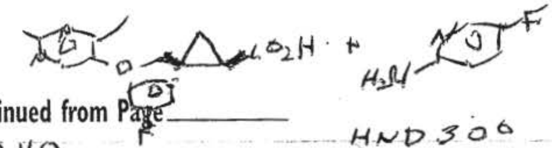
 TITLE  **PROJECT NO.**  T3P 318.2

BOOK NO. iPr₂NEt 129.25 d = 0.742

Work continued from Page

HND110 316.30 HND300 112.11

Ref: US 9,416,109 col 46–47.

HND110 + HND300 were rec'd on Dry Ice from [illegible] via FedEx 8571 2723 3144 on 9/18/20. Stored in freezer at −20 °C. Warmed to 25° briefly before use.

HND110 = (1R,2S)-2-((2,4-Dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)cyclopropane-carboxylic acid, CAS 1369769-35-6 mp 133–135°. MS m/e 317 $(M+H)^+$. ^1H, ^{13}C NMR (DMSO) OK = 9,416,109 patent

HND300 = 5-Fluoropyridin-2-amine, CAS 21717-96-4. mp 96–100° (lit 93–97° aldr). NMR OK (DMSO)

9/29/20 HND110 (1280 mg, 4.05 mmol) + HND300 (476 mg, 4.25 105 mol%) dissolved in EtOAc (10.2 ml) under N_2. Cool 5° (int), add iPr₂NEt (Aldrich 1.41 ml, 1.045 g, 8.084 mmol, 200 mol%) (not exothermic, T ≤ 5° (int)). Stir 20 min at 5°. Add T3P (Aldrich, ≥50% soln in EtOAc 3.61 g, 5.67 mmol, (140 mol%) 6:45 over ~1 min (T(int) → 10°). Stir ~20–25° 22 h. → yellow

9/30/20 Cool 5° (int), add H_2O (6.4 ml) slowly → T int max < 15°. Separate. Ext. aq 1x MTBE (7.68 ml). Wash combined org layers w sat. $NaHCO_3$ (3.84 ml), H_2O (3.84 ml) vac filter through Celite 545 (500 mg), rinse filter w/ →

Heptane 50 EtOAc 50 (UV) faint .3 .35 .25 HND110 300 -1 -1 wu 13-112-1 2 h 15 min -1 -1 -113 -113 1x 15

EtOAc (UV) .4 .5 .5 .5 .5 .65 13-112-1 300 -112-1 100 -113 -113-15 HND110 2 h 1x

Work continued to Page

SIGNATURE DATE

DISCLOSED TO AND UNDERSTOOD BY DATE WITNESS DATE

 410.33 Lemborexant

MTBE (1.28 ml). Evap in vacuo → pt amber oil (1.90 g). Dissolve in EtOAc (6.08 ml) at 50° (b). Add Heptane (8.63 ml) slowly w stirring (all sol'd at 50°. Cool to 20-25° w stirring for 17 h (→ crystals in < 10 min) then 5° for 2h.
9/30/20 5:50
Vac filter, rinse pt. w. heptane-EtOAc (5:1, 2x 1.28 ml) Dry in vacuo → 667 mg (40%) white solid, mp 177-178° 13-113-1X

Filtrate = much product (TLC). Strip → 588 mg -1S pt. beige off-white solid (35%)

10/8/20 Repeat 13-112-1. Follow by TLC + HPLC. ~90% complete in 2h. 8:20 21h (HPLC - complete). Extract etc. Evap MTBE + EtOAc 12/19/20 3:45 to 1.70 g. Reevpt from EtOAc + Heptane (→ crystals in ~1 min at 50°) cool to 24° + stir 1h. Cool 5° w. stirring for 2h. Vac filter pt → white solid, mp 177-178° 13-113-2X 877 mg (53%) Store -20°. Strip w. ice pack in foam container -2S 10/20/20
Filtrate → 432 mg (26%) pt. beige solid

