Letters

Potent, Orally Bioavailable Delta Opioid Receptor Agonists for the Treatment of Pain: Discovery of *N,N*-Diethyl-4-(5-hydroxyspiro-[chromene-2,4′-piperidine]-4-yl)benzamide (ADL5859)

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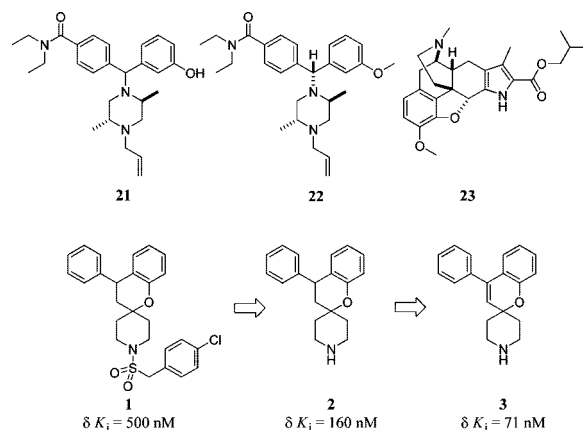
Abstract: Selective δ opioid receptor agonists are promising potential therapeutic agents for the treatment of various types of pain conditions. A spirocyclic derivative was identified as a promising hit through screening. Subsequent lead optimization identified compound **20** (ADL5859) as a potent, selective, and orally bioavailable δ agonist. Compound **20** was selected as a clinical candidate for the treatment of pain.

Endogenous opioid peptides exert their effects through G-protein-coupled seven transmembrane receptors, designated μ, κ, and δ opioid receptors. δ selective agonists have demonstrated efficacy in various animal models of pain.[1−5] In addition, these agents may possess potential clinical benefits compared with the μ agonists currently used for pain relief, including reduced respiratory depression,[6] constipation,[3] physical dependence,[7] and abuse liability.[6]

A major breakthrough in identifying small molecule non-peptidic δ agonists was disclosed by Burroughs Wellcome in 1993 with the identification of BW373U86 (**21**)[8] (Chart 1). The structure−activity relationships (SAR[a]) of this series have formed the basis of much of the research activity in the area of δ agonists.[9−11] SNC80 (**22**),[12] the optically pure enantiomer of the methyl ether analogue of **21**, exhibits remarkable selectivity for δ over μ and κ opioid receptors in both receptor binding and in vitro bioassays.[12,13] Unfortunately, **21** and **22** produce characteristic convulsions in animals at doses similar to the doses required to elicit analgesic activity.[14] The convulsions induced

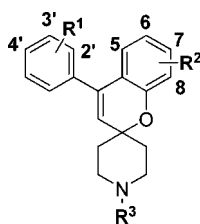* To whom correspondence should be addressed. Phone: 1-484-595-1061. Fax: 1-484-595-1551. E-mail: blebourdonnec@adolor.com.
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[a] Abbreviations: SAR, structure−activity relationships; LQT, long QT syndrome; hERG, human ether-a-go-go related gene; FCA, Freund's complete adjuvant; DOR, δ opioid receptor; CYP: cytochrome P450; EEG: electroencephalogram.

Chart 1. Structures of **21−23**, **1−3**

$\delta K_i = 500$ nM $\delta K_i = 160$ nM $\delta K_i = 71$ nM

by compounds **21** and **22** can be blocked with δ antagonists in all species tested, and the absence of these convulsions in mice lacking the δ receptor strongly suggests the requirement for δ receptor activation in this effect.[15] In contrast to **21** and **22**-like compounds, peptide δ selective agonists have not generally produced convulsions in rodents.[16,17] Furthermore, SB-235863 (**23**),[18] a selective δ agonist of the morphinan class, does not produce seizures up to 70 mg/kg po and fails to decrease maximum electroshock seizure threshold (MEST) or potentiate metrazol-induced seizures.[3]

