Pharmacomodulations around the 4-Oxo-1,4-dihydroquinoline-3-carboxamides, a Class of Potent CB_2-Selective Cannabinoid Receptor Ligands: Consequences in Receptor Affinity and Functionality

Eric Stern,[†,‡] Giulio G. Muccioli,[‡] Barbara Bosier,[‡] Laurie Hamtiaux,[‡] Régis Millet,[†] Jacques H. Poupaert,[‡] Jean-Pierre Hénichart,[†] Patrick Depreux,[†] Jean-François Goossens,[§] and Didier M. Lambert*[,‡]

Institut de Chimie Pharmaceutique Albert Lespagnol, Université de Lille 2, EA 2692, 3 rue du Pr. Laguesse, B.P. 83, F-59006 Lille, France, Unité de Chimie Pharmaceutique et de Radiopharmacie, Ecole de Pharmacie, Faculté de Médecine, Université catholique de Louvain, 73 avenue E. Mounier UCL-CMFA (7340), B-1200 Bruxelles, Belgium, and Laboratoire de Chimie Analytique, EA 4034, Faculté des Sciences Pharmaceutiques et Biologiques, Université de Lille 2, 3 rue du Pr. Laguesse, B.P. 83, F-59006 Lille, France

Received April 3, 2007

CB_2 receptor selective ligands are becoming increasingly attractive drugs due to the potential role of this receptor in several physiopathological processes. Thus, the development of our previously described series of 4-oxo-1,4-dihydroquinoline-3-carboxamides was pursued with the aim to further characterize the structure−affinity and structure−functionality relationships of these derivatives. The influence of the side chain was investigated by synthesizing compounds bearing various carboxamido and keto substituents. On the other hand, the role of the quinoline central scaffold was studied by synthesizing several 6-, 7-, or 8-chloro-4-oxo-1,4-dihydroquinolines, as well as 4-oxo-1,4-dihydronaphthyridine and 4-oxo-1,4-dihydrocinnoline derivatives. The effect of these modifications on the affinity and functionality at the CB_2 receptor was studied and allowed for the characterization of new selective CB_2 receptor ligands.

Introduction

The cannabinoid CB_2 receptor, a G protein-coupled receptor (GPCR), is expressed throughout the immune cell system[1,2] and was recently described in the central nervous system (CNS) under both pathological[3] and physiological conditions.[4] Along with the CB_1 cannabinoid receptor,[5] they represent so far the two cloned GPCRs of the endocannabinoid system (ECS[a]). The ECS comprises, in addition to the two cannabinoid receptors, several endocannabinoids (2-arachidonoylglycerol, *N*-arachidonoylethanolamine) as well as the enzymes responsible for their production and inactivation (fatty acid amide hydrolases I and II, monoglyceride lipase, and *N*-acylethanolamine acid amidase).[6] The therapeutic potential of modulating the activity of the ECS is now well established, with selective receptor ligands or enzyme inhibitors being tested clinically or preclinically.[7,8] The interest for the CB_2 cannabinoid receptors has been growing recently, with proposed indications in alleviating pain[9,10] and inflammation,[11,12] cough,[13] and dermatitis[14] and treating cancers of different origins (glioblastomas,[15] lymphomas[16]). In light of these applications, the development of potent and selective CB_2 ligands results in powerful therapeutic tools devoid of CB_1 receptor-mediated psychotropic side effects. Quite surprisingly, only a limited number of CB_2 receptor selective ligands was described so far. SR-144528 (**1**), JTE-907, and Sch225336 are antagonist/inverse agonists based on a pyrazole, an oxoquinoline, and a phenylsulfonyl scaffold, respectively. On the other hand, CB_2 receptor agonists were developed based on diterpenes (HU-308, JWH-133 (**2**)) and indoles (AM1241, JWH-007, GW405833).[17,18] Along these lines, we previously described the synthesis, pharmacological characterization, and molecular modeling studies of a novel series of 4-oxo-1,4-dihydroquinoline-3-carboxamide derivatives acting as selective and potent CB_2 receptor agonists (e.g., *N*3-(1-(3,5-dimethyl)adamantyl)-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (ALICB179, **3**), Chart 1).[19]

Here, we report the synthesis and structure−activity relationship studies of new 4-oxo-1,4-dihydroquinoline derivatives that confirm the CB_2 selectivity of this class of compounds as well as the molecular modeling studies previously reported.[19] As shown in Chart 1, various structural modifications were realized using the previously reported **3** as template. Replacement of the 4-oxo-quinoline moiety by different naphthyridine isomers was also investigated (Chart 2). The new chiral compounds synthesized here confirm the described enantioselectivity of the interaction.[19] Interestingly enough, the [^{35}S]-GTPγS data showed that small changes in the position of the substituents around the 4-oxo-1,4-dihydroquinoline core result in modifications of the compounds functionality, suggesting that, similarly to the pyrazole derivatives, both agonist and antagonists/inverse agonist series can be developed from the 4-oxo-1,4-dihydroquinoline derivatives.

Results

Chemistry. The synthetic route to obtain the target 4-oxo-1,4-dihydroquinoline-3-carboxamide derivatives **10**−**25** was previously described[19] and is briefly outlined in Scheme 1. Compounds **10**−**25** were obtained by a coupling reaction between selected amines and 4-oxo-1,4-dihydroquinoline-3-carboxylic acids **9a**−**i**, using polystyrene-supported 1-hydroxy-1*H*-benzotriazole (HOBt) as coupling reagent, obtained in three steps following Gould−Jacobs' procedure.[20]

The target 2-substituted-4-oxo-1,4-dihydroquinoline-3-carboxamide derivatives **29**−**35** were obtained by a similar coupling reaction between amines and the desired 2-substituted quinoline-3-carboxylic acids **28a**,**b**, previously synthesized in three steps (Scheme 2). *N*-Alkylation of isatoic anhydride with 1-bromopentane in anhydrous *N*,*N*-dimethylformamide (DMF), in the presence of sodium hydride, gave 1-*n*-pentyl-1*H*-benzo-

* To whom correspondence should be addressed. Phone: +32-2-764-7347. Fax: +32-2-764-7363. E-mail: didier.lambert@uclouvain.be.

† Institut de Chimie Pharmaceutique Albert Lespagnol, Université de Lille 2.

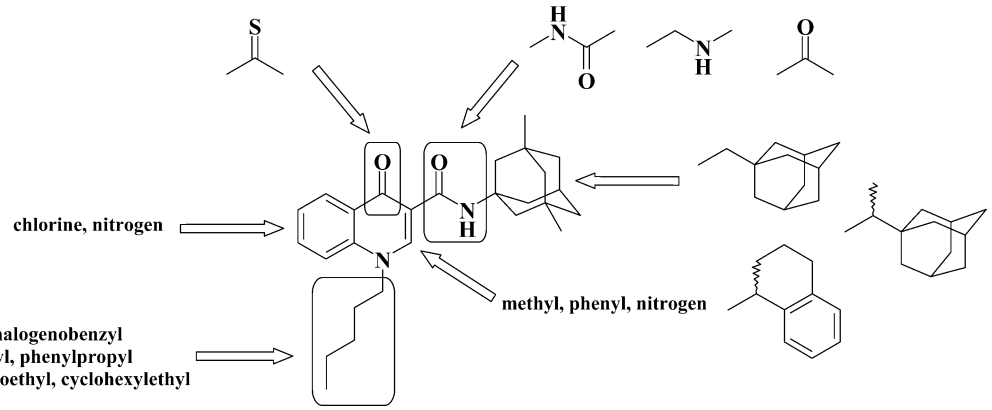
‡ Université catholique de Louvain.

§ Laboratoire de Chimie Analytique, Université de Lille 2.

[a] Abbreviations: ECS, endocannabinoid system; [^{35}S]-GTPγS, [^{35}S]-guanosine-5′-(γ-thio)-triphosphate; hCB_2, human cannabinoid receptor 2; CHO, chinese hamster ovarian cells.

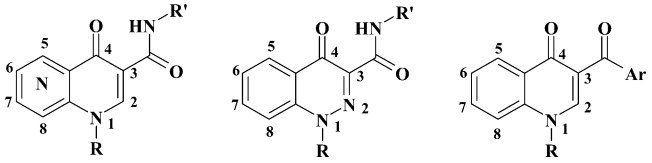
10.1021/jm070387h CCC: $37.00
Published on Web 10/04/2007

Chart 1. Structural Modifications Considered on the 4-Oxo-1,4-dihydroquinoline-4-carboxamide Template[a]



[a] Our lead compound, *N*3-(1-(3,5-dimethyl)adamantyl)-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (ALICB179, **3**), is shown.

Chart 2. General Structures of 4-Oxo-1,4-dihydronaphthyridine, 4-Oxo-1,4-dihydrocinnoline, and 3-Aroyl-4-oxo-1,4-dihydroquinoline Derivatives



[*d*][1,3]oxazine-2,4-dione (**26**).[21] Selected β-ketoesters reacted with **26** in anhydrous DMF in the presence of sodium hydride, yielding the desired 4-oxo-1-pentyl-2-substituted-1,4-dihydroquinoline-3-carboxylic acid ethyl esters **27a**,**b**.[22] Hydrolysis in 10% aqueous NaOH resulted in the corresponding 4-oxo-1-pentyl-2-substituted-1,4-dihydroquinoline-3-carboxylic acids **28a**,**b**.[23]

As shown in Scheme 3, "retro-amide" isomers **38**−**40** were synthesized starting from 4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxylic acid **9a** using a Curtius reaction in the presence of diphenylphosphorylazide (DPPA).[24] This reaction was conducted in *tert*-butanol in the presence of potassium *tert*-butanolate to obtain the corresponding amine derivative protected by a butoxycarbonyl moiety (**36**), which is easily cleaved in acidic conditions. Treatment of **36** with hydrochloric acid in isopropanol yielded the 3-amino-4-oxo-1,4-dihydroquinoline hydrochloride **37**. Addition of the desired acyl chloride, under classical conditions, lead to the corresponding carboxamide derivatives **38**−**40**.

3-Aminomethyl-4-oxo-1-pentyl-1,4-dihydroquinoline derivatives **42**−**44** were also synthesized starting from the carboxylic acid **9a** (Scheme 3). Compound **9a** was first converted into its carbaldehyde analogue **41**, using tributyltin hydride in the presence of tetrakis(triphenylphosphine)palladium(0) in dry toluene,[25] which was then engaged into a reductive amination reaction with selected amines in the presence of sodium cyanoborohydride in dry methanol to afford the target 3-aminomethyl-quinoline derivatives (**42**−**44**).[26]

1-Pentyl-4-thioxo-1,4-dihydroquinoline-3-carboxamide derivative **47** was obtained from 1-pentyl-4-thioxo-1,4-dihydroquinoline-3-carboxylic acid **46** using the same coupling procedure (Scheme 4). To obtain the 4-thioxo-1,4-dihydroquinoline nucleus, the 4-oxo-1-pentyl-1,4-dihydroquinoline-3-yl carboxylic acid ethyl ester **8a** was treated with phosphorus pentasulfide in pyridine furnishing its 4-thioxo isomer **45** with very good yield.[27] Hydrolysis by lithium hydroxide in a tetrahydrofurane/water mixture resulted in the corresponding 1-pentyl-4-thioxo-1,4-dihydroquinoline-3-carboxylic acid **46**.

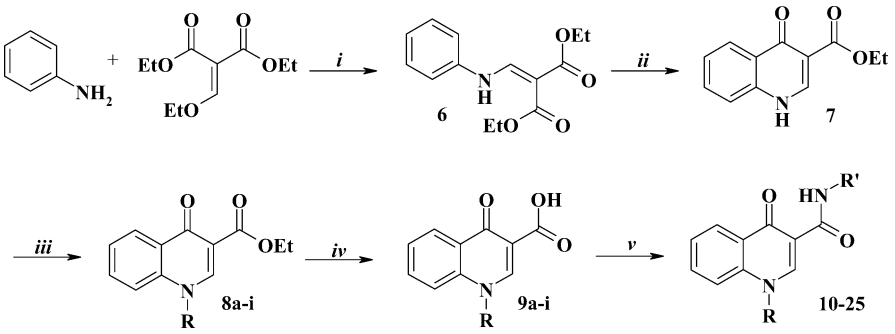
Chloro-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide derivatives **52**−**58** were synthesized by a general procedure similar to the method described earlier for the synthesis of **10**−**25** (Scheme 5) but starting from the corresponding chloroaniline.[28] Enantiopure forms of **55** and **56** (noted **59**−**62**) were obtained by enantiomeric separation with HPLC on polysaccharide-based chiral stationary phases (amylase carbamate derivatives, Chiralpak AD) used in normal phase mode by adapting an analytical procedure previously described.[29]

[1,5]-Naphthyridine-3-carboxamide (**67**) and [1,6]-naphthyridine-3-carboxamide (**68**) derivatives (Scheme 6) were synthesized by a general procedure similar to the synthetic approach used to obtain 4-oxo-1,4-dihydroquinoline-3-carboxamide derivatives **10**−**25** but starting from the corresponding aminopyridine.[30]

The [1,8]-naphthyridine derivative **71** was synthesized using the three-step procedure outlined in Scheme 7. 4-Oxo-1-pentyl-1,4-dihydro-[1,8]-naphthyridine-3-carboxylic acid ethyl ester **69** was first formed using a one-pot method involving 2-chloronicotinoyl chloride and dimethylaminoacrylate in dry acetonitrile. This first step provided an acyclic intermediate that was converted into the desired [1,8]-naphthyridine derivative **69** by addition of *n*-pentylamine.[31] Hydrolysis in aqueous NaOH yielded the corresponding 4-oxo-1-pentyl-1,4-dihydro-[1,8]-naphthyridine-3-carboxylic acid **70**, which was coupled with 1-amino-3,5-dimethyladamantane to afford the 4-oxo-1-pentyl-1,4-dihydro-[1,8]-naphthyridine-3-carboxamide **71**.

