Supporting Information

Application of the Dakin-West Reaction for the Synthesis of Oxazole-containing Dual PPAR α / γ agonists.

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Contents: Preparation and characterization for compounds **11a-g** and **23**; ^1H NMR spectra for compounds **11f**, **12a**, **12c**, **12d**, **12f**, **13a**, **13c**, **14d**, **14f**, **21a**, **22b-d**, **1b-e**, **23-25**.

2-(Cyclohexanecarbonyl-amino)-succinic acid 4-benzyl ester (11a).

A sample of sodium carbonate (3.80 g, 36 mmol, 3.5 equiv) was dissolved in 10 mL of water then chilled in a 0 °C bath followed by addition of the beta-benzyl aspartic acid (2.28 g, 10.2 mmol) and 5 mL of acetone. A 5 mL acetone solution of cyclohexyl carbonyl chloride was then slowly added to the chilled solution. The cooling bath was removed and the mixture allowed to stir at rt for 2 h. The mixture was then placed back

in the 0 °C bath and quenched to pH ~3 with 5 N hydrochloric acid then extracted with methylene chloride (3 x 100 mL). The combined organic phases were dried over solid sodium chloride, decanted and concentrated to yield an oil. The residue was subjected to chromatography on a reversed phase C-18 column ISCO Sg100c apparatus using a water / acetonitrile gradient program yielding 1.75 g (51%) of the desired product as a white solid. mp 132.4 °C; HPLC (100 area%, RT = 8.4 min @ 40% ISO); ¹H NMR (400 MHz, CDCl₃) δ 7.27 (m, 5 H), 6.52 (d, *J*=7.8 Hz, 1 H), 5.82 (br. s., 1 H), 4.79 (m, 1 H) 5.07 (s, 2 H), 3.02 (dd, *J*=17.4, 4.4 Hz, 1 H), 2.82 (B of ABX, *J*_{BA} = 17.4 Hz, *J*_{BX} = 4.9 Hz, 1H), 2.04 (A of ABX, *J*_{AB} = 17.4 Hz, *J*_{AX} = 4.4 Hz, 1H), 1.68 (m, 5 H), 1.22 (m, 5 H); ¹³C NMR (100 MHz, CDCl₃) δ 176.50, 173.96, 170.89, 135.05, 128.48, 128.34, 128.18, 67.01, 48.47, 45.07, 35.98, 29.43, 29.38, 25.72, 25.67; MS *m/z*: 334.25 (M+H)⁺, 356.25 (M+H+Na)⁺.

2-[(Cyclohex-1-enecarbonyl)-amino]-succinic acid 4-benzyl ester (11b). A sample of cyclohex-1-enecarboxylic acid (2.54 g, 20.1 mmol) was combined with the 2-chloro-4,6-dimethoxy-[1,3,5]triazine (3.51 g, 20.1mmol) in 40 mL of THF at rt followed by addition of N-methylmorpholine (2.2 mL, 20.1 mmol, 1.0 equiv) and then allowed to stir for 2 h. A sample of solid beta-benzyl aspartate (4.50 g, 20.1 mmol) was then added to this mixture followed by additional N-methylmorpholine (202 mL, 20.1 mmol, 1.0 equiv). The reaction mixture was stirred overnight at rt then partitioned between 200 mL of methylene chloride and 50 mL of 5 N hydrochloric acid. The organic phase was dried over solid sodium chloride, decanted and concentrated under reduced pressure to yield an oil. The residue was subjected to chromatography on a reversed phase C-18 column ISCO Sg100c apparatus using a water / acetonitrile gradient program yielding 4.39 g

(66%) of the desired product as a white solid. mp 119.9 °C; HPLC (100 area%, RT = 2.8 min @ 60% ISO); ^1H NMR (400 MHz, CDCl_3) δ 7.34 (m, 4 H), 7.06 (m, 1 H), 6.85 (d, J = 7.5 Hz, 1 H), 6.69 (m, 1 H), 5.15 (m, 2 H), 4.93 (ddd, J = 7.7, 4.6, 4.4 Hz, 1 H), 3.02 (B of ABX, J_{BA} = 16.7 Hz, J_{BX} = 4.8 Hz, 1H), 2.82 (A of ABX, J_{AB} = 16.7 Hz, J_{AX} = 4.4 Hz, 1H), 2.18 (m, 4 H), 1.64 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.21, 172.82, 171.86, 140.44, 128.70, 128.51, 126.47, 52.56, 48.70, 38.43, 36.09, 31.90; MS m/z : 332.22 ($\text{M}+\text{H}$) $^+$, 354.24 ($\text{M}+\text{H}+\text{Na}$) $^+$.

