

SUPPORTING INFORMATION

INHIBITION OF NAV1.7: THE POSSIBILITY OF IDEAL ANALGESICS

Yutaka Kitano^a and Tsuyoshi Shinozuka^{*,a}

^aR&D Division, Daiichi Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan

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1. Calculation of the free plasma concentration and Nav1.7 coverage in Tables 5-7

Compound 6¹

CFA model

Free plasma concentration at 1 mg/kg: $7.8 \text{ [ng/mL]} \times 1000/314.35 = 24.8 \text{ [nM]}$

CCI model (subchronic)

Free plasma concentrations on Day 8 after administration for 0.5 h/day at 0.5 mg/kg: $1.9 \text{ [ng/mL]} \times 1000/314.35 = 6.0 \text{ [nM]}$

Free plasma concentrations on Day 8 after administration for 0.5 h/day at 5 mg/kg: $23.4 \text{ [ng/mL]} \times 1000/314.35 = 74.4 \text{ [nM]}$

Compound 9²

Rat SNL model

Free in vivo EC₅₀: $72 \text{ (in vivo EC}_{50} \text{ [}\mu\text{M])} \times 0.01 = 0.72 \text{ [}\mu\text{M]}$

Compound 10 (Mw: 436.48)³

Rat MIA model

In vivo acute EC₅₀: $2.5 \text{ [}\mu\text{g/mL]} = 2.5 \times 1000/436.48 = 5.7 \text{ [}\mu\text{M]}$

In vivo subchronic EC₅₀: $0.8 \text{ [}\mu\text{g/mL]} = 0.8 \times 1000/436.48 = 1.8 \text{ [}\mu\text{M]}$

Compound 13 (Mw: 391.46)⁴

Thermal hyperalgesia in PSNL mouse

Free plasma concentration: $0.10 \text{ (}C_{max} \text{ [}\mu\text{g/mL])} \times 1000/391.46 \times 0.0104 = 0.0027 \text{ [}\mu\text{M]@30 mg/kg}$

Nav1.7 coverage: $(0.0027 \times 3.3/30)/11.8 = 0.000025\text{-fold@3.3 mg/kg}$

Compound 14 (Mw: 434.41)⁵

Phase 1 rat formalin: 65%@43 mg/kg

Nav1.7 coverage@43 mg/kg: $400 \text{ (Free plasma concentration at the end of the formalin experiment [nM])}/1600 = 0.25\text{-fold}$

Compound 15

Phase 2 rat formalin⁶

Nav1.7 coverage@3 mg/kg: $0.5 \text{ (mean plasma concentration in the formalin experiment [}\mu\text{M])} \times 0.027/0.39 = 0.035\text{-fold}$

Nav1.7 coverage@10 mg/kg: $1.4 \text{ (mean plasma concentration in the formalin experiment [}\mu\text{M])} \times 0.027/0.39 = 0.097\text{-fold}$

Rat CFA model⁷

Nav1.7 coverage@3 mg/kg: $0.78 \text{ (terminal plasma concentration [}\mu\text{M])} \times 0.027/0.39 = 0.054\text{-fold}$

Nav1.7 coverage@10 mg/kg: $2.48 \text{ (terminal plasma concentration [}\mu\text{M])} \times 0.027/0.39 = 0.17\text{-fold}$

Compound 16

Aconitine-induced nociceptive events in IEM mouse⁸

Nav1.7 coverage@in vivo IC₅₀: $24.5 \text{ (in vivo IC}_{50} \text{ [}\mu\text{M])} \times 0.013/0.0039 = 82\text{-fold}$

Odorant-induced olfaction at 9.50 mg/kg (i.v. infusion)⁹

Nav1.7 coverage@9.50 mg/kg: $107 \text{ (plasma concentration [}\mu\text{M])} \times 0.001/0.926 = 0.12\text{-fold}$

Compound 17¹⁰

Phase 2 rat formalin

Nav1.7 coverage@100 mg/kg: 250–260 (free plasma concentration [nM])/26 = 9.6–10-fold

Acute pain evoked by aconitine in rat

Nav1.7 coverage@100 mg/kg: 250–260 (free plasma concentration [nM])/26 = 9.6–10-fold

Compound 18¹¹

Phase 2 rat formalin: 36%@3 mg/kg

Nav1.7 coverage@3 mg/kg: 343 (unbound drug concentration [nM])/33 = 10-fold

Phase 2 rat formalin: 61%@10 mg/kg

Nav1.7 coverage@10 mg/kg: 18,000 (C_{max} at PK study [nM]) \times 0.071/33 = 39-fold

