	hydroxypropyl}isothiazole-3-carboxamide
2098	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^5-(1,3-thiazol-2-yl)pentanediamide
2099	N-acetyl-4-chloro-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}phenylalaninamide
2100	8-chloro-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-hydroxycinnoline-3-carboxamide
2101	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,6-dioxohexahydropyrimidine-4-carboxamide
2102	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(5-methyl-4-phenyl-1,3-oxazol-2-yl)benzamide
2103	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-phenylimidazo[1,2-a]pyridine-6-carboxamide
2104	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]propanamide
2105	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3-thiazole-4-carboxamide
2106	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-2-phenyl-2H-1,2,3-triazole-4-carboxamide
2107	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(3-pyridin-2-yl-1,2,4-oxadiazol-5-yl)butanamide
2108	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,3-dimethyl-1H-thieno[2,3-c]pyrazole-5-carboxamide
2109	4-(1,3-benzodioxol-5-yl)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}butanamide
2110	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-(4-methyl-1,2,3-thiadiazol-5-yl)isoxazole-4-carboxamide
2111	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[2-(dimethylamino)-1-methylethyl]amino}-2-hydroxypropyl)-5-methyl-N^3,N^3-dipropylisophthalamide
2112	N^1-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(2-methylmorpholin-4-yl)propyl]-5-methyl-

	N^3,N^3-dipropylisophthalamide
2113	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{2-[hydroxy(phenyl)methyl]-4-methylpiperazin-1-yl}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide
2114	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(2R)-2-methylbutyl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide
2115	N^1-[(1S,2R)-3-{[4-(diethylamino)-1-methylbutyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2116	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-hydroxy-1,1-dimethylethyl)amino]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide
2117	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(2-methylpiperidin-1-yl)propyl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide
2118	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide
2119	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methyl-4,5,6,7-tetrahydro-3H-3lambda4-[1,3]thiazolo[5,4-c]pyridin-2-yl)amino]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide
2120	N^1-[(1S,2R)-3-[(3-ethylbenzyl)amino]-2-hydroxy-1-(1H-pyrazol-1-ylmethyl)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2121	3,5-bis(acetylamino)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide
2122	N^1-[4-(aminosulfonyl)phenyl]-N^4-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}succinamide
2123	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[methyl(methylsulfonyl)amino]benzamide
2124	1-acetyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}piperidine-4-carboxamide
2125	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(4-methoxyphenoxy)propanamide
2126	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^4-

	methylsuccinamide
2127	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^4-(2,6-dimethylphenyl)succinamide
2128	N-acetyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-phenylalaninamide
2129	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(4-methylphenyl)sulfonyl]acetamide
2130	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-{[(ethylamino)carbonyl]amino}benzamide
2131	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-phenyl-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxamide
2132	4-(cyclopentyloxy)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide
2133	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^4-pyridin-3-ylsuccinamide
2134	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^4-phenylsuccinamide
2135	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dihydroxybenzamide
2136	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1H-1,2,4-triazol-1-yl)pentanamide
2137	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-phenyl-1,3-oxazole-4-carboxamide
2138	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-7-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxamide
2139	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-{4-[(methylsulfonyl)amino]phenyl}-4-oxobutanamide
2140	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-hydroxy-7-methoxy-1-benzofuran-5-carboxamide
2141	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-hydroxy-7-methoxy-1-benzothiophene-5-carboxamide

2142	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-2-carboxamide
2143	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5,6-dihydro-4H-cyclopenta[b]thiophene-2-carboxamide
2144	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,3-thiazole-4-carboxamide
2145	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(2-pyridin-2-yl-1,3-thiazol-4-yl)acetamide
2146	N^1-[5-(aminosulfonyl)-1,3,4-thiadiazol-2-yl]-N^4-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}succinamide
2147	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-hydroxy-6-neopentylpyridine-2-carboxamide
2148	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(4-fluorophenyl)-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxamide
2149	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepine-3-carboxamide
2150	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-methyl-3-furamide
2151	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-furamide
2152	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(2-hydroxyethoxy)benzamide
2153	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}thiophene-2-carboxamide
2154	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^2,N^2-dimethylphthalamide
2155	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-2-phenyl-1,3-oxazole-4-carboxamide
2156	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-

	hydroxybutanamide
2157	2-(2H-1,2,3-benzotriazol-2-yl)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}butanamide
2158	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indazole-3-carboxamide
2159	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-hydroxyquinoxaline-2-carboxamide
2160	2-(acetylamino)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4,5-dimethylthiophene-3-carboxamide
2161	N^1-(2-cyanophenyl)-N^4-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}succinamide
2162	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-ethyl-1H-indole-2-carboxamide
2163	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-benzofuran-2-carboxamide
2164	1-benzyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,5-dimethyl-1H-pyrazole-4-carboxamide
2165	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^2-[(4-methylphenyl)sulfonyl]glycinamide
2166	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4,8-dihydroxyquinoline-2-carboxamide
2167	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(1,1-dioxidotetrahydrothien-3-yl)acetamide
2168	methyl 5-[({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)carbonyl]-1H-benzimidazol-2-ylcarbamate
2169	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(2-methyl-1,3-benzoxazol-5-yl)acetamide
2170	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[ethyl(methyl)amino]-4-hydroxypyrimidine-5-carboxamide
2171	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(2-pyridin-4-yl-1,3-benzoxazol-5-yl)acetamide
2172	4-[2-(diethylamino)ethoxy]-N-{(1S,2R)-1-(3,5-

	difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide
2173	3-(aminosulfonyl)-4-chloro-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide
2174	2-(diethylamino)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-hydroxypyrimidine-5-carboxamide
2175	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5,6,7,8-tetrahydro-4H-cyclohepta[c]isoxazole-3-carboxamide
2176	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^4,N^4-diphenylsuccinamide
2177	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-hydroxy-4-methylpyridine-2-carboxamide
2178	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-phenylimidazo[1,2-a]pyridine-7-carboxamide
2179	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}quinoline-4-carboxamide
2180	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)acetamide
2181	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methoxy-1H-indole-2-carboxamide
2182	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(3,5-dimethyl-1H-pyrazol-1-yl)benzamide
2183	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylisoxazole-3-carboxamide
2184	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methylisoxazole-5-carboxamide
2185	2-(1-benzothien-4-yl)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}acetamide
2186	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxamide
2187	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-

	benzothiophene-2-carboxamide
2188	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-hydroxynicotinamide
2189	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-[(4-methylphenyl)sulfonyl]-beta-alaninamide
2190	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-hydroxyquinoline-4-carboxamide
2191	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(5-phenyl-1H-tetraazol-1-yl)acetamide
2192	4-{[(cyclobutylcarbonyl)amino]methyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide
2193	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(2-oxo-1,3-benzoxazol-3(2H)-yl)butanamide
2194	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(1,3-dioxooctahydro-2H-isoindol-2-yl)butanamide
2195	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^2-(tetrahydrofuran-2-ylmethyl)phthalamide
2196	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(2,3-dihydro-1H-indol-1-yl)-4-oxobutanamide
2197	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}thieno[3,2-b]pyridine-6-carboxamide
2198	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(6-methoxy-1H-benzimidazol-2-yl)thio]acetamide
2199	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}thieno[2,3-c]pyridine-2-carboxamide
2200	2-(1H-benzimidazol-2-ylthio)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}propanamide
2201	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(2,4-difluorobenzyl)oxy]propanamide
2202	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5,6-dimethyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-carboxamide

2203	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(2-fluorophenyl)-5-oxopyrrolidine-3-carboxamide
2204	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(5-methyl-1H-tetraazol-1-yl)benzamide
2205	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)thiophene-3-carboxamide
2206	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(trifluoromethoxy)-1H-indole-2-carboxamide
2207	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-phenyl-5-propyl-1H-pyrazole-4-carboxamide
2208	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(pyridin-2-ylthio)methyl]-2-furamide
2209	5-chloro-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-morpholin-4-ylpyrimidine-4-carboxamide
2210	5-chloro-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-1-phenyl-1H-pyrazole-4-carboxamide
2211	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-methyl-1,2,3-thiadiazole-5-carboxamide
2212	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,1,3-benzoxadiazole-5-carboxamide
2213	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(imidazo[1,2-a]pyridin-2-ylmethyl)thio]acetamide
2214	2-(acetylamino)-N-{(1R,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-1,3-oxazole-4-carboxamide
2215	N-{(1S,2R)-1-[3-(cyclohexylmethyl)benzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}acetamide
2216	1 2-{[({(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}amino)carbonyl]amino}-N,N-dipropylethanesulfonamide hydrochloride
2217	2-(3-azabicyclo[3.2.2]non-3-yl)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}acetamide
2218	2-(4-benzoylphenoxy)-N-{(1S,2R)-1-(3,5-

	difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}propanamide
2219	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-4-(7-methoxy-2,3-dihydro-1-benzofuran-4-yl)-4-oxobutanamide
2220	N-{(1S,2R)-1-[3-(cyclohexylmethyl)benzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-{[(trifluoromethyl)sulfonyl]amino}benzamide hydrochloride
2221	N^1-{(1S,2R)-1-[3-(cyclohexylmethyl)benzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide hydrochloride
2222	3-chloro-N-((1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)benzamide
2223	3-chloro-N-{(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}benzamide
2224	3-chloro-N-((1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)benzamide
2225	3-chloro-N-{(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}benzamide
2226	N-((1S,2S)-1-benzyl-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-3-chlorobenzamide
2227	N-{(1S,2S)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-chlorobenzamide
2228	3-{[(3-chlorobenzyl)amino]sulfonyl}-N-((1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)benzamide
2229	3-{[(3-chlorobenzyl)amino]sulfonyl}-N-{(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}benzamide
2230	3-{[(3-chlorobenzyl)amino]sulfonyl}-N-((1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)benzamide
2231	3-{[(3-chlorobenzyl)amino]sulfonyl}-N-{(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}benzamide
2232	N-{(1S,2S)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-{[(3-

	chlorobenzyl)amino]sulfonyl}benzamide
2233	N-{(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-{[(3-methoxybenzyl)amino]sulfonyl}benzamide
2234	N-((1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-3-{[(3-methoxybenzyl)amino]sulfonyl}benzamide
2235	N-{(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-{[(3-methoxybenzyl)amino]sulfonyl}benzamide
2236	N-{(1S,2S)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-{[(3-methoxybenzyl)amino]sulfonyl}benzamide
2237	N^1-[(1R,2S)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(4-methylbenzyl)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2238	N^1-[(1R,2S)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2239	N^1-[(1R,2S)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(4-methylbenzyl)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2240	N^1-[(1R,2S)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2241	N^1-[(1R,2S)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(4-methylbenzyl)propyl]-N^5,N^5-dipropylpentanediamide
2242	N^1-[(1R,2S)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl)propyl]-N^5,N^5-dipropylpentanediamide
2243	3-[(dipropylamino)sulfonyl]-N-[(1R,2S)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(4-methylbenzyl)propyl]propanamide
2244	3-[(dipropylamino)sulfonyl]-N-[(1R,2S)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl)propyl]propanamide
2245	N^1-[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(4-methylbenzyl)propyl]-N^5,N^5-dipropylpentanediamide
2246	N^1-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-methylbenzyl)propyl]-N^5,N^5-dipropylpentanediamide
2247	N^1-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl)propyl]-N^5,N^5-dipropylpentanediamide

2248	N-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-methylbenzyl)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2249	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl)propyl]propanamide
2250	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-(4,5-dimethyl-2-furoyl)-5-methylbenzamide
2251	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-hydroxy-3-(isopentylsulfonyl)propanamide hydrochloride
2252	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-{[(2-methoxyethyl)(propyl)amino]sulfonyl}propanamide hydrochloride
2253	N^1-{(1R,2R)-3-(benzylamino)-2-hydroxy-1-[(phenylthio)methyl]propyl}-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2254	N^1-{(1R,2R)-2-hydroxy-3-(isopentylamino)-1-[(phenylthio)methyl]propyl}-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2255	N^1-{(1S,2R)-3-(benzylamino)-1-[4-(benzyloxy)benzyl]-2-hydroxypropyl}-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2256	N^1-[(1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2257	N^1-[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(1-naphthylmethyl)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2259	N^1-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(1-naphthylmethyl)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2260	N^1-[(1S,2R)-1-(2-furylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2261	N^1-{(1S,2R)-3-(benzylamino)-1-[3-(benzyloxy)benzyl]-2-hydroxypropyl}-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2262	N^1-[(1S,2R)-2-hydroxy-1-(4-hydroxybenzyl)-3-(isopentylamino)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2263	N^1-((1S)-1-{(1R)-1-hydroxy-2-[(3-methoxybenzyl)amino]ethyl}but-3-ynyl)-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2264	N^1-{(1S)-1-[(1R)-2-(benzylamino)-1-hydroxyethyl]but-3-ynyl}-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide

2265	N^1-{(1S)-1-[(1R)-1-hydroxy-2-(isopentylamino)ethyl]but-3-ynyl}-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2266	N^1-[(1S,2R)-3-(benzylamino)-1-(cyclohexylmethyl)-2-hydroxypropyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2267	N^1-[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2268	N^1-((1S)-1-{(1R)-1-hydroxy-2-[(3-methoxybenzyl)amino]ethyl}-3-methylbutyl)-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2270	N^1-{(1S)-1-[(1R)-1-hydroxy-2-(isopentylamino)ethyl]-3-methylbutyl}-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2271	N^1-{(1R,2R)-3-(benzylamino)-2-hydroxy-1-[(phenylthio)methyl]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide
2272	N^1-{(1R,2R)-2-hydroxy-3-(isopentylamino)-1-[(phenylthio)methyl]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide
2273	N^1-{(1S,2R)-3-(benzylamino)-1-[4-(benzyloxy)benzyl]-2-hydroxypropyl}-5-methyl-N^3,N^3-dipropylisophthalamide
2274	N^1-[(1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2275	N^1-[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(1-naphthylmethyl)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2277	N^1-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(1-naphthylmethyl)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2278	N^1-[(1S,2R)-1-(2-furylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2279	N^1-{(1S,2R)-3-(benzylamino)-1-[3-(benzyloxy)benzyl]-2-hydroxypropyl}-5-methyl-N^3,N^3-dipropylisophthalamide
2280	N^1-[(1S,2R)-1-[3-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2281	N^1-[(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2282	N^1-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(thien-2-ylmethyl)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2283	N^1-((1S)-1-{(1R)-1-hydroxy-2-[(3-

	methoxybenzyl)amino]ethyl}but-3-ynyl)-5-methyl-N^3,N^3-dipropylisophthalamide
2284	N^1-{(1S)-1-[(1R)-2-(benzylamino)-1-hydroxyethyl]but-3-ynyl}-5-methyl-N^3,N^3-dipropylisophthalamide
2285	N^1-{(1S)-1-[(1R)-1-hydroxy-2-(isopentylamino)ethyl]but-3-ynyl}-5-methyl-N^3,N^3-dipropylisophthalamide
2286	N^1-[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2288	N^1-{(1S)-1-[(1R)-1-hydroxy-2-(isopentylamino)ethyl]-3-methylbutyl}-5-methyl-N^3,N^3-dipropylisophthalamide
2289	N^1-{(1R,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-[(phenylthio)methyl]propyl}-N^5,N^5-dipropylpentanediamide
2290	N^1-{(1R,2R)-3-(benzylamino)-2-hydroxy-1-[(phenylthio)methyl]propyl}-N^5,N^5-dipropylpentanediamide
2291	N^1-{(1R,2R)-2-hydroxy-3-(isopentylamino)-1-[(phenylthio)methyl]propyl}-N^5,N^5-dipropylpentanediamide
2292	N^1-{(1S,2R)-3-(benzylamino)-1-[4-(benzyloxy)benzyl]-2-hydroxypropyl}-N^5,N^5-dipropylpentanediamide
2293	N^1-[(1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-N^5,N^5-dipropylpentanediamide
2295	N^1-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(1-naphthylmethyl)propyl]-N^5,N^5-dipropylpentanediamide
2296	N^1-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(1-naphthylmethyl)propyl]-N^5,N^5-dipropylpentanediamide
2298	N^1-[(1S,2R)-3-(benzylamino)-1-(2-furylmethyl)-2-hydroxypropyl]-N^5,N^5-dipropylpentanediamide
2299	N^1-[(1S,2R)-1-(2-furylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-N^5,N^5-dipropylpentanediamide
2300	N^1-{(1S,2R)-1-[3-(benzyloxy)benzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^5,N^5-dipropylpentanediamide
2301	N^1-{(1S,2R)-3-(benzylamino)-1-[3-(benzyloxy)benzyl]-2-hydroxypropyl}-N^5,N^5-dipropylpentanediamide
2302	N^1-[(1S,2R)-1-[3-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-N^5,N^5-dipropylpentanediamide