2-(3-Methoxy-benzoylamino)-succinic acid 4-benzyl ester (11c). The title compound was prepared in 86% yield by the method described for **11a**. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.79 (d, J = 8.1 Hz, 1H), 7.42 (m, 3H), 7.32 (m, 5H), 7.12 (m, 1H), 5.13 (s, 2H), 4.85 (m, 1H), 3.80 (s, 3H), 2.97 (A of ABX, J_{AB} = 16.1 Hz, J_{AX} = 4.2 Hz, 1H), 2.94 (B of ABX, J_{BA} = 16.1 Hz, J_{BX} = 2.7 Hz, 1H); ^{13}C NMR (60 MHz, $\text{DMSO}-d_6$) δ 172.14, 170.10, 165.81, 159.12, 135.95, 135.11, 129.37, 128.25, 127.85, 127.65, 119.54, 117.21, 112.56, 65.67, 55.24, 49.27, 35.70; HRMS-ES (m/z): [$\text{M}+\text{H}$] $^+$ calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_6$, 358.1291; found, 358.1302; Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 64.09; H, 5.36; N, 3.77.

2-(4-Methoxy-benzoylamino)-succinic acid 4-benzyl ester (11d). The title compound was prepared in 93% yield by the method described for **11a**. HPLC (98.3 area%, RT = 1.8 min @ 80% ISO); ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.63 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.32 (m, 5H), 7.01 (d, J = 8.7 Hz, 2H), 5.12 (s, 2H), 4.83 (m, 1H), 3.81 (s, 3H), 2.95 (A of ABX, J_{AB} = 16.1 Hz, J_{AX} = 4.2 Hz, 1H), 2.92 (B of ABX, J_{BA} = 16.1 Hz, J_{BX} = 2.7 Hz, 1H); ^{13}C NMR (60 MHz, $\text{DMSO}-d_6$) δ 176.00, 173.84, 169.21, 165.37, 139.65, 134.92, 132.81, 131.92, 131.28, 129.61, 117.38,

117.09, 65.71, 55.40, 49.35, 35.92; HRMS-ES (m/z): $[M+H]^+$ calcd for $C_{19}H_{20}NO_6$, 358.1291; found, 358.1293; Anal. Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.32; H, 5.29; N, 3.46.

2-Phenylacetyl-amino-succinic acid 4-methyl ester (11e). The title compound was prepared by the method described for **11a** and was obtained as an oil after RP-chromatographic purification. (40% yield); HPLC (100 area%, RT = 2.4 min @ 40% ISO); 1H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5 H), 6.97 (m, 1 H), 6.70 (d, J = 7.8 Hz, 1 H), 4.85 (ddd, J = 7.8, 4.6, 4.6 Hz, 1 H), 3.63 (s, 5 H), 3.02 (B of ABX, J_{BA} = 16.7 Hz, J_{BX} = 4.8 Hz, 1H), 2.85 (A of ABX, J_{AB} = 16.7 Hz, J_{AX} = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.85, 171.94, 171.58, 134.26, 129.55, 129.16, 127.66, 52.53, 49.04, 43.63, 36.08; MS m/z : 266.02 ($M+H$) $^+$, 288.02 ($M+H+Na$) $^+$.

2-(3-Phenyl-propionyl-amino)-succinic acid 4-methyl ester (11f). (521315)

The title compound was prepared by the method described for **11a** and was obtained as an oil after RP-chromatographic purification. (86% yield); HPLC (100 area%, RT = 2.8 min @ 40% ISO); 1H NMR (400 MHz, $CDCl_3$) δ 7.90 (m, 1 H), 7.23 (m, 5 H), 6.60 (d, J = 5.5 Hz, 1 H), 4.87 (ddd, J = 8.1, 4.4, 4.2 Hz, 1 H), 3.67 (s, 3 H), 3.02 (B of ABX, J_{BA} = 17.6 Hz, J_{BX} = 4.4 Hz, 1H), 2.97 (t, J = 7.8 Hz, 2 H), 2.76 (A of ABX, J_{AB} = 17.6 Hz, J_{AX} = 4.4 Hz, 1H), 2.57 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.21, 172.82, 171.86, 140.44, 128.70, 128.51, 126.47, 52.56, 48.70, 38.43, 36.09, 31.90; MS m/z : 280.05 ($M+H$) $^+$.