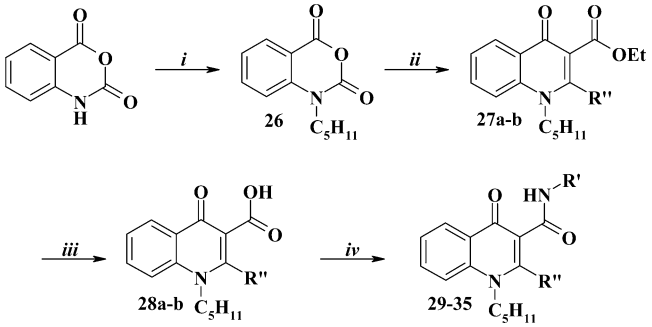
The cinnoline derivative **76** was obtained using a five-step synthetic route (Scheme 8). Diethylmalonate was added to a freshly synthesized phenyl diazonium chloride, obtained by action of sodium nitrite on aniline hydrochloride, in the presence of sodium acetate in ethanol to give the malonate derivative **72**, which was converted into its diacid analogue **73** by hydrolysis in aqueous NaOH.[32] In a one-pot procedure, the diacid **73** was quantitatively converted into diacyl chloride using thionyl chloride in 1,2-dichlorobenzene. After evaporation of the excess of thionyl chloride, and without isolation of the diacyl chloride intermediate, titanium tetrachloride was added to conclude the cyclization and to furnish the 4-oxo-1,4-dihydrocinnoline-3-carboxylic acid **74**. The introduction of the amide substituent was performed using the desired amine and *O*-benzotriazol-1-yl-tetramethyluronium hexafluorophosphate (HBTU) as coupling reactant using triethylamine in dry DMF, affording the 4-oxo-1,4-dihydrocinnoline-3-carboxamide **75**.[33] *N*-Alkylation of **75** with 1-bromopentane in anhydrous DMF, in the presence of sodium hydride, gave the desired 4-oxo-1-pentyl-1,4-dihydrocinnoline-3-carboxamide **76**.

Scheme 1. Synthesis of the 4-Oxo-1,4-dihydroquinoline-3-carboxamide Derivatives **10**−**25**[a]



[a] Reagents and conditions: (*i*) 100 °C, 91%; (*ii*) Ph−O−Ph, reflux, 77%; (*iii*) R-X, NaH, DMF, 90 °C, 50−96%; (*iv*) NaOH, EtOH, 100 °C, 65−90%; (*v*) R′-NH_2, PyBRoP, PS-HOBt (HL), DIEA, DMF, rt, 25−80%.

Scheme 2. Synthesis of the 2-Substituted-4-Oxo-1,4-dihydroquinoline-3-carboxamide Derivatives **29**−**35**[a]



[a] Reagents and conditions: (*i*) R-X, NaH, atm N_2, rt, 65%; (*ii*) R″−CO−CH_2−CO_2Et, NaH, DMF, 120 °C, 75−76%; (*iii*) NaOH, EtOH, 100 °C, 70−76%; (*iv*) R′-NH_2, PyBRoP, PS-HOBt (HL), DIEA, DMF, rt, 30−74%.

The synthetic route to obtain the target 1-alkyl-3-aroyl-1,4-dihydroquinolin-4-one derivatives **80**−**98** was previously described[34] and is outlined in Scheme 9. The key step of the 1-alkyl-3-aroyl-1,4-dihydroquinolin-3-one synthesis was the cyclization reaction of 2-((*Z*)-3-oxo-3-aryl-propenylamino)-benzoic acid methyl esters **78a**−**g** leading to the 3-aroyl-quinolin-4-one derivatives **79a**−**g**. This reaction was carried out by refluxing **78a**−**g** in a methanol/phenyl ether mixture (1:8 ratio) in the presence of sodium methanolate. The final *N*-alkylation leading to the derivatives **80**−**98** was performed using halogenoalkyl derivatives in dry DMF in the presence of sodium hydride.

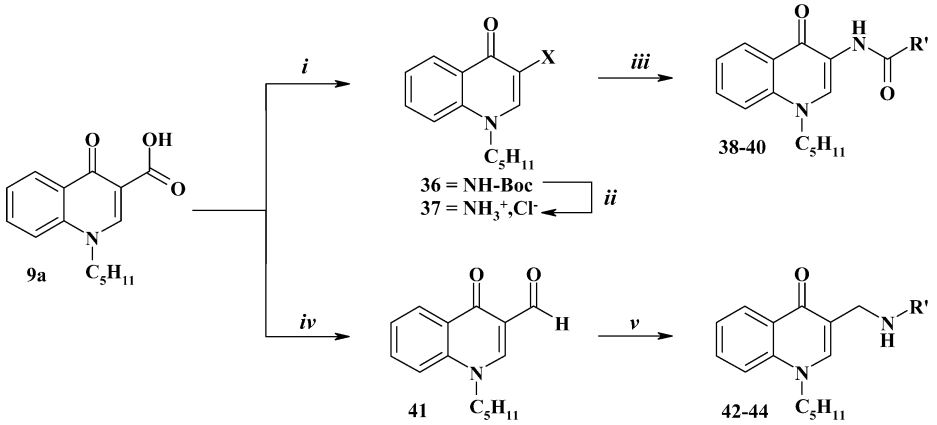
Pharmacology. Structure−**Affinity Relationships.** The 4-oxo-1,4-dihydroquinoline, 4-oxo-1,4-dihydronaphthyridine, and 4-oxo-1,4-dihydrocinnoline derivatives were first screened at 10 μM for their affinity toward the *h*CB_2 and *h*CB_1 cannabinoid receptors in a competitive binding experiment as previously described.[19] *h*CB_2−CHO or *h*CB_1−CHO cell membranes were used in conjunction with [^{3}H]-CP-55,940 and [^{3}H]-SR-141716A as radioligands for the *h*CB_2 and *h*CB_1 cannabinoid receptors, respectively. The results expressed as the displacement percentages of the radioligand from its binding site are summarized in Tables 1−3. The K_i values at the CB_2 cannabinoid receptor were then determined for the compounds exhibiting a displacement of the specific binding superior to 60%. Taken together, these results indicated that the tested compounds possess fair to good selectivity for the *h*CB_2 cannabinoid receptors.

Our initial studies showed that 4-oxo-1,4-dihydroquinoline-3-carboxamide derivatives constitute a suitable template in the design of potent and selective CB_2 cannabinoid ligands.[19] To define the structural elements required for the cannabinoid receptor affinity of our derivatives, different pharmacomodulations starting from our leading compound **3** (K_i CB_2 = 15.8 nM)[19] have been carried out, as shown in Chart 1.

The adopted strategy was to prepare analogues by stepwise introduction of structural modifications on positions 1−3 and 5−8 of the 4-oxo-quinoline template of compound **3**. Replacement of the *N*1-*n*-pentyl side chain by various aromatic, arylalkyl, cycloalkyl-alkyl, or morpholino-alkyl moieties was investigated. We previously showed that introducing a benzyl group on the *N*1-nitrogen (cmpd **31** in ref 19, K_i = 664 nM) instead of the *n*-pentyl moiety resulted in a reduced affinity (44-fold) for the CB_2 cannabinoid receptor.[19] Similarly, the introduction of a 4-halogeno-benzyl substituent resulted in the same reduction of affinity, as shown with 4-chloro- (**11**) and 4-bromobenzyl (**12**)-substituted derivatives, which only displaced 48% and 30%, respectively, of the [^{3}H]-CP-55,940 bound to the *h*CB_2 receptor. Only the 4-fluorobenzyl derivative (**10**) preserves a nanomolar affinity (K_i = 83 nM). Increasing the distance between the phenyl and the 4-oxo-quinoline resulted in an enhancement of the affinity as shown by **13** (phenylethyl) and **14** (phenylpropyl), with K_i values of 333 nM and 160 nM, respectively. Replacement of the 2-phenylethyl substituent (**13**) by its nonaromatic analog 2-(cyclohexyl)ethyl resulted in a lower affinity, as shown with compound **15**, which only displaced 38% of radioligand. Finally, the introduction of a 2-(morpholin-4-yl)ethyl substituent (**16**−**18**), mimicking the morpholinoethyl substituent characterizing WIN-55,212-2 (**4**), did not improve the affinity. Indeed **16**, with a K_i value of 221 nM, has a 14-times lower affinity than the *n*-pentyl analogue **3**. To confirm the effect observed with the 2-(morpholin-4-yl)ethyl substituent, we also synthesized compounds **17** and **18** bearing different carboxamido substituents, 2-phenylethyl (**17**) and (−)-1-phenylethyl (**18**), respectively. With these two amide substituents too a marked decrease in affinity has been observed in comparison with the *n*-pentyl analogs previously reported.[19] For example, with the (−)-1-(phenyl)ethyl substituent on the carboxamido link, we reported for the *N*1-*n*-pentyl derivative an affinity of 37 nM (cmpd **32*R*** in ref 19), whereas the K_i value of the *N*1-2-(morpholin-4-yl)ethyl derivative (**18**) is up to 2000 nM. Taken together, these results clearly demonstrate that the affinity is very sensitive to changes in the *N*1-substituent. Thus, because the *n*-pentyl residue appears to be the preferred one, the subsequent pharmacomodulations were performed while keeping this *N*1-substituent constant.

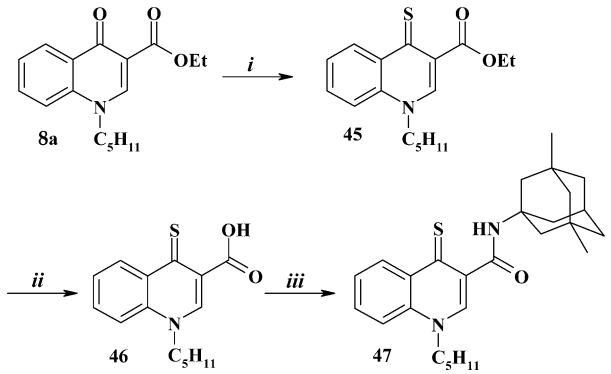
The second step in our strategy was to study the effect of substituting the position-2 of the 4-oxo-quinoline template. A methyl or a phenyl group were introduced at this position leading to compounds **29** and **30**, which possess K_i values of 200 nM and 119 nM, respectively. It seemed, therefore, that the

Scheme 3. Synthesis of the Carboxylic Acid (4-Oxo-1,4-dihydroquinolin-3-yl)-amide Derivatives **38**−**40** and the 3-Aminomethyl-1*H*-quinolin-4-one Derivatives **42**−**44**[a]



[a] Reagents and conditions: (*i*) DPPA, *t*-BuOK, *t*-BuOH, atm N_2, reflux, 65%; (*ii*) HCl 6 N, isoOH, rt, 70%; (*iii*) R′−CO−Cl, Et_3N, CH_2Cl_2, atm N_2, 0 °C, 35−56%; (*iv*) (a) $SOCl_2$, CH_2Cl_2; (b)$HSnBu_3$, $Pd(PPh_3)_4$, toluene, atm N_2, rt, 65%; (*v*) (a) R′-NH_2, Et_3N, MeOH, atm N_2, 50 °C; (b) $NaBH_3CN$, Et_3N, MeOH, atm N_2, 50 °C, 32−35%.

Scheme 4. Synthesis of the 4-Thioxo-1,4-dihydroquinoline-3-carboxamide Derivative **47**[a]



[a] Reagents and conditions: (*i*) P_4S_{10}, pyridine, reflux, 94%; (*ii*) LiOH, THF/H_2O, rt, 83%; (*iii*) 1-amino-3,5-dimethyladamantane, PyBRoP, PS-HOBt (HL), DIEA, DMF, rt, 60%.

introduction of a substituent, leading to a marked reduction in affinity (compared to **3**), is unfavorable. To confirm this hypothesis, compounds **31**−**35** have been synthesized and are characterized by the presence of a substituent in position-2 and by selected carboxamido substituents known to impart good affinity in our series. In all cases, the affinity was strongly decreased. Taken together, these data demonstrate that the introduction of a substituent in position 2 results in a drastic reduction of the affinity for the CB_2 cannabinoid receptor.

Optically active 4-oxo-1,4-dihydroquinoline-3-carboxamide derivatives previously reported showed a stereoselectivity in the binding at the *h*CB_2 receptor.[19] In accordance with our previous results, the eutomers of this novel series exhibit about 10-fold higher affinity than the distomers. For instance, (+)-*N*3-(1-(1,2,3,4-tetrahydronaphthyl))-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (**19**) possesses a K_i value of 41.7 nM, whereas the affinity of the (−)-enantiomer (**20**) is markedly reduced (K_i = 1010 nM). Because the adamantyl substituent was shown to favor the affinity, we decided to combine this structural requirement with a chiral center between the carboxamido function and the 1-adamantyl group (**23**). The steric constraint and the distance imposed by the methyl group on the methylene spacer does not affect the affinity as shown by compound **23** (K_i = 28.5 nM), which was first assayed as racemate. The adamantylmethyl derivative (**22**) was also synthesized as the comparison compound and showed a slight decrease of affinity, with a K_i value of 50.6 nM.

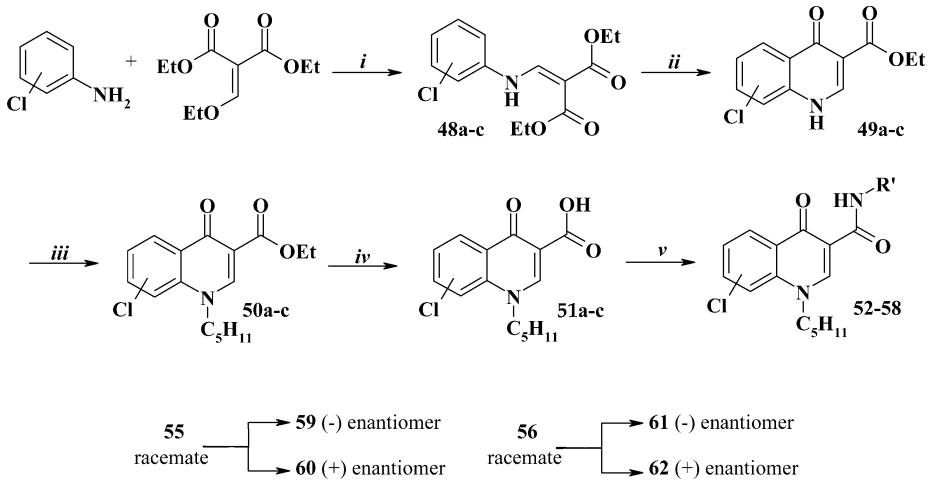
The two enantiopure forms of **23**, referenced as **24** and **25**, were obtained as recently described[29] and showed an affinity of 14.0 nM and 202 nM, respectively. These results highlight a stereoselective ligand−receptor interaction regardless of the nature of the amide substituent. The affinity of **24** for the CB_1 receptor was also determined to further assess the selectivity of this potent CB_2 cannabinoid receptor ligand. A K_i value of 416 nM, resulting in a selectivity ratio for the CB_2 cannabinoid receptor of 30, has been determined.

