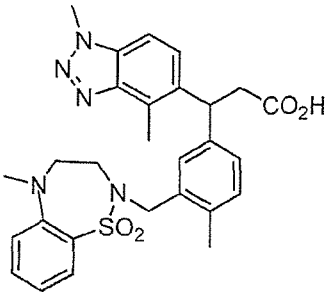
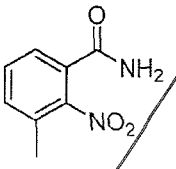
Example 2

3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(4-methyl-3-((5-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2,5]thiadiazepin-2(3H)-yl)methyl)phenyl)propanoic acid

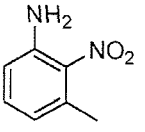


(E)-Ethyl 3-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)acrylate 3-Methyl-2-nitrobenzamide



To a solution of 3-methyl-2-nitrobenzoic acid (100 g, 552 mmol) in DCM (1000 mL), oxalyl chloride (72.5 mL, 828 mmol) was added at 25 °C. The reaction mixture was stirred at RT for 1 h. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL). The solvent was added to NH_4OH (1000 mL, 7704 mmol) at RT and was stirred for 30 min. Then the reaction mixture was extracted with EtOAc (3 x 500 mL). The combined organic layer was dried over MgSO4 and concentrated to give 67 g (60.6%) of the title compound. LC-MS *m/z* 181.1 $(M+H)^+$, 1.40 (ret. time).

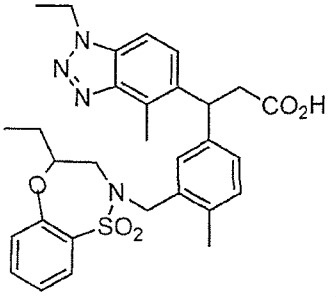
3-Methyl-2-nitroaniline



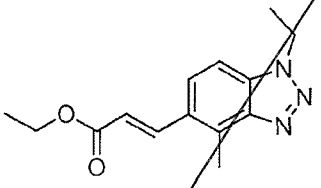
To a mixture of NaOH (2.220 g, 55.5 mmol) in water (12 mL), Br_2 (0.322 mL, 6.26 mmol) was added at 0 °C. Then 3-methyl-2-nitrobenzamide (1g, 5.55 mmol) was added in one portion, and the mixture is warmed slowly in a water bath. The material soon darkens in color, and at 50-55° C (internal temperature) oil droplets begin to separate. The

Example 35

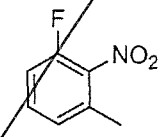
3-(3-((4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-3-(1-ethyl-4-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid



(E)-Ethyl 3-(1-ethyl-4-methyl-1H-benzo[d][1,2,3]triazol-5-yl)acrylate,

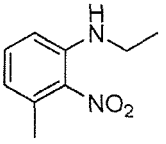


Fluoro-3-methyl-2-nitrobenzene



To a solution of 2-fluoro-6-methylaniline (8.5 g, 67.9 mmol) in DCE (150 mL), m-CPBA (58.6 g, 272 mmol) was added slowly under nitrogen at RT. The reaction mixture was stirred at 70 °C for 4 h. DCM (500 mL) was added. Then it was washed with 1N NaOH (200 mL x4). The combined organic layers was dried and concentrated under a stream of nitrogen at 50 °C to give 11.2 g (65.9%) of the title compound.

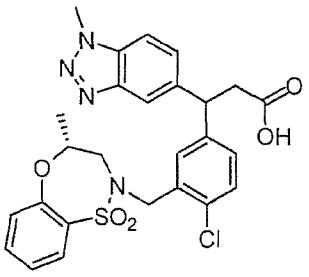
N-Ethyl-3-methyl-2-nitroaniline



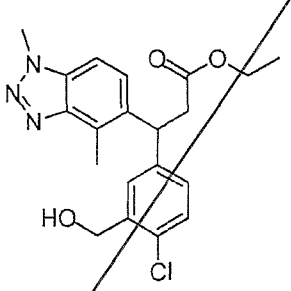
To a solution of 1-fluoro-3-methyl-2-nitrobenzene (11.2 g, 72.2 mmol) in EtOH (80 mL), ethanamine (80 mL, 911 mmol) was added slowly under nitrogen at RT. The reaction mixture was stirred at 60 °C for 16 h. Water (100 mL) was added. Then it was extracted with EtOAc (3x80 mL). The combined organic layers was dried and concentrated under a stream of nitrogen at 50 °C. The crude product was purified by

Example 72

3-(4-chloro-3-(((R)-4-methyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)phenyl)-3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid



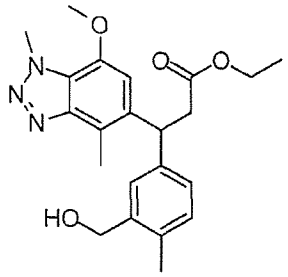
Ethyl 3-(4-chloro-3-(hydroxymethyl)phenyl)-3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate



To a suspension of (E)-ethyl 3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)acrylate (300 mg, 1.223 mmol),(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (657 mg, 2.446 mmol) Et_3N (0.707 mL, 5.10 mmol) in 1,4-dioxane (20 mL) and water (10 mL) at RT was added $[RhCl(cod)]_2$ (33.8 mg, 0.061 mmol). The resulting suspension was heated at 95 °C for 1 h. The reaction mixture was diluted with water and extracted with EtOAc (3x). The combined organic phases were washed with water (3x), brine (1x), dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified on a silica cartridge (40 g) with a Combiflash Companion, eluting at 35 mL/min with a gradient running from 0 % EtOAc/hexanes to 70 % over 35 min. LC-MS *m/z* 388.0 $(M+H)^+$, 0.92 (ret. time).

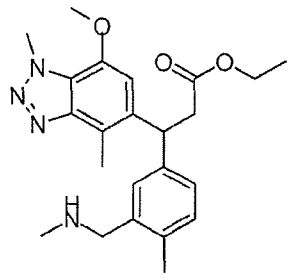
to 80% EtOAc/Hexanes over 35 min) to give 950 mg (88%) of the title compound. LC-MS *m/z* 276.0 $(M+H)^+$, 0.97 (ret. time).

Ethyl 3-(3-(hydroxymethyl)-4-methylphenyl)-3-(7-methoxy-1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate



To (E)-ethyl 3-(7-methoxy-1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)acrylate (150 mg, 0.545 mmol) in 1,4-dioxane (10 mL) and water (5.00 mL) was added (3-(hydroxymethyl)-4-methylphenyl)boronic acid (163 mg, 0.981 mmol), Et_3N (83 mg, 0.817 mmol) and $[RhCl(cod)]_2$ (13.43 mg, 0.027 mmol). The result reaction mixture was stirred at 95 °C for 1 h. The reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated then, the product was purified over a silica cartridge (40 g) using Combiflash Companion eluting at 18 mL/min running a gradient of 0-30% EtOAc/hexane over 30 min then, 30% to 100% over 20 min to give 170 mg (70%) of the title compound. LC-MS m/z 398.2$(M+H)^+$, 0.93 (ret. time).

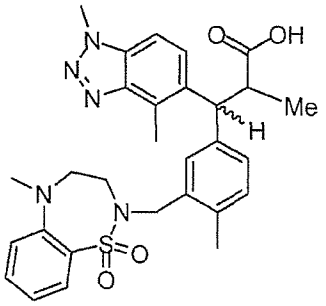
Ethyl 3-(3-(chloromethyl)-4-methylphenyl)-3-(7-methoxy-1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate



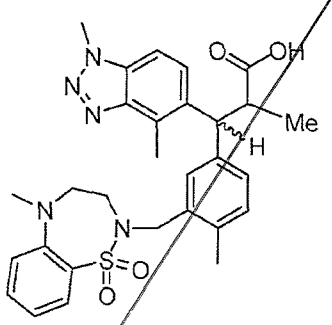
To a solution of ethyl 3-(3-(hydroxymethyl)-4-methylphenyl)-3-(7-methoxy-1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate (350 mg, 0.881 mmol) dissolved in DCM (6 mL) was added thionyl chloride (0.096 mL, 1.321 mmol) and the mixture was stirred at RT for 48 h. After checking LC-MS. the mixture was evaporated down with V10 evaporator under vacuum to get 326 mg crude of ethyl 3-(3-(chloromethyl)-4-

Example 120

2-methyl-3-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(4-methyl-3-((N-methylphenylsulfonamido)methyl)phenyl)propanoic acid

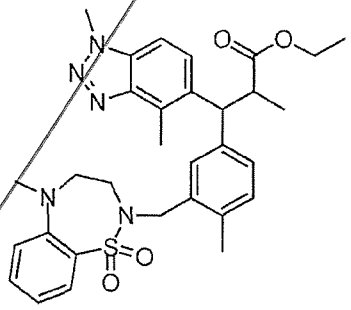


Diastereomer 1
Example 121



Diastereomer 2
Example 122

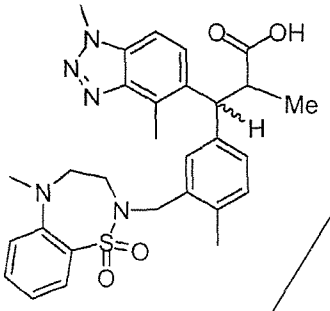
Ethyl 3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-2-methyl-3-(4-methyl-3-((5-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2,5]thiadiazepin-2(3H)-yl)methyl)phenyl)propanoate



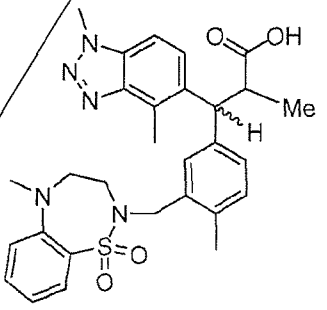
A 2M n-BuLi in hexanes solution (1.100 mL, 2.200 mmol) is added to a dry-ice acetone bath cooled solution (~ - 70 °C) of diisopropylamine (0.381 mL, 2.67 mmol) in THF (2 mL). The clear solution was stirred at dry-ice acetone bath temp for 10 min and then was warmed on an ice-water bath and stirred for 10 min to afford 0.63 M LDA.

A portion of the 0.63M LDA (0.367 mL, 0.231 mmol) diluted with THF (1 mL) was cooled on a dry-ice acetone bath and ethyl 3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(4-methyl-3-((5-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2,5]thiadiazepin-2(3H)-yl)methyl)phenyl)propanoate (100 mg, 0.178 mmol) dissolved in THF (2 mL) was added dropwise (T < -65 °C). The red solution was stirred with dry-ice acetone cooling for 30 min and then the dry-ice acetone bath was replaced with a dry-ice CH_3CN bath (~ -40 °C)

and the red solution was stirred for 15 min, MeI (0.223 mL, 3.56 mmol) was added in one portion and the yellow solution was warmed to 23 °C and stirred 15 min. The volatiles were removed *in vacuo* and the residue was diluted with EtOAc (75 mL) and washed with 0.5 M aqueous HCl (25 mL) and saturated aq NaCl (25 mL), dried Na_2SO_4 and concentrated to afford 103 mg of a brown foam. The crude product was dissolved in CH_3CN (4 mL), filtered through a 0.45 mm acrodisc, and purified by reverse-phase HPLC (YMC C18 S-5 mm/12 nm 50 x 20 mm preparatory column), eluting at 20 mL/min with a linear gradient running from 20% CH_3CN/H_2O (0.1% TFA) to 90% CH_3CN/H_2O (0.1% TFA) over 10 min. The desired fractions were concentrated *in vacuo* to afford 99 mg (97 %) of the title compound as a mixture of isomers. LC-MS *m/z* 576.3 $(M+H)^+$, 1.20 (ret. time).



