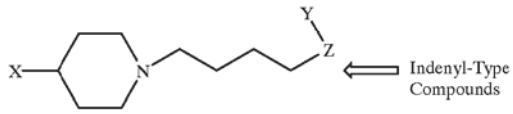
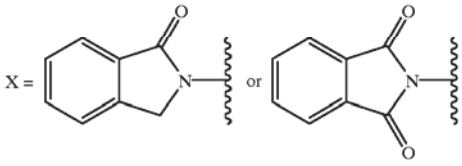
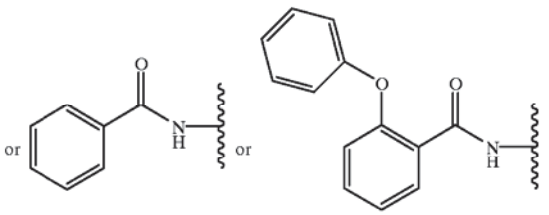
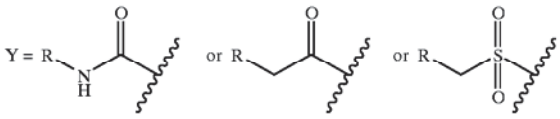
TABLE G-continued

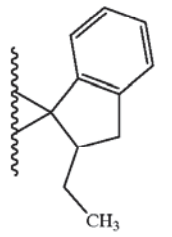


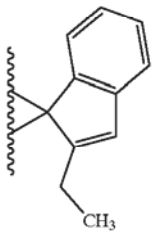


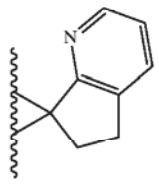


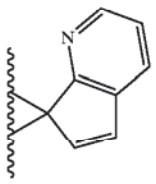


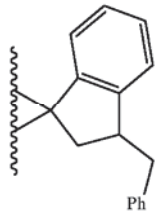
R = propyl or CF_3CH_2

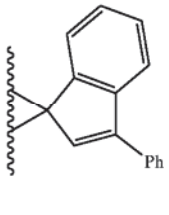


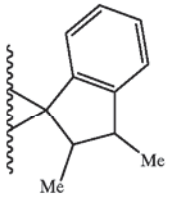












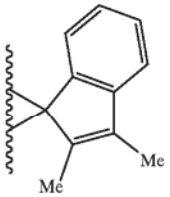
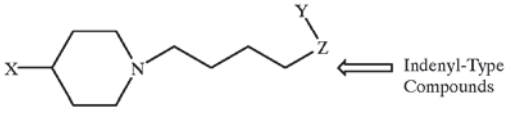
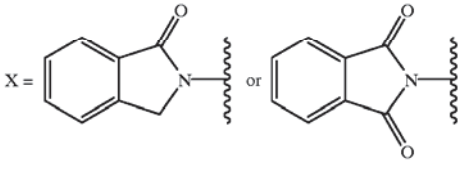
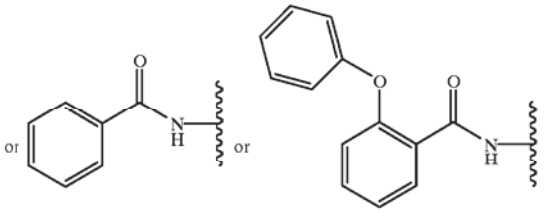
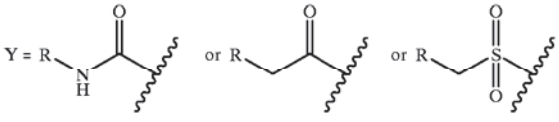