To investigate the hypothesis previously suggested by molecular modeling studies, that is, **3** interacts with the *h*CB_2 receptor through a combination of hydrogen bonds with the residue Ser-193 and aromatic/hydrophobic interactions,[19] compounds with different modifications of the carboxamide link were synthesized. The amide link was first replaced by its "retro-amide" isomer, giving compound **38**. This modification did not elicit a clear effect on the affinity, as **3** and **38** possess affinities of the same magnitude (K_i value of 15.8 nM and 25.5 nM, respectively). The carbonyl group of the amide link was also replaced by a methylene, resulting in "reduced-analogues" of the amide (**42**−**44**). This modification induced in a dramatic reduction in affinity (up to 100-fold), as illustrated by compound **42** (K_i = 1670 nM). These results support the importance of the amide/Ser-193 hydrogen bond. The similar affinities found for compounds **38** and **3** could be explained by the establishment of a hydrogen bond between the amide hydrogen atom of **3** and the Ser-193 hydroxyl oxygen atom.

Recently, Muccioli and co-workers showed, for some selective CB_1 imidazolidine-2,4-diones, that the introduction of a sulfur atom resulted in an enhanced affinity.[35−37] Here, the oxygen atom replacement by a sulfur atom, yielding the 4-thioxo-quinoline derivative (**47**), did not modify the affinity for the *h*CB_2 receptor because **47** possesses a K_i value of 18.2 nM compared to 15.8 nM for the oxo analogue (**3**).

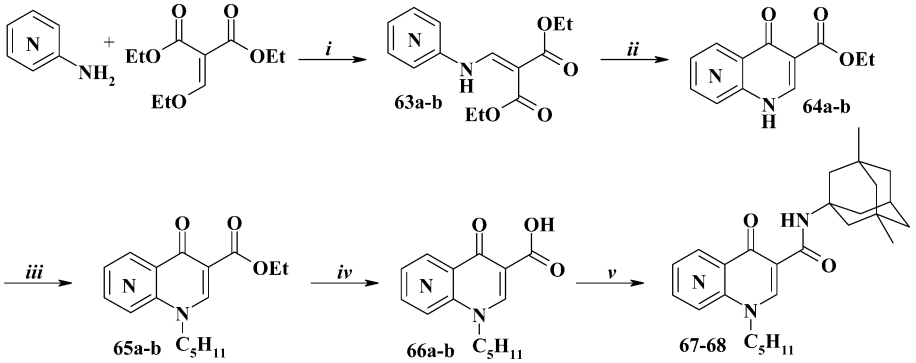
It is well-established that the presence of halogen atoms on the structure of cannabinoid ligands represents an important requirement to increase the affinity (e.g. **1**, tricyclic pyrazoles, AM630). Besides the effect of introducing such halogen on the N_1-benzyl moiety (**10**−**12**), a set of chloro analogs of **3** were synthesized to study the effect of introducing a halogen atom on the 4-oxo-quinoline moiety (**52**−**58**, Table 2). Introduction of a chlorine in position 6 (**52**) or 8 (**54**) resulted in a moderate reduction of the affinities, K_i = 54.6 nM or K_i = 27.4 nM, respectively. However, the introduction of a chlorine atom in

Scheme 5. Synthesis of the Chloro-4-oxo-1,4-dihydroquinoline-3-carboxamide Derivatives **52**−**58**[a]



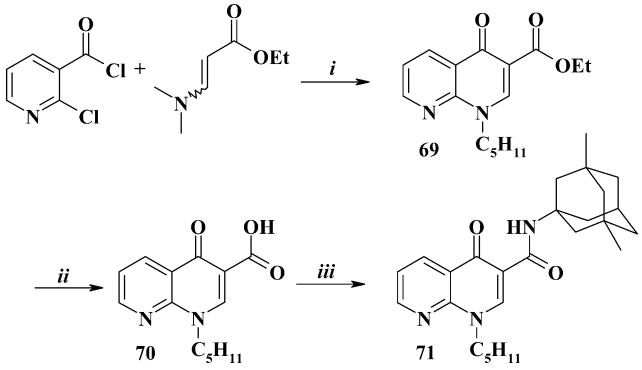
[a] Reagents and conditions: (*i*) 100 °C, 70−91%; (*ii*) Ph−O−Ph, reflux, 72−83%; (*iii*) R-X, NaH, DMF, 90 °C, 50−96%; (*iv*) NaOH, EtOH, 100 °C, 65−90%; (*v*) R′-NH_2, PyBRoP, PS-HOBt (HL), DIEA, DMF, rt, 25−80%.

Scheme 6. Synthesis of the 4-Oxo-1,4-dihydro-[1,5]-naphthyridine-3-carboxamide Derivative **67** and the 4-Oxo-1,4-dihydro-[1,6]-naphthyridine-3-carboxamide Derivative **68**[a]



[a] Reagents and conditions: (*i*) toluene, reflux, 90−95%; (*ii*) Ph−O−Ph, reflux, 85−90%; (*iii*) C_5H_{11}−Br, NaH, DMF, 90 °C, 85%; (*iv*) NaOH, EtOH, 100 °C, 70−75%; (*v*) 1-amino-3,5-dimethyladamantane, PyBRoP, PS-HOBt (HL), DIEA, DMF, rt, 25−30%.

Scheme 7. Synthesis of the 4-Oxo-1,4-dihydro-[1,8]-naphthyridine-3-carboxamide Derivative **71**[a]



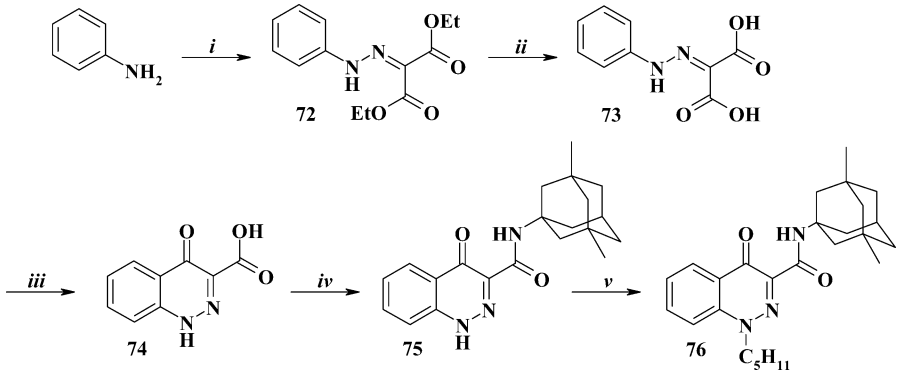
[a] Reagents and conditions: (*i*) (a) Et_3N, acetonitrile, atm N_2, reflux; (b) C_5H_{11}−NH_2, Et_3N, acetonitrile, atm N_2, reflux, 60%; (*ii*) NaOH, EtOH, 100 °C, 74%; (*iii*) 1-amino-3,5-dimethyladamantane, PyBRoP, PS-HOBt (HL), DIEA, DMF, rt, 40%.

position 7 of the quinoline template appears to be the more favorable substitution, with **53** showing a K_i value of 5.3 nM. The structure−affinity relationships on the introduction of the chlorine were also confirmed with other carboxamido-substituted quinoline derivatives (**55**−**62**). For instance, when considering the (−)-1-(1-adamantyl)ethyl derivatives **59** and **61**, the 7-chloro derivative **61** showed an increased affinity compared to the 6-chloro derivative **59** (K_i values of 26.1 nM and 235 nM, respectively). Because **61** displaced over 90% of the radioligand bound to the CB_1 receptor, the K_i value was also determined and found to be of 615 nM, over 1 order of magnitude higher than the CB_2 receptor affinity.

Since a recent series of [1,8]-naphthyridine were published as potent CB_2-selective cannabinoid receptor ligands,[38] the influence of the second nitrogen atom present in the naphthyridine nuclei was investigated with the syntheses of the [1,5]-, [1,6]-, and [1,8]-naphthyridine derivatives of **3** (compounds **67**, **68**, and **71**, respectively) as well as the cinnoline derivative **76** (Table 2). Binding data revealed that the introduction of a nitrogen in position 5 (**67**, K_i = 259 nM) resulted in a decrease of the affinity (16-fold), whereas the [1,6]- (**68**, K_i = 30.9 nM) and [1,8]-naphthyridines (**71**, K_i = 23.5 nM) gave affinities of the same magnitude compared to that of **3**. Finally, the cinnoline **76** exhibits a K_i value of 93.0 nM.

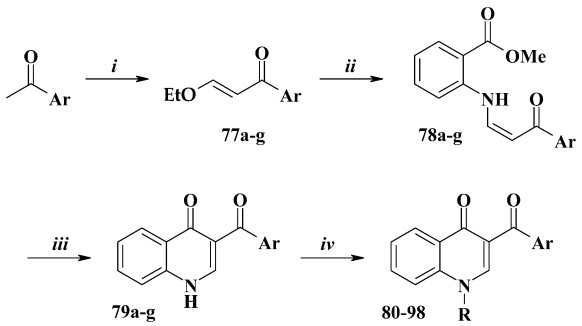
We next decided to keep the 4-oxo-1,4-dihydroquinoline template constant and to replace the carboxamido link by a ketone link, similar to the one present in **4**. As for the amide series, various structural modifications have been introduced, starting with the substituent linked on the quinoline *N*1-position. Different alkyl, aryl-alkyl, and cycloalkyl-alkyl were branched on this new 3-(naphth-1-oyl)-4-oxo-1,4-dihydroquinoline template. As shown in Table 3, the substitution of the *N*1-nitrogen was mandatory to bind to the CB_2 cannabinoid receptor because **79a** (at 10 μM) only displaced 31% of the radioligand from its

Scheme 8. Synthesis of the 4-Oxo-1,4-dihydro-cinnoline-3-carboxamide Derivative **76**[a]



[a] Reagents and conditions: (*i*) (a) HCl 12 N, rt, quant; (b) $NaNO_2$, H_2O, 0 °C; (c) diethylmalonate, AcONa, H_2O, EtOH, 0 °C to rt, 95%; (*ii*) NaOH, EtOH, 100 °C, 81%; (*iii*) (a) $SOCl_2$, 1,2-dichlorobenzene, 70 °C; (b) $TiCl_4$, 1,2-dichlorobenzene, 90 °C, 65%; (*iv*) 1-amino-3,5-dimethyladamantane, HBTU, Et_3N, DMF, rt, 68%; (*v*) C_5H_{11}−Br, NaH, DMF, 90 °C, 40%.

Scheme 9. Synthesis of the 3-Aroyl-1,4-dihydroquinolin-4-one Derivatives **80**−**98**[a]



[a] Reagents and conditions: (*i*) (a) EtONa, Et_2O, rt; (b) C_2H_5−Br, DMF, rt, 39−85%; (*ii*), methyl anthranylate, $ZnCl_2$, THF, rt, 40−84%; (*iii*), MeONa, MeOH/Ph−O−Ph (1/8), 120 °C or reflux, 37−66%; (*iv*) R-X, NaH, DMF, 90 °C, 17−68%.

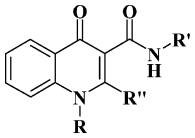
binding site. A first set of 11 compounds variously substituted in position 1 was synthesized (**80**−**90**). In this series, as for the carboxamide derivatives, the highest CB_2 affinity was obtained with an *n*-pentyl chain (**81**; K_i = 154 nM). This compound possesses a strong CB_2 selectivity because it only displaced 56% of the [^{3}H]-SR-141716A CB_1 specific binding at 10 μM. Replacement of this alkyl chain by a benzyl (**83**, K_i = 656 nM) or a benzyl substituted by a chlorine (**85**, K_i = 1120 nM) or bromine (**86**, K_i = 966 nM) resulted in reduction of the CB_2 affinity. Note that the 4-fluorobenzyl derivative possesses a higher affinity than the other benzyl derivatives (**84**, K_i = 225 nM). In addition, the presence of a 4-halogenated-benzyl moiety on the *N*1-position of the quinoline nucleus results in an increased displacement of the [^{3}H]-SR-141716A CB_1 specific binding (e.g., **84** at 10 μM displaced 70% of [^{3}H]-SR-141716A binding). Thus, the K_i value of **84** at the CB_1 receptor was determined and found to be higher than 2000 nM. However, the significance of this selectivity is reduced by the lower CB_2 affinities of these ketone derivatives.

Increasing the benzyl methylene spacer into an ethyl (**87**) or a propyl (**88**) did not result in an enhancement of the affinity. Replacement of the aromatic moiety of 2-(phenyl)ethyl by a 2-cyclohexylethyl (**89**, K_i = 1670 nM) or by a 2-(morpholin-4-yl)ethyl (**90**) led to a loss of affinity. By keeping the *N*1-*n*-pentyl side chain constant, a library of compounds with various aroyl substituents in position 3 of the quinoline template has been developed. The 1-naphthyl (**81**, K_i = 154 nM) moiety proved to be more favorable compared to its 2-naphthyl isomer (**91**, K_i = 1288 nM) or the bulkier 9-anthracenyl (**98**, K_i = 1500 nM). Similarly, replacing the naphthyl moiety by a phenyl one (**92**, K_i = 446 nM) did not improve the affinity. And finally, substitution of the phenyl with polar substituents (**93**−**96**) induced in all cases a decrease in the affinity toward the CB_2 cannabinoid receptor. Finally, as the ketone derivatives possess lower affinities than their carboxamide analogues, it appears that, in this quinoline chemical series, the presence of an H-bond donor/acceptor group results in increased CB_2 affinity.