Compound 19¹²

Thermal hyperalgesia in PSNL mouse: 89%@1 mg/kg

Nav1.7 coverage@1 mg/kg: 105 (C_{max} at PK study [nM]) \times 0.033/59.4 = 0.058-fold

Thermal hyperalgesia in PSNL mouse: 89%@3 mg/kg

Nav1.7 coverage@3 mg/kg: 464 (C_{max} at PK study [nM]) \times 0.033/59.4 = 0.26-fold

Compound 20¹³

Mouse histamine-induced pruritus model: 81%@30 mg/kg

Nav1.7 coverage@30 mg/kg: 490 (unbound plasma concentration [nM])/30 = 16-fold

Capsaicin-induced nociception pain model: 55%@100 mg/kg

Nav1.7 coverage@100 mg/kg: 1300 (unbound plasma concentration [nM])/30 = 43-fold

Capsaicin-induced nociception pain model: 74%@300 mg/kg

Nav1.7 coverage@100 mg/kg: 1700 (unbound plasma concentration [nM])/30 = 57-fold

Compound 21¹⁴

Reduction in nociceptive events in the IEM mouse model

Nav1.7 coverage@EC₅₀: 9.6 (unbound EC₅₀ [nM])/0.38 (K_d) = 25-fold

Compound 22¹⁵

Phase 2 rat formalin: 17%@10 mg/kg

Nav1.7 coverage@10 mg/kg (calculated based on rNav1.7 PX IC₅₀): 0.027 (unbound plasma concentration [μ M])/0.067 = 0.40-fold

Phase 2 rat formalin: 39%@30 mg/kg

Nav1.7 coverage@30 mg/kg (calculated based on rNav1.7 PX IC₅₀): 0.065 (unbound plasma concentration [μ M])/0.067 = 0.97-fold

Phase 2 rat formalin: 70%@100 mg/kg

Nav1.7 coverage@100 mg/kg (calculated based on rNav1.7 PX IC₅₀): 0.18 (unbound plasma concentration [μ M])/0.067 = 2.7-fold

Compound 24

Aconitine-induced pain in IEM mouse⁸

Nav1.7 coverage@in vivo IC₅₀: 0.40 (in vivo IC₅₀ [μ M]) \times 0.22/0.0031 = 28-fold

Phase 2 mouse formalin@30 mg/kg¹⁶

Plasma Nav1.7 coverage@30 mg/kg: 340 (free plasma concentration [nM])/3.9 = 87-fold

DRG Nav1.7 coverage@30 mg/kg: 340 (free DRG concentration [nM])/1.8 = 189-fold

Phase 2 mouse formalin@60 mg/kg¹⁷

Plasma Nav1.7 coverage@60 mg/kg: 1270 (free plasma concentration [nM])/3.9 = 326-fold

DRG Nav1.7 coverage@60 mg/kg: 340 (DRG concentration [nM]) \times 0.24/3.9 = 21-fold (the plasma protein binding as an estimate of tissue binding)

Compound 25¹⁸

Mouse histamine-induced pruritus model

Nav1.7 coverage@60 mg/kg: 5100 (unbound plasma concentration [nM])/180 = 28-fold

Compound 29⁹

Odorant-induced olfaction at 12.06 and 24.12 mg/kg

Nav1.7 coverage@1.34 mg/kg (i.v. infusion): 2.0 (plasma concentration [μM]) $\times 0.0737/0.295 = 0.50$ -fold

Nav1.7 coverage@2.68 mg/kg (i.v. infusion): 13.8 (plasma concentration [μM]) $\times 0.0737/0.295 = 3.4$ -fold

Nav1.7 coverage@4.02 mg/kg (i.v. infusion): 23 (plasma concentration [μM]) $\times 0.0737/0.295 = 5.7$ -fold

Nav1.7 coverage@12.06 mg/kg (i.v. infusion): 48.4 (plasma concentration [μM]) $\times 0.0737/0.295 = 12$ -fold

Nav1.7 coverage@24.12 mg/kg (i.v. infusion): 169 (plasma concentration [μM]) $\times 0.0737/0.295 = 42$ -fold

Withdrawal responses to noxious heat in rhesus monkeys

Nav1.7 coverage@20 mg/kg (s.c.): 7.74 (plasma concentration [μM]) $\times 0.0737/0.295 = 1.9$ -fold

