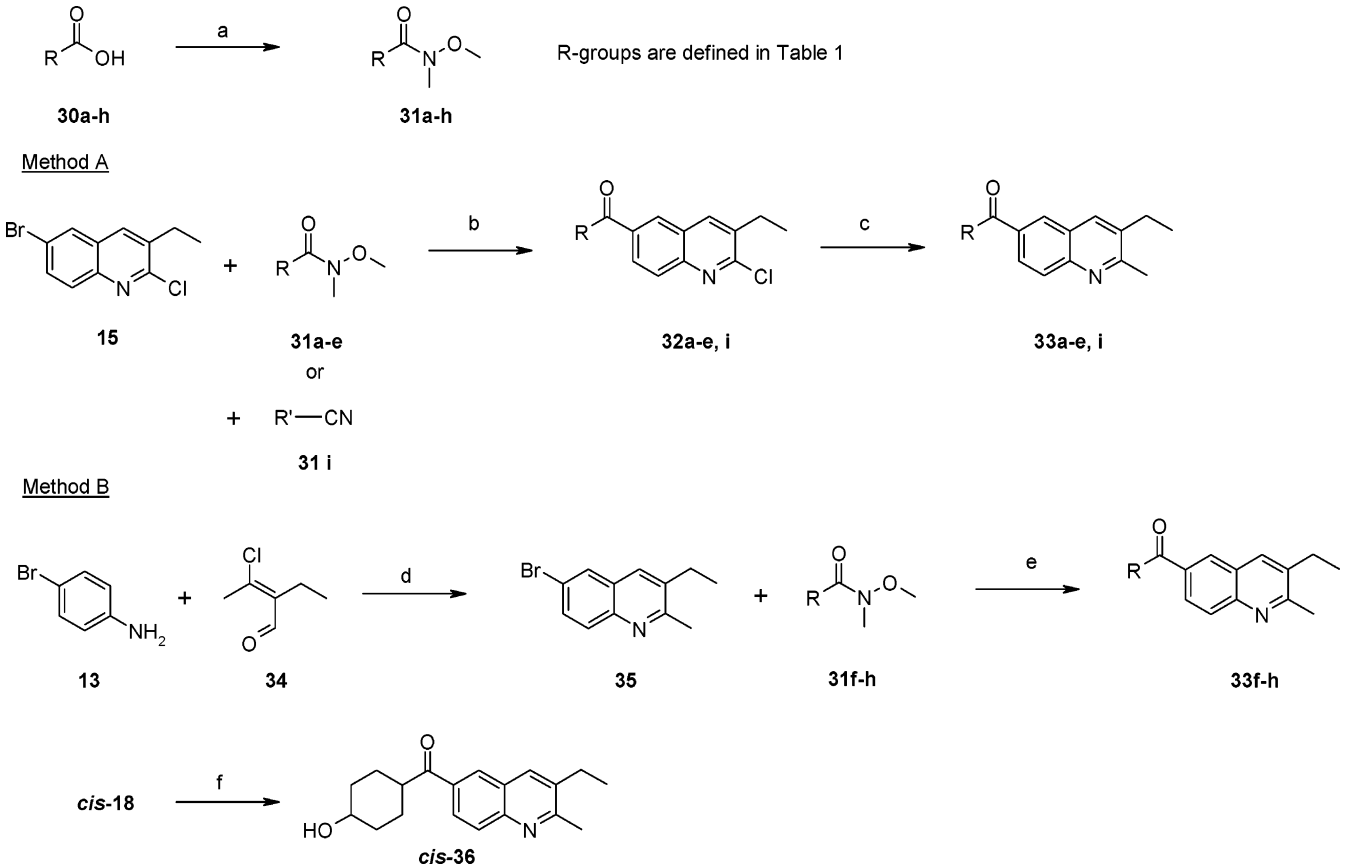
are shown in Table 1. An additional modification of this part of the molecule was obtained when compound ***cis*-18** was subjected to cleavage of the methyl ether with 48% HBr to give the corresponding hydroxy derivative ***cis*-36** with a low yield. (Scheme 2)

Other 2-methyl-3-ethylquinolines were prepared as described in Scheme 3. 1-(4-Aminophenyl)-2-phenylethanone **37**[29] was condensed with 3-chloro-2-ethyl-2-butenal **34**[30] to afford quinoline **38**. The quinoline **16** was treated with butyllithium and the resulting lithium salt reacted with Weinreb amide **39**[31] to give **40**. Acidic cleavage of the methyl ether followed by chlorination with phosphoroxychloride and methylation gave compound **43**. Treatment of **15** with butyllithium led to the corresponding organometallic reagent that was reacted either with isoamylaldehyde **44** or with Weinreb amide **48**[32] to give the secondary alcohol **(±)45** and the ketone **49**, respectively. The alcohol **(±)45** was oxidized with potassium permanganate to afford **46**, which was methylated to produce **47**, whereas **49** was first methylated before its deprotection under acidic conditions to give **51**. Finally, **35** underwent both a Suzuki and a Stille reaction with furan derivatives to provide **52** and **53**,[33] respectively.

Scheme 4 illustrates some of the experiments performed in order to explore the replacement of the keto function at position 6 of the quinoline derivatives. Condensation of ***cis*-10** with hydroxylamine gave the oximes ***cis*-54** and ***cis*-55**, whereas condensation with hydrazine afforded the hydrazone ***cis*-56**. Finally, ***cis*-10** was subjected to a Wittig reaction to give alkene ***cis*-57**.

Modification of the quinoline ring was also investigated (Scheme 5). Vilsmeier−Haack reaction on amide **58**[34,35] afforded compound **59** which, under acidic hydrolysis, gave a mixture of **60a** and **61**. Condensation of **59** with benzylamine at high temperature led to a mixture of **60b** and **62**. Alternatively, 2-amino-5-bromobenzaldehyde **63**[36] was subjected to Friedländer reaction,[36,37] under either basic or acidic conditions, to provide bromoquinoline derivatives **60c−e.** Treatment of bromoquinolines **60a−f** with butyllithium followed by the addition of the resulting aryllithium salt on the Weinreb amide ***cis/trans*-12** afforded ***cis/trans*-64a−f** (Table 2). Starting from the bromoanilide derivative

Scheme 2. Replacement of the 4-Methoxycyclohexyl Moiety[a]



[a] Reagents and reaction conditions: (a) CDI, $H_3CNHOCH_3$·HCl, CH_2Cl_2, rt; (b) *n*-BuLi, THF, −70 °C; (c) $SnMe_4$, $Pd(PPh_3)_4$, toluene, reflux; (d) CH_3COOH, reflux (54%); (e) *n*-BuLi, THF, −78 °C up to −20 °C; (f) 48% HBr, 60 °C, (5%).

65,[39] compound ***cis*-68** was prepared by a sequence of reactions similar to the one used for ***cis*-18**. The 2-chloroquinoline ***cis*-17** was also reacted with sodium azide to give tetrazole ***cis*-69**.

Various aryl alkyl ketones derivatives were synthesized as outlined in Scheme 6. Lithium−bromo exchange on compound **60a** followed by the addition on the Weinreb amides **71** and **31c** gave the quinoline derivatives **72a** and **72b**, respectively, with low to moderate yields. The carboxylic acid **73** was prepared from **60a**, esterified, and condensed with benzylmagnesium chloride to afford **72c** in high yield. 3-Bromoaniline **75** was acylated to give **76**, which was subjected to Vilsmeier−Haack conditions to afford a mixture of isomers **77** and **78**. Hydrolysis of the mixture afforded the quinolones **79** and **80**. Their cyclization in the presence of polyphosphoric acid produced the quinoline **81** and **82**. After separation, **81** was treated with butyllithium and *N*-methoxy-*N*-methylphenylacetamide to afford **83**.

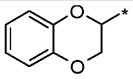
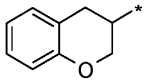
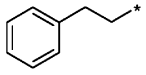
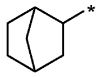
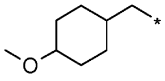
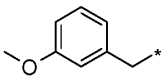
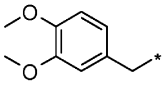
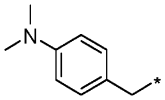
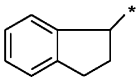
A series of 4-methylcyclohexyl keto derivatives was also prepared as exemplified in Scheme 7. Standard conditions afforded the Weinreb amide ***cis*/*trans*-85** from a cis/trans mixture of commercially available 4-methylcyclohexylcarboxylic acid. Addition of the lithium salts prepared from **60a** and **60c** afforded, after separation, compounds ***cis*-86** and ***cis*-87**, respectively.

Discussion

Compound ***cis*-10**, a quinoline derivative, has been identified as a potent antagonist by means of a cell-based signal transduction assay on rat mGlu1 receptor in CHO-K1 cells. To investigate the SAR within this new chemical series, all compounds were tested for their ability to antagonize the activation of the rat mGlu1 receptor. Most of the active compounds were also tested on the human mGlu1 receptor and for their in vitro metabolic stability in human liver microsomes. IC_{50} values indicating the potency at which the compounds antagonize activation of the rat and human mGlu1 receptors are shown in Tables 3−7. Metabolic stability in human liver microsomes is expressed as a percentage of the parent compound metabolized compared to the control incubation.

We first investigated the effect of the substitution at position 2 of the quinoline moiety in the lead compound ***cis*-10**. Our strategy to prepare such compounds was based on the extensive use of compound ***cis*-17**, a 2-chloroquinoline derivative, as intermediate that was subjected to various reaction conditions. In vitro activity and metabolic stability of these compounds are reported in Table 3. From this study it was apparent that the introduction of small lipophilic substituents such as Cl, Me, and F (***cis*-17**, ***cis*-18**, ***cis*-20**) gave highly potent antagonists. At this position, small hydrophilic substituents such as NH_2 and OH (***cis*-25**, ***cis*-29**) also gave potent antagonists, suggesting a possible interaction with the receptor through a hydrogen bond. Unfortunately, the quinolone derivatives were suffering from very poor aqueous solubility (data not shown) and were not considered as potential candidates for further investigation. The good activity of compound ***cis*-26**, substituted with a methoxy ethylamine, suggested that

Table 1. Method of Preparation of Diverse 2-Methyl-3-ethylquinoline Derivatives According to Scheme 2

COMPD	R	Method
(±)**33a**		A
(±)**33b**		A
33c		A
(±)**33d**		A
cis/trans-**33e**		A
33f		B
33g		B
33h		B
	R'	
(±)**33i**		A

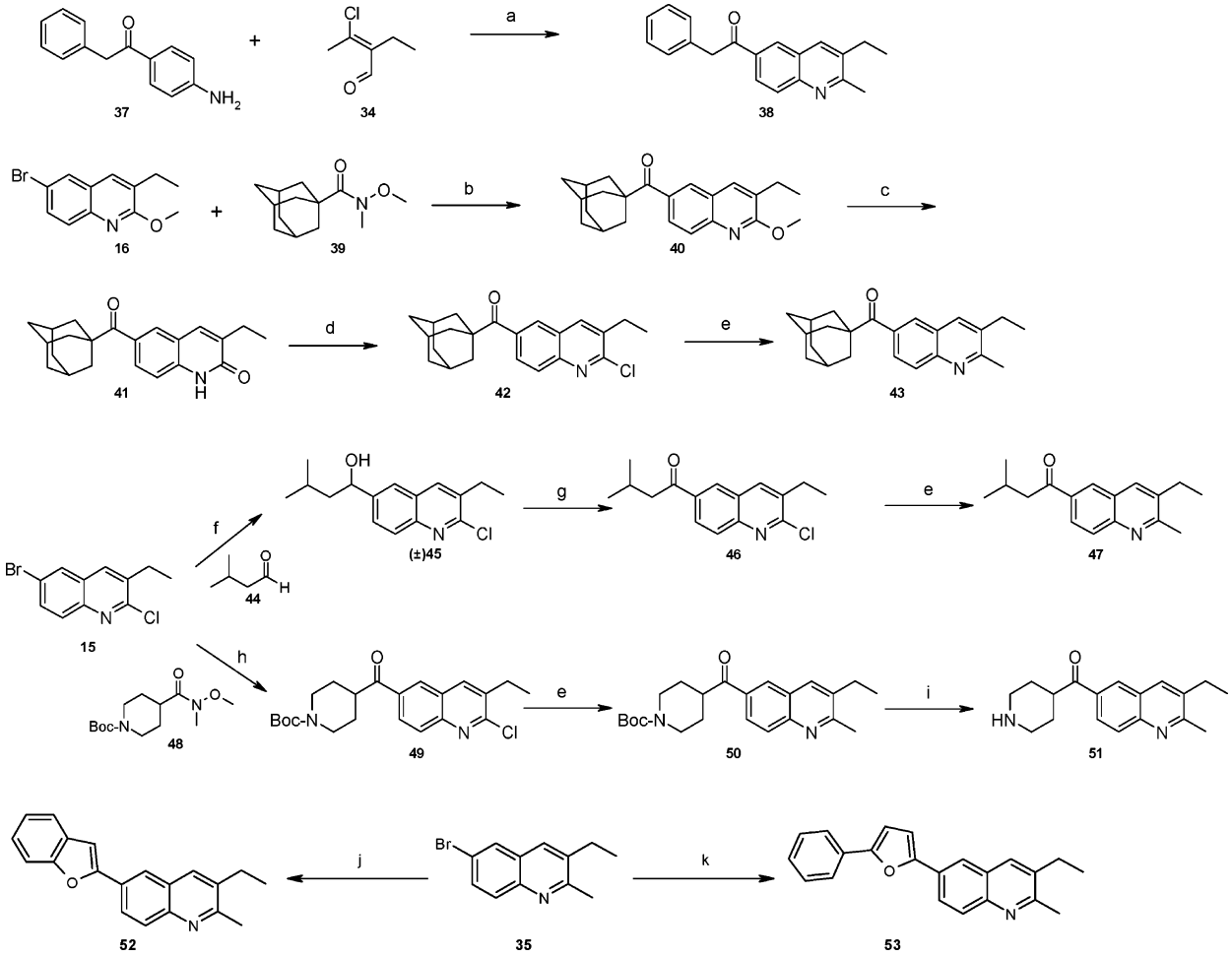
the introduction of a hydrogen-bond acceptor at that position was still tolerated. The introduction of more bulky substituents, such as heteroaryl rings (***cis*-21**, ***cis*-27**, ***cis*-28**), typically induced a loss of activity. The isopropyl ester derivative ***cis*-24** was also only weakly active and it can be pointed out that, for ***cis*-24**, ***cis*-27**, and ***cis*-28**, the presence of at least one heteroatom in the β position relative to the quinoline ring was detrimental to the activity. This was not the case for **23**, a nitrile derivative that remained active and for which the β nitrogen was differently oriented. These trends were observed to a large extent for both the rat and the human mGlu1 receptors. It was also remarkable to note that the activity resided in the compounds having a cis configuration on the cyclohexyl ring, the trans derivatives being less active or inactive (for instance ***cis*-10** versus ***trans*-10**). The measurement of the metabolic stability in human liver microsomes showed that the compounds were generally not stable. The hit compound ***cis*-10** remained one of the most stable as only 32% of the parent compound was metabolized under experimental conditions (Table 3). For this particular compound, the major metabolic pathways were *O*-demethylation of the methoxy group on the quinoline moiety, oxidation at the quinoline ring, and a combination of *O*-demethylation of the methoxy group on the cyclohexyl ring with oxidation at the quinoline. Carbonyl reduction combined with *O*-demethylation were minor metabolic pathways.

The replacement of the cyclohexyl moiety was then investigated while the 2-methyl-3-ethylquinoline remained unchanged (Table 4). Our strategy was to explore the effect of various bulky/lipophilic substituents as well as the potential role of a heteroatom (N or O) that could act as hydrogen-bond acceptor. The high potency of compounds **(±)33d** and **38** and the decrease of activity of compound **47** confirmed the need for a bulky lipophilic group at this position. Indanyl substitution (**(±)33i**) gave a potent antagonist, while phenethyl substitution (**33c**) was less tolerated. Both compounds were less active on human mGlu1 receptor. Introduction of an oxygen atom between the carbonyl function and the aromatic ring (**(±)33a** and **(±)33b**) was also tolerated, whereas, in the benzyl series, the mono- and dimethoxy substitutions (**33f** and **33g**, respectively) as well as substitution with a weak basic nitrogen (**33h**) lowered the activity. Apparently, the presence of a heteroatom, which could act as a hydrogen-bond acceptor, in this particular lipophilic area of the receptor was not always well-tolerated either for electronic or steric effects. The presence of a free hydroxy group (***cis*-36**) was well-accepted, whereas the introduction of a basic nitrogen (**51**) led to an inactive compound. A steric effect due to the *tert*-butoxycarbonyl protecting group could probably explain the lack of activity of compound **50**. These results, in agreement with literature data,[24] suggest that the region where these derivatives bind in the receptor might be rich in lipophilic residues, which often tolerate hydrogen-bond acceptors but tend to repel protonated/charged basic groups. All these compounds except the norbornyl derivative **(±)33d** were metabolically unstable in vitro.