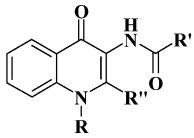
Structure−Functionality Relationships. The derivatives functionality was investigated by using a [^{35}S]-GTPγS binding assay as previously described.[37] This assay constitutes a functional measure of the direct interaction between the receptor and the G protein, the first step in the activation of GPCRs. Although the first series of 4-oxo-quinoline-3-carboxamide derivatives behaved as agonists,[19] quite unexpected results were obtained with the new derivatives described here, which comprised agonists, antagonists, and inverse agonists compounds (Table 4).

Although increasing the spacer length between the quinoline moiety and the phenyl from 1 (cmpd **31** in ref 19) to 3 (**14**) methylenes resulted in an enhanced affinity, the functionality of the resulting 3-phenylpropyl is also affected because **14** behaved as a neutral antagonist rather than as agonist. An interesting switch in functionality was also observed when a phenyl substituent was introduced in position 2 of the quinoline. Indeed, **30** and **35** both behaved as inverse agonists at the CB_2 receptor decreasing the [^{35}S]-GTPγS binding by 75%, while their unsubstituted analogues, **30**[39] and **28** in ref 19, activate the receptor. Similarly, compound **47**, characterized by a 4-thioxoquinoline template, significantly decreased the [^{35}S]-GTPγS binding (65% compared to control). Analogously, the introduction of a chlorine in position 6 (**52**) or 7 (**53**) of the *N*3-(1-(3,5-dimethyl)adamantyl)-quinoline-3-carboxamide moiety completely modifies the derivatives functionality, as these two compounds strongly reduced the [^{35}S]-GTPγS binding, thus acting as inverse agonists of the CB_2 receptor (49% and 51% of control, respectively). On the contrary, the 8-chloro-substituted **54** retained an agonist profile (187% of control). The introduction of an additional nitrogen in the quinoline nucleus, leading to [1,5]-, [1,6]-, and [1,8]-naphthyridine (**67**, **68**, and **71**, respectively), did not influence the functionality because all three compounds kept their agonist profile, with some changes in the efficacy though because **68** and **71** act as partial agonists. However, introduction of the nitrogen in position 2 as for the cinnoline **76**, resulted in a neutral antagonist because no significant stimulation of the [^{35}S]-GTPγS binding was observed.

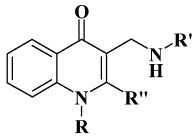
Table 1. Structure and Binding Data of Compounds **10**−**25**, **29**−**35**, **38**−**40**, **42**−**44**, and **47** and Reference Cannabinoid Ligands on *h*CB_1 and *h*CB_2 Cannabinoid Receptors[a]



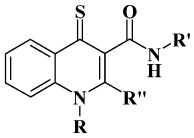
10-25, 29-35



38-40



42-44



47

cmpd	R	R″	R′	% of displacement *h*CB_1-R	% of displacement *h*CB_2-R	K_i (nM) *h*CB_2-R
10	4-fluorobenzyl	H	1-(3,5-dimethyl)adamantyl	59.3 ± 2.9	93.2 ± 1.1	83.4 ± 6.9
11	4-chlorobenzyl	H	1-(3,5-dimethyl)adamantyl	38.7 ± 2.7	48.1 ± 1.8	N.D.
12	4-bromobenzyl	H	1-(3,5-dimethyl)adamantyl	<10	30.5 ± 1.6	N.D.
13	2-phenylethyl	H	1-(3,5-dimethyl)adamantyl	<20	95.8 ± 1.4	333 ± 51
14	3-phenylpropyl	H	1-(3,5-dimethyl)adamantyl	<10	101.2 ± 2.5	160 ± 21
15	2-cyclohexylethyl	H	1-(3,5-dimethyl)adamantyl	<10	38.8 ± 2.4	N.D.
16	2-(morpholin-4-yl)ethyl	H	1-(3,5-dimethyl)adamantyl	<10	95.6 ± 1.3	221 ± 38
17	2-(morpholin-4-yl)ethyl	H	2-phenylethyl	<10	46.7 ± 3.7	N.D.
18	2-(morpholin-4-yl)ethyl	H	(−)-1-phenylethyl	<10	66.5 ± 1.1	>2000
19	pentyl	H	(+)-1-(1,2,3,4-tetrahydronaphthyl)	82.1 ± 4.0	98.0 ± 1.6	41.7 ± 0.4
20	pentyl	H	(−)-1-(1,2,3,4-tetrahydronaphthyl)	44.5 ± 5.3	90.9 ± 0.9	1010 ± 71
21	2-(morpholin-4-yl)ethyl	H	1-adamantyl	<10	101.2 ± 5.1	152 ± 30
22	pentyl	H	1-(adamantyl)methyl	36.7 ± 3.6	87.2 ± 1.8	50.6 ± 5.2
23	pentyl	H	(±)-1-(adamantyl)ethyl	72.2 ± 0.7	99.1 ± 1.5	28.5 ± 1.4
24	pentyl	H	(−)-1-(adamantyl)ethyl	83.6 ± 6.6	101.0 ± 1.4	14.0 ± 0.7
25	pentyl	H	(+)-1-(adamantyl)ethyl	31.0 ± 1.8	64.3 ± 3.5	202 ± 65
29	pentyl	methyl	1-(3,5-dimethyl)adamantyl	39.8 ± 5.8	96.7 ± 1.3	200 ± 13
30	pentyl	phenyl	1-(3,5-dimethyl)adamantyl	40.0 ± 4.1	97.2 ± 0.5	119 ± 8
31	pentyl	methyl	2-phenylethyl	<20	57.3 ± 3.5	N.D.
32	pentyl	methyl	(−)-1-(phenylethyl)	27.2 ± 4.3	91.7 ± 3.2	663 ± 105
33	pentyl	methyl	(−)-1-(2-naphthyl)ethyl	<20	62.6 ± 2.5	>2000
34	pentyl	methyl	(−)-1-(1-naphthyl)ethyl	23.6 ± 4.3	70.4 ± 3.1	>3000
35	pentyl	phenyl	1-adamantyl	29.1 ± 4.5	94.9 ± 1.8	338 ± 29
38	pentyl	H	1-adamantyl	52.3 ± 3.3	99.9 ± 0.1	25.5 ± 1.3
39	pentyl	H	2-phenylethyl	28.1 ± 4.8	83.4 ± 1.4	1130 ± 102
40	pentyl	H	1-naphthyl	59.0 ± 3.5	97.4 ± 1.4	265 ± 12
42	pentyl	H	1-adamantyl	27.0 ± 4.0	81.3 ± 2.5	1670 ± 163
43	pentyl	H	2-phenylethyl	24.0 ± 6.3	25.9 ± 4.6	>4000
44	pentyl	H	(±)-1-(1,2,3,4-tetrahydronaphthyl)	41.0 ± 3.5	63.9 ± 2.1	>4000
47	pentyl	H	1-(3,5-dimethyl)adamantyl	35.1 ± 3.0	95.7 ± 9.9	18.2 ± 2.8
			Reference Compounds			
1				N.D.	N.D.	60.2 ± 5.5[b]
2				N.D.	N.D.	20.3 ± 2.6[b]
3				54.6 ± 2.4	95.6 ± 5.4	15.8 ± 1.4[b]
4				N.D.	N.D.	9.1 ± 0.8[b]
5[c]				N.D.	N.D.	15.4 ± 1.4[b]

[a] The K_i values were obtained from nonlinear analysis of competition curves using [^{3}H]-CP-55,940 as radioligand. Data are mean ± SEM of three to four experiments performed in duplicate. [b] From ref 19. [c] CP-55,940.

These observations open the way for further molecular pharmacology research in terms of which key amino acid residues are involved in the binding and the efficacy of these compounds in the cannabinoid CB_2 receptor.

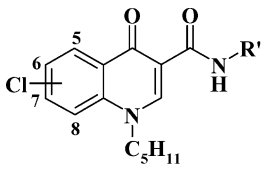
Conclusion

The present study allowed us to extend the structure−affinity relationship studies of the 4-oxo-1,4-dihydroquinolines, a class of potent and selective CB_2 cannabinoid receptor ligands. Reversing the amide bond or introducing an additional nitrogen in the quinoline nucleus, leading to [1,6]-naphthyridine or [1,8]-naphthyridine, did not elicit major changes in the affinity of the compounds. However, the consequences of such modifications deeply affected the functionality of these ligands. Indeed, small changes in the compound structure, like the replacement of the 4-oxo-dihydroquinoline by a 4-thioxo-1,4-dihydroquinoline or the introduction of a chlorine atom, resulted in the switch of the functionality from agonist to antagonist or inverse agonist. This information will be very useful in the future development of this class of derivatives, allowing for the targeted synthesis of potent and selective agonist or antagonist/inverse agonist of the CB_2 cannabinoid receptor.

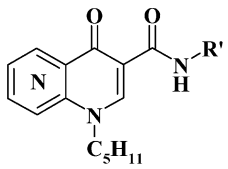
Experimental Section

Chemistry. All commercial reagents and solvents were used without further purification. Analytical thin layer chromatography was performed on precoated Kieselgel 60F_{254} plates (Merck); the spots were located by UV (254 and 366 nm) and with iodine; R_f values are given for guidance. Silica gel 60 230−400 mesh purchased from Merck was used for column chromatography. Preparative thick-layer chromatography (PTLC) was performed using silica gel from Merck, the compounds were extracted from silica gel by the following solvent system: CH_2Cl_2/MeOH 7:3 (v/v). All melting points were measured with a Büchi 535 capillary apparatus and remain uncorrected. ^{1}H NMR spectra were obtained using a Brücker 300 MHz spectrometer, chemical shifts (δ) were expressed in ppm relative to the tetramethylsilane peak used as internal standard, J values are in Hertz, and the splitting patterns were designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet. IR spectra were determined with a Brücker Vector 22 spectrometer on a germanium crystal. APCI$^+$ (atmospheric pressure

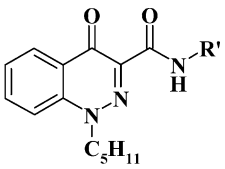
Table 2. Structure and Binding Data of Compounds **52**−**62**, **67**, **68**, **71**, and **76** on *h*CB_1 and *h*CB_2 Cannabinoid Receptors[a]



52-62



67-68, 71

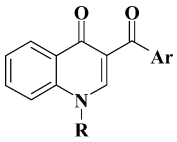


76

cmpd		R′	% of displacement *h*CB_1-R	% of displacement *h*CB_2-R	K_i (nM) *h*CB_2-R
52	6-chloro	1-(3,5-dimethyl)adamantyl	<20	86.7 ± 0.2	54.6 ± 8.2
53	7-chloro	1-(3,5-dimethyl)adamantyl	59.6 ± 5.1	105.8 ± 9.0	5.3 ± 0.7
54	8-chloro	1-(3,5-dimethyl)adamantyl	23.8 ± 13.1	98.7 ± 2.6	27.4 ± 9.1
55	6-chloro	(±)-1-(adamantyl)ethyl	42.4 ± 0.9	81.8 ± 13.0	222 ± 32
59	6-chloro	(−)-1-(adamantyl)ethyl	56.3 ± 6.6	87.7 ± 7.7	235 ± 77
60	6-chloro	(+)-1-(adamantyl)ethyl	<20	97.2 ± 0.5	144 ± 45
56	7-chloro	(±)-1-(adamantyl)ethyl	88.2 ± 5.1	102.1 ± 2.8	41.1 ± 3.4
61	7-chloro	(−)-1-(adamantyl)ethyl	91.6 ± 6.0	102.4 ± 1.3	26.1 ± 3.5
62	7-chloro	(+)-1-(adamantyl)ethyl	22.4 ± 3.8	92.9 ± 6.5	265 ± 66
57	6-chloro	(±)-1-(1,2,3,4-tetrahydronaphthyl)	60.4 ± 1.6	98.2 ± 4.7	506 ± 88
58	6-chloro	(+)-1-(1,2,3,4-tetrahydronaphthyl)	59.1 ± 4.3	92.8 ± 2.4	121 ± 5.6
67	[1,5]-naphthyridine	1-(3,5-dimethyl)adamantyl	26.3 ± 5.6	93.4 ± 7.0	259 ± 22
68	[1,6]-naphthyridine	1-(3,5-dimethyl)adamantyl	30.0 ± 11.8	95.0 ± 2.1	30.9 ± 3.9
71	[1,8]-naphthyridine	1-(3,5-dimethyl)adamantyl	50.0 ± 11.5	101.8 ± 1.4	23.5 ± 1.8
76	cinnoline	1-(3,5-dimethyl)adamantyl	26.1 ± 8.6	94.6 ± 0.4	93.0 ± 13.0

[a] The K_i values were obtained from nonlinear analysis of competition curves using [^{3}H]-CP-55,940 as radioligand. Data are mean ± SEM of three to four experiments performed in duplicate.