Diastereomer 1
Example 121



Diastereomer 2
Example 122

2-methyl-3-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(4-methyl-3-((N-methylphenylsulfonamido)methyl)phenyl)propanoic acid

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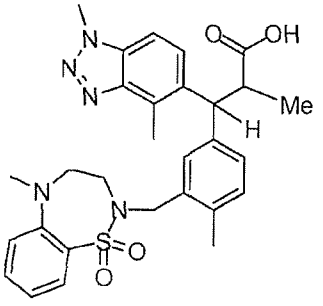
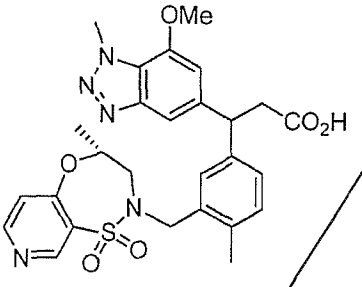


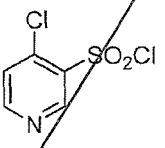
Ethyl 3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-2-methyl-3-(4-methyl-3-((5-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2,5]thiadiazepin-2(3H)-yl)methyl)phenyl)propanoate (99 mg, 0.172 mmol) was dissolved in THF (3 mL) and then

Example 128

3-(7-Methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(4-methyl-3-(((R)-4-methyl-1,1-dioxido-3,4-dihydro-2H-pyrido[4,3-b][1,4,5]oxathiazepin-2-yl)methyl)phenyl)propanoic acid

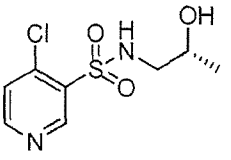


4-Chloropyridine-3-sulfonyl chloride



Pentachlorophosphorane (7.29 g, 35 mmol), phosphoryl trichloride (1.86 mL, 20 mmol) were added to 4-hydroxypyridine-3-sulfonic acid (1.75 g, 10 mmol). The mixture was stirred at 125 °C for 1 h. The solution was allowed to cool to 23 °C and then concentrated to remove excess $POCl_3$, diluted with Et_2O and poured onto ice. The residue was stirred for 5 min and then was neutralized with solid $NaHCO_3$, the mixture was extracted with EtOAc and combined extracts were dried (Na_2SO_4) and concentrated giving 2.02 g (95%) of the title compound. LC-MS *m/z* 211.8 $(M+H)^+$, 0.74 (ret. time).

3-(1-Benzyl-1H-1,2,3-triazol-4-yl)propanal



K_2CO_3 (0.36 g, 2.59 mmol) and 2-chloropyridine-3-sulfonyl chloride (0.5 g, 2.36 mmol) were added slowly to a solution of (R)-1-aminopropan-2-ol (0.2 g, 2.59 mmol) in THF (5 mL) and Water (2 mL). The reaction mixture was stirred at 23 °C for 1 h. The reaction mixture was diluted with H_2O, extracted with EtOAc. The combined extracts were

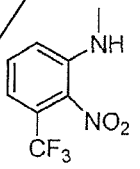
layers were dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (Hexane: EtOAc: 4:1) to give 1.0 g (6.37 %) of title compound.

N-Methyl-N-(2-nitro-3-(trifluoromethyl)phenyl)acetamide



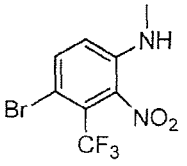
NaH (0.484 g, 20.15 mmol) was added to a solution of N-(2-nitro-3-(trifluoromethyl)phenyl)acetamide (5.0g, 20.15 mmol) in DMF (3 mL), NaH (0.484 g, 20.15 mmol). After 30 min, MeI (1.254 mL, 20.15 mmol) was added. The reaction mixture was stirred at RT for 1 h. A solution of aqueous $NaHCO_3$ was added, and then it was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and was filtered. The filtrate was concentrated under the reduced pressure. The crude product was purified by silica gel chromatography (hexane: EtOAc = 2: 1) to give 4.6 g (87 %) of title compound. LC-MS *m/z* 263.0 $(M+H)^+$, 1.65 (ret. time).

N-Methyl-2-nitro-3-(trifluoromethyl)aniline



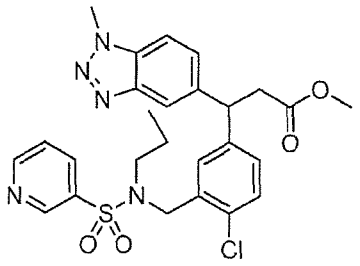
To a solution of N-methyl-N-(2-nitro-3-(trifluoromethyl)phenyl)acetamide (100 mg, 0.381 mmol) in EtOH (5 mL), solution of NaOH (100 mg, 2.500 mmol) in 2 mL of water was added. Then the reaction mixture was stirred at reflux temperature for 1 h. Then the reaction mixture was cooled to RT and the solvent was evaporated under reduced pressure. The crude product was diluted with water (50 mL), extracted with EtOAc (2x). The combined organic layers were dried over $MgSO_4$ and concentrated to give 40 mg, (47.6 %) of title compound.

4-Bromo-N-methyl-2-nitro-3-(trifluoromethyl)aniline

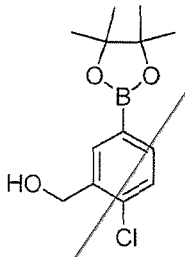


Example 137

Methyl 3-{4-chloro-3-[(N-propylpyridine-3-sulfonamido)methyl]phenyl}-3-(1-methyl-1H-1,2,3-benzotriazol-5-yl)propanoate

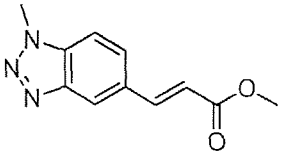


[2-Chloro-5-(3,3,4,4-tetramethyl-borolan-1-yl)-phenyl]-methanol



A stirred mixture of 5-bromo-2-chlorobenzyl alcohol (4.10 g, 18.0 mmol), bis(pinacolato)diboron (5.53 g, 21.6 mmol) and KOAc (7.05 g, 71.8 mmol) in dioxane was degassed with N_2, treated with $(PPh_3)_2PdCl_2$ (0.756 g, 1.08 mmol), and heated under reflux for 2.5 h. The reaction was diluted with water and extracted with EtOAc (x2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to dryness. The residue was purified by silica gel chromatography (50% DCM/petrol) to yield a colourless solid (3.5 g, 73%). A further fraction of slightly less pure material was isolated as a yellow oil (1.0 g, 12%). LCMS (M+18)+ 286/288(Cl), RT 1.38 min.

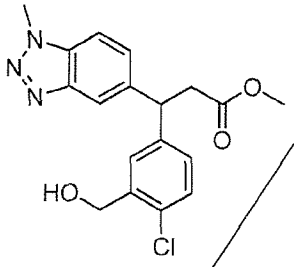
(E)-3-(1-Methyl-1H-benzotriazol-5-yl)-acrylic acid methyl ester



A stirred solution of t-BuOK (2.10 g, 18.6 mmol) in THF (100 mL) at 0 °C under N_2 was treated with trimethyl phosphonoacetate (4.30 g, 23.3 mmol). After 30 mins, 1-methyl-1H-1,2,3-benzotriazole-5-carbaldehyde (2.50 g, 15.5 mmol) was added slowly in

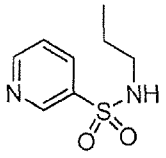
portions. After 1 h, the mixture was treated with NH_4Cl (aq., sat.), diluted with water and then extracted with n-heptane (x3), resulting in a precipitate which was isolated by filtration. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated to dryness, giving a beige solid which was washed with toluene and dried under vacuum. This material was combined with the precipitate above to give the product as a beige solid (3.1 g, 92%). LCMS $(M+H)^+$ 218, RT 1.12 min.

3-(4-Chloro-3-hydroxymethyl-phenyl)-3-(1-methyl-1H-benzotriazol-5-yl)-propionic acid methyl ester



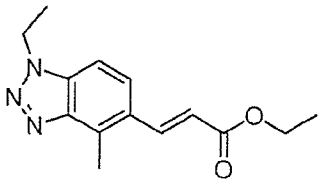
A stirred mixture of [2-Chloro-5-(3,3,4,4-tetramethyl-borolan-1-yl)-phenyl]-methanol (0.927 g, 3.45 mmol), (E)-3-(1-Methyl-1H-benzotriazol-5-yl)-acrylic acid methyl ester (0.500 g, 2.30 mmol),$[RhCl(cod)]_2$ (0.057 g, 0.12 mmol), Et_3N (0.349 g, 3.45 mmol), 1,4-dioxane (1.2 mL) and water (7.7 mL) was heated at 95 °C for 6 h. Additional [2-Chloro-5-(3,3,4,4-tetramethyl-borolan-1-yl)-phenyl]-methanol (0.5 eq) and $[RhCl(cod)]_2$ (0.050 g, 0.10 mmol) were added and the mixture heated again for 16 h. The mixture was diluted with water and extracted with $CHCl_3$:IPA (3:1, x3). The combined organic layers were washed successively with water and brine, dried over $MgSO_4$, filtered and concentrated to dryness. The residue was taken up into MeOH and the solution treated with 2 drops conc. HCl, then stirred under reflux for 4 h. Concentration to dryness followed by purification by silica gel chromatography (100% DCM) gave the product as a white solid (0.560 g, 68%). LCMS $(M+H)^+$ 360/362(Cl), RT 1.18 min.

Pyridine-3-sulfonic acid propylamide



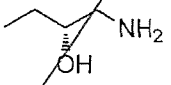
A stirred solution of 3-pyridylsulfonyl chloride hydrochloride (0.240 g, 1.12 mmol) and iPr_2NEt (0.217 g, 1.68 mmol) in DCM (4 mL) at 4°C was treated with n-propylamine

(E)-ethyl 3-(1-ethyl-4-methyl-1H-benzo[d][1,2,3]triazol-5-yl)acrylate



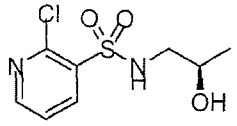
A mixture of tri-o-tolylphosphine (0.849 g, 2.79 mmol), ethyl acrylate (5.59 g, 55.8 mmol), 5-bromo-1-ethyl-4-methyl-1H-benzo[d][1,2,3]triazole (6.7 g, 27.9 mmol), $Pd(OAc)_2$ (0.313 g, 1.395 mmol), and K_2CO_3 (7.71 g, 55.8 mmol) in DMF (50 mL) was stirred at 120 °C for 12 h. The reaction mixture was poured into water and extracted with EtOAc (3 x 30 mL). The organic layer was dried and concentrated. The product was purified over a silica gel column and eluted with hexane:EtOAc (4: 1) to give the title compound (E)-ethyl 3-(1-ethyl-4-methyl-1H-benzo[d][1,2,3]triazol-5-yl)acrylate (5 g, 18.50 mmol, 66.3 % yield). LC-MS *m/z* 260.2 $[(M+H)^+$, 1.63 (ret. time).

(R)-1-aminobutan-2-ol



To a solution of NH_4OH (~28% solution in H_2O) (21.60 mL, 555mmol) was added (R)-2-ethyloxirane (4 g, 55.5 mmol). The resulting reaction mixture was stirred at RT for 20 h. The reaction mixture was concentrated under reduced pressure to afford the desired product (R)-1-aminobutan-2-ol (4.5 g, 50.5 mmol, 91 % yield). ^1H NMR (400 MHz, CHLOROFORM-d) δppm 0.97 (t, J=7.53 Hz, 3 H) 1.42 - 1.53 (m, 2 H) 1.71 (br. s., 3 H) 2.47 - 2.59 (m, 1 H) 2.85 (dd, J=12.80, 3.26 Hz, 1 H) 3.39 - 3.49 (m, 1 H).

(R)-2-chloro-N-(2-hydroxypropyl)pyridine-3-sulfonamide

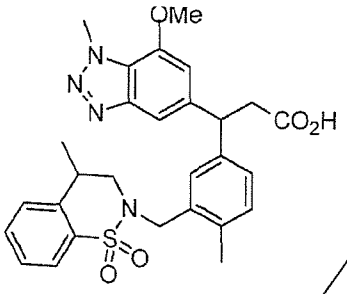


To a solution of (R)-1-amino-2-butanol (2.5 g, 28.0 mmol) in THF (80 mL) and water (16 mL) was added K_2CO_3 (2.477 g, 17.92 mmol) followed by 2-chloropyridine-3-sulfonyl chloride (3.8 g, 17.92 mmol). The resulting reaction mixture was stirred at RT for 5 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with brine (15 mL), dried over $MgSO_4$ and

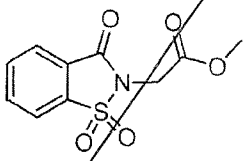
neutral conditions to provide the title compound (0.023 g, 0.043 mmol, 63%) LC-MS *m/z* 514.0 $(M+H)^+$, 0.90 min (ret. time).