Data in Table 5 show that the replacement of the oxygen atom of the keto function by an isostere (CH_2) only gave a weakly active compound (***cis*-57**). These results suggested that the oxygen atom of the keto function probably plays an important role as hydrogen-bond acceptor. Oxime ***cis*-54** and ***cis*-55** derivatives were inactive and hydrazone ***cis*-56** was weakly active. Compounds **52** and **53** (not shown in the table), where the position 6 on the quinoline was directly substituted by a benzofuran and a phenylfuran, respectively, were both inactive on the rat mGlu1 receptor.

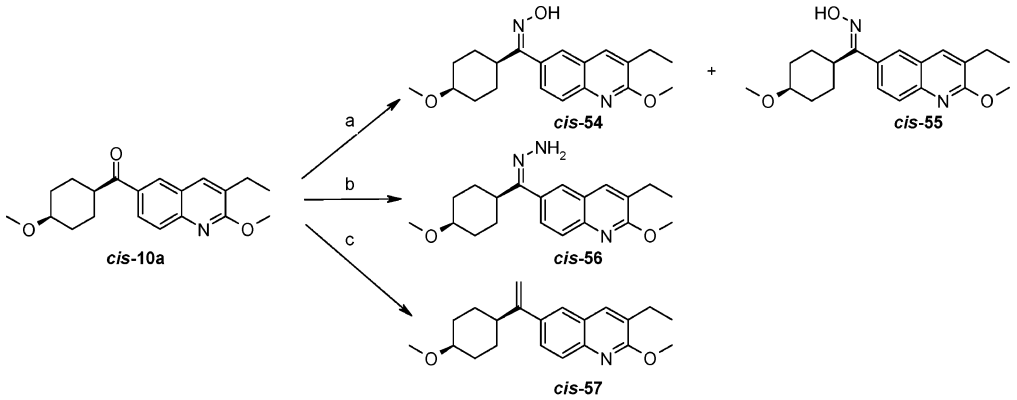
The quinoline ring itself was also modified, and data are shown in Table 6. 2,3-Annulated quinoline derivatives were highly potent on the human receptor. For instance, compounds ***cis*-64a** and ***cis*-64d** had subnanomolar potency. The presence of a heteroatom atom directly attached to the quinoline ring (***cis*-64a**, ***cis*-64b**, ***cis*-64f**) was tolerated as well as cyclic or acyclic alkyl chains (***cis*-64c**, ***cis*-64d**, ***cis*-64e**, ***cis*-68**). In this particular cyclohexyl series, we prepared 4-methylcyclohexyl derivatives, as exemplified by ***cis*-86** and ***cis*-87**, to avoid the metabolic demethylation of the methoxy group at the 4-position of the cyclohexyl ring. Both compounds retained a potency on the human mGlu1

Scheme 3. Synthesis of 2-Methyl-3-ethylquinoline Derivatives[a]



[a] Reagents and reaction conditions: (a) CH_3COOH, reflux (39%); (b) *n*-BuLi, THF, −78 °C (44%); (c) 3 N HCl, THF, reflux (71%); (d) $POCl_3$, reflux (63%); (e) $(CH_3)_4Sn$, $Pd(PPh_3)_4$, toluene, reflux (42%); (f) *n*-BuLi, THF, −70 °C (67%); (g) $KMnO_4$, TDA1, CH_2Cl_2, rt (33%); (h) *n*-BuLi, THF, −70 °C (26%); (i) 3 N HCl, THF, 60 °C (46%); (h) *n*-BuLi, THF, −70 °C (26%); (i) 3 N HCl, THF, 60 °C (46%); (j) benzofuran-2-boronic acid, $Pd(PPh_3)_4$, dioxane, Na_2CO_3, 2,6-di-*tert*-butyl-4-methylphenol, reflux, (7%); (k) tributyl-(5-phenyl)furan-2-yl)stannane, $Pd(PPh_3)_4$, dioxane, LiCl, reflux (31%).

Scheme 4. Replacement of the Keto Group in ***cis*-10**[a]

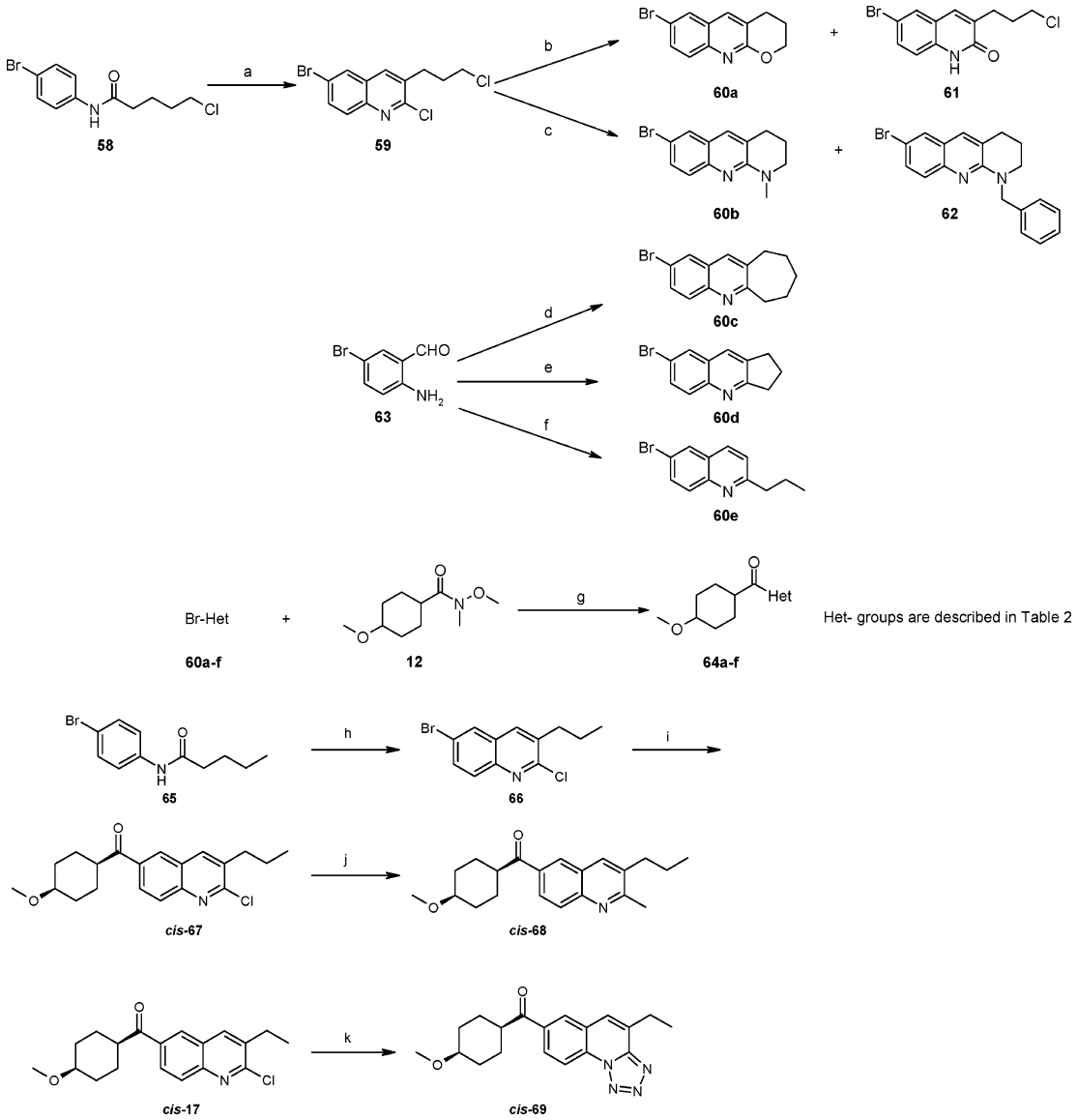


[a] Reagents and reaction conditions: (a) $NH_2OH{\cdot}HCl$, Et_3N, EtOH, reflux (38%, 36%); (b) NH_2NH_2, EtOH, reflux (15%); (c) $Ph_3P^+CH_3,Br^-$, THF, NaH 60%, rt (34%).

receptor similar to that of their 4-methoxycyclohexyl analogues ***cis*-64a** and ***cis*-64c**, respectively. However, if the in vitro metabolic stability of ***cis*-87** was substantially improved when compared to ***cis*-64c**, this was not the case for ***cis*-86** versus ***cis*-64a** (Table 6).

Several aryl alkyl ketones were also prepared (Table 7), and most of them were potent on the human mGlu1 receptor when the substitution took place at position 6 of the quinoline ring. The same substitution at position 7 of the quinoline gave inactive compounds, as shown with **83**. This result reinforced the idea that the oxygen atom of the keto function has to point to the right direction in order to interact with the receptor, probably through a hydrogen bond. The major drawback within this particular series of arylalkyl ketone derivatives was the extremely high rate of in vitro metabolism.

Scheme 5. Synthesis of Modified Quinoline Rings[a]



[a] Reagents and reaction conditions: (a) $POCl_3$, DMF, 75 °C (78%); (b) 12 N HCl, H_2O (28%); (c) Bn-NH_2, DMF, 160 °C (37%); (d) cycloheptanone, EtOH, NaOH, (56%); (e) cyclopentanone, EtOH, KOH, 60 °C (63%); (f) 2-pentanone, pyrrolidine, H_2SO_4, EtOH, rt (56%); (g) *n*-BuLi, THF, −78 to 0 °C (for yields, see Table 2); (h) $POCl_3$, DMF, rt (86%); (i) *n*-BuLi, THF, ***cis/trans*-12**, −78 to 0 °C (8%); (j) $(CH_3)_4Sn$, $Pd(PPh_3)_4$, toluene, reflux (23%); (k) NaN_3, DMF, 140 °C (33%).

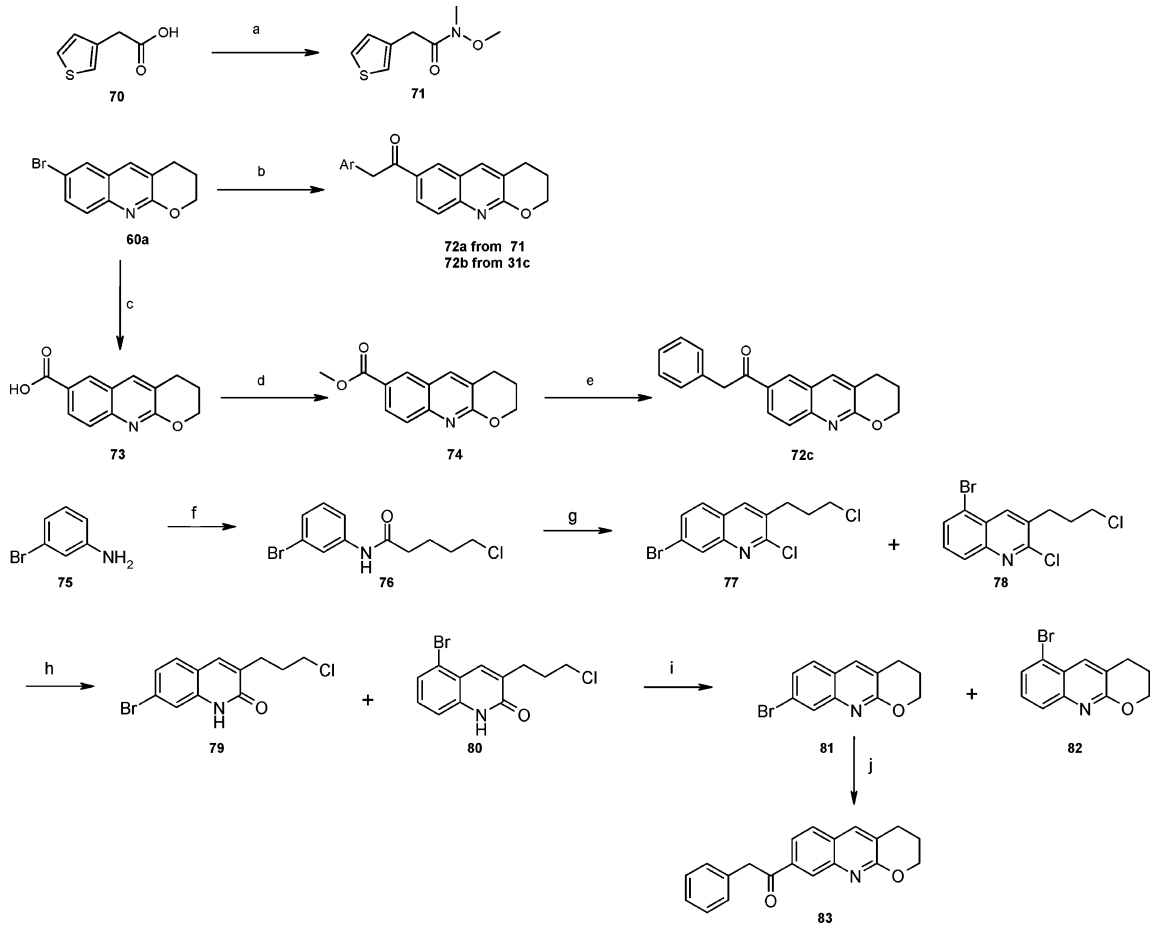
We already reported[41] the synthesis of the radiolabeled [^{3}H]-**72c** ([^{3}H]R214127), where our study supported the notion that CPCCOEt, BAY 36-7620, and **72c** act on a site different from the Glu binding pocket and that they presumably competed for the same transmembrane segment VII. To ascertain the antagonistic mechanism of action of ***cis*-64a**, our most potent compound, concentration−response curves for glutamate-induced Ca^{2+} mobilization in rat mGlu1a receptor-expressing CHO-dhfr$^-$ cells were generated in the presence of ***cis*-64a**. The results of this Schild analysis have been reported recently[42] and showed unambiguously that ***cis*-64a** blocks mGlu1 receptor-mediated signaling in a noncompetitive fashion.

We have also reported that, following subcutaneous administration in rat, ***cis*-64a** rapidly crossed the blood−brain barrier and occupied central mGlu1 receptors at very low doses.[42] Preliminary studies were performed in order to determine the plasma kinetics and absolute bioavailability of ***cis*-64a** in the rat. After a single intravenous administration at 2.5 mg/kg, ***cis*-64a** had a short half-life ($t_{1/2} = 0.32$ h) and a high total plasma clearance (CL = 5.5 l/h/kg). After a single oral dose of 10 mg/kg, very low plasma concentrations were observed. An oral bioavailability of less than 1% could be estimated for ***cis*-64a**. This can be due to bad absorption and/or extensive first-pass metabolism, and further studies have to be carried out to elucidate this issue. Nevertheless, in vivo experiments were performed and ***cis*-64a** has been found to be effective in the lick suppression test, an animal model of anxiety,[43] and to reduce pain behavior in the formalin model of hyperalgesia.[44]

Conclusion

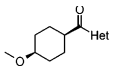
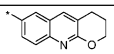
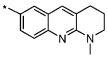
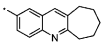
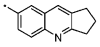
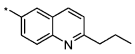
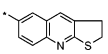
We have discovered a new series of quinoline derivatives acting as selective noncompetitive mGlu1 antagonists, and at least one of those compounds, ***cis*-64a**, had sub-nanomolar in vitro antagonist potency on the human mGlu1 receptor and was centrally active. In view of the various effects elicited by the mGlu1 receptor and

Scheme 6. Synthesis of Arylalkyl Ketone Derivatives[a]



[a] Reagents and reaction conditions: (a) CDI, $H_3CNHOCH_3$·HCl, Et_3N, CH_2Cl_2, rt (89%); (b) 2.5 N BuLi, THF, −78 °C, **71** or **31c**, −78 to −20 °C (6% from **71**, 38% from **31c**); (c) 2.5 N BuLi, THF, −78 °C, CO_2 (solid), −78 °C to room temperature (35%); (d) CH_3OH, H_2SO_4, 80 °C (30%); (e) $PhCH_2MgCl$, THF, rt (100%); (f) $ClCO(CH_2)_4Cl$, Et_3N, CH_2Cl_2, 5 °C (100%); (g) $POCl_3$, DMF, 5−75 °C (91%, two isomers); (h) 6 N HCl, THF, reflux (84%, two isomers), (i) PPA, 160 °C; (**81**, 39%; **82**, 9%); (j) *n*-BuLi, THF, −78 °C, $PhCH_2NCH_3OCH_3$, −78 to 0 °C (35%).

Table 2. Yields of Step g According to Scheme 5[a]

Br-Het	Het		Yields
60a		***cis*-64a**	35%
60b		***cis*-64b**	33%
60c		***cis*-64c**	30%
60d		***cis*-64d**	35%
60e		***cis*-64e**	15%
60f[40]		***cis*-64f**	30 %

[a] Cis product isolated.

the widespread distribution of the receptor in the CNS, we believe that ***cis*-64a** may lead to important progress in elucidating the function of the mGlu1 receptor in physiological and pathological states of the CNS and hence to new therapeutic strategies involving the mGlu1 receptor.

