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SUPPLEMENTARY INFORMATION

for

Synthesis of C-11 Methyl Substituted Benzocycloheptapyridine Inhibitors of Farnesyl Protein Transferase

by

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Experimental Section:

Melting points were determined with an Electrothermal Digital Melting point apparatus and are uncorrected. Elemental analyses were performed by the Physical-Analytical Chemistry Department, Schering-Plough Research Institute on either a Leeman CE 440 or a FISONS EA 1108 elemental analyzer. FT-IR spectra were recorded using a BOMEN Michelson 120 spectrometer. Mass Spectra were recorded using either EXTREL 401 (Chemical Ionization), JEOL,or MAT-90 (FAB), VG ZAB-SE (SIMS), or Finnigan MAT-CH-5 (EI), spectrometer. In general, structures of the compounds were determined by coupling constants, coupling information from the COSY spectra and 1D NOE experiments. The ^{1}H and ^{13}C NMR spectra were obtained on either Varian VXR-200 (200 MHz, ^{1}H) , Varian Gemini-300 (300 MHz, ^{1}H; 75.5 MHz, ^{13}C) or XL-400 (400 MHz, ^{1}H; 100 MHz, ^{13}C)and are reported as ppm down field from

Me_4Si with number of protons, multiplicities, and coupling constants in Hertz (Hz) indicated parenthetically. For ^{13}C NMR, a Nalorac Quad nuclei probe was used. Rotations were recorded on Perkin-Elmer 243B polarimeter.

8-Chloro-11-(1-methyl-piperidyl)-6,11-dihydro-5h-benzo[5,6]-cyclohepta[1,2-b]pyridine (4).

Tricyclic amine **3** [6] (80 g, 0.26 mol) was dissolved in formic acid 160 g (160 mL, 6.84 eq.). To this solution was added 151 g (140 mL) of 37% formaldehyde. The reaction mixture was heated to ~80 °C for 2 h, cooled to room temperature and then basified to pH = 12 with 25% NaOH . The aqueous phase was extracted with ethyl acetate (3 X 1.3 L), dried over Na_2SO_4 and concentrated to give 75.5 g (90% yield) of an oil that was recrystallized from isopropyl ether and diethyl ether to afford the title compound **4**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.20-1.55 (m, 4H), 1.70-1.95 (m, 3H), 2.05-2.20 (m, 1H), 2.25 (s, 3H), 2.70-3.00 (m, 4H), 3.30-3.55(m, 2H), 3.90 (m, 1H), 7.05-7.15 (m, 3H), 7.40 (d, J = 2.5 Hz, 1H), 8.35 (d, J = 2.5 Hz, 1H); MS m/z (rel intens) 326 (100, MH^+); Anal. Calcd. for $C_{26}H_{23}N_3O_2BrCl$: C, 73.49; H, 7.09; N, 8.57. Found: C, 73.52; H, 7,09; N, 8.56.

4-(8-Chloro-5,6-dihydro-11-methyl-benzo[5,6]-cyclohepta[1,2-b]pyridin-11-yl)-1-methyl piperidine (5).

To a solution of tricyclic amine **4** (15.0 g, 45.9 mmol) in 230 mL of THF at -75 °C was added n-Buli (22. 06 mL, 55.1 mmol, 1.2 equiv. 2.5 M in hexanes). The reaction mixture was allowed to stir for 1h, warmed to -30 °C and stirred at that temperature for 1h. The reaction mixture was then cooled to -50 °C and methyliodide (9.46 g, 4.3 mL, 66.5 mmol) was added. The reaction mixture was warmed up to -10 °C, treated with diethylether (1.5 mL) followed by 10 mL of

NH_4OH. The reaction mixture was extracted with EtOAc, dried over MgSO4 and concentrated to give a gummy material that was purified by chromatography using a silica gel column and eluting with 2-5% MeOH-CH_2Cl_2 (Saturated with ammonia) to give 10.69 g (71% yield) of compound **5** as a light yellow solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10-1.30 (m, 3H), 1.20 (t, J = 7.5 Hz, 3H), 1.85 (s, 3H), 2.50-2.60 (m, 2H), 2.80 (m, 1H), 3.00 (m, 2H), 3.30-3.60 (m, 2H), 4.10 (q, J = 7.5 Hz, 2H), 4.10-4.15 (m, 3H),7.00-7.15 (m, 3H), 7.35 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 8.40 (m, 1H); MS (CI) m/z (rel intens) 341 (100, MH^+); Anal. Calcd. for $C_{21}H_{25}N_2Cl$ .0.11CH_2Cl_2, : C, 72.39; H, 7.26; N, 8.00. Found: C, 72.68; H, 7.50; N, 8.12.