On the basis of this information, our objective was to identify a novel series of δ opioid receptor agonists that were not only potent and highly selective over the μ and κ opioid receptors but also orally available and, unlike **21** and **22**, not convulsive. A proprietary chemotype, compound **1**, was identified as a promising hit through screening. This agent was subjected to hit-to-lead, leading to the discovery of the low molecular weight compound **3** (Chart 1) displaying moderate δ affinity ($K_i = 71$ nM), good selectivity over μ and κ opioid receptors, and full δ agonist activity in vitro (Table 1). Optimization of **3** was then initiated to further improve the affinity at the δ receptor and establish nascent SAR in this 4-phenylspiro[chromene-2,4′-piperidine] series. Compounds **3−20** were tested for their affinities toward the cloned human δ, κ, and μ opioid receptors as measured by their abilities to displace [³H]-diprenorphine from its specific binding sites. The agonist potencies of the target compounds were assessed by their abilities to stimulate guanosine 5′-*O*-(3-[³⁵S]thio)triphosphate ([³⁵S]GTPγS) binding to membranes containing cloned human δ opioid receptors.[19] As indicated in Table 1, introduction of electron withdrawing groups at the 4′ position of the pendant phenyl group of **3** led to a substantial improvement in the δ opioid receptor affinity. The best compound identified from this early lead optimization campaign was the diethylcarboxamide derivative **11**, which bound to the δ opioid receptor with an affinity of 1.8 nM and demonstrated greater than 1000-fold selectivity for the δ receptor compared to the μ and κ receptors. As shown in Table 1, displacement of the diethylcarboxamide moiety of **11** from the 4′- to the 3′- (**12**) and 2′-position (**13**) resulted in a significant decrease, i.e., 180-fold and 270-fold, respectively, in the δ opioid receptor affinity. The effect of *N*-substitution of the piperidine nitrogen of **11** was then investigated. Substitution of the NH

Table 1. In Vitro Profile of Compounds 3−20 at Opioid Receptors (δ, μ, and κ); Inhibitory Activity of Selected Compounds at the hERG Channel[a]

compd	R^1	R^2	R^3	$K_i(\delta)$ (nM)	$EC_{50}(\delta)$ (nM)	$K_i(\mu)$ (nM) or %inh.@10 μM	$K_i(\kappa)$ (nM) or %inh.@10 μM	IC_{50}(hERG) (nM)[c]
3	H	H	H	71 (56−89)	380 (110−1300)	42 ± 5%	3400 (550−21000)	680
4	4′-CH$_3$	H	H	72 (40−130)	810 (190−3400)	49 ± 8%	57 ± 7%	462
5	4′-CF$_3$	H	H	150 (81−290)	nd[b]	42 ± 5%	2000 (1500−2600)	379[e]
6	4′-OCH$_3$	H	H	58 (45−74)	190 (110−350)	42 ± 4%	42 ± 13%	585
7	4′-OH	H	H	59 (30−120)	220 (110−440)	54 ± 3%	58 ± 8%	643[e]
8	4′-CN	H	H	18 (10−32)	200 (130−320)	60 ± 2%	63 ± 2%	<100
9	4′-CO$_2$CH$_3$	H	H	9.3 (3.7−23)	81 (38−170)	54 ± 10%	520 (360−760)	663
10	4′-CO$_2$H	H	H	11 (5.5−22)	220 (140−360)	13 ± 1%	14 ± 7%	>100000
11	4′-CON(C$_2$H$_5$)$_2$	H	H	1.8 (1.1−2.8)	19 (11−32)	32 ± 5%	29 ± 5%	7900
12	3′-CON(C$_2$H$_5$)$_2$	H	H	330 (270−400)	nd[b]	12 ± 8%	10 ± 4%	303
13	2′-CON(C$_2$H$_5$)$_2$	H	H	480 (310−740)	nd[b]	12 ± 8%	45 ± 8%	6450
14	4′-CON(C$_2$H$_5$)$_2$	H	COCH$_3$	1300	nd[b]	14%	2%	47440
15	4′-CON(C$_2$H$_5$)$_2$	H	CH$_3$	3.5 (2.3−5.1)	89 (51−150)	12 ± 6%	24 ± 5%	766
16	4′-CON(C$_2$H$_5$)$_2$	H	C$_2$H$_5$	68 (17−270)	nd[b]	13 ± 3%	13 ± 2%	1814
17	4′-CON(C$_2$H$_5$)$_2$	8-OH	H	360 (100−1300)	nd[b]	4 ± 6%	28 ± 3%	18310
18	4′-CON(C$_2$H$_5$)$_2$	7-OH	H	1.5 (0.54−4.2)	140 (79−240)	35 ± 0.3%	39 ± 4%	60000
19	4′-CON(C$_2$H$_5$)$_2$	6-OH	H	0.43 (0.32−0.58)	1.4 (1.0−2.1)	36 ± 7%	830 (590−1200)	19750
20	4′-CON(C$_2$H$_5$)$_2$	5-OH	H	0.84 (0.73−0.96)	20 (10−41)	32 ± 3%	37 ± 2%	78000
21				0.32 (0.25−0.52)	0.40 (0.30−0.52)	260 (180−390)	130 (71−250)	nd[b]
22				1.2 (0.80−1.7)	10 (6.8−15)	25 ± 3%	28 ± 3%	nd[b]

