7-Oxo-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxamides as Selective CB₂ Cannabinoid Receptor Ligands: Structural Investigations around a Novel Class of Full Agonists

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Ⓢ *Supporting Information*

ABSTRACT: Cannabinoid receptor agonists have gained attention as potential therapeutic targets of inflammatory and neuropathic pain. Here, we report the identification and optimization of a series of 7-oxo-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxamide derivatives as a novel chemotype of selective cannabinoid CB₂ receptor agonists. Structural modifications led to the identification of several compounds as potent and selective cannabinoid receptor agonists (**20**, hCB₂ K_i = 2.5 nM, SI = 166; **21**, hCB₂ K_i = 0.81 nM, SI = 383; **38**, hCB₂ K_i = 15.8 nM, SI > 633; **56**, hCB₂

21, hK_iCB₂ = 0.81 nM, hK_i CB₁= 310 nM

56, hK_iCB₂ = 8.12 nM, hK_i CB₁ > 10000 nM

(R)-58, hK_iCB₂ = 9.24 nM, hK_i CB₁ > 10000 nM

K_i = 8.12 nM, SI > 1231; (*R*)-**58**, hCB₂ K_i = 9.24 nM, SI > 1082). The effect of a chiral center on the biological activity was also investigated, and it was found that the (*R*)-enantiomers exhibited greater affinity at the CB₂ receptor than the (*S*)-enantiomers. In 3,5-cyclic adenosine monophosphate assays, the novel series behaved as agonists, exhibiting functional activity at the human CB₂ receptor.
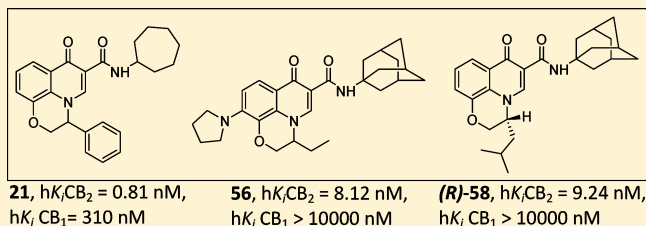
■ INTRODUCTION

Cannabinoids are the pharmacologically active components of *Cannabis sativa*, or marijuana, and are known to mediate some of their actions through the cannabinoid receptors. Two distinct cannabinoid receptors, named CB₁ and CB₂, have been cloned and characterized from mammalian tissues.[1,2] The CB₁ receptor is abundantly expressed in the central nervous system (CNS) and is responsible for the psychotropic side effects.[3−5] The CB₂ receptor is mainly found in cells of the immune system, though it may be up-regulated in the CNS under pathological conditions.[6,7] The main signal transduction pathway triggered is through Gi proteins, resulting in an inhibition of adenylate cylase activity and a decrease in cyclic adenosine monophosphate (cAMP) levels.[8]
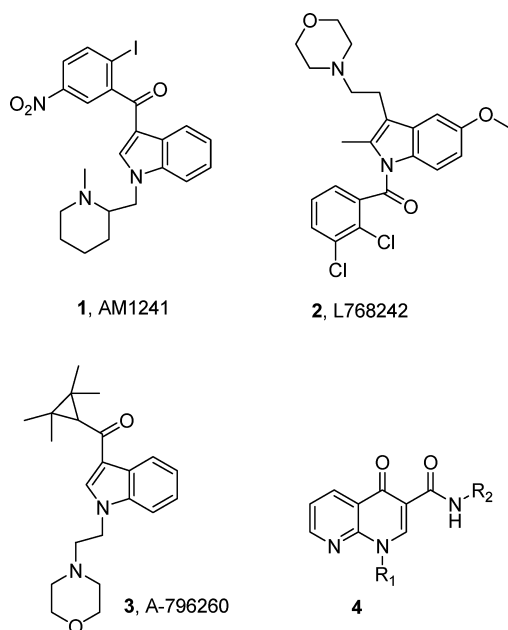
At the present time, CB₂ receptor agonists have gained attention as potential therapeutic targets in the management of neuropathic pain.[9] The available data suggest that CB₂-selective agonists show promise for suppressing inflammatory and neuropathic pain states. Behavioral, electrophysiological, and neurochemical studies all support a role for CB₂ receptor activation in modulating inflammatory nociception. Effects of CB₂-selective agonists in different inflammatory pain models (carrageenan, capsaicin, complete Freund's adjuvant, formalin, and arachidonic acid) have been demonstrated in many studies.[10] These considerations suggest that novel pharmacotherapies

targeting CB₂ receptors may have considerable therapeutic potential. Significant drug discovery efforts have been directed toward developing and characterizing CB₂-selective agonists, both in vitro and in vivo. Indeed, several CB₂-selective agonists have been described previously.[11−17] The selective ligands belong to a number of structural classes. Classical cannabinoids and cannabimimetic indoles have been the most systematically studied, and there are sufficient data available to permit some insight into the structural features of these compounds that lead to high affinity for the CB₂ receptor with little affinity for the CB₁ receptor. The chemical structures of a number of indole-derived CB₂ selective-agonists are shown in Figure 1. Compounds **1** (AM1241)[18] and **2** (L768242)[19] have condition-dependent CB₂ functional activities, while compound **3** (A-796260),[20] developed by Abbott Laboratories, was found to be a highly selective CB₂ agonist with little affinity for CB₁. These compounds have potent analgesic and anti-inflammatory activity in animal models, being especially effective in models of neuropathic pain.[18]

Several recently published studies also disclosed the 4(1*H*)-oxo-1,8-naphthyridine-3-carboxamide scaffold[16,21] (general structure **4**, Figure 1) and 4-oxo-1,4-dihydroquinoline-3-carboxamide

Figure 1. Representative cannabimimetic indoles and naphthyridine scaffold as CB$_2$-selective agonists.

K_i = 2.52, hCB$_1$ K_i = 420 nM, selectivity index (SI) = 168). This result led us to initiate a pharmacophore exploration and optimization effort around the oxazinoquinolin-4-one central scaffold. The novel target compounds are characterized by a chiral center and were initially obtained as racemates. The enantiopure forms of **31**, **33**, **35**, **36**, **51**, **58**, and **59** were also synthesized, starting from the corresponding enantiopure amino alcohols, to investigate the effect of the chiral center on the CB$_2$ receptor affinities.

The newly synthesized compounds were tested in competition binding assays toward both rat CB$_1$ (rCB$_1$) and CB$_2$ (rCB$_2$) receptors expressed in native tissues as rat brain or spleen and human CB$_1$ (hCB$_1$) and CB$_2$ (hCB$_2$) receptors expressed in CHO cells. Affinity data (K_i, nM) were used to calculate the selectivity of these novel compounds versus CB$_2$ receptors. These ligands were also examined in cAMP assays on hCB$_2$ CHO cells, with the aim of evaluating the inhibition of the adenylate cyclase activity and consequently the potency values (IC$_{50}$, nM).

■ CHEMISTRY

The target 7-oxo-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxamides **19**−**59** were prepared following two synthetic routes, depending upon the availability of the requisite α-halo ketone or amino alcohol to form the desired substitution patterns at C-2 and C-3 of the oxazine moiety. Racemic compounds **19**−**33** and **42**−**50** were obtained as depicted in Scheme 1. The benzoxazine[25] precursors **9a**−**g,i,j** were prepared in two steps by deprotonation of 2-nitrophenols **7a**−**c**, followed by alkylation with the appropriate α-halo ketones to give nitro ketones **8a**−**h**. In the second step, catalytic hydrogenation of the nitro ketones **8a**−**h** using 10% palladium-on-carbon in methanol (or methanol/THF (85:15) for 3-aryl derivatives) gave the intermediates **9a**−**g,i,j** by a concomitant reduction−reductive amination sequence. The intermediates **9i** and **9j** were apparently formed by a catalytic ring-opening reaction of the 2-(2-nitrophenoxy)-1-cyclopropylethanone (**8g**) and 2-(4-methyl-2-nitrophenoxy)-1-cyclopropylethanone (**8h**), respectively. Subsequent reaction with diethyl (ethoxymethylene)-malonate (DEEM) at 140 °C furnished the corresponding methylenemalonate derivatives **10a**−**g,i,j** in 70−90% yields. A thermally induced cyclization of **10a**−**g,i,j** in poly(phosphoric acid) (PPA)[26] for 1 h afforded the oxazinoquinoline ester

derivatives (example **5**, Figure 2)[17,22,23] as structurally diverse ligands endowed with high affinity and selectivity toward the CB$_2$ receptor. Some of these analogues were demonstrated to act as agonists or inverse agonists in functional activity assays, depending on the nature of the substituents on the different positions of the heterocyclic scaffold.
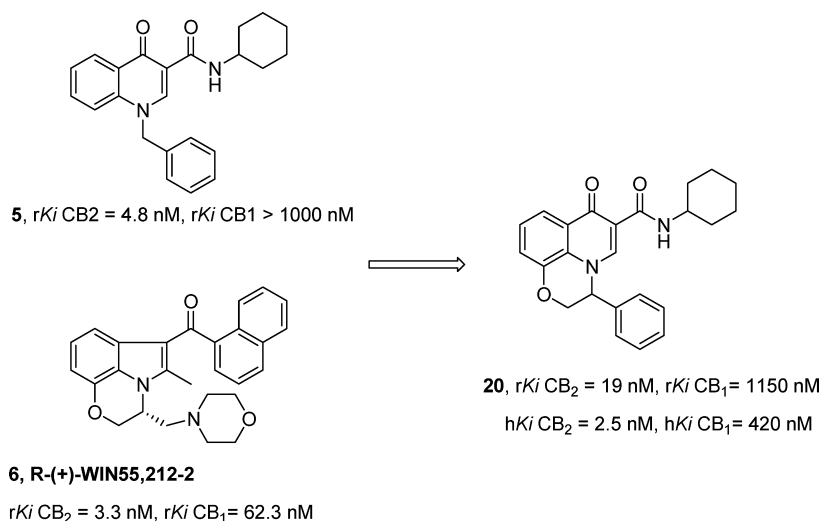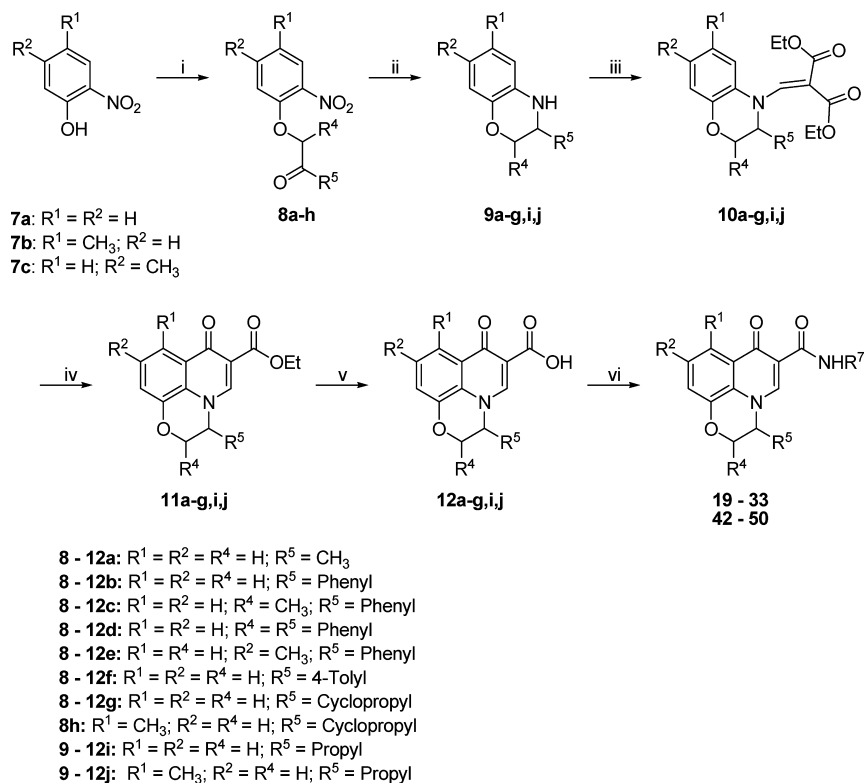
Within a research program to identify novel CB$_2$ agonists, we designed a hybrid chemical structure that incorporated the structural features of known cannabinoid ligands. Indeed, the design of the new oxazinoquinoline **20** (Figure 2) was based on the quinolone compound **5**[16] and the cannabimimetic indole **6** (WIN55,212-2, Figure 2), which is a potent cannabinoid agonist and has approximately a 19-fold selectivity for the CB$_2$ versus CB$_1$ receptor.[24] The new *N*-cyclohexyl-3,7-dihydro-7-oxo-3-phenyl-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxamide (**20**) was synthesized and tested in binding assays, exhibiting high affinity and selectivity for the CB$_2$ receptor (hCB$_2$

5, r*Ki* CB2 = 4.8 nM, r*Ki* CB1 > 1000 nM

6, R-(+)-WIN55,212-2

r*Ki* CB$_2$ = 3.3 nM, r*Ki* CB$_1$= 62.3 nM

20, r*Ki* CB$_2$ = 19 nM, r*Ki* CB$_1$= 1150 nM

h*Ki* CB$_2$ = 2.5 nM, h*Ki* CB$_1$= 420 nM

Figure 2. Rational design of novel CB$_2$ ligands.

Scheme 1[a]

7a: R^1 = R^2 = H
7b: R^1 = CH$_3$; R^2 = H
7c: R^1 = H; R^2 = CH$_3$

8 - 12a: R^1 = R^2 = R^4 = H; R^5 = CH$_3$
8 - 12b: R^1 = R^2 = R^4 = H; R^5 = Phenyl
8 - 12c: R^1 = R^2 = H; R^4 = CH$_3$; R^5 = Phenyl
8 - 12d: R^1 = R^2 = H; R^4 = R^5 = Phenyl
8 - 12e: R^1 = R^4 = H; R^2 = CH$_3$; R^5 = Phenyl
8 - 12f: R^1 = R^2 = R^4 = H; R^5 = 4-Tolyl
8 - 12g: R^1 = R^2 = R^4 = H; R^5 = Cyclopropyl
8h: R^1 = CH$_3$; R^2 = R^4 = H; R^5 = Cyclopropyl
9 - 12i: R^1 = R^2 = R^4 = H; R^5 = Propyl
9 - 12j: R^1 = CH$_3$; R^2 = R^4 = H; R^5 = Propyl

[a]Reagents and conditions: (i) α-halo ketone, K$_2$CO$_3$, acetone (anhydrous), rt, 16 h; (ii) H$_2$ (4 atm), 10% Pd/C, MeOH, 4 h; (iii) diethyl (ethoxymethylene)malonate, 140 °C, 2 h; (iv) poly(phosphoric acid), 140 °C, 1 h; (v) 10% NaOH, CH$_3$OH, 80 °C, 1 h; (vi) amine, EDC, HOBt, DMF, rt, 6 h or amine, DIEA, HBTU, DMF, rt, 16 h.

derivatives 11a−g,i,j in 75−95% yields. After saponification of the ethyl ester functionality of compounds 11a−g,i,j (sodium hydroxide), the resulting carboxylic acids 12a−g,i,j were engaged in an amidation reaction with the appropriate amines under peptide coupling conditions to afford the target amide compounds 19−33 and 42−50.

The synthesis of target compounds 34−41, 51−54, 58, and 59 was accomplished using a procedure similar to that utilized for preparing optically active ofloxacine (Scheme 2).[27] Ethyl 3-(2,3-difluorophenyl)-, 3-(2,3,4-trifluorophenyl)-, and 3-(2,3,4,5-tetrafluorophenyl)-3-oxopropanoates (14a−c, respectively) were prepared from the corresponding benzoic acids (13a−c) by reaction with carbonyldiimidazole (CDI) in THF to afford the imidazolide, followed by condensation with the magnesium salt of monoethyl malonate under essentially neutral conditions (90% yield).[28] Subsequent condensation with triethyl orthoformate in refluxing acetic anhydride produced the ethyl 2-(ethoxymethylene)propionates 15a−c. These intermediates were reacted with the appropriate amino alcohols in dry methylene chloride in an addition−elimination sequence to afford the intermediates 16a−i. Cyclization using potassium carbonate (K$_2$CO$_3$) in dimethylformamide (DMF) at 130 °C followed by saponification afforded the carboxylic acids 18a−i that were coupled with the appropriate amines (in the same manner as reported in Scheme 1) to afford the final compounds 34−41, 51−54, 58, and 59. In an identical fashion, reaction of intermediate 15a with the appropriate (R)- or (S)-amino alcohol led to the preparation of the corresponding enantiomerically pure derivatives itemized in Table 3.
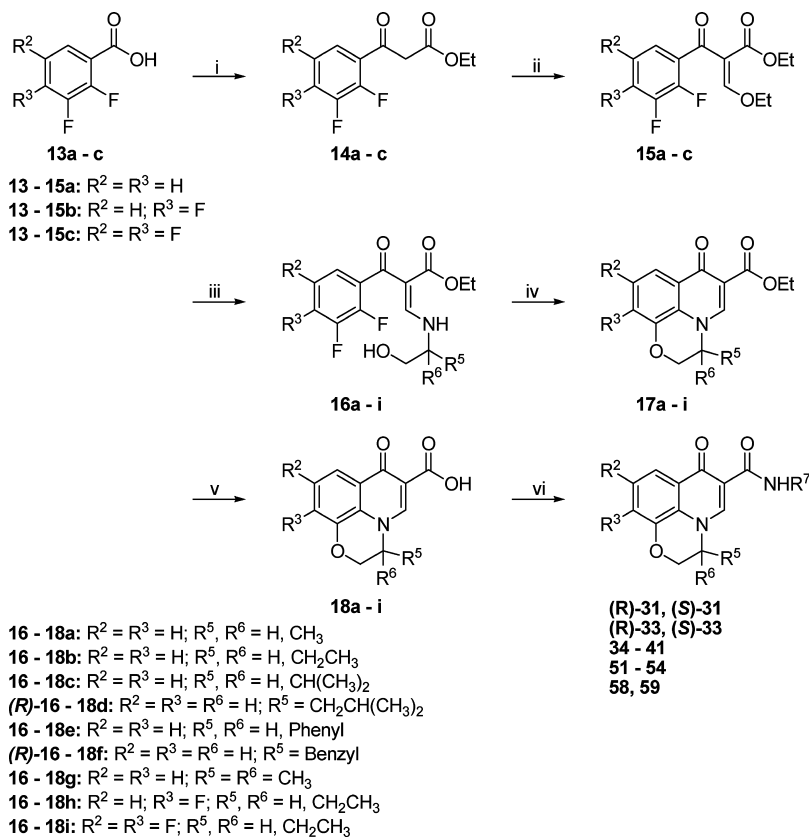
The target compounds 55−57 were obtained by displacement of the fluorine substituent at C-10 by treating the amide 53 with different nucleophiles (sodium methoxide, pyrrolidine, N-methylpiperazine) in alkaline conditions (Scheme 3). The 4-methylpiperazine derivative 57 was converted to the hydrochloride salt by treatment with 1,4-dioxane saturated with gaseous hydrogen chloride.