4-(8-Chloro-5,6-dihydro-11-methyl-benzo[5,6]-cyclohepta[1,2-b]pyridin-11-yl)-piperidine-1-carboxylic acid ethyl ester (6).

To a solution of tricyclic amine **5** (7.19 g, 21.1 mmol) in toluene (120 mL) was added Et_3N (2.14 g, 63.3 mmol, 3 mL, 3 equiv.) and the mixture was heated to reflux. Ethyl chloroformate (11.44g, 105 mmol, 10.10 mL, 5.0 equiv.) was slowly added over a period of 45 min. After 5h the reaction was poured into ice and then basified with IN NaOH. The aqueous phase was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated to give 6.4 g (76% yield) of **6** as a yellow solid that was used in the next experiment without further purification: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20 (t, J = 7.0 Hz, 3H), 1.25-1.23 (m, 5H), 1.90 (s, 3H), 1.90 (d, J = 5.4 Hz, 1H), 2.50-2.70 (m, 2H), 2.75-3.10 (m, 3H), 3.20-3.70 (m, 2H), 4.20 (q, J = 7.0, 2H), 7.00-7.50 (m, 5H), 8.40 (m, 1H); MS m/z (rel intens) 399 (100, MH^+)

4-(8-Chloro-3-nitro-5,6-dihydro-11-methyl-benzo[5,6]cyclo-hepta[1,2-b]pyridin-11-yl)-piperidine-1-carboxylic acid ethyl ester (7).

Tetrabutylammonium nitrate (6.52 g, 21.4 mmol) was dissolved in dichloromethane (50 mL) and trifluoroacetic anhydride (4.50 g, 21.4 mmol, 3 mL) was then added. The solution was cooled to 0 °C and then added by cannulation to a solution of tricyclic carbamate **6** (6.4 g, 19.4 mmol) in methylene chloride (100 mL) also cooled to 0 °C. The reaction mixture was stirred at 0 °C for 3h and then allowed to warm to room temperature (25°C) overnight. The reaction mixture was then extracted with saturated sodium bicarbonate, dried over magnesium sulfate and concentrated to give a semi-solid material that was chromatographed on silica gel eluting with 10-20% ethyl acetate -hexane. Removal of the organic solvents gave 3-nitro carbamate **7** in 40% yield as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, J = 7.0 Hz, 3H), 1.10-1.30 (m, 5H), 1.90 (s, 3H), 2.50-2.65 (m, 2H), 2.75-2.90 (m, 1H), 2.95-3.30 (m, 2H), 3.45-3.65 (m, 2H), 4.10 (q, J = 7.0 Hz, 2H),4.15 (m, 1H), 7.15-7.20 (m, 2H), 7.45 (d, J = 7.5 Hz, 1H), 8.15 (d, J = 2.5 Hz, 1H), 9.15 (d, J = 2.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.7, 22.6, 27.8, 33.4, 33.5, 44.5, 44.7, 44.9, 54.6, 61.3, 126.5, 130.3, 130.2, 130.3, 130.7, 132.9, 133.5, 135.7, 140.2, 141.1, 145.4, 142.3, 155.3, 168.0. IR (film) υ_{max} 1107, 1434, 1572 , 1694 2950,, 3064, 3500; MS m/z (rel intens) 444.1 (100, MH^+).