TABLE G-continued

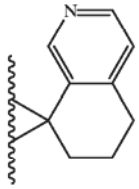


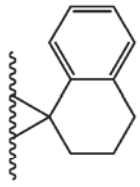


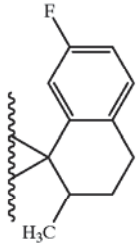


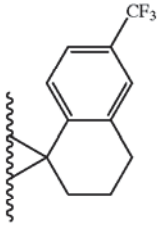


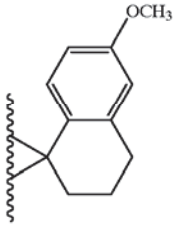
R = propyl or CF_3CH_2

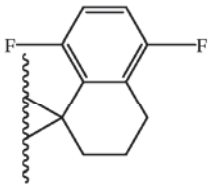


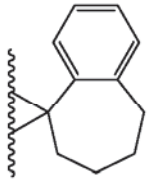












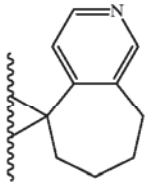
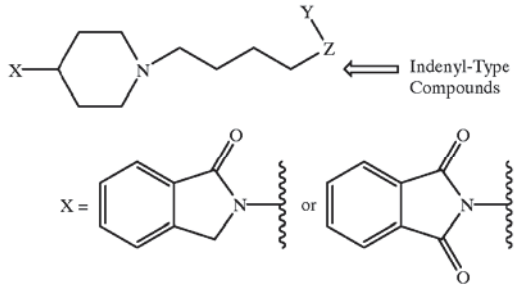
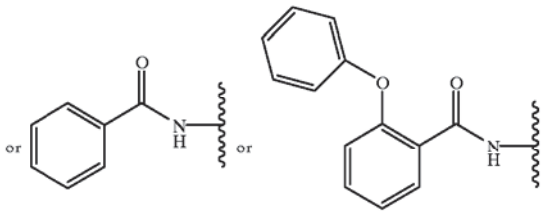
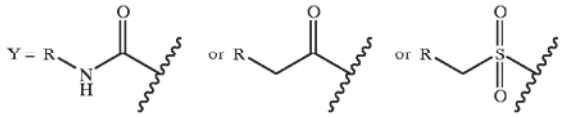


TABLE G-continued







R = propyl or CF_3CH_2

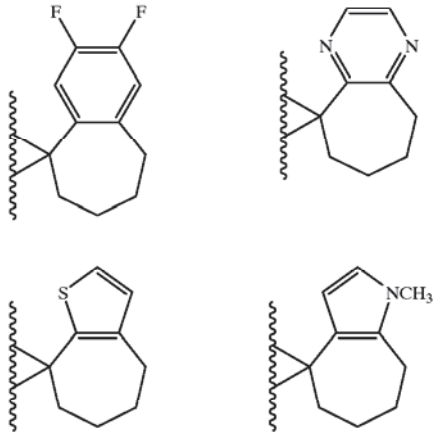
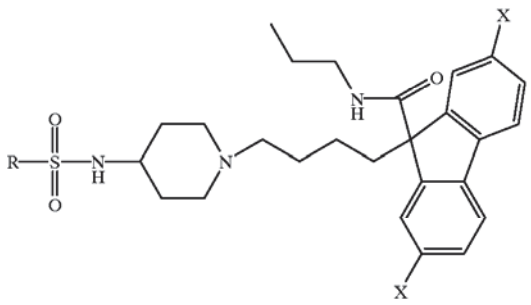
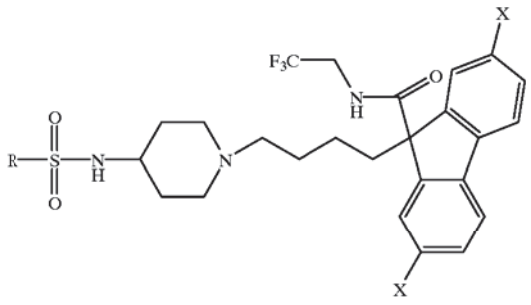
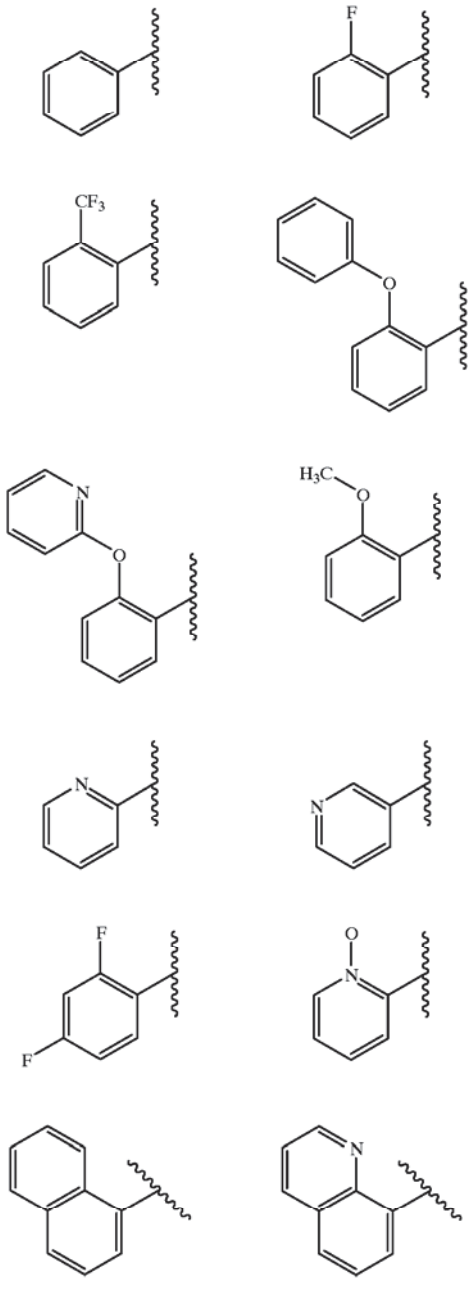


