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)

Bertrand Le Bourdonnec,*,† Rolf T. Windh,‡ Christopher W. Ajello,† Lara K. Leister,† Minghua Gu,† Guo-Hua Chu,† Paul A. Tuthill,† William M. Barker,† Michael Koblish,‡ Daniel D. Wiant,‡ Thomas M. Graczyk,‡ Serge Belanger,‡ Joel A. Cassel,‡ Marina S. Feschenko,‡ Bernice L. Brogdon,§ Steven A. Smith,§ David D. Christ,§ Michael J. Derelanko,|| Steve Kutz,|| Patrick J. Little,‡ Robert N. DeHaven,‡ Diane L. DeHaven-Hudkins,‡ and Roland E. Dolle†

Departments of Chemistry, Pharmacology, DMPK, and Preclinical Safety Assessment, Adolor Corporation, 700 Pennsylvania Drive, Exton, Pennsylvania 19341

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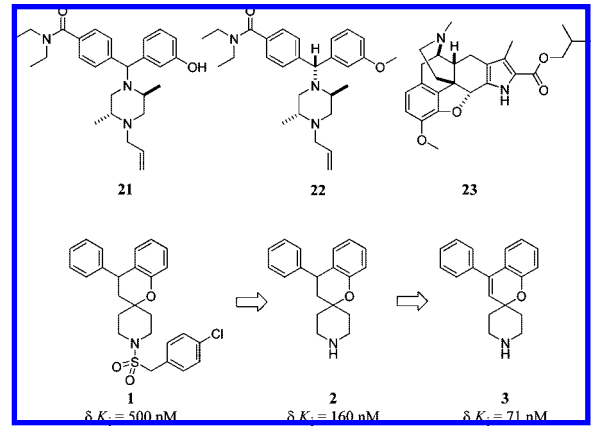
Abstract: Selective δ opioid receptor agonists are promising potential therapeutic agents for the treatment of various types of pain conditions. A spirocyclic derivative was identified as a promising hit through screening. Subsequent lead optimization identified compound **20** (ADL5859) as a potent,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

Chart 1. Structures of **21**−**23**, **1**−**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 [^{3}H]-diprenorphine from its specific binding sites. The agonist potencies of the target compounds were assessed by their abilities to stimulate guanosine 5′-*O*-(3-[^{35}*S*]thio)triphosphate ([^{35}S]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

* To whom correspondence should be addressed. Phone: 1-484-595-1061. Fax: 1-484-595-1551. E-mail: blebourdonnec@adolor.com.
† Department of Chemistry, Adolor Corporation.
‡ Department of Pharmacology, Adolor Corporation.
§ Department of DMPK, Adolor Corporation.
|| Department of Preclinical Safety Assessment, Adolor Corporation.

[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.

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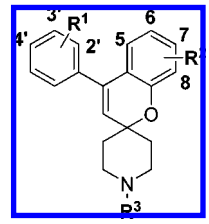
Table 1. In Vitro Profile of Compounds **3**−**20** at Opioid Receptors (δ, μ, and κ); Inhibitory Activity of Selected Compounds at the hERG Channel[a]



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_2CH_3	H	H	9.3 (3.7−23)	81 (38−170)	54 ± 10%	520 (360−760)	663
10	4′-CO_2H	H	H	11 (5.5−22)	220 (140−360)	13 ± 1%	14 ± 7%	>100000
11	4′-$CON(C_2H_5)_2$	H	H	1.8 (1.1−2.8)	19 (11−32)	32 ± 5%	29 ± 5%	7900
12	3′-$CON(C_2H_5)_2$	H	H	330 (270−400)	nd[b]	12 ± 8%	10 ± 4%	303
13	2′-$CON(C_2H_5)_2$	H	H	480 (310−740)	nd[b]	12 ± 8%	45 ± 8%	6450
14	4′-$CON(C_2H_5)_2$	H	$COCH_3$	1300	nd[b]	14%	2%	47440
15	4′-$CON(C_2H_5)_2$	H	CH_3	3.5 (2.3−5.1)	89 (51−150)	12 ± 6%	24 ± 5%	766
16	4′-$CON(C_2H_5)_2$	H	C_2H_5	68 (17−270)	nd[b]	13 ± 3%	13 ± 2%	1814
17	4′-$CON(C_2H_5)_2$	8-OH	H	360 (100−1300)	nd[b]	4 ± 6%	28 ± 3%	18310
18	4′-$CON(C_2H_5)_2$	7-OH	H	1.5 (0.54−4.2)	140 (79−240)	35 ± 0.3%	39 ± 4%	60000
19	4′-$CON(C_2H_5)_2$	6-OH	H	0.43 (0.32−0.58)	1.4 (1.0−2.1)	36 ± 7%	830 (590−1200)	19750
20	4′-$CON(C_2H_5)_2$	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**