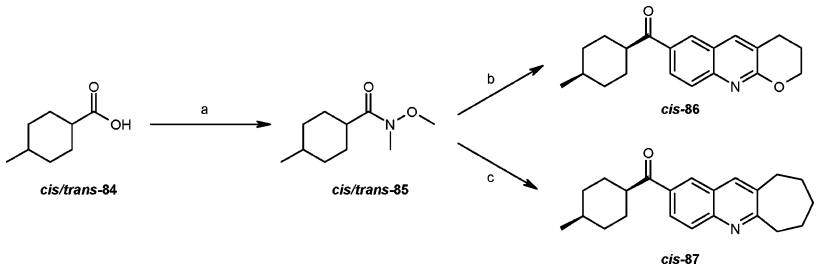
Experimental Section

Chemistry. Progress of the reactions was monitored by TLC-plates (Merck type 60 F254). Melting points were measured on a Leica VMHB System Kofler and are not corrected. All reagents and solvents were used as purchased from commercial sources (Sigma-Aldrich Co., Fluka Chemie AG, Lancaster Synthesis GmbH, Acros Organics). Moisture-sensitive reactions were carried out under a nitrogen atmosphere. Proton NMR spectra were recorded on a Bruker Avance 300 (300 MHz) and a Bruker Avance 400 (400 MHz) spectrometers using internal deuterium lock. Chemicals shifts are reported in reference to internal DMSO (δ 2.54) or $CHCl_3$ (δ 7.26) in parts per million (ppm, δ) and coupling constants (J) in hertz (Hz). Elemental analyses were determined with a Thermo Electron Corporation instruments EA 1110 or EA 1108 and were within ±0.4% unless otherwise stated.

Note: In many cases, the last step leading to the 4-methoxycyclohexyl end products afforded a mixture of cis and trans isomers, even if it started from a pure adduct (as from ***cis*-17** for instance). The isomers were separated by column chromatography. The yields reported under the synthetic schemes referred exclusively to the isolated cis isomer unless otherwise specified. In the Experimental Section only the analytical data for the cis isomers are given unless otherwise specified.

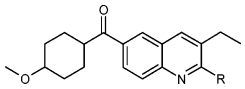
***N*,4-Dimethoxy-*N*-*cis*/*trans*-methylcyclohexanecarboxamide (*cis*/*trans*-12).** CDI (12 g, 0.074 mol) was added portionwise to ***cis*/*trans*-11** (10 g, 0.063 mol) in CH_2Cl_2 (200 mL). The mixture was stirred at room temperature for 1 h. Then *N*,*O*-dimethylhydroxylamine hydrochloride (6.8 g, 0.074 mol) was added. The mixture was stirred at room temperature over-

Scheme 7[a]



[a] Reagents and reaction conditions: (a) CDI, $H_3CNHOCH_3$·HCl, CH_2Cl_2 (100%); (b) **60a**, BuLi, THF, −78 to 0 °C (22%); (c) **60c**, BuLi, THF, −78 to 0 °C (16%).

Table 3. In Vitro Activity and Metabolic Stability of Diverse 2-Substituted Quinolines



		signal transduction IC_{50} (nM)		
compd	R	rmGlu1[a]	hmGlu1[b]	met. stab.[c]
***cis*-10**	OMe	19	94	43 (32[d])
***trans*-10**	OMe	2370	nd	nd
***cis*-17**	Cl	5	4	48[d]
***trans*-17**	Cl	145	nd	nd
***cis*-18**	Me	3	8	92
***trans*-18**	Me	65	nd	90
***cis*-19**	H	4	nd	85
***cis*-20**	F	4	9	75
***cis*-21**	3-thienyl	832	191	nd
***cis*-22**	I	13	162	73
***cis*-23**	CN	11	174	71
***cis*-24**	CO_2iPr	3428	6310	nd
***cis*-25**	NH_2	7	1	68
***cis*-26**	$NHCH_2CH_2OMe$	78	105	35
***cis*-27**	2-thiazoyl	>10000	nd	nd
***cis*-28**	2-thienyl	3311	nd	nd
***cis*-29**	OH	15	85	60

[a] Rat mGlu1. [b] Human mGlu1; IC_{50} values are the mean of two or three independent experiments performed on both rat and human mGlu1 receptors. [c] In vitro metabolic stability expressed as a percentage of converted parent compound (30 μM) after 30 min. [d] Metabolic stability expressed as a percentage of converted parent compound (5 μM) after 5 min.

night, poured out into H_2O, and extracted with CH_2Cl_2. The organic layer was separated, washed several times with H_2O, dried ($MgSO_4$), and filtered, and the solvent was evaporated to afford ***cis/trans*-12** as a colorless oil (12.6 g, 99%): ^{1}H NMR ($CDCl_3$) δ 1.10−1.60 (4H, m), 1.80−2.20 (4H, m), 2.6−2.8 (1H, m), 3.18 (3H, s), 3.18−3.37(1H, m), 3.31 (3H, s), 3.75 (3H, s).

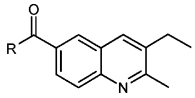
***N*-(4-Bromophenyl)butanamide (14).** A mixture of 4-bromoaniline (100 g, 0.58 mol) and Et_3N (88 g, 0.87 mol) in CH_2Cl_2 (800 mL) was stirred at 5 °C. A mixture of butyryl chloride (60.7 mL, 0.58 mol) in CH_2Cl_2 (400 mL) was slowly added dropwise and then the reaction mixture was allowed to reach room temperature and was stirred overnight at room temperature. H_2O was added, the separated organic layer was dried, and finally the solvent was evaporated. The residue was triturated in petroleum ether and filtered off to afford **14** as a white solid (140 g, 100%): mp 126 °C; ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, t, J = 7.3 Hz), 1.74 (2H, s, J = 7.3 Hz), 2.82 (2H, t, J = 7.3 Hz), 7.40 (4H, m), 7.59 (1H, br s). Anal. ($C_{10}H_{12}BrNO$) C, H, N

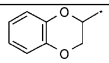
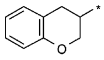
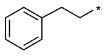
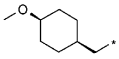
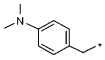
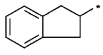
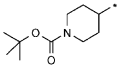
6-Bromo-2-chloro-3-ethylquinoline (15). $POCl_3$ (190 mL, 2.03 mol) was stirred at 10 °C under N_2, and DMF (65 mL, 0.87 mol) was added dropwise (exothermic reaction). The mixture was allowed to reach room temperature, **14** (140 g, 0.58 mol) was slowly added (exothermic reaction), and then the reaction mixture was stirred for 4 h at 85 °C. The mixture was cooled to room temperature and poured out carefully into ice H_2O. The resulting solids were filtered off, washed with H_2O, and dried to afford **15** (115 g, 73%): mp 106 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (3 H, t, J = 7.50 Hz), 2.93 (2H, q, J = 7.5 Hz), 7.75 (1H, dd, J = 2.1, 8.8 Hz), 7.87−7.89 (2H, m), 7.96 (1H, d, J = 2.1 Hz). Anal. ($C_{11}H_9BrClN$) C, H, N.

6-Bromo-3-ethyl-2-methoxyquinoline (16). A mixture of **15** (44 g, 0.162 mol) in $NaOCH_3$ (154 mL, 0.812 mol) and MeOH (600 mL) was stirred and refluxed overnight. The mixture was poured out on ice. The precipitate was filtered off, washed with a small amount of H_2O, and taken up in CH_2Cl_2. The organic phase was washed with a 10% aqueous solution of K_2CO_3. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), and filtered, and the solvent was evaporated to afford **16** (31.9 g, 74%) as a white solid: mp 70 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (3H, t, J = 7.3 Hz), 2.72 (2H, q, J = 7.3 Hz), 4.08 (3H, s), 7.61 (1H, dd, J = 8.8, 2.2 Hz), 7.65 (1H, s), 7.69 (1H, d, J = 8.8 Hz), 7.81 (1H, d, J = 2.2 Hz). Anal. ($C_{12}H_{12}BrNO$) C, H, N

3-Ethyl-2-methoxyquinolin-6-yl *cis*-4-Methoxycyclohexyl Ketone (*cis*-10) and 3-Ethyl-2-methoxyquinolin-6-yl *trans*-4-Methoxycyclohexyl Ketone (*trans*-10). *n*-BuLi (1.6 M) in hexane (69 mL, 0.107 mol) was added dropwise at −78 °C under N_2 flow to a solution of **16** (23.7 g, 0.089 mol) in THF (150 mL). The mixture was stirred at −78 °C for 1 h. A solution of ***cis/trans*-12** (17.9 g, 0.089 mol) in THF (150 mL) was added at −78 °C under N_2 flow. The mixture was stirred at −78 °C for 2 h, brought to 0 °C, poured out into H_2O, and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (31 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/15; 20−45 μm). Two pure fractions were collected and their solvents were evaporated to afford ***cis*-10** (11 g, 38%) and ***trans*-10** (8.2 g, 28%). ***cis*-10**: mp 116 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (3H, t, J = 7.5 Hz), 1.60−1.80 (4H, m), 1.89−2.10 (4H, m), 2.76 (2H, q, J = 7.5 Hz), 3.35 (3H, s), 3.36−3.48 (1H, m), 3.5−3.56 (1H, m),

Table 4. In Vitro Activity and Metabolic Stability of Diverse 2-Methyl-3-ethyl Quinolines Derivatives



COMPD	R	Signal transduction IC_{50} (nM) rmGlu1[a]	Signal transduction IC_{50} (nM) hmGlu1[b]	Met. Stab[c].
(±)**33a**		83	7	98
(±)**33b**		115	nd	nd
33c		230	>1000	nd
(±)**33d**		13	11	34
cis/trans-33e		16	85	83
33f		435	nd	nd
33g		>10000	nd	nd
33h		645	nd	nd
(±)**33i**		56	1175	96
***cis*-36**		50	80	nd
38		10	51	96
43		126	nd	nd
47		162	724	nd
50		>10000	nd	nd
51		>10000	nd	nd

[a] Rat mGlu1. [b] Human mGlu1; IC_{50} values are the mean of two or three independent experiments performed on both rat and human mGlu1 receptors. [c] In vitro metabolic stability expressed as a percentage of converted parent compound (30 μM) after 30 min.

4.14 (3H, s), 7.85−7.88 (2H, m), 8.11 (1H, dd, J = 8.8, 1.9 Hz), 8.32 (1H, d, J = 1.92 Hz). Anal. ($C_{20}H_{25}NO_3$) C, H, N. ***trans*-10**: mp 91 °C; ^{1}H NMR ($CDCl_3$) δ 1.25−1.77 (7H, m), 1.98−2.32 (4H, m), 2.76 (2H, q, J = 7.5 Hz), 3.15−3.48 (5H, m), 4.15 (3H, s), 7.82−7.92 (2H, m), 8.15 (1H, dd, J = 1.9, 6.7 Hz), 8.34 (1H, d, J = 1.9 Hz). Anal. ($C_{20}H_{25}NO_3$) C, H, N.

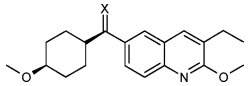
2-Chloro-3-ethylquinolin-6-yl *cis*-4-Methoxycyclohexyl Ketone (*cis*-17) and 2-Chloro-3-ethylquinolin-6-yl *trans*-4-Methoxycyclohexyl Ketone (*trans*-17). *n*-BuLi (1.6 M) in hexane (13.9 mL, 0.022 mol) was added slowly at −70 °C to a solution of **15** (5 g, 0.018 mol) in THF (50 mL). The mixture was stirred at −70 °C for 1 h, brought to −40 °C, and then cooled to −70 °C. A solution of **12** (3.7 g, 0.018 mol) in THF (40 mL) was added slowly. The mixture was stirred at −70 °C for 1 h, brought to −20 °C, hydrolyzed with H_2O, and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (6.5 g) was purified by column chromatography over silica gel (eluent: toluene/EtOAc 90/10; 15−40 μm). Two fractions were collected and the solvent was evaporated. Fraction 1 (2.4 g) was precipitated from diethyl ether. The precipitate was filtered off and dried to afford ***cis*-17** (1.8 g, 29%): mp 123 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (3H, t, J = 7.5 Hz), 1.50−1.8 (4H, m), 1.90−2.10 (4H, m), 2.96 (2H, q, J = 7.5 Hz), 3.35 (3H, s), 3.35−3.50 (1H, m), 3.50−3.60 (1H, m), 8.05−8.11 (2H, m), 8.19−8.22 (1H, dd, J = 2.1, 8.8 Hz), 8.40 (1H, d, J = 2.1 Hz). Anal. ($C_{19}H_{22}ClNO_2$) C, H, N. Fraction 2 (0.9 g) was precipitated from diethyl ether. The precipitate was filtered off and dried to afford ***trans*-17** (0.2 g, 3%): mp 120 °C; ^{1}H NMR ($CDCl_3$) δ 1.47 1.41 (3H, t, J = 7.5 Hz), 1.55−1.70 (4H, m), 2.00−2.29 (4H, m), 2.96 (2H, q, J = 7.5 Hz), 3,15−3.45 (5H, m), 8.02−8.12 (2H, m), 8.22 (1H, dd, J = 1.7, 8.8 Hz), 8.41 (1H, d, J = 1.7 Hz). Anal. ($C_{19}H_{22}ClNO_2$) C, H, N.

3-Ethyl-2-methylquinolin-6-yl *cis*-4-Methoxycyclohexyl Ketone (*cis*-18). A mixture of ***cis*-17** (5 g, 0.015 mol), tetramethyltin (4.2 mL, 0.03 mol), and tetrakis(triphenylphosphine)palladium(0) (1.7 g, 0.002 mol) in toluene (50 mL) was stirred and refluxed for 48 h. A 10% aqueous solution of K_2CO_3 was added and the mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (6.6 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 75/25; 15−40 μm). Different fractions were collected and the solvent was evaporated. The residue (3.4 g, 72%) was precipitated from diethyl ether to afford ***cis*-18** (2.63 g, 56%): mp 112 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, t, J = 7.5 Hz), 1.55−1.80 (4H, m), 1.90−2.10 (4H, m), 2.77 (3H, s), 2.86 (2H, q, J = 7.5 Hz), 3.35 (3H, s), 3.35−3.50 (1H, m), 3.50−3.55 (1H, m), 7.98 (1H, s), 8.03−8.06 (1H, d, J = 8.8 Hz), 8.10−8.19 (1H, dd, J = 2.1, 8.8 Hz), 8.38 (1H, d, J = 2.1 Hz). Anal. ($C_{20}H_{25}NO_2$) C, H, N.

3-Ethyl-2-methylquinolin-6-yl *trans*-4-Methoxycyclohexyl Ketone (*trans*-18). A mixture of ***trans*-17** (0.5 g, 1.502 mol), tetramethyltin (0.42 mL, 3.004 mol), and tetrakis(triphenylphosphine)palladium(0) (0.17 g, 0.151 mol) in toluene (5 mL) was stirred and refluxed for 8 h. H_2O was added. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (0.65 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 70/30; 15−40 μm). Different fractions were collected, and the solvent was evaporated. The residue was precipitated from petroleum ether to afford ***trans*-18** (0.12 g, 25%). ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, t, J = 7.5 Hz), 1.56−1.71 (4H, m), 2.00−2.30 (4H, m), 2.77 (3H, s), 2.86 (2H, q, J = 7.5 Hz), 3.18−3.48 (5H, m), 8.00 (1H, s), 8.06 (1H, d, J = 8.8 Hz), 8.16 (1H, dd, J = 1.8, 8.8 Hz), 8.39 (1H, J = 1.8 Hz). Anal. ($C_{20}H_{25}NO_2$) C, H, N.

3-Ethylquinolin-6-yl *cis*-4-Methoxycyclohexyl Ketone (*cis*-19). A mixture of ***cis*-17** (10 g, 0.03 mol) and Zn (5.92 g, 0.09 mol) in AcOH (100 mL) was stirred at 60 °C for 4 h, filtered over Celite, and washed with CH_2Cl_2. The solvent was evaporated. The residue was taken up in CH_2Cl_2 and washed with a 10% aqueous solution of K_2CO_3. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (15.5 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 80/20; 15−35 μm). The pure fractions were collected and the solvent was evaporated. (3.4 g, 38%). The residue was precipitated from petroleum ether to afford ***cis*-19** (2.47 g, 28%): mp 80 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, t, J = 7.5 Hz), 1.57−1.78 (4H, m), 2.89 (2H, q, J = 7.5 Hz), 1.91−2.10 (4H, m), 3.34 (3H, s), 3.40−3.49 (1H, m), 3.50−3.56 (1H, m), 8.05 (1H, s), 8.11−8.23 (2H, m), 8.40 (1H, s), 8.89 (1H, s). Anal. ($C_{19}H_{23}NO_2$) C, H, N.