■ RESULTS AND DISCUSSION

Each of the newly synthesized compounds was examined in [³H]CP-55,940 competition binding experiments for their affinity and selectivity toward the rat and human recombinant CB$_1$ and CB$_2$ receptors (Tables 1−3). Among the 51 novel 7-oxooxazinoquinoline-6-carboxamide derivatives, 40 of the compounds displayed high affinity for the CB$_2$ receptors (K_i values less than 100 nM).

An initial set of 12 compounds (19−30, Table 1) was synthesized possessing an aromatic moiety (phenyl or 4-tolyl) at C-3 of the heterocycle. The substituents on the carboxamide moiety at C-6 were initially selected on the basis of other cannabinoid pharmacophores, such as those present in the naphthyridine[16,21,29] (4) and quinolone[17,22,23] (5) derivatives.

The 3-phenyl analogues bearing a cyclohexyl (20), cycloheptyl (21), adamant-1-yl (22), or 3,5-dimethyladamant-1-yl (23) carboxamide displayed high affinity at the CB$_2$ and low affinity at the CB$_1$ receptors. In particular, the oxazinoquinolinones 21 and 23 were the most potent and selective compounds in this group (21, h K_i = 0.81 nM, SI = 383; 23, h K_i = 3.45, SI = 133). The cyclopentyl carboxamide derivative 19 showed lower affinity and poor selectivity at the CB

Scheme 2[a]

13 - 15a: $R^2 = R^3 = H$
13 - 15b: $R^2 = H$; $R^3 = F$
13 - 15c: $R^2 = R^3 = F$

16 - 18a: $R^2 = R^3 = H$; R^5, $R^6 = H$, CH_3
16 - 18b: $R^2 = R^3 = H$; R^5, $R^6 = H$, CH_2CH_3
16 - 18c: $R^2 = R^3 = H$; R^5, $R^6 = H$, $CH(CH_3)_2$
(R)-16 - 18d: $R^2 = R^3 = R^6 = H$; $R^5 = CH_2CH(CH_3)_2$
16 - 18e: $R^2 = R^3 = H$; R^5, $R^6 = H$, Phenyl
(R)-16 - 18f: $R^2 = R^3 = R^6 = H$; $R^5 = $ Benzyl
16 - 18g: $R^2 = R^3 = H$; $R^5 = R^6 = CH_3$
16 - 18h: $R^2 = H$; $R^3 = F$; R^5, $R^6 = H$, CH_2CH_3
16 - 18i: $R^2 = R^3 = F$; R^5, $R^6 = H$, CH_2CH_3

(R)-31, (S)-31
(R)-33, (S)-33
34 - 41
51 - 54
58, 59

[a]Reagents and conditions: (i) CDI, THF, $(C_2H_5O)_2Mg$, monoethyl malonate, rt, 16 h; (ii) $CH(OEt)_3$, Ac_2O, 110 °C, 3 h; (iii) appropriate (R)-, (S)-, or (R,S)-amino alcohol, CH_2Cl_2, rt, 1 h; (iv) K_2CO_3, DMF, 130 °C, 7 h; (v) 10% NaOH, CH_3OH, 80 °C, 1 h; (vi) amine, EDC, HOBt, DMF, rt, 6 h or amine, DIEA, HBTU, DMF, rt, 16 h.
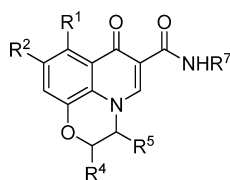
Scheme 3[a]
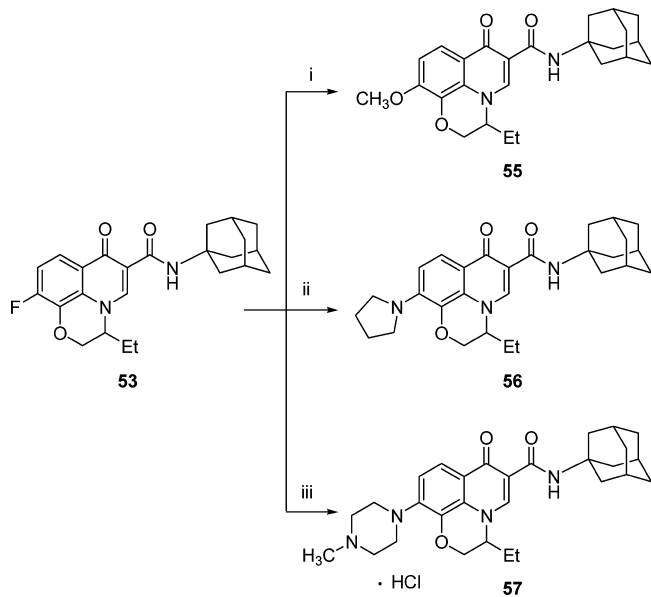
[a]Reagents and conditions: (i) CH_3ONa, THF, 50 °C, 16 h; (ii) K_2CO_3, DMF, pyrrolidine, 100 °C, 10 h; (iii) K_2CO_3, DMF, 1-methylpiperazine, 100 °C, 10 h, then 1,4-dioxane saturated with HCl gas, 0 °C, 30 min.

receptors, suggesting the important role of the carboxamide moiety, as previously reported by Corelli et al.[22]

Introduction of a methyl group at C-2 of the oxazine moiety, as with compounds **24** and **25**, resulted in a 24–27-fold decrease of affinity (h K_i = 536 and 332 nM, respectively) relative to that of the analogous compounds lacking the methyl group (compounds **20** and **22**, respectively). Compound **26** with a phenyl group at C-2 was inactive at both CB receptors, confirming that the affinity of this class of molecules is quite sensitive to modifications at C-2 of the oxazinoquinoline nucleus. Interestingly, the introduction of a methyl group at the *para*-position of the aryl moiety at C-3 (**27** and **28**) resulted in a significant loss of affinity and selectivity for the CB_2 and CB_1 receptors in comparison with those of the corresponding compounds **20** and **22** lacking this substituent, suggesting a less severe steric constraint at this position. Introduction of a methyl group at C-9 of the heterocyclic nucleus (**29**, h K_i of 18.4 nM) resulted in a modest decrease in affinity and selectivity compared to those of the analogue lacking the methyl group (**20**). The C-9 methyl derivative **30** was not tested due to its low solubility in DMSO/water.

The structure–activity relationship (SAR) studies were extended by replacement of the C-3 phenyl ring with a series of aliphatic moieties to evaluate the effect of the chain length and branching (Table 2, compounds **31–51**). Introduction of a methyl group at this position seems to indicate that this may be a site for enhancement in selectivity, although with an apparent loss in affinity. Derivatives **31–33** each displayed a lower affinity for both CB_2 and CB_1 receptors relative to compounds **20–22** bearing a phenyl moiety at this position, although the selectivity for the CB_2 receptor was improved with the

Table 1. Affinity (K_i, nM) and Selectivity Index (SI) of Novel 5-Aryl CB Compounds on Rat and Human CB_1 and CB_2 Receptors and Potency (IC_{50}, nM) of the Novel CB Compounds in hCB_2 CHO Cells on cAMP Assays[a]

19-30

compd	R^1	R^2	R^4	R^5	R^7	rat CB_1[b]	rat CB_2[c]	hCB_1[d]	hCB_2[e]	SI	hCB_2 IC_{50}[f] (nM)
								K_i (nM)			
6				(R)-(+)-WIN55,212-2		15.6 ± 1.4	7.58 ± 0.72	12.4 ± 1.3	4.53 ± 0.42	2.74	15.7 ± 1.3
19	H	H	H	phenyl	cyclopentyl	150 ± 16	110 ± 12	132 ± 12	98 ± 10	1.35	472 ± 43
20	H	H	H	phenyl	cyclohexyl	1150 ± 110	19.3 ± 2.3	420 ± 38	2.52 ± 0.21	166	15.2 ± 1.7
21	H	H	H	phenyl	cycloheptyl	372 ± 36	14.7 ± 1.5	310 ± 29	0.81 ± 0.07	383	5.23 ± 0.42
22	H	H	H	phenyl	adamant-1-yl	670 ± 65	18.3 ± 2.4	265 ± 24	14.2 ± 1.5	19	26 ± 3
23	H	H	H	phenyl	3,5-dimethyladamant-1-yl	545 ± 53	46 ± 3	460 ± 48	3.45 ± 0.42	133	18.3 ± 1.9
24	H	H	Me	phenyl	cyclohexyl	3520 ± 320	710 ± 44	3126 ± 288	536 ± 58	5.83	2749 ± 245
25	H	H	Me	phenyl	adamant-1-yl	2640 ± 225	443 ± 26	2435 ± 231	332 ± 28	7.33	1684 ± 152
26	H	H	phenyl	phenyl	adamant-1-yl	>10000	>10000	>10000	>10000	ND	ND
27	H	H	H	4-tolyl	cyclohexyl	4566 ± 425	547 ± 32	4108 ± 380	468 ± 42	8.78	2457 ± 213
28	H	H	H	4-tolyl	adamant-1-yl	4154 ± 410	482 ± 43	3877 ± 362	412 ± 40	9.41	2215 ± 211
29	H	Me	H	phenyl	cyclohexyl	1568 ± 164	25 ± 3	1346 ± 125	18.4 ± 1.9	73	110 ± 9
30	H	Me	H	phenyl	adamant-1-yl	ND	ND	ND	ND	ND	472 ± 43

[a]The data are expressed as the mean ± SEM of n = 4 independent experiments. [b]The affinity values were calculated by using [³H]CP-55,940 as a radioligand on rat brain for CB_1 receptors. [c]The affinity values were calculated by using [³H]CP-55,940 as a radioligand on rat spleen for CB_2 receptors. [d]The affinity values were calculated by using [³H]CP-55,940 as a radioligand on human CB_1 CHO membranes. [e]The affinity values were calculated by using [³H]CP-55,940 as a radioligand on human CB_2 CHO membranes. [f]IC_{50} values were calculated on cAMP experiments performed on human CB_2 CHO cells.

cycloheptyl and adamant-1-yl amides (**32** and **33**, respectively). The addition of a *gem*-dimethyl group at C-3 (compound **52**) maintained affinity relative to that of analogue **33**, while the selectivity was dramatically reduced (K_i = 56 nM, SI = 4). Optimal activity with this group of compounds was obtained with the cycloheptyl moiety on the carboxamide chain (compound **32**, h K_i = 38 nM, SI > 263), in analogy to the 3-phenyl series.
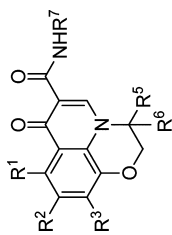
Extending the aliphatic chain to an ethyl group (**34−36**) enhanced affinity for both the CB_1 and CB_2 receptors, although there was an apparent loss in selectivity. Further extension of the aliphatic chain at C-3 to a propyl group (**42−45**) provided further improvements in receptor affinity without significantly affecting selectivity relative to those of the corresponding ethyl derivatives, although the compound with a cycloheptyl amide lacked sufficient solubility in DMSO/water mixtures to permit evaluation. In particular, the 3-propyl derivative with a cyclohexyl carboxamide (compound **42**) proved to have the greatest affinity for the CB_2 receptor affinity in this series, with an h K_i value of 0.32 nM. Replacing the *n*-propyl moiety at C-3 with a cyclopropyl (**48−50**) or 2-propyl (compound **51**) group led to a loss in affinity compared to that of the analogous compounds with the *n*-propyl moiety.

In the 3-ethyl series of compounds, additional modifications on the heterocyclic nucleus were introduced. The introduction of a fluorine atom at the C-10 position (compound **53**) did not significantly alter affinity at the CB_2 receptor relative to that of compound **36**, although the selectivity decreased about 1.5-fold. The 9,10-difluoro derivative **54** was found to be less active than the 10-fluoro compound **53** (h K_i = 33 vs 7.34 nM) without

impacting selectivity. Similarly, the introduction of a methyl at C-8 (**46** and **47**) in the 3-propyl series led to a significant reduction in affinity, particularly at the CB_2 receptor, leading also to reduced selectivity relative to that of the corresponding compounds lacking the methyl moiety (**42** and **44**, respectively). Together, these compounds indicate that the two receptor subtypes are quite sensitive to modifications in this portion of the molecular scaffold. Additional substitutions at C-10 allowed us to explore this sensitivity further. Compounds **55** and **57**, in which the fluorine atom of compound **53** is displaced by a methoxy or *N*-methylpiperazine moiety, retain high receptor binding affinity, especially compound **55** at the CB_2 receptor, suggesting a difference between the two receptor subtypes in steric tolerance at this position. Better results were obtained with compound **56**, in which the 10-fluorine atom was replaced by a pyrrolidine moiety, showing high affinity and remarkable selectivity at the CB_2 receptor (h K_i = 8.12, SI > 1231). Such a result is in accordance with Manera's findings[16] regarding the increased CB_2 selectivity for their 7-substituted quinolones.

