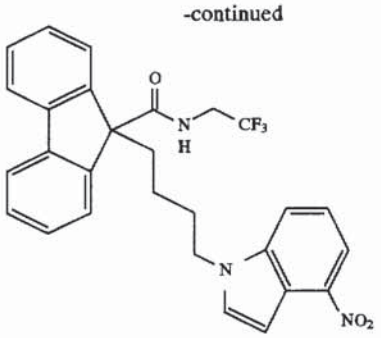
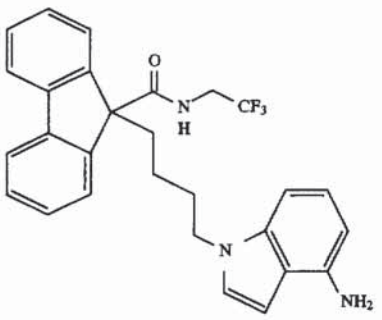
-continued



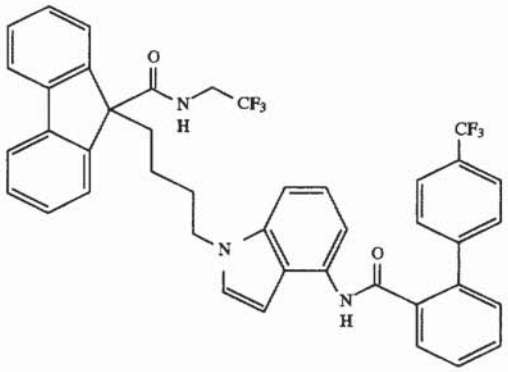
A solution of 4-nitroindole (4.0 g, 24.7 mmol) in DMF (20 mL) was added slowly over 5 min to a suspension of unwashed sodium hydride (1.09 g, 60 wt. % in mineral oil, 27.2 mmol) in DMF (50 mL) at 0° C. An immediate color change to deep red occurred with bubbling of escaping gasses. The reaction mixture was stirred at 0° C. for 5 min and then at RT for 40 min. A solution of Example 273 Part A(2) compound (12.6 g, 29.6 mmol) in DMF (20 mL) was added and the reaction mixture was stirred at RT over a weekend (64 h total). The solvent was removed under high vacuum on a rotary evaporator, and the resulting orange residue was partitioned between EtOAc (200 mL) and H_2O (50 mL). The organic layer was washed with H_2O (2×50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated to give a yellow foam. The crude product was purified by flash chromatography on silica gel (600 g) eluting with a step gradient of 20% to 25% to 30% EtOAc/hexane to give title compound (10.9 g, 73%) as a yellow foam.

B.



A mixture of Part A compound (7.47 g, 14.7 mmol) and 10% palladium on carbon (780 mg, 0.737 mmol) in EtOAc (50 mL) was hydrogenated under a balloon of H_2 at RT for 5 h, filtered through Celite®, and washed with EtOAc (2×50 mL). The filtrate was concentrated and dried under high vacuum to give title compound (7.12 g, 100%) as a white foam.

C.

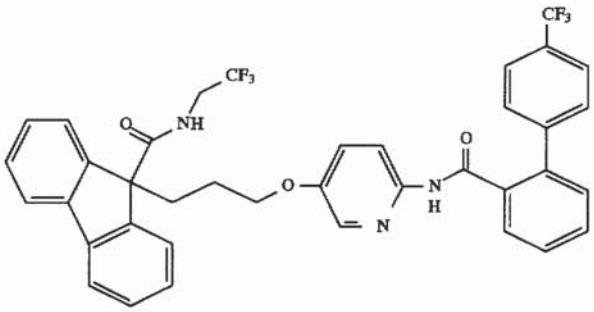


To a solution of Part B compound (5.2 g, 10.9 mmol) and triethylamine (2.0 mL, 14.2 mmol) in CH_2Cl_2 (30 mL) at 0° C. was added Example 415 Part A compound (12 mL, 1.0M in CH_2Cl_2, 12.0 mmol) over 5 min. The cloudy reaction mixture was stirred at 0° C. for 10 min, diluted with EtOAc (200 mL), washed with saturated $NaHCO_3$ (2×50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated to give a golden foam. The crude product was dissolved in a minimal amount of CH_2Cl_2 and then purified by flash chromatography on silica gel (400 g) eluting with a step gradient of 30% to 40% EtOAc/hexane to give title compound (7.74 g, 89%) as a pale yellow foam. NMR shows product to contain EtOAc.