4-(3-Amino-8-chloro--5,6-dihydro-11-methyl-benzo[5,6]cyclo-hepta[1,2-b]pyridin-11-yl)-piperidine-1-carboxylic acid ethyl ester (8). Nitrocarbamate **7** (3.20 g, 7.20 mmol) was dissolved in 85% aqueous ethanol (100 mL). To this solution was added iron filings (3.6 g, 64.6 mmol) and calcium chloride(0.36 g, 3.2 mmol) and refluxed for 16 h. The reaction mixture

was filtered through a bed of celite® while hot and then washed with hot EtOH-CH_2Cl_2. The organic solvents were rotary evaporated to give the title compound in 100% yield as an off-white solid. An analytical sample was prepared by flash column chromatography (silica gel eluting with 80% ethyl acetate-hexane) to afford product **8** as a white foam: mp 111.2-112.1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, J = 7.0 Hz, 3H), 1.10-1.30 (m, 5H), 1.85 (s, 3H), 2.50-2.65 (m, 2H), 2.70-2.80 (m, 1H), 2.85-3.00 (m, 2H), 3.30-3.35 (m, 1H), 3.40-3.55 (m, 1H), 4.10 (q, J = 7.0 Hz, 2H), 3.30-3.35 (m, 1H), 6.80 (brs, 1H), 7.10-7.15 (m, 2H), 7.40 (d, J = 7.5 Hz, 1H), 8.00 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.7, 22.5, 27.6, 27.8, 33.4, 34.1, 44.6, 44.7, 45.4, 52.4, 61.2, 126.0, 130.0, 130.6, 132.0, 132.1, 132.2, 141.1, 155.3. IR (film) υ_{max} 1235, 1451, 1629, 1680 2855, 2946, 3234, 3438. MS (FAB) (rel intens) *m/z* 414 (100%); Calcd. for $C_{23}H_{28}N_3O_2Cl$ .0.51H_2O : C, 65.25; H, 6.70; N, 9.93. Found: C, 65.12; H, 7.20; N, 9.84.

4-(3-Bromo-8-chloro-5,6-dihydro-11-methyl-benzo[5,6]-cyclohepta[1,2-b]pyridin-11-yl)-piperidine-1-carboxylic acid ethyl ester (9). Tricyclic amine **8** (3.3 g, 8.1 mmol) was dissolved in 48% hydrobromic acid (32 mL). The reaction mixture was cooled to -5 °C (ice-ethylene- glycol bath) and bromine (2.3 mL) was added dropwise. The reaction mixture was stirred at -5 °C for 15 minutes. Sodium nitrite (1.7 g, 24.3 mmol) dissolved in water (15 mL) was slowly added to the mixture. The mixture was stirred for 45 minutes and neutralized with 50% NaOH to pH ~10. The aqueous phase was then extracted with CH_2Cl_2. Combined CH_2Cl_2 fractions were dried over magnesium sulfate and concentrated. Purification on silica gel eluting with 10% EtOAc-hexanes afforded 2.43 g (63%) of compound **9** as a white solid: mp 85-86; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, J = 7.0 Hz, 3H), 1.10-1.30 (m, 5H),

1.85 (s, 3H), 2.50-2.65 (m, 2H), 2.70-2.80 (m, 1H), 2.90-3.10 (m, 2H), 3.30-3.65 (m, 2H), 4.10 (q, J = 7.0 Hz, 2H),4.15 (m, 1H), 7.15-7.20 (m, 2H), 7.45 (d, J = 7.5 Hz, 1H), 7.00 (s, 1H), 8.45 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.7, 22.4, 27.8, 33.3, 33.9, 44.6, 44.7, 45.0, 53.4, 61.2, 115.5, 118.4, 126.2, 130.2, 130.6, 132.4, 136.5, 141.0, 141.2, 141.5, 146.2, 155.3, 160.0. IR (film) υ_{max} 1038 1432, 1469,1694, 2855, 2948, 3463; MS (FAB) (rel intens) *m/z* 479.1 (100%); Calcd. for $C_{23}H_{26}N_2O_2BrCl$ .0.2H_2O : C, 57,81; H, 5.85; N, 5.98. Found: C, 57.29; H, 5.85; N, 5.96.

4-(8-Chloro-6,11-dihydro-11-methyl-benzo[5,6]cyclohepta-[1,2-b]pyridin-11-yl)-1-(4-pyridinylacetyl)-piperidine N1-oxide (+)-11 and (-)-11.