2304	N^1-[(1S,2R)-3-(benzylamino)-1-(4-fluorobenzyl)-2-hydroxypropyl]-N^5,N^5-dipropylpentanediamide
2305	N^1-[(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N^5,N^5-dipropylpentanediamide
2306	N^1-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(thien-2-ylmethyl)propyl]-N^5,N^5-dipropylpentanediamide
2307	N^1-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(thien-2-ylmethyl)propyl]-N^5,N^5-dipropylpentanediamide
2308	N^1-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-hydroxybenzyl)propyl]-N^5,N^5-dipropylpentanediamide
2309	N^1-[(1S,2R)-2-hydroxy-1-(4-hydroxybenzyl)-3-(isopentylamino)propyl]-N^5,N^5-dipropylpentanediamide
2310	N^1-((1S)-1-{(1R)-1-hydroxy-2-[(3-methoxybenzyl)amino]ethyl}but-3-ynyl)-N^5,N^5-dipropylpentanediamide
2311	N^1-{(1S)-1-[(1R)-2-(benzylamino)-1-hydroxyethyl]but-3-ynyl}-N^5,N^5-dipropylpentanediamide
2312	N^1-{(1S)-1-[(1R)-1-hydroxy-2-(isopentylamino)ethyl]but-3-ynyl}-N^5,N^5-dipropylpentanediamide
2313	N^1-{(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^5,N^5-dipropylpentanediamide
2314	N^1-[(1S,2R)-3-(benzylamino)-1-(cyclohexylmethyl)-2-hydroxypropyl]-N^5,N^5-dipropylpentanediamide
2315	N^1-[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-N^5,N^5-dipropylpentanediamide
2316	N^1-((1S)-1-{(1R)-1-hydroxy-2-[(3-methoxybenzyl)amino]ethyl}-3-methylbutyl)-N^5,N^5-dipropylpentanediamide
2317	N^1-{(1S)-1-[(1R)-2-(benzylamino)-1-hydroxyethyl]-3-methylbutyl}-N^5,N^5-dipropylpentanediamide
2318	N^1-{(1S)-1-[(1R)-1-hydroxy-2-(isopentylamino)ethyl]-3-methylbutyl}-N^5,N^5-dipropylpentanediamide
2319	3-[(dipropylamino)sulfonyl]-N-{(1R,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-[(phenylthio)methyl]propyl}propanamide
2320	N-{(1R,2R)-3-(benzylamino)-2-hydroxy-1-[(phenylthio)methyl]propyl}-3-

	[(dipropylamino)sulfonyl]propanamide
2321	3-[(dipropylamino)sulfonyl]-N-{(1R,2R)-2-hydroxy-3-(isopentylamino)-1-[(phenylthio)methyl]propyl}propanamide
2322	N-{(1S,2R)-3-(benzylamino)-1-[4-(benzyloxy)benzyl]-2-hydroxypropyl}-3-[(dipropylamino)sulfonyl]propanamide
2323	N-[(1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2324	N-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(1-naphthylmethyl)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2325	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(1-naphthylmethyl)propyl]propanamide
2326	N-[(1S,2R)-3-(benzylamino)-1-(2-furylmethyl)-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
2327	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-1-(2-furylmethyl)-2-hydroxy-3-(isopentylamino)propyl]propanamide
2328	N-{(1S,2R)-1-[3-(benzyloxy)benzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[(dipropylamino)sulfonyl]propanamide
2329	N-{(1S,2R)-3-(benzylamino)-1-[3-(benzyloxy)benzyl]-2-hydroxypropyl}-3-[(dipropylamino)sulfonyl]propanamide
2330	N-[(1S,2R)-1-[3-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2331	N-[(1S,2R)-3-(benzylamino)-1-(4-fluorobenzyl)-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
2332	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]propanamide
2333	N-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(thien-2-ylmethyl)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2334	3-[(dipropylamino)sulfonyl]-N-((1S)-1-{(1R)-1-hydroxy-2-[(3-methoxybenzyl)amino]ethyl}but-3-ynyl)propanamide
2335	N'-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({3-[(1Z)-prop-1-en-1-yl]benzyl}amino)propyl]-5-methyl-N,N-dipropylisophthalamide
2335	N-{(1S)-1-[(1R)-2-(benzylamino)-1-hydroxyethyl]but-3-ynyl}-3-

	[(dipropylamino)sulfonyl]propanamide
2336	3-[(dipropylamino)sulfonyl]-N-{(1S)-1-[(1R)-1-hydroxy-2-(isopentylamino)ethyl]but-3-ynyl}propanamide
2337	N-{(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[(dipropylamino)sulfonyl]propanamide
2338	N-[(1S,2R)-3-(benzylamino)-1-(cyclohexylmethyl)-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
2339	methyl [3-({[(2R,3S)-4-(3,5-difluorophenyl)-3-({3-[(dipropylamino)carbonyl]-5-methylbenzoyl}amino)-2-hydroxybutyl]amino}methyl)phenyl]methylcarbamate
2339	N-[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2340	3-[(dipropylamino)sulfonyl]-N-((1S)-1-{(1R)-1-hydroxy-2-[(3-methoxybenzyl)amino]ethyl}-3-methylbutyl)propanamide
2341	N-{(1S)-1-[(1R)-2-(benzylamino)-1-hydroxyethyl]-3-methylbutyl}-3-[(dipropylamino)sulfonyl]propanamide
2342	3-[(dipropylamino)sulfonyl]-N-{(1S)-1-[(1R)-1-hydroxy-2-(isopentylamino)ethyl]-3-methylbutyl}propanamide
2343	N^1-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(3-methoxybenzyl)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2346	N^1-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-isopropylbenzyl)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2348	N^1-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-methoxybenzyl)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2349	N^1-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-methoxybenzyl)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2350	N^1-[(1S,2R)-3-(benzylamino)-1-(4-fluoro-3-methylbenzyl)-2-hydroxypropyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2351	N^1-[(1S,2R)-1-(3-fluoro-4-methoxybenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2352	N^1-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-isopropylbenzyl)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2353	N^1-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-isopropylbenzyl)propyl]-5-methyl-N^3,N^3-

	dipropylisophthalamide
2354	N^1-{(1S,2R)-2-hydroxy-3-(isopentylamino)-1-[3-(trifluoromethoxy)benzyl]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide
2355	N^1-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-methoxybenzyl)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2356	N^1-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-methoxybenzyl)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2357	N^1-[(1S,2R)-3-(benzylamino)-1-(4-fluoro-3-methylbenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2358	N'-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4R)-2,2-dioxido-3,4-dihydro-1H-2,1-benzothiazin-4-yl]amino}-2-hydroxypropyl)-5-methyl-N,N-dipropylisophthalamide
2359	N'-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(4S)-2,2-dioxido-3,4-dihydro-1H-2,1-benzothiazin-4-yl]amino}-2-hydroxypropyl)-5-methyl-N,N-dipropylisophthalamide
2358	N^1-[(1S,2R)-1-(4-fluoro-3-methylbenzyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2359	N^1-{(1S,2R)-3-(benzylamino)-2-hydroxy-1-[3-(trifluoromethyl)benzyl]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide
2360	N^1-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(3-methylbenzyl)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2361	N^1-{(1S,2R)-3-(benzylamino)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxypropyl}-5-methyl-N^3,N^3-dipropylisophthalamide
2362	N^1-[(1S,2R)-3-(benzylamino)-1-(3-fluoro-4-methoxybenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2363	N^1-{(1S,2R)-2-hydroxy-1-(3-methoxybenzyl)-3-[(3-methoxybenzyl)amino]propyl}-N^5,N^5-dipropylpentanediamide
2364	N^1-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(3-methoxybenzyl)propyl]-N^5,N^5-dipropylpentanediamide
2365	N^1-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(3-methoxybenzyl)propyl]-N^5,N^5-dipropylpentanediamide
2366	N^1-[(1S,2R)-3-(benzylamino)-1-(3-chloro-5-fluorobenzyl)-2-hydroxypropyl]-N^5,N^5-dipropylpentanediamide
2367	N^1-[(1S,2R)-1-(3-chloro-5-fluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N^5,N^5-

	dipropylpentanediamide
2368	N^1-{(1S,2R)-1-(3,5-dichlorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^5,N^5-dipropylpentanediamide
2369	N^1-[(1S,2R)-3-(benzylamino)-1-(3,5-dichlorobenzyl)-2-hydroxypropyl]-N^5,N^5-dipropylpentanediamide
2370	N^1-[(1S,2R)-1-(3,5-dichlorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N^5,N^5-dipropylpentanediamide
2371	N^1-{(1S,2R)-2-hydroxy-1-(4-isopropylbenzyl)-3-[(3-methoxybenzyl)amino]propyl}-N^5,N^5-dipropylpentanediamide
2311	N^1-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-isopropylbenzyl)propyl]-N^5,N^5-dipropylpentanediamide
2312	N^1-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-isopropylbenzyl)propyl]-N^5,N^5-dipropylpentanediamide
2313	N^1-{(1S,2R)-1-[3-fluoro-5-(trifluoromethyl)benzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^5,N^5-dipropylpentanediamide
2314	N^1-{(1S,2R)-3-(benzylamino)-1-[3-fluoro-5-(trifluoromethyl)benzyl]-2-hydroxypropyl}-N^5,N^5-dipropylpentanediamide
2315	N^1-[(1S,2R)-1-[3-fluoro-5-(trifluoromethyl)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-N^5,N^5-dipropylpentanediamide
2316	N^1-{(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-[3-(trifluoromethoxy)benzyl]propyl}-N^5,N^5-dipropylpentanediamide
2317	N^1-{(1S,2R)-3-(benzylamino)-2-hydroxy-1-[3-(trifluoromethoxy)benzyl]propyl}-N^5,N^5-dipropylpentanediamide
2318	N^1-{(1S,2R)-2-hydroxy-3-(isopentylamino)-1-[3-(trifluoromethoxy)benzyl]propyl}-N^5,N^5-dipropylpentanediamide
2319	N^1-[(1S,2R)-3-(benzylamino)-1-(3-fluoro-4-methylbenzyl)-2-hydroxypropyl]-N^5,N^5-dipropylpentanediamide
2320	N^1-[(1S,2R)-1-(3-fluoro-4-methylbenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N^5,N^5-dipropylpentanediamide
2321	N^1-{(1S,2R)-2-hydroxy-1-(4-methoxybenzyl)-3-[(3-methoxybenzyl)amino]propyl}-N^5,N^5-dipropylpentanediamide
2322	N^1-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-

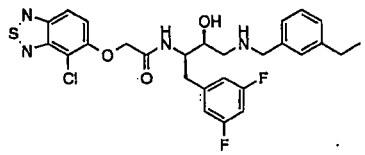
	methoxybenzyl)propyl]-N^5,N^5-dipropylpentanediamide
2323	N^1-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-methoxybenzyl)propyl]-N^5,N^5-dipropylpentanediamide
2324	N^1-{(1S,2R)-1-(4-chlorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^5,N^5-dipropylpentanediamide
2325	N^1-[(1S,2R)-3-(benzylamino)-1-(4-chlorobenzyl)-2-hydroxypropyl]-N^5,N^5-dipropylpentanediamide
2326	N^1-[(1S,2R)-1-(4-chlorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N^5,N^5-dipropylpentanediamide
2327	N^1-{(1S,2R)-1-(1,3-benzodioxol-5-ylmethyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^5,N^5-dipropylpentanediamide
2328	N^1-[(1S,2R)-1-(1,3-benzodioxol-5-ylmethyl)-3-(benzylamino)-2-hydroxypropyl]-N^5,N^5-dipropylpentanediamide
2329	N^1-[(1S,2R)-1-(1,3-benzodioxol-5-ylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-N^5,N^5-dipropylpentanediamide
2330	N^1-{(1S,2R)-1-(4-fluoro-3-methylbenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^5,N^5-dipropylpentanediamide
2331	N^1-[(1S,2R)-3-(benzylamino)-1-(4-fluoro-3-methylbenzyl)-2-hydroxypropyl]-N^5,N^5-dipropylpentanediamide
2332	N^1-[(1S,2R)-1-(4-fluoro-3-methylbenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N^5,N^5-dipropylpentanediamide
2333	N^1-{(1S,2R)-3-(benzylamino)-2-hydroxy-1-[3-(trifluoromethyl)benzyl]propyl}-N^5,N^5-dipropylpentanediamide
2335	N^1-[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(3-methylbenzyl)propyl]-N^5,N^5-dipropylpentanediamide
2336	N^1-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(3-methylbenzyl)propyl]-N^5,N^5-dipropylpentanediamide
2337	N^1-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(3-methylbenzyl)propyl]-N^5,N^5-dipropylpentanediamide
2338	N^1-{(1S,2R)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^5,N^5-dipropylpentanediamide
2339	N^1-{(1S,2R)-3-(benzylamino)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxypropyl}-N^5,N^5-

	dipropylpentanediamide
2340	N^1-[(1S,2R)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxy-3-(isopentylamino)propyl]-N^5,N^5-dipropylpentanediamide
2341	N^1-{(1S,2R)-1-(3-fluoro-4-methoxybenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^5,N^5-dipropylpentanediamide
2342	N^1-[(1S,2R)-3-(benzylamino)-1-(3-fluoro-4-methoxybenzyl)-2-hydroxypropyl]-N^5,N^5-dipropylpentanediamide
2343	N^1-[(1S,2R)-1-(3-fluoro-4-methoxybenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N^5,N^5-dipropylpentanediamide
2344	N^1-[(1S,2R)-3-(benzylamino)-1-(3-bromobenzyl)-2-hydroxypropyl]-N^5,N^5-dipropylpentanediamide
2345	N^1-[(1S,2R)-1-(3-bromobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N^5,N^5-dipropylpentanediamide
2346	N-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(3-methoxybenzyl)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2347	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(3-methoxybenzyl)propyl]propanamide
2348	N-[(1S,2R)-3-(benzylamino)-1-(3,5-dichlorobenzyl)-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
2349	3-[(dipropylamino)sulfonyl]-N-{(1S,2R)-2-hydroxy-1-(4-isopropylbenzyl)-3-[(3-methoxybenzyl)amino]propyl}propanamide
2350	N-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-isopropylbenzyl)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2351	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-isopropylbenzyl)propyl]propanamide
2352	N-{(1S,2R)-3-(benzylamino)-1-[3-fluoro-5-(trifluoromethyl)benzyl]-2-hydroxypropyl}-3-[(dipropylamino)sulfonyl]propanamide
2353	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-1-[3-fluoro-5-(trifluoromethyl)benzyl]-2-hydroxy-3-(isopentylamino)propyl]propanamide
2354	N-{(1S,2R)-3-(benzylamino)-2-hydroxy-1-[3-(trifluoromethoxy)benzyl]propyl}-3-[(dipropylamino)sulfonyl]propanamide
2355	N-[(1S,2R)-3-(benzylamino)-1-(3-fluoro-4-methylbenzyl)-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
2356	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-1-(3-fluoro-4-methylbenzyl)-2-hydroxy-3-

	(isopentylamino)propyl]propanamide
2357	3-[(dipropylamino)sulfonyl]-N-{(1S,2R)-2-hydroxy-1-(4-methoxybenzyl)-3-[(3-methoxybenzyl)amino]propyl}propanamide
2358	N-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(4-methoxybenzyl)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2359	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(4-methoxybenzyl)propyl]propanamide
2360	N-[(1S,2R)-3-(benzylamino)-1-(4-chlorobenzyl)-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
2314	N-[(1S,2R)-1-(4-chlorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2315	N-[(1S,2R)-1-(1,3-benzodioxol-5-ylmethyl)-3-(benzylamino)-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
2316	N-[(1S,2R)-1-(1,3-benzodioxol-5-ylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2317	3-[(dipropylamino)sulfonyl]-N-{(1S,2R)-1-(4-fluoro-3-methylbenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}propanamide
2318	N-[(1S,2R)-3-(benzylamino)-1-(4-fluoro-3-methylbenzyl)-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
2319	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-1-(4-fluoro-3-methylbenzyl)-2-hydroxy-3-(isopentylamino)propyl]propanamide
2320	N-{(1S,2R)-3-(benzylamino)-2-hydroxy-1-[3-(trifluoromethyl)benzyl]propyl}-3-[(dipropylamino)sulfonyl]propanamide
2321	3-[(dipropylamino)sulfonyl]-N-{(1S,2R)-2-hydroxy-3-(isopentylamino)-1-[3-(trifluoromethyl)benzyl]propyl}propanamide
2322	N-[(1S,2R)-3-(benzylamino)-2-hydroxy-1-(3-methylbenzyl)propyl]-3-[(dipropylamino)sulfonyl]propanamide
2323	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-2-hydroxy-3-(isopentylamino)-1-(3-methylbenzyl)propyl]propanamide
2324	N-{(1S,2R)-3-(benzylamino)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxypropyl}-3-[(dipropylamino)sulfonyl]propanamide
2325	3-[(dipropylamino)sulfonyl]-N-{(1S,2R)-1-(3-fluoro-4-methoxybenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}propanamide
2326	N-[(1S,2R)-3-(benzylamino)-1-(3-fluoro-4-

	methoxybenzyl)-2-hydroxypropyl]-3-[(dipropylamino)sulfonyl]propanamide
2327	3-[(dipropylamino)sulfonyl]-N-[(1S,2R)-1-(3-fluoro-4-methoxybenzyl)-2-hydroxy-3-(isopentylamino)propyl]propanamide
2328	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-phenyl-2-(4H-1,2,4-triazol-3-ylthio)acetamide
2329	1-acetyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-phenylprolinamide

A compound of the formula:

Compound #	Compound Structure
2330	

The compounds in the table immediately below were prepared essentially using the methods described above and illustrated below in the schemes.

