Supplementary Materials

Importance of the proximity and orientation of ligand-linkage to the design of cinnamate-GW9662 hybrid compounds as covalent PPARy agonists

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|----|--|---|
| 2. | ¹ H and ¹³ C NMR spectra | 3 |

(**A**)



Supplemntary Figure 1. Validation of docking protocol. (A) The indicated ligands were docked into the original protein crystal structures. The reported binding manners and predicted docking poses were displayed in green and yellow, respectively. (B) The ligands were docked in the crystal structures other than originally reported structural data. The reported binding manners and predicted docking poses were displayed in green and yellow, respectively.



400 MHz ¹H NMR spectrum of compound 6a in CDCl₃

8.5 8.0

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6.5 6.0 5.5 5.0

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100 MHz ¹³C NMR spectrum of compound **6a** in CDCl₃

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| 210 | 200 | 190 | 180 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 | 0 | ppm |



1721.5093 1714.3852 1707.2612 1700.0970

818.3103 652.6551 545.7937 538.6295 531.5055

400 MHz ¹H NMR spectrum of compound 7a in CDCl₃



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100 MHz ¹³C NMR spectrum of compound 7a in CDCl₃

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ppm

-14.2964

77.3174 77.2025 76.9997 76.6818



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125 MHz ¹³C NMR spectrum of compound 8a in CDCl₃

-60.53

ppm



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536.5484 529.4243 522.2601

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400 MHz ¹H NMR spectrum of compound 4a in CDCl₃



| 0.2 | 46 | 75 | 62 | - 25 | 76 | 32 | 18 | 19 | 45 | 67 | 91 | 50 | 44 | 57 | 60 | 38 | 24 | 60 | 10 | 26 |
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100 MHz ¹³C NMR spectrum of compound **4a** in CDCl₃

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60.5053

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| 190 | 180 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 | 0 |

400 MHz ¹H NMR spectrum of compound 4b in CDCl₃



| 5365 | 7867 | 0902 | 3297 | 0514 | 2405 1611 4619 | 7923 5727 2098 9748 7231 7231 | 1704 1704 1704 1961 1961 1961 1677 1967 99199 8204 8204 |
|------|------|------|------|------|----------------------|--|---|
| 167. | 163. | 159. | 148. | 144. | 139. 139. 136. | 133. 130. 129. 129. | 122. 119. 119. 116. 116. 116. 1116. 1111. |
| 1. | 1 | | 1 | | VI | W | INVER |

100 MHz ^{13}C NMR spectrum of compound 4b in CDCl3

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10 ppm



400 MHz ¹H NMR Spectrum of compound 9 in CDCl₃

| | | | | | | | | | | | | | | · · · · · · | | | | | | · · · · · · · · · |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-------------|-----|------|-----|-----|-----|-------------------|
| 9.5 | 9.0 | 8.5 | 8.0 | 7.5 | 7.0 | 6.5 | 6.0 | 5.5 | 5.0 | 4.5 | 4.0 | 3.5 | 3.0 | 2.5 | 2.0 | 1.5 | 1.0 | 0.5 | 0.0 | ppm |
| | | | | | 200 | NU | 5 | | | | 6 | 101 | | 4 | | | 6 | | | |
| | | | | | 1.0 | 1.9 | | | | | 2.2 | 1.00 | 2.0 | 2.0 | | 28.8 | 3.2 | | | |

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| | | | | 11 | | 11-1- | | VZ | T 1121 | | 1. | | |

100 MHz ¹³C NMR spectrum of compound 9 in CDCl₃

| 210 | 200 | 190 | 180 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 | 0 | ppn |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|----|----|----|---|-----|
| | | | | | | | | | | | | | | | | | | | | | | |