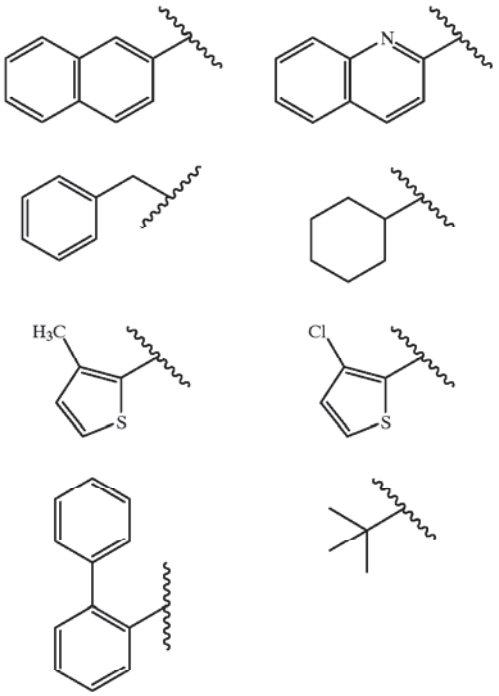
TABLE H





Example of R





In the foregoing Tables which set out compounds of the invention of formulae I and II, that is compounds which include the 4-substituted piperidine isomers, it will be understood that the formulae I and II compounds may be substituted with compounds of the invention of formulae Ii and IIi, that is compounds which include the 3-substituted piperidine isomers.

EXAMPLE 339

cis-9-[4-[4-(2,3-Dihydro-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, N-oxide

A slurry of 3-chloroperoxybenzoic acid (approx. 50%) (341 mg, 0.99 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a solution of Example 310 compound (524 mg, 0.99 mmol) in CH_2Cl_2 (1 mL) at 0° C. under argon. The reaction was stirred at 0° C. for 20 min, diluted with CH_2Cl_2 (15 mL), washed with saturated $NaHCO_3$ (5 mL) and brine (5 mL), then dried over $MgSO_4$. Evaporation gave 612 mg of a white foam, which was purified by flash chromatography on silica gel (75 g) eluting with a step gradient of 4% to 5% to 7% to 10% MeOH/CH_2Cl_2 to give title compound (308 mg, 58%) as a white foam.