2-(4-Phenyl-butrylamino)-succinic acid 4-methyl ester (11g). The title was prepared the method described for **11b** and was obtained as an oil after RP-chromatographic purification. (53% yield); HPLC (96.8 area%, RT = 3.6 min @ 40% ISO); 1H NMR (400

MHz, CDCl₃) δ 7.88 (m, 1 H), 7.23 (m, 4 H), 6.65 (d, J = 7.34 Hz, 1 H), 4.89 (ddd, J = 8.19, 4.65, 4.28 Hz, 1 H), 3.70 (s, 3 H), 3.07 (B of ABX, J_{BA} = 17.5 Hz, J_{BX} = 4.4 Hz, 1H), 2.87 (A of ABX, J_{AB} = 17.5 Hz, J_{AX} = 4.4 Hz, 1H), 2.65 (m, 2 H), 2.27 (m, 2 H), 1.98 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 174.21, 173.52, 171.94, 141.42, 128.69, 128.60, 126.21, 52.59, 48.78, 36.16, 35.91, 35.42, 27.38; MS m/z : 294.09 (M+H)⁺, 316.08 (M+H+Na)⁺.

2-Amino-4-[4-(1-ethoxycarbonyl-1-methyl-ethoxy)-phenoxy]-butyric acid ethyl ester

(23). Compound **19** (6.39 g, 13.56 mmol) was dissolved in EtOH (130 mL) and 50% NaOH (5.21 g, 65.13 mmol) was added. After heating at reflux for 45 min, the solution was acidified to pH=1 with conc HCl, and heating continued at reflux for 16 h. After cooling to ambient temperature the solvent was removed under reduced pressure and the residue dissolved in H₂O (40 mL). The solution was extracted with Et₂O (2x40 mL), and then the organic layer was washed with 1N HCl (25 mL), brine, and dried over MgSO₄, filtered and concentrated to a yellow oil (1.23 g). The acidic aqueous layers were neutralized with 5N NaOH and extracted with Et₂O (2x50 mL), and then the organic layer was washed with brine, and dried over MgSO₄, filtered and concentrated to a colorless oil (1.81 g) that was used without further purification. Combined yield provided 3.04 g (63%) of compound **23**: ¹H NMR (300 MHz, DMSO-*d*₆) δ 6.78 (m, 4H), 4.15 (q, J = 7.3 Hz, 2H), 4.08 (q, J = 7.3 Hz, 2H), 3.99 (m, 2H), 3.46 (dd, J = 8.4, 5.1 Hz, 2H), 1.82 (m, 2H), 1.44 (s, 6H, 1.19 (t, J = 7.3 Hz, 3H), 1.17 (t, J = 7.3 Hz, 3H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 175.48, 173.13, 153.97, 148.35, 121.23, 114.76, 79.08, 64.40, 60.75, 59.96, 51.10, 33.84, 24.85, 13.85; MS m/z : 354.33 (M+H)⁺.

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dmsco-d6

Pulse Sequence: s2pul

Solvent: DMSO

Ambient temperature
INOVA-500 "inova500"

PULSE SEQUENCE

Relax. delay 1.000 sec

Pulse 34.3 degrees

Acq. time 2.752 sec

Width 7501.2 Hz

16 repetitions

OBSERVE H1, 500.1770077 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 65536

Total time 1 min, 0 sec

Acquisition Time (sec)	2.0469	Comment	STANDARD 1H OBSERVE		Date	Jan 6 2000			
Frequency (MHz)	400.21	Nucleus	1H	Number of Transients	16	Original Points Count	15968	Points Count	16384
Solvent	CDCl3	Sweep Width (Hz)	8004.11	Temperature (grad C)	29.000				