Table 5. In Vitro Activity and Metabolic Stability of Non-Keto Derivatives



compd	X	signal transduction IC_{50} (nM) rmGlu1[a]	signal transduction IC_{50} (nM) hmGlu1[b]	met. stab.[c]
***cis*-10**	O	19	94	32
***cis*-54**	NOH	>10000	nd	nd
***cis*-55**	NOH	5011	nd	nd
***cis*-56**	NNH_2	320	4360	nd
***cis*-57**	CH_2	2630	nd	nd

[a] Rat mGlu1. [b] Human mGlu1; IC_{50} values are the mean of two or three independent experiments performed on both rat and human mGlu1 receptors. [c] In vitro metabolic stability expressed as a percentage of converted parent compound (5 μM) after 15 min.

3-Ethyl-2-fluoroquinolin-6-yl *cis*-4-Methoxycyclohexyl Ketone (*cis*-20). A mixture of ***cis*-17** (2 g, 0.006 mol) and KF (1.4 g, 0.0241 mol) in DMSO (20 mL) was stirred at 140 °C for 4 h. The solvent was evaporated to dryness. The residue was solidified in H_2O and diethyl ether. The mixture was extracted with diethyl ether. The organic layer was separated, washed with H_2O and with a saturated solution of NaCl, dried ($MgSO_4$), filtered, and concentrated in a vacuum. The residue (1.7 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/15; 15−40 μm). Fractions were collected, and the solvent was evaporated. The residue was precipitated from petroleum ether to afford ***cis*-20** (0.21 g, 11%): mp 92 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, t, J = 7.5 Hz), 1.52−1.80 (4H, m), 1.89−2.10 (4H, m), 2.87 (2H, q, J = 7.5 Hz); 3.35 (3H, s), 3.36−46 (1H, m), 3.47−3.57 (1H, m), 7.98 (1H, d, J = 8.8 Hz), 8.12−8.22 (2H, m), 8.42 (1H, d, J = 1.5 Hz). Anal. ($C_{19}H_{22}FNO_2$) C, H, N.

3-Ethyl-2-(3-thienyl)quinolin-6-yl *cis*-4-Methoxycyclohexyl Ketone (*cis*-21). A mixture of ***cis*-17** (0.5 g, 0.0015 mol), 3-thienylboronic acid (0.3 g, 0.0023 mol), tetrakis(triphenylphosphine)palladium(0) (0.17 g, 0.0002 mol), and dioxane was stirred and refluxed for 24 h. A 10% aqueous solution of K_2CO_3 was added. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (0.8 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 80/20; 15−40 μm). The pure fractions were collected, and the solvent was evaporated. The residue (0.4 g, 70%) was precipitated from petroleum ether to afford ***cis*-21** (0.39 g, 68%): mp 113 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (3H, t, J = 7.4 Hz), 1.58−1.81 (4H, m), 1.90−2.13 (4H, m), 2.97 (2H, q, 7.4 Hz), 3.36 (3H, s), 3.37−3.58 (2H, m), 7.41−7.51 (2H, m), 7.51 (1H, s), 8.11−8.20 (3H, m), 8.43 (1H, s). Anal. Calcd ($C_{23}H_{25}NO_2S$): C, 72.79; H, 6.64; N, 3.69. Found: C, 71.84; H, 6.76; N, 3.58.

3-Ethyl-2-iodoquinolin-6-yl *cis*-4-Methoxycyclohexyl Ketone (*cis*-22). A mixture of ***cis*-17** (3 g, 0.009 mol), AcCl (0.75 mL, 0.01 mol), and NaI (2.7 g, 0.018 mol) in CH_3CN (30 mL) was stirred and refluxed for 1 h. A 10% aqueous solution of K_2CO_3 was added. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (4.2 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc; 85/15; 15−40 μm). Fractions were collected, and the solvent was evaporated off. The residue was precipitated from petroleum ether to afford ***cis*-22** (0.7 g, 18%): mp 100 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, t, J = 7.4 Hz), 1.53−1.79 (4H, m), 1.88−2.11 (4H, m), 2.89 (2H, q, J = 7.44 Hz), 3.45 (3H, s), 3.36−3.46 (1H, m), 3.47−53 (1H, m), 7.93 (1H, s), 8.09 (1H, d, J = 8.8 Hz), 8.18 (1H, J = 8.8 Hz), 8.38 (1H, s). Anal. ($C_{19}H_{22}INO_2$) C, H, N.

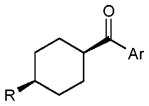
3-Ethyl-6-[(*cis*-4-methoxycyclohexyl)carbonyl]quinoline-2-carbonitrile (*cis*-23). A mixture of ***cis*-22** (6.34 g, 0.015 mol), trimethylsilyl cyanide (3 mL, 0.023 mol), and tetrakis(triphenylphosphine)palladium(0) (1.7 g, 0.002 mol) in Et_3N (50 mL) was stirred and refluxed for 2 h. A 10% aqueous solution of K_2CO_3 was added and the mixture was extracted with EtOAc. The organic layer was separated, filtered ($MgSO_4$), and dried, and the solvent was evaporated. The residue (7 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 75/25; 15−40 μm). Fractions were collected, and the solvent was evaporated. The residue was precipitated from diethyl ether/petroleum ether to afford ***cis*-23** (0.75 g, 15%): mp 137 °C; ^{1}H NMR ($CDCl_3$) δ 1.47 (3H, t, J = 7.5 Hz), 1.54−1.80 (4H, m), 1.90−2.11 (4H, m), 3.12 (2H, q, J = 7.5 Hz), 3.35 (3H, s), 3.36−3.45 (1H, m), 3.47−3.57 (1H, m), 8.17−8.26 (3H, m), 8.43 (1H, d, J = 1.5 Hz). Anal. ($C_{20}H_{22}N_2O_2$) C, H, N.

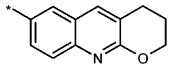
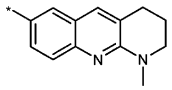
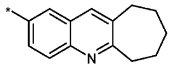
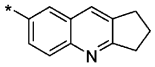
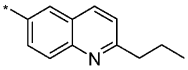
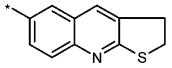
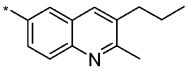
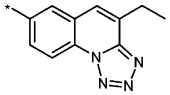
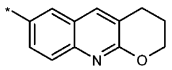
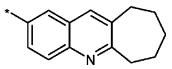
Isopropyl 3-Ethyl-6-[(*cis*-4-methoxycyclohexyl)carbonyl]quinoline-2-carboxylate (*cis*-24). A mixture of ***cis*-17** (1 g, 0.0036 mol), $Pd(OAc)_2$ (0.07 g, 0.0003 mol), triphenylphosphine (1.2 g, 0.0045 mol), and K_2CO_3 (0.83 g, 0.006 mol) in 2-propanol (10 mL) and DMF (10 mL) was stirred overnight at 90 °C under 5 bar pressure of CO, filtered over Celite, and washed with EtOAc.·H_2O was added to the filtrate and the mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (2.8 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 75/25; 15−40 μm). The pure fractions were collected, and the solvent was evaporated. The residue was precipitated from petroleum ether to afford ***cis*-24** (0.07 g, 6%): mp 105 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, t, J = 7.9 Hz), 1.47 (6H, d, J = 7.7 Hz), 1.54−1.79 (4H, m), 1.88−2.09 (4H, m), 2.99 (2H, q, J = 7.9 Hz), 3.33 (3H, s), 3.36−3.47 (1H, m), 3.49−3.56 (1H, m), 5.42 (1H, m), 8.16 (1H, s), 8.18−8.22 (2H, m), 8.38 (1H, s). Anal. Calcd ($C_{23}H_{29}NO_4$): C, 72.04; H, 7.62; N, 3.65. Found. C, 71.56; H, 7.65; N, 3.63.

2-Amino-3-ethylquinolin-6-yl *cis*-4-Methoxycyclohexyl Ketone (*cis*-25). A mixture of ***trans*-17** (2 g, 0.006 mol), acetamide (7.1 g, 0.12 mol), and K_2CO_3 (4.15 g, 0.03 mol) was stirred at 200 °C for 1 h and cooled at room temperature, and H_2O was added. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (3.68 g) was purified by column chromatography over silica gel (eluent: toluene/isopropyl alcohol/NH_4OH 92/8/0.1; 15−35 μm). Fractions were collected, and the solvent was evaporated. The residue (1.5 g, 40%) was separated by column chromatography over Kromasil (eluent:CH_3CN/$AcNH_4$ 40/60). The pure fractions were collected, and the solvent was evaporated. The residue was precipitated from diethyl ether to afford ***cis*-25** (0.07 g, 4%): mp 203 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, t, J = 7.9 Hz), 1.54−1.74 (4H, m), 1.88−2.09 (4H, m), 2.62 (2H, q, J = 7.9 Hz), 3.32 (3H, s), 3.33−3.43 (1H, m), 3.49−3.54 (1H, m), 5.09 (2H, br s), 7.65 (1H, d, J = 9.2 Hz), 7.79 (1H, s), 8.06 (1H, dd, J = 2.5, 9.2 Hz), 8.25 (1H, d, J = 2.5 Hz). Anal. ($C_{19}H_{24}N_2O_2$) C, H, N.

3-Ethyl-2-[(2-methoxyethyl)amino]quinolin-6-yl *cis*-4-Methoxycyclohexyl Ketone (*cis*-26). A solution of ***trans*-17** (0.018 mol) in 2-methoxyethylamine (30 mL) was stirred and refluxed for 8 h. The solvent was evaporated to dryness. The residue was dissolved in EtOAc. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (7.7 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc; 70/30; 15−40 μm). The fractions were collected and the solvent was evaporated. The residue was precipitated from

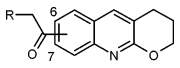
Table 6. In Vitro Activity and Metabolic Stability of Diverse Cyclohexyl Quinolin-6-yl Ketone Derivatives



COMPD	R	Ar	Signal transduction IC_{50} (nM) rmGlu1[a]	Signal transduction IC_{50} (nM) hmGlu1[b]	Met. Stab[c].
***cis*-64a**	OMe		3	0.55	77 (66[d])
***cis*-64b**	OMe		8	29	70
***cis*-64c**	OMe		80	18	60 (61[d])
***cis*-64d**	OMe		4	0.56	85
***cis*-64e**	OMe		5	3	49 (37[d])
***cis*-64f**	OMe		2	2	78
***cis*-68**	OMe		7	6	67
***cis*-69**	OMe		45	450	68
***cis*-86**	Me		11	1.6	73[d]
***cis*-87**	Me		125	16	35[d]

[a] Rat mGlu1. [b] Human mGlu1; IC_{50} values are the mean of two or three independent experiments performed on both rat and human mGlu1 receptors. [c] In vitro metabolic stability expressed as a percentage of converted parent compound (30 μM) after 30 min. [d] Metabolic stability expressed as a percentage of converted parent compound (5 μM) after 5 min.

Table 7. In Vitro Activity and Metabolic Stability of Diverse Aryl Alkyl Ketones



compd	position	R	signal transduction IC_{50} (nM) rmGlu1[a]	signal transduction IC_{50} (nM) hmGlu1[b]	met. stab.[c]
72a	6	3-thienyl	7	74	100
72b	6	toluyl	85	160	87
72c	6	phenyl	6	14	99
83	7	phenyl	8300	nd	nd

[a] Rat mGlu1. [b] Human mGlu1; IC_{50} values are the mean of two or three independent experiments performed on both rat and human mGlu1 receptors. [c] In vitro metabolic stability expressed as a percentage of converted parent compound (30 μM) after 30 min.

petroleum ether to afford ***cis*-26** (1.15 g, 17%): mp 109 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, t, J = 7.5 Hz), 1.54−1.74 (4H, m), 1.88−2.08 (4H, m), 2.57 (2H, q, J = 7.5 Hz), 3.32 (3H, s), 3.33−3.41 (1H, m), 3.42 (3H, s), 3.47−3.54 (1H, m), 3.67 (2H, t, J =

6.4 Hz), 3.87 (2H, q, J = 7.7 Hz), 5.25 (1H, br m), 7.65−7.70 (2H, m), 8.05 (1H, dd, J = 1.8, 8.8 Hz), 8.21 (1H, d, J = 2.5 Hz). Anal. Calcd ($C_{22}H_{30}N_2O_3$): C, 71.32; H, 8.16; N, 7.56. Found: C, 70.74; H, 8.22; N,7.52.

3-Ethyl-2-(1,3-thiazol-2-yl)quinolin-6-yl *cis*-4-Methoxycyclohexyl Ketone (*cis*-27). A mixture of ***cis*-17** (0.5 g, 0.0015 mol), 2-tributylstannylthiazole (0.85 g, 0.0023 mol), and tetrakis(triphenylphosphine)palladium(0) (0.17 g, 0.0002 mol) in dioxane (5 mL) was stirred at 80 °C for 2 h. H_2O was added and the mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (1.6 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 80/20; 15−40 μm). Fractions were collected, and the solvent was evaporated off. The residue was precipitated from petroleum ether and pentane to afford ***cis*-27** (0.12 g, 21%): mp 108 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (3H, t, J = 7.4 Hz), 1.60−1.81 (4H, m), 1.91−2.13 (4H, m), 3.36 (3H, s), 3.40−3.60 (4H, m), 7.53 (1H, d, J = 3.2 Hz), 8.03 (1H, d, J = 3.2 Hz), 8.11−8.25 (3H, m), 8.41 (1H, s). Anal. ($C_{22}H_{24}N_2O_2S$) C, H, N.

3-Ethyl-2-(2-thienyl)quinolin-6-yl *cis*-4-Methoxycyclohexyl Ketone (*cis*-28). A mixture of ***cis*-17** (0.5 g, 0.0015 mol), 2-tributylstannylthiophene (0.72 mL, 0.0022 mol), and tetrakis(triphenylphosphine)palladium(0) (0.17 g, 0.0002 mol) in dioxane (5 mL) was stirred at 80 °C for 8 h. A 10% aqueous solution of K_2CO_3 was added. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (1.6 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 80/20; 15−40 μm). Fractions were collected, and the solvent was evaporated off. The residue was precipitated from petroleum ether and pentane to afford ***cis*-28** (0.35 g, 61%): mp 142 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (3H, t, J = 7.4 Hz), 1.55−1.81 (4H, m), 1.90−2.11 (4H, m), 3.14 (2H, q, J = 7.4 Hz), 3.36 (3H, s), 3.37−50 (1H, m) 3.51−3.59 (1H, m), 7.20 (1H, m), 7.54 (1H, d, J = 5.2 Hz), 7.64 (1H, d, J = 3.8 Hz). Anal. ($C_{23}H_{25}NO_2S$) C, H, N.

3-Ethyl-6-[(*cis*-4-methoxycyclohexyl)carbonyl]quinolin-2(1*H*)-one (*cis*-29). A mixture of ***cis*-10** (4 g, 0.0122 mol) in 3 N HCl (40 mL) and THF (40 mL) was stirred and refluxed overnight, poured out into H_2O, basified with a 10% aqueous solution of K_2CO_3, and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 40/60; 15−40 μm). The pure fractions were collected, and the solvent was evaporated to afford ***cis*-29** (2 g, 52%): mp 224 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, t, J = 7.4 Hz), 1.5−2.15 (8H, m), 2.78 (2H, q, J = 7.4 Hz), 3.22−3.42 (4H, m), 3.50−3.60 (1H, m), 7.47 (1H, d, J = 10.0 Hz), 7.73 (1H, s), 8.08 (1H, dd, J = 1.9, 10.9 Hz), 8.19 (1H, d, J = 1.9 Hz), 12.10 (1H, br s). Anal. ($C_{19}H_{23}NO_3$) C, H, N.

(±)-*N*-Methoxy-*N*-methyl-2,3-dihydro-1,4-benzodioxine-2-carboxamide ((±)31a). CDI (5.6 g, 0.035 mol) was added portionwise at room temperature to a solution of **(±)30a** (5.7 g, 0.032 mol) in CH_2Cl_2 (60 mL). The mixture was stirred at room temperature for 1 h. *N,O*-Dimethylhydroxylamine hydrochloride (5.6 g, 0.035 mol) was added. The mixture was stirred at room temperature for 8 h, washed with 1 N HCl and then with a 10% aqueous solution of K_2CO_3. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (6.7 g, 95%) was precipitated from petroleum ether to afford **(±)31a** (5.65 g, 95%): mp 80 °C; ^{1}H NMR ($CDCl_3$) δ 3.29 (3H, s), 3.82 (3H, s), 4.23−4.31 (1H, m), 4.44 (1H, dd, J = 2.5, 8 Hz), 5.05 (1H, d, J = 8 Hz), 6.84−7.02 (4H, m). Anal. ($C_{11}H_{13}NO_4$), C, H, N.

(±)-*N*-Methoxy-*N*-methylchromane-3-carboxamide((±)31b). Compound **(±)31b** was prepared in 92% yield from **(±)30b** by a method similar to that described for **(±)-31a**: ^{1}H NMR ($CDCl_3$) δ 2.85−3.21 (2H, m), 3.26 (3H, s), 3.31−3.45 (1H, m), 3.77 (3H, s), 4.04 (1H, t, J = 7 Hz), 4.40−4.46 (1H, m), 6.81−6.92 (2H, m), 7.08−7.17 (2H, m).