Example 155

3-(7-Methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(4-methyl-3-((4-methyl-1,1-dioxido-3,4-dihydro-2H-benzo[e][1,2]thiazin-2-yl)methyl)phenyl)propanoic acid

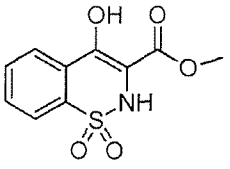


Methyl 2-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)acetate



To a solution of sodium 3-oxo-3H-benzo[d]isothiazol-2-ide 1,1-dioxide (15g, 73.1 mmol) in DMF (30 mL) was added sodium 3-oxo-3H-benzo[d]isothiazol-2-ide 1,1-dioxide (15g, 73.1 mmol).The mixture was stirred at 100 °C for 3 h, cooled to RT and poured into cooled water, resulting in an immediate formation of solid. The solid was filtered and washed with water,dried and recrystallized from MeOH. LC-MS: *m/z* 256$(M+H)^+$ 1.43 min (ret. time).

Methyl 4-hydroxy-2H-benzo[e][1,2]thiazine-3-carboxylate 1,1-dioxide

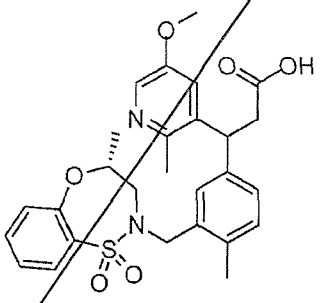


NaOMe (8.25 g, 153 mmol) was suspended in dry DMF (20 mL). and then added to a solution of methyl 2-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)acetate (13 g, 50.9 mmol) in DMF (5 mL) at 0 °C over 7 min. Upon complete addition of the NaOMe the reaction mixture was allowed to stir for additional 30 min. The product was precipitated

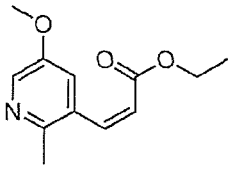
methylphenyl)propanoate (300 mg, 0.503 mmol) in EtOH (20 mL)was added 10% NaOH (20 mL) at 0 °C. Then the reaction mixture was stirred at RT for 2 h. The reaction mixture was then evaporated under reduced pressure, neutralized with 1N HCl, and extracted with DCM (2X). The organic layer was dried under anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure to get 280 mg of crude compound. The crude compound was purified by flash column chromatography(2X) using MeOH:DCM (0.5:9.5) as solvent system, to afford 3-(2-((dimethylamino)methyl)-4-fluoro-6-methylphenyl)-3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)propanoic acid (53 mg, 0.091 mmol). LC-MS *m/z* 569.28 $(M+H)^+$, 2.14 min (ret. time).

Example 161

3-(5-Methoxy-2-methylpyridin-3-yl)-3-(4-methyl-3-(((R)-4-methyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)phenyl)propanoic acid



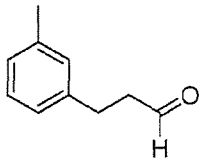
(Z)-Ethyl 3-(5-methoxy-2-methylpyridin-3-yl)acrylate



To a solution of 3-bromo-5-methoxy-2-methylpyridine (500 mg, 2.475 mmol) in DMF (3 mL) was added methyl acrylate ethyl acrylate (1239 mg, 12.37 mmol), tri-o-tolylphosphine (226 mg, 0.742 mmol), DIPEA (1.729 mL, 9.90 mmol) and $Pd(OAc)_2$ (5.56 mg, 0.025 mmol) at RT and stirred under microwave irradiation at 120 °C for 1.30 h. The reaction was cooled to RT, filtered through celite and washed with EtOAc (50 mL). The filtrate was washed with a brine solution (100 mL) and dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under vacuum. The residue was purified by flash

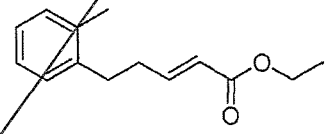
To a solution of 3-(m-tolyl)propanoic acid (2 g, 12.18 mmol) in THF (50 mL) was added 2 M LAH in THF (30 mL, 30.5 mmol) at 0 °C under nitrogen atmosphere and strirred at RT for 2 h. The reaction mixture was quenched with saturated, extracted with EtOAc (2X), the organic layer was dried under anhydrous Na_2SO_4 and filtered. The filtrate was evaporated and the crude residue was purified by flash column chromtography by using EtOAc : hexane (20:80) to afford 3-(m-tolyl)propan-1-ol (1.4 g, 9.29 mmol, 76 % yield). LC-MS *m/z* 151 $(M+H)^+$, 2.03min (ret. time).

3-(m-Tolyl)propanal



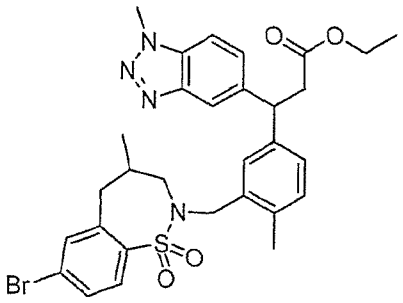
To a solution of 3-(m-tolyl)propan-1-ol (1.4 g, 9.32 mmol) in DCM (20 mL), at 0 °C was added PCC (3.01 g, 13.98 mmol) then brought RT and stirred at RT for 3 h. The crude residue was filterd through celite, and the solvent was evaporated to afford 3-(m-tolyl)propanal (1.2 g, 8.10 mmol, 87 % yield). ^1H NMR (400 MHz, DMSO-d6) δ ppm 9.65 (bs, 1H), 6.85-7.20 (m, 4H), 2.90-2.20 (m, 7H).

(E)-Ethyl 5-(o-tolyl)pent-2-enoate



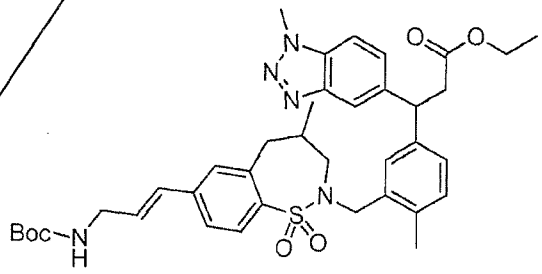
To a suspension of NaH (0.486 g, 20.24 mmol) in THF (15 mL) was added triethyl phosphonoacetate (1.945 mL, 9.72 mmol) at 0 °C and stirred for 15 min.Then 3-(o-tolyl)propanal (1.2 g, 8.10 mmol) in THF (3 mL) was added to the reaction mixture and stirred at RT and stirred for 2 h. The reaction mixture was quenched with cold water, extracted with EtOAc (2X), brine, the organic layer was dried under anhydrous Na_2SO_4 and filtered. The filtrate was concentrated. the crude residue was purified on flash column chromtography by using EtOAc : hexane (80:20) to afford (E)-ethyl 5-(o-tolyl)pent-2-enoate (500 mg, 1.397 mmol, 17.25 % yield) LC-MS *m/z* 219 $(M+H)^+$, 2.82min (ret. time).

2,4-Dibromo-N-(2-methylallyl)benzenesulfonamide



To a solution of 7-bromo-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-dioxide (500 mg, 1.723 mmol) in THF (20 mL) was added ethyl 3-(3-(hydroxymethyl)-4-methylphenyl)-3-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate (609 mg, 1.723 mmol), triphenylphosphine (452 mg, 1.723 mmol) and DEAD (0.273 mL, 1.723 mmol) at 0 °C. The reaction was stirred at RT for 3 h. The reaction mixture was cooled to 0 °C and quenched with water, extracted with EtOAc (2X). The organic layer washed with brine, dried under anhydrous Na_2SO_4 and filtered. The filtrate was evaporated and was purified by column chromatography using EtOAc : hexane (30:70) to afford ethyl 3-(3-((7-bromo-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)methyl)-4-methylphenyl)-3-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate (400 mg, 0.613 mmol, 35.6 % yield). LC-MS *m/z* 624 $(M+H)^+$, 2.83 min (ret. time).

(E)-Ethyl 3-(3-((7-(3-((tert-butoxycarbonyl)amino)prop-1-en-1-yl)-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)methyl)-4-methylphenyl)-3-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate

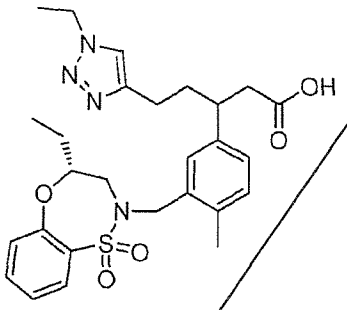


To solution of ethyl 3-(3-((7-bromo-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)methyl)-4-methylphenyl)-3-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl) propanoate (1.5 g, 2.398 mmol) in DMF (4 mL) was added tert-butyl allylcarbamate (0.565 g, 3.60 mmol), tri-o-tolylphosphine (0.219 g, 0.719 mmol) and DIPEA (1.256 mL, 7.19 mmol) in a microwave reactor. The mixture was degassed with

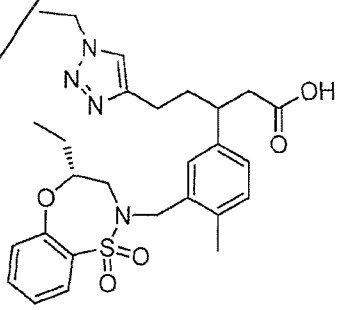
The desired fractions were pooled based on LCMS analysis of all the fractions individually and then pooling those fractions from the major peak with > 90% of the m/z = 541 peak. The pooled fractions were concentrated *in vacuo* to afford 3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)-2-methylpentanoic acid (12 mg, 0.022 mmol, 33.1 % yield) LC-MS *m/z* = 542.4 $(M+H)^+$, 1.02 min (ret time). Analytical sfc analysis indicates the product is a mixture of two isomers presumeably with the same relative stereochemistry at the pentanoate C-2 and C-3 but with opposite absolute stereochemistry at these atoms.

Example 194

3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)pentanoic acid (isomer M1) and 3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)pentanoic acid (isomer N1)

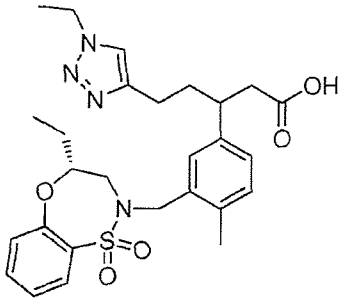


isomer M1



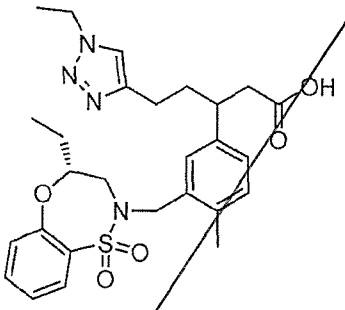
isomer N1

3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)-2-methylpentanoate

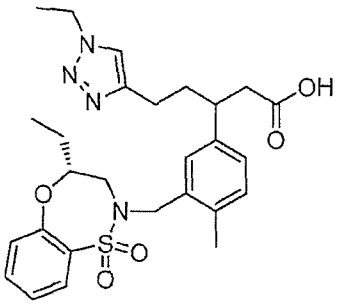


60 mg of ethyl 3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)-2-methylpentanoate was dissolved in MeOH (2 mL). 2M LiOH (3.09 mL, 6.18 mmol) was added and the reaction mixture was heated in a Biotage microwave at high absorption for 30 min at 80 °C. 0.8 mL of 1 N HCl and 1.5 mL of DMSO were added. Most of the solvent was removed at reduced pressure and the sample was purified via reverse phase chromatography (Sunfire C18, 19x100mm, 5u; mobile phase A = Water+0.1% TFA:Mobile phase B = MeCN +0.1% TFA; 18 mL/min; 35%B to 65% B in 10 min) to afford 62 mg of the mixture of isomers 3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)-2-methylpentanoate.