400 MHz ¹H NMR Spectrum of compound 4e in CDCl₃

| 8.5 | 8.0 | 7.5 | 7.0 | 6.5 | 6.0 | 5.5 | 5.0 | 4.5 | 4.0 | 3.5 | 3.0 | 2.5 | 2.0 | 1.5 | 1.0 | 0.5 | ppm |
|------|------|------|----------------------|------------------|-----|-----|-----|-----|------|-----|------|------|------|-----|-----|-----|-----|
| 0.92 | 0.48 | 0.47 | 0.35 0.99 0.95 |) <mark>.</mark> | | | | | 1.14 | | 1.00 | 1.01 | 0.22 | | 001 | | |

| 6291.6V1 | 162.6573 | 158.3345 | 155.0887 | 146.5283 | 138.5317 137.9282 136.7117 136.7117 136.7112 131.6261 131.6261 130.3485 139.7930 125.9727 125.9727 | 119.4735 | 115.3255 114.9302 | 110.6847 | 77.5461 77.4298 77.2282 76.9101 | 60.6677 60.6106 | | 36.1008 | 30.3588 | 21.1802 | 14.3507 | |
|----------|----------|----------|----------|----------|--|----------|----------------------|----------|--|--------------------|--------|---------|---------|---------|---------|--|
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100 MHz ¹³C NMR spectrum of compound **4e** in CDCl₃

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|--|-----------------------|
| 1/0 160 150 140 130 120 110 100 90 80 70 | b0 50 40 30 20 10 ppr |
| | |



400 MHz ¹H NMR Spectrum of compound **6b** in CDCl₃



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| 1.1 | | | | 2.4 | 10 A 11 | 1 1 | 11 1 | |
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100 MHz ¹³C NMR spectrum of compound **6b** in CDCl₃

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|-----|-----|-----|-----|-----|-----|-----|-----|-------|-----|-----|----|----|----|----|----|----|---|-----|----|-----|
| 200 | 190 | 180 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 | ppm |



1717.4270 1710.3429 1703.2588 1696.0547

817.2697 666.6231 535.5478 533.3477 533.3477 533.3477 533.3478 503.4528 503.4528 503.4941 503.0491

0.0000

400 MHz ¹H NMR Spectrum of compound 7b in CDCl₃



| 67.0857 | 58.0497 | 49.6929 | 43.5364 | 34.5312 | 30.7441 | 26.0528 24.4172 21.9332 | 18.8734 |
|---------|---------|---------|---------|---------|-------------------------|-------------------------------|---------|
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77.5478 77.4318 77.2298 76.9127 -60.6946

14.4992

100 MHz ¹³C NMR spectrum of compound **7b** in CDCl₃

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| 180 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 | nnm |
| 100 | | 100 | 100 | 140 | 100 | 120 | 110 | 100 | 50 | 00 | 10 | 00 | 50 | | | 20 | 10 | ppm |



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0.5

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400 MHz ¹H NMR Spectrum of compound **8b** in CDCl₃

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|-----|-----|-----|-----|-----|-----|-----|-----|------------|-----|-----|-----|---------|-----|
| 8.0 | 7.5 | 7.0 | 6.5 | 6.0 | 5.5 | 5.0 | 4.5 | 4.0 007 | 3.5 | 3.0 | 2.5 | 2.0 | 1.5 |

| 3651 | 5502 | 0688 2584 | 1102 | 9699 1232 3772 | 1837 1218 1104 1138 | 197 | 178 |
|-------|-------|--------------|-------|----------------------|------------------------------|-------|-------|
| 167.3 | 159.6 | 144.0 | 139.1 | 129.9 | 119.1 | 77.25 | 50.61 |
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100 MHz ¹³C NMR spectrum of compound **8b** in CDCl₃

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| 180 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 |



400 MHz ¹H NMR Spectrum of compound 4c in CDCl₃



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130

120

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170

160

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140

100 MHz ¹³C NMR spectrum of compound **4c** in CDCl₃

60.5146

14.2947

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400 MHz ¹H NMR Spectrum of compound 6c in CDCl₃

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100 MHz ¹³C NMR Spectrum of compound 6c in CDCl₃

400 MHz ¹H NMR Spectrum of compound 7c in CDCl₃

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| 8.5 | . 8.0 | 7.5 | 7.0 | 6.5 | 6.0 | 5.5 | 5.0 | 4.5 | 4.0 | 3.5 | 3.0 | 2.5 | 2.0 | 1.5 | 1.0 | 0.5 | ppm |
|-----|-------|------|------|------|-----|-----|-----|------|-----|-----|-----|-----|-----|------|-----|-----|-----|
| | 0.30 | 0.16 | 1.32 | 0.17 | | 1 | | 0.67 | | | | | | 0.17 | | | |

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100 MHz ^{13}C NMR Spectrum of compound 7c in CDCl_3

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4301

132.