(±)-*N*-Methoxy-*N*-methylbicyclo[2.2.1]heptane-2-carboxamide ((±)31d). Compound **(±)31d** was prepared in 76% yield from **(±)30d** by a method similar to that described for **(±)31a**: ^{1}H NMR ($CDCl_3$) δ 1.08−1.58 (7H, m), 1.70−1.85 (1H, m), 2.17−2.26 (1H, m), 2.49−2.62 (1H, m), 2.91−3.03 (1H, m), 3.16 (3H, s), 3.65 (3H, s).

***N*-Methoxy-2-(*cis/trans*-4-methoxycyclohexyl)-*N*-methylacetamide (*cis/trans*-31e).** Compound ***cis/trans*-31e** was prepared in 100% yield from ***cis/trans*-30e** by a method similar to that described for **(±)31a** and was used without further purification.

2-[4-(Dimethylamino)phenyl]-N-methoxy-*N*-methylacetamide (31h). Compound **31h** was prepared in 100% yield from **30h** by a method similar to that described for **(±)31a** and was used without further purification.

(±)-2-Chloro-3-ethylquinolin-6-yl 2,3-Dihydro-1,4-benzodioxin-2-yl Ketone ((±)32a). *n*-BuLi (1.6 M) in hexane (17 mL, 0.027 mol) was added slowly at −70 °C to a solution of **15** (6 g, 0.022 mol) in THF (60 mL). The mixture was stirred at −70 °C for 30 min. A solution of **(±)31a** (5.45 g, 0.024 mol) in THF (60 mL) was added slowly. The mixture was stirred at −70 °C for 1 h and then brought slowly to room temperature, poured out into H_2O, and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (9.7 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 99/1; 15−35 μm). The pure fractions were collected, and the solvent was evaporated. The residue (2.6 g, 33%) was precipitated from diethyl ether to afford **(±)32a** (2 g, 25%): mp 150 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, t, J = 7.5 Hz), 2.87 (2H, q, J = 7.5 Hz), 4.41−4.51 (1H, m), 4.63 (1H, dd, J = 2.6, 11.6 Hz), 5.54−5.60 (1H, m), 6.85−7.05 (4H, m), 8.05−8.14 (2H, m), 8.28 (1H, dd, J = 1.7, 8.9 Hz), 8.58 (1H, d, J = 1.7 Hz). Anal. Calcd ($C_{20}H_{16}ClNO_3$): C, 67.90; H, 4.56; N, 3.96. Found: C, 67.12; H, 4.45; N, 3.86.

(±)-2-Chloro-3-ethylquinolin-6-yl 3,4-Dihydro-2*H*-chromen-3-yl Ketone ((±)32b). Compound **(±)32b** was prepared in 24% yield from **(±)31b** by a method similar to that described for **(±)32a**: mp 138 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, t, J = 7.4 Hz), 2.98 (2H, q, J = 7.4 Hz), 3.00−3.10 (1H, m), 3.20−3.31 (1H, m), 4.05−4.21 (2H, m), 4.51−4.64 (1H, m), 6.88−6.97 (2H, m), 7.10−7.21 (2H, m), 8.08−8.14 (2H, m), 8.28 (1H, dd, J = 1.9, 8.9 Hz), 8.51 (1H, d, J = 1.9 Hz). Anal. ($C_{21}H_{18}ClNO_2$) C, H, N.

1-(2-Chloro-3-ethylquinolin-6-yl)-3-phenylpropan-1-one (32c). Compound **32c** was prepared in 37% yield from **31c**[45] by a method similar to that described for **(±)32a**: mp 100 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, t, J = 7.5 Hz), 8.94 (2H, q, J = 7.5 Hz), 3.15 (2H, t, J = 7.6 Hz), 3.45 (2H, t, J = 7.6 Hz), 7.20−7.38 (5H, m), 8.01−8.07 (2H, m), 8.24 (1H, dd, J = 1.9, 8.9 Hz), 8.41(1H, d, J = 1.9 Hz). Anal. ($C_{20}H_{18}ClNO$) C, H, N.

(±)-Bicyclo[2.2.1]hept-2-yl 2-Chloro-3-ethylquinolin-6-yl Ketone ((±)32d). Compound **(±)32d** was prepared in 40% yield from **(±)31d** by a method similar to that described for **(±)32a**: mp 131 °C; mixture of diastereoisomers 70/30; ^{1}H NMR ($CDCl_3$) δ 1.10−1.74 (10H, m), 1.99−2.12 (1H, m), 2.32−2.41(1H, m), 2.53−2.72 (1H, m), 2.92 (2H, q, J = 7.5 Hz), 3.30 (0.5H, m), 3.78−3.90 (0.5H, m), 8.00−8.10 (2H, m), 8.19−8.28 (1H, m), 8.38−8.43 (1H, m). Anal. ($C_{19}H_{20}ClNO$) C, H, N.

1-(2-Chloro-3-ethylquinolin-6-yl)-2-(*cis/trans*-4-methoxycyclohexyl)ethanone (32e). Compound ***cis/trans*-32e** was prepared in 29% yield from ***cis/trans*-31e** by a method similar to that described for **(±)32a**: mp 136 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, m), 1.55 (6H, m), 1.9 (2H,m), 2.15 (1H, m), 3 (4H, m), 3.45 (3H, s), 3.45 (1H, m), 8.08 (1H, m), 8.12 (1H, s), 8.25 (1H, m), 8.42 (1H, s). Anal. Calcd ($C_{20}H_{24}ClNO_2$): C, 69.45; H, 6.99; N, 4.05. Found: C, 68.75; H, 6.92; N, 3.92.

(±)-2-Chloro-3-ethylquinolin-6-yl 2,3-Dihydro-1*H*-inden-2-yl Ketone ((±)32i). Compound **(±)32i** was prepared in 5% yield from **(±)31i** by a method similar to that described for **(±)32a**: mp 145 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, t, J = 7.4 Hz), 7.98 (2H, q, J = 7.4 Hz), 3.28−3.55 (4H, m), 4.35−4.51 (1H, m), 7.11−7.35 (4H, m), 8.05−8.8.18 (2H, m), 8.29 (1H, d, J = 8.8 Hz), 8.50 (1H, s). Anal. ($C_{21}H_{18}ClNO$) C, H, N.

(±)-2,3-Dihydro-1,4-benzodioxin-2-yl 3-Ethyl-2-methylquinolin-6-yl Ketone ((±)33a). A mixture of **(±)32a** (0.5

g, 0.0014 mol), tetramethyltin (0.4 mL, 0.0028 mol), and tetrakis(triphenylphosphine)palladium(0) (0.16 g, 0.0001 mol) in toluene (5 mL) was stirred and refluxed for 48 h. A 10% aqueous solution of K_2CO_3 was added. The mixture was filtered over Celite, washed with EtOAc, and the filtrate was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (0.84 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 70/30; 15−40 μm). The pure fractions were collected, and the solvent was evaporated. The residue (0.2 g, 42%) was precipitated from diethyl ether/petroleum ether to afford **(±)33a** (0.09 g, 19%): mp 149 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, t, J = 7.5 Hz), 2.79 (3H, s), 2.85 (2H, q, J = 7.5 Hz), 4.41−4.5 (1H, m), 4.65 (1H, dd, J = 2.4, 9 Hz), 5.57−5.63 (1H, m), 6.87−7.05 (4H, m), 8.00 (1H, s), 8.09 (1H, d, J = 8.8 Hz), 8.24 (1H, d, J = 10 Hz), 8.55 (1H, d, J = 1.6 Hz). Anal. Calcd ($C_{21}H_{19}NO_3$): C, 75.66; H, 5.74; N, 4.20. Found: C, 74.3; H, 5.74; N, 4.08.

(±)-3,4-Dihydro-2*H*-chromen-3-yl 3-Ethyl-2-methylquinolin-6-yl Ketone ((±)33b). Compound **(±)33b** was prepared in 33% yield from **(±)32b** by a method similar to that described for **(±)33a**: mp 143 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (3H, t, J = 7.4 Hz), 2.70 (3H, s), 2.83 (2H, q, J = 7.4 Hz), 2.95−3.15 (2H, m), 4.05−4.14 (1H, m), 4.20−4.32 (1H, m), 4.48−4.56 (1H, m), 6.78−6.92 (2H, m), 7.06−7.17 (2H, m), 8.00 (1H, d, J = 8.8 Hz), 8.14 (1H, dd, J = 1.8, 8.8 Hz), 8.27 (1H, s), 8.84 (1H, d, J = 1.8 Hz). Anal. Calcd ($C_{22}H_{21}NO_2$): C, 68.40; H, 5.50; N, 3.32. Found: C, 67.33; H, 5.32; N, 3.17.

1-(3-Ethyl-2-methylquinolin-6-yl)-3-phenylpropan-1-one (33c). Compound **33c** was prepared in 53% yield from **32c** by a method similar to that described for **(±)33a**: mp 53 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, t, J = 7.5 Hz), 2.77 (3H, s), 2.83 (2H, q, J = 7.5 Hz), 3.15 (2H, t, J = 7.7 Hz), 3.46(2H, t, J = 7.7 Hz), 7.20−7.38 (5H, m), 7.95 (1H, s), 8.05 (1H, d, J = 8.8 Hz), 8.20 (1H, dd, J = 1.9, 8.8 Hz), 8.40 (1H, d, J = 1.9 Hz). Anal. Calcd ($C_{21}H_{21}NO$): C, 83.13; H, 6.98; N, 4.62. Found: C, 82.71; H, 6.83; N, 4.56.

(±)-Bicyclo[2.2.1]hept-2-yl 3-Ethyl-2-methylquinolin-6-yl Ketone ((±)33d). Compound **(±)33d** was prepared in 32% yield from **(±)32d** by a method similar to that described for **(±)33a**: mp 87 °C; mixture of diastereoisomers 70/30; ^{1}H NMR ($CDCl_3$) δ 1.11−1.75 (9H, m), 2.01−2.13 (1H, m), 2.32−2.41 (1H, m), 2.70−2.90 (7H, m), 3.32−3.40 (0.5H, m), 3.84−3.92 (0.5H, m), 7.99 (1H, s), 8.04 (1H, d, J = 8.8 Hz), 8.16−8.24 (1H, m), 8.38−8.43 (1H, m). Anal. Calcd ($C_{20}H_{23}NO$): C, 81.87; H, 7.90; N, 4.77. Found: C, 81.22; H, 8.11; N, 4.72.

1-(3-Ethyl-2-methylquinolin-6-yl)-2-(*cis*-4-methoxycyclohexyl)ethanone (*cis*-33e). Compound ***cis*-33e** was prepared in 35% yield from ***cis*/*trans*-32e** by a method similar to that described for **(±)33a**: mp 80 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, t, J = 7.5 Hz), 1.40−1.61 (6H, m), 1.86−1.94 (2H, m), 2.08−2.19 (1H, m), 2.75 (3H, s), 2.84 (2H, q, J = 7.5 Hz), 2.98 (2H, d, J = 9.2 Hz), 3.32 (3H, s), 3.41−3.46 (1H, m), 7.97 (1H, s), 8.03 (1H, d, J = 10 Hz), 8.15−8.21 (1H, m), 8.38 (1H, m). Anal. Calcd ($C_{21}H_{27}NO_2$): C, 77.50; H, 8.36; N, 4.30. Found: C, 76.62; H, 8.41; N, 4.29.

(±)-2,3-Dihydro-1*H*-inden-2-yl 3-Ethyl-2-methylquinolin-6-yl Ketone ((±)33i). Compound **(±)33i** was prepared in 67% yield from **(±)32i** by a method similar to that described for **(±)33a**: mp 120 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, t, J = 7.5 Hz), 2.79 (3H, s), 2.87 (2H, q, J = 7.5 Hz), 3.30−3.53 (4H, m), 4.40−4.51 (1H, m), 7.15−7.30 (4H, m), 8.00 (1H, s), 8.09 (1H, d, 8.8 Hz), 8.25 (1H, dd, J = 1.9, 8.8 Hz), 8.47 (1H, d, J = 1.9 Hz). Anal. ($C_{22}H_{21}NO$) C, H, N.

6-Bromo-3-ethyl-2-methylquinoline (35). 13 (5.8 g, 0.034 mol) was added at room temperature to a solution of **34** (5.4 g, 0.041 mol) in AcOH (60 mL). The mixture was stirred and refluxed for 8 h, brought to room temperature, and evaporated to dryness. The product was precipitated from EtOAc. The precipitate was filtered, washed with a 10% aqueous solution of K_2CO_3, and taken up in CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated to afford **35** (4.6 g, 54%) which was used without further purification: ^{1}H NMR (DMSO-d_6) δ 1.32 (3H, t, J = 7.5 Hz), 2.81−2.95 (5H, m), 8.08 (1H, d, J = 9.6 Hz), 8.28 (1H, d, J = 9.6 Hz), 8.48 (1H, s), 8.65 (1H, s).

1-(3-Ethyl-2-methylquinolin-6-yl)-2-(3-methoxyphenyl)-ethanone (33f). *n*-BuLi (1.6 M) in hexane (6 mL, 0.0096 mol) was added dropwise at −78 °C to a solution of **35** (2 g, 0.008 mol) in THF (20 mL) under N_2 flow. The mixture was stirred for 30 min. A mixture of **31f**[1] (2.5 g, 0.012 mol) in THF (10 mL) was added slowly. The mixture was stirred from −78 to −20 °C, poured out into H_2O/NH_4Cl, and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated to dryness. The residue (3.9 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc; 70/30; 15−40 μm). Fractions were collected and evaporated off. The residue was precipitated from diethyl ether/petroleum ether to afford **33f** (0.24 g, 25%): mp 60 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (3H, t, J = 7.7 Hz), 2.69 (3H, s), 2.82 (2H, q, J = 7.7 Hz), 3.73 (3H, s), 4.48 (2H, s), 6.78−6.83 (1H, m), 6.86 (2H, m), 7.24 (1H, t, J = 7.9 Hz), 7.96 (1H, d, J = 10 Hz), 8.14−8.18 (1H, m), 6.24 (1H, s), 8.75 (1H, m).

2-(3,4-Dimethoxyphenyl)-1-(3-ethyl-2-methylquinolin-6-yl)ethanone (33g). Compound **33g** was prepared in 13% yield from **31g**[47] by a method similar to that described for **33f**: mp 105 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (3H, t, J = 7.5 Hz), 2.68 (3H, s), 2.81 (2H, q, J = 7.5 Hz), 3.71 (3H, s), 3.73 (3H, s), 4.43 (2, s), 6.80−6.85 (1H, m), 6.87−6.91 (1H, m), 6.92−6.96 (1H, m), 7.96 (1H, d, J = 8.9 Hz), 8.15 (1H, dd, J = 1.9, 8.9 Hz), 8.24 (1H, s), 8.76 (1H, m).

2-[4-(Dimethylamino)phenyl]-1-(3-ethyl-2-methylquinolin-6-yl)ethanone (33h). Compound **33h** was prepared in 15% yield from **31h** by a method similar to that described for **33f**: mp 130 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (3H, t, J = 7.7 Hz), 2.74 (3H, s), 2.82 (2H, q, J = 7.7 Hz), 2.91 (6H, s), 4.30 (2H, s), 6.71 (2H, d, J = 4.5 Hz), 7.18 (2H, d, J = 4.5 Hz), 7.94 (1H, s), 8.00 (1H, d, J = 8.9 Hz), 8.21 (1H, dd, J = 1.8, 8.9 Hz), 8.45 (1H, d, J = 1.8 Hz).

3-Ethyl-2-methylquinolin-6-yl *cis*-4-Hydroxycyclohexyl Ketone (*cis*-36). A solution of ***cis*-18** (2.4 g, 0.0078 mol) in a 48% aqueous solution of HBr (21 mL) was stirred at 60 °C for 2 h. The mixture was poured out into H_2O, basified with a 10% aqueuos solution of K_2CO_3, and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc; 35/65; 15−40 μm). Fractions were collected and evaporated off. The residue was precipitated from DIPE to afford ***cis*-36** (0,-12 g, 5%): mp 170 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (3 H, t, J = 7.7 Hz), 1.5 (1 H, br s), 1.75 (4H, m), 1.9 (2 H, m), 2.05 (2 H, m), 2.75 (3H, s), 2.85 (2H, t, J = 7.7 Hz), 3.45 (1H, m), 4.1 (1H, m), 7.95 (1H, s), 8.05 (1H, d, J = 10.2 Hz), 8.15 (1H, d, J = 10.2 Hz), 8.38 (1H, s). Anal. ($C_{19}H_{23}NO_2$) C, H, N.