Table 3. Structure and Binding Data of Compounds **79a** and **80**−**98** on *h*CB_1 and *h*CB_2 Cannabinoid Receptors[a]



79a, 80-98

cmpd	R	Ar	% of displacement *h*CB_1-R	% of displacement *h*CB_2-R	K_i (nM) *h*CB_2-R
79a	H	1-naphthyl	<10	31.0 ± 4.3	N.D.
80	butyl	1-naphthyl	33.0 ± 3.5	77.7 ± 5.7	1550 ± 529
81	pentyl	1-naphthyl	55.8 ± 4.3	97.0 ± 3.8	154 ± 18
82	hexyl	1-naphthyl	35.8 ± 3.2	89.5 ± 0.8	582 ± 60
83	benzyl	1-naphthyl	47.1 ± 2.3	100.2 ± 4.2	656 ± 19
84	4-fluorobenzyl	1-naphthyl	70.8 ± 11.7	111.6 ± 0.3	225 ± 85
85	4-chlorobenzyl	1-naphthyl	73.8 ± 6.3	96.5 ± 6.6	1120 ± 222
86	4-bromobenzyl	1-naphthyl	79.8 ± 2.8	93.7 ± 4.3	966 ± 148
87	2-phenylethyl	1-naphthyl	29.3 ± 5.2	56.8 ± 16.0	N.D.
88	3-phenylpropyl	1-naphthyl	31.3 ± 0.2	80.4 ± 0.4	>2000
89	2-cyclohexylethyl	1-naphthyl	28.7 ± 3.3	78.5 ± 3.2	1670 ± 256
90	2-(morpholin-4-yl)ethyl	1-naphthyl	<10	46.1 ± 2.4	N.D.
91	pentyl	2-naphthyl	35.7 ± 4.5	74.3 ± 2.6	1288 ± 92
92	pentyl	phenyl	49.5 ± 5.1	94.5 ± 5.4	446 ± 80
93	butyl	4-methoxyphenyl	<10	<10	N.D.
94	pentyl	4-methoxyphenyl	<20	46.9 ± 6.4	N.D.
95	hexyl	4-methoxyphenyl	39.9 ± 5.9	68.8 ± 2.0	>2000
96	pentyl	3,4-methylenedioxyphenyl	27.2 ± 5.4	70.2 ± 8.0	>2000
97	pentyl	2-(6-methoxy)naphthyl	<20	44.1 ± 4.0	N.D.
98	pentyl	9-anthracenyl	52.9 ± 3.2	76.5 ± 3.1	1500 ± 223

[a] The K_i values were obtained from nonlinear analysis of competition curves using [^{3}H]-CP-55,940 as radioligand. Data are mean ± SEM of three to four experiments performed in duplicate.

chemical ionization) mass spectra were obtained on an LC-MS system Thermo Electron Surveyor MSQ. Optical rotations ($[\alpha]_D$) were measured on a Perkin-Elmer 343 polarimeter. Specific rotations are given as deg/dm, and the concentration values are reported as g/mL of the specified solvent and were recorded at 25 °C. Elemental analyses were performed by the "Service Central d'Analyses" at the CNRS, Vernaison (France). Chiral separations were carried out using a gradient Waters 600E metering pump model equipped with a Waters 996 photodiode array spectrophotometer. Chromatographic data were collected and processed on a computer running with Millennium 2010. The column eluate was monitored at 220 and 230 nm. The sample loop was 20 μL (Rheodyne 7125 injector). Chiral chromatography was carried out on a Chiralpak AD-H (Tris-3,5-dimethylphenylcarbamate; 250 mm

Table 4. [^{35}S]-GTPγS Binding Stimulation Assays of Selected Compounds and Reference Compounds for the *h*CB_2 Cannabinoid Receptors[a]

cmpd	[^{35}S]-GTPγS specific binding (control = 100%)	cmpd	[^{35}S]-GTPγS specific binding (control = 100%)
10	157.1 ± 4.7**	**54**	187.4 ± 4.0**
13	140.6 ± 8.1**	**55**	97.3 ± 4.3
14	98.8 ± 3.56	**59**	86.1 ± 2.3**
16	141.0 ± 4.9**	**60**	76.7 ± 2.5**
19	182.9 ± 6.7**	**56**	56.3 ± 6.1**
22	155.0 ± 3.25**	**61**	53.5 ± 3.2**
23	155.6 ± 3.8**	**62**	42.7 ± 2.6**
24	174.6 ± 3.5**	**57**	98.5 ± 4.3
25	172.5 ± 1.9**	**58**	123.7 ± 2.7**
29	128.2 ± 4.5**	**67**	170.4 ± 3.4**
30	27.1 ± 3.2**	**68**	135.6 ± 3.4**
32	185.9 ± 9.0**	**71**	123.5 ± 2.8**
35	26.5 ± 2.9**	**76**	109.3 ± 3.1
38	119.7 ± 10.1	**1**	21.6 ± 2.7**
39	183.3 ± 7.4**	**2**	201.4 ± 7.5**
40	139.4 ± 4.9**	**3**	130.7 ± 1.8**
47	65.6 ± 1.8**	**4**	207.1 ± 10.1**
52	49.6 ± 1.8**	**5**	230.5 ± 13.7**
53	51.6 ± 0.8**		

[a] Results are expressed as the percentages of stimulation of [^{35}S]-GTPγS binding (basal value set at 100%) obtained for a concentration of ligands of 10 μM. Data are the mean ± SEM of three experiments performed in duplicate. Statistical significance assessed by one-way ANOVA followed by a Dunett post-test (*P < 0.05 and **P < 0.01).

× 4.6 mm i.d.; 10 μm; Daicel Chemical Industries, Baker, France). The mobile phase consisting of hexane/propan-2-ol (9:1, v/v) was degassed with a Waters inline degasser apparatus and delivered at a flow rate of 1.0 mL·min^{-1}. All the separations were carried out at 20 °C. The peak of the solvent front was considered to be equal to the dead time (t_0) and was about 3.70 min. For preliminary studies, compounds were dissolved in propan-2-ol at a concentration of 0.50 mmol·L^{-1} (concentration 100%) and passed through a 0.45 μm membrane filter prior to loading the column.

Procedures for the preparation of 2-phenylaminomethylenemalonic acid diethyl ester (**6**) and 4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester (**7**) have been previously described.[19]

The procedures for the synthesis of 1-alkyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester (**8a**−**i**) and 1-alkyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**9a**−**i**), as well as their characterization, are described in the Supporting Information.

General Procedure for the Preparation of *N*3-Aryl-1-alkyl-4-oxo-1,4-dihydroquinoline-3-carboxamide (10−**25).** To a solution of PybrOP (1.5 mmol) in 3 mL of dry DMF were added at room temperature compounds **9a**−**i** and diisopropylethylamine (3.0 mmol). The preswollen resin (0.75 g) in dry DMF was treated with the above mixture at room temperature for 3 h, after which time the resin was washed three times with dry DMF and three times with dichloromethane. The same activation procedure was repeated once. The appropriate amine (0.67 mmol) dissolved in dry DMF was reacted with the polymer-bound activated ester for 24 h at room temperature. The supernatant was then separated from the resin by filtration and the polymer beads were washed three times with dry DMF and three times with dichloromethane. The combined solutions were concentrated and the residue was purified either by crystallization or preparative TLC.

***N*3-(1-(3,5-Dimethyl)adamantyl)-4-oxo-1-(4-fluorobenzyl)-1,4-dihydroquinoline-3-carboxamide (10).** Compound **10** was purified by TLC (dichloromethane/methyl alcohol 99:1), white solid (185 mg, 45%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS (APCI$^+$) *m*/*z* 459 (MH^+). Anal. ($C_{29}H_{31}FN_2O_2$) C, H, N.

***N*3-(1-(3,5-Dimethyl)adamantyl)-4-oxo-1-(4-chlorobenzyl)-1,4-dihydroquinoline-3-carboxamide (11).** Compound **11** was purified by TLC (dichloromethane/methanol 99:1), white solid (235 mg, 55%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS (APCI$^+$) *m*/*z* 476 (MH^+). Anal. ($C_{29}H_{31}ClN_2O_2$) C, H, N.

***N*3-(1-(3,5-Dimethyl)adamantyl)-4-oxo-1-(4-bromobenzyl)-1,4-dihydroquinoline-3-carboxamide (12).** Compound **12** was purified by TLC (dichloromethane/methanol 99:1), white solid (280 mg, 60%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS (APCI$^+$) *m*/*z* 520 (MH^+). Anal. ($C_{29}H_{31}BrN_2O_2$) C, H, N.

***N*3-(1-(3,5-Dimethyl)adamantyl)-4-oxo-1-(2-phenylethyl)-1,4-dihydroquinoline-3-carboxamide (13).** Compound **13** was purified by TLC (dichloromethane/methanol 98:2), white solid (102 mg, 25%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS (APCI$^+$) *m*/*z* 455 (MH^+). Anal. ($C_{30}H_{34}N_2O_2$) C, H, N.

***N*3-(1-(3,5-Dimethyl)adamantyl)-4-oxo-1-(3-phenylpropyl)-1,4-dihydroquinoline-3-carboxamide (14).** Compound **14** was purified by TLC (dichloromethane/methanol 98:2), white solid (147 mg, 35%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS (APCI$^+$) *m*/*z* 469 (MH^+). Anal. ($C_{31}H_{36}N_2O_2$) C, H, N.

***N*3-(1-(3,5-Dimethyl)adamantyl)-4-oxo-1-(2-cyclohexylethyl)-1,4-dihydroquinoline-3-carboxamide (15).** Compound **15** was purified by TLC (cyclohexane/ethyl acetate 7:3), white solid (248 mg, 60%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS (APCI$^+$) *m*/*z* 461 (MH^+). Anal. ($C_{30}H_{41}N_2O_2$) C, H, N.

***N*3-(1-(3,5-Dimethyl)adamantyl)-4-oxo-1-(2-(morpholin-4-yl)-ethyl)-1,4-dihydroquinoline-3-carboxamide Hydrochloride (16).** Compound **16** was purified by TLC (dichloromethane/methanol 98:2), white solid (217 mg, 65%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS (APCI$^+$) *m*/*z* 464 (MH^+). Anal. ($C_{28}H_{38}ClN_3O_3$) C, H, N.

***N*3-(1-(2-Phenylethyl))-4-oxo-1-(2-(morpholin-4-yl)ethyl)-1,4-dihydroquinoline-3-carboxamide Hydrochloride (17).** Compound **17** was purified by TLC (cyclohexane/ethyl acetate 6:4), white solid (178 mg, 45%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS (APCI$^+$) *m*/*z* 406 (MH^+). Anal. ($C_{24}H_{28}ClN_3O_3$) C, H, N, Cl.

***(-)-N*3-(1-(1-Phenylethyl))-4-oxo-1-(2-(morpholin-4-yl)ethyl)-1,4-dihydroquinoline-3-carboxamide Hydrochloride (18).** Compound **18** was purified by TLC eluting from dichloromethane/methanool 95:5, white solid (262 mg, 66%); mp; $[\alpha]^{25}_D = -75°$ (c = 0.01, CH_2Cl_2); IR; ^{1}H NMR ($CDCl_3$); LC-MS (APCI$^+$) *m*/*z* 406 (MH^+). Anal. ($C_{24}H_{28}ClN_3O_3$) C, H, N, Cl.

***(+)-N*3-(1-(1,2,3,4-Tetrahydronaphthyl))-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (19).** Compound **19** was purified by TLC (cyclohexane/ethyl acetate 7:3), white oil (209 mg, 60%); $[\alpha]^{25}_D = +1.8°$ (c = 0.01, CH_2Cl_2); IR; ^{1}H NMR ($CDCl_3$); LC-MS (APCI$^+$) *m*/*z* 389 (MH^+). Anal. ($C_{25}H_{28}N_2O_2$) C, H, N.

***(−)-N*3-(1-(1,2,3,4-Tetrahydronaphthyl))-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (20).** Compound **20** was purified by TLC (cyclohexane/ethyl acetate 7:3), white oil (216 mg, 62%); $[\alpha]^{25}_D = -1.8°$ (c = 0.01, CH_2Cl_2); IR; ^{1}H NMR ($CDCl_3$); LC-MS (APCI$^+$) *m*/*z* 389 (MH^+). Anal. ($C_{25}H_{28}N_2O_2$) C, H, N.

***N*3-(1-Adamantyl)-4-oxo-1-(2-(morpholin-4-yl)ethyl)-1,4-dihydroquinoline-3-carboxamide Hydrochloride (21).** Compound **21** was purified by TLC (dichloromethane/methanol 98:2), white solid (156 mg, 40%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS (APCI$^+$) *m*/*z* 436 (MH^+). Anal. ($C_{26}H_{33}N_3O_3$) C, H, N.

***N*3-((1-Adamantyl)methyl)-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (22).** Compound **22** was purified by TLC (cyclohexane/ethyl acetate 7:3), white solid (201 mg, 55%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS (APCI$^+$) *m*/*z* 407 (MH^+). Anal. ($C_{26}H_{34}N_2O_2$) C, H, N.

***(±)-N*3-(1-(1-Adamantyl)ethyl)-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (23).** Compound **23** was purified by TLC (cyclohexane/ethyl acetate 7:3), white solid (208 mg, 55%); mp; $[\alpha]^{25}_D = +0°$ (c = 0.01, CH_2Cl_2); IR; ^{1}H NMR ($CDCl_3$); LC-MS (APCI$^+$) *m*/*z* 422 (MH^+). Anal. ($C_{27}H_{36}N_2O_2$) C, H, N.

***(−)-N*3-(1-(1-Adamantyl)ethyl)-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (24).** Compound **24** was prepared by chiral preparative HPLC (stationary phase: Chiralpak AD (20 μm); mobile phase: *n*-hexane/propan-2-ol, 90/10; separation yield: 94%), white solid (245 mg); mp; $[\alpha]^{25}_D = -93°$ (c = 0.01, CH_2Cl_2); IR; ^{1}H NMR ($CDCl_3$); LC-MS (APCI$^+$) *m*/*z* 422 (MH^+). Anal. ($C_{27}H_{36}N_2O_2$) C, H, N.

***(+)-N*3-(1-(1-Adamantyl)ethyl)-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (25).** Compound **25** was prepared by chiral preparative HPLC (stationary phase: Chiralpak AD (20 μm);

mobile phase: *n*-hexane/propan-2-ol, 90/10; separation yield: 91%), white solid (235 mg); mp; $[\alpha]^{25}_D = +93°$ ($c = 0.01$, CH_2Cl_2); IR; ^1H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 422 (MH^+). Anal. ($C_{27}H_{36}N_2O_2$) C, H, N.

Synthesis and Characterization of 26, 27a,b, and 28a,b. The synthesis and characterization of **26**, **27a**,**b**, and **28a**,**b** are described in the Supporting Information.

General Procedure for the Preparation of *N*3-Aryl-1-alkyl-4-oxo-1,4-dihydroquinoline-3-carboxamide (29−35). To a solution of PybrOP (1.5 mmol) in 3 mL of dry DMF were added at room temperature compounds **28a**,**b** and diisopropylethylamine (3.0 mmol). The preswollen resin (0.75 g) in dry DMF was treated with the above mixture at room temperature for 3 h, and after this time, the resin was washed three times with dry DMF and three times with dichloromethane. The same activation procedure was repeated a second time. The appropriate amine (0.67 mmol) dissolved in dry DMF was reacted with the polymer-bound activated ester for 24 h at room temperature. The supernatant was then separated from the resin by filtration, and the polymer beads were washed three times with dry DMF and three times with dichloromethane. The combined solutions were concentrated and the residue was purified either by crystallization or preparative TLC.