Within the 3-ethyl series, we also examined the effect on receptor affinity and selectivity of structural modifications at the 6-carboxamide side chain (compounds **34−41**). As seen with the 3-phenyl series, the cycloheptyl amide **35** shows greater affinity and selectivity for the CB_2 receptor than the cyclohexyl amide **34**. In contrast, the adamant-1-yl amide **36** retains affinity for the CB_2 receptor equivalent to that of the cycloheptyl derivative while showing a significant increase in selectivity. Moving the point of attachment of the adamantane ring from the bridgehead 1-position (**36**) to the bridging 2-position (**37**)

Table 2. Affinity (K_i, nM) and Selectivity Index (SI) of the Novel CB Compounds on Rat and Human CB_1 and CB_2 Receptors and Potency (IC_{50}, nM) of the Novel CB Compounds in hCB_2 CHO Cells on cAMP Assays[a]
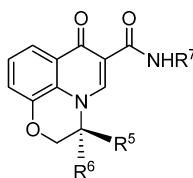

31-57

compd	R¹	R²	R³	R⁵	R⁶	R⁷	K_i (nM) rat CB_1[b]	rat CB_2[c]	hCB_1[d]	hCB_2[e]	SI	hCB_2 IC_{50}[f] (nM)
6				(R)-(+)-WIN55,212-2			15.6 ± 1.4	7.58 ± 0.72	12.4 ± 1.3	4.53 ± 0.42	2.74	15.7 ± 1.3
31	H	H	H	Me	H	cyclohexyl	2630 ± 254	65 ± 6	2150 ± 207	60 ± 8	36	245 ± 28
32	H	H	H	Me	H	cycloheptyl	>10000	52 ± 3	>10000	38 ± 4	>263	210 ± 23
33	H	H	H	Me	H	adamant-1-yl	>10000	55 ± 4	>10000	47 ± 4	>212	230 ± 22
34	H	H	H	ethyl	H	cyclohexyl	972 ± 83	24 ± 2	821 ± 78	22 ± 2	37	62 ± 7
35	H	H	H	ethyl	H	cycloheptyl	498 ± 52	11.4 ± 1.3	433 ± 42	9.24 ± 0.92	47	42 ± 3
36	H	H	H	ethyl	H	adamant-1-yl	725 ± 73	13.5 ± 1.5	689 ± 64	7.83 ± 0.82	88	38 ± 4
37	H	H	H	ethyl	H	adamant-2-yl	425 ± 39	16.1 ± 1.5	389 ± 35	13.2 ± 1.2	30	57 ± 6
38	H	H	H	ethyl	H	5-methylhexan-2-yl	>10000	196 ± 17	>10000	15.8 ± 1.4	>633	62 ± 6
39	H	H	H	ethyl	H	pyridin-4-yl	1375 ± 112	183 ± 16	1150 ± 104	152 ± 14	8	683 ± 66
40	H	H	H	ethyl	H	thiazol-2-yl	1622 ± 157	324 ± 28	1365 ± 115	265 ± 21	5	1127 ± 104
41	H	H	H	ethyl	H	N,N-disopropyl	>10000	104 ± 10	>10000	85 ± 9	>118	423 ± 37
42	H	H	H	propyl	H	cyclohexyl	13.4 ± 1.5	1.84 ± 0.16	10.2 ± 0.9	0.32 ± 0.03	32	1.53 ± 0.16
43	H	H	H	propyl	H	cycloheptyl	ND	ND	ND	ND	ND	ND
44	H	H	H	propyl	H	adamant-1-yl	240 ± 25	2.73 ± 0.25	215 ± 20	2.34 ± 0.21	92	15.3 ± 1.4
45	H	H	H	propyl	H	3,5-dimethyladamant-1-yl	476 ± 44	10.7 ± 1.1	200 ± 23	3.62 ± 0.41	55	20 ± 3
46	Me	H	H	propyl	H	cyclohexyl	874 ± 78	43 ± 4	756 ± 72	38 ± 4	20	122 ± 11
47	Me	H	H	propyl	H	adamant-1-yl	476 ± 45	13.2 ± 1.1	450 ± 43	10.4 ± 1.1	43	42 ± 5
48	H	H	H	cyclopropyl	H	cyclohexyl	123 ± 12	18.2 ± 1.7	102 ± 9	15.3 ± 1.4	7	67 ± 6
49	H	H	H	cyclopropyl	H	cycloheptyl	101 ± 10	3.52 ± 0.36	91 ± 9	3.12 ± 0.27	29	12.4 ± 1.3
50	H	H	H	cyclopropyl	H	adamant-1-yl	482 ± 46	10.3 ± 1.2	389 ± 37	8.92 ± 0.91	44	32 ± 3
51	H	H	H	isopropyl	H	adamant-1-yl	366 ± 31	4.22 ± 0.38	323 ± 28	3.74 ± 0.32	86	12.4 ± 1.7
52	H	H	H	Me	Me	adamant-1-yl	276 ± 22	68 ± 6	221 ± 18	56 ± 5	4	242 ± 23
53	H	H	F	ethyl	H	adamant-1-yl	452 ± 44	9.51 ± 0.88	389 ± 34	7.34 ± 0.68	53	27 ± 2
54	H	F	F	ethyl	H	adamant-1-yl	1824 ± 176	37 ± 4	1752 ± 165	33 ± 3	53	145 ± 12
55	H	H	OMe	ethyl	H	adamant-1-yl	589 ± 51	9.12 ± 0.86	521 ± 48	6.78 ± 0.62	77	24 ± 3
56	H	H	pyrrolidin-1-yl	ethyl	H	adamant-1-yl	>10000	10.5 ± 1.1	>10000	8.12 ± 0.83	>1231	29 ± 3
57	H	H	4-methylpiperazin-1-yl	ethyl	H	adamant-1-yl	>10000	61 ± 5	>10000	42 ± 3	>238	196 ± 17

[a]The data are expressed as the mean ± SEM of n = 4 independent experiments. [b]The affinity values were calculated by using [³H]CP-55,940 as a radioligand on rat brain for CB_1 receptors. [c]The affinity values were calculated by using [³H]CP-55,940 as a radioligand on rat spleen for CB_2 receptors. [d]The affinity values were calculated by using [³H]CP-55,940 as a radioligand on human CB_1 CHO membranes. [e]The affinity values were calculated by using [³H]CP-55,940 as a radioligand on human CB_2 CHO membranes. [f]IC_{50} values were calculated on cAMP experiments performed on human CB_2 CHO cells.

Table 3. Affinity (K_i, nM) and Selectivity Index (SI) of the Novel Chiral CB Compounds on Rat and Human CB$_1$ and CB$_2$ Receptors and Potency (IC$_{50}$, nM) of the Novel CB Compounds in hCB$_2$ CHO Cells on cAMP Assays[a]

31, 33, 35, 36, 51, 58, 59

				K_i (nM)					
compd	R^5	R^6	R^7	rat CB$_1$[b]	rat CB$_2$[c]	hCB$_1$[d]	hCB$_2$[e]	SI	hCB$_2$ IC$_{50}$[f] (nM)
(R)-31	H	Me	cyclohexyl	3560 ± 355	30 ± 4	2866 ± 245	24 ± 3	119	90 ± 8
(S)-31	Me	H	cyclohexyl	5242 ± 534	250 ± 27	4652 ± 425	188 ± 16	25	724 ± 75
(R)-33	H	Me	adamant-1-yl	>10000	52 ± 5	>10000	47 ± 3	>212	153 ± 14
(S)-33	Me	H	adamant-1-yl	>10000	86 ± 8	>10000	78 ± 7	>128	250 ± 23
(R)-35	H	ethyl	cyclohepty	126 ± 11	6.03 ± 0.52	105 ± 9	4.12 ± 0.38	25	17.2 ± 1.6
(S)-35	ethyl	H	cycloheptyl	913 ± 87	203 ± 19	843 ± 77	187 ± 16	4.5	682 ± 67
(R)-36	H	ethyl	adamant-1-yl	242 ± 21	6.17 ± 0.53	197 ± 15	4.93 ± 0.45	40	18.1 ± 1.7
(S)-36	ethyl	H	adamant-1-yl	653 ± 58	97 ± 8	578 ± 44	88 ± 7	7	413 ± 38
(R)-51	H	isopropyl	adamant-1-yl	95 ± 9	1.75 ± 0.14	88 ± 7	1.24 ± 0.11	71	9.84 ± 0.91
(S)-51	isopropyl	H	adamant-1-yl	864 ± 82	19.3 ± 1.9	858 ± 79	16.2 ± 1.8	53	55 ± 6
(R)-58	H	isobutyl	adamant-1-yl	>10000	10.2 ± 1.1	>10000	9.24 ± 0.84	>1082	36 ± 3
(R)-59	H	benzyl	adamant-1-yl	121 ± 10	4.65 ± 0.43	105 ± 9	3.72 ± 0.32	28	17.5 ± 1.8

[a]The data are expressed as the mean ± SEM of n = 4 independent experiments. [b]The affinity values were calculated by using [^{3}H]CP-55,940 asa radioligand on rat brain for CB$_1$ receptors. [c]The affinity values were calculated by using [^{3}H]CP-55,940 as a radioligand on rat spleen for CB$_2$ receptors. [d]The affinity values were calculated by using [^{3}H]CP-55,940 as a radioligand on human CB$_1$ CHO membranes. [e]The affinity values were calculated by using [^{3}H]CP-55,940 as a radioligand on human CB$_2$ CHO membranes. [f]IC$_{50}$ values were calculated on cAMP experiments performed on human CB$_2$ CHO cells.

resulted in less affinity and selectivity. Replacing the aliphatic carbocyclic cycloheptyl amide moiety with a heteroaromatic 4-pyridyl (39) or thiazol-2-yl (40) moiety caused a dramatic loss of affinity and almost complete loss of selectivity for the CB$_2$ receptor. Similarly, replacing the cycloheptyl amide with the bulky, noncyclic N,N-diisopropyl amide (41) led to a significant loss of affinity at the CB$_2$ receptor, although selectivity was retained or even enhanced. Optimal activity and selectivity in this series of 3-ethyl derivatives were obtained with the 5-methylhexan-2-yl carboxamide chain (38, h K_i = 15.8 nM, SI > 633). These data show that affinity and selectivity for the CB$_2$ receptor are quite sensitive to modifications of the 6-carboxamido group.

As noted above, the presence of a *gem*-dimethyl group (compound 52, h K_i = 56 nM, SI = 4) does not significantly alter affinity for the CB$_2$ receptor relative to that of the monomethyl analogue 33 (h K_i = 47 nM, SI > 212), but has a profound effect on selectivity. This suggested the possibility of a difference between the two receptor subtypes in the stereofacial preference for substituents at this position. To evaluate this possibility, we prepared a number of compounds (31, 33, 35, 36, and 51) as single enantiomers rather than racemic mixtures (Table 3). With the two compounds bearing a C-3 methyl group (31 and 33), a stereochemical preference for the (R)-enantiomers over the corresponding (S)-enantiomers is observed. Interestingly, the (R)-31 enantiomer (h K_i = 24 nM, SI = 119) displays a greater affinity for the CB$_2$ receptor than the racemic mixture (h K_i = 60 nM, SI = 36), but apparently poorer affinity for the CB$_1$ receptor. As a consequence, (R)-31 also shows greater selectivity than the racemic mixture. Similarly, the (R)-enantiomer of 33 binds with greater affinity than the (S)-enantiomer, although the (R)-enantiomer does not appear to offer any improvement in affinity or selectivity over the

racemic compound. Extending this analysis to compounds bearing an ethyl group at C-3, we found that the (R)-enantiomers of 35 and 36 both show approximately a 2-fold enhancement in affinity over the racemic compounds. However, there is also an approximately 2-fold loss in selectivity of the (R)-enantiomers for the CB$_2$ receptor. This reflects a nearly 4-fold improvement in affinity of the (R)-enantiomers for the CB$_1$ receptor. In contrast, the (S)-enantiomers of 35 and 36 displayed an 11−20-fold loss in affinity for the CB$_2$ receptor with almost complete loss of selectivity. Similarly, with the C-3 isopropyl derivative 51, the (R)-enantiomer bound with greater affinity to both the CB$_1$ and CB$_2$ receptors than the (S)-enantiomer or the racemic mixture ((R)-51, hCB$_1$ K_i = 88 nM, hCB$_2$ K_i = 1.24 nM; (S)-51, hCB$_1$ K_i = 858 nM, hCB$_2$ K_i = 16.2 nM; 51, hCB$_1$ K_i = 323 nM, hCB$_2$ K_i = 3.74 nM). However, the affinity enhancement was slightly greater for the CB$_1$ receptor, resulting in an apparent loss in selectivity relative to that of the racemic mixture.

Recognizing that a significant enhancement in both affinity and selectivity had been seen only with (R)-31 and (R)-33, compounds bearing a methyl at C-3, we hypothesized that introducing a methylene spacer between the oxazine nucleus and the bulky isopropyl moiety may lead to further enhancements in affinity and selectivity. This led to the synthesis and evaluation of (R)-58, the enantiopure derivative bearing an isobutyl moiety at C-3. Indeed, this compound was found to bind to the CB$_2$ receptor with high affinity and exceptional selectivity (h K_i = 9.24 nM, SI > 1082). In light of this finding, we prepared (R)-59 by introduction of a benzyl moiety at C-3, effectively placing a methylene spacer between the oxazine ring and the phenyl moiety of compound 22. As expected, the compound had improved affinity at the CB$_2$ receptor, with a

K_i of 3.72 nM, and a modest improvement in selectivity (SI = 28) relative to those of the C-3 phenyl derivative **22**.

The potency of the novel compounds was measured in a functional assay, evaluating the capability of the compounds to inhibit forskolin-induced cAMP production in hCB$_2$ CHO cells (Tables 1−3). The competition binding curves obtained from receptor binding experiments (Figure 3A) and the dose−response
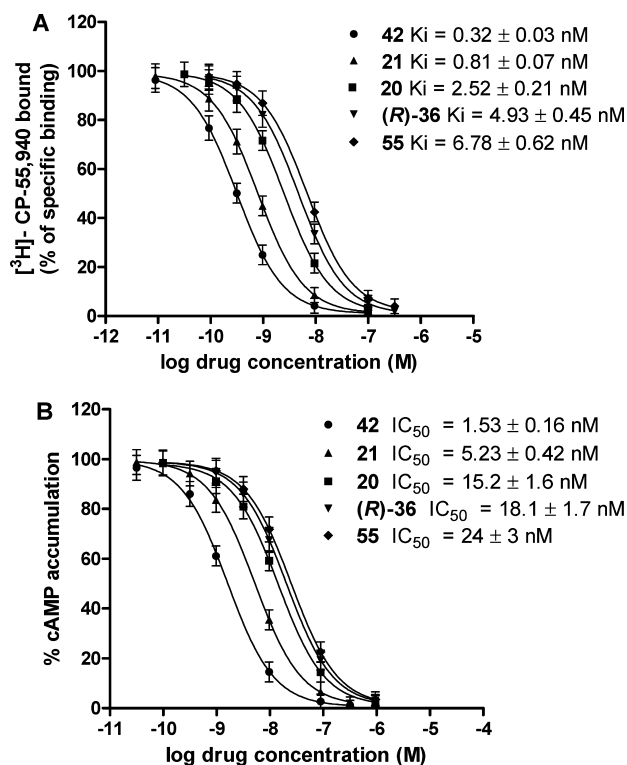
Figure 3. Affinity (K_i, nM) and potency (IC$_{50}$, nM) of selected novel CB compounds: (A) competition curves on hCB$_2$ receptors; (B) inhibition curves of forskolin-stimulated cAMP accumulation in hCB$_2$ CHO cells. Results are given as the mean ± SEM (n = 4 independent experiments).

curves (Figure 3B) from cAMP assays are shown for select compounds (**42**, **20**, **21**, (*R*)-**36**, and **55**). High affinity values, expressed as K_i values, are seen to be closely associated with high potency, represented by IC$_{50}$ values (Tables 1−3 and Figure 3). The affinity and potency of the novel compounds were also compared with those of the reference cannabimimetic compound **6** that is characterized by high affinity and potency but very low selectivity (Tables 1−3). The functionality of this new series of oxazinoquinolones was not affected by several modifications, showing agonistic behavior, not in accordance with the Stern et al. investigations.[23] Interestingly, the affinity values of the examined compounds at the respective rat and human receptors were not significantly different, suggesting a high degree of similarity between the two receptor subtypes across the two species. As such, these data support the evaluation of in vivo efficacy in rodent animal models of inflammatory and/or neuropathic pain.

CONCLUSION

We have discovered the 7-oxo-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxamide chemotype as a novel series possessing significant cannabinoid CB$_2$ receptor affinity. A major focus of the optimization effort was to increase selectivity to avoid or

reduce the potential CB$_1$-associated CNS adverse effects of this novel series.

The potency of the novel compounds was measured in functional assays, with high potency values (represented by IC$_{50}$) that are closely correlated with the high affinity values (expressed as K_i), revealing that the novel series behaves as CB$_2$ receptor agonists. This novel series of compounds offers an attractive starting point for further optimization and represents novel pharmacological tools to evaluate the therapeutic potential of CB$_2$ agonists in various disease settings, especially inflammatory pain.

EXPERIMENTAL SECTION

Pharmacology. Competition binding experiments were performed by using [^{3}H]CP-55,940 (specific activity 180 Ci/mmol) that was obtained from Perkin-Elmer Life and Analytical Sciences (Waltham, MA). Human CB$_1$ and CB$_2$ receptors expressed in CHO cells were purchased from Perkin-Elmer Life and Analytical Sciences. All other reagents were of analytical grade and were obtained from commercial sources.

Competition Binding Experiments on CB$_1$ and CB$_2$ Receptors. To study CB$_1$ receptors, rat brain (male Sprague−Dawley rats, Charles River, Wilmington, MA) was removed, frozen in liquid nitrogen, and stored at −80 °C. The rat brain tissue was suspended in 50 mM Tris−HCl buffer, pH 7.4, at 4 °C. The suspension was homogenized with a Polytron and centrifuged for 10 min at 2000g, and the supernatant was centrifuged again for 20 min at 40000g. The pellet was resuspended in a buffer containing 50 mM Tris−HCl, 1 mM EDTA, 3 mM MgCl$_2$, and 0.5% fatty acid free bovine serum albumin (BSA), pH 7.4, at 30 °C.

Competition binding experiments to rat CB$_1$ receptors were carried out using [^{3}H]CP-55,940 (1.0 nM), a membrane suspension containing 40 μg of protein/100 μL and different concentrations (1 nM to 10 μM) of the examined compounds.[30]

To investigate CB$_2$ receptors, a [^{3}H]CP-55,940 binding assay was performed by using rat spleen (male Sprague−Dawley rats, Charles River) that was homogenized in 50 mM Tris−HCl buffer, pH 7.4, at 4 °C with a Polytron and centrifuged for 10 min at 2000g, and the supernatant was centrifuged for 20 min at 40000g. The pellet was resuspended in a buffer containing 50 mM Tris−HCl, 1 mM EDTA, 3 mM MgCl$_2$, and 0.5% fatty acid free BSA, pH 7.4, at 30 °C. Competition binding experiments to rat CB$_2$ receptors were performed using [^{3}H]CP-55,940 (0.5 nM), a membrane suspension containing 80 μg of protein/100 μL and different concentrations (1 nM to 10 μM) of the examined compounds.[30]

Human CB$_1$ and CB$_2$ receptors expressed in CHO cells were grown adherently and maintained in Ham's F12 containing 10% fetal bovine serum, penicillin (100 U/mL), streptomycin (100 μg/mL), and Geneticin (G418; 0.4 mg/mL) at 37 °C in 5% CO$_2$/95% air.[24,31,32] For membrane preparation the culture medium was removed, and the cells were washed with PBS and scraped off T75 flasks in ice-cold hypotonic buffer (5 mM Tris−HCl, 2 mM EDTA, pH 7.4). The cell suspension was homogenized with a Polytron and centrifuged for 10 min at 1000g, and the supernatant was then centrifuged for 30 min at 100000g. The membrane pellet was suspended in 50 mM Tris−HCl buffer, 0.5% BSA (pH 7.4) containing 5 mM MgCl$_2$, and 2.5 mM EDTA or 1 mM EDTA for hCB$_1$ or hCB$_2$ receptors, respectively.