The following compounds were named using the Advanced Chemistry Development Inc. (ACD) nomenclature program, IUPAC Name Batch Version 4.5. The website for ACD is www.acdlabs.com.

2332	*N'*-((1*S*,2*R*)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(3*R*,4*S*)-3-(hydroxymethyl)-6-isopropyl-2,2-dioxido-3,4-dihydro-1*H*-isothiochromen-4-yl]amino}propyl)-5-methyl-*N*,*N*-dipropylisophthalamide
2333	*N'*-((1*S*,2*R*)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(3*R*,4*S*)-6-isopropyl-3-methyl-2,2-dioxido-3,4-dihydro-1*H*-isothiochromen-4-yl]amino}propyl)-5-methyl-*N*,*N*-dipropylisophthalamide
2334	*N'*-((1*S*,2*R*)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(3*R*,4*S*)-6-isopropyl-2,2-dioxido-3-propyl-3,4-dihydro-1*H*-isothiochromen-4-yl]amino}propyl)-5-methyl-*N*,*N*-dipropylisophthalamide

2336	*N'*-((1*S*,2*R*)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(3*S*,4*R*)-3-(hydroxymethyl)-6-isopropyl-2,2-dioxido-3,4-dihydro-1*H*-isothiochromen-4-yl]amino}propyl)-5-methyl-*N*,*N*-dipropylisophthalamide
2337	*N'*-((1*S*,2*R*)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(3*S*,4*R*)-3-(2-hydroxyethyl)-6-isopropyl-2,2-dioxido-3,4-dihydro-1*H*-isothiochromen-4-yl]amino}propyl)-5-methyl-*N*,*N*-dipropylisophthalamide
2339	*N'*-((1*S*,2*R*)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(3*S*,4*S*)-6-isopropyl-2,2-dioxido-3-propyl-3,4-dihydro-1*H*-isothiochromen-4-yl]amino}propyl)-5-methyl-*N*,*N*-dipropylisophthalamide
2340	*N'*-((1*S*,2*R*)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(3*S*,4*S*)-6-isopropyl-3-methyl-2,2-dioxido-3,4-dihydro-1*H*-isothiochromen-4-yl]amino}propyl)-5-methyl-*N*,*N*-dipropylisophthalamide
2341	*N'*-((1*S*,2*R*)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4*R*)-6-isopropyl-2,2-dioxido-3,4-dihydro-1*H*-isothiochromen-4-yl]amino}propyl)-5-methyl-*N*,*N*-dipropylisophthalamide

The compounds in the table immediately below were prepared essentially using the methods described above and illustrated below in the schemes.

The following compounds were named using the Advanced Chemistry Development Inc. (ACD) nomenclature program, IUPAC Name Batch Version 4.5. The website for ACD is www.acdlabs.com.

2342	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(3-methoxypropyl)(methylsulfonyl)amino]benzamide
2343	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(3-methoxypropyl)(methylsulfonyl)amino]benzamide
2344	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(2-methoxyethyl)(methylsulfonyl)amino]benzamide
2345	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-[(2-methoxyethyl)(methylsulfonyl)amino]nicotinamide
2346	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-[(3-hydroxypropyl)(methylsulfonyl)amino]nicotinamide

2347	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-[(2-hydroxyethyl)(methylsulfonyl)amino]nicotinamide
2348	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-[(2-methoxyethyl)(methylsulfonyl)amino]nicotinamide
2349	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(2-methoxyethyl)(methylsulfonyl)amino]isonicotinamide
2350	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(2-methoxyethyl)(methylsulfonyl)amino]nicotinamide
2351	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(3-hydroxypropyl)(methylsulfonyl)amino]isonicotinamide
2352	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(2-hydroxyethyl)(methylsulfonyl)amino]isonicotinamide
2353	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(2-hydroxyethyl)(methylsulfonyl)amino]nicotinamide
2354	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(3-hydroxypropyl)(methylsulfonyl)amino]nicotinamide
2355	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(3-methoxypropyl)(methylsulfonyl)amino]isonicotinamide
2356	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(3-methoxypropyl)(methylsulfonyl)amino]nicotinamide
2357	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(methylsulfonyl)-1H-indole-5-carboxamide
2358	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(methylsulfonyl)indoline-5-carboxamide
2359	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(methylsulfonyl)indoline-4-carboxamide
2360	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(methylsulfonyl)indoline-6-carboxamide
2361	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-

	(methylsulfonyl)-1H-indole-4-carboxamide
2362	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[1-methyl-1-(methylsulfonyl)ethyl]benzamide
2363	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[1-methyl-1-(methylsulfonyl)ethyl]benzamide
2364	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(ethylsulfonyl)benzamide
2365	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(propylsulfonyl)benzamide
2366	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(pentylsulfonyl)benzamide
2367	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(2-hydroxyethyl)sulfonyl]benzamide
2368	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(2-methoxyethyl)sulfonyl]benzamide
2369	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(2-ethoxyethyl)sulfonyl]benzamide
2370	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(3-hydroxypropyl)sulfonyl]benzamide
2371	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,3-dihydro-1-benzothiophene-5-carboxamide; 1,1-dioxide
2372	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-benzothiophene-5-carboxamide; 1,1-dioxide
2374	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,3-dihydro-1-benzothiophene-6-carboxamide; 1,1-dioxide
2375	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-benzothiophene-6-carboxamide; 1,1-dioxide
2376	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-methyl-2,3-dihydro-1,2-benzisothiazole-6-carboxamide; 1,1-dioxide
2377	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-methyl-2,3-dihydro-1,2-benzisothiazole-5-carboxamide; 1,1-dioxide

2378	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-methyl-1,3-dihydro-2,1-benzisothiazole-6-carboxamide; 2,2-dioxide
2343	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-methyl-1,3-dihydro-2,1-benzisothiazole-5-carboxamide; 2,2-dioxide
2344	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,2-dimethylchromane-6-carboxamide
2345	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,2-dimethylchromane-7-carboxamide

The compounds in the table immediately below were prepared essentially using the methods described above and illustrated below in the schemes.

The following compounds were named using the Advanced Chemistry Development Inc. (ACD) nomenclature program, IUPAC Name Batch Version 4.5. The website for ACD is www.acdlabs.com.

	Compound Name(s)
2346	benzyl (3R)-4-({(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}amino)-2,2,3-trimethyl-4-oxobutanoate
2347	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-4-(phenylsulfonyl)butanamide
2348	(3S)-tetrahydrofuran-3-yl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
2349	N^1-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^3-(phenylsulfonyl)-beta-alaninamide
2350	N^1-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^3-[(4-methylphenyl)sulfonyl]-beta-alaninamide
2351	N^1-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^3-[(4-fluorophenyl)sulfonyl]-beta-alaninamide
2352	N^1-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^3-[(4-methoxyphenyl)sulfonyl]-beta-alaninamide

2353	N^1-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^2-[(4-methylphenyl)sulfonyl]glycinamide
2354	N^1-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^2-[(4-fluorophenyl)sulfonyl]glycinamide
2355	N^1-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^2-[(4-methoxyphenyl)sulfonyl]glycinamide
2356	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[(4-chlorophenyl)sulfonyl]propanamide
2357	N^1-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^2-(benzylsulfonyl)glycinamide
2358	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[(4-fluorophenyl)sulfonyl]propanamide
2359	N^1-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^3-[(4-chlorophenyl)sulfonyl]-beta-alaninamide
2360	N^1-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^3-(benzylsulfonyl)-beta-alaninamide
2361	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[(4-methoxyphenyl)sulfonyl]propanamide
2362	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[(4-methylphenyl)sulfonyl]propanamide
2363	N^1-benzyl-N^4-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2,2-dimethylsuccinamide
2364	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)propanamide
2365	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanamide
2366	(2R)-N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-methyl-3-(phenylsulfonyl)propanamide
2367	(2S)-N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-methyl-3-(phenylsulfonyl)propanamide
2368	N^1-benzyl-N^5-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}pentanediamide
2369	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-[(phenylsulfonyl)methyl]acrylamide

2370	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-[(isopentylsulfonyl)methyl]acrylamide
2371	N^1-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^3-[(dipropylamino)carbonyl]-beta-alaninamide
2372	N^1-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^2-[(dipropylamino)carbonyl]glycinamide
2373	benzyl (4R)-4-{[((1S,2R)-1-benzyl-3-{[3-(dimethylamino)-2,2-dimethylpropyl]amino}-2-hydroxypropyl)amino]carbonyl}-1,3-oxazolidine-3-carboxylate compound with methyl hydroperoxide (1:2)
2374	tert-butyl (2R,3S)-2-hydroxy-3-({2-hydroxy-3-[(3-methoxyphenyl)sulfonyl]propanoyl}amino)-4-phenylbutyl(3-methoxybenzyl)carbamate
2383	N^1-[(1S,2R)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2386	N^1-[(1S,2R)-1-[3-(benzyloxy)-5-fluorobenzyl]-2-hydroxy-3-(isopentylamino)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2405	N^1-[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2406	N^1-[(1S,2R)-3-(benzylamino)-1-(cyclohexylmethyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2411	N^1-[(1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2413	N^1-[(1S,2R)-1-(cyclohexylmethyl)-2-hydroxy-3-(isopentylamino)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2414	N^1-[(1S,2R)-3-(benzylamino)-1-(cyclohexylmethyl)-2-hydroxypropyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2419	N^1-[(1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-(isopentylamino)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2421	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[hydroxy(2-methylphenyl)methyl]-5-methylbenzamide
2426	N^1-[(1R,2S)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2427	N^1-[(1R,2S)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(4-methylbenzyl)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide

2428	N^1-[(1R,2S)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2429	N^1-[(1R,2S)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(4-methylbenzyl)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide
2440	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-hydroxy-4-(phenylsulfonyl)butanamide
2442	benzyl (2R,3S)-4-(3,5-difluorophenyl)-3-[(3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-{[(1-propylbutyl)sulfonyl]methyl}propanoyl)amino]-2-hydroxybutyl(3-ethylbenzyl)carbamate
2445	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-7-(1H-imidazol-1-yl)-5,6-dihydronaphthalene-2-carboxamide
2446	2-{[({(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}amino)carbonyl]amino}-N,N-dipropylethanesulfonamide hydrochloride
2447	benzyl (2R,3S)-4-(3,5-difluorophenyl)-2-hydroxy-3-({N-(3-phenylpropanoyl)-3-[(1-propylbutyl)sulfonyl]alanyl}amino)butyl(3-ethylbenzyl)carbamate
2448	N^1-[(1S,2R)-3-[[(benzyloxy)carbonyl](3-ethylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-N^2-{[(3S)-tetrahydrofuran-3-yloxy]carbonyl}-D-leucinamide
2449	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-([1,3]oxazolo[4,5-b]pyridin-2-ylthio)acetamide
2450	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(imidazo[1,2-a]pyridin-2-ylmethyl)thio]acetamide
2451	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(5,7-dimethyl[1,2,4]triazolo[4,3-a]pyrimidin-3-yl)thio]acetamide
2452	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,3-dihydro-1H-cyclopenta[b]quinoline-9-carboxamide
2453	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-hydroxy-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxamide
2454	1817 or N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,3-dioxoisoindoline-5-carboxamide

2455	1-benzyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-imidazole-2-carboxamide
2456	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)thiophene-3-carboxamide
2457	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-isobutyl-1,3-dioxoisoindoline-5-carboxamide
2458	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-oxo-2-phenylpyrazolidine-3-carboxamide
2459	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5,6-dimethyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-carboxamide
2460	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(2,4-difluorobenzyl)oxy]propanamide
2461	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}thieno[2,3-c]pyridine-2-carboxamide
2463	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(2-methyl-1H-benzimidazol-1-yl)-4-oxobutanamide
2464	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2,5-dioxopyrrolidin-1-yl)-4-methylbenzamide
2465	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}thieno[3,2-b]pyridine-6-carboxamide
2466	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(2,3-dihydro-1H-indol-1-yl)-4-oxobutanamide
2468	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(1,3-dioxooctahydro-2H-isoindol-2-yl)butanamide
2469	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-[(4-methylphenyl)sulfonyl]-beta-alaninamide
2470	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(1H-indol-3-yl)-4-oxobutanamide
2471	N^2-(anilinocarbonothioyl)-N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}glycinamide
2472	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxamide

2473	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5,6,7,8-tetrahydro-4H-cyclohepta[c]isoxazole-3-carboxamide
2475	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^2-[(4-methylphenyl)sulfonyl]glycinamide
2477	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(3,5-dioxo-1,2,4-triazolidin-4-yl)benzamide
2478	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(2-hydroxyethoxy)benzamide
2479	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(1,3-dithian-2-yl)-3-furamide
2481	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepine-3-carboxamide
2482	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(4-fluorophenyl)-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxamide
2484	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5,6-dihydro-4H-cyclopenta[b]thiophene-2-carboxamide
2485	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-2-carboxamide
2486	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-7-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxamide
2487	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-carboxamide
2488	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4,5,6,7-tetrahydro-2H-indazole-3-carboxamide
2489	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxamide
2490	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-7-fluoro-4H-imidazo[5,1-c][1,4]benzoxazine-3-carboxamide
2491	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(3-fluoro-4-methoxyphenyl)-4-oxobutanamide

2492	methyl 4-({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)-4-oxobutyl-(dithiocarbamate)
2493	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}[1,2,4]triazolo[4,3-a]pyridine-6-carboxamide
2494	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-phenyl-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxamide
2495	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(4-methylphenyl)sulfonyl]acetamide
2496	3-(2-chlorophenyl)-2-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}propanamide
2498	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(4-methylphenyl)-4-oxobutanamide
2499	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(2-hydroxy-5-methylphenyl)-4-oxobutanamide
2500	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzamide
2501	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-oxo-4-thien-2-ylbutanamide or 2379
2502	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-hydroxybenzamide
2503	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(2,5-dioxopyrrolidin-1-yl)benzamide
2507	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(trifluoroacetyl)amino]butanamide
2510	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(1-hydroxycyclopentyl)thio]acetamide
2511	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2-oxocyclohexyl)propanamide
2512	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(2-naphthyl)-4-oxobutanamide

2513	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-oxo-2,3-dihydro-1H-indazole-4-carboxamide
2514	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,3-dimethyl-1H-thieno[2,3-c]pyrazole-5-carboxamide
2515	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^2-[(dimethylamino)sulfonyl]valinamide
2516	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(2-furyl)-4-oxobutanamide
2517	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(5-methyl-4-phenyl-1,3-oxazol-2-yl)benzamide
2518	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,6-dioxohexahydropyrimidine-4-carboxamide
2519	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5,7-dimethoxy-1-oxoindane-2-carboxamide
2521	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^5-(2-pyridin-2-ylethyl)pentanediamide
2522	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[4-(2-furoyl)piperazin-1-yl]-4-oxobutanamide
2523	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide
2524	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-oxo-1-(thien-2-ylmethyl)pyrrolidine-3-carboxamide
2525	2-[(cyanomethyl)thio]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}nicotinamide
2526	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(2-furoyl)-4-hydroxyprolinamide
2527	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4,5-dihydrofuro[2,3-g][2,1]benzisoxazole-8-carboxamide
2528	methyl 3-[({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)carbonyl]-5-methylthiophene-2-sulfenate
2529	2-(acetylamino)-2-(1H-1,2,3-benzotriazol-1-yl)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}acetamide

2530	1-{[(cyclohexylamino)carbonyl]amino}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}cyclopropanecarboxamide
2531	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(2-ethyl-4H-[1,2,4]triazolo[1,5-a]benzimidazol-4-yl)acetamide
2532	(2E)-N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^4-[4-(1,3-oxazol-5-yl)phenyl]but-2-enediamide
2533	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,3,4,5-tetrahydrothiopyrano[4,3-b]indole-8-carboxamide
2535	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)-4-oxobutanamide
2536	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(1-oxidothiomorpholin-4-yl)butanamide
2537	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-oxo-4-(2-thioxo-1,3-benzothiazol-3(2H)-yl)butanamide
2538	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-8H-thieno[2,3-b]indole-2-carboxamide
2539	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dihydro-2H-1,5-benzodioxepine-7-carboxamide
2540	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4H-chromeno[3,4-d]isoxazole-4-carboxamide
2542	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(3,4-difluorophenyl)-4-oxobutanamide
2543	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(3,4-difluorophenyl)-2-methyl-4-oxobutanamide
2544	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(3,4-difluorophenyl)-2-methoxy-4-oxobutanamide
2545	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-hydroxy-4-oxo-4-[3-(trifluoromethyl)phenyl]butanamide
2546	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-hydroxy-4-oxo-4-thien-2-ylbutanamide