(R)-3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)pentanoic acid (isomer M1) and (S)-3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)pentanoic acid (isomer N1)



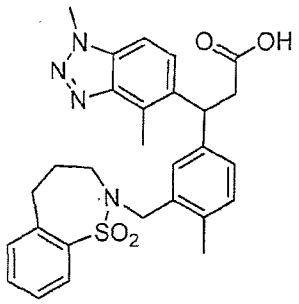
isomer M1



isomer N1

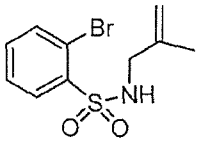
62 mg of the mixture of isomers 3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)-2-methylpentanoate was separated by chiral supercritical fluid chromatography (Chiralpak AD, 20x250mm, 5µ; 20% EtOH; 50g/min; 100bar) to afford:
isomer M1 (15mg) 3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)pentanoic acid LC-MS *m/z* 527.4 $(M + H)^+$, 1.02 (ret. time). **isomer N1** (15 mg) (S)-3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)pentanoic acid LC-MS *m/z* 527.4 $(M + H)^+$, 1.02 (ret. time)

3-(1,4-Dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(3-((1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)methyl)-4-methylphenyl)propanoic acid



To a solution of ethyl 3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(3-((1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)methyl)-4-methylphenyl)propanoate (101 mg, 0.185 mmol), ethyl 3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(4-methyl-3-((4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)methyl)phenyl)propanoate (100 mg, 0.178 mmol) in MeOH (2 mL) at RT was added 2 M LiOH (0.554 mL, 1.109 mmol). The reaction mixture was heated in a Biotage microwave at high absorption for 30 min at 85 °C. 1N HCl (1.109 mL, 1.109 mmol) and 1 mL of DMSO were added and concentrated. The reaction mixture was purified with reverse-phase HPLC under acidic conditions to give the title compound (82.2 mg, 0.154 mmol, 84 % yield). LC-MS *m/z* 519.2 $(M+H)^+$, 1.05 min (ret. time)

2-Bromo-N-(2-methylallyl)benzenesulfonamide

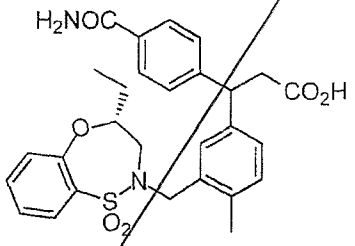


To a solution of 2-bromobenzene-1-sulfonyl chloride (5 g, 19.6 mmol) in DCM (100 mL) was added TEA (5.5 mL, 39.2 mmol) at 0 °C. After 10 min, 2-methyl allylamine (1.3 g, 21.5 mmol) was added at 0 °C, then stirred at RT overnight. The reaction mixture was diluted with water (100 mL) and extracted with DCM (2 x 100 mL). The combined organic layer washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the title compound (3.5 g, 62 %) as solid. LC-MS *m/z* 287.99 $(M)^+$, 1.993 min (ret. time)

0.300 mmol), Et_3N (0.084 mL, 0.600 mmol) and $[RhCl(cod)]_2$ (3.70 mg, 7.50 µmol). The resulting reaction mixture was stirred at 90 °C for 2 h. The reaction mixture was evaporated down under vacuum. This intermediate was redissolved in MeOH (2 mL). To the resulting solution was added NaOH (3 N) (0.400 mL, 1.200 mmol) and the mixture heated with microwave irradiation at 80 °C for 20 min. The reaction mixture was acidified with HCl (3 N) to pH 4~5, evaporated down under vacuum, and purified with reverse phase HPLC to afford desired product 3-(4-chlorophenyl)-3-(4-methyl-3-(((R)-4-methyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)phenyl)propanoic acid (44.9 mg, 0.090 mmol, 59.9 % yield). LC-MS *m/z* 500.3 $(M+H)^+$, 1.18 min (ret. time).

Example 241

3-(4-Carbamoyl-2-methylphenyl)-3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)propanoic acid



To a solution of methyl 3-(4-cyano-2-methylphenyl)-3-(3-(hydroxymethyl)-4-methylphenyl)propanoate (50 mg, 0.155 mmol) in THF (2 mL) was added (R)-4-ethyl-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide (52.7 mg, 0.232 mmol), PS-PPh_3 (193 mg, 0.309 mmol) and DIAD (0.060 mL, 0.309 mmol). The resulting reaction mixture was stirred at RT for 30 min. The reaction mixture was filtered, evaporated down under vacuum. This intermediate was redissolved in EtOH (2 mL). To the resulting solution was added NaOH (2 N) (0.541 mL, 1.082 mmol) and H_2O_2 (~30%) (0.111 mL, 1.082 mmol). The resulting reaction mixture was stirred at RT for 17 h. The reaction mixture was acidified with HCl (1 N) to pH ~5, evaporated down under vacuum, and purified with reverse phase HPLC to afford desired product 3-(4-carbamoyl-2-methylphenyl)-3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)propanoic acid (29.5 mg, 0.055 mmol, 35.6 % yield). LC-MS *m/z* 537.3 $(M+H)^+$, 0.97 min (ret. time).

or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising the compound or pharmaceutically acceptable salt according to any one of claims 1-13 and a pharmaceutically acceptable carrier or excipient.

15. A method of treating respiratory and non-respiratory disorders, including COPD, asthma, fibrosis, chronic and acute asthma, lung disease secondary to environmental exposures, acute lung infection, chronic lung infection, α1 antitrypsin disease, cystic fibrosis, autoimmune diseases, diabetic nephropathy, chronic kidney disease, sepsis-induced acute kidney injury, acute kidney injury (AKI), kidney disease or malfunction seen during kidney transplantation, Pulmonary Arterial Hypertension, atherosclerosis, hypertension, heart failure, Parkinson's disease (PD), Alzheimer's disease (AD), autism, Friedreich's Ataxia (FA), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), inflammatory bowel disease, colon cancer, neovascular (dry) AMD and neovascular (wet) AMD, eye injury, Fuchs Endothelial Corneal Dystrophy (FECD), uveitis or other inflammatory eye condtions, Nonalcoholic Steatohepatitis (NASH), toxin-induced liver disease (e.g., acetaminophen-induced hepatic disease), viral hepatitis, cirrhosis, psoriasis, dermatitis/topical effects of radiation, immunosuppression due to radiation exposure, Preeclampsia, and high altitude sickness, which comprises administering to a human in need thereof, the compound or pharmaceutically acceptable salt according to any one of claims 1-13.

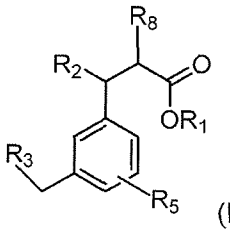
16. The method according to claim 15 wherein the compound is administered orally.

17. The method according to claim 15 wherein the compound is administered intravenously.

18. The method according to claim 15 wherein the compound is administered by inhalation.

19. The method according to claim 15 wherein the disorder is COPD.

20. A compound of formula (Ia)



(Ia)

Wherein:

R_1 is hydrogen, CH_2 $C(O)N(R_7)_2$, CH_2-(4- methyl-1,3 dioxol-2-one), C_{1-3} alkyl-OH, C_{1-3} alkyl, C_{1-5} alkyl-$N(R_7)_2$, $(CH_2)_n$–morpholinyl, $(CH_2)_n$-furyl, CH_2-O-C(O)–C_{1-5} alkyl, $(CH_2)_n$–imidazolyl, $(CH_2)_n$–pyrrolidinyl, $(CH_2)_n$-Piperidyl or 2-oxotetrahydrofura-3-nyl;

Wherein the morpholinyl, and piperidyl may be substituted by one or two C_{1-3} alkyl;

and the pyrrolidinyl, imidazolyl and furyl may be substituted by one or two C_{1-3} alkyl, halo, or O-C_{1-3} alkyl;

R_2 is Phenyl, which may be substituted by one, two, or three CN, F, $C(O)NH_2$, $C(O)CH_3$), O-C_{1-3} alkyl, C_{1-3} alkyl, CF_3, or O-CF_3;

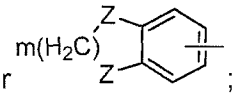
Benzotriazolyl, which may be substituted by one, two or three -O-C_{1-3} alkyl, F, Cl, CF_3, OCF_3 or C_{1-3} alkyl;

$(CH_2)_n$-Triazolyl which may be substituted by one or two C_{1-3} alkyl or -CH_2-phenyl;

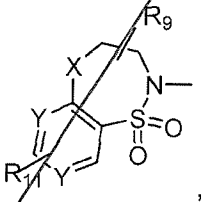
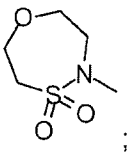
Pyridyl which may be substituted by one, two, or three C_{1-3} alkyl, F, OCH_3, or =O;

or triazolo pyridyl which may be substituted by one or two -O-C_{1-3} alkyl, F, or C_{1-3} alkyl;

R_3 is R_4-SO_2–$N(R_6)$-;

R_4 is Phenyl, C_{5-6} cycloalkyl, Thienyl, Imidazolyl, Pyridyl, Piperidyl, Tetrahydro–2H-pyranyl, C_{1-3} alkyl or  ;

All of which may be substituted by one or two C_{1-3} alkyl, NH–C (O)-CH_3, O-C_{1-3}alkyl, C(O)-CH_3, =O, or OH;

or R_3 is  ,or  ;

X is CH_2, NR_6 or O;

Y is independently N or CH; provided one Y is CH;

Z is independently O, CH_2, or NR_{10};

R_5 is hydrogen, C_{1-3} alkyl, Cl, F, or CF_3

R_6 is independently hydrogen or C_{1-3} alkyl;

R_7 is independently hydrogen or C_{1-3} alkyl;

R_8 is hydrogen or C_{1-3} alkyl;

R_9 is hydrogen or C_{1-3} alkyl;

R_{10} is $C(O)$-CH_3;

R_{11} is hydrogen or F;

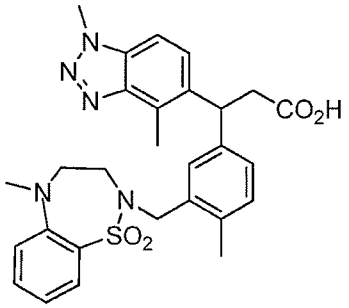
n is independently 0, 1, 2, or 3; and

m is 1 or 2;

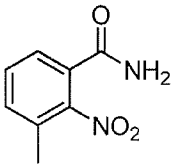
or a pharmaceutically acceptable salt thereof.or a pharmaceutically acceptable salt thereof.

Example 2

3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(4-methyl-3-((5-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2,5]thiadiazepin-2(3H)-yl)methyl)phenyl)propanoic acid

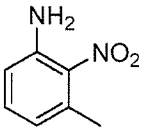


3-methyl-2-nitrobenzamide



To a solution of 3-methyl-2-nitrobenzoic acid (100 g, 552 mmol) in DCM (1000 mL), oxalyl chloride (72.5 mL, 828 mmol) was added at 25 °C. The reaction mixture was stirred at RT for 1 h. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL). The solvent was added to NH_4OH (1000 mL, 7704 mmol) at RT and was stirred for 30 min. Then the reaction mixture was extracted with EtOAc (3 x 500 mL). The combined organic layer was dried over MgSO4 and concentrated to give 67 g (60.6%) of the title compound. LC-MS *m/z* 181.1 $(M+H)^+$, 1.40 (ret. time).

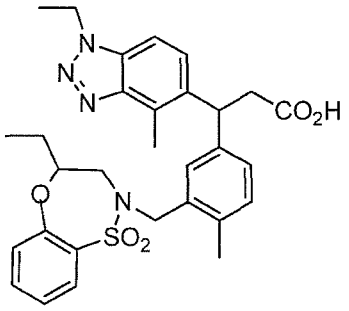
3-Methyl-2-nitroaniline



To a mixture of NaOH (2.220 g, 55.5 mmol) in water (12 mL), Br_2 (0.322 mL, 6.26 mmol) was added at 0 °C. Then 3-methyl-2-nitrobenzamide (1g, 5.55 mmol) was added in one portion, and the mixture is warmed slowly in a water bath. The material soon darkens in color, and at 50-55° C (internal temperature) oil droplets begin to separate. The

Example 35

3-(3-((4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-3-(1-ethyl-4-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid

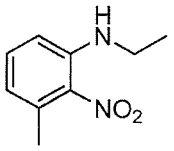


1-Fluoro-3-methyl-2-nitrobenzene



To a solution of 2-fluoro-6-methylaniline (8.5 g, 67.9 mmol) in DCE (150 mL), m-CPBA (58.6 g, 272 mmol) was added slowly under nitrogen at RT. The reaction mixture was stirred at 70 °C for 4 h. DCM (500 mL) was added. Then it was washed with 1N NaOH (200 mL x4). The combined organic layers was dried and concentrated under a stream of nitrogen at 50 °C to give 11.2 g (65.9%) of the title compound.

