Synthesis of T785

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Method Article

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Abstract

Chemical synthesis procedure and methods for T785 small molecule

Introduction

T785 was prepared via an eight step synthesis starting from commercially available starting materials. Commercially available 3-nitroquinoline-2,4-diol undergoes nitration and chlorination followed by a regioselective addition of tert-butyl N-(4-aminobutyl)carbamate. Aniline formation via hydrogenation and subsequent acylation undergoes imidazoquinoline ring formation under acidic conditions. Finally, displacement of the chloroquinoline by (2,4-dimethoxyphenyl)methanamine and acidic deptrotection yields T785 in ~36% overall yield.

Reagents

Acetic acid

Nitric Acid

POCl3

Pet ether

ethyl acetate

water

THF

Triethylamine

Pt/C

Nitrogen gas

pentanoyl chloride

Sodium sulfate (Na2SO4)

MeOD

d-DMSO

NaHCO3

HCl

MeOH

quinoline-2,4-diol

tert-butyl N-(4-aminobutyl)carbamate

(2,4-dimethoxyphenyl)methanamine

Equipment

Rotoevaporary

Flask

Seperatory funnel

Stir plate

NMR

Thin Layer Chromotagraphy

HPLC

LCMS

Procedure

3-nitroquinoline-2,4-diol (**1**). To a solution of quinoline-2,4-diol (260 g, 1.61 mol, 1 eq) in AcOH (1.2 L) is added fuming nitric acid (152.49 g, 2.42 mol, 108.92 mL, 1.5 eq) dropwise at 0°C. The mixture is stirred at 65°C for 5 hours. The mixture is cooled to 25°C and quenched by the addition of ice-water (500 mL). The product is separated by filtration and washed with water (500 mL x 3), and dried to give 3-nitroquinoline-2,4-diol (320 g, 1.52 mol, 94.29% yield) as yellow solid. The crude product was used in the next step without further purification. LC/MS: m/z = 207.0 $[M+H]^+$ 1H NMR (DMSO-d_6, 400 MHz) δ 11.96 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 7.2 Hz,1H), 7.34 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 7.2 Hz, 1H).

2,4-dichloro-3-nitroquinoline (**2**). 3-nitroquinoline-2,4-diol (365 g, 1.77 mol, 1 eq) is added slowly to $POCl_3$ (2.44 kg, 15.93 mol, 1.48 L, 9 eq) at 65°C and further heated to 90°C for 12 h. The mixture is concentrated under vacuum. The residue is then poured into ice-water (3 L) and stirred for an additional 0.5 h. The aqueous phase is filtered, washed by water (500 mL x 5) and the filter cake is collected and further purified by silica gel chromatography (Petroleum ether/Ethyl acetate=20/1, 3/1) to obtain 2,4-dichloro-3-nitro-quinoline (330 g, 1.32 mol, 74.39% yield, 97% purity) as yellow solid. LC/MS: m/z = 243.0 $[M+H]^+$ 1H

NMR ($CDCl_3$, 400 MHz) δ 8.29 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.96 (t, J =8.4 Hz, 1H), 7.82 (t, J = 8.4 Hz, 1H).

Tert-butyl N-[4-[(2-chloro-3-nitro-4-quinolyl) amino]butyl]carbamate (**3**). To a mixture of 2,4-dichloro-3-nitro-quinoline (330 g, 1.36 mol, 1 eq) and tert-butyl N-(4-aminobutyl)carbamate (281.18 g, 1.49 mol, 1.1 eq) in THF (1.5 L) is added Et_3N (206.09 g, 2.04 mol, 283.48 mL, 1.5 eq) slowly at 0°C and stirred for 2 h. TLC (Petroleum ether: Ethyl acetate = 1:1, Rf = 0.43) showed the starting materials is consumed completely and one main spot is detected. The reaction is quenched by water (2 L) and extracted with EtOAc (800 mL x 3). The combined organic layer is washed by brine (1000 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product is washed by petroleum ether (1000 mL) and filtered to give tert-butyl N-[4-[(2-chloro-3-nitro-4-quinolyl) amino]butyl]carbamate (500 g, crude) as yellow solid. LC/MS: m/z = 395.2 $[M+H]^+$ 1H NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, J = 7.2 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.75 (t, J =7.2 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H), 6.43 (s, 1H), 4.70 (s, 1H), 3.50-3.45 (m, 2H), 3.22-3.17(m, 2H), 1.80-1.75 (m, 2H), 1.67-1.61 (m, 2H), 1.44 (s, 9H).