6925 8798 6289 0110 8127

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-143.3563

- 167.0403 - 162,6462 - 156.6954

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| 400 | 470 | 400 | 450 | 440 | 400 | 400 | 440 | 400 | 00 | 00 | 70 | 00 | =0 | 40 | 20 | 20 | 40 | • | |
| 100 | 170 | 100 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 10 | 60 | 50 | 40 | 30 | 20 | 10 | U | ppm |
| | | | | | | | | | | | | | | | | | | 100 | |

77.5480 77.2308 76.9132

-60.8266



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400 MHz ¹H NMR Spectrum of compound 8c in CDCl₃

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|-----|-------------|-----------|-----|-----|------|-----------|------|-----|-----|-----|-----|-----|-----|-----|-----|--------------------------|
| 8.0 | 7.5 | 7.0 | 6.5 | 6.0 | 5.5 | 5.0 | 4.5 | 4.0 | 3.5 | 3.0 | 2.5 | 2.0 | 1.5 | 1.0 | 0.5 | 0.0 ppm |
| | 00. 06. 62. | 12 | .93 | | | | (88) | | E. | | | 60 | .83 | | | |

| 167.4395 | 161.1590 | .47.7283 .44.2364 .43.5233 | 129.8268 128.4790 121.7511 117.2185 116.5388 116.4355 | 77.5456 77.4301 77.2276 76.9105 |
|----------|----------|----------------------------------|--|--|
| Ï | T.S. | ΪŴ | N IN | V |

60.5702

14.5367

100 MHz ¹³C NMR Spectrum of compound 8c in CDCl₃



-1.6478 1.3453 1.3097 1.2096 1.2728 1.2549

400 MHz ¹H NMR Spectrum of compound 4d in CDCl₃

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|-----------|-------------|-----------|-------|-----|-----|-----|-----|-----|-----|---------|----------|-----|-----|-----|-------|-----|-----|-----|-----|
| 9.0 | 8.5 | 8.0 | 7.5 | 7.0 | 6.5 | 6.0 | 5.5 | 5.0 | 4.5 | 4.0 | 3.5 | 3.0 | 2.5 | 2.0 | 1.5 | 1.0 | 0.5 | 0.0 | ppm |
| | 1_1 | V.I | 1.125 | 115 | 1 | | | | 1 | 1 5 15% | 1. 1. 18 | | | | 11 61 | 5 | | | |
| | 00. | 01 | .07 | 11 | .03 | 1 | | | 1 | 1. 1. | | | | | 2.08 | 7. | | | |

74.2644 74.2466 74.2288 74.2109

| 167.3995 | 162.4973 | 159.5707 | 153.5564 | 146.7780 | 143.9817 | L37.8332 L36.6879 | 133.3066 | 129.5800 | 126.1387 | 122.4116 | 118.4869 |
|----------|----------|----------|----------|----------|----------|----------------------|----------|----------|-------------------------|----------|----------|
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100 MHz ¹³C NMR Spectrum of compound 4d in CDCl₃

77.4329

ppm





 $\overbrace{1149.9469}^{1156.9449}$ -966.9957

508.7324 501.5682 494.4442

400 MHz ¹H NMR Spectrum of compound **12** in CDCl₃

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|---|------|-----|-------|------|------------|-------|-----|-----|-----|-----|---------|------|--------|------------|-----|-----|------|-----|-----|-----|----------|
| | 9.5 | 9.0 | 8.5 | 8.0 | 7.5 | 7.0 | 6.5 | 6.0 | 5.5 | 5.0 | 4.5 | 4.0 | 3.5 | 3.0 | 2.5 | 2.0 | 1.5 | 1.0 | 0.5 | 0.0 | -0.5 ppm |
| | | | | | 11 1 | | 11 | | | | | 11 . | | 11 | 11 | Л | 111 | L | | | |
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100 MHz 13 C NMR Spectrum of compound 12 in CDCl₃

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1235.3500 1228.3860 1221.3819

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400 MHz ¹H NMR Spectrum of compound 13 in CDCl₃