***N*3-(1-(3,5-Dimethyl)adamantyl)-2-methyl-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (29).** Compound **29** was purified by TLC (cyclohexane/ethyl acetate 6:4), yellow oil (140 mg, 36%); IR; ^1H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 435 (MH^+). Anal. ($C_{28}H_{38}N_2O_2$) C, H, N.

***N*3-(1-(3,5-Dimethyl)adamantyl)-4-oxo-2-phenyl-1-pentyl-1,4-dihydroquinoline-3-carboxamide (30).** Compound **30** was purified by TLC (dichloromethane/methanol 98:2), white solid (134 mg, 30%); mp; IR; ^1H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 497 (MH^+). Anal. ($C_{33}H_{40}N_2O_2$) C, H, N.

***N*3-(2-Phenylethyl)-2-methyl-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (31).** Compound **31** was purified by TLC (cyclohexane/ethyl acetate 4:6), white oil (250 mg, 74%); IR; ^1H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 377 (MH^+). Anal. ($C_{24}H_{28}N_2O_2$) C, H, N.

(−)-*N*3-(1-Phenylethyl)-2-methyl-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (32). Compound **32** was purified by TLC (cyclohexane/ethyl acetate 6:4), white oil (170 mg, 50%); $[\alpha]^{25}_D = -90°$ ($c = 0.01$, CH_2Cl_2); IR; ^1H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 377 (MH^+). Anal. ($C_{24}H_{28}N_2O_2$) C, H, N.

(−)-*N*3-(1-(2-Naphthyl)ethyl)-2-methyl-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (33). Compound **33** was purified by TLC (cyclohexane/ethyl acetate 4:6), white oil (130 mg, 34%); $[\alpha]^{25}_D = -148°$ ($c = 0.01$, CH_2Cl_2); IR; ^1H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 427 (MH^+). Anal. ($C_{28}H_{30}N_2O_2$) C, H, N.

(−)-*N*3-(1-(1-Naphthyl)ethyl)-2-methyl-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (34). Compound **34** was purified by TLC (cyclohexane/ethyl acetate 4:6), white oil (130 mg, 34%); $[\alpha]^{25}_D = -175°$ ($c = 0.01$, CH_2Cl_2); IR; ^1H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 427 (MH^+). Anal. ($C_{28}H_{30}N_2O_2$) C, H, N.

***N*3-(1-Adamantyl)-4-oxo-1-pentyl-2-phenyl-1,4-dihydroquinoline-3-carboxamide (35).** Compound **35** was purified by TLC (dichloromethane/methanol 98:2), white solid (130 mg, 34%); mp; IR; ^1H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 469 (MH^+). Anal. ($C_{31}H_{36}N_2O_2$) C, H, N.

Synthesis and Characterization of Intermediates 36, 37, and 41. The synthesis and characterization of intermediates **36**, **37**, and **41** are described in the Supporting Information.

General Procedure for the Preparation of *N*-(4-Oxo-1-pentyl-1,4-dihydroquinolin-3-yl)-aryl-carboxamide (38−40). A mixture of selected carboxylic acid (5.00 mmol) and thionyl chloride (10 mL) was refluxed for 2 h. Excess of thionyl chloride was evaporated under reduced pressure, and dry toluene (20 mL) was added (solution A). A mixture of amine **37** (7.5 mmol) and ethyldiisoproyl amine (7.5 mmol) in dry toluene (30 mL) under nitrogen was cooled at 0 °C. A solution of freshly prepared acyl chloride (solution A) was added dropwise. The mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The residue was dissolved in ethyl acetate (50 mL) and washed with saturated aqueous sodium hydrogenocarbonate (2 × 50 mL), water (2 × 50 mL), and brine (2 × 50 mL). The organic layer was separated and dried over anhydrous magnesium sulfate. The concentrate was purified by flash chromatography (dichloromethane/methanol 98:2, v/v) to afford the corresponding carboxamide derivatives **38**−**40**.

Adamantane-1-carboxylic Acid (4-Oxo-1-pentyl-1,4-dihydroquinolin-3-yl)amide (38). White solid (686 mg, 40%); mp; IR; ^1H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 393 (MH^+). Anal. ($C_{25}H_{32}N_2O_2$) C, H, N.

***N*-(4-Oxo-1-pentyl-1,4-dihydroquinolin-3-yl)-3-phenyl-propionamide (39).** White solid (727 mg, 40%); mp; IR; ^1H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 363 (MH^+). Anal. ($C_{23}H_{26}N_2O_2$) C, H, N.

Naphthalene-1-carboxylic Acid (4-Oxo-1-pentyl-1,4-dihydroquinolin-3-yl)amide (40). White solid (1.07 g, 56%); mp; IR; ^1H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 385 (MH^+). Anal. ($C_{25}H_{24}N_2O_2$) C, H, N.

General Procedure for the Preparation of 3-(Substituted-aminomethyl)-1-pentyl-1*H*-quinolin-4-one (42−44). A mixture of aldehyde **41** (0.30 g, 1.23 mmol) in dry methanol (30 mL) was stirred at room temperature under nitrogen in the presence of 3 Å molecular sieve. Selected amine (1.85 mmol) and triethylamine (0.70 mL, 4.93 mmol) were added, and the resulting mixture was stirred overnight at 50 °C under nitrogen. Then sodium cyanoborohydride (0.08 g, 1.35 mmol) was added, and the stirring was continued at 50 °C for 24 h. The molecular sieve was eliminated by filtration, and the solvent was removed by evaporation under reduced pressure. The residue was dissolved in ethyl acetate (50 mL) and washed with saturated aqueous sodium hydrogenocarbonate (2 × 50 mL), water (2 × 50 mL), and brine (2 × 50 mL). The organic layer was separated and dried over anhydrous magnesium sulfate. The concentrate was purified by flash-chromatography, using specified eluent, to afford the corresponding amines, which were isolated as hydrochloride except for compound (**42**).

3-((1-Adamantyl)aminomethyl)-1-pentyl-1*H*-quinolin-4-one (42). Compound **42** was purified by chromatography (dichloromethane/methanol 9:1, v/v), white solid (163 mg, 35%); mp; IR; ^1H NMR (DMSO-d_6); LC-MS ($APCI^+$) *m/z* 379 (MH^+). Anal. ($C_{25}H_{34}N_2O$) C, H, N.

1-Pentyl-(3-phenylethylaminomethyl)-1*H*-quinolin-4-one Hydrochloride (43). Compound **43** was purified by chromatography (dichloromethane/methanol 9:1, v/v), white solid (151 mg, 32%); mp; IR; ^1H NMR (DMSO-d_6); LC-MS ($APCI^+$) *m/z* 349 (MH^+). Anal. ($C_{23}H_{29}ClN_2O$) C, H, N.

(±)1-Pentyl-(3-(1,2,3,4-tetrahydronaphthyl)aminomethyl)-1*H*-quinolin-4-one Hydrochloride (44). Compound **44** was purified by chromatography (dichloromethane/methanol 9:1, v/v), white solid (167 mg, 33%); mp; IR; ^1H NMR (DMSO-d_6); LC-MS ($APCI^+$) *m/z* 375 (MH^+). Anal. ($C_{25}H_{30}ClN_2O$) C, H, N.

1-Pentyl-4-thioxo-1,4-dihydroquinoline-3-carboxylic Acid Ethyl Ester (45). A mixture of **8a** (2.00 g, 6.96 mmol) and phosphorus pentasulfide (3.09 g, 13.92 mmol) was refluxed for 12 h in pyridine (40 mL). After cooling, the solvent was removed under reduced pressure and the residue was taken up in water and then extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, concentrated under reduced pressure, and finally purified by flash chromatography (cyclohexane/ethyl acetate 9:1) to provide 1.98 g (94%) of compound **45** as a yellow oil; IR; ^1H NMR ($CDCl_3$).

1-Pentyl-4-thioxo-1,4-dihydroquinoline-3-carboxylic Acid (46). A mixture of **45** (2.00 g, 6.59 mmol) and lithium hydroxide (1.10 g, 26.36 mmol) was stirred (RT, N_2) in a mixture of tetrahydrofuran/water 50:50 (100 mL). Tetrahydrofuran was removed under reduced pressure. The solution was adjusted to pH 4 with aqueous 10% hydrochloric acid. The resulting precipitate was collected by filtration, washed with water, and recrystallized from diisopropyl ether to afford 1.50 g (83%) of carboxylic acid **46** as a yellow solid; mp; IR; ^1H NMR (DMSO-d_6).

***N*3-(1-(3,5-Dimethyl)adamantyl)-1-pentyl-4-thioxo-1,4-dihydroquinoline-3-carboxamide (47).** This compound was obtained using the same methodology previously described for 1-pentyl-4-oxo-1,4-dihydroquinoline-3-carboxamide (**10**−**25**). Purified by TLC (cyclohexane/ethyl acetate 8:2), white solid (235 mg, 60%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m*/*z* 437 (MH^+). Anal. ($C_{27}H_{36}N_2OS$) C, H, N.

Synthesis and Characterization of Intermediates 48a−**c, 49a**−**c, 50a**−**c, and 51a**−**c.** The synthesis and characterization of intermediates **48a**−**c**, **49a**−**c**, **50a**−**c**, and **51a**−**c** are described in the Supporting Information.

General Procedure for the Preparation of *N*3-Aryl-1-alkyl-4-oxo-1,4-dihydroquinoline-3-carboxamide (52−**58).** These compounds were obtained using the same methodology previously described for 1-pentyl-4-oxo-1,4-dihydroquinoline-3-carboxamide (**10**−**25**).

***N*3-(1-(3,5-Dimethyl)adamantyl)-6-chloro-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (52).** Compound **52** was purified by TLC (cyclohexane/ethyl acetate 7:3), white solid (167 mg, 55%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m*/*z* 456 (MH^+). Anal. ($C_{27}H_{35}ClN_2O_2$) C, H, N.

***N*3-(1-(3,5-Dimethyl)adamantyl)-7-chloro-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (53).** Compound **53** was purified by TLC (cyclohexane/ethyl acetate 7:3), white solid (219 mg, 72%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m*/*z* 456 (MH^+). Anal. ($C_{27}H_{35}ClN_2O_2$) C, H, N.

***N*3-(1-(3,5-Dimethyl)adamantyl)-8-chloro-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (54).** Compound **54** was purified by TLC (cyclohexane/ethyl acetate 7:3), white solid (225 mg, 74%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m*/*z* 456 (MH^+). Anal. ($C_{27}H_{35}ClN_2O_2$) C, H, N.

(±)-*N*3-(1-(1-Adamantyl)ethyl)-6-chloro-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (55). Compound **55** was purified by TLC (cyclohexane/ethyl acetate 7:3), white solid (140 mg, 46%); mp; $[\alpha]^{25}_D = +0°$ ($c = 0.01$, CH_2Cl_2); IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m*/*z* 456 (MH^+). Anal. ($C_{27}H_{35}ClN_2O_2$) C, H, N.

(−)-*N*3-(1-(1-Adamantyl)ethyl)-6-chloro-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (59). Compound **59** was prepared by chiral preparative HPLC (stationary phase: Chiralpak AD (20 μm); mobile phase: *n*-hexane/propan-2-ol, 92/8, v/v; separation yield: 94%), white solid (235 mg); mp; $[\alpha]^{25}_D = -101°$ ($c = 0.01$, CH_2Cl_2); IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m*/*z* 422 (MH^+).

(+)-*N*3-(1-(1-Adamantyl)ethyl)-6-chloro-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (60). Prepared by chiral preparative HPLC (stationary phase: Chiralpak AD (20 μm); mobile phase: *n*-hexane/propan-2-ol, 92/8, v/v; separation yield: 91%), white solid (227 mg); mp; $[\alpha]^{25}_D = +101°$ ($c = 0.01$, CH_2Cl_2); IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m*/*z* 422 (MH^+).

(±)-*N*3-(1-(1-Adamantyl)ethyl)-7-chloro-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (56). Compound **56** was purified by TLC (cyclohexane/ethyl acetate 7:3), white solid (164 mg, 54%); mp; $[\alpha]^{25}_D = +0°$ ($c = 0.01$, CH_2Cl_2); IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m*/*z* 456 (MH^+). Anal. ($C_{27}H_{35}ClN_2O_2$) C, H, N.

(−)-*N*3-(1-(1-Adamantyl)ethyl)-7-chloro-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (61). Prepared by chiral preparative HPLC (stationary phase: Chiralpak AD (20 μm); mobile phase: *n*-hexane/propan-2-ol, 90/10, v/v; separation yield: 96%), white solid (240 mg); mp; $[\alpha]^{25}_D = -95°$ ($c = 0.01$, CH_2Cl_2); IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m*/*z* 422 (MH^+).

(+)-*N*3-(1-(1-Adamantyl)ethyl)-7-chloro-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (62). Compound **62** was prepared by chiral preparative HPLC (stationary phase: Chiralpak AD (20 μm); mobile phase: *n*-hexane/propan-2-ol, 90/10, v/v; separation yield: 93%), white solid (232 mg); mp; $[\alpha]^{25}_D = +95°$ ($c = 0.01$, CH_2Cl_2); IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m*/*z* 422 (MH^+).

(±)-*N*3-(1-(1,2,3,4-Tetrahydronaphthyl))-6-chloro-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (57). Compound **57** was purified by TLC (cyclohexane/ethyl acetate 7:3), white solid (226 mg, 80%); $[\alpha]^{25}_D = +0°$ ($c = 0.01$, CH_2Cl_2); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m*/*z* 423 (MH^+). Anal. ($C_{25}H_{27}ClN_2O_2$) C, H, N.

(+)-*N*3-(1-(1,2,3,4-Tetrahydronaphthyl))-6-chloro-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (58). Purified by TLC (cyclohexane/ethyl acetate 7:3), white solid (232 mg, 82%); $[\alpha]^{25}_D = +2.0°$ ($c = 0.01$, CH_2Cl_2); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m*/*z* 423 (MH^+). Anal. ($C_{25}H_{27}ClN_2O_2$) C, H, N.