2548	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(2-ethyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]propanamide
2549	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-oxoisoindoline-1-carboxamide
2550	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(7-methoxy-1-benzofuran-2-yl)-4-oxobutanamide
2551	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4H-chromeno[3,4-d]isoxazole-8-carboxamide
2552	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-methyl-4-oxo-4H-chromene-6-carboxamide
2553	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-([1,2,4]triazolo[4,3-b]pyridazin-6-ylthio)acetamide
2554	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(1,1-dioxidotetrahydrothien-2-yl)acetamide
2555	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(3,4-dihydro-2H-chromen-6-yl)-4-oxobutanamide
2556	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-ethyl-3-oxoisoindoline-1-carboxamide
2558	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(4-hydroxyphenyl)-4-oxobutanamide
2559	2-[(6-chloro[1,2,4]triazolo[4,3-b]pyridazin-3-yl)oxy]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}acetamide
2560	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-hydroxy-4-(3-methoxyphenyl)-4-oxobutanamide
2561	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-hydroxy-4-oxo-4-thien-3-ylbutanamide
2562	3-chlorophenyl 4-({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)-4-oxobutanoate
2563	4-(4-chloro-2-hydroxyphenyl)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-oxobutanamide
2565	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-{[(4-methylphenyl)sulfonyl]amino}-4-oxohexanamide

2566	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(6-hydroxy-3-oxo-2,3-dihydroimidazo[2,1-b][1,3]thiazol-2-yl)acetamide
2567	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(4,5-dihydro-1,3-thiazol-2-ylthio)acetamide
2568	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-imidazo[1,2-b]pyrazole-6-carboxamide
2570	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(6-methoxy-1,1'-biphenyl-3-yl)-4-oxobutanamide
2571	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(4-methoxyphenyl)-4-oxobutanamide
2572	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-oxobutanamide
2573	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)acetamide
2574	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)acetamide
2575	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-9-oxo-1,2,3,9-tetrahydrocyclopenta[b]chromene-7-carboxamide
2576	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-methyl-1H-benzo[g]indazole-3-carboxamide
2577	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxamide
2578	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(tetraazolo[1,5-b]pyridazin-6-ylthio)acetamide
2580	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(5-methyl-1H-pyrrol-2-yl)-4-oxobutanamide
2581	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-{[(trifluoromethyl)sulfonyl]amino}butanamide
2582	N-[(1S,2R)-3-(2-acetyl-1-ethylhydrazino)-1-benzyl-2-hydroxypropyl]-2-[(methylsulfonyl)amino]-1,3-thiazole-4-carboxamide

2583	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(1-hydroxy-2-propylpentyl)benzamide
2587	N^1-[(1S,2R)-3-[(2-{4-[(3-chlorobenzyl)oxy]phenyl}ethyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2589	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-morpholin-4-ylpropyl)amino]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide
2597	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^2-[(methylsulfonyl)acetyl]-N^2-pentylglycinamide
2598	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonyl}propanamide
2599	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonyl}propanamide
2600	ethyl 4-{[(2R,3S)-3-({3-[(dipropylamino)carbonyl]benzoyl}amino)-2-hydroxy-4-phenylbutyl]amino}piperidine-1-carboxylate
2601	N^1-((1S,2R)-1-benzyl-3-{[(3R)-1-benzylpyrrolidin-3-yl]amino}-2-hydroxypropyl)-N^3,N^3-dipropylisophthalamide
2602	methyl (2E)-2-[2-({(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}amino)-2-oxoethyl]-4-methylpent-2-enoate
2603	N^1-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^4-(4-methoxybenzyl)succinamide
2604	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-{[(4-fluorophenyl)sulfonyl]amino}-3-methylbutanamide
2605	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-9,10-dioxo-9,10-dihydroanthracene-2-carboxamide
2606	N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-4-(benzyloxy)benzamide
2607	N'-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N-methyl-N-phenylurea
2608	N'-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N,N-diisopropylurea
2609	N'-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N,N-diphenylurea

2610	N'-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N,N-dimethylurea
2611	methyl 2-{[({(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}amino)carbonyl]amino}benzoate
2613	2-methoxyethyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
2612	phenyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
2614	2-(benzyloxy)ethyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
2615	prop-2-ynyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
2616	(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
2617	pentyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
2618	neopentyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
2621	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(4-oxo-4H-chromen-3-yl)methyl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide
2622	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)amino]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide
2623	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-4-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide
2625	N^1-[(1S,2R)-3-[(1-acetylpiperidin-3-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide
2627	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-ethoxy-5-methylisophthalamide
2628	N^1-(allyloxy)-N^3-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylisophthalamide
2629	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-isobutoxy-5-methylisophthalamide
2630	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^3-(2,2,3,3,3-pentafluoropropyl)isophthalamide
2631	ethyl 4-({3-[({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)carbonyl]-5-methylbenzoyl}amino)butanoate

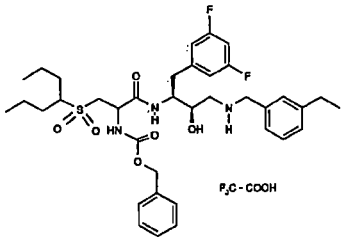
2632	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^3,N^3-bis(2,2,2-trifluoroethyl)isophthalamide
2633	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-ethyl-N^3-[(1-ethylpiperidin-4-yl)carbonyl]-5-methylisophthalamide
2634	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-(2,2,3,3,4,4,4-heptafluorobutyl)-5-methylisophthalamide
2635	N^1-(1-benzylpyrrolidin-3-yl)-N^3-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^1-ethyl-5-methylisophthalamide
2636	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^3-(tetrahydrofuran-2-ylmethyl)isophthalamide
2638	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(3R)-2-oxoazepan-3-yl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide
2639	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(1,1-dioxido-3,4-dihydro-2H-1,2-benzothiazin-4-yl)amino]-2-hydroxypropyl}-5-methyl-N^3,N^3-dipropylisophthalamide
2640	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[2-(4-methylpentanoyl)hydrazino]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide
2641	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(3-ethylphenyl)sulfonyl]propanamide
2642	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,2,3,3,4,4-hexafluoro-N^5,N^5-dipropylpentanediamide
2643	N^5-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-phenyl-N^1,N^1-dipropylpentanediamide
2644	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(3-hydroxypropyl)(methylsulfonyl)amino]benzamide
2645	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(2-hydroxyethyl)(methylsulfonyl)amino]benzamide
2646	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonyl}-N^3,N^3-dipropylisophthalamide
2647	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(3-hydroxypropyl)(methylsulfonyl)amino]benzamide

The compounds in the table immediately below were prepared essentially using the methods described above and illustrated below in the schemes.

The following compounds were named using the Advanced Chemistry Development Inc. (ACD) nomenclature program, IUPAC Name Batch Version 4.5. The website for ACD is www.acdlabs.com.

	Compound Name(s)	mass spec
2648	5-bromo-N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-N^3,N^3-dipropylisophthalamide	
2649	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(trifluoromethyl)sulfonyl]amino}benzamide	586.1
2657	N^1-{(1S,2R)-1-(3,5-dichlorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide	643.2
2664	N^1-[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(thien-2-ylmethyl)propyl]-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide	581.3
2665	N^1-{(1S,2R)-1-(4-fluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N^3,N^3-dipropylbenzene-1,3,5-tricarboxamide	593.3
2666	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(4-methyl-1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide	647
2667	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide	649
2668	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(methylsulfonyl)amino]benzamide	532.2
2671	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide	633
2672	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide hydrochloride	633.4
2675	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]propanamide hydrochloride	553

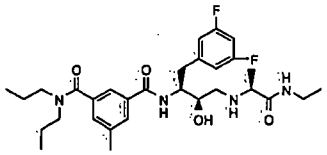
2677	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide	635
2678	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-2-[(methylsulfonyl)amino]-1,3-thiazole-4-carboxamide	637.6
2679	N^1-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-N^3,N^3-dipropyl-5-{[(trifluoromethyl)sulfonyl]amino}isophthalamide	665
2680	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(isopentylsulfonyl)propanamide	525
2681	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(1-methyl-1H-imidazol-4-yl)sulfonyl]amino}benzamide trihydrochloride	598.1
2682	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-{[(trifluoromethyl)sulfonyl]amino}benzamide	586
2684	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2-hydroxyethyl)(propyl)amino]sulfonyl}propanamide	556
2685	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(1,3-oxazol-2-yl)benzamide hydrochloride	506
2686	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-{[(2-hydroxy-1,1-dimethylethyl)amino]sulfonyl}-N^3,N^3-dipropylisophthalamide	717
2687	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2-hydroxy-1,1-dimethylethyl)amino]sulfonyl}benzamide	590
2688	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-{[(3-hydroxypropyl)amino]sulfonyl}-N^3,N^3-dipropylisophthalamide	703
2689	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(methylsulfonyl)amino]-1,3-thiazole-4-carboxamide	539.1

2690	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^2-(phenylacetyl)-3-[(1-propylbutyl)sulfonyl]alaninamide	686
2691	 racemic	702
2692	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(3-methylisoxazol-4-yl)-N^3,N^3-dipropylisophthalamide hydrochloride	647
2693	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-({[2-(methylamino)ethyl]amino}sulfonyl)-N^3,N^3-dipropylisophthalamide hydrochloride	702
2694	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-{[(2-hydroxyethyl)amino]sulfonyl}-N^3,N^3-dipropylisophthalamide	689
2695	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(methylsulfonyl)amino]butanamide	499
2696	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(piperazin-1-ylsulfonyl)-N^3,N^3-dipropylisophthalamide	714
2697	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[methyl(methylsulfonyl)amino]benzamide	546
2698	5-{[bis(2-hydroxyethyl)amino]sulfonyl}-N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-dipropylisophthalamide	733
2699	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,8-dimethylquinoline-3-carboxamide	518.3
2702	2-{[(2R,3S)-4-(3,5-difluorophenyl)-3-({3-[(dipropylamino)carbonyl]-5-methylbenzoyl}amino)-2-hydroxybutyl]amino}ethyl 2,4-difluorophenylcarbamate	661.7
2704	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-dipropyl-5-(1H-pyrazol-4-yl)isophthalamide	632

2706	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-hydroxyisoxazole-5-carboxamide	446.2
2707	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1-methyl-1H-imidazol-2-yl)-N^3,N^3-dipropylisophthalamide	646
2708	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-methylbenzamide hydrochloride	594.3
2709	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-{[(2-hydroxyethyl)amino]sulfonyl}-N^3-propylisophthalamide	647
2710	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-({[(1S)-2-hydroxy-1-methylethyl]amino}sulfonyl)-N^3,N^3-dipropylisophthalamide	703
2711	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-diethyl-5-(1,3-oxazol-2-yl)isophthalamide	605.4
2712	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-methylbenzamide hydrochloride	594.3
2713	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-{[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]sulfonyl}-N^3,N^3-dipropylisophthalamide	729
2714	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-({[(1R)-2-hydroxy-1-methylethyl]amino}sulfonyl)-N^3,N^3-dipropylisophthalamide	703
2716	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2-ethyl-1-hydroxybutyl)benzamide	539.3
2717	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(dimethylamino)sulfonyl]-N^3,N^3-dipropylisophthalamide	673.1
2719	N^1-[(1S,2R)-3-{[2-(aminosulfonyl)ethyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	569.6

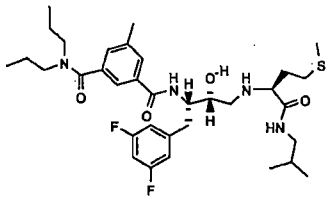
2723	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(4-phenylbutyl)amino]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide	594.5
2729	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-ethyl-N^3-methyl-5-(1,3-oxazol-2-yl)isophthalamide	591.4
2730	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-methyl-5-(1,3-oxazol-2-yl)-N^3-propylisophthalamide	605.4
2731	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-dipropyl-5-(pyrrolidin-1-ylsulfonyl)isophthalamide hydrochloride	699.1
2732	N^1-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-5-{[(2-hydroxy-1,1-dimethylethyl)amino]sulfonyl}-N^3,N^3-dipropylisophthalamide	669
2733	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-5-yl)-N^3,N^3-dipropylisophthalamide hydrochloride	633
2734	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide hydrochloride	629
2735	N^1-butyl-N^3-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^1-methyl-5-(1,3-oxazol-2-yl)isophthalamide	619.4
2736	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-dimethyl-5-(1,3-oxazol-2-yl)isophthalamide	577.3
2737	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-ethyl-5-(1,3-oxazol-2-yl)-N^3-propylisophthalamide	619.4
2738	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide hydrochloride	645
2739	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(1-propylbutyl)amino]sulfonyl}propanamide	568
2740	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-{[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]sulfonyl}-N^3,N^3-dipropylisophthalamide	729

2741	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-5-{[(2-hydroxy-1,1-dimethylethyl)amino]sulfonyl}-N^3,N^3-dipropylisophthalamide	713
2742	N^1-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(isobutylamino)propyl]-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide hydrochloride	571
2743	5-bromo-N^1-((1S,2R)-1-[3-fluoro-4-(trifluoromethyl)benzyl]-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-N^3,N^3-dipropylisophthalamide	734.1
2744	5-bromo-N^1-((1S,2R)-2-hydroxy-1-(2,3,4-trifluorobenzyl)-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-N^3,N^3-dipropylisophthalamide	
2745	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2-ethylbutanoyl)-5-methylbenzamide hydrochloride	551.3
2746	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-[(2-propylpiperidin-1-yl)carbonyl]benzamide hydrochloride	606.3
2747	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-[(2-methylpyrrolidin-1-yl)carbonyl]benzamide hydrochloride	564.4
2748	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(2,6-dimethylpiperidin-1-yl)carbonyl]-5-methylbenzamide hydrochloride	592.3
2749	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-{[(2-methoxyethyl)amino]sulfonyl}-N^3,N^3-dipropylisophthalamide	703
2750	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-N^3,N^3-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide dihydrochloride	689.6
2751	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-5-{[(2-hydroxyethyl)amino]sulfonyl}-N^3,N^3-dipropylisophthalamide	685.2
2752	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-(2-propylpentanoyl)benzamide hydrochloride	579.3

2753	N^1-(sec-butyl)-N^3-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^1-propylisophthalamide	594.6
2754	N^1-butyl-N^3-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^1-propylisophthalamide	594.6
2755	N^1-allyl-N^1-cyclopentyl-N^3-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylisophthalamide	600.5
2756	N^1,N^1-dibutyl-N^3-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylisophthalamide	608.6
2757	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-diisobutyl-5-methylisophthalamide	608.6
2758	N^1-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({3-[(1Z)-prop-1-enyl]benzyl}amino)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide	
2759	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[3-(ethylsulfonyl)benzyl]amino}-2-hydroxypropyl)-5-methyl-N^3,N^3-dipropylisophthalamide	644.2
2760	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-iodophenyl)cyclopropyl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide	704.1
2761		561.2
2762	N^1-[(1S,2R)-3-[(1,1'-biphenyl-3-ylmethyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	
2763	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-hydroxy-1-phenylpropyl)amino]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide	593.3
2764	N^1-cyclohexyl-N^3-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^1,5-dimethylisophthalamide	594.6
2765	N^1-cyclohexyl-N^3-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^1-ethyl-5-methylisophthalamide	606.6

2766	N^1-[(1S,2R)-3-{[3-(1-benzothien-2-yl)benzyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	684.5
2767	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-5-ethynyl-N^3,N^3-dipropylisophthalamide	630.2
2768	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-thien-3-ylbenzyl)amino]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide	633.0
2769	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(5-methylthien-2-yl)benzyl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide	647.0
2770	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-pyridin-4-ylbenzyl)amino]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide	629.6
2771	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(4-methylthien-2-yl)benzyl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide	648.5
2772	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[3-(2,4-dimethoxypyrimidin-5-yl)benzyl]amino}-2-hydroxypropyl)-5-methyl-N^3,N^3-dipropylisophthalamide	690.6
2773	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[3-(3,5-dimethylisoxazol-4-yl)benzyl]amino}-2-hydroxypropyl)-5-methyl-N^3,N^3-dipropylisophthalamide	647.6
2774	N^4-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-methyl-N^2,N^2-dipropylpyridine-2,4-dicarboxamide	581.3
2775	N^1-[(1S,2R)-3-{[3-(cyclopropylamino)benzyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	607.3
2776	N^1-[(1S,2R)-3-{[3-(cyclopropylamino)benzyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-ethynyl-N^3,N^3-dipropylisophthalamide	617.3
2777	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(2-isobutyl-1,3-thiazol-5-yl)cyclopropyl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide	641.3