-3950.7505





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2.197

4

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| 102 | 241 | 970 | | 952 679 562 434 | 060 | 78 178 178 | |
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100 MHz ¹³C NMR Spectrum of compound **13** in CDCl₃

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| | | | | | | | | | | 1.00 | | |
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710

684.1 684.1 592.724 529.944 529.944 529.944 509.3721 495.2046 .8694

0.0000

400 MHz ¹H NMR Spectrum of compound 14 in CDCl₃

| | | | | · · · · · · · · | · · · · · | · · · · · | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----------------|-----------|-----------|-----|-----|-----|-----|------|-----|------|-----|-----|------|-----|-----|-----|-----|
| 9.5 | 9.0 | 8.5 | 8.0 | 7.5 | 7.0 | 6.5 | 6.0 | 5.5 | 5.0 | 4.5 | 4.0 | 3.5 | 3.0 | 2.5 | 2.0 | 1.5 | 1.0 | 0.5 | 0.0 | ppm |
| | | | | 2.00 | 2.02 | 0.94 | | | | ĺ | 2.37 | | 2.02 | | | 9.20 | | | | |

| 167.3074 | 160.5310 | 152.7850 | 144.2216 | 136.8897 | 132.4999 129.6285 129.4253 129.4253 | 118.7554 115.6687 114.8257 | 80.4011 77.3157 77.2009 76.9987 |
|----------|----------|----------|----------|----------|--|----------------------------------|--|
| | | 1 | | | 14/ | \/ . | 1VV |

77.2009 76.9987 76.6804 68.7912 68.7912 60.3434

-34.9277

~ 14.3043 14.1464

100 MHz ¹³C NMR Spectrum of compound 14 in CDCl3

| | | 1 A C C C C C C C C C C C C C C C C C C | | | | | | | | | | | | | | | | | | | | |
|-----|-----|---|-----|-----|-----|-------|-------|-----|-----|-----|-----|----|----|----|-----|----|----|-----|----|----|---|-----|
| | 000 | 100 | 100 | 4 | 100 | 4 - 0 | 4 4 0 | 100 | 100 | 440 | 400 | 00 | 00 | 70 | 00 | 50 | 40 | 20 | 20 | 10 | 0 | |
| 210 | 200 | 100 | 180 | 1/0 | 160 | 150 | 140 | 130 | 120 | 110 | 300 | 90 | 80 | 70 | bu. | 20 | 40 | -50 | 20 | 10 | | DDM |
| 210 | 200 | 150 | 100 | 110 | 100 | 100 | 1-10 | 100 | 120 | | 100 | 00 | 00 | | 00 | | | | | | | P P |





-505.9307 -491.7226 766.3604

400 MHz ¹H NMR Spectrum of compound 15 in CDCl₃

4099.2758

11

10

2.125

9





5

2

1

3.049

3

1.988

0 ppm

| | | | | | 68.0279 | | 14.2264 |
|--|----------------|-----------|-------------------------------|---|--|-----------|---|
| 00 MHz ¹³ C NMR in CDCl3 | Spectrum of co | mpound 15 | | | | | |
| | | | | | | | |
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| house and house device his body patho his a pho- news poper participants for house in page 1 pho- | | | Difail pointifi an his she de | na ha na ana kana ka kana hina ka sa kana sa kana sa Mana sa pana kana ka | ole enoughling a beneficient a source in a source of a | | , kon dalla (b. y. kond bills, di dilaran Menanga produktion (bills) |
| 190 180 170 | 0 160 150 | 0 140 130 | 120 110 | 100 90 80 | 70 60 50 |) 40 30 ; | 20 10 0 |



400 MHz ¹H NMR spectrum of compound 16 in CDCl₃



 - 68.7657 - 60.5664 -

14.5105

ppm

35.2938

100 MHz ^{13}C NMR spectrum of compound 16 in CDCl_3

- 167.6164 - 162.5337 - 160.7101

| 210 | 200 | 100 | 100 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 | 0 | |
|-----|-----|-----|-----|-----|-----|-----|------|-----|------|-----|-----|----|----|----|----|----|----|----|----|-----------------|---|--|
| 210 | 200 | 150 | 100 | 110 | 100 | 100 | 1-40 | 100 | 14.4 | | | | | | | | | | | 1.1.1.1.1.1.1.1 | | |