Compound 31¹⁷

Phase 2 mouse formalin

Nav1.7 coverage@100 mg/kg: 0.32 (free plasma concentration [μM])/ $0.0075 = 43$ -fold

DRG Nav1.7 coverage in DRG@100 mg/kg: 72 (DRG concentration [nM]) $\times 0.08/7.5 = 0.77$ -fold (the plasma protein binding as an estimate of tissue binding)

Compound 32¹⁹

Mouse CCI-induced cold hyperalgesia model

Nav1.7 coverage@100 mg/kg: 0.74 (free plasma concentration [μM])/ $0.054 = 14$ -fold

Mouse CFA thermal hyperalgesia model

Nav1.7 coverage@30 mg/kg: 26 (free plasma concentration [nM])/ $54 = 0.5$ -fold

Nav1.7 coverage@60 mg/kg: 59 (free plasma concentration [nM])/ $54 = 1$ -fold

Phase 2 mouse formalin

Nav1.7 coverage@30 mg/kg: 0.17 (free plasma concentration@60 min [μM])/ $0.054 = 3$ -fold

Nav1.7 coverage@30 mg/kg in DRG: 0.07 (free DRG concentration@60 min [μM])/ $0.054 = 1$ -fold

Compound 36⁸

Aconitine-induced nociceptive events in IEM mouse

Nav1.7 coverage@in vivo IC₅₀: 7.3 (in vivo IC₅₀ [μM]) $\times 0.007/0.0151 = 3.4$ -fold

Compound 37⁸

Aconitine-induced nociceptive events in IEM mouse

Nav1.7 coverage@in vivo IC₅₀: 0.97 (in vivo IC₅₀ [μM]) $\times 0.002/0.0032 = 0.61$ -fold

Compound 38²⁰

Aconitine-induced nociceptive events in IEM mouse

Nav1.7 coverage@in vivo EC₅₀: 0.42 (free in vivo EC₅₀ [nM])/ $0.4 = 1.1$ -fold

Compound 39²¹

Mouse histamine-induced scratching

Nav1.7 coverage@300 mg/kg: 4.15 (free plasma concentration [μM])/ 0.27 (native TTX-S currents inhibition in the mouse DRG) = 15 -fold

Nav1.7 coverage@300 mg/kg: 4.15 (free plasma concentration [μM])/ 0.115 (mouse Nav1.7) = 36 -fold

Compound 40¹⁶

Phase 2 mouse formalin

Plasma Nav1.7 coverage@30 mg/kg i.p.: $59,000$ (plasma concentration [nM]) $\times 0.002/35 = 3.4$ -fold

DRG Nav1.7 coverage@30 mg/kg i.p.: 2724 (plasma concentration [nM]) $\times 0.035/11 = 8.7$ -fold

Mouse CFA model

Plasma Nav1.7 coverage@30 mg/kg i.p.: $63,000$ (plasma concentration [nM]) $\times 0.002/35 = 3.6$ -fold

Mouse CCI model

Plasma Nav1.7 coverage@30 mg/kg i.p.: $68,000$ (plasma concentration [nM]) $\times 0.002/35 = 3.9$ -fold

Compound 41²²

Aconitine-induced pain in IEM mouse

Plasma Nav1.7 coverage@0.3 mg/kg: 3100 (plasma concentration [nM]) × 0.001/0.6 = 5-fold

Plasma Nav1.7 coverage@3 mg/kg: 25,000 (plasma concentration [nM]) × 0.001/0.6 = 42-fold

Plasma Nav1.7 coverage@10 mg/kg: 79,000 (plasma concentration [nM]) × 0.001/0.6 = 132-fold

Phase 2 mouse formalin test

Plasma Nav1.7 coverage@10 mg/kg i.p.: 50,000 (plasma concentration [nM]) × 0.001/2.2 = 23-fold

Compound 42²³

Aconitine-induced pain in IEM mouse

Plasma Nav1.7 coverage@30 mg/kg: 2800 (plasma concentration [nM]) × 0.001/3 = 0.93-fold

Plasma Nav1.7 coverage@EC₅₀: 500 (plasma concentration [nM]) × 0.001/3 = 0.17-fold

Plasma Nav1.7 coverage@10 mg/kg: 79,000 (plasma concentration [nM]) × 0.001/0.6 = 132-fold

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