Supporting Information

An Improved Synthesis of the Selective EP4-receptor Agonist ONO-4819

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General Information

Unless otherwise noted, all reagents and solvents were used as received from commercial suppliers. All reactions were carried out under argon atmosphere unless otherwise noted.

^1H NMR and ^{13}C NMR spectra were measured on 400 MHz or 200 MHz instrument as indicated. The chemical shifts (δ) on ^1H NMR spectra were reported in parts per million relative to tetramethylsilane. Infrared spectra were recorded on a FT-IR spectrometer. Purity of compounds and assay were measured using reverse HPLC. Analytical TLC was performed on commercially available preparative plates.

NAME: 050168
 Pulse Sequence: zgpg
 Solvent: CDCl3
 Ambient temperature
 File: 050168

DATA PROCESSING
 FT size 32768
 Total time 1 minute

CHENYU NI, 139.9750689

PULSE SEQUENCE
 Pulse 45.0 degrees
 Acq. time 4.000 sec
 Width 3000.3 Hz
 16 repetitions

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: HN10501829
INOVA-400 "sumf3"

DATA PROCESSING
PT size 65536
total time 5 minutes

RESERVE 81, 399.9519350

PULSE SEQUENCE
Relax. delay 1.256 sec
Pulse 45.0 degrees
Acq. time 3.744 sec
Width 6000.6 Hz
68 repetitions

PULSE SEQUENCE: zgpg30
 Solvent: CDCl3
 Ambient temperature
 File: HM10501832
 INOVA-400 "gms3"

DATA PROCESSING
 FT size 65536
 Total time 1 minute

OBSERVE H1, 399.9519516

PULSE SEQUENCE
 Relax. delay 1.256 sec
 Pulse 45.0 degrees
 Acq. time 3.744 sec
 Width 6000.6 Hz
 16 repetitions

HN10501824
 Pulse sequence: zgpg30
 Solvent: CDCl3
 Ambient temperature
 File: HN10501824
 INOVA-400 "sum3"

DATA PROCESSING
 FT size 63336
 Total time 1 minute

CONSERVE H1, 399.9519324

PULSE SEQUENCE
 Relax delay 1.256 sec
 Pulse 45.0 degrees
 Acq. time 3.744 sec
 Width 6000.5 Hz
 16 repetitions

HN10501753
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 File: HN10501753
 INOVA-400 "sunf3"

DATA PROCESSING
 FT size 65536
 Total time 1 minute

OBSERVE H1, 399.9819326

PULSE SEQUENCE
 Relax delay 1.256 sec
 Pulse 45.0 degrees
 Acq. time 3.744 sec
 Width 6000.6 Hz
 16 repetitions

HN10501780
Pulse Sequence: zgpg30
Solvent: CDCl3
Ambient temperature
File: HN10501780
INOVA-400 "mud3"

DATA PROCESSING
F2 size 65536
Total time 1 minute

OBSERVE H1, 399.9519335

PULSE SEQUENCE
Relax. delay 1.256 sec
Pulse 45.0 degrees
Acq. time 3.744 sec
Width 6000.6 Hz
16 repetitions

ONO-4819

HN1000193
Pulse Sequence: zgpg30
Solvent: CDCl3
Ambient temperature
File: HN1000193
INOVA-400 "nmf3"

DATA PROCESSING
F2 size 65536
Total time 1 minute

OBSERVE M1, 399.9519322

PULSE SEQUENCE
Relax. delay 1.256 sec
Pulse 45.0 degrees
Acq. time 3.744 sec
Width 6000.6 Hz
16 repetitions

PULSE SEQUENCE Pulse Sequence: s2pul Pulse 45.0 degrees Acq. time 4.000 sec Width 3000.3 Hz 16 repetitions	OBSERVE H1, 159.5710689	DATA PROCESSING 377 size 32768 Total time 1 minute	Solvent: CDCl ₃ Subst: H22390044 File: H22390044 NAME: 200 "s2pul" Tue Jun 9 15:51:27 JST 2009	NAME: H22390044 EXPNO: 271 Pulse Sequence: s2pul
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<p>PULSE SEQUENCE</p> <p>Pulse sequence: #2pul</p> <p>Pulse 45.0 degrees</p> <p>Acq. time 4.000 sec</p> <p>Width 3000.3 Hz</p> <p>16 repetitions</p>	<p>CONVENT RI, 159.9750689</p>	<p>DATA PROCESSING</p> <p>Pr size 32768</p> <p>Total time 1 minute</p>	<p>Solvent: CDCl₃</p> <p>Ambient temperature</p> <p>File: H20900045</p> <p>GMINI-200 "nucl2"</p> <p>Tue Jun 9 19:52:49 JPT 2009</p>	<p>H20900045</p> <p>ONC-0000-273</p> <p>Pulse sequence: #2pul</p>
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PULSE SEQUENCE Pulse sequence: #2pul Pulse 45.0 degrees Acq. time 4.000 sec Width 3000.3 Hz 16 repetitions	OBSERVE H1, 159.9780689	DATA PROCESSING FT size 32768 Total time 1 minute	SOLVENT: CDCl3 Acquire temperature 40.000000 Date: Jun 9 20:03:48 JST 2009	PULSE SEQUENCE: #2pul	0.03
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3