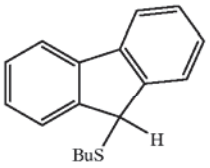
MS (ES): 538 [M+H]

Anal. Calcd. for $C_{34}H_{39}N_3O_3.1.5\ H_2O$: C, 72.29; H, 7.50; N, 7.44 Found: C, 72.32; H, 7.28; N, 7.41.

EXAMPLE 340

2-[1-[4-[9-(Butylsulfonyl)-9H-fluoren-9-yl]butyl]-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one

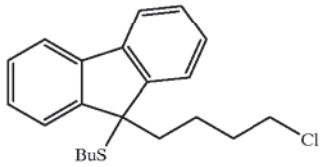
A.



A solution of 9-hydroxy-(9H)-flourene (1.58 g, 10.0 mmol) and butanethiol (0.72 g, 8.00 mmol) in 10 mL of dichloromethane at −20° C. was treated with borontrifluoride etherate (1.28 g, 9.00 mmol). The reaction was stirred for 1 h at −20° C. and warmed to room temperature. After stirring for 18 h the contents of the flask were purified by column chromatography on silica gel (100 g) with hexanes followed by 1:9 dichloromethane/hexanes to give 1.54 g (75%) of title compound as a colorless oil.

TLC Silica gel (1:9 dichloromethane/hexanes) R_f=0.5.

B.

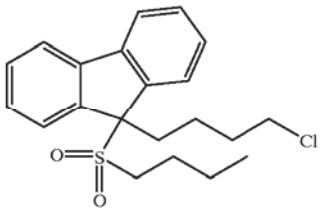


A solution of Part A compound (1.0 g, 3.93 mmol) in 10 mL of THF at −78° C. was treated with n-butyllithium in hexanes (1.75 mL, 4.40 mmol) followed by 1-chloro-4-bromo-butane (0.81 g, 4.70 mmol). The reaction was stirred for 0.5 h and warmed to room temperature for 18 h. The contents of the flask were diluted with 30 mL of aqueous NH_4Cl solution and 30 mL of ethyl acetate. The organic fraction was dried (Na_2SO_4) and concentrated. The remainder was purified by column chromatography on silica gel (50 g) with 2:98 acetone/dichloromethane (500 mL) followed by 15:85 dichloromethane/hexanes to give 1.00 (73%) of title compound as a colorless oil.

TLC Silica gel (2:8 dichloromethane/hexanes) R_f=0.4.

Mass Spec. (ES, + ions) m/e 255 (M—SC_4H_9).

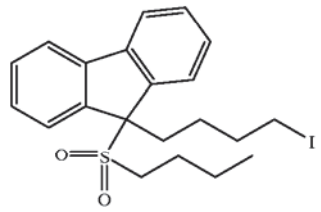
C.



To a solution of Part B compound (0.30 g, 0.86 mmol) in dichloromethane (5 mL) at 0° C. was added 3-chloroperoxybenzoic acid (m-CPBA) (0.37 g, 80% by weight ≈0.1.72 mmol) in one portion. The mixture was stirred for 1 h when it was diluted with 0.1 M K_2CO_3 (20 mL) and ether (30 mL). The organic fraction was dried (Na_2SO_4) and concentrated. The remainder was purified by column chromatography on silica gel (50 g) with 15:85 ethyl acetate/hexanes to give 0.24 g (75%) of title compound as a colorless oil.

TLC Silica gel (2:8 dichloromethane/hexanes) R_f=0.07.

D.



To a solution of Part C compound (0.24 g, 0.64 mmol) in 2-butanone (10 mL) at RT was added NaI (1.00 g, 6.66 mmol) in one portion. The mixture was refluxed for 30 h when it was diluted with water (20 mL) and ether (30 mL). The organic fraction was dried (Na_2SO_4) and concentrated. The remainder was purified by column chromatography on silica gel (50 g) with 15:85 ethyl acetate/hexanes to give 0.24 g (81%) of title compound as a colorless oil.