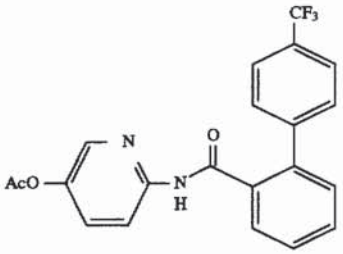
Anal. Calcd for $C_{42}H_{33}F_6N_3O_2$+0.5 $C_4H_8O_2$: C, 68.65; H, 4.84; N, 5.46; F, 14.81 Found: C, 68.38; H, 4.55; N, 5.44; F, 14.82.

EXAMPLE 419

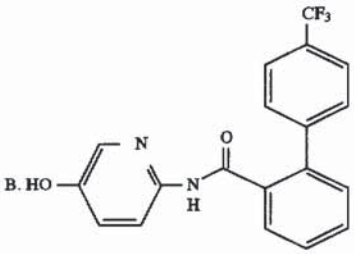
N-(2,2,2-Trifluoroethyl)-9-[3-[[2-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-5-pyridinyl]oxy]propyl]-9H-fluorene-9-carboxamide



A.

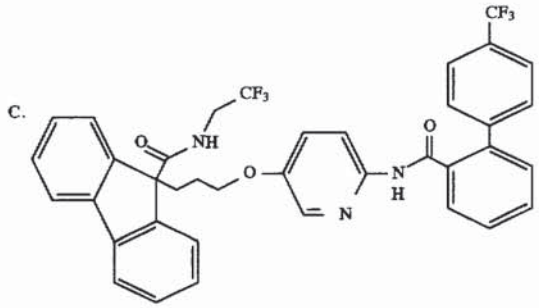


Sodium nitrite (587 mg, 8.5 mmol) was added in portions to a stirred solution of 2.02 g (5.66 mmol) of Example 415 Part D compound in 40 mL of glacial AcOH at room temperature under N_2. The reaction was stirred at room temperature for 45 minutes, then 408 mg (6.8 mmol) of urea was added to destroy excess HONO and stirring was continued for 2 hours. The reaction was gradually heated to 90° C. (N_2 evolution) and then 115° C., over the course of 3 hours, and then cooled to room temperature. The solvent was removed in vacuo and the residue was taken up in CH_2Cl_2 and dilute $NaHCO_3$. The CH_2Cl_2 was washed with dilute $NaHCO_3$ (2x) and water (2x), dried (Na_2SO_4), and concentrated to an oily residue (2.29 g). Flash chromatography over 200 g of silica gel packed in $CHCl_3$ by eluting with title compound (fraction A, 265 mg and fraction B, 763 mg), which was used without further purification.



B.

A solution of Part A compound (763 mg) in 10 mL of CH_3OH and 6 mL of 2N KOH was stirred at room temperature for 20 hours and concentrated to a residue, which was taken up in Et_2O and water and extracted twice with Et_2O. The aqueous phase was layered with Et_2O and adjusted to pH 5.2 with dilute HCl. After two extractions with Et_2O, the acidic Et_2O extract was dried (Na_2SO_4) and concentrated to a residue. Crystallization of this residue from CH_2Cl_2 gave 439 mg of title compound. Similar treatment of the above 265 mg fraction of Part A compound provided an additional 87 mg of title compound for a total of 526 mg (26%, 2 steps) of title compound.