1-(3-Ethyl-2-methylquinolin-6-yl)-2-phenylethanone (38). A mixture of **37** (27 g, 0.128 mol) and **34** (20.3 g, 0.154 mol) in AcOH (270 mL) was stirred and refluxed for 15 h and then cooled to room temperature. AcOH was evaporated. The residue was taken up in EtOAc. The precipitate was filtered and taken up in CH_2Cl_2. H_2O was added. The mixture was basified with K_2CO_3. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 90/10; 10−35 μm). Fractions were collected, and the solvent was evaporated off. The residue was precipitated from diethyl ether to afford **38** (14 g, 39%): mp 89 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, t, J = 7.7 Hz), 2.93 (2 H, q, J = 7.5 Hz), 2.75 (3H, s), 4.41 (2H, s), 7.35 (4H, m), 7.95 (1H, s), 8.03 (1H, d, J = 10.2 Hz), 8.21 (1H, d, J = 10.2 Hz), 8.45 (1H, s). Anal. ($C_{20}H_{19}NO$) C, H, N.

1-Adamantyl 3-Ethyl-2-methoxyquinolin-6-yl Ketone (40). *n*-BuLi (1.6 M) in hexane (68 mL, 0.108 mol) was added dropwise at −78 °C under N_2 flow to a mixture of **16** (24 g, 0.09 mol) in THF (270 mL). The mixture was stirred at −30 °C for 1 h. A solution of **39**[31] (20 g, 0.09 mol) in THF (80 mL) was added at −78 °C. The mixture was stirred for 2.5 h while the temperature was brought to room temperature, hydrolyzed

with H_2O, and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 96/4; 15−35 μm). Fractions were collected, and the solvent was evaporated off. The residue was precipitated from diethyl ether to afford **40** (13.9 g, 44%): mp 116 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (3H, t, J = 7.5 Hz), 1.81 (6H, s), 2.13 (9H, s), 2.75 (2H, q, J = 7.5 Hz), 4.14 (3H, s), 7.85 (3H, m), 8.02 (1H, s). Anal. ($C_{23}H_{27}NO_2$) C, H, N.

6-(1-Adamantylcarbonyl)-3-ethylquinolin-2(1*H*)-one (41). A mixture of **40** (3 g, 0.0086 mol) in 3 N HCl (30 mL) and THF (30 mL) was stirred and refluxed overnight, poured out into H_2O, basified with K_2CO_3 (solid), and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (9 g) was reprecipitated from 2-propanone and diethyl ether to afford **41** (2.04 g, 71%): mp 148 °C; ^{1}H NMR (DMSO-d_6) δ 1.18 (3H, t, J = 7.4 Hz), 1.74 (6H, s), 1.99 (6H, s), 2.04 (3H, s), 2.51 (2H, q, J = 7.4 Hz), 7.30 (1H, d, J = 6 Hz), 7.78 (1H, d, J = 6 Hz, 1.81 (6H, s), 2.13 (9H, s) 2.75 (2H, q, J = 7.5 Hz), 4.14 (3H, s) 7.89 (1H, s), 8.09 (1H, s), 11.9 (1H, br s). Anal. Calcd ($C_{22}H_{25}NO_2$): C, 78.77; H, 7.51; N, 4.18. Found: C, 77.52; H, 7.55; N, 4.01.

1-Adamantyl 2-Chloro-3-ethylquinolin-6-yl Ketone (42). A solution of **41** (6 g, 0.018 mol) in $POCl_3$ (60 mL) was stirred and refluxed for 1 h. The solvent was evaporated to dryness. The mixture was poured out on ice, basified with NH_4OH, and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated to give **42** (4 g, 63%): ^{1}H NMR (DMSO-d_6) δ 1.33 (3 H, t, J = 7.4 Hz), 2.0 (15H, m), 2.89 (2H, q, J = 7.4 Hz), 7.88 (1H, d, J = 8.7 Hz),7.98 (1H, d, J = 8.7 Hz), 8.32 (1H, s), 8.52 (1H, s).

1-Adamantyl 3-Ethyl-2-methylquinolin-6-yl Ketone (43). A mixture of **42** (0.5 g, 0.0014 mol), tetramethyltin (0.4 mL, 0.0028 mol), and tetrakis(triphenylphosphine)palladium(0) (0.16 g, 0.0001 mol) in toluene (5 mL) was stirred and refluxed for 48 h. A 10% aqueous solution of K_2CO_3 was added. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (0.55 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 75/25; 15−40 μm). The pure fractions were collected, and the solvent was evaporated. The residue was precipitated from diethyl ether to afford **43** (0.2 g, 42%): mp 180 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, t, J = 7.3 Hz), 1.79 (6H, s), 2.11 (9H, s), 2.76 (3H, s), 2.83 (2 H, q, J = 7.3 Hz), 7.84 (1H, d, J = 9 Hz), 7.91 (1H, s), 7.99 (2H, m). Anal. Calcd ($C_{23}H_{27}NO$): C, 82.84; H, 8.16; N, 4.2. Found: C, 80.68; H, 8.01; N, 4.02.

(±)-1-(2-Chloro-3-ethylquinolin-6-yl)-3-methylbutan-1-ol ((±)45). *n*-BuLi (1.6 M) in hexane (28 mL, 0.044 mol) was added slowly at −70 °C to a solution of **15** (10 g, 0.037 mol) in THF (100 mL). The mixture was stirred at −70 °C for 30 min. A solution of **44** (4.8 mL, 0.044 mol) in THF (50 mL) was added. The mixture was stirred at −70 °C for 1 h and then brought slowly to room temperature, hydrolyzed with H_2O, and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (9.5 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 92/08; 15−35 μm). The pure fractions were collected, and the solvent was evaporated. The residue was precipitated from diethyl ether/petroleum ether to afford **(±)45** (6.9 g, 67%): mp 92 °C; ^{1}H NMR (DMSO-d_6) δ 1.27 (6H, m), 1.44 (3H, t, J = 6 Hz), 1.46 (1H, m), 1.58 (2H, m), 2.84 (2H, q, J = 6 Hz), 4.76 (1H, m), 5.3 (1H, d, J = 3 Hz), 7.74 (1H, m), 7.89 (1H, m), 8.31 (1H, s). Anal. ($C_{16}H_{20}ClNO$) C, H, N.

1-(2-Chloro-3-ethylquinolin-6-yl)-3-methylbutan-1-one (46). $KMnO_4$ (10 g) was added portionwise at room temperature to a solution of **(±)45** (6 g, 0.022 mol) in TDA1 (1 mL) and CH_2Cl_2 (100 mL). The mixture was stirred at room temperature for 8 h, filtered over Celite, washed with CH_2Cl_2, and dried. The residue was precipitated from diethyl ether/petroleum ether to afford **46** (2 g, 33%): mp 82 °C; ^{1}H NMR (DMSO-d_6) δ 0.96 (6H, s), 1.31 (3H, t, J = 6 Hz), 2.21 (1H, m), 2.85 (2H, q, J = 6 Hz), 3 (2H, d, J = 9 Hz), 7.99 (1H, d, J = 9 Hz), 8.17 (1H, d, J = 9 Hz), 8.49 (1H, s), 8.71 (1H, s). Anal. Calcd ($C_{16}H_{18}ClNO$): C, 69.68; H, 6.58; N, 5.08. Found: C, 69.07; H, 6.76; N, 5.10.

1-(3-Ethyl-2-methylquinolin-6-yl)-3-methylbutan-1-one (47). Compound **47** was prepared in 64% yield from **46** by a method similar to that described for **43**: mp 68 °C; ^{1}H NMR (DMSO-d_6) δ 0.96 (6H, m), 1.31 (3H, t, J = 9 Hz), 2.21 (1H, m), 2.77 (3H, s), 2.83 (2H, q, J = 9 Hz), 3 (2H, d, J = 9 Hz), 7.97 (1H, d, J = 9 Hz), 8 (1H, d, J = 9 Hz), 8.23 (1H, s), 8.64 (1H, s). Anal. Calcd ($C_{17}H_{21}NO$): C, 79.96; H, 8.29; N, 5.49. Found: C, 78.79; H, 8.43; N, 5.11.

***tert*-Butyl 4-[(2-Chloro-3-ethylquinolin-6-yl)carbonyl]-piperidine-1-carboxylate (49).** *n*-BuLi (1.6 M) in hexane (92 mL, 0.112 mol) was added slowly at −70 °C to a solution of **15** (25 g, 0.092 mol) in THF (250 mL). The mixture was stirred at −70 °C for 30 min and a solution of **48** (30 g, 0.110 mol) in THF (300 mL) was added slowly. The mixture was stirred at −70 °C for 30 min, brought to room temperature, hydrolyzed with H_2O, and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (40 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 75/25; 15−35 μm). Fractions were collected, and the solvent was evaporated to afford **49** (9.9 g, 26%) which was used without further purification.

***tert*-Butyl 4-[(3-Ethyl-2-methylquinolin-6-yl)carbonyl]-piperidine-1-carboxylate (50).** Compound **50** was prepared in 63% yield from **49** by a method similar to that described for **43**: mp 162 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (3H, t, J = 7.7 Hz), 1.4 (9H, s), 1.5 (2H, m), 1.85 (2H, m), 2.7 (3H, s), 2.8 (2H, m), 2.9 (2H, m), 3.8 (1H, m), 4.03 (2H, m), 7.95 (1H, d, J = 8 Hz), 8.12 (1H, d, J = 8 Hz), 8.25 (1H, s), 8.72 (1H, s). Anal. Calcd ($C_{23}H_{30}N_2O_3$): C, 72.22; H, 7.91; N, 7.32. Found: C, 71.77; H, 7.96; N, 7.26.

3-Ethyl-2-methylquinolin-6-yl Piperidin-4-yl Ketone (51). A mixture of **50** (2.9 g, 0.008 mol) in 3 N HCl (30 mL) and THF (10 mL) was stirred at 60 °C for 1 h, poured out on ice, basified with NH_4OH, and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue was recrystallized from CH_3CN to afford **51** (1 g, 46%): mp 132 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (3H, t, J = 7.7 Hz), 1.5 (2H, m), 1.75 (2H, m), 2.15 (1H, br s), 2.68 (5H, m), 2.8 (2H, q, J = 7.7 Hz), 3 (2H, m), 3.65 (1H, m), 7.95 (1H, d, J = 10.2 Hz), 8.1 (1H, d, J = 10.2 Hz), 8.25 (1H, s), 8.68 (1H, s). Anal. Calcd ($C_{18}H_{22}N_2O$): C, 76.56; H, 7.85; N, 9.92. Found: C, 76.11; H, 7.90; N, 9.96.

6-(1-Benzofuran-2-yl)-3-ethyl-2-methylquinoline (52). A mixture of **35** (4.7 g, 0.019 mol), benzofuran-2-boronic acid (5 g, 0.028 mol), tetrakis(triphenylphosphine)palladium(0) (0.55 g, 0.001 mol), and 2,6-di-*tert*-butyl-4-methylphenol (a few milligrams) in dioxane (25 mL) and Na_2CO_3 (25 mL) was stirred and refluxed for 8 h and extracted with EtOAc. The aqueous layer was basified with NH_4OH and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (3.6 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1; 15−40 μm). The pure fractions were collected, and the solvent was evaporated. The residue was precipitated from 2-propanone/diethyl ether to afford **52** (0.39 g, 7%): mp 134 °C; ^{1}H NMR (DMSO-d_6) δ 1.3 (3H, t, J = 7.7 Hz), 2.68 (3H, s), 2.8 (2H, q, J = 7.7 Hz), 7.3 (1H, m), 7.37 (1H, m), 7.58 (1H, s), 7.7 (2H, m), 7.98 (1H, d, J = 9.2 Hz), 8.18 (1H, s), 8.2 (1H, m), 8.42 (1H, s). Anal. ($C_{20}H_{17}NO$), C, H, N.

3-Ethyl-2-methyl-6-(5-phenyl-2-furyl)quinoline (53). A mixture of **35** (1 g, 0.004 mol), tributyl-((5-phenyl)furan-2-yl)-stannane[31] (2.1 g, 0.005 mol), LiCl (a few milligrams), and tetrakis(triphenylphosphine)palladium(0) (0.45 g, 0.001 mol) in dioxane (10 mL) was stirred and refluxed for 8 h. A 10% aqueous solution of KF was added. The mixture was filtered over Celite and washed with EtOAc. The filtrate was extracted

with EtOAc and then with 3 N HCl. The aqueous layer was basified with NH_4OH and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (1 g) was recrystallized from 2-propanone/diethyl ether to afford **53** (0.39 g, 31%): mp 134 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, t, J = 7.7 Hz), 2.75 (3H, s), 2.82 (2H, q, J = 7.7 Hz), 6.8 (1H, d, J = 3.5 Hz), 6.88 (1H, d, J = 3.5 Hz), 7.3 (1H, m), 7.45 (2H, m), 7.8 (2H, m), 7.9 (1H, s), 8 (2H, m), 8.13 (1H, s). Anal. ($C_{22}H_{19}NO$) C, H, N.

(*Z*)-3-Ethyl-2-methoxyquinolin-6-yl *cis*-4-Methoxycyclohexyl Ketone Oxime (*cis*-54) and (*E*)-3-Ethyl-2-methoxyquinolin-6-yl *cis*-4-Methoxycyclohexyl Ketone Oxime (*cis*-55). A mixture of ***cis*-10** (7.5 g, 0.0229 mol), NH_2OH (1.75 g, 0.0252 mol), and Et_3N (3.5 mL, 0.0252 mol) in EtOH (100 mL) was stirred and refluxed for 6 h, poured out into H_2O, and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue was recrystallized from CH_3CN. The precipitate was filtered off and dried. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 80/20; 15−40 μm). Fractions were collected, and the solvent was evaporated to afford ***cis*-54** (3 g, 38%) and ***cis*-55** (2.8 g, 36%). ***cis*-54**: mp 133 °C; ^{1}H NMR (DMSO-d_6) δ 1.24 (3H, t, J = 7.4 Hz), 1.45 (4H, m), 1.88 (4H, m), 2.68 (2H, q, J = 7.4 Hz), 3.18 (3H, s), 3.33 (1H, m), 3.41 (1H, m), 4.03 (1H, s), 7.58 (1H, m), 7.60 (1H, m), 7.72 (1H, m), 8.04 (1H, s), 11.02 (1H, br s). Anal. ($C_{20}H_{26}N_2O_3$) C, H, N. ***cis*-55**: mp 142 °C; ^{1}H NMR (DMSO-d_6) δ 1.24 (3H, t, J = 7.4 Hz), 1.54 (4H, m), 1.88 (4H, m), 2.67 (2H, q, J = 7.4 Hz), 2.7 (1H, m), 3.17 (3H, s), 3.33 (1H, m), 4.03 (3H, s), 7.49 (1H, m), 7.73 (2H, m), 8.03 (1H, s), 10.54 (1H, br s). Anal. ($C_{20}H_{26}N_2O_3$) C, H, N.

(*Z*)-3-Ethyl-2-methoxyquinolin-6-yl *cis*-4-Methoxycyclohexyl Ketone Hydrazone (*cis*-56). NH_2NH_2 (20 mL, 0.41 mol) was added at room temperature to a solution of ***cis*-10** (5 g, 0.015 mol) in EtOH (75 mL). The mixture was stirred and refluxed overnight, poured out into H_2O, and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH/NH_4OH 98/2/0.1). The pure fractions were collected, and the solvent was evaporated (2.7 g, 52%). The residue was precipitated from diethyl ether to afford ***cis*-56** (0.8 g, 15%): mp 110 °C; ^{1}H NMR (DMSO-d_6) δ 1.27 (3H, t, J = 14.9 Hz), 1.50 (6H, m), 1.79 (2H, m), 2.51 (1H, m), 2.68 (2H, q, J = 7.4 Hz), 3.16 (1H, s), 3.33 (1H, m), 4.03 (3H, s), 7.58 (1H, m), 5.54 (2H, br s), 7.39 (1H, m), 7.64 (1H, s), 7.83 (1H, d, J = 8.5 Hz), 8.05 (1H, s). Anal. ($C_{20}H_{27}N_3O_2$) C, H, N.

3-Ethyl-2-methoxy-6-[1-(*cis*-4-methoxycyclohexyl)vinyl]-quinoline (*cis*-57). NaH 60% (0.3 g, 0.0073 mol) was added portionwise at room temperature to a solution of ***cis*-10** (2 g, 0.0061 mol) in THF (20 mL). The mixture was stirred at room temperature for 30 min. Methyltriphenylphosphonium bromide (2.6 g, 0.0073 mol) was added portionwise. The mixture was stirred at room temperature for 12 h and then at 60 °C for 1 h, hydrolyzed with H_2O, and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (3.3 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 90/10; 15−40 μm). Fractions were collected, and the solvent was evaporated off. The residue was solidified in 2-propanol. HCl/2-propanol was added. The precipitate was filtered off, washed with diethyl ether, and dried to afford ***cis*-57** (0.77 g, 34%): mp 118 °C; ^{1}H NMR (DMSO-d_6) δ 1.24 (3H, t, J = 9.6 Hz), 1.50 (4H, m), 1.88 (2H, m), 2.68 (2H, m), 2.70 (1H, m), 3.39 (3H, s), 3.43 (1H, m), 4.00 (3H, s), 5.08 (1H, s), 5.29 (1H, s), 6.56 (1H, m), 7.62(1H, d, J = 9.6 Hz), 7.7 (1H, d, J = 9.6 Hz), 7.81 (1H, s), 8.02 (1H, s). Anal. ($C_{21}H_{27}NO_2$·HCl) C, H, N.