No.	(ppm)	Height	No.	(ppm)	Height
1	0.95	0.126	32	3.21	0.031
2	0.97	0.257	33	3.68	0.064
3	0.98	0.093	34	3.77	0.618
4	0.99	0.137	35	3.97	0.033
5	1.00	0.044	36	3.98	0.032
6	1.40	0.032	37	3.99	0.027
7	1.53	1.000	38	4.03	0.023
8	1.67	0.036	39	4.05	0.042
9	1.68	0.040	40	4.06	0.037
10	1.69	0.054	41	4.07	0.025
11	1.70	0.058	42	4.89	0.048
12	1.71	0.053	43	4.91	0.046
13	1.72	0.051	44	6.70	0.112
14	1.72	0.045	45	6.73	0.180
15	1.73	0.027	46	6.79	0.177
16	1.74	0.025	47	6.82	0.106
17	2.32	0.024	48	6.83	0.046
18	2.34	0.043	49	7.26	0.671
19	2.36	0.034	50	7.37	0.066
20	2.40	0.024	51	7.39	0.090
21	2.55	0.029	52	7.41	0.053
22	2.57	0.043	53	7.45	0.085
23	2.59	0.041	54	7.47	0.137
24	2.59	0.039	55	7.48	0.068
25	2.60	0.026	56	7.61	0.135
26	2.61	0.057	57	7.62	0.114
27	2.63	0.029	58	7.65	0.135
28	2.70	0.027	59	7.68	0.165
29	2.72	0.042	60	7.88	0.157
30	2.74	0.031	61	7.90	0.134
31	3.20	0.024

Acquisition Time (sec)	1.9950	Comment	STANDARD 1H OBSERVE		Date	Jan 30 2000			
Frequency (MHz)	400.21	Nucleus	1H	Number of Transients	16	Original Points Count	15968	Points Count	16384
Solvent	CDCI3	Sweep Width (Hz)	8004.11	Temperature (grad C)	29.000

Acquisition Time (sec)	1.9950	Comment STANDARD 1H OBSERVE		Date Jan 15 2000	
Frequency (MHz)	400.21	Nucleus 1H	Number of Transients 16	Original Points Count 15968	Points Count 16384
Solvent	CDCl3	Sweep Width (Hz) 8004.11	Temperature (grad C) 29.000		

8.02
7.63
7.61
7.60
7.58
7.43
7.41
7.40
7.35
7.33
7.22
6.87
6.85
6.75
6.72

4.15
4.13
4.12

2.99
2.97
2.96
2.68
2.66
2.65

1.73
1.72
1.70
1.68
1.49
1.48

0.99
0.98
0.96

No.	(ppm)	Height
1	0.96	0.176
2	0.98	0.411
3	0.99	0.197
4	1.48	0.051
5	1.49	1.000
6	1.68	0.060
7	1.70	0.114
8	1.72	0.116
9	1.73	0.062
10	2.65	0.104
11	2.66	0.174
12	2.68	0.093
13	2.96	0.073
14	2.97	0.165
15	2.99	0.076
16	4.12	0.085
17	4.13	0.180
18	4.15	0.078
19	6.72	0.129
20	6.75	0.188
21	6.85	0.145
22	6.87	0.096
23	7.22	0.554
24	7.33	0.086
25	7.35	0.073
26	7.40	0.114
27	7.41	0.198
28	7.43	0.093
29	7.58	0.170
30	7.60	0.162
31	7.61	0.227
32	7.63	0.219
33	8.00	0.196
34	8.02	0.188

Acquisition Time (sec) 1.9950		Comment STANDARD 1H OBSERVE			Date Jan 17 2000		
Frequency (MHz) 400.21		Nucleus 1H	Number of Transients 16		Original Points Count 15968		Points Count 16384
Solvent CDCl3		Sweep Width (Hz) 8004.11	Temperature (grad C) 29.000				

No.	(ppm)	Height	No.	(ppm)	Height
1	1.18	0.014	30	2.50	0.014
2	1.42	0.008	31	2.51	0.024
3	1.47	1.000	32	2.52	0.012
4	1.49	0.029	33	2.54	0.011
5	1.50	0.027	34	2.80	0.011
6	1.52	0.034	35	2.86	0.026
7	1.53	0.032	36	2.87	0.049
8	1.55	0.016	37	2.89	0.025
9	1.56	0.015	38	4.02	0.035
10	1.62	0.011	39	4.04	0.069
11	1.63	0.013	40	4.05	0.031
12	1.65	0.026	41	6.66	0.010
13	1.66	0.026	42	6.67	0.100
14	1.68	0.023	43	6.69	0.038
15	1.69	0.024	44	6.70	0.158
16	1.71	0.008	45	6.71	0.015
17	1.72	0.008	46	6.80	0.016
18	1.95	0.035	47	6.81	0.154
19	1.97	0.027	48	6.83	0.112
20	1.98	0.026	49	6.84	0.009
21	2.13	0.028	50	7.11	0.021
22	2.14	0.029	51	7.13	0.047
23	2.17	0.026	52	7.14	0.065
24	2.17	0.025	53	7.15	0.038
25	2.22	0.272	54	7.16	0.107
26	2.26	0.016	55	7.19	0.875
27	2.47	0.008	56	7.22	0.077
28	2.48	0.013	57	7.23	0.074
29	2.49	0.008	58	7.25	0.038