Synthesis and Characterization of Intermediates 63a,b, 64a,b, 65a,b, 66a,b, 69, and 70. The synthesis and characterization of intermediates **63a**,**b**, **64a**,**b**, **65a**,**b**, **66a**,**b**, **69**, and **70** are described in the Supporting Information.

General Procedure for the Preparation of *N*3-Aryl-1-alkyl-4-oxo-1,4-dihydronaphthyridine-3-carboxamide (67, 68, and 71). These compounds were obtained using the same methodology previously described for 1-pentyl-4-oxo-1,4-dihydroquinoline-3-carboxamide (**10**−**25**).

***N*3-(1-(3,5-Dimethyl)adamantyl)-4-oxo-1-pentyl-1,4-dihydro-[1,5]-naphthyridine-3-carboxamide (67).** Purified by TLC (dichloromethane), white solid (40 mg, 25%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m*/*z* 422 (MH^+). Anal. ($C_{26}H_{35}N_3O_2$) C, H, N.

***N*3-(1-(3,5-Dimethyl)adamantyl)-4-oxo-1-pentyl-1,4-dihydro-[1,6]-naphthyridine-3-carboxamide (68).** Compound **68** was purified by TLC (dichloromethane), white solid (47 mg, 30%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m*/*z* 422 (MH^+). Anal. ($C_{26}H_{35}N_3O_2$) C, H, N.

***N*3-(1-(3,5-Dimethyl)adamantyl)-4-oxo-1-pentyl-1,4-dihydro-[1,8]-naphthyridine-3-carboxamide (71).** Compound **71** was purified by TLC (dichloromethane), white solid (63 mg, 40%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m*/*z* 422 (MH^+). Anal. ($C_{26}H_{35}N_3O_2$) C, H, N.

Diethyl 2-(Phenylhydrazono)malonate (72). Aniline (9.78 mL, 107.37 mmol) was added to aqueous HCl 37% (23.30 mL). The resulting aniline hydrochloride solution was cooled to −10 °C. Then a solution of sodium nitrite (7.58 g, 109.88 mmol) in water (30 mL) was added keeping the reaction temperature below 0 °C. Because the reaction was exothermic, the addition has to proceed very slowly under rigorous cooling. The resulting orange solution was added to a solution consisting of sodium acetate and diethyl malonate. The latter solution was freshly prepared by dissolution of sodium acetate (20.19 g, 246.25 mmol) in water (40 mL). Then diethyl malonate (16.68 mL, 109.88 mmol) was dissolved in ethanol (215 mL). Both solutions were combined and brought to 0 °C, which is accompanied by some precipitations. To the resulting slurry stirred at 0 °C was slowly added the previously prepared cold solution of phenyl diazonium chloride. After this addition, the reaction mixture was allowed to reach room temperature and stirred for 5 h. After keeping the mixture at −13 °C overnight, a white inorganic solid and the crude product (dark red oil) precipitated. The solid was removed by filtration. The filtrate was evaporated to give a red, viscous oil, which was taken up in ethyl acetate and extracted twice with water. The combined organic layers were dried over anhydrous magnesium sulfate, evaporated under reduce pressure, and finally purified by flash chromatography (dichloromethane) the afford 26.95 g (95%) of compound **72** as an orange oil: IR; ^{1}H NMR ($CDCl_3$).

2-(Phenylhydrazono)malonic Acid (73). To diethyl 2-(phenylhydrazono)malonate **72** (5.00 g, 18.92 mmol) dissolved in refluxing ethyl alcohol (95%, 20 mL) was added dropwise aqueous sodium hydroxide (2 N, 21 mL). The resulting mixture was heated to reflux for 30 min, then allowed to reach room temperature and evaporated under reduced pressure. The resulting concentrate was precipitated into aqueous HCl (10%). The resulting precipitate was collected by filtration, washed with water, and dried in vacuo over P_2O_5 to afford 3.19 g (81%) of **73** as a yellow solid: mp; IR; ^{1}H NMR (DMSO-d_6).

4-Oxo-1,4-dihydrocinnoline-3-carboxylic Acid (74). To 2-(phenylhydrazono)malonic acid **73** (2.00 g, 9.61 mmol) suspended in 1,2-dichlorobenzene (20 mL) was added dropwise a solution of thionyl chloride (2 mL) in 1,2-dichlorobenzene (10 mL). The resulting mixture was heated to 70 °C for 5 h. The excess of thionyl chloride was distilled off under ambient pressure. To this solution

was added a solution of titanium tetrachloride (2 mL) in 1,2-dichlorobenzene (30 mL) within 15 min. The reaction suspension was stirred at 90 °C for 14 h. Subsequently, the excess of titanium tetrachloride and then the 1,2-dichlorobenzene were evaporated under reduced pressure. The resulting brown solid was extracted several times with small portions of boiling hot aqueous sodium hydroxide (4 M, total volume: 30 mL). The resulting suspension was passed through cellite. The product precipitated into concentrated HCl (37%, 150 mL) while being agitated. The resulting solid was filtered off and then dried under reduced pressure over P_2O_5, offering 1.19 g (65%) of **74** as a brown solid: mp; IR; ^{1}H NMR (DMSO-d_6).

***N*3-(1-(3,5-Dimethyl)adamantyl)-4-oxo-1,4-dihydrocinnoline-3-carboxamide (75).** To a stirred solution of carboxylic acid **74** (0.50 g, 2.63 mmol) in dry DMF (30 mL) was added diisopropylethyl amine (1.83 mL, 10.52 mmol). The resulting solution was stirred at room temperature for 10 min before adding HBTU (1.49 g, 3.94 mmol) and stirring for 3 more hours. 1-Amino-3,5-dimethyladamantane (0.85 g, 3.94 mmol) was then added, and the solution was stirred for 24 h. DMF was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate and successively washed with aqueous saturated sodium bicarbonate, water, and brine. The organic phase was dried over anhydrous magnesium sulfate, evaporated, and finally purified by flash chromatography using dichloromethane/methanol 98:2 (v/v) as eluent, yielding 0.63 g (68%) of **75** as an orange solid: mp; IR; ^{1}H NMR (DMSO-d_6).

***N*3-(1-(3,5-Dimethyl)adamantyl)-4-oxo-1-pentyl-1,4-dihydrocinnoline-3-carboxamide (76).** This compound was obtained using the same methodology previously described for 1-pentyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl esters (**8a**−**i**), purified by TLC, eluting from cyclohexane/ethyl acetate 6:4 (v/v), white solid (775 mg, 40%); mp 121−122 °C; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 422 (MH^+). Anal. ($C_{26}H_{35}N_3O_2$) C, H, N.

Synthesis and Characterization of 77a−g, 78a−g, and 79a−g. The synthesis and characterization of **77a**−**g**, **78a**−**g**, and **79a**−**g** are reported in the Supporting Information.

General Procedure for the Preparation of *N*-Alkyl-3-aroyl-1,4-dihydroquinolin-4-one (80−98). These compounds were obtained using the same methodology previously described for 1-pentyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl esters (**8a**−**i**).

1-Butyl-3-(naphthalene-1-carbonyl)-1,4-dihydroquinolin-4-one (80). Compound **80** was purified by TLC (dichloromethane/methanol 98:2, v/v), white solid (490 mg, 30%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 356 (MH^+). Anal. ($C_{24}H_{21}NO_2$) C, H, N.

3-(Naphthalene-1-carbonyl)-1-pentyl-1,4-dihydroquinolin-4-one (81). Compound **81** was purified by TLC (cyclohexane/ethyl acetate 7:3, v/v), white solid (1155 mg, 68%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 370 (MH^+). Anal. ($C_{25}H_{23}NO_2$) C, H, N.

1-Hexyl-3-(naphthalene-1-carbonyl)-1,4-dihydroquinolin-4-one (82). Compound **82** was purified by TLC (dichloromethane/methanol 98:2, v/v), white solid (917 mg, 52%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 384 (MH^+). Anal. ($C_{26}H_{25}NO_2$) C, H, N.

1-Benzyl-3-(naphthalene-1-carbonyl)-1,4-dihydroquinolin-4-one (83). Compound **83** was purified by TLC (dichloromethane/methanol 98:2, v/v), white solid (358 mg, 20%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 390 (MH^+). Anal. ($C_{27}H_{19}NO_2$) C, H, N.

1-(4-Fluorobenzyl)-3-(naphthalene-1-carbonyl)-1,4-dihydroquinolin-4-one (84). Compound **84** was purified by TLC (dichloromethane/methanol 98:2, v/v), white solid (1105 mg, 59%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 408 (MH^+). Anal. ($C_{27}H_{18}FNO_2$) C, H, N.

1-(4-Chlorobenzyl)-3-(naphthalene-1-carbonyl)-1,4-dihydroquinolin-4-one (85). Compound **85** was purified by TLC (dichloromethane/methanol 98:2, v/v), white solid (1267 mg, 65%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 424 (MH^+). Anal. ($C_{27}H_{18}ClNO_2$) C, H, N.

1-(4-Bromobenzyl)-3-(naphthalene-1-carbonyl)-1,4-dihydroquinolin-4-one (86). Compound **86** was purified by TLC (dichloromethane/methanol 98:2, v/v), white solid (1400 mg, 65%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 469 (MH^+). Anal. ($C_{27}H_{18}BrNO_2$) C, H, N.

3-(Naphthalene-1-carbonyl)-1-phenylethyl-1,4-dihydroquinolin-4-one (87). Compound **87** was purified by TLC (dichloromethane/methanol 98:2, v/v), white solid (371 mg, 30%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 404 (MH^+). Anal. ($C_{28}H_{21}NO_2$) C, H, N.

3-(Naphthalene-1-carbonyl)-1-phenylpropyl-1,4-dihydroquinolin-4-one (88). Compound **88** was purified by TLC (dichloromethane/methanol 98:2, v/v), white solid (691 mg, 36%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 418 (MH^+). Anal. ($C_{29}H_{23}NO_2$) C, H, N.

3-(Naphthalene-1-carbonyl)-1-(2-(cyclohexyl)ethyl)-1,4-dihydroquinolin-4-one (89). Compound **89** was purified by TLC (dichloromethane/methanol 98:2, v/v), white solid (376 mg, 20%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 410 (MH^+). Anal. ($C_{28}H_{27}NO_2$) C, H, N.

3-(Naphthalene-1-carbonyl)-1-(2-(morpholin-4-yl)ethyl)-1,4-dihydroquinolin-4-one Hydrochloride (90). Compound **90** was purified by TLC (dichloromethane/methanol 97:3, v/v), white solid (681 mg, 33%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 413 (MH^+). Anal. ($C_{26}H_{25}ClN_2O_3$) C, H, N.

3-(Naphthalene-2-carbonyl)-1-pentyl-1,4-dihydroquinolin-4-one (91). Compound **91** was purified by TLC (cyclohexane/ethyl acetate 7:3, v/v) ,white oil (681 mg, 40%); ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 370 (MH^+). Anal. ($C_{25}H_{23}NO_2$) C, H, N.

3-Benzoyl-1-pentyl-1,4-dihydroquinolin-4-one (92). Compound **92** was purified by TLC (dichloromethane/methanol 95:5, v/v), white oil (631 mg, 43%); IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 320 (MH^+). Anal. ($C_{21}H_{21}NO_2$) C, H, N.

1-Butyl-3-(4-methoxybenzoyl)-1,4-dihydroquinolin-4-one (93). Compound **93** was purified by TLC (dichloromethane/methanol 98:2, v/v), white oil (416 mg, 27%); IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 336 (MH^+). Anal. ($C_{21}H_{21}NO_3$) C, H, N.

3-(4-Methoxybenzoyl)-1-pentyl-1,4-dihydroquinolin-4-one (94). Compound **94** was purified by TLC (dichloromethane/methanol 98:2, v/v), white oil (562 mg, 35%); IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 350 (MH^+). Anal. ($C_{22}H_{23}NO_3$) C, H, N.

1-Hexyl-3-(4-methoxybenzoyl)-1,4-dihydroquinolin-4-one (95). Compound **95** was purified by TLC (dichloromethane/methanol 98:2, v/v), white oil (769 mg, 46%); IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 364 (MH^+). Anal. ($C_{23}H_{25}NO_3$) C, H, N.

3-(Benzo[1,3]dioxole-5-carbonyl)-1-pentyl-1,4-dihydroquinolin-4-one (96). Compound **96** was purified by TLC (dichloromethane/methanol 95:5, v/v), white oil (417 mg, 25%); IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 364 (MH^+). Anal. ($C_{22}H_{21}NO_4$) C, H, N.

3-((6-Methoxy)naphthalene-2-carbonyl)-1-pentyl-1,4-dihydroquinolin-4-one (97). Compound **97** was purified by TLC (dichloromethane/methanol 98:2, v/v), white oil (459 mg, 25%); IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 400 (MH^+). Anal. ($C_{26}H_{25}NO_3$) C, H, N.

3-(Anthracene-9-carbonyl)-1-pentyl-1,4-dihydroquinolin-4-one (98). Compound **98** was purified by TLC (dichloromethane/methanol 98:2, v/v), yellow solid (482 mg, 25%); mp; IR; ^{1}H NMR ($CDCl_3$); LC-MS ($APCI^+$) *m/z* 420 (MH^+). Anal. ($C_{29}H_{25}NO_2$) C, H, N.

Pharmacology. Fatty acid free bovine serum albumin (BSA) was purchased from Sigma Chemical Co. (St. Louis, MO). Compound **4** was purchased from RBI (Natick, MA), **2**, HU-210, and CP-55,940 (**5**) were acquired from Tocris (Bristol, U.K.). SR-141716A and **1** were kindly donated by Sanofi Recherche (Montpellier, France).

Cell Culture and Preparation of *h*CB_1- or *h*CB_2-Transfected CHO Cell Membranes. CHO cells stably transfected with the

cDNA sequences encoding either the human CB_1 or the human CB_2 cannabinoid receptors were kindly provided by Dr. M. Detheux and Dr. P. Nokin, respectively (Euroscreen s.a., Gosselies, Belgium). Cell cultures and membrane preparation were reported previously.[19]

Competition Binding Assay. [^{3}H]-SR-141716A (52 Ci/mol) was purchased from Amersham (Roosendaal, The Netherlands) and [^{3}H]-CP-55,940 (101 Ci/mol) from NEN Life Science (Zaventem, Belgium). Binding assay procedure was previously reported,[19] under those conditions, using [^{3}H]-SR-141716A, the B_{max} value was 57 pmoles/mg protein and the K_d value was 1.13 ± 0.13 nM for the *h*CB_1 cannabinoid receptor, and using [^{3}H]-CP-55,940, the B_{max} value was 194 pmoles/mg protein and the K_d value was 4.3 ± 0.13 nM for the *h*CB_2 cannabinoid receptor. The results are expressed as mean ± SEM of at least three experiments performed in duplicate.