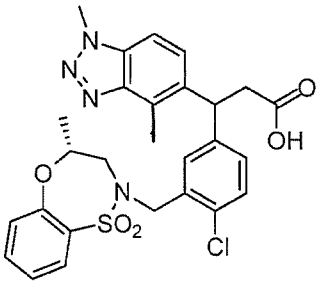
N-Ethyl-3-methyl-2-nitroaniline



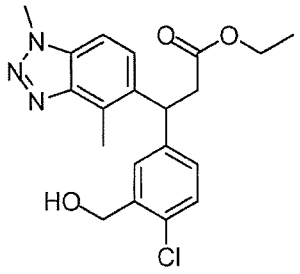
To a solution of 1-fluoro-3-methyl-2-nitrobenzene (11.2 g, 72.2 mmol) in EtOH (80 mL), ethanamine (80 mL, 911 mmol) was added slowly under nitrogen at RT. The reaction mixture was stirred at 60 °C for 16 h. Water (100 mL) was added. Then it was extracted with EtOAc (3x80 mL). The combined organic layers was dried and concentrated under a stream of nitrogen at 50 °C. The crude product was purified by

Example 72

3-(4-chloro-3-(((R)-4-methyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)phenyl)-3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid



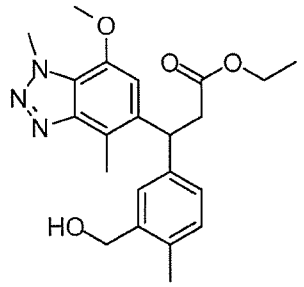
Ethyl 3-(4-chloro-3-(hydroxymethyl)phenyl)-3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate



To a suspension of (E)-ethyl 3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)acrylate (300 mg, 1.223 mmol),(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (657 mg, 2.446 mmol) Et_3N (0.707 mL, 5.10 mmol) in 1,4-dioxane (20 mL) and water (10 mL) at RT was added $[RhCl(cod)]_2$ (33.8 mg, 0.061 mmol). The resulting suspension was heated at 95 °C for 1 h. The reaction mixture was diluted with water and extracted with EtOAc (3x). The combined organic phases were washed with water (3x), brine (1x), dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified on a silica cartridge (40 g) with a Combiflash Companion, eluting at 35 mL/min with a gradient running from 0 % EtOAc/hexanes to 70 % over 35 min. LC-MS *m/z* 388.0 $(M+H)^+$, 0.92 (ret. time).

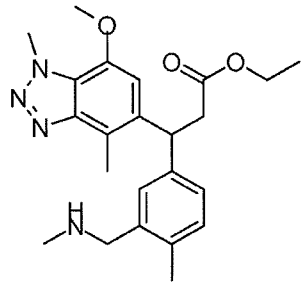
to 80% EtOAc/Hexanes over 35 min) to give 950 mg (88%) of the title compound. LC-MS *m/z* 276.0 $(M+H)^+$, 0.97 (ret. time).

Ethyl 3-(3-(hydroxymethyl)-4-methylphenyl)-3-(7-methoxy-1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate



To (E)-ethyl 3-(7-methoxy-1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)acrylate (150 mg, 0.545 mmol) in 1,4-dioxane (10 mL) and water (5.00 mL) was added (3-(hydroxymethyl)-4-methylphenyl)boronic acid (163 mg, 0.981 mmol), Et_3N (83 mg, 0.817 mmol) and $[RhCl(cod)]_2$ (13.43 mg, 0.027 mmol). The result reaction mixture was stirred at 95 °C for 1 h. The reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated then, the product was purified over a silica cartridge (40 g) using Combiflash Companion eluting at 18 mL/min running a gradient of 0-30% EtOAc/hexane over 30 min then, 30% to 100% over 20 min to give 170 mg (70%) of the title compound. LC-MS m/z 398.2$(M+H)^+$, 0.93 (ret. time).

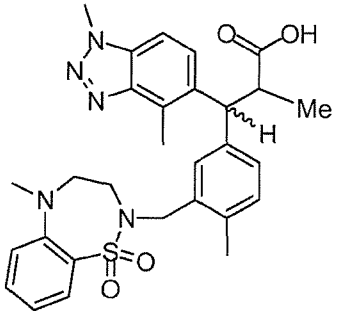
Ethyl 3-(7-methoxy-1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(4-methyl-3-((methylamino)methyl)phenyl)propanoate



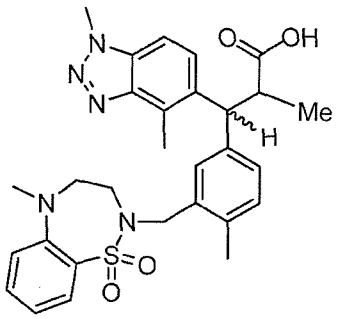
To a solution of ethyl 3-(3-(hydroxymethyl)-4-methylphenyl)-3-(7-methoxy-1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate (350 mg, 0.881 mmol) dissolved in DCM (6 mL) was added thionyl chloride (0.096 mL, 1.321 mmol) and the mixture was stirred at RT for 48 h. After checking LC-MS, the mixture was evaporated down with V10 evaporator under vacuum to get 326 mg crude of ethyl 3-(3-(chloromethyl)-4-

Example 120

3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(4-methyl-3-((5-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2,5]thiadiazepin-2(3H)-yl)methyl)phenyl)propanoic acid

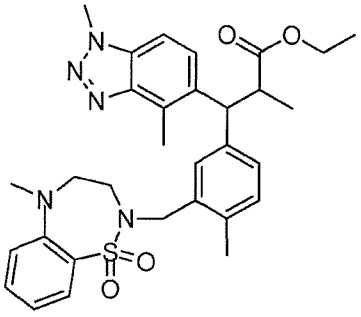


Diastereomer 1
Example 121



Diastereomer 2
Example 122

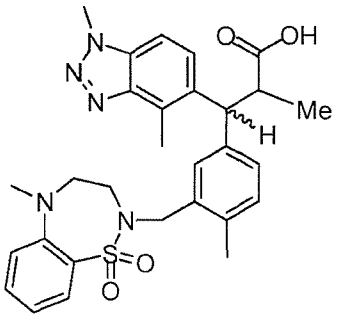
Ethyl 3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-2-methyl-3-(4-methyl-3-((5-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2,5]thiadiazepin-2(3H)-yl)methyl)phenyl)propanoate



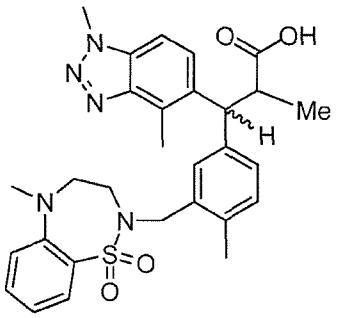
A 2M n-BuLi in hexanes solution (1.100 mL, 2.200 mmol) is added to a dry-ice acetone bath cooled solution (~ - 70 °C) of diisopropylamine (0.381 mL, 2.67 mmol) in THF (2 mL). The clear solution was stirred at dry-ice acetone bath temp for 10 min and then was warmed on an ice-water bath and stirred for 10 min to afford 0.63 M LDA.

A portion of the 0.63M LDA (0.367 mL, 0.231 mmol) diluted with THF (1 mL) was cooled on a dry-ice acetone bath and ethyl 3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(4-methyl-3-((5-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2,5]thiadiazepin-2(3H)-yl)methyl)phenyl)propanoate (100 mg, 0.178 mmol) dissolved in THF (2 mL) was added dropwise (T < -65 °C). The red solution was stirred with dry-ice acetone cooling for 30 min and then the dry-ice acetone bath was replaced with a dry-ice CH_3CN bath (~ -40 °C)

and the red solution was stirred for 15 min, MeI (0.223 mL, 3.56 mmol) was added in one portion and the yellow solution was warmed to 23 °C and stirred 15 min. The volatiles were removed *in vacuo* and the residue was diluted with EtOAc (75 mL) and washed with 0.5 M aqueous HCl (25 mL) and saturated aq NaCl (25 mL), dried Na_2SO_4 and concentrated to afford 103 mg of a brown foam. The crude product was dissolved in CH_3CN (4 mL), filtered through a 0.45 mm acrodisc, and purified by reverse-phase HPLC (YMC C18 S-5 mm/12 nm 50 x 20 mm preparatory column), eluting at 20 mL/min with a linear gradient running from 20% CH_3CN/H_2O (0.1% TFA) to 90% CH_3CN/H_2O (0.1% TFA) over 10 min. The desired fractions were concentrated *in vacuo* to afford 99 mg (97 %) of the title compound as a mixture of isomers. LC-MS *m/z* 576.3 $(M+H)^+$, 1.20 (ret. time).

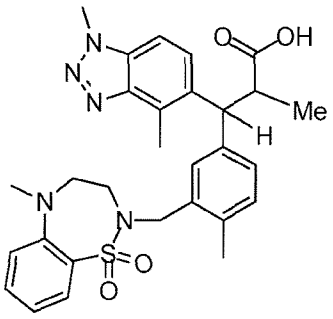


Diastereomer 1
Example 121



Diastereomer 2
Example 122

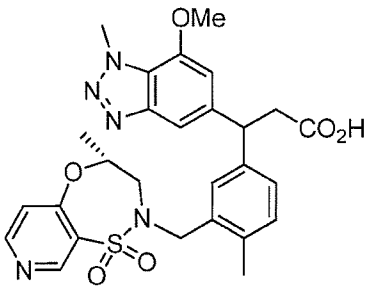
3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(4-methyl-3-((5-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2,5]thiadiazepin-2(3H)-yl)methyl)phenyl)propanoic acid



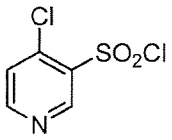
Ethyl 3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-2-methyl-3-(4-methyl-3-((5-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2,5]thiadiazepin-2(3H)-yl)methyl)phenyl)propanoate (99 mg, 0.172 mmol) was dissolved in THF (3 mL) and then

Example 128

3-(7-Methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(4-methyl-3-(((R)-4-methyl-1,1-dioxido-3,4-dihydro-2H-pyrido[4,3-b][1,4,5]oxathiazepin-2-yl)methyl)phenyl)propanoic acid

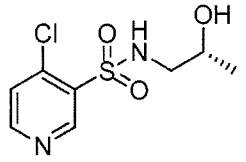


4-Chloropyridine-3-sulfonyl chloride



Pentachlorophosphorane (7.29 g, 35 mmol), phosphoryl trichloride (1.86 mL, 20 mmol) were added to 4-hydroxypyridine-3-sulfonic acid (1.75 g, 10 mmol). The mixture was stirred at 125 °C for 1 h. The solution was allowed to cool to 23 °C and then concentrated to remove excess $POCl_3$, diluted with Et_2O and poured onto ice. The residue was stirred for 5 min and then was neutralized with solid $NaHCO_3$, the mixture was extracted with EtOAc and combined extracts were dried (Na_2SO_4) and concentrated giving 2.02 g (95%) of the title compound. LC-MS *m/z* 211.8 $(M+H)^+$, 0.74 (ret. time).

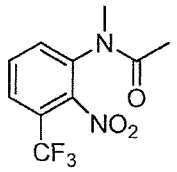
(R)-4-chloro-N-(2-hydroxypropyl)pyridine-3-sulfonamide



K_2CO_3 (0.36 g, 2.59 mmol) and 2-chloropyridine-3-sulfonyl chloride (0.5 g, 2.36 mmol) were added slowly to a solution of (R)-1-aminopropan-2-ol (0.2 g, 2.59 mmol) in THF (5 mL) and Water (2 mL). The reaction mixture was stirred at 23 °C for 1 h. The reaction mixture was diluted with H_2O, extracted with EtOAc. The combined extracts were

layers were dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (Hexane: EtOAc: 4:1) to give 1.0 g (6.37 %) of title compound.