2778	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide	659.3
2779	methyl 3-({[(2R,3S)-4-(3,5-difluorophenyl)-3-({3-[(dipropylamino)carbonyl]-5-methylbenzoyl}amino)-2-hydroxybutyl]amino}methyl)phenyl(methyl)carbamate	639.3
2780	N^1-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({3-[methyl(methylsulfonyl)amino]benzyl}amino)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide	659.3
2781	N^1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-({3-[(dimethylamino)sulfonyl]benzyl}amino)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	659.3
2782	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-methyl-N^3,N^3-dipropylisophthalamide	606.3
2783	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(2-isobutyl-1,3-thiazol-5-yl)methyl]amino}propyl)-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide	668.2
2785	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-1-methylethyl]amino}-2-hydroxypropyl)-5-ethynyl-N^3,N^3-dipropylisophthalamide	618.3
2786	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-1-methylethyl]amino}-2-hydroxypropyl)-5-methyl-N^3,N^3-dipropylisophthalamide	608.3
2787	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide	647.2
2788	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-1-methylethyl]amino}-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide	661.3
2789	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isobutylisoxazol-5-yl)cyclopropyl]amino}propyl)-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide	678.3

2790	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isobutylisoxazol-5-yl)cyclopropyl]amino}propyl)-5-ethynyl-N^3,N^3-dipropylisophthalamide	635.2
2791	N^1-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({3-[(methylsulfonyl)amino]benzyl}amino)propyl]-5-methyl-N^3,N^3-dipropylisophthalamide	645.2
2792	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3-isobutylisoxazol-5-yl)cyclopropyl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide	625.3
2793	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide	629.2
2794	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide	673.2
2795	N^1-[(1S,2R)-3-[(3-cyanobenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	577.2
2796		649.0
2797	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide	655.3
2799	N^1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-({3-[(1E)-hex-1-enyl]benzyl}amino)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	634.6
2800	N^1-[(1S,2R)-3-{[3-(5-acetylthien-2-yl)benzyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	676.5
2801	N^1-[(1S,2R)-3-[(3-allylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	592.6
2802	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(6-methoxypyridin-3-yl)benzyl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide	659.6

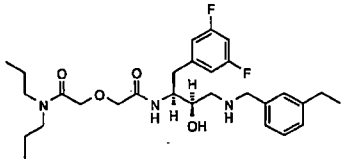
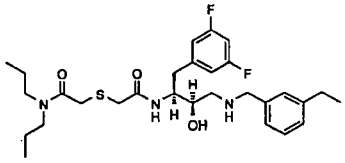
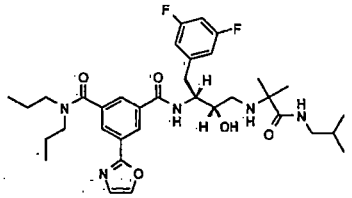
2803	N^1-[(1S,2R)-3-{[(2-tert-butylpyrimidin-4-yl)methyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	610.3
2804	N^4-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-6-methyl-N^2,N^2-dipropylpyridine-2,4-dicarboxamide	595.3
2805	N^1-[(1S,2R)-3-[(3-butylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	608.6
2806	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-pentylbenzyl)amino]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide	622.6
2807	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-pent-4-enylbenzyl)amino]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide	620.6
2808	N^1-[(1S,2R)-3-[(3-cyclopentylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	620.6
2809	N^1-[(1S,2R)-3-[(3-cyclohexylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	634.6
2810	N^1-[(1S,2R)-3-{[3-(cyclohexylmethyl)benzyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	648.6
2811	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-hex-5-enylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^3,N^3-dipropylisophthalamide	634.6
2812	methyl (2S)-3-[3-({[(2R,3S)-4-(3,5-difluorophenyl)-3-({3-[(dipropylamino)carbonyl]-5-methylbenzoyl}amino)-2-hydroxybutyl]amino}methyl)phenyl]-2-methylpropanoate	2812
2813	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(3-methylthien-2-yl)benzyl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide	648.5
2814	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(3-methylpyridin-2-yl)benzyl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide	643.6
2815	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(4-methylpyridin-2-yl)benzyl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide	643.6

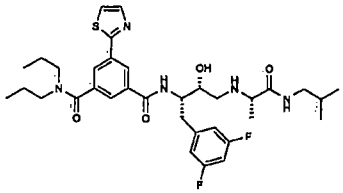
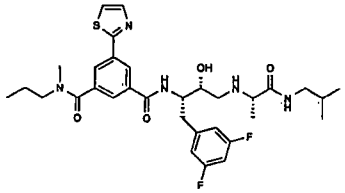
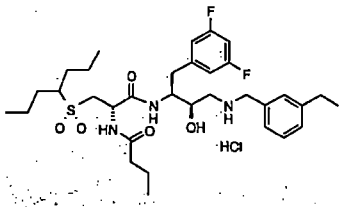
2816	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(5-methylpyridin-2-yl)benzyl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide	643.6
2817	N^1-[(1S,2R)-3-{[3-(4-chlorobutyl)benzyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	642.6
2818	N^1-[(1S,2R)-3-{[3-(3-cyanopropyl)benzyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	619.6
2819	N^1-[(1S,2R)-3-{[3-(4-cyanobutyl)benzyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	633.6
2820	N^1-[(1S,2R)-3-{[3-(6-cyanohexyl)benzyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	661.6
2821	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(6-methylpyridin-2-yl)benzyl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide	643.6
2822	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(1,3-oxazol-2-yl)benzyl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide	619.2
2823	methyl 3-{[((2R,3S)-4-(3,5-difluorophenyl)-3-{[3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoyl]amino}-2-hydroxybutyl)amino]methyl}phenyl(methyl)carbamate	
2824	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(1S)-1-[(isobutylamino)carbonyl]-3-(methylsulfonyl)propyl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide	681.0
2825	N^1-butyl-N^3-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-N^1,5-dimethylisophthalamide	580.3
2826	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-1-methylethyl]amino}-2-hydroxypropyl)-5-{[(2-hydroxy-1,1-dimethylethyl)amino]sulfonyl}-N^3,N^3-dipropylisophthalamide	745.1

2827	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-{methyl[(trifluoromethyl)sulfonyl]amino}-N^3,N^3-dipropylisophthalamide	727
2828	N^1-[(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-{[(2-hydroxy-1,1-dimethylethyl)amino]sulfonyl}-N^3,N^3-dipropylisophthalamide	639
2829	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-1-methylethyl]amino}-2-hydroxypropyl)-N^3,N^3-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide	677.1
2830	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[methyl(methylsulfonyl)amino]-N^3,N^3-dipropylisophthalamide	673.2
2831	N^1-butyl-N^3-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)-1-methylethyl]amino}-2-hydroxypropyl)-N^1,5-dimethylisophthalamide	594.3
2832	N^1-((1S,2R)-1-(2,4-difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-5-methyl-N^3,N^3-dipropylisophthalamide	620.2
2833	5-bromo-N^1-((1S,2R)-1-(2,4-difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-N^3,N^3-dipropylisophthalamide	684.1
2834	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(2-ethylpiperidin-1-yl)sulfonyl]propanamide	566
2835	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-ethynyl-N^3,N^3-dipropylisophthalamide	616.3
2836	N^1-cyclobutyl-N^3-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylisophthalamide	550.1
2837	N^1-cyclopentyl-N^3-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylisophthalamide	564.1
2838	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^3-pentylisophthalamide	566.1
2839	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-isopentyl-5-methylisophthalamide	566.1

2840	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-ethyl-N^3-(2-hydroxyethyl)-5-methylisophthalamide	568.1
2841	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-(2-ethoxyethyl)-5-methylisophthalamide	568.1
2842	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-(2-methoxyethyl)-N^3,5-dimethylisophthalamide	568.1
2843	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-(2-furylmethyl)-N^3,5-dimethylisophthalamide	590.1
2844	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2R,5R)-2,5-dimethylpyrrolidin-1-yl]carbonyl}-5-methylbenzamide	578.1
2845	N^1-cyclopentyl-N^3-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^1,5-dimethylisophthalamide	578.1
2846	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,5-dimethyl-N^3-pentylisophthalamide	580.1
2847	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-(2-hydroxyethyl)-5-methyl-N^3-propylisophthalamide	582.1
2848	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-ethyl-N^3-(2-methoxyethyl)-5-methylisophthalamide	582.1
2849	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^3-(2-methylcyclohexyl)isophthalamide	592.1
2850	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-(2-methoxyethyl)-5-methyl-N^3-propylisophthalamide	596.1
2851	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-bis(2-methoxyethyl)-5-methylisophthalamide	612.1
2852	N^1-allyl-N^1-cyclohexyl-N^3-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylisophthalamide	618.1
2853	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^3,N^3-dipentylisophthalamide	636.2

2854	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-bis(2-ethoxyethyl)-5-methylisophthalamide	640.1
2855	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-naphthylmethyl)amino]propyl}-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide	655.2
2856	N^1-butyl-N^3-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-N^1,5-dimethylisophthalamide	592.3
2857	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-{[(2-hydroxy-1,1-dimethylethyl)amino]sulfonyl}-N^3,N^3-dipropylisophthalamide	743.2
2860	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(3-hydroxypropyl)sulfonyl]-N^3,N^3-dipropylisophthalamide	688
2861	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1H-imidazol-4-yl)-N^3,N^3-dipropylisophthalamide trifluoroacetate	632
2862	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-isoxazol-3-yl-N^3,N^3-dipropylisophthalamide	633
2863	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-(1,3-oxazol-2-yl)benzamide	647
2864	N^4-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-6-methyl-N^2,N^2-dipropylpyridine-2,4-dicarboxamide	577.2
2865	N^4-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-6-methyl-N^2,N^2-dipropylpyridine-2,4-dicarboxamide	621.2
2866	N^4-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-6-methyl-N^2,N^2-dipropylpyridine-2,4-dicarboxamide	607.3
2867	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-N^3,N^3-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide	675.4

2868	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[methyl(thien-2-ylsulfonyl)amino]-N^3,N^3-dipropylisophthalamide	741
2869	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-({[(2R)-2-hydroxypropyl]amino}sulfonyl)-N^3,N^3-dipropylisophthalamide	703
2870	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(2-isobutyl-1,3-thiazol-5-yl)cyclopropyl]amino}propyl)-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide	694.2
2871	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-hydroxy-N^5,N^5-dipropylpentanediamide	548.1
2872		534.1
2873		550.1
2874		656.3
2875	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(methylsulfonyl)methyl]benzamide	531
2876	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-(2-methylpentanoyl)benzamide hydrochloride	551.3
2877	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(methylsulfonyl)amino]-N^3,N^3-dipropylisophthalamide	659.2
2878	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide dihydrochloride	568

2879	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^2-propionyl-3-[(1-propylbutyl)sulfonyl]-D-alaninamide	624
2880		658.3
2881		630.3
2882	N^1-butyl-N^3-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^1-methyl-5-(1,3-thiazol-2-yl)isophthalamide	635.4
2883	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(3-hydroxypropyl)(methylsulfonyl)amino]benzamide	590.2
2884	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(methylsulfonyl)benzamide	517.2
2885	 as drawn	638
2886	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-dipropyl-5-pyrimidin-2-ylisophthalamide	644
2887	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-({[(2S)-2-hydroxypropyl]amino}sulfonyl)-N^3,N^3-dipropylisophthalamide	703
2888	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-methyl-N^3-propyl-5-(1,3-thiazol-2-yl)isophthalamide	621.3
2889	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2-methylpentanoyl)-5-(1,3-oxazol-2-yl)benzamide	604.3

2890	N^1-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({3-[(methylsulfonyl)amino]benzyl}amino)propyl]-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide	698.2
2891	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^2-(2,2-dimethylpropanoyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride	652
2892	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonyl}-N^3,N^3-dipropylisophthalamide	743
2893	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(3-hydroxypropyl)(methylsulfonyl)amino]benzamide	590.0
2894	N^2-acetyl-N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride	610
2895	2-[allyl(methylsulfonyl)amino]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,3-thiazole-5-carboxamide	579.2
2896	3-(butylsulfonyl)-N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide bis(trifluoroacetate)	526
2897	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide bis(trifluoroacetate)	594
2898	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^2-isobutyryl-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride	638

The compounds in the table immediately below were prepared essentially using the methods described above and illustrated below in the schemes.

The following compounds were named using the Advanced Chemistry Development Inc. (ACD) nomenclature program, IUPAC

Name Batch Version 4.5. The website for ACD is www.acdlabs.com.

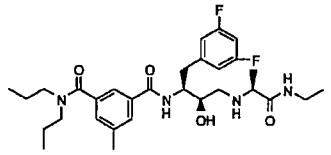
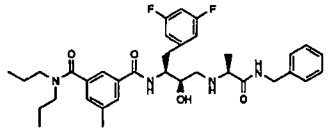
	Compound Name(s)	mass spec
2899	N-[(1S,2R)-3-(butylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-4-(ethylthio)benzamide	
2900	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(2-fluorophenyl)-5-oxopyrrolidine-3-carboxamide	540.2
2901	N^1-(4-tert-butyl-1,3-thiazol-2-yl)-N^4-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}succinamide	
2902	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-hydroxy-6-(1-hydroxy-2,2-dimethylpropyl)pyridine-2-carboxamide	542.3
2903	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-{[(ethylamino)carbonyl]amino}benzamide	525.3
2908	3-acetyl-N-[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]benzamide	
2909	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)amino]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide	
2913	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2,2-dioxido-3,4-dihydro-1,2-benzoxathiin-4-yl)amino]-2-hydroxypropyl}-5-methyl-N^3,N^3-dipropylisophthalamide	
2916	N^1-{(1S,2R)-1-{[5-(cyanomethyl)-1H-imidazol-1-yl]methyl}-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^3,N^3-dipropylisophthalamide	
2918	N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(2-ethylpyrimidin-4-yl)methyl]amino}-2-hydroxypropyl)-5-methyl-N^3,N^3-dipropylisophthalamide	
2920	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-{[ethyl(methyl)amino]sulfonyl}-N^3,N^3-dipropylisophthalamide	687.3

2921	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(2-hydroxyethyl)(methylsulfonyl)amino]benzamide	575.9
2922	5-bromo-N^1-{(1S,2R)-1-(2,4-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-dipropylisophthalamide	646.4
2923	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(2-methoxyethyl)(methylsulfonyl)amino]benzamide hydrochloride	590.0
2924	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(methylsulfonyl)methyl]benzamide	531.2
2925	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(4-hydroxybutyl)sulfonyl]-N^3,N^3-dipropylisophthalamide hydrochloride	702.4
2926	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(dipropylamino)isoquinoline-7-carboxamide	589.4
2927	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-{[(2-hydroxyethyl)(methyl)amino]sulfonyl}-N^3,N^3-dipropylisophthalamide	703.4
2928	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(ethylamino)sulfonyl]-N^3,N^3-dipropylisophthalamide	673.4
2929	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(5-methyl-1,2,4-oxadiazol-3-yl)-N^3,N^3-dipropylisophthalamide hydrochloride	648.4
2930	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4-carboxamide	
2931	3-(butylsulfonyl)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}propanamide	511
2932	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-dipropylmalonamide	
2933	N^2-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-dipropylbicyclo[2.2.1]hept-5-ene-2,3-dicarboxamide	
2934	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-dipropylcyclopentane-1,3-dicarboxamide	

2935	N^2-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dimethyl-N^5,N^5-dipropylthieno[2,3-b]thiophene-2,5-dicarboxamide	
2936	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-phenyl-N^5,N^5-dipropylpentanediamide	
2937	N^2-benzyl-N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^2-[2-(dipropylamino)-2-oxoethyl]glycinamide	
2938	3-(4-chlorophenyl)-N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^5,N^5-dipropylpentanediamide	
2939	(2E)-N^5-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(methoxyimino)-N^1,N^1-dipropylpentanediamide	
2940	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^2-[2-(dipropylamino)-2-oxoethyl]-N^2-phenylglycinamide	
2941	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^2,N^2-dipropylcyclohexane-1,2-dicarboxamide	
2942	N^1-[(1S,2R)-3-[(benzyloxy)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide	
2943	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-phenylpropanamide	
2945	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1H-imidazol-2-yl)-N^3,N^3-dipropylisophthalamide	632.3
2946	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(1-hydroxy-2-propylpentyl)benzamide	567.3
2947	N-{(1R,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-isobutyrylbenzamide hydrochloride	536.2
2948	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2-propylpentanoyl)benzamide	565.3
2949	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2-ethylbutanoyl)benzamide hydrochloride	537.3

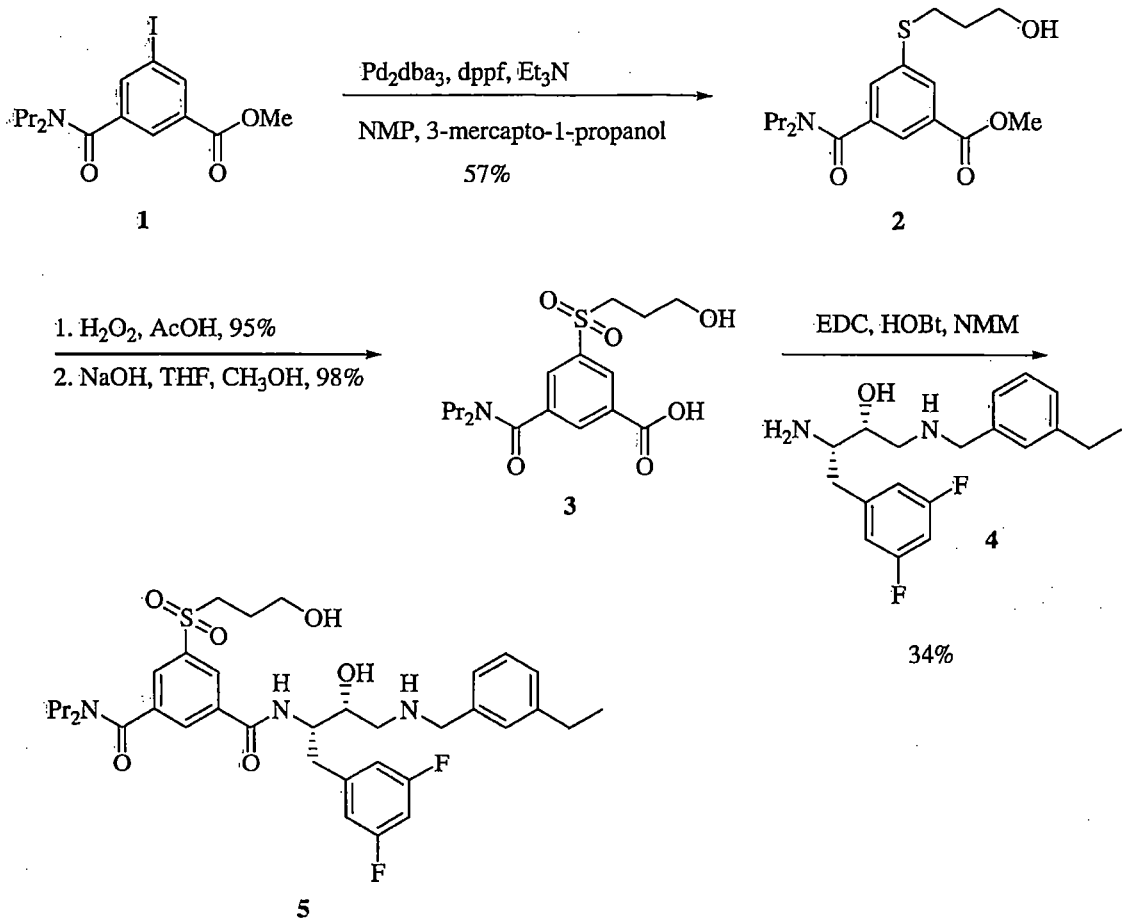
The compounds in the table immediately below were prepared essentially using the methods described above and illustrated below in the schemes.