[^{35}S]GTPγS Assay. [^{35}S]-GTPγS (1173 Ci/mmol) was obtained from Amersham (Roosendaal, The Netherlands). The experiments were performed as previously described.[19] Gpp(NH)p 100 μM was used to determine the nonspecific binding. The results are expressed as mean ± SEM of at least three experiments performed in duplicate and are reported for a concentration of ligand of 10 μM.

Data Analysis. IC_{50} values were determined by nonlinear regression analysis performed using the GraphPad prism 4.0 program (GraphPad Software, San Diego). The K_i values were calculated from the IC_{50}, based on the Cheng−Prusoff equation: $K_i = IC_{50}/(1 + L/K_d)$. The statistical significance of [^{35}S]-GTPγS assay results was assessed using a one-way ANOVA followed by a Dunett post-test.

Acknowledgment. Dr. Laurence Goossens is acknowledged for her contribution to the chiral preparative HPLC separation of **24**, **25**, and **59**−**62**. GGM is a postdoctoral researcher from the National Fund for Scientific Research (FNRS, Belgium). This work was partially supported by Charcot Foundation (Bruxelles, Belgium) and by the National Fund for Scientific Research (FNRS, Crédit aux chercheurs. Belgium).

Supporting Information Available: Elemental analysis of compounds **10**−**25**, **29**−**35**, **38**−**40**, **42**−**44**, **47**, **52**−**58**, **67**, **68**, **71**, **76**, and **80**−**98**, spectroscopic data and melting point for all compounds, and procedures for the synthesis of intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Munro, S.; Thomas, K. L.; Abu-Shaar, M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* **1993**, *365*, 61−65.
(2) Galiegue, S.; Mary, S.; Marchand, J.; Dussossoy, D.; Carriere, D.; Carayon, P.; Bouaboula, M.; Shire, D.; Le, Fur, G.; Casellas, P. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *Eur. J. Biochem.* **1995**, *232*, 54−61.
(3) Benito, C.; Nunez, E.; Tolon, R. M.; Carrier, E. J.; Rabano, A.; Hillard, C. J.; Romerio, J. Cannabinoid CB_2 receptors and fatty acid amide hydrolase are selectively overexpressed in neuritic plaque-associated glia in Alzheimer's disease brains. *J. Neurosci.* **2003**, *23*, 11136−11141.
(4) Van, Sickle, M. D.; Duncan, M.; Kingsley, P. J.; Mouihate, A.; Urbani, P.; Mackie, K.; Stella, N.; Makriyannis, A.; Piomelli, D.; Davison, J. S.; Marnett, L. J.; Di, Marzo, V.; Pittman, O. J.; Patel, K. D.; Sharkey, K. A. Identification and functional characterization of brainstem cannabinoid CB_2 receptors. *Science* **2005**, *310*, 329−332.
(5) Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* **1990**, *346*, 561−564.
(6) Lambert, D. M.; Fowler, C. J. The endocannabinoid system: Drug targets, lead compounds, and potential therapeutic applications. *J. Med. Chem.* **2005**, *48*, 5069−5087.
(7) Mackie, K. Cannabinoid receptors as therapeutic targets. *Annu. Rev. Pharmacol. Toxicol.* **2006**, *46*, 101−122.
(8) Pacher, P.; Batkai, S.; Kunos, G. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol. Rev.* **2006**, *58*, 389−462.
(9) Malan, T. P.; Jr.; Ibrahim, M. M.; Deng, H.; Liu, Q.; Mata, H. P.; Vanderah, T.; Porreca, F.; Makriyannis, A. CB_2 cannabinoid receptor-mediated peripheral antinociception. *Pain* **2001**, *93*, 239−245.
(10) Ibrahim, M. M.; Deng, H.; Zvonok, A.; Cockayne, D. A.; Kwan, J.; Mata, H. P.; Vanderah, T. W.; Lai, J.; Porreca, F.; Makriyannis, A.; Malan, T. P., Jr. Activation of the CB_2 cannabinoid receptors by AM1241 inhibits experimental neuropathic pain: Pain inhibition by receptors not present in the CNS. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 10529−10533.
(11) Clayton, N.; Marshall, F. H.; Bountra, C.; O'Shaughnessy, C. T. CB_1 and CB_2 cannabinoid receptors are implicated in inflammatory pain. *Pain* **2002**, *96*, 253−260.
(12) Nackley, A. G.; Makriyannis, A.; Hohmann, A. G. Selective activation of cannabinoid CB(2) receptors suppresses spinal fos protein expression and pain behavior in a rat model of inflammation. *Neuroscience* **2003**, *119*, 747−757.
(13) Patel, H. J.; Birrell, M. A.; Crispino, N.; Hele, D. J.; Venkatesan, P.; Barnes, P. J.; Yacoub, M. H.; Belyisi, M. G. Inhibition of guinea-pig and human sensory nerve activity and the cough reflex in guinea-pigs by cannabinoid (CB_2) receptor activation. *Br. J. Pharmacol.* **2003**, *140*, 261−268.
(14) Maekawa, T.; Nojima, H.; Kuraishi, Y.; Aisaka, K. The cannabinoid CB_2 receptor inverse agonist JTE-907 suppresses spontaneous itch-associated responses of NC mice, a model of atopic dermatitis. *Eur. J. Pharmacol.* **2006**, *542*, 179−183.
(15) Sánchez, C.; De Ceballos, M. L.; Gómez del Pulgar, T.; Rueda, D.; Corbacho, C.; Velasco, G.; Galve-Roperh, I.; Huffman, J. W.; Y Cajal, S. R.; Guzmán, M. "Inhibition of glioma growth in vivo by selective activation of the CB_2 cannabinoid receptor". *Cancer Res.* **2001**, *61*, 5784−5789.
(16) McKallip, R. J.; Lombard, C.; Fisher, M.; Martin, B. R; Ryu, S.; Grants, S.; Nagarkatti, P. S.; Nagarkatti, M. Targeting CB_2 cannabinoid receptors as a novel therapy to treat malignant lymphoblastic disease. *Blood* **2002**, *100*, 627−634.
(17) Raitio, K. H.; Salo, O. M.; Nevalainen, T.; Poso, A.; Jarvinen, T. Targeting the cannabinoid CB_2 receptor: mutations, modeling and development of CB_2 selective ligands. *Curr. Med. Chem.* **2005**, *12*, 1217−1237.
(18) Muccioli, G. G.; Lambert, D. M. Current knowledge on the antagonists and inverse agonists of cannabinoid receptors. *Curr. Med. Chem.* **2005**, *12*, 1361−1394.
(19) Stern, E.; Muccioli, G. G.; Millet, R.; Goossens, J.-F.; Farce, A.; Chavatte, P.; Poupaert, J. H.; Lambert, D. M.; Depreux, P.; Hénichart, J.-P. Novel 4-oxo-1,4-dihydroquinoline-3-carboxamide derivatives as new CB_2 cannabinoid receptors agonists: Synthesis, pharmacological properties, and molecular modeling. *J. Med. Chem.* **2006**, *49*, 70−79.
(20) Gould, R. G. and Jacobs, W. A. The synthesis of certain substituted quinolines and 5,6-benzoquinolines. *J. Am. Chem. Soc.* **1939**, *61*, 2890−2895.
(21) Mitscher, L. A.; Gracey, H. E.; Clark, G. W.; Suzuki, T. Quinolone antimicrobial agents. 1. Versatile new synthesis of 1-alkyl-1,4-dihydro-4-oxo-3-quinoline carboxylic acids. *J. Med. Chem.*, **1978**, *21*, 485−489.
(22) Hayashi, H.; Miwa, Y.; Ichikawa, S.; Yoda, N.; Miki, I.; Ishii, A.; Kono, M.; Yasuzawa, T.; Suzuki, F. 5-HT_3 receptor antagonists. 2. 4-Hydroxy-3-quinolinecarboxylic acid derivatives. *J. Med. Chem.* **1993**, *36*, 617−626.
(23) Jung, J.-C.; Jung, Y.-J.; Park, O.-S. Synthesis of 4-hydroxyquinolin-2(1*H*)-one analogues and 2-substituted quinolone derivatives. *J. Heterocycl. Chem.* **2001**, *38*, 61−67.
(24) White, J. D.; Yager, K. M.; Yakura, T. Synthetic studies of the pyrroloquinoline nucleus of the makaluvamine alkaloids. Synthesis of the topoisomerase II inhibitor makaluvamine D. *J. Am. Chem. Soc.* **1994**, *116*, 1831−1838.
(25) Four, P.; Guibe, F. Palladium-catalyzed reaction of tributyltin hydride with acyl chlorides. A mild, selective, and general route to aldehydes. *J. Org. Chem.* **1981**, *46*, 4439−4445.
(26) Chan, L.; Reddy, T. J.; Proulx, M.; Das, S. K.; Pereira, O.; Wang, W.; Siddiqui, A.; Yannopoulos, C. G.; Poisson, C.; Turcotte, N.; Drouin, A.; Alaoui-Ismaili, M. H.; Bethell, R.; Hamel, M.; L'Heureux, L.; Bilimoria, D.; Nguyen-Ba, N. Identification of *N*,*N*-disubstituted phenylalanines as a novel class of inhibitors of hepatitis C NS5B polymerase. *J. Med. Chem.* **2003**, *46*, 1283−1285.
(27) Crespo, M, I.; Gràcia, J.; Puig, C.; Vega, A.; Bou, J.; Beleta, J.; Doménech, T.; Ryder, H.; Segarra, V.; Palacios, J. M. Synthesis and biological evaluation of 2,5-dihydropyrazolo[4,3-*c*]quinolin-3-ones, a novel series of PDE 4 inhibitors with low emetic potential and antiasthmatic properties. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2661−2664.

(28) Podányi, B.; Keresztúri, G.; Vasvári-Debreczy, L.; Hermecz, I. An NMR study of halogenated 1,4-dihydro-1-ethyl-4-oxoquinoline-3-carboxylates. *Magn. Reson. Chem.* **1998**, *34*, 972−978.
(29) Stern, E.; Goossens, L.; Vaccher, C.; Bonte, J.-P.; Depreux, P.; Hénichart, J.-P. Goossens, J.-F. Chiral resolution of the enantiomers of new selective CB_2 receptor agonists by liquid chromatography on amylose stationary phases. *J. Pharm. Biomed. Anal.* **2007**, in press, doi: 10.1016/j.jpba.2007.01.044.
(30) Adams, J. T.; Bradsher, C. K.; Breslow, D. S.; Amore, T.; Hauser, C. R. Synthesis of antimalarials. VI. Synthesis of certain 1,5- and l,8-naphthyridine derivatives. *J. Am. Chem. Soc.* **1946**, *68*, 1317−1319.
(31) Springfield, S. A.; Marcantonio, K.; Ceglia, S.; Albaneze-Walker, J.; Dormer, P. G.; Nelson, T. D.; Murry, J. A. A convenient one-pot synthesis of 1,8-naphthyridones. *J. Org. Chem.* **2003**, *68*, 4598−4599.
(32) Sereni, L.; Tató, M.; Sola, F.; Brill, W. K.-D. Solid phase synthesis of 6-acylamino-1-alkyl/aryl-4-oxo-1,4-dihydrocinnoline-3-carboxamides. *Tetrahedron* **2005**, *60*, 8561−8577.
(33) Coste, J.; Frérot, E.; Jouin, P. Oxybenzotriazole free peptide coupling reagents for N-methylated amino acids. *Tetrahedron Lett.* **1991**, *32*, 1967−1970.
(34) Stern, E.; Millet, R.; Depreux, P.; Hénichart, J.-P. A versatile and efficient synthesis of 3-aroyl-1,4-dihydroquinolin-4-ones. *Tetrahedron Lett.* **2004**, *45*, 9257−9259.
(35) Muccioli, G. G.; Martin, D.; Scriba, G. K. E.; Poppitz, W.; Poupaert, J. H.; Wouters, J.; Lambert, D. M. Substituted 5,5′-diphenyl-2-thioxoimidazolidin-4-one as CB_1 cannabinoid receptor ligands: Synthesis and pharmacological evaluation. *J. Med. Chem.* **2005**, *48*, 2509−2517.
(36) Muccioli, G. G.; Wouters, J.; Scriba, G. K. E.; Poppitz, W.; Poupaert, J. H.; Lambert, D. M. 1-Benzhydryl-3-phenylurea and 1-benzhydryl-3-phenylthiourea derivatives: New templates among the CB_1 cannabinoid receptor inverse agonists. *J. Med. Chem.* **2005**, *48*, 7486−7490.
(37) Muccioli, G. G.; Wouters, J.; Charlier, C.; Scriba, G. K. E.; Pizza, T.; Di, Pace, P.; De Martino, P.; Poppitz, W.; Poupaert, J. H.; Lambert, D. M. Synthesis and activity of 1,3,5-triphenylimidazolidine-2,4-diones and 1,3,5-triphenyl-2-thioxoimidazolindin-4-ones: Characterization of new CB_1 cannabinoid receptor inverse agonists/antagonists. *J. Med. Chem.* **2006**, *49*, 872−882.
(38) Manera, C.; Benetti, V.; Castelli, M. P.; Cavallini, T.; Lazzarotti, S.; Pibiri, F.; Saccomanni, G.; Tuccinardi, T.; Vannacci, A.; Martinelli, A.; Ferrarini, P. L. Design, synthesis, and biological evaluation of new 1,8-naphthyridin-4(1*H*)-on-3-carboxamide and quinolin-4(1*H*)-on-3-carboxamide derivatives as CB_2 selective agonists. *J. Med. Chem.* **2006**, *49*, 5947−5957.
(39) Compound **30** in ref 19 corresponds to ALICB-179 (compound **3** in the present study).

JM070387H