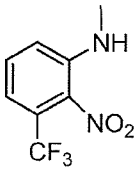
N-Methyl-N-(2-nitro-3-(trifluoromethyl)phenyl)acetamide



NaH (0.484 g, 20.15 mmol) was added to a solution of N-(2-nitro-3-(trifluoromethyl)phenyl)acetamide (5.0g, 20.15 mmol) in DMF (3 mL).

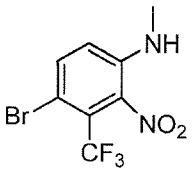
After 30 min, MeI (1.254 mL, 20.15 mmol) was added. The reaction mixture was stirred at RT for 1 h. A solution of aqueous $NaHCO_3$ was added, and then it was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and was filtered. The filtrate was concentrated under the reduced pressure. The crude product was purified by silica gel chromatography (hexane: EtOAc = 2: 1) to give 4.6 g (87 %) of title compound. LC-MS *m/z* 263.0 $(M+H)^+$, 1.65 (ret. time).

N-Methyl-2-nitro-3-(trifluoromethyl)aniline



To a solution of N-methyl-N-(2-nitro-3-(trifluoromethyl)phenyl)acetamide (100 mg, 0.381 mmol) in EtOH (5 mL), solution of NaOH (100 mg, 2.500 mmol) in 2 mL of water was added. Then the reaction mixture was stirred at reflux temperature for 1 h. Then the reaction mixture was cooled to RT and the solvent was evaporated under reduced pressure. The crude product was diluted with water (50 mL), extracted with EtOAc (2x). The combined organic layers were dried over $MgSO_4$ and concentrated to give 40 mg, (47.6 %) of title compound.

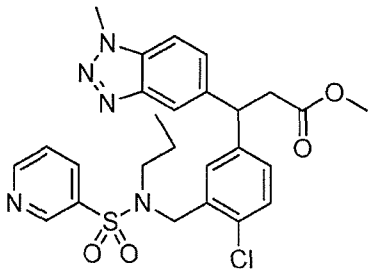
4-Bromo-N-methyl-2-nitro-3-(trifluoromethyl)aniline



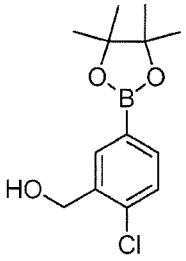
305

Example 137

Methyl 3-{4-chloro-3-[(N-propylpyridine-3-sulfonamido)methyl]phenyl}-3-(1-methyl-1H-1,2,3-benzotriazol-5-yl)propanoate

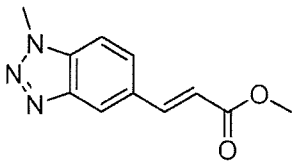


[2-Chloro-5-(3,3,4,4-tetramethyl-dioxaborolan-1-yl)-phenyl]-methanol



A stirred mixture of 5-bromo-2-chlorobenzyl alcohol (4.10 g, 18.0 mmol), bis(pinacolato)diboron (5.53 g, 21.6 mmol) and KOAc (7.05 g, 71.8 mmol) in dioxane was degassed with N_2, treated with $(PPh_3)_2PdCl_2$ (0.756 g, 1.08 mmol), and heated under reflux for 2.5 h. The reaction was diluted with water and extracted with EtOAc (x2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to dryness. The residue was purified by silica gel chromatography (50% DCM/petrol) to yield a colourless solid (3.5 g, 73%). A further fraction of slightly less pure material was isolated as a yellow oil (1.0 g, 12%). LCMS (M+18)+ 286/288(Cl), RT 1.38 min.

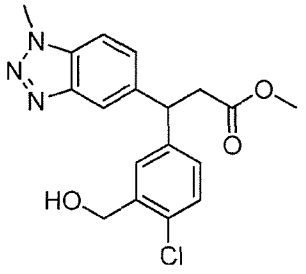
(E)-3-(1-Methyl-1H-benzotriazol-5-yl)-acrylic acid methyl ester



A stirred solution of t-BuOK (2.10 g, 18.6 mmol) in THF (100 mL) at 0 °C under N_2 was treated with trimethyl phosphonoacetate (4.30 g, 23.3 mmol). After 30 mins, 1-methyl-1H-1,2,3-benzotriazole-5-carbaldehyde (2.50 g, 15.5 mmol) was added slowly in

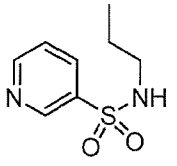
portions. After 1 h, the mixture was treated with NH_4Cl (aq., sat.), diluted with water and then extracted with n-heptane (x3), resulting in a precipitate which was isolated by filtration. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated to dryness, giving a beige solid which was washed with toluene and dried under vacuum. This material was combined with the precipitate above to give the product as a beige solid (3.1 g, 92%). LCMS $(M+H)^+$ 218, RT 1.12 min.

3-(4-Chloro-3-hydroxymethyl-phenyl)-3-(1-methyl-1H-benzotriazol-5-yl)-propionic acid methyl ester



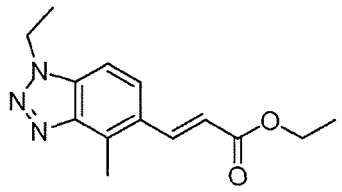
A stirred mixture of [2-Chloro-5-(3,3,4,4-tetramethyl-dioxaborolan-1-yl)-phenyl]-methanol (0.927 g, 3.45 mmol), (E)-3-(1-Methyl-1H-benzotriazol-5-yl)-acrylic acid methyl ester (0.500 g, 2.30 mmol),$[RhCl(cod)]_2$ (0.057 g, 0.12 mmol), Et_3N (0.349 g, 3.45 mmol), 1,4-dioxane (1.2 mL) and water (7.7 mL) was heated at 95 °C for 6 h. Additional [2-Chloro-5-(3,3,4,4-tetramethyl-borolan-1-yl)-phenyl]-methanol (0.5 eq) and $[RhCl(cod)]_2$ (0.050 g, 0.10 mmol) were added and the mixture heated again for 16 h. The mixture was diluted with water and extracted with $CHCl_3$:IPA (3:1, x3). The combined organic layers were washed successively with water and brine, dried over $MgSO_4$, filtered and concentrated to dryness. The residue was taken up into MeOH and the solution treated with 2 drops conc. HCl, then stirred under reflux for 4 h. Concentration to dryness followed by purification by silica gel chromatography (100% DCM) gave the product as a white solid (0.560 g, 68%). LCMS $(M+H)^+$ 360/362(Cl), RT 1.18 min.

Pyridine-3-sulfonic acid propylamide



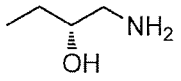
A stirred solution of 3-pyridylsulfonyl chloride hydrochloride (0.240 g, 1.12 mmol) and iPr_2NEt (0.217 g, 1.68 mmol) in DCM (4 mL) at 4°C was treated with n-propylamine

(E)-ethyl 3-(1-ethyl-4-methyl-1H-benzo[d][1,2,3]triazol-5-yl)acrylate



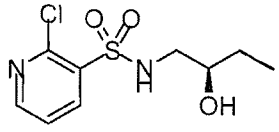
A mixture of tri-o-tolylphosphine (0.849 g, 2.79 mmol), ethyl acrylate (5.59 g, 55.8 mmol), 5-bromo-1-ethyl-4-methyl-1H-benzo[d][1,2,3]triazole (6.7 g, 27.9 mmol), $Pd(OAc)_2$ (0.313 g, 1.395 mmol), and K_2CO_3 (7.71 g, 55.8 mmol) in DMF (50 mL) was stirred at 120 °C for 12 h. The reaction mixture was poured into water and extracted with EtOAc (3 x 30 mL). The organic layer was dried and concentrated. The product was purified over a silica gel column and eluted with hexane:EtOAc (4: 1) to give the title compound (E)-ethyl 3-(1-ethyl-4-methyl-1H-benzo[d][1,2,3]triazol-5-yl)acrylate (5 g, 18.50 mmol, 66.3 % yield). LC-MS *m/z* 260.2 $[(M+H)^+$, 1.63 (ret. time).

(R)-1-aminobutan-2-ol



To a solution of NH_4OH (~28% solution in H_2O) (21.60 mL, 555mmol) was added (R)-2-ethyloxirane (4 g, 55.5 mmol). The resulting reaction mixture was stirred at RT for 20 h. The reaction mixture was concentrated under reduced pressure to afford the desired product (R)-1-aminobutan-2-ol (4.5 g, 50.5 mmol, 91 % yield). ^1H NMR (400 MHz, CHLOROFORM-d) δppm 0.97 (t, J=7.53 Hz, 3 H) 1.42 - 1.53 (m, 2 H) 1.71 (br. s., 3 H) 2.47 - 2.59 (m, 1 H) 2.85 (dd, J=12.80, 3.26 Hz, 1 H) 3.39 - 3.49 (m, 1 H).

(R)-2-chloro-N-(2-hydroxybutyl)pyridine-3-sulfonamide

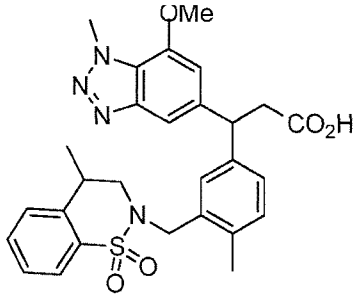


To a solution of (R)-1-amino-2-butanol (2.5 g, 28.0 mmol) in THF (80 mL) and water (16 mL) was added K_2CO_3 (2.477 g, 17.92 mmol) followed by 2-chloropyridine-3-sulfonyl chloride (3.8 g, 17.92 mmol). The resulting reaction mixture was stirred at RT for 5 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with brine (15 mL), dried over $MgSO_4$ and

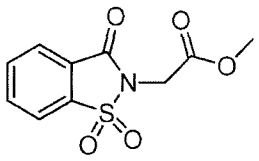
neutral conditions to provide the title compound (0.023 g, 0.043 mmol, 63%) LC-MS *m/z* 514.0 $(M+H)^+$, 0.90 min (ret. time).

Example 155

3-(7-Methoxy-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(4-methyl-3-((4-methyl-1,1-dioxido-3,4-dihydro-2H-benzo[e][1,2]thiazin-2-yl)methyl)phenyl)propanoic acid



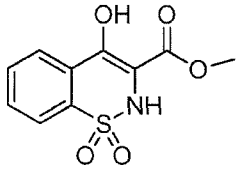
Methyl 2-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)acetate



To a solution of sodium 3-oxo-3H-benzo[d]isothiazol-2-ide 1,1-dioxide (15g, 73.1 mmol) in DMF (30 mL) was added methyl bromoacetate (14.54 g, 95 mmol).

The mixture was stirred at 100 °C for 3 h, cooled to RT and poured into cooled water, resulting in an immediate formation of solid. The solid was filtered and washed with water,dried and recrystallized from MeOH. LC-MS: *m/z* 256$(M+H)^+$ 1.43 min (ret. time).

Methyl 4-hydroxy-2H-benzo[e][1,2]thiazine-3-carboxylate 1,1-dioxide

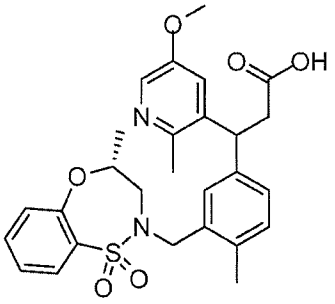


NaOMe (8.25 g, 153 mmol) was suspended in dry DMF (20 mL). and then added to a solution of methyl 2-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)acetate (13 g, 50.9 mmol) in DMF (5 mL) at 0 °C over 7 min. Upon complete addition of the NaOMe the reaction mixture was allowed to stir for additional 30 min. The product was precipitated

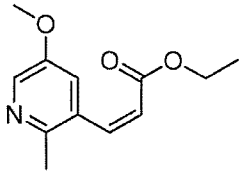
methylphenyl)propanoate (300 mg, 0.503 mmol) in EtOH (20 mL)was added 10% NaOH (20 mL) at 0 °C. Then the reaction mixture was stirred at RT for 2 h. The reaction mixture was then evaporated under reduced pressure, neutralized with 1N HCl, and extracted with DCM (2X). The organic layer was dried under anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure to get 280 mg of crude compound. The crude compound was purified by flash column chromatography(2X) using MeOH:DCM (0.5:9.5) as solvent system, to afford 3-(2-((dimethylamino)methyl)-4-fluoro-6-methylphenyl)-3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)propanoic acid (53 mg, 0.091 mmol). LC-MS *m/z* 569.28 $(M+H)^+$, 2.14 min (ret. time).