The following compounds were named using the Advanced Chemistry Development Inc. (ACD) nomenclature program, IUPAC Name Batch Version 4.5. The website for ACD is www.acdlabs.com.

2951		561.2
2953		623.2
2954	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,3-dimethyl-N^2,N^2-dipropylcyclopropane-1,2-dicarboxamide	558.4
2956	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-N^5,N^5-dipropylpentanediamide	546.5
2957	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,3-dimethyl-N^5,N^5-dipropylpentanediamide	560.5
2958	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-ethyl-3-methyl-N^5,N^5-dipropylpentanediamide	574.5
2959	N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-hydroxy-3-methyl-N^5,N^5-dipropylpentanediamide	562.5
2960	2-[allyl(methylsulfonyl)amino]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,3-oxazole-4-carboxamide	563.2
2962	N^1-[(1S,2R)-3-({2-[bis(2-hydroxyethyl)amino]ethyl}amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide	593.5
2963	N^1-[(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide dihydrochloride	

2964	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[4-(hydroxymethyl)-1,3-oxazol-2-yl]benzamide hydrochloride	536.3

EXAMPLE SP-131



Step 1: A solution of iodide **1** (1.70 g, 4.36 mmol), Pd_2dba_3 (80 mg, 0.087 mmol), dppf (193 mg, 0.349 mmol), and triethylamine (882 mg, 8.72 mmol) in *N*-methylpyrrolidine (10 mL) was degassed under nitrogen for 15 min. 3-Mercapto-1-propanol (402 mg, 4.36 mmol) was added and the reaction mixture was heated at 60 °C for 2 h. The reaction mixture was cooled to room temperature and then partitioned between ethyl acetate and saturated sodium chloride. The organic layer was washed (2x) with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:1 hexanes/ethyl acetate) gave sulfide **2** (880 mg, 57%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.85 (s, 1H), 7.50 (s, 1H), 3.92 (s, 3H), 3.77 (m, 2H), 3.47 (m, 4H),

3.11 (m, 4H), 1.92 (m, 2H), 1.70 (m, 2H), 0.98 (m, 3H), 0.78 (m, 3H); ESI MS *m/z* 354 $[M + H]^+$.

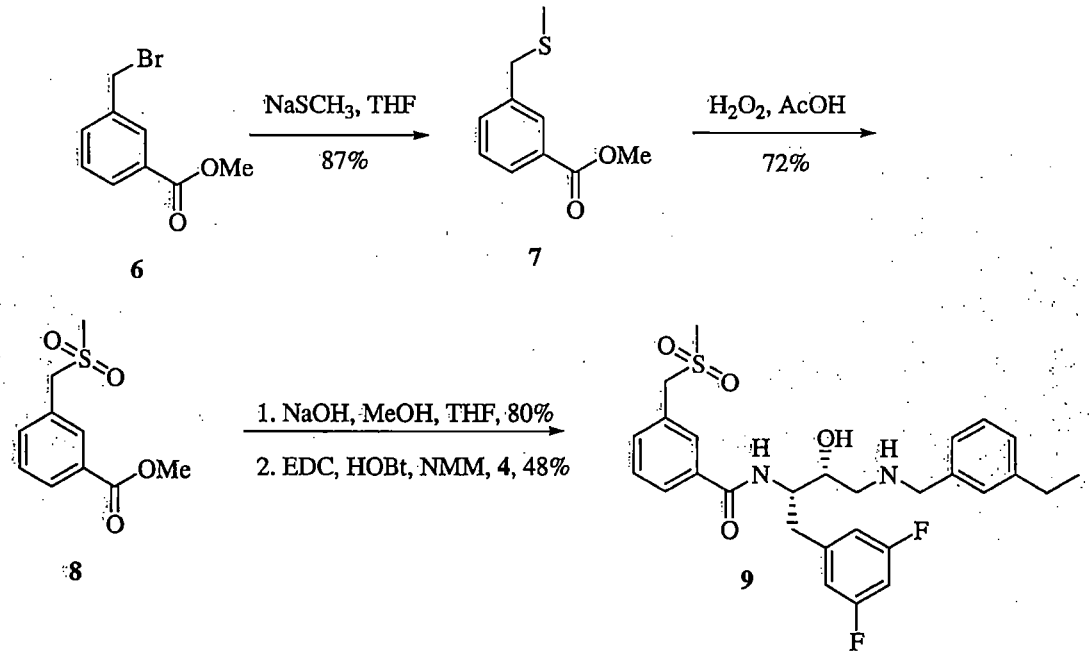
Step 2: To a stirred solution of sulfide **2** (880 mg, 2.49 mmol) in 1:1 acetic acid/water (15 mL) was added excess 30% hydrogen peroxide. The reaction mixture was stirred overnight and then partitioned between ethyl acetate and water. The organic layer was washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a sulfone (912 mg, 95%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 8.28 (s, 1H), 8.11 (s, 1H), 3.99 (s, 3H), 3.71 (m, 2H), 3.55 (m, 2H), 3.44 (m, 2H), 3.38 (m, 2H), 2.11 (m, 2H), 1.88 (m, 2H), 1.78 (m, 2H), 0.77 (m, 3H), 0.56 (m, 3H); APCI MS *m/z* 387 $[M + H]^+$.

Step 3: A solution of the sulfone from step 2 (912 mg, 2.36 mmol) in 3:1:1 methanol/tetrahydrofuran/1 N sodium hydroxide (20 mL) was stirred at room temperature for 2 h. The reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was acidified to pH 3 with 1 N hydrochloric acid and extracted with chloroform. The organic layer was dried (sodium sulfate), filtered, and concentrated to give acid **3** (860 mg, 98%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.24 (s, 1H), 8.08 (s, 1H), 4.11 (m, 2H), 3.69 (m, 2H), 3.33 (m, 2H), 3.13 (m, 2H), 1.98 (m, 2H), 1.75 (m, 2H), 1.58 (m, 2H), 1.03 (m, 3H), 0.79 (m, 3H).

Step 4: To a stirred solution of acid **3** (630 mg, 1.69 mmol), amine **4** (688 mg, 1.69 mmol), HOBt (251 mg, 1.86 mmol), and *N*-methylmorpholine (855 mg, 8.45 mmol) in methylene chloride (15 mL) was added EDC (583 mg, 3.04 mmol). The reaction mixture was stirred overnight and then partitioned between ethyl acetate and water. The organic layer was washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and saturated

sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 93:7:1 methylene chloride/methanol/ammonium hydroxide) gave ALB 8198 (**5**) (400 mg, 34%) as a white solid: mp 62-66 □C; IR (ATR) 3293, 2964, 2874, 1614 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.06 (s, 1H), 7.85 (s, 1H), 7.28 (m, 2H), 7.15 (m, 2H), 6.85 (m, 2H), 6.62 (m, 1H), 4.31 (m, 1H), 3.79 (m, 2H), 3.67 (m, 2H), 3.55 (m, 2H), 3.24 (m, 2H), 3.05 (m, 2H), 2.91 (m, 4H), 2.86 (m, 1H), 2.60 (m, 2H), 1.95 (m, 2H), 1.73 (m, 2H), 1.56 (m, 2H), 1.22 (m, 3H), 1.03 (m, 3H), 0.72 (m, 3H); APCI MS *m/z* 688 $[M + H]^+$; HPLC: Method A, 8.36 min (>99%, AUC). Anal. Calcd for $C_{36}H_{47}F_2N_3O_6S \cdot 0.25H_2O$: C, 62.45; H, 6.92; N, 6.07. Found: C, 62.21; H, 6.69; N, 5.97.

EXAMPLE SP-132



Step 1: A mixture of benzoate **6** (870 mg, 3.79 mmol) and sodium thiomethoxide (292 mg, 4.18 mmol) was stirred in THF (20 mL) at 40 □C. After 48 h, the reaction mixture was cooled to room

temperature and then partitioned between ethyl acetate and water. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure to give sulfide **7** (650 mg, 87%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.88 (d, J = 8 Hz, 1H), 7.40 (d, J = 8 Hz, 1H), 7.27 (m, 1H), 3.92 (s, 3H), 3.71 (s, 2H), 1.99 (s, 3H).

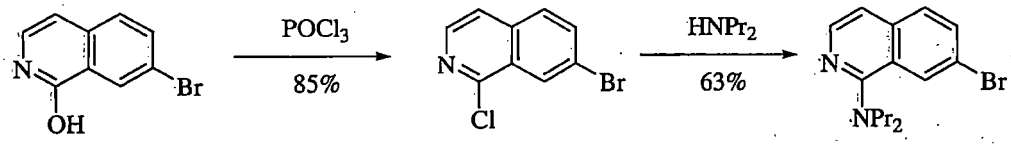
Step 2: To a stirred solution of sulfide **7** (650 mg, 3.31 mmol) in 1:1 acetic acid/water (25 mL) was added excess 30% hydrogen peroxide. The reaction mixture was stirred overnight and then partitioned between ethyl acetate and water. The organic layer was washed with sodium bicarbonate, water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give sulfone **8** (540 mg, 72%) as a clear oil: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.12 (s, 1H), 8.04 (d, J = 7 Hz, 1H), 7.74 (d, J =7 Hz, 1H), 7.54 (m, 1H), 4.62 (s, 2H), 3.98 (s, 3H), 2.98 (s, 3H).

Step 3: A mixture of sulfide **8** (540 mg, 2.37 mmol) in 3:1:1 methanol/THF/2 N sodium hydroxide (10 mL) was stirred overnight. The reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was acidified to pH 3 with 1 N HCl and extracted with chloroform. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide an acid (406 mg, 80%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.96 (d, J = 7 Hz, 1H), 7.64 (d, J = 7 Hz, 1H), 7.57 (m, 1H), 4.59 (s, 2H), 2.92 (s, 3H).

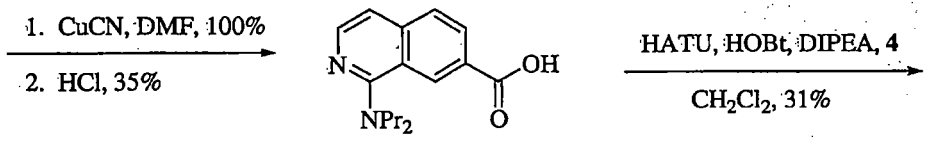
Step 4: To a stirred solution of acid from step 3 (260 mg, 1.21 mmol), HOBt (163 mg, 1.21 mmol), amine **4** (495 mg, 1.21 mmol), and *N*-methylmorpholine (612 mg, 6.05 mmol) was added EDC (418 mg, 2.18 mmol). The reaction mixture was stirred

overnight and then partitioned between ethyl acetate and water. The organic layer was washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 93:7:1 methylene chloride/methanol/ammonium hydroxide) gave ALB 8653 (**9**) (308 mg, 48%): mp 147-149 □C; IR (ATR) 3286, 2961, 1633, 1596 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.39 (d, J = 9 Hz, 1H), 7.77 (s, 1H), 7.72 (d, J = 7 Hz, 1H), 7.54 (d, J = 7 Hz, 1H), 7.48 (m, 1H), 7.18 - 6.93 (m, 7H), 5.03 (br s, 1H), 4.51 (s, 2H), 4.18 (br s, 1H), 3.68 (s, 2H), 3.67 (m, 1H), 3.12 (m, 1H), 2.91 (s, 3H), 2.88 (m, 1H), 2.61 (m, 1H), 2.45 (m, 2H), 2.43 (m, 2H), 1.13 (m, 3H); ESI MS m/z 531 $[M + H]^+$; HPLC: Method A, 6.81 min (>99%, AUC). Anal. Calcd for $C_{31}H_{40}F_2N_4O_4 \bullet 0.25H_2O$: C, 62.85; H, 6.12; N, 5.23. Found: C, 62.96; H, 5.83; N, 5.09.

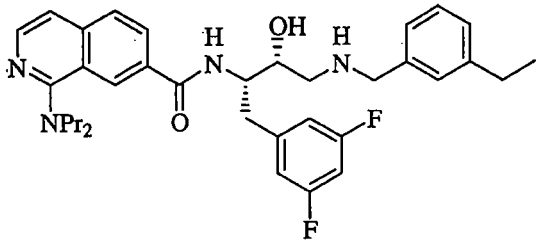
EXAMPLE SP-133



10 **11** **12**



13



14

Step 1: A solution of hydroxide **10** (2.5 g, 11.1 mmol) and $POCl_3$ (10.4 mL, 111 mmol) was stirred at 70 °C for 2.5 h. The reaction mixture was cooled to room temperature, poured into ice water and the solution was stirred overnight. The aqueous mixture was diluted with $CHCl_3$, washed with a saturated solution of $NaHCO_3$, saturated NaCl, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford chloride **11** (2.3 g, 85%) as a tan solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.39-8.36 (m, 2H), 8.09-8.02 (m, 2H), 7.95 (d, J = 6 Hz, 1H).

Step 2: A solution of chloride **11** (500 mg, 2.1 mmol) and dipropylamine (2.8 mL, 21 mmol) was heated at 150 °C in a sealed tube for 2 d. The reaction mixture was cooled, and the solvent was removed under reduced pressure to provide amine **12** (400 mg, 63%) as a brown oil: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.55 (s, 1H), 7.90 (d, J = 6 Hz, 1H), 7.75-7.64 (m, 2H), 6.87 (d, J = 6 Hz, 1H), 3.42 (q, J = 7 Hz, 4H), 1.65 (q, J = 7 Hz, 4H), 0.94 (t, J = 7 Hz, 6H).

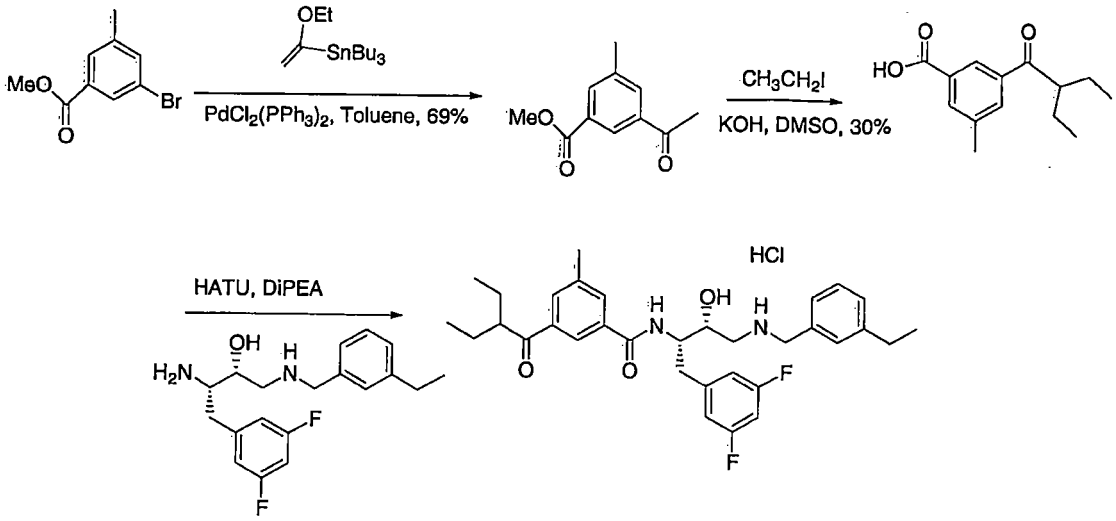
Step 3: A solution of amine **12** (350 mg, 1.1 mmol) and CuCN (204 mg, 2.2 mmol) in DMF (2 mL) was stirred at reflux for 24 h. The reaction mixture was cooled to room temperature, diluted with water, and extracted with EtOAc (3 x 50 mL). The combined organics were washed with saturated NaCl, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a nitrile (279, mg, 100%) as a brown oil, which was used without any further characterization.