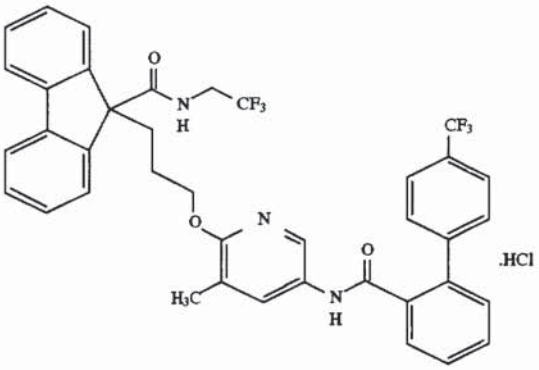
C.

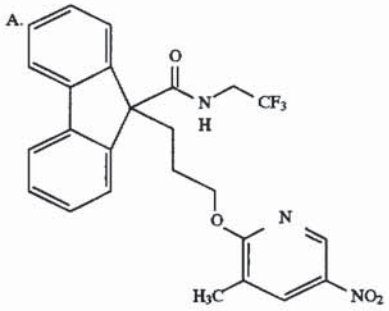
50 mg (0.143 mmol) of Example 417 Part B compound, 64 mg (0.179 mmol) of Part B compound and 41 mg of triphenylphosphine were azeotropically evaporated with toluene (3X), then dried in vacuo for 2 hours before dissolved in 0.5 mL of freshly distilled THF. To above solution cooled at 0° C. was added dropwise diethylazodicarboxylate (24.8 µL, 0.157 mmol), and the resulting mixture was stirred at room temperature under argon for 18 hours, then diluted with EtOAc, washed with water, brine, dried over $MgSO_4$. The filtrate was concentrated, absorbed on Celite, flash chromatographed eluting with 20–30% EtOAc/hexane to give 76.4 mg of the product as an oily residue. Further purication using preparative HPLC, after lyophilization afforded 56.5 mg (57% yield) of the pure title product as a white powder.

MICROANALYSIS: Calculated for $C_{38}H_{29}N_3F_6O_3$+0.60 H_2O: C, 65.16; H, 4.35; N, 6.00; F, 16.27 Found: C, 64.86; H, 4.04; N, 5.77; F, 16.59. MS: (electrospray, +ions) m/e @ 690 (M+H).

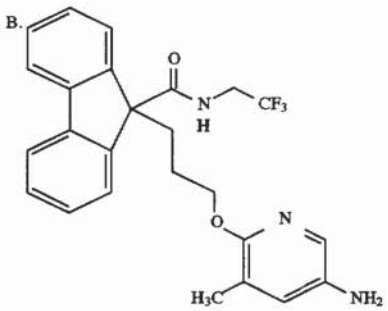
EXAMPLE 420

9-[3-[[3-Methyl-5-[[[4'-(trifluoromethyl)[1.1'-biphenyl]-2-yl]carbonyl]amino]-2-pyridinyl]oxy]propyl]-N-(2.2.2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