[a] See detailed pharmacological methods in the Supporting Information. [b] nd: not determined. [c] Inhibition of hERG channel currents in voltage-clamped HEK293 cells stably expressing hERG potassium channels; IC_{50} values are geometric means from at least three separate determinations.

group of **11** with an *N*-acetyl (**14**) functionality resulted in a 720-fold decrease in δ receptor binding, suggesting that the basic nitrogen functionality of **11**, protonated at physiological pH, is an essential pharmacophoric point, presumably involved in electrostatic interaction with an anionic residue of the δ opioid receptor. Replacement of the NH group of **11** with an *N*-methyl functionality (**15**) was found to be well tolerated. However, larger *N*-substituents resulted in a decrease in the affinity of the ligand for the δ receptor. As an example, substitution of the methyl group of **15** with an ethyl moiety (**16**) resulted in a 20-fold decrease in the δ binding affinity. This SAR distinguishes our 4-phenylspiro[chromene-2,4′-piperidine] class of δ agonists from the compound **22** series.[20]

With regard to ancillary activity, we found that **11** moderately inhibited (IC_{50} = 7900 nM) hERG channel currents in vitro (experiments performed in voltage-clamped HEK293 cells that stably expressed hERG potassium channels). The blocking of this cardiac K$^+$ channel (I_{Kr}) has been linked to drug-induced long QT syndrome (LQT), which can lead to Torsades de Pointes, a life threatening form of arrhythmia, and subsequent ventricular fibrillation.[21] Therefore, lead optimization efforts were focused on further minimizing hERG channel inhibitory activity while preserving potent affinity at the δ receptor. We adopted the approach of incorporating polar substituent into the structure of **11** as a means of controlling log P and to attenuate hERG inhibitory activity. This strategy has already been successfully employed in a number of optimization campaigns designed to reduce the hERG liability of a lead series.[22] As indicated in Table 1, introduction of a hydroxyl group at the 8-position of the spiro[chromene-2,4′-piperidine] core of compound **11** resulted in 200-fold decrease in the affinity toward the δ opioid receptor. In contrast, the 6- and 5-hydroxy analogues of compound **11**, i.e., compounds **19** and **20** (ADL5859) respectively, displayed subnanomolar binding affinity at the δ opioid receptor, potent δ agonist activity, and excellent opioid receptor selectivity. In addition, **19** and **20**
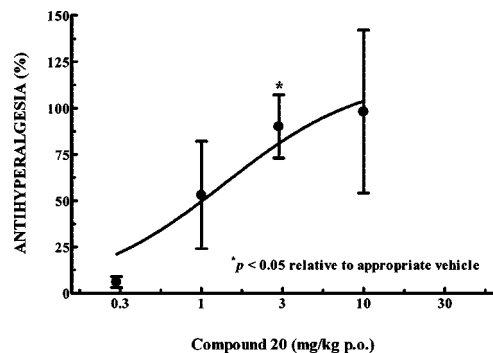
Figure 1. Effect of compound **20** in the rat FCA mechanical hyperalgesia assay. Values on the graph represent the mean and standard error of the mean (SEM) using $n = 11-12$.
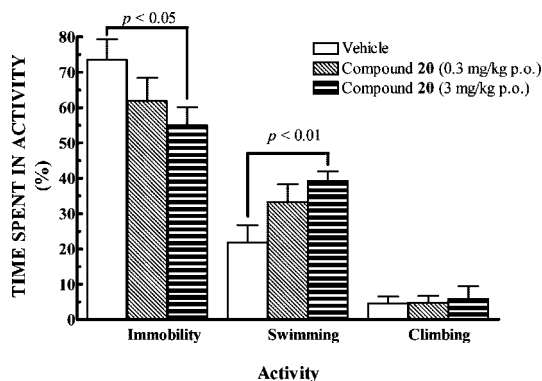