Step 4: A solution of the nitrile from step 4 (279 mg, 1.1 mmol) in concentrated HCl (4 mL) was heated at 150 °C in a sealed tube for 14 h. The reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure,

and the residue was dissolved in a 25% NH_4OH/H_2O solution and stirred for 1 h. The solution was acidified to pH 4, and extracted with $CHCl_3$ (3 x 50mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide acid **13** (104 mg, 35%) as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.15 (d, J = 8 Hz, 1H), 8.01 (d, J = 6 Hz, 1H), 7.79 (d, J = 7 Hz, 1H), 7.21 (d, J = 6 Hz, 1H), 3.47 (m, 4H), 1.68 (m, 4H), 0.83 (m, 6H); ESI MS m/z 273 $[M + H]^+$.

Step 5: To a stirred solution of acid **13** (103 mg, 0.38 mmol), amine **4** (154 mg, 0.38 mmol), HOBt (77 mg, 0.57 mmol), and DIPEA (0.2 mL, 1.1 mmol) in methylene chloride (4 mL) was added HATU (216 mg, 0.57 mmol). The reaction mixture was stirred overnight and then partitioned between methylene chloride and 1 N hydrochloric acid. The organic layer was washed with saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9:1 methylene chloride/methanol) gave a ALB 8655 (70 mg, 31): mp: 142-151 °C; IR (ATR): 3222, 1621, 1585, 1114, 848, 700 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.46 (s, 1H), 9.09 (s, 2H), 8.57 (s, 1H), 8.35 (s, 1H), 8.09 (s, 1H), 7.29 (s, 1H), 7.46 (d, J = 6 Hz, 1H), 7.40 (s, 1H), 7.35 (d, J = 7 Hz, 1H), 7.27 (t, J = 7 Hz, 1H), 7.19 (d, J = 7 Hz, 1H), 7.04-6.97 (m, 3H), 4.24-4.08 (m, 4H), 3.73 (br s, 4H), 3.54 (br s, 8H), 3.18 (d, J = 8 Hz, 1H), 3.10 (br s, 1H), 3.00 (m, 1H), 2.87 (d, J = 8 Hz, 1H), 2.56-2.50 (m, 2H), 1.75 (d, J = 6 Hz, 4H), 1.12 (t, J = 7 Hz, 3H), 0.88 (t, J = 7 Hz, 6H); APCI MS m/z 589 $[M + H]^+$; HPLC: Method A, 7.21 min (99%, AUC). Anal. Calcd for $C_{35}H_{42}F_2N_4O_2 \cdot 2HCl \cdot 0.5H_2O$: C, 62.68; H, 6.76; N, 8.35. Found: C, 62.60; H, 6.89; N, 8.29.

EXAMPLE SP-134



Ketones used in this EXAMPLE can be generally prepared as shown in chart U.

Step 1.

To a stirred solution of the halide (4.68 g, 20 mmol) in anhydrous toluene (10 mL) was added (α-ethyoxyvinyl)-tributyltin (7.66 ml, 22 mmol) and dichlorobis(triphenylphosphine)palladium (0.715 g, 1 mmol). The reaction was heated under nitrogen at 100 °C for 14 hours. After hydrolysis of the reaction mixture with 1N HCl (100 ml), the organic layer was extracted with diethyl ether (100 mL x 2), washed with aqueous potassium fluoride (10%, 100 mL), dried with magnesium sulfate, and concentrated under vacuo. The crude product was purified by flash column chromatography (10 - 20% ethyl acetate: hexane) to afford 2.5 g of 3-Acetyl-5-methyl-benzoic acid methyl ester as a white solid (65% yield). IR (drift) 3090, 3078, 3019, 2998, 2952, 2920, 1716, 1681, 1608, 1596, 1448, 1435, 1273, 1237, 1234, 1197, 1118, 893 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.44 (s, 1 H), 8.10 (s, 1 H), 8.01 (s, 1 H), 3.99 (s, 3 H), 2.68 (s, 3 H), 2.51 (s, 3 H); HRMS (FAB) calcd for $C_{11}H_{12}O_3 + H^+$= 193.0865, found 193.0868.

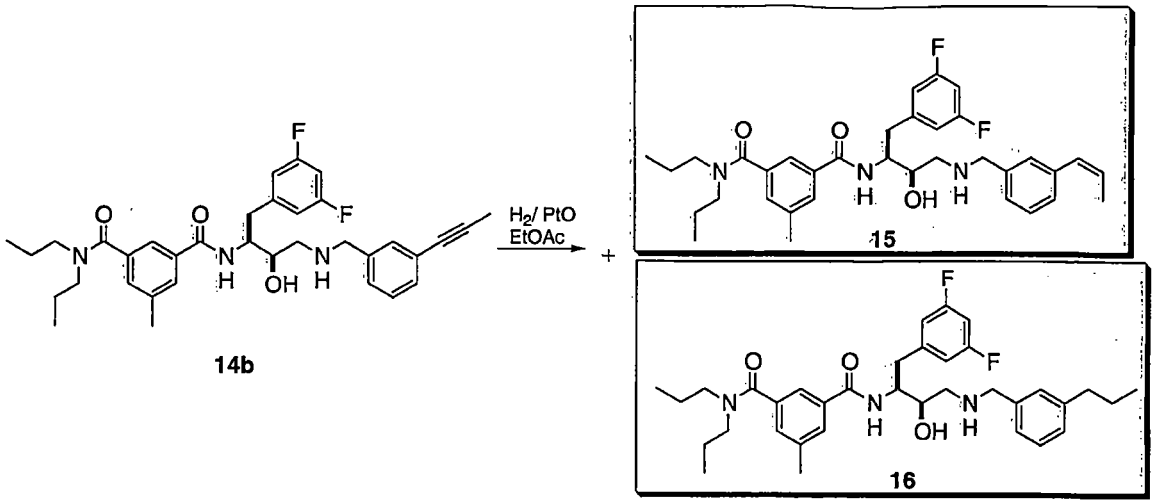
Step 2.

To a stirred suspension of potassium hydroxide (pellets) (5.0 g, 90.0 mmol) in dimethylsulfoxide (10 mL) was added 3-Acetyl-5-methyl-benzoic acid methyl ester (0.8 g, 4.5 mmol) and 1 - iodopropane (2.9mL, 36 mmol) at room temperature. The reaction mixture was heated to 50 - 60 °C and stirred for additional 1 hour. After cooled to room temperature, the reaction was poured into 1N aqueous HCl solution (100 mL). The aqueous solution was extracted with diethyl ether (80 mL x 2). The combined organic layer was washed with brine (80 mL x 2), dried with magnesium sulfate, and concentrated under *vacuo*. The crude product was purified by flash column chromatography (30 - 40% ethyl acetate: hexane) to afford 0.316 g of the benzoic acid as a pale yellow solid (30% yield).

Step 3

To a stirred solution of acid the benzoic acid (138.2 mg, 0.59 mmol) in DMF (3 mL) was added HATU (281 mg, 0.74 mmol), diisopropylethylamine (0.31 mL, 1.77 mmol), and then the amine (240 mg, 0.59 mmol) at room temperature. After stirred for 1 hour at room temperature, the reaction mixture was poured into 40 mL water. The aqueous solution was extracted with chloroform (50 mL x 2), and then organic layers were collected, washed with water (40 mL x 2), 1N HCl (40 mL x 2), sat. aq. sodium bicarbonate (40 mL x 2) and brine (40 mL x 2), dried over sodium sulfate, and concentrated under *vacuo*. The crude product was purified by flash column chromatography (10% methanol: dichloromethane) to afford 198 mg of the desired product as a pale yellow solid (61% yield).

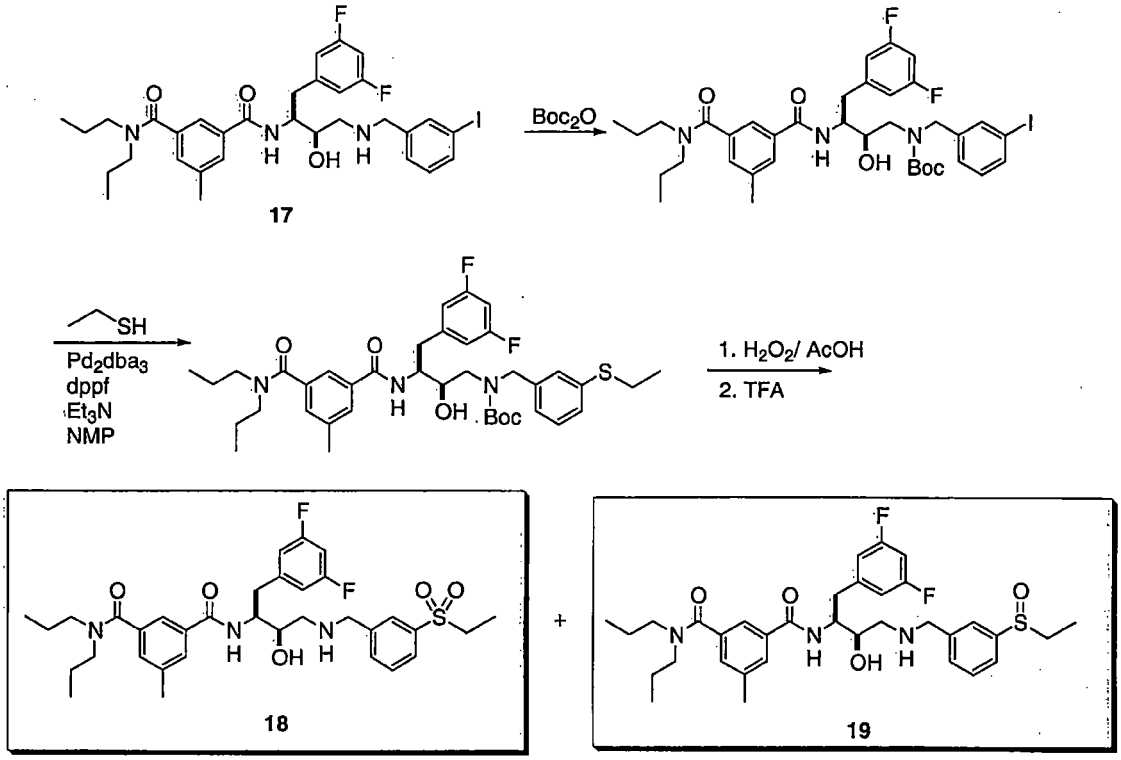
EXAMPLE SP-135



14b

Compound **14b** (1 equiv, 0.064 mmol, 37.6 mg) was dissolved in EtOAc before the addition of PtO (catalytic) and an H_2 balloon. The reaction was stirred for 4 hours at ambient temperature before LC-MS determined the two products: **15** and **16**. The crude mixture was filtered through celite and the solvent was removed *in vacuo* before isolation by HPLC of each of the products: **15** (13 mg, 34 %, $M+H^+$ = 592.3) and **16** (16 mg, 42 %, $M+H^+$ = 594.3).

EXAMPLE SP-136



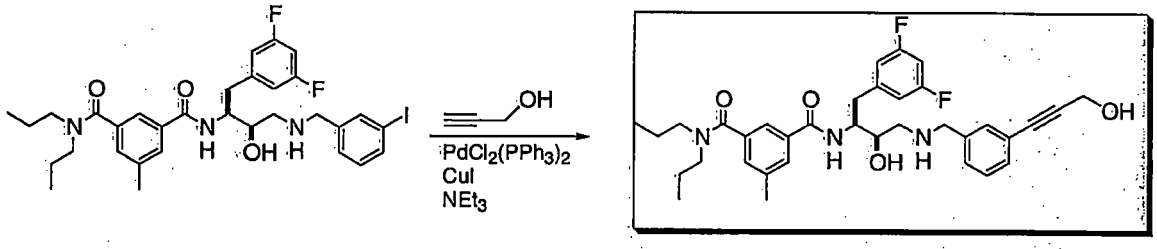
Compound **17** (1 equiv, 0.46 mmol, 0.31 g) was dissolved in CH_2Cl_2 and cooled to 0 °C before the addition of Boc_2O (1 equiv, 0.46 mmol, 0.1 g) and catalytic DMAP. After the reaction was judged to be done by TLC (4 h), the solvent was simply removed *in vacuo* and the product was used crude in the next step.

The iodo compound (1 equiv, 0.13 mmol, 100 mg), Pd_2dba_3 (0.02 equiv, 0.002 mmol, 2.4 mg), dppf (0.08 equiv, 0.01 mmol, 5.8 mg), Et_3N (2 equiv, 0.26 mmol, 0.04 mL), and NMP (0.3 M, 0.4 mL) were added to a sealed tube and flushed / bubbled with N_2 (g) for 15 minutes. Ethanethiol was then added and the tube was sealed and stirred for 3h at 60 °C. At this point the reaction was cooled to ambient temperature, diluted with brine, and extracted 3x with EtOAc. The combined organic extracts were then washed with brine (2x), dried over Na_2SO_4, filtered, and rotovapped to give the crude brown desired thioether. Column chromatography through SiO_2 with 25 % EtOAc

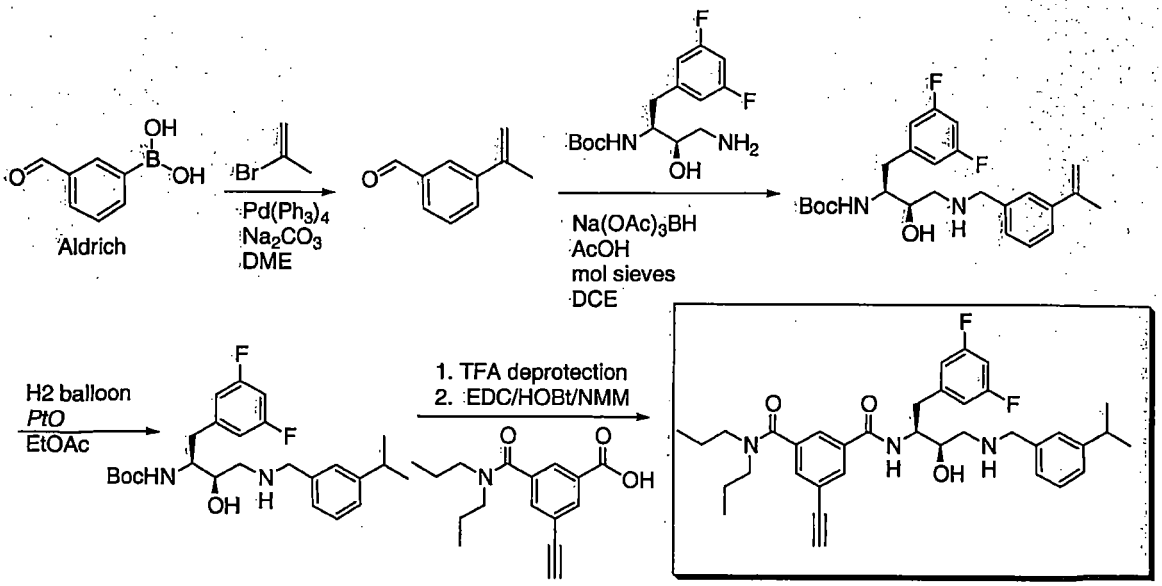
in hexanes gave the purified product (71.5 mg, 0.1 mmol, 77 %).

The thioether (1 equiv, 0.08 mmol, 56.3 mg) was dissolved in AcOH (0.4 mL) and treated with 30 % H2O2 (0.2 mL). The reaction was stirred 2 h. At this point, the crude mixture was partitioned between EtOAc and H_2O, and the products were extracted 3x with EtOAc. The organic extracts were dried over Na_2SO_4, filtered, and rotovapped before column chromatography purification through SiO_2 with 50 % EtOAc in hexanes gave the separated Boc protected sulfone and sulfoxide. After TFA deprotection and HPLC purification, the final products **18** (17 mg, 33%, $M+H^+$ = 644.2) and **19** (18 mg, 35 %, $M+H^+$ = 628.3) were achieved.