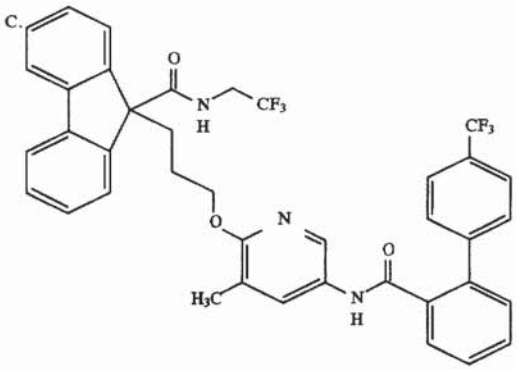




A solution of Example 417 Part B compound (1.25 g, 3.58 mmol) in THF (5 mL) was treated with NaH (173 mg, 60% mineral oil dispersion, 4.3 mmol) and stirred for 15 min at RT. After all the gray solid was consumed, 2-chloro-3-methyl-5-nitropyridine (742 mg, 4.3 mmol) was added to the reaction mixture. The resulting black mixture was stirred at RT for 18 h. Additional 2-chloro-3-methyl-5-nitropyridine (74 mg, 0.43 mmol) was added and stirring was continued for 6 h longer. The mixture was diluted with 5% aq. $NaHCO_3$ (10 mL) and extracted with EtOAc (3×50 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated to give a foam. Flash chromatography on Merck silica gel K-60 (50 g) eluting with EtOAc/hexane (0.5:9.5 to 1:4) to give title compound (1.53 g, 90%) as a solid, m.p. 102°–104° C.



A mixture of Part A compound (250 mg, 0.51 mmol) and 10% palladium on carbon (15 mg) in ethyl acetate (5 mL) was hydrogenated (balloon pressure) at RT for 24 h. The catalyst was removed by filtration through nylon 66 filter, and concentrated in vacuo to give crude title amine (240 mg, quantitative) as an oil.

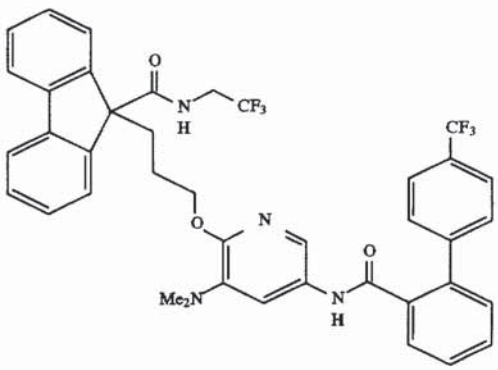


To a solution of crude Part B compound (240 mg, 0.50 mmol) and triethylamine (221 µl, 1.5 mmol) in CH_2Cl_2 (5 mL) at 0° C. was added dropwise 540 µl (0.54 mmol) of 1.0M 4'-(trifluoromethyl)-2-biphenyl carboxylic acid chloride (Example 415 Part A) solution in CH_2Cl_2. The reaction was stirred at 0° C. for 1 h. Dichloromethane (20 mL) was added and the solution was washed with sat. $NaHCO_3$ solution (2×10 mL), then dried over Na_2SO_4 and concentrated to give an oil. Purification by flash chromatography on Merck silica gel K-60 (20 g) eluting with CH_2Cl_2/MeOH (10:0 to 9.8:0.2) to give 300 mg of title compound as a free base. To the stirred solution of free base title compound (281 mg, 0.4 mmol) in THF was added 4N HCl in dioxane (415 µl, 1.6 mmol). After stirring for 3 min, the clear solution was diluted with Et_2O (50 mL). The separated solid was collected and dried in vacuo (0.5 mm) at RT for 2 h to give title compound (260 mg, 90%) as off white solid.

MS (ESI, +ions) m/z 704 (M+H).

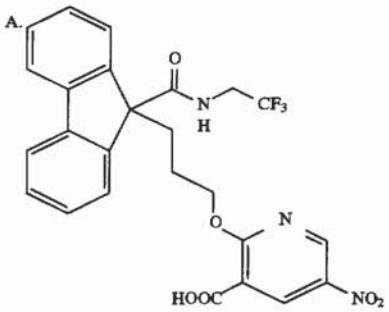
EXAMPLE 421

9-[3-[[3-(Dimethylamino)-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-2-pyridinyl]oxy]propyl]-N-(2,2.2-trifluoroethyl)-9H-fluorene-9-carboxamide

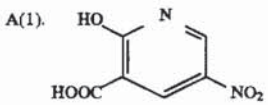


For compounds of Part A(1) and Part A(2), the procedure described in J. Med. Chem. 1992 35, 1895, was followed.

A.

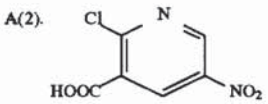


A(1).