Tert-butyl N-[4-[(3-amino-2-chloro-4-quinolyl)amino]butyl]carbamate (**4**). To a solution of tert-butyl N-[4-[(2-chloro-3-nitro-4-quinolyl)amino]butyl]carbamate (150 g, 379.89 mmol, 1 eq) in EtOAc (800 mL) is added Pt/C (40 g, 10% purity) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 psi) at 25°C for 3 hours. LCMS and HPLC showed the starting material is consumed completely. The reaction mixture was filtered and the filtrate is concentrated to give tert-butyl N-[4-[(3-amino-2-chloro-4-quinolyl)amino]butyl]carbamate (110 g, crude) as an off-white solid. LC/MS: m/z = 365.2 $[M+H]^+$ 1H NMR ($CDCl_3$, 400 MHz) δ 7.90 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 7.6 Hz, 1H) 7.49-7.45 (m,2H), 4.59 (s, 1H), 4.15-4.10 (m, 2H), 3.29-3.26 (m, 2H), 3.18-3.16 (m, 2H), 1.70-1.60 (m, 4H), 1.45 (s, 9H).

Tert-butyl N-[4-[[2-chloro-3-(pentanoylamino)-4-quinolyl]amino]butyl] carbamate (**5**). To a mixture of tert-butyl N-[4-[(3-amino-2-chloro-4-quinolyl)amino]butyl] carbamate (500 g, 1.37 mol, 1 eq) and Et_3N (208.00 g, 2.06 mol, 286.11 mL, 1.5 eq) in THF (1000 mL) is
added pentanoyl chloride (247.85 g, 2.06 mol, 249.10 mL, 1.5 eq) dropwise at 0°C. The mixture is stirred at 0°C for 1 h. The mixture is poured into ice water (1000 mL) and stirred for 2 min. The aqueous phase is extracted with ethyl acetate (500 mL x 3). The combined organic phase was washed with brine (1000 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue is purified by re-crystallization from EtOAc/petroleum ether (1/1, 800 mL) to give the pure tert-butyl N-[4-[[2-chloro-3-(pentanoylamino)-4-quinolyl]amino] butyl] carbamate (550 g, 1.16 mol, 84.92% yield, 95% purity) as light yellow solid. LC/MS: m/z = 449.3 $[M+H]^+$ 1H NMR (MeOD, 400 MHz) δ 8.14 (d, J = 8.4 Hz, 1H), 7.72 (d, J =

7.6 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.46 (t, J = 6.8 Hz, 1H), 3.56 (t, J = 7.2 Hz, 2H), 3.07 (t, J = 7.2 Hz, 2H), 2.51 (t, J = 7.6 Hz, 2H), 1.77-1.66 (m, 4H), 1.54-1.41 (m, 4H), 1.41 (s, 9H), 1.01 (t, J = 7.2 Hz, 3H).

Tert-butyl N-[4-(2-butyl-4-chloro-imidazo[4,5-c]quinolin-1-yl)butyl]carbamate (**6**). To a solution of tert-butyl N-[4-[[2-chloro-3-(pentanoylamino)-4-quinolyl]amino] butyl]carbamate (490 g, 1.09 mol, 1 eq) in toluene (1000 mL) is added AcOH (65.54 g, 1.09 mol, 62.42 mL, 1 eq) at 25°C. The mixture is stirred at 100°C for 15 hours. The mixture is concentrated in vacuum. The residue is poured into ice water (1000 mL) and stirred for 5 min. The aqueous phase is extracted with ethyl acetate (500 mL x 3). The combined organic phase is washed with $NaHCO_3$.aq (500 mL) and brine (800 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue is purified by re-crystallized from EtOAc/ petroleum ether (1/50, 500 mL) to give tert-butyl N-[4-(2-butyl-4-chloro-imidazo[4,5-c]quinolin-1- yl)butyl]carbamate (400 g, 928.14 mmol, 85.05% yield) as a white solid. LC/MS: m/z = 431.1 $[M+H]^+$ 1H NMR ($CDCl_3$, 400 MHz) δ 8.19 (d, J = 6.8 Hz, 1H), 8.09 (d, J = 7.6 Hz, 1H) 7.66-7.62 (m,2H), 4.61 (s, 1H), 4.54 (t, J = 7.6 Hz, 2H), 3.21-2.20 (m, 2H), 3.00 (t, J = 8.0 Hz, 2H), 1.97-1.88 (m, 4H), 1.71-1.69 (m, 2H), 1.55-1.49 (m, 2H), 1.42 (s, 9H), 1.01 (t, J = 7.2 Hz, 3H).