Hydrolysis of the carbamate **9** was carried out according to the procedure previously described [5] : Resolution of 10 on Chiralpak® AD column eluting with 20% isopropanol-80% hexane-0.2% diethylamine afforded the enantiomeric amines **(+) 10**: (Retention time = 18.24 min), and **(-) 10**: (Retention time = 45.47 min). Coupling of amines **(+)-10** and **(-)-10** with pyridine acetic acid N-oxide using previously described procedure[5] afforded the tricyclic pyridylacetyl N- oxides **(+)-11** and **(-)-11** in 54 and 97% yields respectively.

Compound (+)-11: mp 134-135; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90-1.45 (m, 4H), 1.80 (s, 3H), 2.30-3.10 (m, 5H), 3.20-3.80 (m, 5H), 4.60 (m, 1H), 7.10-7.20 (m, 4H), 7.40 (d, J = 7.5 Hz, 1H), 7.05 (s, 1H), 8.15 (d, J = 5.0 Hz, 1H), 8.45 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.3, 27.4, 27.6, 28.5, 28.6, 33.6, 33.7, 33.4, 34.2, 38.7, 38.8, 43.0, 43.1, 45.4, 45.5, 46.8, 46.9, 53.6, 118.4, 126.3, 127.0, 127.1,130.4, 130.5, 132.6, 135.7, 136.7, 136.8, 138.9 140.5, 140.7, 141.1, 141.9, 142.0, 146.4, 159.5, 159.6, 166.6. IR (film) υ_{max} 1035, 1447,1485,

1639, 2856, 2946, 3428; MS (FAB) (rel intens) *m/z* 542 (100%); Calcd. for $C_{27}H_{27}N_3O_2BrCl$ .1.0 H_2O ; C, 57.97; H, 5.01; N, 7.51. Found: C, 58.09; H, 5.30; N, 7.71; $[\alpha]_D^{25}$ +41.8° (c = 0.28, MeOH).

Compound (-)-11: mp 139-140; ^1H NMR, ^{13}C and IR spectra identical to that of **(+)-10**; Calcd. for $C_{27}H_{27}N_3O_2BrCl$ .1.0 H_2O ; C, 57.97; H, 5.01; N, 7.51. Found: C, 58.00; H, 5.20; N, 7.48; $[\alpha]_D^{25}$ -36.3° (c = 0.32, MeOH);

8-chloro-11-(1-methyl-3-piperidylidene)-6,11-dihydro-5h-benzo[5,6]-cyclohepta[1,2-b]pyridine (13).

To a solution of tricyclic amine **12** (20 g, 61.6 mmol) in THF under nitrogen and cooled to -15 °C was 2.5M n-Butyllithium (4.0g, 25 mL, 61.6 mmol) and stirred for 1.5 hours. The reaction mixture was further cooled to -78 °C and add MeI (9.61g, 4.2 mL, 68 mmol) and stirred from -78 °C to room temperature overnight. The reaction mixture was then quenched with H_2O (300 mL) and exhaustively extracted with EtOAc. The organic phase was dried over $MgSO_4$ and concentrated. Purification by flash chromatography, eluting with 4% triethyl amine in EtOAc afforded compound **13** as an amber solid (6.91 g, yield 32%); ^1H NMR (400 MHz, $CDCl_3$) δ 1.90 (m, 2H), 2.05 (s, 3H), 2.30 (s, 3H), 2.45 (m, 2H), 2.75-2.95 (m, 4H), 3.30-3.60 (m, 2H), 5.00 (m, 1H), 7.05-7.15 (m, 3H), 7.35 (d, J = 7.0 Hz, 1H), 7.45 (d, J = 7.0 Hz, 1H), 8.35 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 27.0, 27.6, 31.9, 32.0, 45.9, 52.8, 54.7, 55.1, 120.2, 122.1, 126.1,128.7, 130.1, 132.6, 134.4, 138.7, 141.7, 141.8, 142.8, 145.6, 160.6. IR (film) υ_{max} 1026, 1435, 1563, 2778, 2937, 3434; MS (FAB) (rel intens) *m/z* 339 (100%); Calcd. for $C_{21}H_{23}N_2Cl$ .0.2 H_2O ; C, 73.58; H, 6.83; N, 8.18. Found: C, 73.83; H, 6.98; N, 8.27.