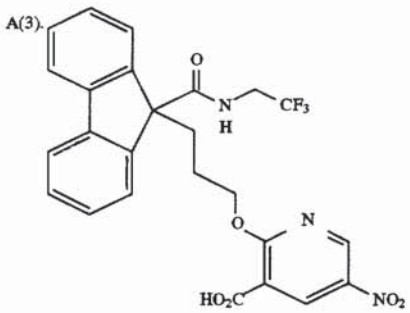
Fuming nitric acid (10 mL, 240 mmol) was added to a suspension of 2-hydroxynicotinic acid (13.9 g, 100 mmol) in concentrated sulfuric acid (40 mL) and the reaction mixture was heated gradually to 50° C., at which point all solids had dissolved. After 5 min at 50° C., the reaction mixture began to exotherm violently, whereupon the heating bath was removed. The reaction mixture turned dark red and emitted red fumes, and within a few minutes, began to cool down. Once at RT (HPLC indicated complete reaction), the yellow solution was poured into ice water (600 mL), and the resulting solid was filtered, washed with ice water (2×100 mL), and air-dried for 1 h to give 12.1 g of a yellow solid. The crude product was recrystallized from H_2O (200 mL) and then dried in a vacuum oven at 90° C. to give title compound (10.4 g, 57%) as a yellow solid (mp 238.5°–240.5° C., lit mp 240° C.).

A(2).



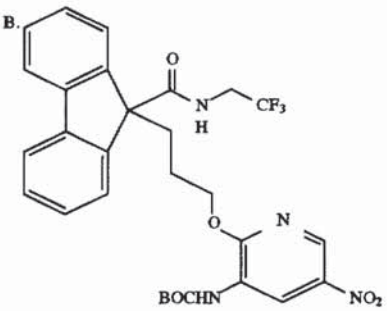
A suspension of Part A(1) compound (7.0 g, 38 mmol) in phosphorus oxychloride (20 mL) was heated at reflux for 2 h, cooled to RT, and added slowly to H_2O (100 mL) with stirring, maintaining the temperature below 40° C. with added ice. Following addition, the mixture was stirred at RT for 30 min, whereupon a precipitate formed. The mixture was extracted with Et_2O/THF (2:1, 2×200 mL), and the combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, and concentrated to give an oily yellow solid. The crude product was taken up in hot Et_2O/hexane (1:1, 200 mL), filtered, and the filtrate was concentrated to give title compound (5.78 g, 75%) as a yellow solid (mp 140°–141° C., lit mp 142°–143° C.).

A(3).



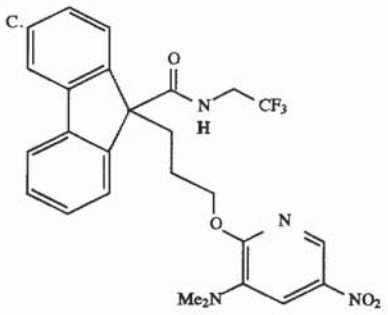
Sodium hydride (124 mg, 60 wt % in mineral oil, 3.09 mmol) was added all at once to a solution of Example 417 Part B compound (430 mg, 1.23 mmol) in DMF (2 mL). After evolution of gasses, the reaction mixture was stirred for 30 min at RT, followed by addition of Part A(2) compound (208 mg, 1.03 mmol) all at once. Bubbling ensued and the reaction mixture was stirred at RT for 30 min, diluted with H_2O, and then acidified with 1N HCl (3 mL). The solid mass that formed was extracted with EtOAc (20 mL), washed with a large amount of brine, dried over Na_2SO_4, and concentrated to give 750 mg crude title carboxylic acid as a yellow oil.

B.