Example 161

3-(5-Methoxy-2-methylpyridin-3-yl)-3-(4-methyl-3-(((R)-4-methyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)phenyl)propanoic acid



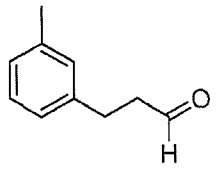
(Z)-Ethyl 3-(5-methoxy-2-methylpyridin-3-yl)acrylate



To a solution of 3-bromo-5-methoxy-2-methylpyridine (500 mg, 2.475 mmol) in DMF (3 mL) was added ethyl acrylate (1239 mg, 12.37 mmol), tri-o-tolylphosphine (226 mg, 0.742 mmol), DIPEA (1.729 mL, 9.90 mmol) and $Pd(OAc)_2$ (5.56 mg, 0.025 mmol) at RT and stirred under microwave irradiation at 120 °C for 1.30 h. The reaction was cooled to RT, filtered through celite and washed with EtOAc (50 mL). The fitrate was washed with a brine solution (100 mL) and dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under vacuum. The residue was purified by flash

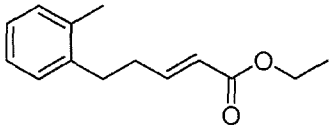
To a solution of 3-(m-tolyl)propanoic acid (2 g, 12.18 mmol) in THF (50 mL) was added 2 M LAH in THF (30 mL, 30.5 mmol) at 0 °C under nitrogen atmosphere and strirred at RT for 2 h. The reaction mixture was quenched with saturated sodium sulfate, extracted with EtOAc (2X), the organic layer was dried under anhydrous Na_2SO_4 and filtered. The filtrate was evaporated and the crude residue was purified by flash column chromtography by using EtOAc : hexane (20:80) to afford 3-(m-tolyl)propan-1-ol (1.4 g, 9.29 mmol, 76 % yield). LC-MS *m/z* 151 $(M+H)^+$, 2.03min (ret. time).

3-(m-Tolyl)propanal



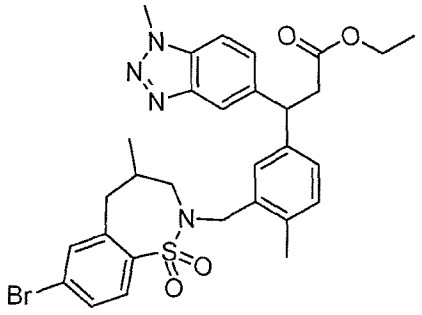
To a solution of 3-(m-tolyl)propan-1-ol (1.4 g, 9.32 mmol) in DCM (20 mL), at 0 °C was added PCC (3.01 g, 13.98 mmol) then brought RT and stirred at RT for 3 h. The crude residue was filterd through celite, and the solvent was evaporated to afford 3-(m-tolyl)propanal (1.2 g, 8.10 mmol, 87 % yield). ^1H NMR (400 MHz, DMSO-d6) δ ppm 9.65 (bs, 1H), 6.85-7.20 (m, 4H), 2.90-2.20 (m, 7H).

(E)-Ethyl 5-(o-tolyl)pent-2-enoate



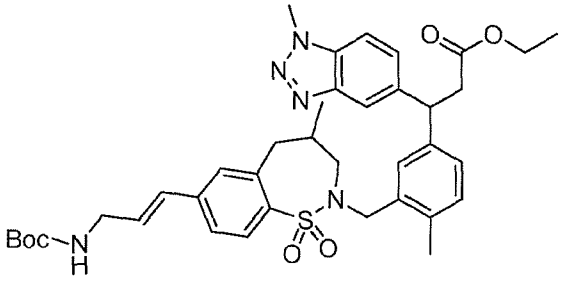
To a suspension of NaH (0.486 g, 20.24 mmol) in THF (15 mL) was added triethyl phosphonoacetate (1.945 mL, 9.72 mmol) at 0 °C and stirred for 15 min.Then 3-(o-tolyl)propanal (1.2 g, 8.10 mmol) in THF (3 mL) was added to the reaction mixture and stirred at RT and stirred for 2 h. The reaction mixture was quenched with cold water, extracted with EtOAc (2X), brine, the organic layer was dried under anhydrous Na_2SO_4 and filtered. The filtrate was concentrated. the crude residue was purified on flash column chromtography by using EtOAc : hexane (80:20) to afford (E)-ethyl 5-(o-tolyl)pent-2-enoate (500 mg, 1.397 mmol, 17.25 % yield) LC-MS *m/z* 219 $(M+H)^+$, 2.82min (ret. time).

Ethyl 3-(3-((7-bromo-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)methyl)-4-methylphenyl)-3-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate



To a solution of 7-bromo-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepine 1,1-dioxide (500 mg, 1.723 mmol) in THF (20 mL) was added ethyl 3-(3-(hydroxymethyl)-4-methylphenyl)-3-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate (609 mg, 1.723 mmol), triphenylphosphine (452 mg, 1.723 mmol) and DEAD (0.273 mL, 1.723 mmol) at 0 °C. The reaction was stirred at RT for 3 h. The reaction mixture was cooled to 0 °C and quenched with water, extracted with EtOAc (2X). The organic layer washed with brine, dried under anhydrous Na_2SO_4 and filtered. The filtrate was evaporated and was purified by column chromatography using EtOAc : hexane (30:70) to afford ethyl 3-(3-((7-bromo-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)methyl)-4-methylphenyl)-3-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate (400 mg, 0.613 mmol, 35.6 % yield). LC-MS *m/z* 624 $(M+H)^+$, 2.83 min (ret. time).

(E)-Ethyl 3-(3-((7-(3-((tert-butoxycarbonyl)amino)prop-1-en-1-yl)-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)methyl)-4-methylphenyl)-3-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoate

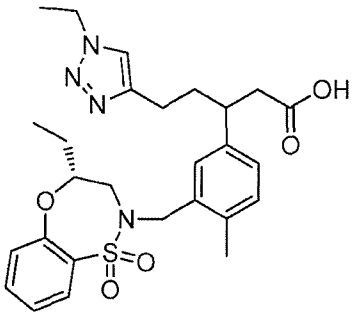


To solution of ethyl 3-(3-((7-bromo-4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)methyl)-4-methylphenyl)-3-(1-methyl-1H-benzo[d][1,2,3]triazol-5-yl) propanoate (1.5 g, 2.398 mmol) in DMF (4 mL) was added tert-butyl allylcarbamate (0.565 g, 3.60 mmol), tri-o-tolylphosphine (0.219 g, 0.719 mmol) and DIPEA (1.256 mL, 7.19 mmol) in a microwave reactor. The mixture was degassed with

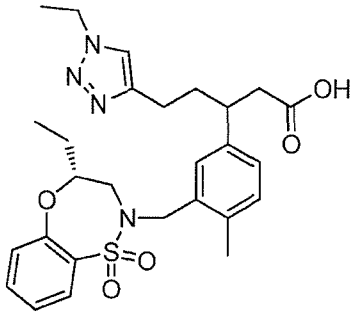
The desired fractions were pooled based on LCMS analysis of all the fractions individually and then pooling those fractions from the major peak with > 90% of the m/z = 541 peak. The pooled fractions were concentrated *in vacuo* to afford 3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)-2-methylpentanoic acid (12 mg, 0.022 mmol, 33.1 % yield) LC-MS *m/z* = 542.4 $(M+H)^+$, 1.02 min (ret time). Analytical sfc analysis indicates the product is a mixture of two isomers presumeably with the same relative stereochemistry at the pentanoate C-2 and C-3 but with opposite absolute stereochemistry at these atoms.

Example 194

3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)pentanoic acid (isomer M1) and 3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)pentanoic acid (isomer N1)

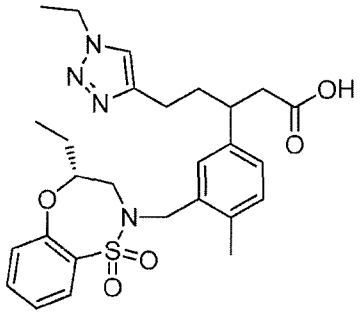


isomer M1



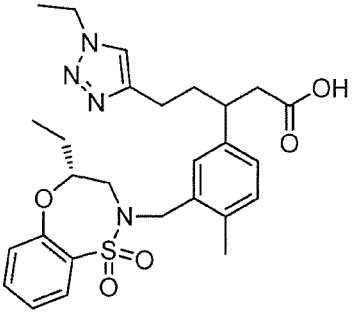
isomer N1

3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl) pentanoic acid

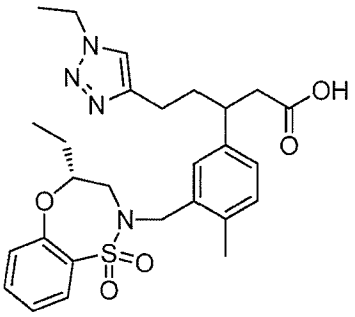


60 mg of ethyl 3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)-2-methylpentanoate was dissolved in MeOH (2 mL). 2M LiOH (3.09 mL, 6.18 mmol) was added and the reaction mixture was heated in a Biotage microwave at high absorption for 30 min at 80 °C. 0.8 mL of 1 N HCl and 1.5 mL of DMSO were added. Most of the solvent was removed at reduced pressure and the sample was purified via reverse phase chromatography (Sunfire C18, 19x100mm, 5u; mobile phase A = Water+0.1% TFA:Mobile phase B = MeCN +0.1% TFA; 18 mL/min; 35%B to 65% B in 10 min) to afford 62 mg of the mixture of isomers 3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)-pentanoic acid .

(R)-3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)pentanoic acid (isomer M1) and (S)-3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)pentanoic acid (isomer N1)



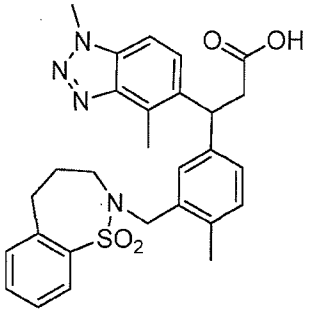
isomer M1



isomer N1

62 mg of the mixture of isomers 3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)-pentanoic acid was separated by chiral supercritical fluid chromatography (Chiralpak AD, 20x250mm, 5μ; 20% EtOH; 50g/min; 100bar) to afford:
isomer M1 (15mg) 3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)pentanoic acid LC-MS *m/z* 527.4 $(M + H)^+$, 1.02 (ret. time). **isomer N1** (15 mg) (S)-3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-5-(1-ethyl-1H-1,2,3-triazol-4-yl)pentanoic acid LC-MS *m/z* 527.4 $(M + H)^+$, 1.02 (ret. time)

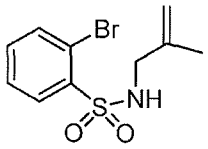
3-(1,4-Dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(3-((1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)methyl)-4-methylphenyl)propanoic acid



To a solution of ethyl 3-(1,4-dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(4-methyl-3-((4-methyl-1,1-dioxido-4,5-dihydrobenzo[f][1,2]thiazepin-2(3H)-yl)methyl)phenyl)propanoate (100 mg, 0.178 mmol) in MeOH (2 mL) at RT was added 2 M LiOH (0.554 mL, 1.109 mmol). The reaction mixture was heated in a Biotage microwave at high absorption for 30 min at 85 °C. 1N HCl (1.109 mL, 1.109 mmol) and 1 mL of DMSO were added and concentrated. The reaction mixture was purified with reverse-phase HPLC under acidic conditions to give the title compound (88.3 mg, 0.17 mmol, 92% yield).