Figure 2. Effect of compound **20** in the rat forced swim test. The data were analyzed by one-way ANOVA with post hoc analysis to compare the behavioral response after vehicle treatment to the behavioral response after drug treatment ($n = 12$ for each group).

displayed weak inhibitory activity at the hERG channel (**19**: hERG IC$_{50}$ = 19.75 μM; **20**: hERG IC$_{50}$ = 78 μM).

On the basis of their favorable profile in vitro, compounds **19** and **20** were tested in the rat Freund's complete adjuvant (FCA) mechanical hyperalgesia assay.[23,24] At the screening dose of 3 mg/kg po, compound **20** produced 100% reversal of hyperalgesia in the inflamed paw (the paw pressure threshold of the inflamed paw returned to that of the uninflamed paw). In contrast, under the same assay conditions, compound **19** when dosed orally at 3 mg/kg displayed only weak activity (35% reversal of hyperalgesia). The oral ED$_{50}$ of compound **20** in the FCA mechanical hyperalgesia assay was 1.4 mg/kg (Figure 1). The onset of action was rapid after oral dosing of 3 mg/kg, with significant antihyperalgesia occurring at 30 and 60 min post-treatment, and the duration of action was relatively short (less than 60 min; data not shown). The antihyperalgesia produced by compound **20** (3 mg/kg, po) was reversed by pretreatment with the δ opioid antagonist naltrindole (0.3 mg/kg sc), thus demonstrating a δ receptor mediated effect (data not shown). Several lines of evidence in animal models support the potential utility of DOR-selective agonists in the treatment of depression.[17,25] In the rat forced swim assay, compound **20** (3 mg/kg po) produced robust antidepressant-like activity, as evidenced by a significant decrease in the time spent immobile and a significant increase in the time spent swimming (Figure 2). As was observed for the FCA mechanical hyperalgesia assay, the effect of compound **20** (3 mg/kg, po) in the forced swim assay was prevented by pretreatment with naltrindole (1 mg/kg sc) (data not shown). The pharmacokinetics of compound **20** after iv and po administration to rats and dogs are summarized in Table 2. The estimated half-life after oral administration in

Table 2. Selected Pharmacokinetic Parameters of Compound **20** in Rats and Dogs[a]

	rat[c]	dog[d]
CLs (L/h/kg)	1.8 ± 0.5	0.4 ± 0.1
Vdss (L/kg)	10.7 ± 1.9	2.5 ± 0.5
$t_{1/2}$[b] (oral, h)	5.3 ± 0.7	4.7 ± 0.2
C_{max} (nM)	117 ± 44	1732 ± 240
F (%)	33.4 ± 3.2	66.5 ± 6.8

[a] Values represent the mean $\pm$ standard deviation of three animals. [b] Expressed as harmonic mean. [c] 0.25 mg/kg intravenous and 3.0 mg/kg oral dose. [d] 1.0 mg/kg intravenous and 3.0 mg/kg oral dose.