<p>PULSE SEQUENCE</p> <p>Pulse Sequence: s2pul</p> <p>Pulse 45.0 degrees</p> <p>Acq. time 4.000 sec</p> <p>Width 3000.3 Hz</p> <p>16 repetitions</p>	<p>OBSERVE H1, 199.8710689</p>	<p>DATA PROCESSING</p> <p>PT size 32768</p> <p>Total time 1 minute</p>	<p>Solvent: CDCl3</p> <p>Acq. temperature</p> <p>File: RM20500047</p> <p>NAME: RM20500047</p> <p>DATE: JUN 9 19:53:48 JST 2009</p>	<p>RM20500047</p> <p>CNO-00000-274</p> <p>Pulse Sequence: s2pul</p>
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<p>PULSE SEQUENCE</p> <p>Pulse sequence: #2pul</p> <p>Relax. delay 2.000 sec</p> <p>Pulse 45.0 degrees</p> <p>Acq. time 2.000 sec</p> <p>Width 13570.9 Hz</p> <p>576 repetitions</p>	<p>OBSERVE C13, 50.2837551</p> <p>RECOUPLE H1, 199.9760737</p> <p>Power 30 dB</p> <p>continuously on</p> <p>WALTZ-16 modulated</p>	<p>DATA PROCESSING</p> <p>Line broadening 1.0 Hz</p> <p>FT size 65536</p> <p>Total time 38 minutes</p>	<p>Solvent: CDCl3</p> <p>Ambient temperature</p> <p>File: MZ09000057</p> <p>ORIGIN: 200 "sumf2"</p> <p>Tue Jun 9 19:32:20 JST 2009</p>	<p>MZ09000057</p> <p>Pulse sequence: #2pul</p>
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INNOVA-400 "sun23"
 Operator: vms1
 Ambient temperature
 Solvent: CDCl3
 Pulse Sequence: #2pul
 BMT0501680

DATA PROCESSING
 Line broadening 1.0 Hz
 FT size 6536
 Total time 7 minutes

OBSERVE C13, 100.6279703
 INCOUPLE H1, 399.933359
 Power 35 dB
 continuously on
 WALTZ-16 Modulated

PULSE SEQUENCE
 Relax. delay 1.01 sec
 Pulse 45.0 degrees
 Acq. time 1.159 sec
 Width 20000.0 Hz
 144 repetitions

<p>PULSE SEQUENCE</p> <p>Pulse Sequence: #2pul</p> <p>Pulse delay 2.000 sec</p> <p>Pulse 41.0 degree</p> <p>Acq. time 2.000 sec</p> <p>Width 1250.9 Hz</p> <p>8320 repetitions</p>	<p>NAME PROCESSTING</p> <p>line broadening 1.0 Hz</p> <p>FT size 6556</p> <p>Total time 9.2 hours</p>	<p>SOLVENT: CDCl3</p> <p>ambient temperature</p> <p>File: RM0900064</p> <p>GBM01-200 "sumf2"</p> <p>Tue Jun 9 18:31:31 JST 2009</p>	<p>NAME PROCESSTING</p> <p>NAME: CL3, 50.3837591</p> <p>PROCESSED: 11, 139.5760737</p> <p>Power 30 dB</p> <p>continuously on</p> <p>WALTZ-16 modulated</p>	<p>NAME PROCESSTING</p> <p>NAME: CL3, 50.3837591</p> <p>PROCESSED: 11, 139.5760737</p> <p>Power 30 dB</p> <p>continuously on</p> <p>WALTZ-16 modulated</p>	<p>PULSE SEQUENCE</p> <p>Pulse Sequence: #2pul</p> <p>Pulse delay 2.000 sec</p> <p>Pulse 41.0 degree</p> <p>Acq. time 2.000 sec</p> <p>Width 1250.9 Hz</p> <p>8320 repetitions</p>
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<p>PULSE SEQUENCE</p> <p>Program: 42pul</p> <p>Pulse sequence: 42pul</p> <p>Relax. delay: 2.000 sec</p> <p>Pulse 45.0 degrees</p> <p>Acq. time: 2.000 sec</p> <p>Width: 11570.9 Hz</p> <p>1024 repetitions</p>	<p>DATA PROCESSING</p> <p>Line broadening: 1.0 Hz</p> <p>FT size: 65536</p> <p>Total time: 68 minutes</p>	<p>EXPERIMENTAL</p> <p>Probe: C13, 50.2837891</p> <p>RECOUPLE H1, 199.9760737</p> <p>Power: 30 dB</p> <p>continuously on</p> <p>WALTZ-16 modulated</p>	<p>Solvent: CDCl3</p> <p>Ambient temperature</p> <p>File: HM20900059</p> <p>NAME: 200 "sumf2"</p> <p>Tue Jun 9 19:35:15 CEST 2009</p>	<p>HM20900059</p> <p>Pulse sequence: 42pul</p>
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FALSE SEQUENCE