Competition binding experiments were performed using 0.5 nM [^{3}H]CP-55,940 and different concentrations (1 nM to 10 μM) of the examined compounds or the reference agonist WIN55,212-2 for an incubation time of 90 or 60 min at 30 °C for CB$_1$ or CB$_2$ receptors, respectively.

Bound and free radioactivities were separated by filtering the assay mixture through Whatman GF/C glass fiber filters using a Brandel cell harvester (Brandel Instruments, Unterföhring, Germany). The filter-bound radioactivity was counted using a Packard Tri Carb 2810 TR scintillation counter from Perkin-Elmer Life and Analytical Sciences.

cAMP Assay to Human CB$_2$ Receptors. CHO cells transfected with human CB$_2$ receptors were washed with phosphate-buffered saline and diluted trypsin and centrifuged for 10 min at 200g. The pellet containing CHO cells (1×10^6 cells/assay) was suspended in 0.5 mL of an incubation mixture, NaCl (150 mM), KCl (2.7 mM), NaH$_2$PO$_4$ (0.37 mM), MgSO$_4$ (1 mM), CaCl$_2$ (1 mM), Hepes (5 mM), MgCl$_2$ (10 mM), glucose (5 mM), pH 7.4, at 37 °C. Then 0.5 mM 4-(3-butoxy-4-methoxybenzyl)-2-imidazolidinone (Ro 20-1724) as a phosphodiesterase inhibitor was added and preincubated for 10 min in a shaking bath at 37 °C.[33] The potency of the novel CB compounds in comparison with a well-known CB agonist (**6**) was studied in the presence of forskolin (1 μM). The reaction was terminated by the addition of cold 6% trichloroacetic acid (TCA). The TCA suspension was centrifuged at 2000g for 10 min at 4 °C, and the supernatant was extracted four times with water-saturated diethyl ether. The final aqueous solution was tested for cAMP levels by a competition protein binding assay. Samples of cAMP standard (0−10 pmol) were added to each test tube containing the incubation buffer (Trizma base (0.1 M), aminophylline (8.0 mM), 2-mercaptoethanol (6.0 mM), pH 7.4) and [^{3}H]cAMP in a total volume of 0.5 mL. The binding protein previously prepared from beef adrenals was added to the samples previously incubated at 4 °C for 150 min, and after the addition of charcoal, the samples were centrifuged at 2000g for 10 min. The clear supernatant was counted by using a Perkin-Elmer 2810 TR scintillation counter (Perkin-Elmer Life and Analytical Sciences).

Data Analysis. The protein concentration was determined according to a Bio-Rad method (Bradford, 1976) with bovine albumin as a standard reference. Inhibitory binding constant values, K_i, were calculated from the IC$_{50}$ according to the Cheng and Prusoff equation[34] $K_i = \mathrm{IC}_{50}/(1 + [C^*]/K_D^*)$, where [$C^*$] is the concentration of the radioligand and K_D^* its dissociation constant. A weighted nonlinear least-squares curve fitting program, LIGAND,[35] was used for computer analysis of inhibition experiments. All the data are expressed as the mean ± SEM of $n = 4$ independent experiments for the in vitro assays. Statistical analysis of the data was performed using unpaired two-sided Student's t test.

Chemistry. Reaction progress and product mixtures were monitored by thin-layer chromatography (TLC) on silica gel (precoated F254 Merck plates) and visualized with aqueous potassium permanganate. ^{1}H NMR data were determined in CDCl$_3$ or DMSO-d_6 solutions with a Varian VXR 200 spectrometer or a Varian Mercury Plus 400 spectrometer. Peak positions are given in parts per million (δ) downfield, and J values are given in hertz. Light petroleum refers to the fractions boiling at 40−60 °C. Melting points were determined on a Buchi-Tottoli instrument and are uncorrected. Chromatography was performed on Merck 230−400 mesh silica gel. Organic solutions were dried over anhydrous sodium sulfate. Elemental analyses were performed by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara, and were within ±0.4% of the theoretical values for C, H, and N. The mass spectra were obtained on an ESI Micromass ZMD 2000 mass spectrometer. The chemical purity of the target compounds was ≥95%.

Synthesis of 2-Nitrophenoxy Ketones 8a−h. General Procedure. To a solution of 2-nitrophenol (14 mmol) in anhydrous acetone (10 mL) were added K$_2$CO$_3$ (15 mmol) and the appropriate halo ketone (15 mmol). After being stirred vigorously at room temperature until the starting material disappeared as determined by thin-layer chromatography (TLC), the reaction mixture was filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in ethyl acetate (150 mL) and washed with water (30 mL). The organic layer was dried over sodium sulfate and concentrated under vacuum. The residue was purified by column chromatography (SiO$_2$) using ethyl acetate/petroleum ether as the eluent or by crystallization to yield the desired compound.

1-(2-Nitrophenoxy)propan-2-one (8a). White solid. Mp: 72 °C. Yield: 72%. MS: m/z 196.0 (M + H). ^{1}H NMR (DMSO-d_6): δ 7.91−7.86 (m, 1H), 7.61−7.57 (m, 1H), 7.24−7.13 (m, 2H), 5.05 (s, 2H), 2.17 (s, 3H).

2-(2-Nitrophenoxy)-1-phenylethanone (8b). Yellow solid. Mp: 116−117 °C. Yield: 71%. MS: m/z 258.2 (M + H). ^{1}H NMR (CDCl$_3$): δ 8.03−7.98 (m, 2H), 7.90−7.85 (m, 1H), 7.61−7.45 (m, 4H), 7.11−6.95 (m, 2H), 5.45 (s, 2H).

2-(2-Nitrophenoxy)-1-phenylpropan-1-one (8c). Yellow oil. Yield: 69%. MS: m/z 272.4 (M + H). ^{1}H NMR (DMSO-d_6): δ 8.08−8.04 (m, 2H), 7.89−7.85 (m, 1H), 7.72−7.59 (m, 3H), 7.15−7.11 (m, 2H), 6.29 (q, J = 6.8 Hz, 1H), 1.57 (d, J = 6.6 Hz, 3H).

2-(2-Nitrophenoxy)-1,2-diphenylethanone (8d). Yellow solid. Mp: 58 °C. Yield: 15%. MS: m/z 334.3 (M + H). ^{1}H NMR (DMSO-d_6): δ 8.08−7.86 (m, 2H), 7.30−7.54 (m, 5H), 7.03−7.19 (m, 7H), 6.48 (s, 1H).

2-(5-Methyl-2-nitrophenoxy)-1-phenylethanone (8e). Yellow solid. Mp: 132−134 °C. Yield: 75%. MS: m/z 272.1 (M + H). ^{1}H NMR (CDCl$_3$): δ 8.03−7.99 (m, 2H), 7.83−7.54 (m, 4H), 7.16 (s, 1H), 6.96−6.91 (m, 1H), 5.83 (s, 2H), 2.32 (s, 3H).

1-(4-Methylphenyl)-2-(2-nitrophenoxy)ethanone (8f). White solid. Mp: 125 °C. Yield: 73%. MS: m/z 272.8 (M + H). ^{1}H NMR (DMSO-d_6): δ 7.92−7.86 (m, 3H), 7.58−7.53 (m, 1H), 7.40−7.36 (m, 2H), 7.28−7.23 (m, 1H), 7.16−7.11 (m, 1H), 5.81 (s, 2H), 2.40 (s, 3H).

1-Cyclopropyl-2-(2-nitrophenoxy)ethanone (8g). White solid. Mp: 58 °C. Yield: 75%. MS: m/z 222.1 (M + H). ^{1}H NMR (DMSO-d_6): δ 7.91−7.86 (m, 1H), 7.61−7.57 (m, 1H), 7.20−7.13 (m, 2H), 5.21 (s, 2H), 2.22 (m, 1H), 1.01−0.90 (m, 4H).

1-Cyclopropyl-2-(4-methyl-2-nitrophenoxy)ethanone (8h). Brown oil. Yield: 69%. MS: m/z 236.2 (M + H). ^{1}H NMR (DMSO-d_6): δ 7.89 (m, 1H), 7.19−7.12 (m, 2H), 5.20 (s, 2H), 2.32 (s, 3H), 2.21 (m, 1H), 1.01−0.90 (m, 4H).

Synthesis of Benzo[1,4]oxazines 9a−g,i,j). General Procedure. To a solution of the nitro ketone **8a−h** (7 mmol) in methanol (100 mL) (in the case of 3-aryl in methanol/THF, 85:15) was added 10% palladium on carbon (0.3 mmol, 0.178 g), and the mixture was shaken under 4 atm of hydrogen at room temperature for 6 h. The reaction was monitored by TLC, and when complete, the suspension was filtered through a pad of Celite to remove the catalyst. The filtrate was concentrated under vacuum to give a yellow residue that was purified by column chromatography (SiO$_2$) using ethyl acetate/petroleum ether (0.5:9.5) to yield the desired compounds. The cyclopropyl derivative **9g** and propyl derivative **9i** were separated by column chromatography using ethyl acetate/petroleum ether (0.2:9.8) as the eluent.

3,4-Dihydro-3-methyl-2H-benzo[b][1,4]oxazine (9a). Colorless oil. Yield: 80%. MS: m/z 150.1 (M + H). ^{1}H NMR (DMSO-d_6): δ 6.68−6.40 (m, 4H), 5.72 (br s, 1H), 4.15−4.07 (m, 1H), 3.65−3.56 (m, 1H), 3.37−3.36 (m, 1H), 1.07 (d, J = 6.4 Hz, 3H).

3,4-Dihydro-3-phenyl-2H-benzo[b][1,4]oxazine (9b). White solid. Mp: 40 °C. Yield: 76%. MS: m/z 212.2 (M + H). ^{1}H NMR (DMSO-d_6): δ 7.43−7.37 (m, 5H), 6.85−6.67 (m, 4H), 5.99 (br s, 1H); 4.53−4.49 (m, 1H), 4.34−4.27 (m, 1H), 4.06−3.95 (m, 1H).

3,4-Dihydro-2-methyl-3-phenyl-2H-benzo[b][1,4]oxazine (9c). Pale yellow oil. Yield: 83%. MS: m/z 226.0 (M + H). ^{1}H NMR (DMSO-d_6): δ 7.34−7.30 (m, 5H), 6.74−6.69 (m, 3H), 6.58−6.43 (m, 1H), 6.38 (br s, 1H), 4.47-4.44 (m, 2H), 0.98 (d, J = 6.4 Hz, 3H).

3,4-Dihydro-2,3-diphenyl-2H-benzo[b][1,4]oxazine (9d). Orange solid. Mp: 161−162 °C dec. Yield: 71%. MS: m/z 288.8 (M + H). ^{1}H NMR (CDCl$_3$): δ 7.18−7.13 (m, 7H), 6.99−6.75 (m, 8H), 5.44 (d, J = 3.2 Hz, 1H), 4.70 (d, J = 3 Hz, 1H).

3,4-Dihydro-7-methyl-3-phenyl-2H-benzo[b][1,4]oxazine (9e). White solid. Mp: 88 °C. Yield: 77%. MS: m/z 226.3 (M + H). ^{1}H NMR (DMSO-d_6): δ 7.41−7.33 (m, 5H), 6.62−6.50 (m, 3H), 6.03 (br s, 1H), 4.48 (m, 1H), 4.17 (m, 1H), 3.91−3.82 (m, 1H), 2.13 (s, 3H).

3,4-Dihydro-3-(4-methylphenyl)-2H-benzo[b][1,4]oxazine (9f). Colorless oil. Yield: 83%. MS: m/z 226.1 (M + H). ^{1}H NMR (DMSO-d_6): δ 7.29 (dd, J = 8 Hz, 2H), 7.17 (dd, J = 8 Hz, 2H), 6.71−6.66 (m, 3H), 6.54−6.48 (m, 1H), 6.20 (br s, 1H), 4.39 (m, 1H), 4.21−4.14 (m, 2H), 3.89−3.80 (m, 1H), 2.30 (s, 3H).

3,4-Dihydro-3-cyclopropyl-2H-benzo[b][1,4]oxazine (9g). Yellow oil. Yield: 38%. MS: m/z 176.5 (M + H). ^{1}H NMR (DMSO-d_6): δ 6.65−6.59 (m, 3H), 6.45−6.41 (m, 1H), 5.80 (br s, 1H), 4.19−4.15

(m, 1H), 3.56−3.81 (m, 1H), 2.58−2.57 (m, 1H), 0.78−0.76 (m, 1H) 0.48−0.32 (m, 4H).

3,4-Dihydro-3-propyl-2H-benzo[b][1,4]oxazine (9i). Yellow oil. Yield: 54%. MS: *m/z* 178.4 (M + H). ¹H NMR (DMSO-*d₆*): δ 6.66−6.58 (m, 3H), 6.46−6.42 (m, 1H), 5.71 (br s, 1H), 4.14−4.10 (m, 1H), 3.72−3.67 (m, 1H), 3.25−3.24 (m, 1H), 1.41−1.37 (m, 4H), 0.91 (t, *J* = 6.8 Hz, 3H).

3,4-Dihydro-6-methyl-3-propyl-2H-benzo[b][1,4]oxazine (9j). Yellow oil. Yield: 81%. MS: *m/z* 192.3 (M + H). ¹H NMR (CDCl₃): δ 6.68 (m, 1H), 6.48−6.42 (m, 2H), 4.22−4.16 (m, 1H), 3.86−3.77 (m, 1H), 3.67 (br s, 1H), 3.40−3.35 (m, 1H), 2.21 (s, 3H), 1.49−1.41 (m, 4H), 1.01−0.94 (m, 3H).

Synthesis of Diethyl 2-[(2,3-Dihydro-2/3-substituted-benzo[b]-[1,4]oxazin-4-yl)methylene]malonates 10a−g,i,j. General Procedure. A mixture of benzo[1,4]oxazine **9a−g,i,j** (4.7 mmol) and diethyl (ethoxymethylene)malonate (4.7 mmol) was heated with stirring at 140 °C for 2 h. The solvent was removed under reduced pressure, and cold diethyl ether was added to form a precipitate that was filtered and subsequently purified by column chromatography (SiO₂) using ethyl acetate/petroleum ether (0.5:9.5).

Diethyl 2-((2,3-Dihydro-3-methylbenzo[b][1,4]oxazin-4-yl)-methylene)malonate (10a). Pale yellow oil. Yield: 73%. MS: *m/z* 320.1 (M + H). ¹H NMR (DMSO-*d₆*): δ 7.71 (s, 1H), 7.21−6.95 (m, 4H), 4.21−3.87 (m, 7H), 1.26−1.16 (m, 9H).

Diethyl 2-((2,3-Dihydro-3-phenylbenzo[b][1,4]oxazin-4-yl)-methylene)malonate (10b). White solid. Mp: 103−104 °C. Yield: 81%. MS: *m/z* 382.2 (M + H). ¹H NMR (CDCl₃): δ 8.12 (s, 1H) 7.38−6.87 (m, 9H), 4.55−3.93 (m, 6H) 3.42−3.21 (m, 1H), 1.26 (t, *J* = 7 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H).

Diethyl 2-((2,3-Dihydro-2-methyl-3-phenylbenzo[b][1,4]oxazin-4-yl)methylene)malonate (10c). White solid. Mp: 130 °C. Yield: 89%. MS: *m/z* 396.2 (M + H). ¹H NMR (DMSO-*d₆*): δ 7.85 (s, 1H), 7.33−7.27 (m, 4H), 7.10−6.93 (m, 5H), 5.02 (d, *J* = 2.6 Hz, 1H), 4.60−4.43 (m, 1H), 4.11−3.95 (m, 3H), 3.64−3.61 (m, 1H), 1.20−1.13 (m, 6H), 0.93 (t, *J* = 7.2 Hz, 3H).

Diethyl 2-((2,3-Dihydro-2,3-diphenylbenzo[b][1,4]oxazin-4-yl)-methylene)malonate (10d). White solid. Mp: 114 °C. Yield: 96%. MS: *m/z* 458.2 (M + H). ¹H NMR (DMSO-*d₆*): δ 7.96 (s, 1H), 7.42−7.30 (m, 4H), 7.18−7.04 (m, 8H), 6.43−6.40 (m, 2H), 5.69 (d, *J* = 2.6 Hz, 1H), 5.34 (d, *J* = 2.8 Hz, 1H), 4.14−4.10 (m, 2H), 3.98−3.81 (m, 1H), 3.56−3.41 (m, 1H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H).