4-(8-chloro-5,6-dihydro-11h-benzo[5,6]-cyclohepta-[1,2-b]pyridin-11-yl)-1,2,5,6-tetrahydropyridine-1-carboxylicacid ethyl ester (14). Following a similar procedure as tha descibed for preparation of compound **6** above, carbamate **14** was prepared: mp 62-63; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20 (t, J = 7.5 Hz, 3H), 1.90 (s, 3H), 2.20 (m, 1H), 2.50-3.60 (m, 7H), 3.60-4.40 (m, 5H), 5.00 (m, 1H), 7.00-7.50 (m, 5H), 8.35 (m, 1H); MS (FAB) (rel intens) *m/z* 397 (100%);

4-(8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta-[1,2-b]pyridin-11-yl)-1-[(3-pyridinyl)acetyl]-1,2,5,6-tetrahydropyridine (15).

Following a similar procedure to that descibed for preparation of compounds **(+)-11** and **(-)-11** above, tricyclic pyridylacetamide compound **15** was prepared: mp 78-79; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.70-1.90 (m, 2H), 2.00 (s, 3H), 2.70-3.50 (m, 5H), 3.65 (m, 1H), 3.70 (s, 2H), 3.90 (m, 1H), 4.10 (m, 1H),74.95-5.10 (m, 1H), 7.00-7.50 (m, 7H), 7.35 (m, 1H), 8.55 (m, 1H); IR (film) υ_{max} 1057, 1435, 1641, 2937, 2989, 3500; MS (FAB) (rel intens) *m/z* 444 (100%); Calcd. for $C_{27}H_{26}N_3OCl$ .0.75 H_2O ; C, 70.96; H, 6.00; N, 9.20. Found: C, 71.27; H, 5.90; N, 9.19.

4-(8-Chloro-6,11-dihydro-11-methyl-benzo[5,6]cyclohepta-[1,2-b]pyridin-11-yl)-1-(4-pyridinylacetyl)-piperidine N1-oxide (16)

To 15 mL of conc. HCl was added tricyclic carbamate **6** (3.5 g, 8.8 mmol). The reaction mixture was refluxed for 16 h. It was then cooled, poured into ice and neutralized with 50% NaOH. The aqueous phase was extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried over MgSO4 and concentrated to give the amine **5** (2.26 g, 79% yield) which was used in the subsequent

reaction without further purification: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10-1.50 (m, 4H), 1.85 (s, 3H), 1.90 (m, 1H), 2.20-2.35 (m, 3H), 2.40-2.60 (m, 2H), 2.70-3.20 (m, 4H), 3.35-3.70 (m, 2H), 7.00-7.20 (m, 3H), 7.35-7.60 (m, 2H), 8.40 (m, 1H); IR (film) υ_{max} 812, 1040, 1117, 1424, 1561, 2941, 3424; MS m/z (rel intens) 306.9 (12.04), 389.0 (82.39), 390.0 (21.32), 391.0 (100 MH^+), 392.0 (24.57), 393.0 (28.62). Calcd. for $C_{20}H_{23}N_2Cl$ .0.11H_2O : C, 71.28; H, 7.13; N, 8.32. Found: C, 71.28; H, 7.16; N, 8.29. This amine was coupled with pyridine acetic acid N-Oxide using a previously described procedure affording the tricyclic pyridylacetyl N-oxide **16** after purification on a C-18 reverse phase eluting with 75% MeOH-H_2O. mp 118-119; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85-1.45 (m, 4H), 1.80 (s, 3H), 2.30-2.55 (m, 1H), 2.75-3.10 (m, 4H), 3.25-3.85 (m, 5H), 4.55 (m, 1H), 7.00-7.50 (m, 7H), 8.10 (d, J = 7.5 Hz, 2H), 8.35 (m, 1H); IR (film) υ_{max} 1036, 1447,1485, 1638, 2945, 3422; MS (FAB) (rel intens) *m/z* 462 (100%).