Scheme 1. Synthesis of Compound **20**[a]
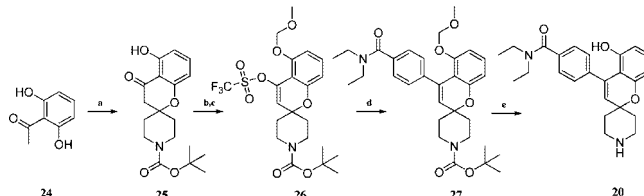
[a] Reagents and conditions: (a) *tert*-butyl 4-oxopiperidine-1-carboxylate, pyrrolidine, MeOH, reflux, 75%; (b) MOMCl, *i*Pr$_2$EtN, DCM, reflux, 83%; (c) C$_6$H$_5$N(SO$_2$CF$_3$)$_2$, LiHMDS, THF, -78 °C to 25 °C, 100%; (d) 4-(*N,N*-diethylaminocarbonyl)phenylboronic acid, Pd[P(C$_6$H$_5$)$_3$]$_4$, LiCl, aq Na$_2$CO$_3$, DME, reflux, 62%; (d) anhyd HCl, dioxane, MeOH, 25 °C, 100%.

rats and dogs was 5.3 and 4.7 h, respectively. There was a greater than proportional increase in AUC$_{0-\infty}$ with increasing dose after oral administration of $1-30$ mg/kg in rats (data not shown). The bioavailability of compound **20** (3 mg/kg po) in rats and dogs was 33% and 66%, respectively. Plasma protein binding of compound **20** (tested at 2 μM concentration) was modest in rat (15.9% unbound), dog (15.2% unbound), and human (41.9% unbound). Compound **20** was moderately metabolized by human and rat hepatic microsomes, with 64.9% and 69.2% remaining, respectively, after a 30 min incubation. Consistent with the low systemic plasma clearance observed in dog, little metabolism of **20** occurred in dog liver microsomes (98.7% remaining after 30 min). Compound **20** showed very little inhibitory activity toward drug-metabolizing CYP enzymes and was metabolized in vitro by the recombinant human P450 isoenzymes CYP3A4 and CYP2D6. Compound **20** is a selective δ agonist, as it did not bind to over 100 nonopioid receptors, channels, or enzymes at a concentration of 10 μM. No overt side effects of compound **20** have been identified. Only modest *suppression* of locomotor activity in rats was produced at a dose 200-fold higher than the ED$_{50}$ in the FCA assay. Importantly, no SNC80-like behaviors, including convulsions, increased locomotor activity, or stereotypic activity, were observed in mice or rats following administration at po doses of compound **20** up to 1000 mg/kg. No EEG disturbances (seizure-like activity) were observed following intravenous administration of 10 and 30 mg/kg of compound **20** in a rat EEG telemetry study. These data highlight a markedly improved CNS safety margin for compound **20** compared to **22** and representatives of this chemical class.

In summary, starting from a screening hit with submicromolar affinity at the δ opioid receptor, compound **20**, a potent and highly selective full agonist at the δ opioid receptor that is structurally distinct from other chemical classes of δ agonists, was discovered. Compound **20** was prepared as indicated in Scheme 1. Compound **20** was selected as a clinical candidate for the management of various pain conditions. In a phase I safety study conducted in normal healthy volunteers, **20** was well tolerated and showed good oral exposure with a pharmacokinetic profile that may be suitable for once or twice daily

dosing.[26] Compound **20** has been advanced to phase II proof of concept studies for the management of pain.

Supporting Information Available: Experimental procedures and characterization data for all compounds and experimental procedure for biological assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Clinical studies with **20** are being conducted under open INDs, indicating FDA approval to conduct clinical studies.