Diethyl 2-((2,3-Dihydro-7-methyl-3-phenylbenzo[b][1,4]oxazin-4-yl)methylene)malonate (10e). White solid. Mp: 105 °C. Yield: 92%. MS: *m/z* 396.2 (M + H). ¹H NMR (DMSO-*d₆*): δ 7.93 (s, 1H), 7.30−7.15 (m, 6H), 6.87−6.82 (m, 1H), 6.64−6.63 (m, 1H), 5.14 (m, 1H), 4.72−4.65 (m, 1H), 4.36−4.29 (m, 1H), 4.11 (q, *J* = 6.2 Hz, 2H), 3.88−3.79 (m, 1H), 3.32−3.23 (m, 1H), 2.20 (s, 3H), 1.17 (t, *J* = 7 Hz, 3H), 0.77 (t, *J* = 7 Hz, 3H).

Diethyl 2-((2,3-Dihydro-3-(4-methylphenyl)benzo[b][1,4]oxazin-4-yl)methylene)malonate (10f). White solid. Mp: 94 °C. Yield: 87%. MS: *m/z* 396.2 (M + H). ¹H NMR (DMSO-*d₆*): δ 7.94 (s, 1H), 7.33 (m, 1H), 7.08−6.99 (m, 6H), 6.83−6.78 (m, 1H), 5.13 (m, 1H), 4.78−4.62 (m, 1H), 4.38−4.31 (m, 1H), 4.11 (q, *J* = 6.2 Hz, 2H), 3.97−3.78 (m, 1H), 3.42−3.21 (m, 1H), 2.23 (s, 3H), 1.82 (t, *J* = 7.4 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H).

Diethyl 2-((3-Cyclopropyl-2,3-dihydrobenzo[b][1,4]oxazin-4-yl)-methylene)malonate (10g). Yellow oil. Yield: 92%. MS: *m/z* 346.1 (M + H). ¹H NMR (DMSO-*d₆*): δ 7.72 (s, 1H), 7.12−6.90 (m, 4H), 4.36−4.35 (m, 1H), 4.20−4.05 (m, 3H), 3.97−3.65 (m, 2H), 3.51−3.47 (m, 1H), 1.19 (t, *J* = 7 Hz, 3H), 1.06 (t, *J* = 7 Hz, 3H), 0.98−0.83 (m, 2H), 0.53−0.43 (m, 3H).

Diethyl 2-((2,3-Dihydro-3-propylbenzo[b][1,4]oxazin-4-yl)-methylene)malonate (10i). Yellow oil. Yield: 84%. MS: *m/z* 348.2 (M + H). ¹H NMR (DMSO-*d₆*): δ 7.70 (s, 1H), 7.14−6.89 (m, 4H), 4.35 (m, 1H), 4.17−3.78 (m, 6H), 1.48−1.05 (m, 10H), 0.85 (t, *J* = 7.4 Hz, 3H).

Diethyl 2-(2,3-Dihydro-6-methyl-3-propylbenzo[b][1,4]oxazin-4-yl)methylene)malonate (10j). Yellow oil. Yield: 78%. MS: *m/z* 362.3 (M + H). ¹H NMR (DMSO-*d₆*): δ 7.84 (s, 1H), 6.88−6.78 (m, 3H),

4.30−4.07 (m, 6H), 3.82 (m, 1H), 2.27 (s, 3H), 1.63−1.59 (m, 4H), 1.32−1.22 (m, 6H), 0.92 (t, *J* = 7 Hz, 3H).

Synthesis of Ethyl 3,7-Dihydro-2/3-substituted-7-oxo-2H-[1,4]-oxazino[2,3,4-ij]quinoline-6-carboxylates 11a−g,i,j. General Procedure. A mixture of diethyl ester **10a−g,i,j** (0.49 g, 1.5 mmol) and poly(phosphoric acid) (3 g) was heated at 140 °C for 1 h. The mixture was poured into ice and water to form a precipitate that was filtered and washed with cold water.

Ethyl 3,7-Dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylate (11a). White solid. Mp: 189 °C dec. Yield: 95%. MS: *m/z* 274.3 (M + H). ¹H NMR (DMSO-*d₆*): δ 8.65 (s, 1H), 7.80−7.75 (m, 1H), 7.40−7.31 (m, 2H), 4.79−4.63 (m, 1H), 4.42−4.34 (m, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.41 (d, *J* = 6.6 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H).

Ethyl 3,7-Dihydro-3-phenyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylate (11b). White solid. Mp: 239 °C. Yield: 87%. MS: *m/z* 336.3 (M + H). ¹H NMR (DMSO-*d₆*): δ 8.55 (s, 1H), 7.87−7.82 (m, 1H), 7.43−7.28 (m, 5H), 7.13−7.08 (m, 2H), 5.91 (m, 1H), 4.76−4.64 (m, 2H), 4.19 (q, *J* = 6.2 Hz, 2H), 1.24 (t, *J* = 7 Hz, 3H).

Ethyl 3,7-Dihydro-2-methyl-7-oxo-3-phenyl-2H-[1,4]oxazino-[2,3,4-ij]quinoline-6-carboxylate (11c). White solid. Mp: 243−244 °C. Yield: 81%. MS: *m/z* 350.2 (M + H). ¹H NMR (DMSO-*d₆*): δ 8.53 (s, 1H), 7.84−7.83 (m, 1H), 7.43−7.34 (m, 5H), 7.11−7.07 (m, 2H), 5.73 (d, *J* = 3 Hz, 1H), 4.82−4.78 (m, 1H), 4.21−4.16 (m, 2H), 1.27−1.18 (m, 6H).

Ethyl 3,7-Dihydro-7-oxo-2,3-diphenyl-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylate (11d). White solid. Mp: 289−290 °C dec. Yield: 75%. MS: *m/z* 412.1 (M + H). ¹H NMR (DMSO-*d₆*): δ 8.63 (s, 1H), 7.93−7.90 (m, 1H), 7.53−7.49 (m, 2H), 7.32−7.13 (m, 8H), 6.66 (d, *J* = 6.4 Hz, 2H), 6.15−5.95 (m, 2H), 4.22−4.17 (m 2H), 1.25 (t, *J* = 7.2 Hz, 3H).

Ethyl 3,7-Dihydro-9-methyl-7-oxo-3-phenyl-2H-[1,4]oxazino-[2,3,4-ij]quinoline-6-carboxylate (11e). White solid. Mp: 199 °C dec. Yield: 79%. MS: *m/z* 350.0 (M + H). ¹H NMR (DMSO-*d₆*): δ 8.49 (s, 1H), 7.63−7.62 (m, 1H), 7.36−7.32 (m, 3H), 7.13−7.04 (m, 3H), 5.87 (m, 1H), 4.72−4.59 (m 2H), 4.16 (q, *J* = 6.4 Hz, 2H), 2.38 (s, 3H), 1.21 (t, *J* = 7 Hz, 3H).

Ethyl 3,7-Dihydro-7-oxo-3-(4-methylphenyl)-2H-[1,4]oxazino-[2,3,4-ij]quinoline-6-carboxylate (11f). White solid. Mp: 183 °C. Yield: 83%. MS: *m/z* 350.2 (M + H). ¹H NMR (DMSO-*d₆*): δ 8.50 (s, 1H), 7.86−7.81 (m, 1H), 7.43−7.27 (m, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.00 (d, *J* = 8 Hz, 2H), 5.84 (m, 1H), 4.72−4.61 (m, 2H), 4.18 (q, *J* = 7 Hz, 2H), 2.27 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H).

Ethyl 3-Cyclopropyl-3,7-dihydro-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylate (11g). White solid. Mp: 190 °C. Yield: 77%. MS: *m/z* 300.3 (M + H). ¹H NMR (DMSO-*d₆*): δ 8.70 (s, 1H), 7.82−7.76 (m, 1H), 7.37−7.32 (m, 2H), 4.58−4.31 (m, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.97 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.18 (m, 1H), 0.59 (m, 4H).

Ethyl 3,7-Dihydro-7-oxo-3-propyl-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylate (11i). White solid. Mp: 133 °C. Yield: 80%. MS: *m/z* 302.2 (M + H). ¹H NMR (DMSO-*d₆*): δ 8.60 (s, 1H); 7.79−7.74 (m, 1H), 7.36−7.30 (m, 2H), 4.60−4.54 (m, 2H), 4.28−4.21 (m, 3H), 1.82−1.63 (m, 2H), 1.48−1.33 (m, 2H), 1.29 (d, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H).

Ethyl 3,7-Dihydro-8-methyl-7-oxo-3-propyl-2H-[1,4]oxazino-[2,3,4-ij]quinoline-6-carboxylate (11j). Pale white solid. Mp: 125−127 °C. Yield: 95%. MS: *m/z* 316.3 (M + H). ¹H NMR (DMSO-*d₆*): δ 8.47 (s, 1H), 7.16−7.07 (m, 2H), 4.79 (m, 1H), 4.53−4.47 (m, 2H), 4.24−4.16 (m, 3H), 2.71 (s, 3H), 1.81−1.68 (m, 4H), 1.31−1.24 (m, 6H), 0.88 (t, *J* = 7.4 Hz, 3H).

Synthesis of Ethyl 3-(2,3-Difluorophenyl)-3-oxopropanoate, Ethyl 3-(2,3,4-Trifluorophenyl)-3-oxopropanoate, and Ethyl 3-(2,3,4,5-Tetrafluorophenyl)-3-oxopropanoate (14a−c). Carbonyldiimidazole (1.78 g, 11 mmol) was added to a solution of the requisite benzoic acid (**13a−c**, 10 mmol) in anhydrous THF (50 mL). After the mixture was stirred at room temperature for 6 h, the magnesium salt of ethyl malonic acid half-ester (prepared by stirring monoethyl malonate (1.2 mL, 10 mmol) and magnesium ethoxide (0.57 g, 5 mmol) in anhydrous THF (25 mL) for 1 h at room temperature) was added, and

the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was partitioned between 5% hydrochloric acid (20 mL) and ether (50 mL). The aqueous layer was further extracted with ether, and the combined extracts were washed with aqueous saturated sodium bicarbonate solution (10 mL) and dried. Evaporation of the solvent in vacuo led to the desired compounds as clear oils (1.9 g, 79%), which were used without further purification in the next step.

Synthesis of Ethyl 2-(2,3-Difluorobenzoyl)-3-((2-hydroxy-1-alkylethyl)amino)acrylates 16a−g, Ethyl 2-(2,3,4-Trifluorobenzo-yl)-3-((2-hydroxy-1-ethylethyl)amino)acrylate (16h), and Ethyl 2-(2,3,4,5-Tetrafluorobenzoyl)-3-((2-hydroxy-1-ethylethyl)amino)-acrylate (16i). A mixture of the appropriate ethyl 3-(2,3-difluorophenyl)-, 3-(2,3,4-trifluorophenyl)-, or 3-(2,3,4,5-tetrafluoro-phenyl)-3-oxopropanoate (14a−c, 7.7 mmol), triethyl orthoformate (2.6 mL, 11.5 mmol), and acetic anhydride (4.6 mL, 45 mmol) was stirred at 110−120 °C for 3 h. The reaction was concentrated under reduced pressure to leave an oily residue, which was diluted with toluene and concentrated. This process was repeated two more times to afford the desired ethyl 2-(ethoxymethylene)-3-oxo-3-(2,3-difluoro-phenyl)-, 3-(2,3,4-trifluorophenyl)-, or 3-(2,3,4,5-tetrafluorophenyl)-propionate (15a−c) as an oil, which was used directly without further purification.

To a solution of ethyl 2-(ethoxymethylene)-3-oxo-3-(2,3-difluorophenyl)propionate (15a; 7.7 mmol) in dry methylene chloride (20 mL) was added a solution of the desired (R,S)-, (R)-, or (S)-2-amino-1-hydroxyalkane (11 mmol) in methylene chloride (5 mL) dropwise under cooling with an ice bath. The whole mixture was stirred at room temperature for 1 h and then concentrated in vacuo to yield the requisite (R,S)-, (R)-, or (S)-ethyl 2-(2,3-difluorobenzoyl)-3-((2-hydroxy-1-alkylethyl)amino)acrylates 16a−g as oils, which were used in the next step without further purification.

In identical fashion, ethyl 2-(ethoxymethylene)-3-oxo-3-(2,3,4-trifluorophenyl)propionate (15b) or ethyl 2-(ethoxymethylene)-3-oxo-3-(2,3,4,5-tetrafluorophenyl)propionate (15c) was reacted with 2-amino-1-hydroxybutane to afford the desired ethyl 2-(2,3,4-trifluor-obenzoyl)-3-((2-hydroxy-1-ethylethyl)amino)acrylate (16h) and ethyl 2-(2,3,4,5-tetrafluorobenzoyl)-3-((2-hydroxy-1-ethylethyl)amino)-acrylate (16i) as oils, which were used in the next step without further purification.

Synthesis of Ethyl 3,7-Dihydro-7-oxo-3-substituted-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylates 17a−i. General Procedure. A mixture of the requisite ethyl 2-(2,3-difluorobenzoyl)-, 2-(2,3,4-trifluorobenzoyl)-, or 2-(2,3,4,5-tetrafluorobenzoyl)-3-((2-hydroxy-1-substituted-ethyl)amino)acrylate (16a−i, 5.5 mmol), K_2CO_3 (2.2 g, 16 mmol), and anhydrous DMF (30 mL) was stirred at 130−140 °C for 7 h. After cooling, ethyl acetate (50 mL) was added to the reaction mixture. The organic phase was washed with water, dried, filtered, and concentrated. The residue was purified by flash chromatography, eluting with ethyl acetate/petroleum ether (7:3) to afford the desired product as a white solid.

(R)-Ethyl 3,7-Dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylate ((R)-17a) and (S)-Ethyl 3,7-Dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylate ((S)-17a). The NMR data and melting points are identical to those reported for compound 11a.

(R,S)-Ethyl 3,7-Dihydro-3-ethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylate (17b), (R)-Ethyl 3,7-Dihydro-3-ethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylate ((R)-17b), and (S)-Ethyl 3,7-Dihydro-3-ethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylate ((S)-17b). White solid. Mp: 157 °C dec. Yield: 86%. MS: m/z 288.3 (M + H). ^{1}H NMR (DMSO-d_6): δ 8.63 (s, 1H), 7.79−7.44 (m, 1H), 7.35−7.30 (m, 2H), 4.61−4.49 (m, 2H), 4.32−4.18 (m, 3H), 1.75−1.72 (m, 2H), 1.28 (t, J = 7 Hz, 3H), 0.93 (t, J = 7.6 Hz, 3H).

(R,S)-Ethyl 3,7-Dihydro-3-isopropyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylate (17c), (R)-Ethyl 3,7-Dihydro-3-isopropyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylate ((R)-17c), and (S)-(−)-Ethyl 3,7-Dihydro-3-isopropyl-7-oxo-2H-[1,4]oxazino-[2,3,4-ij]quinoline-6-carboxylate ((S)-17c). White solid. Mp: 142 °C. Yield: 71%. MS: m/z 302.2 (M + H). ^{1}H NMR (DMSO-d_6): δ

8.60 (s, 1H), 7.79−7.74 (m, 1H), 7.39−7.29 (m, 2H), 4.75 (d, J = 10.8 Hz, 1H), 4.32−4.18 (m, 4H), 2.07−1.91 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H).

(R)-(+)-Ethyl 3,7-Dihydro-3-isobutyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylate ((R)-17d). Colorless oil. Yield: 54%. MS: m/z 316.3 (M + H). ^{1}H NMR (CDCl$_3$): δ 8.33 (s, 1H), 8.08−8.04 (m, 1H), 7.32−7.21 (m, 2H), 4.45−4.17 (m, 4H), 1.95−1.51 (m, 4H), 1.22 (m, 3H), 1.05 (t, J = 6.4 Hz, 3H), 0.98 (d, J = 6 Hz, 3H).

(R)-Ethyl 3,7-Dihydro-3-phenyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylate ((R)-17e) and (S)-Ethyl 3,7-Dihydro-3-phenyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylate ((S)-17e). The NMR data and melting points are identical to those reported for compound 11b.

(R)-Ethyl 3,7-Dihydro-3-benzyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylate ((R)-17f). White solid. Mp: 179−180 °C. Yield: 57%. MS: m/z 350.4 (M + H). ^{1}H NMR (DMSO-d_6): δ 8.74 (s, 1H), 8.07−8.03 (m, 1H), 7.74−7.39 (m, 2H), 7.23−7.16 (m, 5H), 5.33−5.29 (m, 2H), 4.25 (q, J = 6.8 Hz, 2H), 3.83 (m, 2H), 3.26 (m, 1H), 1.30 (t, J = 7.2 Hz, 3H).

Ethyl 3,7-Dihydro-3,3-dimethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylate (17g). Yellow solid. Mp: 216−217 °C. Yield: 28%. MS: m/z 289.3 (M + H). ^{1}H NMR (CDCl$_3$): δ 8.61 (s, 1H), 8.11−8.07 (m, 1H), 7.36−7.23 (m, 2H), 4.40 (q, J = 7.2 Hz, 2H), 4.12 (s, 2H), 1.62 (s, 6H), 1.42 (t, J = 7.2 Hz, 3H).