^1H + ^{13}C NMR OK (DMSO-d_6) compared to patents
MS m/z 433 $(M+Na)^+$

Work continued to Page _____

SIGNATURE DATE

DISCLOSED TO AND UNDERSTOOD BY DATE WITNESS DATE

Work continued from Page________

PROJECT NO. HATU 380.23

BOOK NO. → iPr$_2$NEt 129.25 d = 0.742

Ref: US 9,416,109 Col 49

10/13/20 HND110 (1280 mg, 4.05 mmol) + HND300 (476 mg, 4.25 mmol, 105 mol %) + HATU (1.616 g, 4.25 mmol, 105 mol %) were dissolved in DMF (6.4 mL, distilled over 3A sieves) N_2. Cool 5°

add iPr$_2$NEt (1.41 mL, 1.045 g, 8.084 mmol, 200 mol %)

4:15 T max = 7°. Stir 20°-25° (turns yellow) 24 h.

(Still containing 5% HND110 after 22 h (slow))

10/14/20 4:15 Add HATU (162 mg, 0.425 mmol, 10.5 mol %) cool to 10°, add iPr$_2$NEt (0.14 mL, 20 mol %). Stir 20-25° 24 h (Still contains 5% HND110 after 24 + 22 h)

10/15/20 4:15 Add HND300 (40 mg, 0.357 mmol, 8.8 mol %) Stir 24 h (still contains 5% HND110 after 21 h).

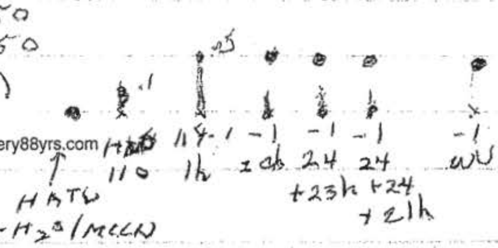
10/16/20 add MTBE (5.12 mL), cool 0-5°. Add H_2O (6.4 mL) (T: 10°). Warm to 20°. Add MTBE (7.68 mL). Separate. Extract aq w MTBE (12.8 mL) + Toluene (10.24 mL). Rinse combined org. layer w. sat $NaHCO_3$ (3.84 mL) + 18% NaCl (2X 3.2 mL) (+1x 3.2 mL). Vac filter through Celite 545 (500 mg). Rinse filter w. MTBE

10/19/20 (1.28 mL). Store @ 4° 3d. Evap in vacuo, high vac (6 mm 1.0) → 1.37 g beige semisolid. (Contains < 0.5% HND110).

13-114-1

EtOAc 50 heptane 50 (UV)

EtOAc 0.5 (UV)



Work continued to Page______

SIGNATURE DATE

DISCLOSED TO AND UNDERSTOOD BY DATE WITNESS DATE

cool to 25°(i)

10/19/20 Dissolve in EtOAc (6.08 ml) at 50°C (i) & add
3:05 heptane (8.63 ml) slowly w. stirring at ~~50°~~ 25° (Note different from p 113?). crystals form in 2 min. Stir 40 mins at 20°, 2.5h at 4°. Vac filter, rinse ppt w heptane-EtOAc (5:1, 2×1.28 ml). Dry in vacuo → 654 mg white solid (39%) mp 177-178°. Store -20° ship 10/20/20 w ice pack in foam container. MS m/z 411 $(M+H)^+$; ^1H + ^{13}C NMR OK (DMSO-d_6) 13-115-1X

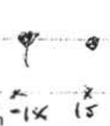
Filtrate (TLC less pure) evap solvent → 689 mg lt. beige solid (41%) 13-115-1S

Transfer 50 mg of -1X by dissolving in $CHCl_3$, evap. in air → larger crystals, mp 176-177° 13-115-1XC

HPLC conditions: 150×4.6mm Lichrospher RP 18-5 5µm. H_2O to MeCN (0.1% TFA) 0 to 100% in 20 min. 1 mL/min. Dilute ~10 µL in 0.6 mL MeCN
approx. ret. times (min)

HND110 11.2
HND300 5.8 (faint)
HATU + H_2O/MeCN 6.1
Product 12.1

EtOAc 5%
Heptane 50
(UV)



SIGNATURE DATE
DISCLOSED TO AND UNDERSTOOD BY DATE WITNESS DATE