ONO-4819

<p>PULSE SEQUENCE</p> <p>Pulse sequence: #2pul Relax. delay 2.000 sec Pulse 45.0 degrees Acq. time 2.000 sec Width 12570.9 Hz 5000 repetitions</p>	<p>DATA PROCESSING</p> <p>Line broadening 1.0 Hz FT size 65536 Total time 10.1 hours</p>	<p>SOLVENT: CDCl3</p> <p>Ambient temperature OSMINT-200 "pmd2" Thu Jun 11 08:36:14 EDT 2009</p>	<p>NOISE SEQUENCE</p> <p>Pulse sequence: #2pul Pulse sequence: #2pul</p>
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<p>PULSE SEQUENCE</p> <p>Pulse Sequence: #2pul</p> <p>Relax. delay 2.000 sec</p> <p>Pulse 15.0 degrees</p> <p>Acq. time 2.000 sec</p> <p>Width 12870.8 Hz</p> <p>576 repetitions</p>	<p>OBSERVE CH3, 50.3497663</p> <p>RECORDING HI, 199.3760737</p> <p>Power 30 dB</p> <p>continuously on</p> <p>WALTZ-16 modulated</p>	<p>DATA PROCESSING</p> <p>time broadening 1.0 Hz</p> <p>PT size 6536</p> <p>Total time 38 minutes</p>	<p>Solvent: CDCl3</p> <p>Ambient temperature</p> <p>File: HM20900048</p> <p>ORIENT-200 "sum2"</p> <p>Tue Jun 9 19:48:06 JST 2009</p>	<p>HM20900048</p> <p>ORIG-0000-371</p> <p>Pulse Sequence: #2pul</p>
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<p>PULSE SEQUENCE</p> <p>Pulse sequence: w2pul</p> <p>Relax. delay 2.000 sec</p> <p>Pulse 45.0 degrees</p> <p>Acq. time 2.000 sec</p> <p>Width 12770.9 Hz</p> <p>512 repetitions</p>	<p>DATA PROCESSING</p> <p>Line broadening 1.0 Hz</p> <p>FT size 65536</p> <p>Total time 34 minutes</p>	<p>Solvent: CDCl3</p> <p>Ambient temperature</p> <p>File: RM20900050</p> <p>ORIGIN: 200 "sumf2"</p> <p>Tue Jun 9 19:47:16 JET 2009</p>	<p>RM20900050</p> <p>ONC-00000-473</p> <p>Pulse sequence: w2pul</p>
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<p>PULSE SEQUENCE</p> <p>Pulse sequence: s2pul</p> <p>Relax. delay 2.000 sec</p> <p>Pulse 45.0 degrees</p> <p>Acq. time 2.000 sec</p> <p>Width 11570.9 Hz</p> <p>5000 repetitions</p>	<p>DATA PROCESSING</p> <p>CONVERT C13, 50.2837194</p> <p>RECORDING F1, 199.9740137</p> <p>Power 30 dB</p> <p>continuously on</p> <p>WALTZ-16 modulated</p>	<p>SOLVENT: CDCl3</p> <p>Solvent temperature</p> <p>CDCl3-200 °*nmf2*</p> <p>Wed Jun 10 09:26:47 JST 2009</p>	<p>WALTZ-16</p> <p>Pulse sequence: s2pul</p>
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