Ethyl 3,7-Dihydro-3-ethyl-10-fluoro-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylate (17h). White solid. Mp: 190−191 °C dec. Yield: 40%. MS: m/z 306.1 (M + H). ^{1}H NMR (DMSO-d_6): δ 8.66 (s, 1H), 7.82−7.70 (m, 1H), 7.45−7.31 (m, 1H), 4.79−4.54 (m 2H), 4.40−4.31 (m, 1H), 4.23 (q, J = 7 Hz, 2H), 1.91−1.83 (m, 2H), 1.28 (t, J = 7 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H).

Ethyl 3,7-Dihydro-3-ethyl-9,10-difluoro-7-oxo-2H-[1,4]oxazino-[2,3,4-ij]quinoline-6-carboxylate (17i). White solid. Mp: 190−191 °C dec. Yield: 40%. MS: m/z 324.2 (M + H). ^{1}H NMR (DMSO-d_6): δ 8.68 (s, 1H), 7.71−7.57 (m, 1H), 4.79−4.54 (m 2H), 4.40−4.33 (m, 1H), 4.23 (q, J = 7 Hz, 2H), 1.82−1.63 (m, 2H), 1.28 (t, J = 7 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H).

Synthesis of 3,7-Dihydro-2/3-substituted-7-oxo-2H-[1,4]oxazino-[2,3,4-ij]quinoline-6-carboxylic Acids 12a−g,i,j and 18a−i. General Procedure. A solution of the requisite ethyl 3,7-dihydro-2-substituted-3-substituted-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylate (11a−g,i,j, 17a−i, 7.4 mmol), NaOH 10% (10 mL), and methanol (90 mL) was heated at 80 °C for 1 h. The solvent was evaporated under reduced pressure, and the residue was acidified with 10% HCl at 0 °C. The precipitate was collected by filtration to give the desired product as a white solid.

(R,S)-3,7-Dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylic Acid (12a), (R)-3,7-Dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic Acid ((R)-18a), and (S)-3,7-Dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic Acid ((S)-18a). White solid. Mp: 240 °C dec. Yield: 76%. MS: m/z 246.1 (M + H). ^{1}H NMR (DMSO-d_6): δ 15.23 (br s, 1H), 9.05 (s, 1H), 7.95−7.91 (m, 1H), 7.60−7.47 (m, 2H), 4.99−4.84 (m, 1H), 4.50−4.42 (m, 2H), 1.46 (d, J = 7 Hz, 3H).

(R,S)-3,7-Dihydro-3-phenyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylic Acid (12b), (R)-3-Phenyl-3,7-dihydro-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic Acid ((R)-18e), and (S)-3-Phenyl-3,7-dihydro-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic Acid ((S)-18e). White solid. Mp: 284 °C. Yield: 90%. MS: m/z 308.4 (M + H). ^{1}H NMR (DMSO-d_6): δ 15.10 (br s, 1H), 8.90 (s, 1H), 8.02−7.98 (m, 1H),7.64−7.37 (m, 5H), 7.17−7.12 (m, 2H), 6.10 (m, 1H), 4.85−4.83 (m, 1H), 4.73−4.70 (m, 1H).

3,7-Dihydro-2-methyl-7-oxo-3-phenyl-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylic Acid (12c). White solid. Mp: 291−292 °C dec. Yield: 82%. MS: m/z 322.4 (M + H). ^{1}H NMR (DMSO-d_6): δ 15.02 (br s, 1H), 8.93 (s, 1H), 8.02−7.98 (m, 1H), 7.61−7.56 (m, 2H), 7.38−7.34 (m, 3H), 7.11−7.09 (m, 2H), 5.93−5.91 (m, 1H), 4.96−4.84 (m, 1H), 2.03 (m, 3H).

3,7-Dihydro-7-oxo-2,3-diphenyl-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylic Acid (12d). White solid. Mp: >300 °C. Yield: 86%. MS: m/z 384.2 (M + H). ^{1}H NMR (DMSO-d_6): δ 15.03 (br s, 1H), 8.73 (s, 1H), 8.02−7.99 (m, 1H), 7.55−7.51 (m, 2H), 7.29−7.12 (m, 8H), 6.71−6.67 (m, 2H), 6.20 (m, 1H), 5.95 (m, 1H).

3,7-Dihydro-9-methyl-7-oxo-3-phenyl-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylic Acid (12e). White solid. Mp: >300 °C. Yield: 86%. MS: *m/z* 322.5 (M + H). ¹H NMR (DMSO-*d₆*): δ 15.21 (br s, 1H), 8.85 (s, 1H), 7.81−7.79 (m, 1H), 7.39−7.35 (m, 4H), 7.15−7.10 (m, 2H), 6.08 (m, 1H), 4.83−4.69 (m, 2H), 2.48 (s, 3H).

3,7-Dihydro-7-oxo-3-(4-methylphenyl)-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylic Acid (12f). White solid. Mp: 294 °C dec. Yield: 90%. MS: *m/z* 322.2 (M + H). ¹H NMR (DMSO-*d₆*): δ 15.08 (br s, 1H), 8.82 (s, 1H), 8.01−7.96 (m, 1H), 7.63−7.47 (m, 2H), 7.20 (d, *J* = 8 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.02 (m, 1H), 4.80−4.69 (m, 2H), 2.28 (s, 3H).

3-Cyclopropyl-3,7-dihydro-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylic Acid (12g). White solid. Mp: 227−228 °C. Yield: 76%. MS: *m/z* 272.1 (M + H). ¹H NMR (DMSO-*d₆*): δ 15.17 (br s, 1H), 9.06 (s, 1H), 7.95−7.90 (m, 1H), 7.59−7.46 (m, 2H), 4.64−4.46 (m, 2H), 4.14−4.07 (m, 1H), 1.38−1.11 (m, 1H), 0.79−0.52 (m, 4H).

3,7-Dihydro-7-oxo-3-propyl-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic Acid (12i). White solid. Mp: 213 °C. Yield: 82%. MS: *m/z* 274.3 (M + H). ¹H NMR (DMSO-*d₆*): δ 15.21 (br s, 1H), 9.00 (s, 1H), 7.95−7.90 (m, 1H), 7.60−7.46 (m, 2H), 4.85 (m, 1H), 4.69−4.63 (m, 1H), 4.42−4.41 (m, 1H), 1.98−1.11 (m, 4H), 0.88 (t, *J* = 7 Hz, 3H).

3,7-Dihydro-8-methyl-7-oxo-3-propyl-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylic Acid (12j). White solid. Mp: 205 °C dec. Yield: 78%. MS: *m/z* 289.2 (M + H). ¹H NMR (DMSO-*d₆*): δ 15.53 (br s, 1H), 8.91 (s, 1H), 7.36−7.24 (m, 2H), 4.84−4.77 (m, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.29 (d, *J* = 10 Hz, 1H), 2.80 (s, 3H), 1.95−1.20 (m, 4H), 0.87 (t, *J* = 7.4 Hz, 3H).

(R,S)-3,7-Dihydro-3-ethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylic Acid (18b), (R)-3,7-Dihydro-3-ethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic Acid ((R)-18b), and (S)-3,7-Dihydro-3-ethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic Acid ((S)-18b). White solid. Mp: 190 °C. Yield: 78%. MS: *m/z* 260.1 (M + H). ¹H NMR (DMSO-*d₆*): δ 15.21 (br s, 1H), 9.03 (s, 1H), 7.94−7.90 (m, 1H), 7.59−7.45 (m, 2H), 4.81−4.65 (m, 2H), 4.42−4.35 (m, 1H), 1.80−1.75 (m, 2H), 0.93 (t, *J* = 6.6 Hz, 3H).

(R,S)-3,7-Dihydro-3-isopropyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylic Acid (18c), (R)-3,7-Dihydro-3-isopropyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic Acid ((R)-18c), and (S)-3,7-Dihydro-3-isopropyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylic Acid ((S)-18c). White solid. Mp: 210 °C. Yield: 86%. MS: *m/z* 274.2 (M + H). ¹H NMR (DMSO-*d₆*): δ 14.99 (br s, 1H), 8.99 (s, 1H), 8.31−7.44 (m, 3H), 5.28 (m, 1H), 4.99−3.91 (m, 3H), 2.01 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 3H).

(R)-3,7-Dihydro-3-isobutyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylic Acid ((R)-18d). White solid. Mp: 131−132 °C. Yield: 80%. MS: *m/z* 288.3 (M + H). ¹H NMR (DMSO-*d₆*): δ 14.99 (br s, 1H), 8.62 (s, 1H), 8.11−8.06 (m, 1H), 7.52−7.26 (m, 2H), 4.82−4.21 (m, 3H), 1.99−1.38 (m, 3H), 1.07−0.95 (m, 6H).

(R)-3-Benzyl-3,7-dihydro-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylic Acid ((R)-18f). White solid. Mp: 239−240 °C. Yield: 82%. MS: *m/z* 323.2 (M + H). ¹H NMR (DMSO-*d₆*): δ 15.08 (br s, 1H), 8.58 (s, 1H), 7.97−7.92 (m, 1H), 7.63−7.54 (m, 2H), 7.31−7.14 (m, 5H), 5.08 (m, 1H), 4.59−4.15 (m, 2H), 3.13−3.05 (m, 2H).

3,7-Dihydro-3,3-dimethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylic Acid (18g). White solid. Mp: >300 °C. Yield: 68%. MS: *m/z* 260.1 (M + H). ¹H NMR (CDCl₃): δ 15.00 (br s, 1H), 8.88 (s, 1H), 8.15−8.10 (m, 1H), 7.53−7.36 (m, 2H), 4.18 (s, 2H), 1.67 (s, 6H).

3-Ethyl-10-fluoro-3,7-dihydro-7-oxo-2H-[1,4]oxazino[2,3,4-ij]-quinoline-6-carboxylic Acid (18h). White solid. Mp: 230 °C. Yield: 65%. MS: *m/z* 278.1 (M + H). ¹H NMR (DMSO-*d₆*): δ 15.00 (br s, 1H), 9.01 (s, 1H), 7.97−7.90 (m, 1H), 7.64−7.54 (m, 1H), 4.84−4.75 (m, 2H), 4.64−4.39 (m, 1H), 1.85−1.73 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

9,10-Difluoro-3,7-dihydro-3-ethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic Acid (18i). White solid. Mp: 246−248 °C. Yield: 50%. MS: *m/z* 296.3 (M + H). ¹H NMR (DMSO-*d₆*): δ 15.00

(br s, 1H), 9.01 (s, 1H), 7.71−7.65 (m, 1H), 4.84−4.76 (m, 2H), 4.44−4.38 (m, 1H), 1.84−1.76 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).

Synthesis of N-Cycloalkyl- or N,N-Diisopropyl-3,7-dihydro-2/3-substituted-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamides 19−21, 24, 27, 29, 31, 32, 34, 35, 41−43, 46, 48, 49, (R)-31, (S)-31, (R)-35, and (S)-35. General Procedure. To a solution of the appropriate 3,7-dihydro-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (**12a−c,e−g,i,j**, (*R*)-**18a**, (*S*)-**18a**, or **18b**, 0.6 mmol) in DMF (5 mL) were added EDC (0.6 mmol), HOBt (0.6 mmol), and finally the desired amine (0.9 mmol). The reaction mixture was stirred at room temperature for 6 h. The solvent was evaporated, and the residue was purified by column chromatography (SiO₂) to yield a white solid.

N-Cyclopentyl-3,7-dihydro-7-oxo-3-phenyl-2H-[1,4]oxazino-[2,3,4-ij]quinoline-6-carboxamide (19). White solid. Mp: 237 °C. Yield: 64%. MS: *m/z* 375.2 (M + H). ¹H NMR (DMSO-*d₆*): 10.00 (br d, *J* = 7.2 Hz, 1H), 8.67 (s, 1H), 7.96−7.91 (m, 1H), 7.46−7.36 (m, 5H), 7.14−7.09 (m, 2H), 6.01 (m, 1H), 4.82−4.59 (m, 2H), 4.25−4.16 (m, 1H), 1.98−1.30 (m, 8H). Anal. (C₂₃H₂₂N₂O₃) C, H, N.

N-Cyclohexyl-3,7-dihydro-7-oxo-3-phenyl-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (20). White solid. Mp: 207 °C. Yield: 58%. MS: *m/z* 389.5 (M + H). ¹H NMR (DMSO-*d₆*): δ 10.01 (br d, *J* = 7.6 Hz, 1H), 8.69 (s, 1H), 7.96−7.91 (m, 1H), 7.49−7.08 (m, 7H), 6.01 (m, 1H), 4.76 (m, 1H), 4.65 (m, 1H), 3.95 (m, 1H), 1.88−1.30 (m, 10H). Anal. (C₂₄H₂₄N₂O₃) C, H, N.

N-Cycloheptyl-3,7-dihydro-7-oxo-3-phenyl-2H-[1,4]oxazino-[2,3,4-ij]quinoline-6-carboxamide (21). White solid. Mp: 169 °C. Yield: 55%. MS: *m/z* 403.5 (M + H). ¹H NMR (DMSO-*d₆*): δ 10.03 (br d, *J* = 7.8 Hz, 1H), 8.66 (s, 1H), 7.96−7.92 (m, 1H), 7.46−7.34 (m, 5H), 7.14−7.09 (m, 2H), 6.01 (m, 1H), 4.83−4.58 (m, 2H), 3.95 (m, 1H), 1.95−1.35 (m, 12H). Anal. (C₂₅H₂₆N₂O₃) C, H, N.

N-Cyclohexyl-3,7-dihydro-2-methyl-7-oxo-3-phenyl-2H-[1,4]-oxazino[2,3,4-ij]quinoline-6-carboxamide (24). White solid. Mp: 254 °C. Yield: 61%. MS: *m/z* 403.3 (M + H). ¹H NMR (DMSO-*d₆*): δ 9.97 (br d, *J* = 7.4 Hz, 1H), 8.68 (s, 1H), 7.97−7.93 (m, 1H), 7.50−7.35 (m, 5H), 7.10 (m, 2H), 5.88 (m, 1H), 4.89−4.84 (m, 1H), 3.91 (m, 1H), 1.97−1.40 (m, 10H), 1.33 (d, *J* = 6.2 Hz, 3H). Anal. (C₂₅H₂₆N₂O₃) C, H, N.

N-Cyclohexyl-3,7-dihydro-7-oxo-3-p-tolyl-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (27). White solid. Mp: 237 °C. Yield: 64%. MS: *m/z* 403.4 (M + H). ¹H NMR (DMSO-*d₆*): δ 9.99 (br d, *J* = 7.4 Hz, 1H), 8.62 (s, 1H), 7.95−7.90 (m, 1H), 7.49−7.34 (m, 2H), 7.19 (d, *J* = 8.00 Hz, 2H), 7.02 (d, *J* = 8.00 Hz, 2H), 5.94 (m, 1H), 4.72−4.63 (m, 2H), 3.89 (m, 1H), 2.28 (s, 3H), 1.92−1.26 (m, 10H). Anal. (C₂₅H₂₆N₂O₃) C, H, N.

N-Cyclohexyl-3,7-dihydro-9-methyl-7-oxo-3-phenyl-2H-[1,4]-oxazino[2,3,4-ij]quinoline-6-carboxamide (29). White solid. Mp: 286 °C. Yield: 66%. MS: *m/z* 403.5 (M + H). ¹H NMR (DMSO-*d₆*): δ 10.04 (br d, *J* = 7.8 Hz, 1H), 8.63 (s, 1H), 7.74 (s, 1H), 7.38−7.35 (m, 3H), 7.21 (s, 1H), 7.011−7.07 (m, 2H), 5.99 (m, 1H), 4.75−4.59 (m, 2H), 3.89 (m, 1H), 2.43 (s, 3H), 1.92−1.24 (m, 10H). Anal. (C₂₅H₂₆N₂O₃) C, H, N.

N-Cyclohexyl-3,7-dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (31). White solid. Mp: 245 °C. Yield: 58%. MS: *m/z* 327.2 (M + H). ¹H NMR (DMSO-*d₆*): δ 10.05 (br d, *J* = 7.8 Hz, 1H), 8.82 (s, 1H), 7.89−7.85 (m, 1H), 7.46−7.33 (m, 2H), 4.82 (m, 1H), 4.45−4.36 (m, 2H), 3.81 (m, 1H), 1.88−1.28 (m, 13H). Anal. (C₁₉H₂₂N₂O₃) C, H, N.

N-Cycloheptyl-3,7-dihydro-3-methyl-7-oxo-2H-[1,4]oxazino-[2,3,4-ij]quinoline-6-carboxamide (32). White solid. Mp: 208 °C. Yield: 47%. MS: *m/z* 403.3 (M + H). ¹H NMR (CDCl₃): δ 10.05 (br d, *J* = 7.4 Hz, 1H), 8.71 (s, 1H), 8.09−8.04 (m, 1H), 7.41−7.24 (m, 2H), 4.82 (m, 1H), 4.35−4.26 (m, 2H), 4.21−4.08 (m, 1H), 2.04−1.97 (m, 2H), 1.71−1.57 (m, 13H). Anal. (C₂₀H₂₄N₂O₃) C, H, N.