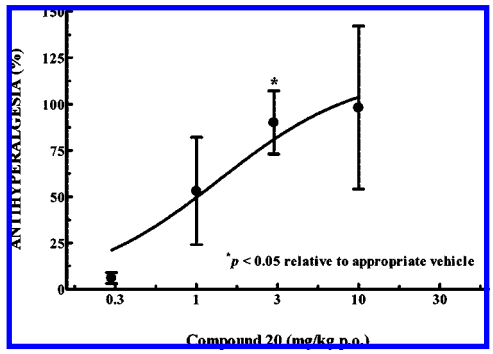


Figure 1. Effect of compound **20** in the rat FCA mechanical hyperalgesia assay. Values on the graph represent the mean and standard error of the mean (SEM) using $n = 11-12$.

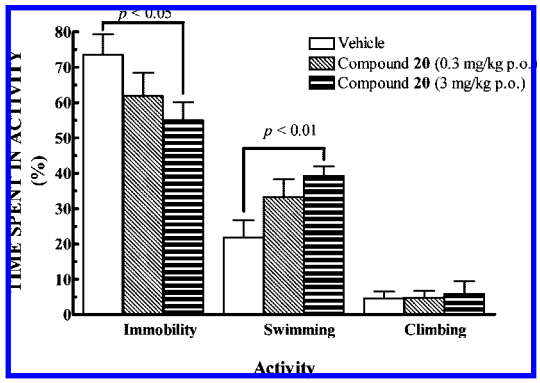


Figure 2. Effect of compound **20** in the rat forced swim test. The data were analyzed by one-way ANOVA with post hoc analysis to compare the behavioral response after vehicle treatment to the behavioral response after drug treatment ($n = 12$ for each group).

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

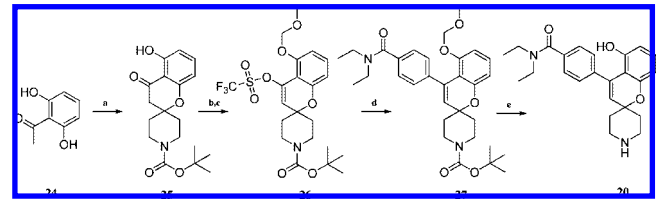
On the basis of their favorable profile in vitro, compounds **19** and **20** were tested in the rat Freund's complete adjuvant (FCA) mechanical hyperalgesia assay.[23,24] At the screening dose of 3 mg/kg po, compound **20** produced 100% reversal of hyperalgesia in the inflamed paw (the paw pressure 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 ± 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_2EtN, DCM, reflux, 83%; (c) $C_6H_5N(SO_2CF_3)_2$, LiHMDS, THF, −78 °C to 25 °C, 100%; (d) 4-(*N*,*N*-diethylaminocarbonyl)phenylboronic acid, $Pd[P(C_6H_5)_3]_4$, LiCl, aq Na_2CO_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.

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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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(24) All housing conditions and experimental procedures were performed in accordance with the "Guide for the Care and Use of Laboratory Animals". Experimental procedures followed the ethical guidelines of the IASP and were approved by the Adolor Corporation Institutional Animal Care and Use Committee.

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

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