E. 2-[1-[4-[9-(Butylsulfonyl)-9H-fluoren-9-yl] butyl]-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one

To a stirred solution of 0.70 g (1.49 mmol) of Part D compound in 6 mL of DMF at RT was added 0.38 g (1.80 mmol) of Example 2 Part A compound. The reaction mixture was warmed to 55° C. and allowed to stir for 24 h. The mixture was diluted with $NaHCO_3$ solution (50 mL) and ethyl acetate (50 mL). The layers were separated, the organics dried (Na_2SO_4) and concentrated. The remainder was purified by flash column chromatography on silica gel (100 g) eluting with 5:95 methanol/dichloromethane (700 mL) followed by 5:95:0.5 methanol/dichloromethane/NH_3 (1 L). Pure fractions were pooled and concentrated to give 0.70 g (85%) of title compound as a thick oil which solidified after standing.

mp: 130–132° C.

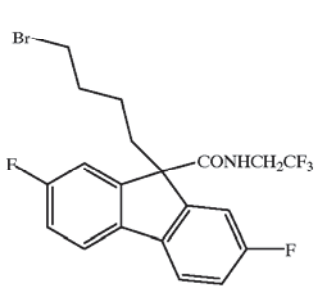
TLC Silica gel (5:95:1 methanol/dichloromethane/NH_3) R_f=0.35.

Anal. Calcd. for $C_{34}H_{40}N_2SO_3$+0.5 H_2O: C, 72.79; H, 7.30; N, 4.96; S, 5.68 Found: C, 72.25; H, 7.15; N, 5.00; S, 5.69.

EXAMPLE 341

9-[4-[[4-[(1,1-Dimethylethoxy)carbonyl]amino]-1-piperidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

A.



A Solution of Example 312 Part B compound (8.00 g, 32.5 mmol) in 100 mL of THF at room temperature was carefully evacuated and then purged with argon four times. The stirred solution was cooled to −25° C. and a solution of n-butyllithium (26.5 mL, 2.5 M in hexanes, 66.3 mmol) was added over 15 min. The resulting slurry was stirred for 1 h and cooled to −78° C. Neat dibromobutane (6.0 mL, 50.0 mmol) was added in one portion and the reaction was allowed to warm to room temperature over the course of 6 h. After an additional 14 h, the reaction mixture was poured into 1 M hydrochloric acid (70 mL) and extracted twice with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and evaporated. The semi-solid residue was triturated with hexanes and filtered to give 11.32 g of an off-white solid.

To a slurry of the above solid (11.0 g) in 25 mL of dichloromethane at room temperature under argon was added a solution of oxalyl chloride (25 mL, 2.0 M in dichloromethane, 50 mmol) followed by 0.5 mL (6.0 mmol) of DMF. After 1 h, the reaction was evaporated at less than 25° C. and the residue redissolved in 30 mL of THF. This solution was added over 20 min to a solution of 2,2,2-trifluoroethyl amine (6.10 g, 61.5 mmol) in 25 mL of THF at −10° C. under argon. After 2 h, the reaction was quenched with 10% citric acid solution and extracted twice with ethyl acetate. The organic extract was dried (Na_2SO_4) and evaporated. Purfication by flash chromatography (12×20 cm column, 7:3 dichloromethane/hexanes as elutant) on silica gel provided title compound as a white solid, 9.03 g, 60% yield from Example 312 Part B compound, mp 147–148° C.

B. 9-[4-[[4-[(1,1-Dimethylethoxy)carbonyl]amino]-1-piperidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

To a stirred solution of Part A compound (5.48 g, 11.9 mmol) in 20 mL of DMF at room temperature under argon was added Example 1 Part B compound (2.85 g, 14.2 mmol). The reaction was heated to 50° C. After 14 h, the reaction was quenched with 10% $NaHSO_3$ solution and extracted with ethyl acetate. The organic extract was dried ($MgSO_4$), evaporated and re-evaporated twice from toluene. Purification by flash chromatography on silica gel (2.5×15 cm column, ethyl acetate elutant) gave title compound, as a white solid, 6.23 g, 90%, mp 152–154° C.