N-Cyclohexyl-3,7-dihydro-3-ethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (34). White solid. Mp: 175 °C. Yield: 69%. MS: *m/z* 341.3 (M + H). ¹H NMR (DMSO-*d₆*): δ 10.05 (br d, *J* = 7.8 Hz, 1H), 8.80 (s, 1H), 7.89−7.84 (m, 1H), 7.46−7.32 (m, 2H), 4.67−4.60 (m, 2H), 4.36−4.30 (m, 1H), 3.99 (m, 1H), 1.87−1.28 (m, 12H), 0.92 (t, *J* = 7.4 Hz, 3H). Anal. (C₂₀H₂₄N₂O₃) C, H, N.

N-Cycloheptyl-3,7-dihydro-3-ethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (35). White solid. Mp: 165 °C. Yield: 51%. MS: *m/z* 355.3 (M + H). ^{1}H NMR (DMSO-d_6): δ 10.09 (br d, *J* = 7.8 Hz, 1H), 8.79 (s, 1H), 7.89−7.84 (m, 1H), 7.41−7.35 (m, 2H), 4.70−4.59 (m, 2H), 4.36−4.29 (m, 1H), 4.07−4.01 (m, 1H), 1.87−1.56 (m, 14H), 0.92 (t, *J* = 7.2 Hz, 3H). Anal. ($C_{21}H_{26}N_2O_3$) C, H, N.

3,7-Dihydro-N,N-diisopropyl-3-ethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (41). White solid. Mp: 187 °C. Yield: 36%. MS: *m/z* 336.2 (M + H). ^{1}H NMR (DMSO-d_6):8.06 (s, 1H), 7.74−7.69 (m, 1H), 7.27−7.23 (m, 2H), 4.63−4.21 (m, 3H), 3.75 (m, 1H), 3.50 (m, 1H), 1.80−1.42 (m, 2H), 1.42 (d, *J* = 6.4 Hz, 6H), 1.08 (m, 6H), 0.90 (t, *J* = 7.2 Hz, 3H). Anal. ($C_{20}H_{26}N_3O_3$) C, H, N.

N-Cyclohexyl-3,7-dihydro-7-oxo-3-propyl-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (42). White solid. Mp: 191 °C. Yield: 68%. MS: *m/z* 355.2 (M + H). ^{1}H NMR (DMSO-d_6): δ 10.04 (br d, *J* = 8 Hz, 1H), 8.77 (s, 1H), 7.87−7.85 (m, 1H), 7.43−7.33 (m, 2H), 4.75−4.59 (m, 2H), 4.34−4.31 (m, 1H), 3.85 (m, 1H), 1.91−1.29 (m, 14H), 0.87 (t, *J* = 7.6 Hz, 3H). Anal. ($C_{21}H_{26}N_2O_3$) C, H, N.

N-Cycloheptyl-3,7-dihydro-7-oxo-3-propyl-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (43). White solid. Mp: >300 °C. Yield: 46%. MS: *m/z* 369.6 (M + H). ^{1}H NMR (DMSO-d_6): δ 10.08 (br d, *J* = 8 Hz, 1H), 8.75 (s, 1H), 7.89−7.84 (m, 1H), 7.45−7.31 (m, 2H), 4.74−4.57 (m, 2H), 4.34−4.29 (m, 1H), 4.04 (m, 1H), 3.98 (m, 1H), 1.89−1.29 (m, 15H), 0.88 (t, *J* = 7.2 Hz, 3H). Anal. ($C_{22}H_{28}N_2O_3$) C, H, N.

N-Cyclohexyl-3,7-dihydro-8-methyl-7-oxo-3-propyl-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (46). White solid. Mp: 213 °C. Yield: 55%. MS: *m/z* 369.4 (M + H). ^{1}H NMR (DMSO-d_6): δ 10.05 (br d, *J* = 7.8 Hz, 1H); 8.67 (s, 1H), 7.22−7.08 (m, 2H); 4.73−4.65 (m, 1H); 4.56−4.50 (m, 1H); 4.26−4.19 (m, 1H); 3.82 (m, 1H); 2.78 (s, 3H); 1.88−1.19 (m, 14H); 0.87 (t, *J* = 7.4 Hz, 3H). Anal. ($C_{22}H_{28}N_2O_3$) C, H, N.

N-Cyclohexyl-3-cyclopropyl-3,7-dihydro-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (48). White solid. Mp: 212 °C. Yield: 63%. MS: *m/z* 353.2 (M + H). ^{1}H NMR (DMSO-d_6): δ 10.05 (br d, *J* = 8 Hz, 1H), 8.90 (s, 1H), 7.90−7.86 (m, 1H), 7.43−7.38 (m, 2H), 4.61−4.46 (m, 2H), 4.10−4.05 (m, 1H), 3.85 (m, 1H), 1.99−1.32 (m, 11H), 0.70.65 (m, 4H). Anal. ($C_{21}H_{24}N_2O_3$) C, H, N.

N-Cycloheptyl-3-cyclopropyl-3,7-dihydro-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (49). White solid. Mp: 185 °C. Yield: 52%. MS: *m/z* 367.6 (M + H). ^{1}H NMR (DMSO-d_6): δ 10.09 (br d, *J* = 8.4 Hz, 1H), 8.90 (s, 1H), 7.89−7.87 (m, 1H), 7.45−7.35 (m, 2H), 4.55−4.46 (m, 2H), 4.05−4.02 (m, 2H), 1.99−1.90 (m, 2H),1.69−1.41 (m, 10H), 1.30−1.19 (m, 1H), 0.75−0.54 (m, 4H). Anal. ($C_{22}H_{26}N_2O_3$) C, H, N.

(R)-N-Cyclohexyl-3,7-dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide ((R)-31). White solid. Mp: 245 °C. Yield: 62%. MS: *m/z* 327.2 (M + H). ^{1}H NMR (DMSO-d_6): δ 10.05 (br d, *J* = 7.8 Hz, 1H), 8.82 (s, 1H), 7.89−7.85 (m, 1H), 7.46−7.33 (m, 2H), 4.82 (m, 1H), 4.45−4.36 (m, 2H), 3.81 (m, 1H), 1.88−1.28 (m, 13H). Anal. ($C_{19}H_{22}N_2O_3$) C, H, N. $[\alpha]_D^{25}$ = +81 (*c* = 0.01, CH$_3$OH).

(S)-N-Cyclohexyl-3,7-dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide ((S)-31). White solid. Mp: 245 °C. Yield: 69%. MS: *m/z* 327.2 (M + H). ^{1}H NMR (DMSO-d_6): δ 10.05 (br d, *J* = 7.8 Hz, 1H), 8.82 (s, 1H), 7.89−7.85 (m, 1H), 7.42−7.37 (m, 2H), 4.82 (m, 1H), 4.49−4.37 (m, 2H), 3.81 (m, 1H), 1.88−1.28 (m, 13H). Anal. ($C_{19}H_{22}N_2O_3$) C, H, N. $[\alpha]_D^{25}$ = −81 (*c* = 0.01, CH$_3$OH).

(R)-(+)-N-Cycloheptyl-3,7-dihydro-3-ethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide ((R)-35). White solid. Mp: 165 °C. Yield: 72%. MS: *m/z* 355.3 (M + H). ^{1}H NMR (DMSO-d_6): δ 10.09 (br d, *J* = 7.8 Hz, 1H), 8.79 (s, 1H), 7.89−7.84 (m, 1H), 7.45−7.35 (m, 2H), 4.71−4.60 (m, 2H), 4.36−4.29 (m, 1H), 4.07−4.01 (m, 1H), 1.87−1.56 (m, 14H), 0.92 (t, *J* = 7.2 Hz, 3H). Anal. ($C_{21}H_{26}N_2O_3$) C, H, N. $[\alpha]_D^{25}$ = +100 (*c* = 0.01, CHCl$_3$).

(S)-(−)-N-Cycloheptyl-3,7-dihydro-3-ethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide ((S)-35). White solid. Mp: 165 °C. Yield: 54%. MS: *m/z* 355.0 (M + H). ^{1}H NMR (DMSO-d_6): δ 10.09 (br d, *J* = 7.8 Hz, 1H), 8.79 (s, 1H), 7.89−7.84 (m, 1H),

7.45−7.32 (m, 2H), 4.70−4.60 (m, 2H), 4.36−4.29 (m, 1H), 4.07−4.03 (m, 1H), 1.87−1.57 (m, 14H), 0.92 (t, *J* = 7.2 Hz, 3H). Anal. ($C_{21}H_{26}N_2O_3$) C, H, N. $[\alpha]_D^{25}$ = −100 (*c* = 0.01, CHCl$_3$).

Synthesis of N-Adamantyl-, N-Alkyl-, and N-Heteroaryl-3,7-dihydro-2/3-substituted-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamides 22, 23, 25, 26, 28, 30, 33, 36−40, 44, 45, 50−54, (R)-33, (S)-33, (R)-36, (S)-36, (R)-51, (S)-51, (R)-58, and (S)-59. General Procedure. To a stirred solution of the respective carboxylic acid (**12a−g,i,j**, **18a−i**, 0.2 mmol) in dry DMF (3 mL) was added diisopropylethylamine (0.8 mmol). The resulting solution was stirred at room temperature for 10 min before addition of HBTU (*o*-benzotriazol-1-yl-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate; 0.3 mmol) and then stirred for another 3 h. 1-Aminoadamantane, 2-aminoadamantane (for **37**), or 1-amino-3,5-dimethyladamantane (for **45**) (0.3 mmol) was then added, and the solution was stirred for 16 h. DMF was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate and successively washed with water-saturated sodium bicarbonate, water, and brine. The organic phase was dried over anhydrous sodium sulfate, evaporated, and finally purified by flash chromatography using ethyl acetate/petroleum ether (8:2) as the eluent.

N-Adamant-1-yl-3,7-dihydro-7-oxo-3-phenyl-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (22). White solid. Mp: >300 °C. Yield: 71%. MS: *m/z* 441.6 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.89 (br s, 1H), 8.59 (s, 1H), 7.95−7.90 (m, 1H), 7.45−7.34 (m, 5H), 7.16−7.11 (m, 2H), 5.96 (m, 1H); 4.92−4.58 (m, 2H), 2.03 (s, 9H), 1.65 (s, 6H). Anal. ($C_{28}H_{28}N_2O_3$) C, H, N.

3,7-Dihydro-N-(3,5-dimethyladamant-1-yl)-7-oxo-3-phenyl-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (23). White solid. Mp: 264 °C. Yield: 63%. MS: *m/z* 469.5 (M + H). ^{1}H NMR (DMSO-d_6): 9.92 (br s, 1H), 8.56 (s, 1H), 7.95−7.90 (m, 1H), 7.45−7.37 (m, 5H), 7.17−7.12 (m, 2H), 5.95 (m, 1H), 4.82−4.59 (m, 2H), 2.10−1.59 (m, 7H), 1.39−1.14 (m, 6H), 0.83 (s, 6H). Anal. ($C_{30}H_{32}N_2O_3$) C, H, N.

N-Adamant-1-yl-3,7-dihydro-2-methyl-7-oxo-3-phenyl-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (25). White solid. Mp: >300 °C. Yield: 71%. MS: *m/z* 455.6 (M + H). ^{1}H NMR (DMSO-d_6): 9.85 (br s, 1H), 8.62 (s, 1H), 7.95−7.91 (m, 1H), 7.52−7.33 (m, 5H), 7.11−7.06 (m, 2H), 5.82 (d, *J* = 2.8 Hz, 1H), 4.83−4.78 (m, 1H), 2.02 (s, 9H), 1.64 (s, 6H), 1.20 (d, *J* = 6.2 Hz, 3H). Anal. ($C_{29}H_{30}N_2O_3$) C, H, N.

N-Adamant-1-yl-3,7-dihydro-7-oxo-2,3-diphenyl-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (26). White solid. Mp: 260 °C. Yield: 45%. MS: *m/z* 517.3 (M + H). ^{1}H NMR (DMSO-d_6): 9.86 (br s, 1H), 8.73 (s, 1H), 8.02−7.98 (m, 1H), 7.58−7.54 (m, 2H), 7.33−7.13(m, 8H), 6.71−6.66 (m, 2H), 6.25 (d, *J* = 2.8 Hz, 1H), 5.96 (d, *J* = 2.8 Hz, 1H), 2.04 (s, 9H), 1.65 (s, 6H). Anal. ($C_{34}H_{32}N_2O_3$) C, H, N.

N-Adamant-1-yl-3,7-dihydro-7-oxo-3-(4-methylphenyl)-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (28). White solid. Mp: 171 °C. Yield: 59%. MS: *m/z* 455.8 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.89 (br s, 1H), 8.53 (s, 1H), 7.94−7.89 (m, 1H), 7.45−7.34 (m, 2H), 7.21 (d, *J* = 8.00 Hz, 2H), 7.06 (d, *J* = 8.00 Hz, 2H), 5.88 (m, 1H), 4.79−4.51 (m, 2H), 2.29 (s, 3H), 2.03 (s, 9H), 1.65 (s, 6H). Anal. ($C_{29}H_{30}N_2O_3$) C, H, N.

N-Adamant-1-yl-3,7-dihydro-9-methyl-7-oxo-3-phenyl-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (30). White solid. Mp: >300 °C. Yield: 48%. MS: *m/z* 455.4 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.93 (br s, 1H), 8.55 (s, 1H), 7.73 (s, 1H), 7.39−7.36 (m, 3H), 7.20 (s, 1H), 7.14−7.10 (m, 2H), 5.94 (m, 1H), 4.82−4.53 (m, 2H), 2.43 (s, 3H), 2.03 (s, 9H), 1.65 (s, 6H). Anal. ($C_{29}H_{30}N_2O_3$) C, H, N.

N-Adamant-1-yl-3,7-dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (33). White solid. Mp: 282 °C. Yield: 55%. MS: *m/z* 379.3 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.95 (br s, 1H), 8.77 (s, 1H), 7.88−7.84 (m, 1H), 7.45−7.33 (m, 2H), 4.82 (m, 1H), 4.52−4.23 (m, 2H), 2.07 (s, 9H), 1.67 (s, 6H), 1.42 (d, *J* = 6.8 Hz, 3H). Anal. ($C_{23}H_{26}N_2O_3$) C, H, N.

N-Adamant-1-yl-3,7-dihydro-3-ethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (36). White solid. Mp: 219 °C. Yield: 66%. MS: *m/z* 393.5 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.93 (br s, 1H), 8.74 (s, 1H), 7.88−7.83 (m, 1H), 7.41−7.34 (m, 2H),

4.65−4.59 (m, 2H), 4.39−4.12 (m, 1H), 2.07 (s, 9H), 1.72 (m, 2H), 1.67 (s, 6H), 0.92 (t, J = 7.4 Hz, 3H). Anal. ($C_{24}H_{28}N_2O_3$) C, H, N.

N-Adamant-2-yl-3,7-dihydro-3-ethyl-7-oxo-2H-[1,4]oxazino-[2,3,4-ij]quinoline-6-carboxamide (37). White solid. Mp: 240 °C. Yield: 45%. MS: *m/z* 393.1 (M + H). ^{1}H NMR (DMSO-d_6): 10.61 (d, J = 8.4 Hz, 1H), 8.81 (s, 1H), 7.92−7.87 (m, 1H), 7.46−7.32 (m, 2H), 4.70−4.60 (m, 2H), 4.36−4.30 (m, 1H), 4.13 (d, J = 8.4 Hz, 1H), 1.98−1.60 (m, 16H), 0.96 (t, J = 7.2 Hz 3H). Anal. ($C_{24}H_{28}N_2O_3$) C, H, N.

3,7-Dihydro-3-ethyl-N-(5-methylhexan-2-yl)-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (38). White solid. Mp: 240 °C. Yield: 24%. MS: *m/z* 357.1 (M + H). ^{1}H NMR (DMSO-d_6): 10.61 (d, J = 8.4 Hz, 1H), 8.80 (s, 1H), 7.88−7.80 (m, 1H), 7.48−7.34 (m, 2H), 4.78−4.66 (m, 2H), 4.40−4.28 (m, 1H), 4.12−3.88 (m, 1H), 1.83−1.40 (m, 5H), 1.18−1.11 (m, 5H), 0.88−0.83 (m, 9H). Anal. ($C_{21}H_{28}N_2O_3$) C, H, N.

3,7-Dihydro-3-ethyl-7-oxo-N-pyridin-4-yl-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (39). White solid. MS: *m/z* 336.2 (M + H). ^{1}H NMR (DMSO-d_6): 12.68 (br s, 1H), 9.00 (s, 1H), 8.50−8.47 (m, 2H), 7.97−7.93 (m, 1H), 7.74−7.70 (m, 2H), 7.54−7.39 (m, 2H), 4.83−4.64 (m, 2H), 4.42−4.31 (m, 1H), 1.96−1.65 (m, 2H), 0.95 (t, J = 7.6 Hz, 3H). Anal. ($C_{19}H_{17}N_3O_3$) C, H, N.