LC-MS *m/z* 519.2 $(M+H)^+$, 1.05 min (ret. time)

2-Bromo-N-(2-methylallyl)benzenesulfonamide

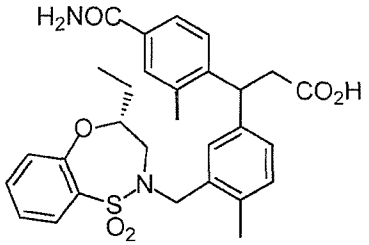


To a solution of 2-bromobenzene-1-sulfonyl chloride (5 g, 19.6 mmol) in DCM (100 mL) was added TEA (5.5 mL, 39.2 mmol) at 0 °C. After 10 min, 2-methyl allylamine (1.3 g, 21.5 mmol) was added at 0 °C, then stirred at RT overnight. The reaction mixture was diluted with water (100 mL) and extracted with DCM (2 x 100 mL). The combined organic layer washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the title compound (3.5 g, 62 %) as solid. LC-MS *m/z* 287.99 $(M)^+$, 1.993 min (ret. time)

0.300 mmol), Et_3N (0.084 mL, 0.600 mmol) and $[RhCl(cod)]_2$ (3.70 mg, 7.50 μmol). The resulting reaction mixture was stirred at 90 °C for 2 h. The reaction mixture was evaporated down under vacuum. This intermediate was redissolved in MeOH (2 mL). To the resulting solution was added NaOH (3 N) (0.400 mL, 1.200 mmol) and the mixture heated with microwave irradiation at 80 °C for 20 min. The reaction mixture was acidified with HCl (3 N) to pH 4~5, evaporated down under vacuum, and purified with reverse phase HPLC to afford desired product 3-(4-chlorophenyl)-3-(4-methyl-3-(((R)-4-methyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)phenyl)propanoic acid (44.9 mg, 0.090 mmol, 59.9 % yield). LC-MS *m/z* 500.3 $(M+H)^+$, 1.18 min (ret. time).

Example 241

3-(4-Carbamoyl-2-methylphenyl)-3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)propanoic acid



To a solution of methyl 3-(4-cyano-2-methylphenyl)-3-(3-(hydroxymethyl)-4-methylphenyl)propanoate (50 mg, 0.155 mmol) in THF (2 mL) was added (R)-4-ethyl-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide (52.7 mg, 0.232 mmol), PS-PPh_3 (193 mg, 0.309 mmol) and DIAD (0.060 mL, 0.309 mmol). The resulting reaction mixture was stirred at RT for 30 min. The reaction mixture was filtered, evaporated down under vacuum. This intermediate was redissolved in EtOH (2 mL). To the resulting solution was added NaOH (2 N) (0.541 mL, 1.082 mmol) and H_2O_2 (~30%) (0.111 mL, 1.082 mmol). The resulting reaction mixture was stirred at RT for 17 h. The reaction mixture was acidified with HCl (1 N) to pH ~5, evaporated down under vacuum, and purified with reverse phase HPLC to afford desired product 3-(4-carbamoyl-2-methylphenyl)-3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)propanoic acid (29.5 mg, 0.055 mmol, 35.6 % yield). LC-MS *m/z* 537.3 $(M+H)^+$, 0.97 min (ret. time).

or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising the compound or pharmaceutically acceptable salt according to any one of claims 1-13 and a pharmaceutically acceptable carrier or excipient.

15. Use of the compound or a pharmaceutically acceptable salt thereof according to claims 1-13 in the manufacture of a medicament for the treatment of respiratory and non-respiratory disorders, including COPD, asthma, fibrosis, chronic and acute asthma, lung disease secondary to environmental exposures, acute lung infection, chronic lung infection, α1 antitrypsin disease, cystic fibrosis, autoimmune diseases, diabetic nephropathy, chronic kidney disease, sepsis-induced acute kidney injury, acute kidney injury (AKI), kidney disease or malfunction seen during kidney transplantation, Pulmonary Arterial Hypertension, atherosclerosis, hypertension, heart failure, Parkinson's disease (PD), Alzheimer's disease (AD), autism, Friedreich's Ataxia (FA), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), inflammatory bowel disease, colon cancer, neovascular (dry) AMD and neovascular (wet) AMD, eye injury, Fuchs Endothelial Corneal Dystrophy (FECD), uveitis or other inflammatory eye conditions, Non-alcoholic Steatohepatitis (NASH), toxin-induced liver disease (e.g., acetaminophen-induced hepatic disease), viral hepatitis, cirrhosis, psoriasis, dermatitis/topical effects of radiation, immunosuppression due to radiation exposure, Preeclampsia, and high altitude sickness.

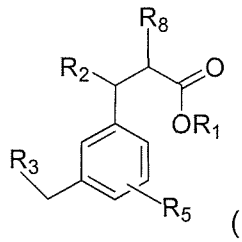
16. The use of the compound or a pharmaceutically acceptable salt thereof according to claim 15, wherein the compound is to be administered orally.

17. The use of the compound or a pharmaceutically acceptable salt thereof according to claim 15, wherein the compound is to be administered intravenously.

18. The use of the compound or a pharmaceutically acceptable salt thereof according to claim 15, wherein the compound is to be administered by inhalation.

19. The use of the compound or a pharmaceutically acceptable salt thereof according to claim 15, wherein the disorder is COPD.

20. A compound of formula (Ia)



(Ia)

wherein:

R_1 is hydrogen, CH_2 $C(O)N(R_7)_2$, CH_2-(4- methyl-1,3 dioxol-2-one), C_{1-3} alkyl-OH, C_{1-3} alkyl, C_{1-5} alkyl-$N(R_7)_2$, $(CH_2)_n$–morpholinyl, $(CH_2)_n$-furyl, CH_2-O-C(O)–C_{1-5} alkyl, $(CH_2)_n$–imidazolyl, $(CH_2)_n$–pyrrolidinyl, $(CH_2)_n$-Piperidyl or 2-oxotetrahydrofura-3-nyl;

Wherein the morpholinyl, and piperidyl may be substituted by one or two C_{1-3} alkyl;

and the pyrrolidinyl, imidazolyl and furyl may be substituted by one or two C_{1-3} alkyl, halo, or O-C_{1-3} alkyl;

R_2 is Phenyl, which may be substituted by one, two, or three CN, F, $C(O)NH_2$, $C(O)CH_3$), O-C_{1-3} alkyl, C_{1-3} alkyl, CF_3, or O-CF_3;

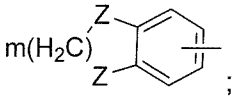
Benzotriazolyl, which may be substituted by one, two or three -O-C_{1-3} alkyl, F, Cl, CF_3, OCF_3 or C_{1-3} alkyl;

$(CH_2)_n$-Triazolyl which may be substituted by one or two C_{1-3} alkyl or -CH_2-phenyl;

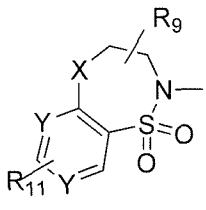
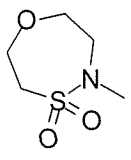
Pyridyl which may be substituted by one, two, or three C_{1-3} alkyl, F, OCH_3, or =O;

or triazolo pyridyl which may be substituted by one or two -O-C_{1-3} alkyl, F, or C_{1-3} alkyl;

R_3 is R_4-SO_2–$N(R_6)$-;

R_4 is Phenyl, C_{5-6} cycloalkyl, Thienyl, Imidazolyl, Pyridyl, Piperidyl, Tetrahydro–2H-pyranyl, C_{1-3} alkyl or  ;

All of which may be substituted by one or two C_{1-3} alkyl, NH–C (O)-CH_3, O-C_{1-3}alkyl, C(O)-CH_3, =O, or OH;

or R_3 is  ,or  ;

X is CH_2, NR_6 or O;

Y is independently N or CH; provided one Y is CH;

Z is independently O, CH_2, or NR_{10};

R_5 is hydrogen, C_{1-3} alkyl, Cl, F, or CF_3

R_6 is independently hydrogen or C_{1-3} alkyl;
R_7 is independently hydrogen or C_{1-3} alkyl;
R_8 is hydrogen or C_{1-3} alkyl;
R_9 is hydrogen or C_{1-3} alkyl;
R_{10} is $C(O)-CH_3$;
R_{11} is hydrogen or F;
n is independently 0, 1, 2, or 3; and
m is 1 or 2;
or a pharmaceutically acceptable salt thereof.

21. A compound which is (S)-3-(3-(((R)-4-ethyl-1,1-dioxido-3,4-dihydro-2H-pyrido[2,3-b][1,4,5]oxathiazepin-2-yl)methyl)-4-methylphenyl)-3-(1-ethyl-4-methyl-1H-benzo[d][1,2,3]triazol-5-yl)propanoic acid or a pharmaceutically acceptable salt thereof.

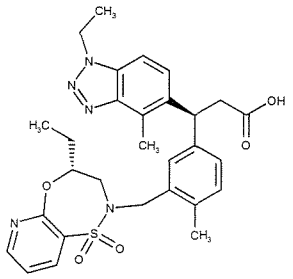
22. A pharmaceutical composition comprising the compound or pharmaceutically acceptable salt according to claim 21 and a pharmaceutically acceptable carrier or excipient.

23. Use of the compound or a pharmaceutically acceptable salt thereof according to claim 21 in the manufacture of a medicament for the treatment of respiratory and non-respiratory disorders, including COPD, asthma, fibrosis, chronic and acute asthma, lung disease secondary to environmental exposures, acute lung infection, chronic lung infection, $\alpha 1$ antitrypsin disease, cystic fibrosis, autoimmune diseases, diabetic nephropathy, chronic kidney disease, sepsis-induced acute kidney injury, acute kidney injury (AKI), kidney disease or malfunction seen during kidney transplantation, Pulmonary Arterial Hypertension, atherosclerosis, hypertension, heart failure, Parkinson's disease (PD), Alzheimer's disease (AD), autism, Friedreich's Ataxia (FA), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), inflammatory bowel disease, colon cancer, neovascular (dry) AMD and neovascular (wet) AMD, eye injury, Fuchs Endothelial Corneal Dystrophy (FECD), uveitis or other inflammatory eye conditions, Non-alcoholic Steatohepatitis (NASH), toxin-induced liver disease (e.g., acetaminophen-induced hepatic disease), viral hepatitis, cirrhosis, psoriasis, dermatitis/topical effects of radiation, immunosuppression due to radiation exposure, Preeclampsia, and high altitude sickness.

24. Use of the compound or a pharmaceutically acceptable salt thereof according to claim 21 in the manufacture of a medicament for the treatment of COPD.

25. Use of the compound or a pharmaceutically acceptable salt thereof according to claim 21 in the manufacture of a medicament for the treatment of heart failure.

26. A compound which is:



27. A pharmaceutical composition comprising the compound or pharmaceutically acceptable salt according to claim 26 and a pharmaceutically acceptable carrier or excipient.

28. Use of the compound or a pharmaceutically acceptable salt thereof according to claim 26 in the manufacture of a medicament for the treatment of respiratory and non-respiratory disorders, including COPD, asthma, fibrosis, chronic and acute asthma, lung disease secondary to environmental exposures, acute lung infection, chronic lung infection, α1 antitrypsin disease, cystic fibrosis, autoimmune diseases, diabetic nephropathy, chronic kidney disease, sepsis-induced acute kidney injury, acute kidney injury (AKI), kidney disease or malfunction seen during kidney transplantation, Pulmonary Arterial Hypertension, atherosclerosis, hypertension, heart failure, Parkinson's disease (PD), Alzheimer's disease (AD), autism, Friedreich's Ataxia (FA), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), inflammatory bowel disease, colon cancer, neovascular (dry) AMD and neovascular (wet) AMD, eye injury, Fuchs Endothelial Corneal Dystrophy (FECD), uveitis or other inflammatory eye conditions, Non-alcoholic Steatohepatitis (NASH), toxin-induced liver disease (e.g., acetaminophen-induced hepatic disease), viral hepatitis, cirrhosis, psoriasis, dermatitis/topical effects of radiation, immunosuppression due to radiation exposure, Preeclampsia, and high altitude sickness.

29. Use of the compound or a pharmaceutically acceptable salt thereof according to claim 26 in the manufacture of a medicament for the treatment of COPD.

30. Use of the compound or a pharmaceutically acceptable salt thereof according to claim 26 in the manufacture of a medicament for the treatment of heart failure.