Tert-butyl N-[4-[2-butyl-4-[(2,4-dimethoxyphenyl)methylamino]imidazo[4,5-c]quinolin-1-yl]butyl]carbamate (**7**). Tert-butyl N-[4-(2-butyl-4-chloro-imidazo[4,5-c]quinolin-1-yl)butyl] carbamate (62 g, 143.86mmol, 1 eq) in (2,4-dimethoxyphenyl)methanamine (120.27 g, 719.31 mmol, 108.35 mL, 5 eq) is stirred at 120°C for 3 hr. LCMS showed the reaction is completed. The reaction is quenched by addition of water (200 mL), acidified by diluted hydrochloride acid and extracted with EtOAc (300 mL x 3). The combined organic layers is washed by brine (500 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue is purified by re-crystallization from EtOAc (200mL) to give tert-butyl N-[4-[2-butyl-4-[(2,4-dimethoxyphenyl)methylamino]imidazo[4,5-c]quinolin-1-yl]butyl]carba mate (70 g, 118.39 mmol, 82.29% yield, 95% purity) as white solid. LC/MS: m/z = 562.4 $[M+H]^+$ 1H NMR (MeOD, 400 MHz) δ 8.22 (d, J = 8.4 Hz, 1H), 8.05 (s, 1H), 7.74 (t, J = 7.6 Hz, 1H),7.66 (t, J = 8.4 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 6.63-6.58 (m, 1H), 6.54 (d, J = 8.0 Hz, 1H) 4.62 (t, J = 7.2 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.12 (t, J = 6.8 Hz, 2H), 3.00 (t, J = 7.6 Hz, 2H), 1.98-1.86 (m, 4H), 1.69-1.65 (m, 2H), 1.53-1.50 (m, 2H), 1.37 (s, 9H), 1.01 (t, J = 7.6 Hz,

1-(4-aminobutyl)-2-butyl-imidazo[4,5-c]quinolin-4-amine (**9**). Tert-butyl N-[4-[2-butyl-4-[(2,4-dimethoxyphenyl)methylamino]imidazo[4,5-c] quinolin-1-yl] butyl]carbamate (30 g, 53.41 mmol, 1 eq) is added to HCl (12M, 200 mL) at 25°C. The mixture is stirred at 25°C for 12 hour. LCMS showed the starting material is consumed completely. The reaction mixture is filtered, washed with MeOH (500 mL) and the filtrate is concentrated to give the crude product, recrystallized from EtOAc (50 mL) to give the pure 1-(4-aminobutyl)-2-butyl-imidazo[4,5-c]quinolin-4-amine (17 g, 48.38 mmol, 90.58% yield, 99% purity, HCl) as

white solid. 1H NMR (MeOD, 400 MHz) δ 8.28 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.75 (t, J =7.6 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H), 4.72 (t, J = 7.6 Hz, 2H), 3.08 (t, J = 7.6 Hz, 2H), 3.01 (t, J = 7.6 Hz, 2H), 2.07-1.85 (m, 6H), 1.62-1.53 (m, 2H), 1.05 (t, J = 7.6 Hz, 3H). LCMS (ESI): $[M+H]^+$. calculated 312.21, $[M+H]^+$ found 312.

Figures

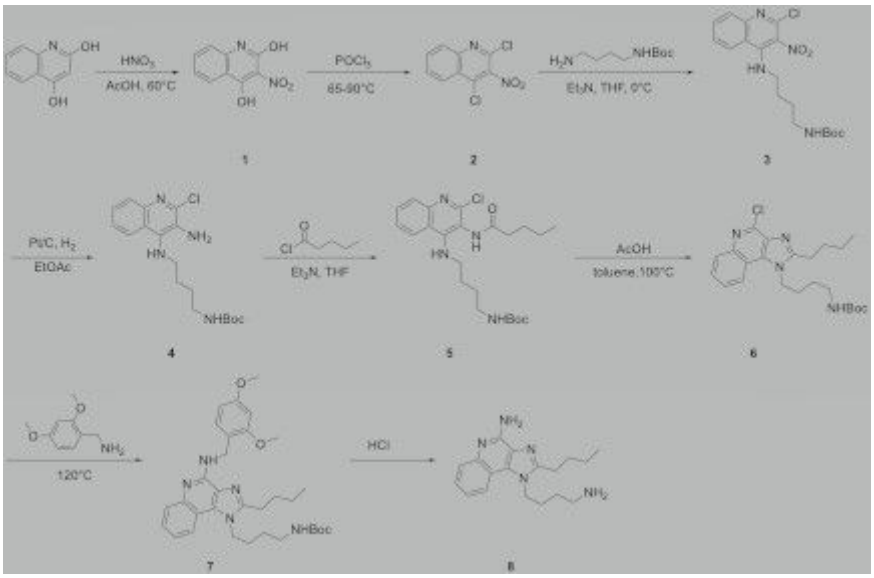

Figure 1

Synthetic scheme for T785

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