3,7-Dihydro-3-ethyl-7-oxo-N-thiazol-2-yl-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (40). White solid. Mp: 221 °C. Yield: 58%. MS: *m/z* 342.2 (M + H). ^{1}H NMR (DMSO-d_6): 13.62 (s, 1H), 9.05 (s, 1H), 7.96−7.94 (m, 1H), 7.54−7.28 (m, 4H), 4.78−4.65 (m, 2H), 4.43−4.3 (m, 1H), 1.92−1.61 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H). Anal. ($C_{17}H_{15}N_3O_3S$) C, H, N.

N-Adamant-1-yl-3,7-dihydro-7-oxo-3-propyl-2H-[1,4]oxazino-[2,3,4-ij]quinoline-6-carboxamide (44). White solid. Mp: 218 °C. Yield: 43%. MS: *m/z* 407.3 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.93 (br s, 1H), 8.71 (s, 1H), 7.86−7.84 (m, 1H), 7.42−7.32 (m, 2H), 4.71 (m, 1H), 4.61−4.58 (m, 1H), 4.33−4.30 (m, 1H), 2.06 (s, 9H), 1.78 (m, 2H), 1.67 (s, 6H), 1.43−1.21 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H). Anal. ($C_{25}H_{30}N_2O_3$) C, H, N.

3,7-Dihydro-N-(3,5-dimethyladaman-1-yl)-7-oxo-3-propyl-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (45). White solid. Mp: 219 °C. Yield: 48%. MS: *m/z* 435.7 (M + H). ^{1}H NMR (DMSO-d_6): 9.96 (br s, 1H), 8.68 (s, 1H), 7.87−7.83 (m, 1H), 7.45−7.31 (m, 2H), 4.79−4.57 (m, 2H), 4.33 (m, 1H), 2.12−1.15 (m, 17H), 0.92−0.85 (m, 9H). Anal. ($C_{27}H_{34}N_2O_3$) C, H, N.

N-Adamant-1-yl-3,7-dihydro-8-methyl-7-oxo-3-propyl-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (47). White solid. Mp: 237 °C. Yield: 53%. MS: *m/z* 421.3 (M + H). ^{1}H NMR (DMSO-d_6): 9.94 (br s, 1H), 8.62 (s, 1H), 7.17−7.05 (m, 2H), 4.85−4.60 (m, 2H), 4.22 (m, 1H), 3.43−3.36 (m, 4H), 2.77 (s, 3H), 2.06 (s, 9H), 1.67 (s, 6H), 0.88 (m, 3H). Anal. ($C_{26}H_{32}N_2O_3$) C, H, N.

N-Adamant-1-yl-3-cyclopropyl-3,7-dihydro-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (50). White solid. Mp: 245 °C. Yield: 55%. MS: *m/z* 405.3 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.94 (br s, 1H), 8.88 (s, 1H), 7.89−7.85 (m, 1H), 7.42−7.36 (m, 2H), 4.63−4.18 (m, 2H), 4.04−3.97 (m, 2H), 2.07 (s, 9H), 1.68 (s, 6H), 1.33−1.15 (m, 1H), 0.66−0.51 (m, 4H). Anal. ($C_{25}H_{28}N_2O_3$) C, H, N.

N-Adamant-1-yl-3,7-dihydro-3-isopropyl-7-oxo-2H-[1,4]oxazino-[2,3,4-ij]quinoline-6-carboxamide (51). White solid. Mp: 220 °C. Yield: 62%. MS: *m/z* 407.5 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.90 (br s, 1H), 8.68 (s, 1H), 7.85−7.81 (m, 1H), 7.42−7.28 (m, 2H), 4.79−4.73 (m, 1H), 4.42−4.24 (m, 2H), 2.04 (s, 10H), 1.92 (m, 1H), 1.65 (s, 6H), 0.99 (d, J = 6.6 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H). Anal. ($C_{25}H_{30}N_2O_3$) C, H, N.

N-Adamant-1-yl-3,7-dihydro-3,3-dimethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (52). Pale white solid. Mp: 223 °C. Yield: 26%. MS: *m/z* 393.1 (M + H). ^{1}H NMR (CDCl$_3$): 9.98 (br s, 1H), 8.95 (s, 1H), 8.10−8.05 (m, 1H), 7.41−7.23 (m, 2H), 4.12 (s, 2H), 2.19−2.11 (m, 9H), 1.73 (s, 6H), 1.62 (s, 6H). Anal. ($C_{24}H_{28}N_2O_3$) C, H, N.

N-Adamant-1-yl-3-ethyl-10-fluoro-3,7-dihydro-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (53). White solid. Mp: 232 °C. Yield: 65%. MS: *m/z* 411.2 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.84 (s, 1H), 8.77 (s, 1H), 7.90−7.82 (m, 1H), 7.48−7.38 (m, 1H),

4.75−4.64 (m, 2H), 4.39−4.32 (m, 1H), 2.06 (s, 9H), 1.82−1.74 (m, 2H), 1.67 (s, 6H), 0.93 (t, J = 7.6 Hz, 3H). Anal. ($C_{24}H_{27}FN_2O_3$) C, H, N.

N-Adamant-1-yl-9,10-difluoro-3,7-dihydro-3-ethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (54). White solid. Mp: 262 °C. Yield: 50%. MS: *m/z* 429.3 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.78 (s, 1H), 8.79 (s, 1H), 7.77−7.68 (m, 1H), 4.82−4.68 (m, 2H), 4.45−4.38 (m, 1H), 2.06 (s, 9H), 1.82−1.78 (m, 2H), 1.67 (s, 6H), 0.92 (t, J = 7.6 Hz, 3H). Anal. ($C_{24}H_{26}FN_2O_3$) C, H, N.

(R)-(+)-N-Adamant-1-yl-3,7-dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide ((R)-33). White solid. Mp: 282 °C. Yield: 56%. MS: *m/z* 379.3 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.95 (br s, 1H), 8.77 (s, 1H), 7.88−7.84 (m, 1H), 7.45−7.33 (m, 2H), 4.82 (m, 1H), 4.52−4.23 (m, 2H), 2.07 (s, 9H), 1.67 (s, 6H), 1.42 (d, J = 6.8 Hz, 3H). Anal. ($C_{23}H_{26}N_2O_3$) C, H, N. $[\alpha]_D^{25}$ = +69 (c = 0.01, CDCl$_3$).

(S)-(−)-N-Adamant-1-yl-3,7-dihydro-3-methyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide ((S)-33). White solid. Mp: 282 °C. Yield: 50%. MS: *m/z* 379.3 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.95 (br s, 1H), 8.77 (s, 1H), 7.88−7.84 (m, 1H), 7.45−7.33 (m, 2H), 4.82 (m, 1H), 4.52−4.23 (m, 2H), 2.07 (s, 9H), 1.67 (s, 6H), 1.42 (d, J = 6.8 Hz, 3H). Anal. ($C_{23}H_{26}N_2O_3$) C, H, N. $[\alpha]_D^{25}$ = −69 (c = 0.01, CDCl$_3$).

(R)-(+)-N-Adamant-1-yl-3,7-dihydro-3-ethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide ((R)-36). White solid. Mp: 219 °C. Yield: 69%. MS: *m/z* 393.1 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.94 (br s, 1H), 8.75 (s, 1H), 7.88−7.83 (m, 1H), 7.41−7.34 (m, 2H), 4.65−4.59 (m, 2H), 4.39−4.12 (m, 1H), 2.07 (s, 9H), 1.72 (m, 2H), 1.67 (s, 6H), 0.92 (t, J = 7.4 Hz, 3H). Anal. ($C_{24}H_{28}N_2O_3$) C, H, N. $[\alpha]_D^{25}$ = +142 (c = 0.01, CHCl$_3$).

(S)-(−)-N-Adamant-1-yl-3,7-dihydro-3-ethyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide ((S)-36). White solid. Mp: 219 °C. Yield: 53%. MS: *m/z* 393.2 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.94 (br s, 1H), 8.75 (s, 1H), 7.88−7.83 (m, 1H), 7.45−7.31 (m, 2H), 4.65−4.59 (m, 2H), 4.39−4.12 (m, 1H), 2.07 (s, 9H), 1.77 (m, 2H), 1.68 (s, 6H), 0.92 (t, J = 7.4 Hz, 3H). Anal. ($C_{24}H_{28}N_2O_3$) C, H, N. $[\alpha]_D^{25}$ = −142 (c = 0.01, CHCl$_3$).

(R)-(+)-N-Adamant-1-yl-3,7-dihydro-3-isopropyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide ((R)-51). White solid. Mp: 212 °C. Yield: 47%. MS: *m/z* 407.5 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.90 (br s, 1H), 8.68 (s, 1H), 7.86−7.81 (m, 1H), 7.42−7.28 (m, 2H), 4.79−4.73 (m, 1H), 4.42−4.24 (m, 2H), 2.04 (s, 10H), 1.92 (m, 1H), 1.65 (s, 6H), 0.98 (d, J = 6.6 Hz, 3H), 0.76 (d, J = 6.6 Hz, 3H). Anal. ($C_{25}H_{30}N_2O_3$) C, H, N. $[\alpha]_D^{25}$ = +42 (c = 0.01, CH$_3$OH).

(S)-(−)-N-Adamant-1-yl-3,7-dihydro-3-isopropyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide ((S)-51). White solid. Mp: 220 °C. Yield: 53%. MS: *m/z* 407.5 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.90 (br s, 1H), 8.68 (s, 1H), 7.85−7.81 (m, 1H), 7.42−7.28 (m, 2H), 4.79−4.73 (m, 1H), 4.42−4.24 (m, 2H), 2.04 (s, 10H), 1.92 (m, 1H), 1.65 (s, 6H), 0.99 (d, J = 6.6 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H). Anal. ($C_{25}H_{30}N_2O_3$) C, H, N. $[\alpha]_D^{25}$ = −42 (c = 0.01, CH$_3$OH).

(R)-(+)-N-Adamant-1-yl-3,7-dihydro-3-isobutyl-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide ((R)-58). White solid. Mp: 130 °C. Yield: 28%. MS: *m/z* 421.3 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.92 (br s, 1H), 8.67 (s, 1H), 7.88−7.83 (m, 1H), 7.45−7.32 (m, 2H), 4.82−4.75 (m, 1H), 4.63−4.57 (m, 1H), 4.35−4.24 (m, 1H), 2.07 (s, 10H), 1.68 (s, 6H),1.44 (m, 1H), 0.99 (d, J = 5.8 Hz, 3H), 0.90 (d, J = 5.8 Hz, 3H). Anal. ($C_{26}H_{32}N_2O_3$) C, H, N.

(R)-(+)-N-Adamant-1-yl-3-benzyl-3,7-dihydro-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide ((R)-59). White solid. Mp: 153 °C. Yield: 55%. MS: *m/z* 455.6 (M + H). ^{1}H NMR (DMSO-d_6): δ 9.85 (br s, 1H), 8.50 (s, 1H), 7.89−7.85 (m, 1H), 7.43−7.19 (m, 7H), 4.99 (m, 1H), 4.41−4.23 (m, 2H), 3.04 (d, J = 7.4 Hz, 2H), 2.03 (s, 9H), 1.66 (s, 6H). Anal. ($C_{29}H_{30}N_2O_3$) C, H, N. $[\alpha]_D^{25}$ = +190 (c = 0.01, CH$_3$OH).

Synthesis of N-Adamant-1-yl-3,7-dihydro-3-ethyl-10-methoxy-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (55). A solution of N-adamant-1-yl-3,7-dihydro-3-ethyl-10-fluoro-7-oxo-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (53; 58 mg, 0.14 mmol) in dry THF (3 mL) was added to a solution of freshly prepared CH$_3$ONa (0.28 mmol) under a nitrogen atmosphere. The

reaction mixture was heated at 50 °C for 16 h and neutralized using 1 N HCl. The mixture was concentrated in vacuo and the residue extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated to dryness. The crude residue was purified by chromatography using petroleum ether/ethyl acetate (1:1) as the eluent, yielding 20 mg (33%) of *N*-adamant-1-yl-3,7-dihydro-3-ethyl-10-methoxy-7-oxo-2*H*-[1,4]oxazino[2,3,4-*ij*]-quinoline-6-carboxamide as a white solid. Mp: 279 °C. MS: *m/z* 423.1 (M + H). ^1H NMR (CDCl$_3$): δ 9.98 (br s, 1H), 8.59 (s, 1H), 8.07 (d, *J* = 9 Hz, 1H), 7.12 (d, *J* = 9 Hz, 1H), 4.65−4.59 (m, 1H), 4.30−4.21 (m, 1H), 4.19 (m, 1H), 4.02 (s, 3H), 2.16−2.10 (m, 9H), 1.91−1.88 (m, 2H), 1.73 (m, 6H), 1.05 (t, *J* = 7.4 Hz, 3H). Anal. ($C_{25}H_{30}N_2O_3$) C, H, N.

Synthesis of N-Adamant-1-yl-3,7-dihydro-3-ethyl-7-oxo-10-pyrrolidin-1-yl-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (56). K_2CO_3 (1 mmol) was added to a mixture of *N*-adamant-1-yl-3,7-dihydro-3-ethyl-10-fluoro-7-oxo-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxamide (**53**; 0.36 mmol), pyrrolidine (2.5 mmol), and anhydrous DMF (5 mL). The resulting mixture was stirred at 100 °C for 10 h. The solvent was removed under vacuum, the residue dissolved in ethyl acetate (30 mL), and the organic layer washed with water (5 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, evaporated, and purified by flash chromatography using ethyl acetate/petroleum ether (3:7) as the eluent. Pale white solid. Mp: 282 °C. Yield: 50%. MS: *m/z* 462.4 (M + H). ^1H NMR (CDCl$_3$): δ 10.01 (br s, 1H), 8.50 (s, 1H), 7.71 (d, *J* = 9 Hz, 1H), 6.80 (d, *J* = 9.2 Hz, 1H), 4.532−4.38 (m, 2H), 4.14−4.07 (m, 1H), 3.51 (m, 4H), 2.06 (s, 9H), 1.96−1.73 (m, 6H), 1.66 (s, 6H), 0.96 (t, *J* = 7.4 Hz, 3H). Anal. ($C_{28}H_{35}N_3O_3$) C, H, N.

Synthesis of N-Adamant-1-yl-3,7-dihydro-3-ethyl-7-oxo-10-(4-methylpiperazin-1-yl)-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxamide (57). K_2CO_3 (1 mmol) was added to a mixture of *N*-adamant-1-yl-3,7-dihydro-3-ethyl-10-fluoro-7-oxo-2*H*-[1,4]oxazino[2,3,4-*ij*]-quinoline-6-carboxamide (**53**; 0.36 mmol), 1-methylpiperazine (2.5 mmol), and anhydrous DMF (5 mL). The resulting mixture was stirred at 100 °C for 10 h. The solvent was removed in vacuo, the residue dissolved in ethyl acetate (30 mL), and the organic layer washed with water (5 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, evaporated, and purified by flash chromatography using ethyl acetate/petroleum ether (3:7) as the eluent. White solid. Mp: 294 °C dec. Yield: 40%. MS: *m/z* 491.3 (M + H). ^1H NMR (DMSO-d_6): δ 9.95 (s, 1H), 8.61 (s, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 4.75−4.67 (m, 2H), 4.45−4.38 (m, 1H), 3.25−3.11 (m, 4H), 2.49−2.46 (m, 4H), 2.21 (s, 3H), 2.03 (s, 9H), 1.84−1.69 (m, 2H), 1.65 (s, 6H), 0.93 (t, *J* = 7.4 Hz, 3H). Anal. ($C_{29}H_{39}N_4O_3$) C, H, N.

Synthesis of N-Adamant-1-yl-3-ethyl-10-(4-methylpiperazin-1-yl)-7-oxo-3,7-dihydro-2H-[1,4]-oxazino[2,3,4-ij]quinoline-6-carboxamide Hydrochloride (57·HCl). A solution of *N*-adamant-1-yl-3-ethyl-10-(4-methylpiperazin-1-yl)-7-oxo-3,7-dihydro-7*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxamide (**47**; 20 mg g, 0.04 mmol) in 1,4-dioxane saturated with gaseous hydrogen chloride (4 mL) was stirred at 0 °C for 30 min. The solvent was concentrated in vacuo, and the residue was suspended in diethyl ether (10 mL), filtered, and washed with cold diethyl ether. Pale yellow solid. Mp: 240 °C dec. Yield: 69%. MS: *m/z* 527.8 (M + H). ^1H NMR (DMSO-d_6): δ 10.48 (br s, 1H), 9.94 (s, 1H), 8.67 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 4.68−4.57 (m, 2H), 4.30−4.25 (m, 1H), 3.70−2.88 (m, 11H), 2.05 (m, 9H), 1.67 (m, 8H), 0.92 (t, *J* = 7.4 Hz, 3H). Anal. ($C_{29}H_{39}ClN_4O_3$) C, H, N.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Table of elemental analysis of compounds **19−59**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

ABBREVIATIONS USED

CHO, Chinese hamster ovary; DEEM, diethyl (ethoxymethylene)-malonate; CDI, 1,1′-carbonyldiimidazole; SI, selectivity index; EDC, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride; HOBt, hydroxybenzotriazole; HBTU, *O*-benzotriazolyl-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate

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