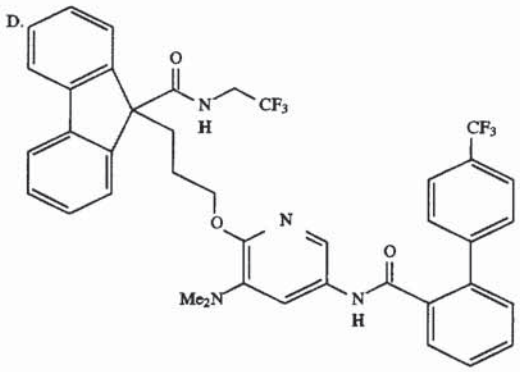
Diphenylphosphoryl azide (477 μL, 2.22 mmol) was added to a solution of Part A compound (955 mg, 1.85 mmol) and triethylamine (385 μL, 2.78 mmol) in freshly distilled tert-butanol. The reaction mixture was heated at 80° C. for 2 h, cooled to RT, and concentrated to give an orange oil. The oil was dissolved in EtOAc (25 mL), washed with saturated $NaHCO_3$ (2×5 mL), H_2O (5 mL), and brine (5 mL), dried over $MgSO_4$, and concentrated to give 1.33 g of an orange thick oil. The crude product was purified by flash chromatography on silica gel (100 g) eluting with a step gradient of 15% to 20% EtOAc/hexane to give title compound (355 mg, 33%) as a yellow foam.

C.



A solution of Part B compound (343 mg, 0.585 mmol) in 4N HCl/dioxane (3 mL) was allowed to stand at RT for 5 h, then concentrated to give the crude amine. To a mixture of the crude free amine, formalin (950 μL, 37%, 11.7 mmol), and AcOH (1 mL, 17.6 mmol) in MeOH (3 mL) was added sodium cyanoborohydride (370 mg, 5.85 mmol) all at once. The reaction mixture was stirred at RT overnight, concentrated, and azeotroped with toluene (15 mL). The residue was dissolved in EtOAc (50 mL), washed with saturated $NaHCO_3$ (2×10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated to give 400 mg of an orange oil. The crude product was purified by flash chromatography on silica gel (50 g) eluting with 15% EtOAc/hexane to give title compound (230 mg, 76%) as a yellow glass.

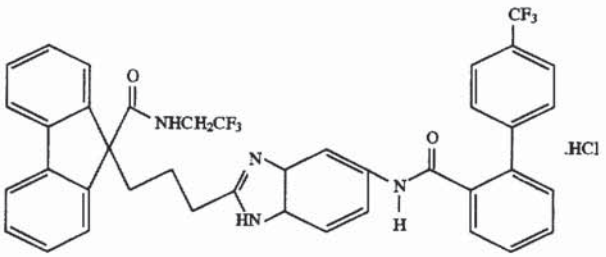
D.



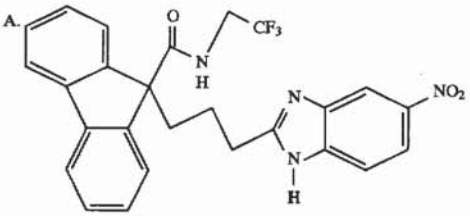
Following the procedure in Example 418 Part C compound(230 mg, 0.447 mmol) was hydrogenated and then acylated with Example 415 Part A compound to give title compound (234 mg, 72%) as a white foam.

MS (ES, +ions) m/z 733 [M+H). Anal. Calcd for $C_{40}H_{34}F_6N_4O_3$+0.5 H_2O: C, 64.77; H, 4.76; N, 7.55; F, 15.37 Found: C, 64.70; H, 4.60; N, 7.28; F, 15.16.

EXAMPLE 422



A.



A mixture of Example 416 Part B compound (400 mg, 1.11 mmoles), 5-nitrophenyldiamine (173 mg, 1.11 mmoles) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (256.3 mg, 1.11 mmoles) in dry CH_3CN (5.0 ml) was stirred at room temperature for 25 hours and stripped to dryness. The crude mixture chromatographed on a silica gel column (Merck), eluting the column with CH_2Cl_2:EtOAc (3:1) to give title compound as a light brick-red solid foam (313 mg, 57.1%).

TLC : R_f 0.47 (Silica gel; EtOAc:CH_2Cl_2-6:4; UV)

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