6-Bromo-2-chloro-3-(3-chloropropyl)quinoline (59). DMF (12.4 mL) was added dropwise at 50 °C to $POCl_3$ (70.3 mL, 0.7536 mol). **58** (30 g, 0.1032 mol) was added and the mixture was stirred at 75 °C for 6 h, cooled at room temperature, and poured out into ice H_2O. The insoluble portion was filtered, washed with H_2O, and dried to afford **59** (25.7 g, 78%), which was used without further purification.

7-Bromo-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinoline (60a). A mixture of **59** (25.5 g, 0.0799 mol) in 12 N HCl (100 mL) and H_2O (100 mL) was stirred and refluxed for 10 h, cooled at room temperature, and neutralized with NH_4OH (concentrated). The insoluble portion was filtered, washed with H_2O and with EtOH, and dried to afford **61** (16 g) The filtrate was evaporated to afford **60a** (5.9 g, 28%): mp 129 °C; ^{1}H NMR (DMSO-d_6) δ 1.97 (2 H, qt, J = 5.8 Hz), 2.96 (2H, t, J = 5.9 Hz), 4.39 (2H, t, J = 5.9 Hz), 7.6 (1H, d, J = 9.2 Hz), 7.68 (1H, dd, J = 9.2 Hz, 2.3 Hz), 8.01 (1H, s), 8.04 (1H, m). Anal. ($C_{12}H_{10}BrNO$) C, H, N.

7-Bromo-1-methyl-1,2,3,4-tetrahydrobenzo[*b*]-1,8-naphthyridine (60b). A mixture of **59** (15 g, 0.047 mol) and benzylamine (7.7 mL, 0.0705 mol) in DMF (250 mL) was stirred at 160 °C for 15 h, cooled at room temperature, poured out into ice H_2O, and extracted with EtOAc. The residue (19 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 80/20; 15−35 μm). Two fractions were collected, and the solvent was evaporated. Each fraction was precipitated separately from petroleum ether. The precipitates were filtered off and dried to afford **62** (2.4 g) and **60b** (3.26 g, 37%): mp 105 °C; ^{1}H NMR (DMSO-d_6) δ 1.9 (2 H, m), 2.85 (2H, t, J = 6.7 Hz), 3.15 (3H, s), 3.45 (2H, t, J = 6.0 Hz), 7.4 (1 H, d, J = 7.7 Hz), 7.47 (1H, d, J = 7.7 Hz), 7.57 (1H, s), 7.77 (1H, d, J = 1.92 Hz). Anal. ($C_{13}H_{13}BrN_2$) C, H, N.

2-Bromo-7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinoline (60c). A mixture of cycloheptanone (1.9 mL, 0.016 mol) and NaOH (0.6 g, 0.016 mol) in EtOH (8 mL) was warmed to 65 °C and a solution of **63** (2.9 g, 0.015 mol) in EtOH (16 mL) was slowly added dropwise. The reaction mixture was stirred for 1 h at 65 °C and cooled to room temperature. The solvent was evaporated and the residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected, and the solvent was evaporated. The residue was precipitated in DIPE to afford **60c** (2.7 g, 56%): ^{1}H NMR (DMSO-d_6) δ 1.60−1.75 (4H, m), 1.80−1.90 (2H, m), 2.90−3.01 (2H, m), 3.09−3.17 (2H, m), 7.75 (1H, dd, J = 2.2, 8.8 Hz), 7.82 (1H, s), 7.85 (1H, s), 8.12 (1H, d, J = 2.2 Hz).

7-Bromo-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (60d). A mixture of **63** (10 g, 0.05 mol), cyclopentanone (4.9 mL, 0.055 mol) and KOH (5.6 g, 0.1 mol) in EtOH (20 mL) was stirred at 60 °C for 1 h and then cooled to room temperature. The solvent was evaporated. The residue was taken up in H_2O. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated to dryness. The residue was precipitated from 2-propanone to afford **60d** (7.8 g, 63%). ^{1}H NMR ($CDCl_3$) δ 2.22 (2H, qt, J = 7.3 Hz), 3.12 (4H, m), 7.67 (1H, dd, J = 2.1, 9.1 Hz), 7.87 (2H, m). Anal. ($C_{12}H_{10}BrNO$) C, H, N.

6-Bromo-2-propylquinoline (60e). 2-Pentanone (2.4 mL, 0.021 mol) was slowly added dropwise to a mixture of **63** (3.9 g, 0.02 mol), pyrrolidine (1.7 mL, 0.021 mol), and H_2SO_4 (0.057 mL, 0.001 mol) in EtOH (18 mL) under N_2 and then the reaction mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2 100%). The product fractions were collected, and the solvent was evaporated to afford **60e** (2.8 g, 56%): ^{1}H NMR (DMSO-d_6) δ 0.93 (3 H, t, J = 7.7 Hz), 1.85 (2H, st, J = 7.7 Hz), 3.20 (2H, t, J = 7.7 Hz), 7.95 (1H, d, J = 9.6 Hz), 8.2 (1 H, m), 8.4 (1H, m), 8.55 (2H, m), 8.85 (1H, m).

3,4-Dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-yl *cis*-4-Methoxycyclohexyl Ketone (*cis*-64a). *n*-BuLi (1.6 M) in hexane (8.5 mL, 0.0137 mol) was added slowly at −78 °C to a solution of **60a** (3 g, 0.0114 mol) in THF (30 mL) under N_2 flow. The mixture was stirred for 30 min and a solution of ***cis*/*trans*-12** (2.74 g, 0.0137 mol) in THF (30 mL) was added dropwise at −78 °C. The mixture was stirred for 1 h, poured out into H_2O/NH_4Cl, and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered and the solvent was evaporated to dryness. The residue (5.8 g) was purified by

column chromatography over silica gel (eluent: toluene/EtOAc 50/50; 15−40 μm). The pure fractions were collected, and the solvent was evaporated. The residue was precipitated from diethyl ether to afford ***cis*-64a** (1.3 g, 35%): mp 115 °C; ^{1}H NMR ($CDCl_3$) δ 1.58 (2 H, m), 1.77 (2H, m), 2.0 (6H, m), 3.03 (2H, t), 3.32 (3H, s), 3.38 (1H, m), 3.52 (1H, m), 4.52 (2H, t, J = 5.1 Hz), 7.85 (1H, d, J = 8.8 Hz), 7.93 (1H, s), 8.10 (1H, dd, J = 8.8, 1.8 Hz), 8.30 (1H, d, J = 1.8 Hz). Anal. ($C_{20}H_{23}NO_3$) C, H, N.

***cis*-4-Methoxycyclohexyl 1-Methyl-1,2,3,4-tetrahydrobenzo[*b*]-1,8-naphthyridin-7-yl Ketone (*cis*-64b).** Compound ***cis*-64b** was prepared in 33% yield from **60b** by a method similar to that described for ***cis*-64a**: mp 127 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 (4 H, m), 2.0 (6H, m), 2.9 (2H, t, J = 6.7), 3.32 (3H, s), 3.35 (1H, s), 3.38 (1H, m), 3.52 (3H, m), 7.54 (1H, s), 7.63 (1H, d, J = 7.7 Hz), 8.1 (1H, dd, J = 7.7, 2.6 Hz), 8.14 (1H, d, J = 2.6 Hz). Anal. ($C_{21}H_{26}N_2O_2$) C, H, N.

***cis*-4-Methoxycyclohexyl 7,8,9,10-Tetrahydro-6*H*-cyclohepta[*b*]quinolin-2-yl Ketone (*cis*-64c).** Compound ***cis*-64c** was prepared in 12% yield from **60c** by a method similar to that described for ***cis*-64a**: mp 121 °C; ^{1}H NMR ($CDCl_3$) δ 1.60 (2H, m), 1.78 (6H, m), 1.93 (4H, m), 2.04 (2H, m), 2.97 (2H, m), 3.23 (2H, m), 3.33 (3H, s), 3.41 (1H, m), 3.52 (1H, m), 7.92 (1H, s), 8.03 (1H, d, J = 8.8 Hz), 8.14 (1H, dd, J = 1.8, 8.8 Hz), 8.33 (1H, d, J = 1.8 Hz). Anal. ($C_{22}H_{27}NO_2$) C, H, N.

2,3-Dihydro-1*H*-cyclopenta[*b*]quinolin-7-yl *cis*-4-Methoxycyclohexyl Ketone (*cis*-64d). Compound ***cis*-64d** was prepared in 35% yield from **60d** by a method similar to that described for ***cis*-64a**: mp 118 °C; ^{1}H NMR ($CDCl_3$) δ 1.58 (2H, m), 1.73 (2H, m), 1.82−2.08 (4H, m), 2.25 (2H, m), 3.12 (2H, t, J = 7.7 Hz), 3.2 (2H, t, J = 7.7 Hz), 3.32 (3H, s), 3.4 (1H, tt, J = 2.6 Hz), 3.52 (1H, q, J = 2.6 Hz), 8.0 (1H, s), 8.05 (1H, d, J = 9.1 Hz), 8.12 (1H, dd, J = 1.8, 9.1 Hz), 8.35 (1H, d, J = 1.8 Hz). Anal. Calcd ($C_{20}H_{23}NO_2$): C, 77.64; H, 7.49; N, 4.53. Found: C, 77.10; H, 7.52; N, 4.49.

(*cis*-4-Methoxycyclohexyl 2-Propylquinolin-6-yl Ketone (*cis*-64e). Compound ***cis*-64e** was prepared in 15% yield from **60e** by a method similar to that described for ***cis*-64a**: ^{1}H NMR ($CDCl_3$) δ 1.03 (3 H, t, J = 7.7 Hz), 1.6 (2H, m), 1.7 (2H, m), 1.9 (4H, m), 3.0 (2H, m), 3.3 (1H, s), 3.4 (1H, tt), 3.5 (1H, q), 7.35 (1H, d, J = 7.7 Hz), 8.08 (1H, d, J = 7.7 Hz), 8.2 (2H, m), 8.4 (1H, m). Anal. ($C_{20}H_{25}NO_2$) C, H, N.

2,3-Dihydrothieno[2,3-*b*]quinolin-6-yl *cis*-4-Methoxycyclohexyl Ketone (*cis*-64f). Compound ***cis*-64f** was prepared in 30% yield from **60f** by a method similar to that described for ***cis*-64a**: mp 145 °C; ^{1}H NMR ($CDCl_3$) δ 1.63 (4H, m), 1.98 (4H, m), 3.32 (3H, s), 3.35 (1H, m), 3.5 (5H, m), 7.85 (1H, s), 7.91 (1H, d, J = 7.7 Hz), 8.11 (1H, dd, J = 7.7, 2.6 Hz), 8.28 (1H, d, J = 2.6 Hz). Anal. ($C_{19}H_{21}NO_2S$) C, H, N.

6-Bromo-2-chloro-3-propylquinoline (66). $POCl_3$ (98.07 mL, 1.05 mol) was added dropwise at 10 °C to DMF (36.02 mL, 0.45 mol). **65** (38.5 g, 0.15 mol) was added at room temperature. The mixture was stirred at 80 °C overnight and then poured out on ice. The precipitate was filtered off and dried to afford **66** (36.51 g, 86%): ^{1}H NMR ($CDCl_3$) δ 1.0 (3H, t, J = 7.3 Hz), 1.80 (2H, q, J = 7.3 Hz)), 2.88 (2H, t, J = 7.3 Hz), 7.75 (1H, m), 7.87 (2H, m), 7.90 (1H, m).

2-Chloro-3-propylquinolin-6-yl *cis*-4-Methoxycyclohexyl Ketone (*cis*-67). *n*-BuLi (1.6 M) in hexane (26.4 mL, 0.042 mol) was added dropwise at −70 °C to a solution of **66** (10 g, 0.035 mol) in THF (100 mL). The mixture was stirred at −70 °C for 30 min. A solution of ***cis*/*trans*-12** (8.5 g, 0.042 mol) in THF (100 mL) was added dropwise. The mixture was stirred at −70 °C for 30 min, brought slowly to room temperature, poured out into H_2O, and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (13.7 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 80/20; 15−35 μm). Fractions were collected, and the solvent was evaporated. The residue was precipitated from diethyl ether to afford ***cis*-67** (1.05 g, 8%): ^{1}H NMR ($CDCl_3$) δ 1.05 (3H, t, J = 6.1 Hz), 1.6 (2H, m), 1.75 (4H, m), 2.0 (4H, m), 2.88 (2H, t, J = 6.1 Hz), 3.3 (3H, s), 3.4 (1H, m), 3.5 (1H, m), 8.05 (2H, m), 8.2 (1H, m), 8.38 (1H, m).

***cis*-4-Methoxycyclohexyl 2-Methyl-3-propylquinolin-6-yl Ketone (*cis*-68).** A mixture of ***cis*-67** (1.6 g, 0.005 mol), tetramethyltin (1.3 mL, 0.009 mol), and tetrakis(triphenylphosphine)palladium(0) (0.5 g, 0.0005 mol) in toluene (20 mL) was stirred and refluxed for 8 h. A 10% aqueous solution of K_2CO_3 was added. The mixture was filtered over Celite and washed with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (2.1 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 75/25; 15−40 μm). The pure fractions were collected, and the solvent was evaporated. The residue was precipitated from petroleum ether to afford ***cis*-68** (0.36 g, 23%): ^{1}H NMR ($CDCl_3$) δ 1.06 (3H, t, J = 7.3 Hz), 1.58 (2H, m), 1.75 (4H, m), 1.93 (2H, m), 2.05 (2H, m), 2.80 (5H, m), 3.33 (3H, s), 3.41 (1H, m), 3.52 (1H, m), 7.95 (1H, s), 8.02 (1H, d, J = 8.8 Hz), 8.14 (1H, dd, J = 2.2, 8.8 Hz), 8.35 (1H, d, J = 2.2 Hz). Anal. ($C_{21}H_{27}NO_2$) C, H, N.

4-Ethyltetrazolo[1,5-*a*]quinolin-7-yl *cis*-4-Methoxycyclohexyl Ketone (*cis*-69). A mixture of ***cis*-17** (1.5 g, 0.0045 mol) and NaN_3 (0.88 g, 0.0135 mol) in DMF (15 mL) was stirred at 140 °C for 3 h and then poured out into H_2O. The precipitate was filtered off, rinsed with H_2O, and dried under vacuum. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 92/8; 15−40 μm). Fractions were collected, and the solvents were evaporated. The residue was precipitated from diethyl ether to afford ***cis*-69** (0.5 g, 33%): mp 172 °C; ^{1}H NMR ($CDCl_3$) δ 1.52 (3H, t, J = 7.5 Hz), 1.73 (4H, m), 2.04 (4H, m), 3.22 (2H, q, J = 7.5 Hz), 3.34 (3H, s), 3.42 (1H, m), 3.54 (1H, m), 7.78 (1H, s), 8.34 (1H, dd, J = 8.7, 1.75 Hz), 8.51 (1H, s), 8.72 (1H, d, J = 8.7 Hz). Anal. ($C_{19}H_{22}N_4O_2$) C, H, N.

***N*-Methoxy-*N*-methyl-2-(3-thienyl)acetamide (71).** CDI (17.1 g, 0.105 mol) was added portionwise at room temperature to a solution of **70a** (10 g, 0.0703 mol) in CH_2Cl_2 (100 mL). The mixture was stirred at room temperature for 1 h. *N*,*O*-Dimethylhydroxylamine hydrochloride (10.3 g, 0.105 mol) was added. The mixture was stirred at room temperature for 5 h. H_2O was added. The organic layer was washed with 3 N HCl, separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated off to afford **71** (11.6 g, 89%).

1-(3,4-Dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-yl)-2-(3-thienyl)ethanone (72a). *n*-BuLi (1.6 M) in hexane (5.7 mL, 0.0091 mol) was added at −70 °C to a solution of **60a** (2 g, 0.0076 mol) in THF (15 mL) under N_2 flow. The mixture was stirred at −70 °C for 1 h. A solution of **71a** (2.1 g, 0.011 mol) in THF (15 mL) was added at −70 °C. The mixture was stirred at −70 °C for 3 h, brought to −20 °C, poured out into H_2O, and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (3.5 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAC 40/60; 15−35 μm). The pure fractions were collected, and the solvent was evaporated. The residue was precipitated from diethyl ether to afford **72a** (0.14 g, 6%): mp 131 °C; ^{1}H NMR (DMSO-d_6) δ 2.0 (2 H, m), 3.01 (2H, m), 3.15 (3H, s), 4.44 (2H, t), 4.48 (2 H, s), 7.07 (1H, d, J = 4.1 Hz), 7.38 (1H, s), 7.48 (1H, m), 7.73 (1H, d, J = 8.7 Hz), 8.22 (1H, s), 8.65 (1H, s). Anal. ($C_{18}H_{15}NO_2S$) C, H, N.