EXAMPLE 342

9-[4-[4-[(2-Phenoxybenzoyl)amino]-1-piperidinyl] butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

Following the procedure in Example 321 Part B, 2-phenoxybenzoic acid (2.0 g, 9.34 mmol) was transformed into the acid chloride then reacted with Example 346 Part D compound (4.84 g, 9.34 mmol) to give a white solid (5.0 g). The product was dissolved in MeOH (5 mL), then 0.77M HCl in ethyl ether (15 mL) was added. The solution was evaporated and heated in a vacuum oven (55° C.) overnight to give title compound (5.1 g, 82%) as a white solid.

m.p. 123–127° C.

MS (ES, + ion): 656 (M+H).

Anal. Calc. for $C_{38}H_{39}ClF_3N_3O_2$.0.7 H_2O: C, 66.07; H, 5.90; N, 6.08; F, 8.25 Found: C, 66.05; H, 5.97; N, 5.96; F, 8.21.

EXAMPLE 343

9-[4-[[4-(Benzoylamino)-1-piperidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

A solution of Example 341 compound (2.07 g, 3.56 mmol) in 10 mL of 4 N hydrogen chloride in dioxane was

stirred, protected by a calcium chloride drying tube, for 3 h. The solution was evaporated at 30° C. and the resulting solid was re-dissolved in 20 mL of THF. To this stirred solution, cooled to −10° C. under argon, was added triethylamine (1.24 mL, 8.9 mmol) and then benzoyl chloride (0.46 mmol, 4.0 mmol) over 10 min. After 1 h, the reaction was quenched with saturated sodium bicarbonate solution and extracted twice with ethyl acetate. The organic extract was dried (Na_2SO_4) and evaporated. Purfication by flash chromatography on silica gel (5×20 cm column, 1:19 methanol/ethylacetate as elutant) provided, after recrystallization from ethyl acetate/hexanes, title compound as a white solid, 1.83 g, 87% yield, mp 177–179° C.

Anal. Calc'd for $C_{32}H_{32}F_5N_3O_2.0.25\ H_2O$: C, 65.13; H, 5.55; F, 16.10; N, 7.12 Found: C, 65.10; H, 5.49; F, 15.85; N, 7.12.

MA (electrospray, + ions) m/e 586 (M+H).

EXAMPLE 344

9-[4-[[4-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-piperidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

A solution of Example 341 compound (2.02 g, 3.47 mmol) in 10 mL of 4 N hydrogen chloride in dioxane was stirred, protected by a calcium chloride drying tube, for 3 h. The solution was evaporated at 30° C. and partitioned between saturated sodium bicarbonate solution and dichloromethane. The organic layer was separated, dried (Na_2SO_4) and evaporated to give a white solid. To this residue was added 550 mg (3.71 mmol) of phthalic anhydride under an argon atmosphere. The solids were melted together at 150° C. for 6 h. On cooling, the resulting solid was recrystallized from ethyl acetate/hexanes to give title compound as a white solid, 1.71 g, 80% yield, mp 186–188° C.

Anal. Calc'd for $C_{38}H_{36}F_5N_3O_3.0.13\ H_2O$: C, 64.56; H, 4.94; N 6.87 Found: C, 64.56; H, 5.03; N 6.81.

MS (electrospray, + ions) m/e 612.2 (M+H).

EXAMPLE 345

2,7-Difluoro-9-[4-[[4-[(2-phenoxybenzoyl)amino]-1-peridinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

To a solution of 565 mg (2.64 mmol) of 2-phenoxybenzoic acid (Aldrich) in 10 mL of dichloromethane under argon, was added 2 mL of oxalyl chloride (2.0 M in dichloromethane, 4.0 mmol) and then 0.1 mL of DMF. After 1 h, the reaction was evaporated and the residue, 2-phenoxybenzoyl chloride, was redissolved in 10 mL of THF.