1d

Acquisition Time (sec)	1.9950	Comment STANDARD 1H OBSERVE		Date	Jan 30 2000	
Frequency (MHz)	400.21	Nucleus	1H	Number of Transients	16	Original Points Count 15968
Solvent	CDCl3	Sweep Width (Hz)	8004.11	Temperature (grad C)	29.000	Points Count 16384

No.	(ppm)	Height
1	1.21	0.096
2	1.48	1.000
3	3.14	0.026
4	3.15	0.055
5	3.17	0.027
6	4.22	0.055
7	4.24	0.110
8	4.25	0.050
9	6.77	0.075
10	6.78	0.034
11	6.79	0.139
12	6.85	0.171
13	6.86	0.038
14	6.87	0.082
15	7.22	0.137
16	7.36	0.045
17	7.37	0.040
18	7.41	0.050
19	7.43	0.091
20	7.45	0.047
21	7.59	0.083
22	7.60	0.075
23	7.66	0.097
24	7.68	0.110
25	8.07	0.104
26	8.09	0.100

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Acquisition Time (sec)	1.9950	Comment STANDARD 1H OBSERVE		Date Jan 18 2000	
Frequency (MHz)	400.21	Nucleus	1H	Number of Transients	16
Solvent CDCl3		Sweep Width (Hz)	8004.11	Original Points Count	15968
		Temperature (grad C)	29.000	Points Count	16384

No.	(ppm)	Height	No.	(ppm)	Height
1	1.20	0.115	40	4.04	0.021
2	1.22	0.306	41	4.04	0.022
3	1.24	0.329	42	4.06	0.018
4	1.24	0.010	43	4.06	0.014
5	1.26	0.102	44	4.08	0.010
6	1.26	0.006	45	4.12	0.032
7	1.31	0.005	46	4.14	0.126
8	1.44	0.007	47	4.16	0.109
9	1.49	1.000	48	4.17	0.047
10	1.50	0.033	49	4.17	0.035
11	1.54	0.007	50	4.19	0.152
12	1.93	0.009	51	4.20	0.007
13	1.94	0.005	52	4.20	0.107
14	1.95	0.014	53	4.21	0.005
15	1.97	0.015	54	4.22	0.050
16	1.97	0.008	55	6.67	0.007
17	1.98	0.008	56	6.68	0.091
18	1.99	0.012	57	6.68	0.030
19	2.00	0.009	58	6.69	0.035
20	2.09	0.006	59	6.70	0.156
21	2.10	0.013	60	6.71	0.016
22	2.12	0.014	61	6.76	0.014
23	2.14	0.011	62	6.76	0.156
24	2.16	0.009	63	6.77	0.038
25	3.44	0.024	64	6.78	0.025
26	3.45	0.027	65	6.79	0.074
27	3.46	0.024	66	6.80	0.006
28	3.47	0.021	67	7.16	0.007
29	3.62	0.034	68	7.18	0.027
30	3.65	0.045	69	7.19	0.010
31	3.80	0.051	70	7.19	0.034
32	3.83	0.037	71	7.21	0.034
33	3.94	0.010	72	7.22	0.148
34	3.95	0.024	73	7.23	0.084
35	3.96	0.018	74	7.24	0.011
36	3.97	0.013	75	7.24	0.040
37	3.98	0.036	76	7.26	0.059
38	3.99	0.016	77	7.28	0.030
39	4.02	0.017

Acquisition Time (sec)	1.9950	Comment	STANDARD 1H OBSERVE		Date	Jan 19 2000			
Frequency (MHz)	400.21	Nucleus	1H	Number of Transients	16	Original Points Count	15968	Points Count	16384
Solvent	CDCI3	Sweep Width (Hz)	8004.11	Temperature (grad C)	29.000