1-(3,4-Dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-yl)-3-phenylpropan-1-one (72b). Compound **72b** was prepared in 38% yield from **31c**[40] by a method similar to that described for **72a**: mp 170 °C; ^{1}H NMR (DMSO-d_6) δ 1.96 (2 H, qt), 2.35 (3H, s), 2.86 (2H, t), 4.38 (2H, t), 5.95 (1H, br s), 6.22 (1H, d), 6.58 (1H, d, J = 2.9 Hz), 6.67 (1H, d, J = 2.9 Hz), 7.58 (2H, m), 7.79 (1H, s), 8.03 (1H, s). Anal. Calcd ($C_{21}H_{19}NO_2$): C, 79.47; H, 6.03; N, 4.41. Found: C, 79.11; H, 5.98; N, 4.38.

3,4-Dihydro-2*H*-pyrano[2,3-*b*]quinoline-7-carboxylic Acid (73). 60a (1 g, 0.0038 mol) in THF (25 mL) was stirred under N_2 at −78 °C on a 2-propanone/CO_2 bath. BuLi (2.5 M) in hexane (1.51 mL) was added and the mixture was stirred for 40 min at −78 °C. CO_2 (solid) was added at −78 °C and the mixture was stirred at the same temperature for 20 min. Then it was allowed to warm to room temperature. NaOH (1 N, 5 mL) was added and the mixture was stirred vigorously. The separated organic layer was washed with NaOH (1 N, 6

mL). The combined aqueous layer was acidified with HCl (1 N, 11 mL). The formed precipitate was filtered off and stirred in 2-propanol. The precipitate was filtered off, washed with DIPE, and dried to afford **73** (0.306 g, 35%), which was used without further purification: ^{1}H NMR (DMSO-d_6) δ 1.95−2.05 (2H, m), 2.90−3.03 (2H, m), 4.35−4.45 (2H, m), 7.71 (1H, d, J = 9.2 Hz), 8.05 (1H, d, J = 9.2 Hz), 8.20 (1H, s), 8.45 (1H, s).

Methyl 3,4-Dihydro-2*H*-pyrano[2,3-*b*]quinoline-7-carboxylate (74). A mixture of **73** (3.5 g, 0.0153 mol) and H_2SO_4 (0.3 mL) in MeOH (25 mL) was stirred overnight at 80 °C under N_2. The solvent was evaporated. The residue was stirred in H_2O/CH_2Cl_2. The separated aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried and filtered, and the solvent was evaporated. The residue was dried (vacuum; 40 °C) and then it was purified by column chromatography over silica gel (eluent: CH_2Cl_2/MeOH 98:2). The desired fractions were collected, and the solvent was evaporated to afford **74** (1.97 g, 30%). The compound was used without further purification.

1-(3,4-Dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-yl)-2-phenylethanone (72c). THF (6 mL) was added to **74** (0.375 g, 0.0015 mol) under N_2. Benzylmagnesium chloride (2 M in THF, 0.8 mL, 0.0016 mol) was added dropwise. The reaction mixture was stirred at room temperature for 90 min under N_2. The mixture was poured out into H_2O (100 mL) and extracted with ether (3 × 50 mL). The combined organic layer was washed with brine. The mixture was filtered over dicalite. The separated organic layer was dried and filtered, and the solvent was evaporated to afford **72c** (0.481 g, 100%): mp 128 °C; ^{1}H NMR (DMSO-d_6) δ 2.01 (2H, m), 3.01 (2H, m), 4.45 (4H, m), 7.24 (1H, m), 7.32 (4H, m), 7.72 (1H, d, J = 8.7 Hz), 8.12 (1H, d, J = 8.7 Hz), 8.22 (1H, s), 8.66 (1H, s). Anal. ($C_{20}H_{17}NO_2$) C, H, N.

***N*-(3-Bromophenyl)-5-chloropentanamide (76).** 5-Chlorovaleryl chloride (82.6 mL, 0.6394 mol) was added dropwise at 5 °C to a solution of **75** (100 g, 0.5813 mol) and Et_3N (97.1 mL, 0.6976 mol) in CH_2Cl_2 (800 mL). The mixture was stirred for 30 min. H_2O was added. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated to afford **76** (178.2 g, 100%). This product was used without further purification in the next step.

7-Bromo-2-chloro-3-(3-chloropropyl)quinoline (77). $POCl_3$ (140 mL, 1.507 mol) was added at 5 °C to DMF (24.8 mL, 0.32 mol). The mixture was stirred until dissolution of the complex. **76** (60 g, 0.206 mol) was added. The mixture was stirred at 75 °C for 6 h, cooled to room temperature, poured out into ice H_2O, filtered, washed with H_2O, and dried to afford an nonseparable mixture of **77** and **78** (60 g, 91%).

7-Bromo-3-(3-chloropropyl)quinolin-2(1*H*)-one (79). A mixture of **77** (30 g, 0.094 mol) and **78** (30 g, 0.094 mol) in HCl (6 N, 600 mL) and THF (100 mL) was stirred and refluxed for 15 h, cooled, poured out on ice, basified with NH_4OH, and filtered. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), and filtered, and the solvent was evaporated to afford a nonseparable 85/15 mixture of **79** and **80**, respectively (47.4 g, 84%).

8-Bromo-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinoline (81). The above mixture (44.6 g, 0.148 mol) and PPA (300 g) were stirred at 160 °C for 15 h, cooled to room temperature, poured out into ice H_2O and NH_4OH, and filtered. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue (44.1 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 97/3; 15−35 μm). The pure fractions were collected, and the solvent was evaporated. The residue was precipitated from diethyl ether to afford **81** (12.9 g, 39%): mp 170 °C; ^{1}H NMR (DMSO-d_6) δ 1.99 (2H, q, J = 5.1 Hz), 2.95 (2H, t, J = 5.1 Hz), 4.41 (2H, t, J = 5.1 Hz), 7.51 (1H, d, J = 9 Hz), 7.77 (1H, d, J = 9 Hz), 7.87 (1H, s), 8.09 (1H, s). Anal. ($C_{12}H_{10}BrNO$) C, H, N. The filtrate was evaporated. The residue was precipitated from diethyl ether to afford **82** (0.5 g, 9%): mp 110 °C; ^{1}H NMR (DMSO-d_6) δ 2.0 (2H, q, J = 5.1 Hz), 3.05 (2H, t, J = 5.1 Hz), 4.43 (2H, t, J = 5.1 Hz), 7.51 (1H, m), 7.70 (2H, m), 8.17 (1H, s). Anal. ($C_{12}H_{10}BrNO$) C, H, N.

1-(3,4-Dihydro-2*H*-pyrano[2,3-*b*]quinolin-8-yl)-2-phenylethanone (83). *n*-BuLi (1.6 M) in hexane (7.8 mL, 0.0125 mol) was added dropwise at −78 °C to a solution of **81** (3 g, 0.0113 mol) in THF (50 mL) under N_2 flow. The mixture was stirred for 1 h. A solution of *N*-methoxy-*N*-methylphenylacetamide (3.05 g, 0.017 mol) in THF (30 mL) was added dropwise at −78 °C. The mixture was stirred from −78 to 0 °C, poured out into H_2O, and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated till dryness. The residue (5.7 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 60/40; 15−35 μm). The pure fractions were collected, and the solvent was evaporated. The residue was precipitated from diethyl ether to afford **83** (1.2 g, 35%): mp 137 °C; ^{1}H NMR (DMSO-d_6) δ 2.01 (2H, q, J = 5.1 Hz), 3.2 (2H, t, J = 5.1 Hz), 4.42 (2H, t, J = 5.1 Hz), 4.51 (2H, s), 7.25 (1H, m), 7.31 (4H, m), 7.89 (2H, s), 8.12 (1H, s), 8.42 (1H, s). Anal. ($C_{20}H_{17}NO_2$) C, H, N.

***cis*/*trans*-*N*-Methoxy-*N*,4-dimethylcyclohexanecarboxamide (*cis*/*trans*-85).** CDI (32 g, 0.19 mol) was added portionwise to a solution of ***cis*/*trans*-84** (25 g, 0.18 mol) in CH_2Cl_2 (500 mL) and the mixture was stirred for 1 h at room temperature. *N*,*O*-Dimethylhydroxylamine hydrochloride (19 g, 0.19 mol) was added and the reaction mixture was stirred overnight at room temperature. H_2O was added and the resulting mixture was stirred for 10 min. The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated to afford ***cis*/*trans*-85** (32.4 g, 100%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, d, J = 6.9 Hz), 1.47−1.59 (6H, m), 1.72−1.85 (3H, m), 2.53−2.75 (1H, m), 3.18 (1H, s), 3.69 (1H, s).

3,4-Dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-yl *cis*-4-Methylcyclohexyl Ketone (*cis*-86). Under N_2, a mixture of **60a** (5.8 g, 0.022 mol) in THF (50 mL) was stirred at −70 °C and *n*-BuLi (2.5 M) in hexane (11 mL, 0.027 mol) was added dropwise, then the mixture was stirred for 30 min at −70 °C and a solution of ***cis*/*trans*-85** (5 g, 0.027 mol) in THF (50 mL) was added dropwise. The reaction mixture was stirred for 30 min at −70 °C and was allowed to slowly reach room temperature. H_2O was added dropwise and the mixture was extracted with EtOAc. The organic layer was separated and dried, and the solvent was evaporated. The residue (8.5 g) was first purified by high-performance liquid chromatography and then separated into its optical isomers by chiral separation. The pure fractions were collected, and the solvent was evaporated to afford ***cis*-86** (1.47 g, 22%): mp 128 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, d, 6.9 Hz), 1.41−1.53 (2H, m), 1.39−1.54 (2H, m), 1.56−1.82 (7H, m), 1.88−2.01 (2H, m), 2.06−2.17 (2H, m), 3.04 (2H, t, J = 6.6 Hz), 3.40−3.51 (1H, m), 4.51 (2H, t, J = 5.1 Hz), 7.84 (1H, d, 8.8 Hz), 7.93 (1H, s), 8.09 (1H, dd, J = 2.2, 8.8 Hz), 8.27 (1H, d, J = 2.2 Hz). Anal. ($C_{20}H_{23}NO_2$) C, H, N.

***cis*-4-Methylcyclohexyl 7,8,9,10-Tetrahydro-6*H*-cyclohepta[*b*]quinolin-2-yl Ketone (*cis*-87).** A solution of **60c** (2.7 g, 0.0098 mol) in THF (60 mL) was cooled to −70 °C on a CO_2 bath, and *n*-BuLi (2.5 M) in hexane (5 mL, 0.012 mol) was slowly added dropwise. The mixture was stirred for 30 min at −70 °C and ***cis*/*trans*-85** (2.3 g, 0.012 mol) was slowly added dropwise. The reaction mixture was stirred for 30 min at −70 °C and was allowed to slowly reach room temperature. The mixture was treated with H_2O. The organic layer was separated, dried ($MgSO_4$), and filtered off, and the solvent was evaporated. The residue was purified and separated into its isomers. Fractions were collected, and the solvent was evaporated to afford ***cis*-87** (0.513 g, 16%): mp 122 °C; ^{1}H NMR (DMSO-d_6) δ 0.91 (3H, d, 6.9 Hz), 1.28−1.41 (2H, m), 1.55−1.76 (9H, m), 1.76−1.93 (4H, m), 2.94−3.01 (2H, m), 3.14−3.21 (2H, m), 3.60−3.70 (1H, m), 7.96 (1H, d, J = 8.8 Hz), 8.09 (1H, dd, J = 2.2, 8.8 Hz), 8.20 (1H, d, J = 2.2 Hz). Anal. ($C_{22}H_{27}NO$) C, H, N.

Cell Transfection and Culture. L929sA cells stably expressing the human mGlu1a receptor were obtained as

described previously[48] and were cultured in GlutaMAX1 medium supplemented with 10% heat-inactivated dialyzed fetal calf serum, 0.1 mg/mL streptomycin sulfate, and 100 units/mL penicillin. CHO-dhfr$^-$ cells stably expressing the rat mGlu1a receptor were a kind gift from S. Nakanishi (Tokyo University, Tokyo, Japan) and were grown in Dulbecco's modified Eagle's medium with GlutaMAX1 with 10% heat-inactivated dialyzed fetal calf serum, 0.4 mM l-proline, 0.2 mg/mL streptomycin sulfate, and 200 units/mL penicillin. Cells were kept in an atmosphere of 37 °C and 5% CO_2.

Intracellular Ca^{2+} Response in Rat and Human mGlu1a Receptor Expressing Cells. Intracellular calcium ion levels ($[Ca^{2+}]_i$) in human mGlu1a receptor-expressing L929sA cells were measured using the fluorometric imaging plate reader (Molecular Devices, Sunnyvale, CA), as described previously.[48] The same procedure was followed for CHO-dhfr$^-$ cells expressing the rat mGlu1a receptor.

Human Liver Microsomal Incubations. Human liver samples obtained from five kidney donors from the Gasthuisberg Hospital, Leuven, Belgium, with the consent of the donor and hospital were used to make microsomal preparations according to a previously described method.[49] All incubations were conducted by shaking reaction mixtures (250 μL) containing 5 μM test compound, 1 mg of microsomal protein/mL, 0.5M Na−K-phosphate buffer pH 7.4, 1.6 mM magnesium chloride, 1.6 mM glucose-6-phosphate and 0.125 unit/mL of glucose-6-phosphate dehydrogenase. The mixture was preincubated at 37 °C for 5 min and followed by addition of 0.16 mM NADP to start the enzymatic reaction. After 15-min incubation, the reaction was terminated by addition of 500 μL of DMSO or acetonitrile. Two sets of controls were used in this experiment. The first set of controls contained all the components as described above, except that the active protein was substituted by heat-inactivated protein; the second set contained all the components but the enzyme was denatured by the addition of DMSO/acetonitrile before the addition of NADP (T_0 min sample). The precipitated material was removed by centrifugation at 1200g for 10 min. The supernatant was transferred into 96-well microplates prior to analysis by LC−MS. The metabolic stability was determined by comparing the peak areas of the parent compound measured at 15 min to that of 0 min and was calculated as follows:

$$\% \text{ remaining} = [\text{area } T_{15} \text{ active/average (area } T_0 \text{ active)}] \times 100$$

$$\% \text{ metabolized} = [100\% - \% \text{ remaining}]$$

The averaged areas of T_0 minute active duplicates are used for calculation. In certain instances whereby the areas decrease at T_0 active due to reasons of esterase, reductase, etc., the averaged T_0 boiled areas are taken for calculation. The chemical compound stability during the microsomal assay is determined with the boiled protein incubations.

Instrumentation. The HPLC system consisted of a Surveyor Solvent Platform, MS pump, and Surveyor autosampler. The system was interfaced to a ThermoFinnigan LCQ DecaXP ion-trap mass spectrometer equipped with an atmospheric pressure chemical ionization (APCI) source (Finnigan Mat, San Jose, CA). The mobile phase consisted of 10 mM aqueous ammonium acetate (95%), acetonitrile (5%) (solvent A), and acetonitrile (solvent B). The flow rate was maintained at 1.2 mL/min. The proportion of B was increased from 0% to 95% over 2.5 min. B was maintained at 95% until 4.5 min and the proportion of B reduced from 95% to 0% from 4.5 to 5 min. A 20 μL sample was injected in full-loop mode. The gradient elution of test compounds and metabolites was achieved on a BDS hypersil C-18 column (4.6 × 50 mm, 5 μm particle size) over a 6 min run time. The entire column eluent was directed to a pneumatically assisted APCI interface. Nitrogen was used both as the nebulizer gas at 85 psi and as the drying gas at a flow rate of 5 L/min and a temperature of 450 °C. The MS data capture was preformed from 1 to 5.5 min. The flow was diverted to waste before 1.5 min and after 5.5 min in order to prevent endogenous material from entering the source.

The mass spectrometer was operated in positive ion mode in a mass range of 100−1000 Da. The MS/MS spectra were acquired using the ion-trap operating in data-dependent scan mode, with events switching between the full scan for the mass range 100−1000 Da (used for quantitative analysis) and MS/MS-dependent scan mode fragmentation (used for qualitative metabolite identification). Helium was used as the collision gas for the tandem mass spectrometric experiments. Fragmentation was induced with a resonant excitation amplitude of 1.0−1.2 V, following isolation of the ion of interest over a given mass window of 5 Da. The ions for the MS/MS were automatically selected for peaks set with a threshold of 10^5 cps. All MS/MS experiments were performed using the ion charge control (ICC) facility to automatically adjust the accumulation time as the ion abundance changed. Instrument control and data acquisition and processing were performed using Xcalibur software version 1.3 (ThermoFinnigan, San Jose, CA).

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Supporting Information Available: Elemental analysis data for the compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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