A solution of Example 341 compound (1.00 g, 1.76 mmol) in 10 mL of 4 N hydrogen chloride in dioxane was stirred, protected by a calcium chloride drying tube, for 3 h. The solution was evaporated at 30° C. and the resulting solid was re-dissolved in 10 mL of THF. To this stirred solution, cooled to −10° C. under argon was added triethylamine (0.95 mL, 6.5 mmol) and then the 2-phenoxybenzoyl chloride solution prepared above over 10 min. After 1 h, the reaction was quenched with saturated sodium bicarbonate solution and extracted twice with ethyl acetate. The organic extract was dried (Na_2SO_4) and evaporated. Purfication by flash chromatography on silica gel (5×20 cm column, 1:19 methanol/ethylacetate as elutant) provided, after recrystallization from ethyl acetate/hexanes, title compound as a white solid, 1.01 g, 85% yield, mp 168–69° C.

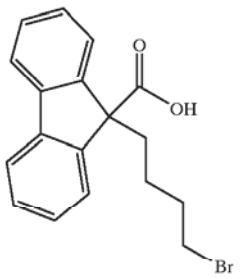
Anal. Calc'd for $C_{38}H_{36}F_5N_3O_3$: C, 67.35; H, 5.35; F, 14.02; N 6.20 Found: C, 67.20; H, 5.35; F, 14.33; N 6.08.

MS (electrospray, − ions) m/e 676.3 (M−H).

EXAMPLE 346

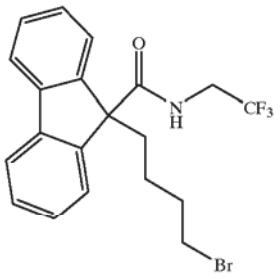
9-[4-[4-(Benzoylamino)-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

A.



To a solution of 9-fluorenecarboxylic acid (50 g, 240 mmol) in THF (1200 mL) at 0° C. was added dropwise a solution of n-butyllithium (2.5M, 211 mL, 530 mmol) in THF. The yellow reaction was stirred at 0° C. for 1 h, then 1,4-dibromobutane (31.3 mL, 260 mmol) was added dropwise over 30 min. The reaction was stirred at 0° C. for 30 min, then the reaction was warmed to RT for 30 h. The reaction was extracted with water (3×750 mL). The combined aqueous layers were extracted with ethyl ether (800 mL). The aqueous layer was made acidic with HCl solution (1N, 500 mL), then extracted with dichloromethane (3×750 mL). The combined organic layers were dried over $MgSO_4$. Evaporation gave title compound (71 g, 85%) as a white solid.

B.



To a solution of Part A acid (60 g, 173 mmol) and DMF (100 μL) in CH_2Cl_2 (600 mL) under argon at 0° C. was added oxalyl chloride (104 mL, 2.0M in CH_2Cl_2, 208 mmol) dropwise. The reaction was stirred at 0° C. for 10 min, then warmed to RT and stirred for 1.5 h. The reaction was concentrated in vacuo to give the crude acid chloride as a yellow oil. To a suspension of 2,2,2-trifluoroethylamine hydrochloride (25.9 g, 191 mmol) in CH_2Cl_2 (500 mL) at 0° C. under argon was added triethylamine (73 mL, 521 mmol) followed by dropwise addition of a solution of the crude acid chloride in CH_2Cl_2 (15 mL). The reaction was stirred at 0° C. for 1 h, diluted with CH_2Cl_2 (500 mL), and washed with water (2×300 mL), 1N HCl (2×300 mL), saturated $NaHCO_3$ (2×300 mL), and brine (2×300 mL), then dried over $MgSO_4$. Evaporation gave 80 g of a oil which was purified by flash

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