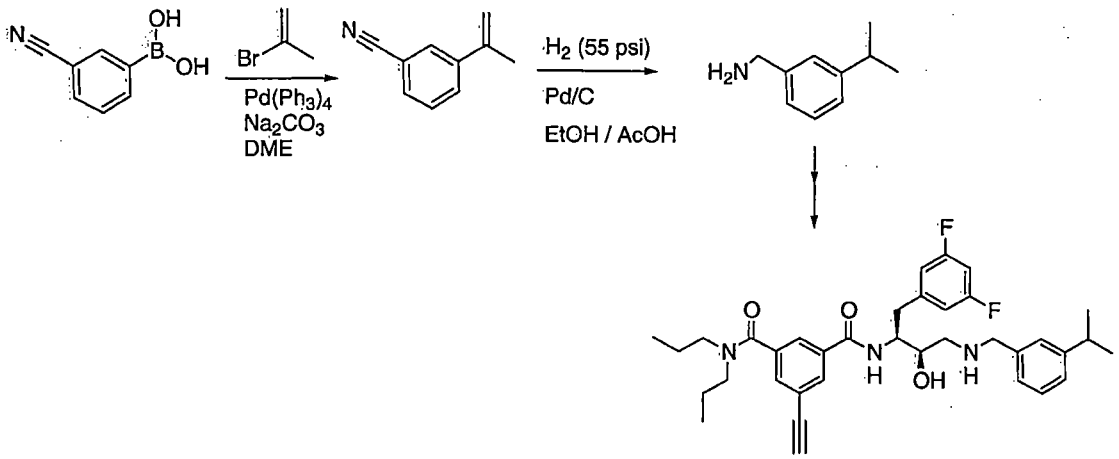
EXAMPLE SP-137



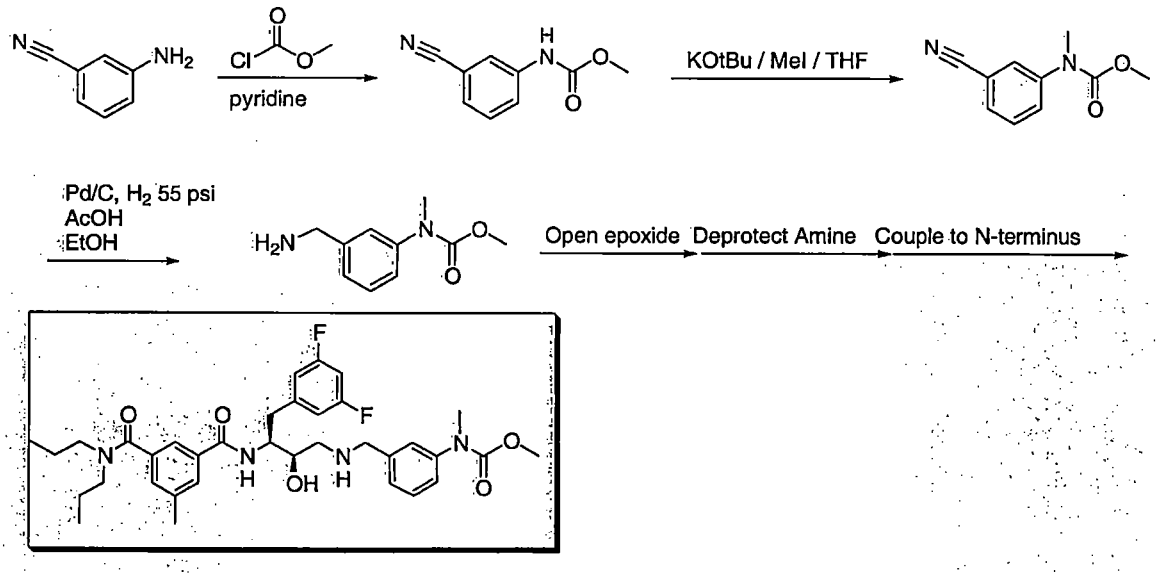
EXAMPLE SP-138



OR



EXAMPLE SP-139



The aniline (1 equiv, 8.46 mmol, 1 g) was dissolved in pyridine (1 M, 8.5 mL) and cooled to 0 °C before the addition of methyl chloroformate (1.2 equiv, 10.2 mmol, 0.96 g, 0.78 mL). The reaction was allowed to warm to room temperature overnight with stirring. The reaction mixture was then rotovapped, and H_2O was added to the residual oil, at which point a white solid precipitated. The white precipitate was

filtered and washed with H_2O, and then dried on the vacuum pump overnight to give the clean crude carbamate (1.4 g, 93%)

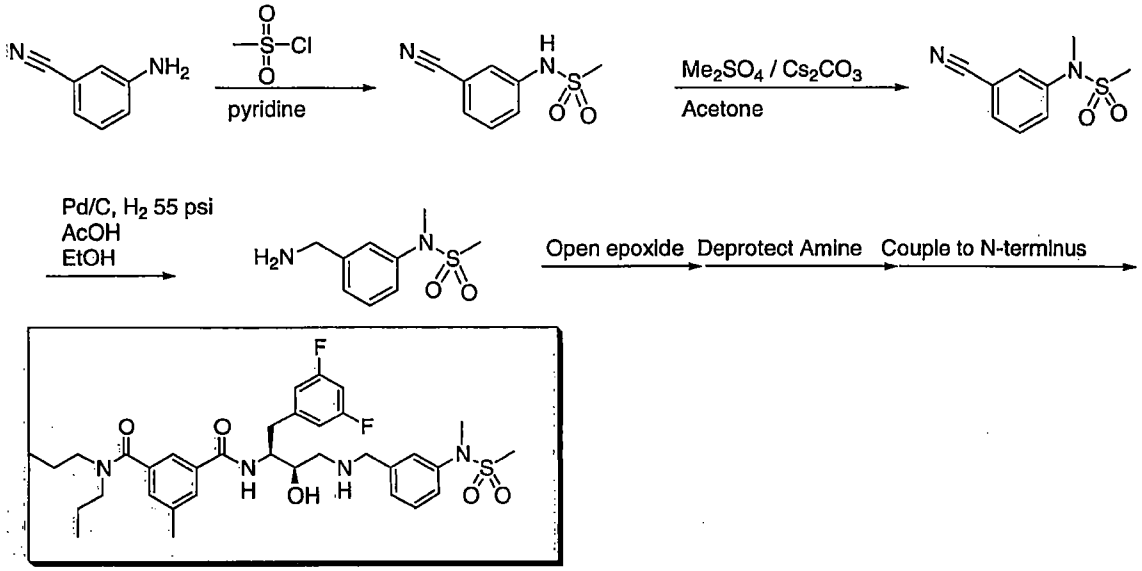
The carbamate (1 equiv, 3.98 mmol, 0.70 g) was dissolved in THF (8 mL) and cooled to 0 °C before the addition of a 1M THF solution of KOtBu (1.1 equiv, 4.37 mmol, 4.37 mL). Upon addition of KOtBu, the starting material crashed out of solution, and so more THF was added (5 mL) along with dioxane (2 mL). At this point, despite the continued lack of solubility, MeI (1.1 equiv, 4.37 mmol, 0.62 g, 0.27 mL) was added and the reaction was allowed to warm to room temperature overnight with stirring. After 12 hours, the reaction was still not in solution, and TLC showed incomplete consumption of starting material. Thus, DMF (5 mL) was added and the reaction finally went into solution. After stirring for 5 additional hours at ambient temperature, the reaction was complete. The crude reaction mixture was filtered through celite, rotovapped, partitioned between H_2O and EtOAc, extracted 3x with EtOAc, and washed with brine. The organic extracts were dried over Na_2SO_4, filtered, and rotovapped. Purification through a short plug of SiO_2 with 30% EtOAc in hexanes gave the desired methylated carbamate which still contained a colored impurity which was undetected by TLC and NMR. (0.76 g, Quantitative)

The nitrile (1 equiv, 3.98 mmol, 0.76 g) was dissolved in ethanol, and N_2 (g) was bubbled through the solution for 5 minutes before the addition of AcOH (1 equiv, 3.98 mmol, 2.27 mL) and 5% DeGussa Pd/C (1 scoop). N_2 (g) was bubbled again for 5 minutes before shaking on Parr Shaker at 55 psi H_2 overnight. The reaction was filtered through celite and rotovapped to give the acetic acid salt of the desired product. The product was then partitioned between 10% NaOH

(aq) and 20% isopropanol / chloroform, and extracted 3x with 20% isopropanol / chloroform to give the desired free-base.

The crude free-base was used to open the epoxide. The $M+H^+$ mass of the final product is 639.3.

EXAMPLE SP-140



The aniline (1 equiv, 16.9 mmol, 2 g) was dissolved in pyridine and cooled to 0 °C before the addition of the sulfonyl chloride (1.5 equiv, 25.4 mmol, 2.91 g, 1.97 mL). Upon addition of the sulfonyl chloride, the reaction turned bright orange. The reaction was allowed to warm to room temperature overnight with stirring. After 12 hours, the reaction mixture was rotovapped, partitioned between CH_2Cl_2 and $NaHCO_3$ (aq), and extracted 3x with CH_2Cl_2. The combined organic extracts were washed with $KHSO_4$ (aq) and brine, dried over Na_2SO_4, filtered, and rotovapped to give the clean crude sulfonamide. (3.34 g, Quantitative)

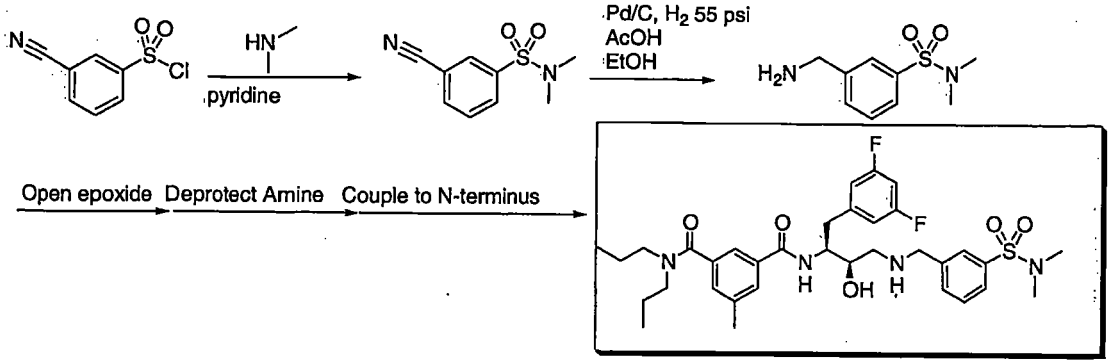
The crude sulfonamide was dissolved in acetone before the addition of *ground* Cs_2CO_3, followed by Me_2SO_4. The Cs_2CO_3 did not dissolve completely. The reaction was stirred overnight

at ambient temperature. After 12 h, the brownish reaction mixture was rotovapped in a fume hood, partitioned between EtOAc and H_2O, and extracted 3x with EtOAc. The combined organic extracts were then washed with $NaHCO_3$ (aq) and $KHSO_4$ (aq), dried over Na_2SO_4, filtered and rotovapped to give the crude methylated sulfonamide. By TLC the R_f values of the starting sulfonamide and the final product were identical, however the spots were different colors. Quick purification through a plug of SiO_2 with 30% - 40% EtOAc in hexanes gave the desired product. (1.88 g, 93 %)

The nitrile (1 equiv, 8.94 mmol, 1.88 g) was dissolved in methanol, and N_2 (g) was bubbled through the solution for 5 minutes before the addition of AcOH (1 equiv, 8.94 mmol, 0.51 mL) and 5% DeGussa Pd/C (one scoop). N_2 (g) was bubbled again for 5 minutes before shaking on Parr Shaker at 55 psi H_2 for 2 hours. The reaction was filtered through celite and rotovapped to give the acetic acid salt of the desired product. The product was then partitioned between 10% NaOH (aq) and 20% isopropanol / chloroform, and extracted 3x with 20% isopropanol / chloroform to give the desired free-base.

The crude free-base was used to open the epoxide. The $M+H^+$ mass of the final product is 659.3.

EXAMPLE SP-141

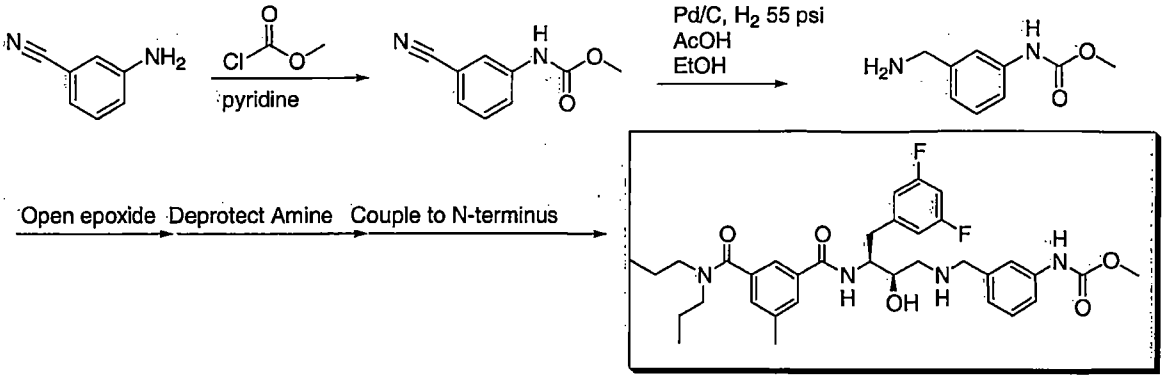


A 2M solution of dimethylamine in THF (1.2 equiv, 11.88 mmol, 5.94 mL) was dissolved in pyridine and cooled to 0 °C before the addition of the sulfonyl chloride (1 equiv, 9.9 mmol, 2 g). The reaction was allowed to warm to room temperature overnight with stirring. After 12 hours, the reaction mixture was rotovapped, partitioned between CH_2Cl_2 and $NaHCO_3$ (aq), and extracted 3x with CH_2Cl_2. The combined organic extracts were washed with $KHSO_4$ (aq) and brine, dried over Na_2SO_4, filtered, and rotovapped to give the clean crude sulfonamide. (2.04 g, 98 %)

The nitrile (1 equiv, 9.7 mmol, 2.04 g) was dissolved in a mixture of ethanol, methanol, and THF until it finally went into solution. N_2 (g) was bubbled through the solution for 5 minutes before the addition of AcOH (1 equiv, 9.7 mmol, 0.56 mL) and 5% DeGussa Pd/C (one scoop). N_2 (g) was bubbled again for 5 minutes before shaking on Parr Shaker at 55 psi H_2 overnight. The reaction was filtered through celite and rotovapped to give the acetic acid salt of the desired product. The product was then partitioned between 10% NaOH (aq) and 20% isopropanol / chloroform, and extracted 3x with 20% isopropanol / chloroform to give the desired free-base.

The crude free-base was used to open the epoxide. The $M+H^+$ mass of the final product is 659.3.

EXAMPLE SP-142

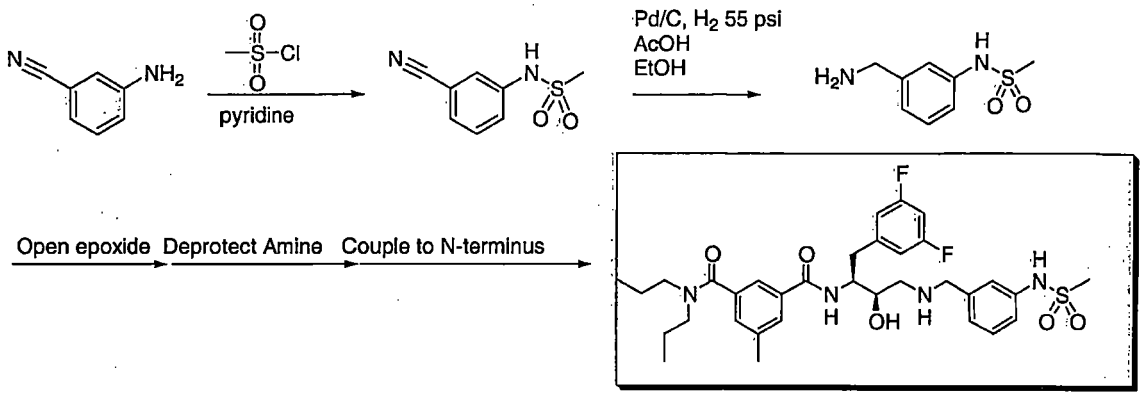


The aniline (1 equiv, 8.46 mmol, 1 g) was dissolved in pyridine (1 M, 8.5 mL) and cooled to 0 °C before the addition of methyl chloroformate (1.2 equiv, 10.2 mmol, 0.96 g, 0.78 mL). The reaction was allowed to warm to room temperature overnight. The reaction mixture was then rotovapped, and H_2O was added to the residual oil, at which point a white solid precipitated. The white precipitate was filtered and washed with H_2O, and then dried on the vacuum pump overnight to give the clean crude carbamate (1.4 g, 93%)

The nitrile (1 equiv, 3.43 mmol, 0.604 g) was dissolved in ethanol, and N_2 (g) was bubbled through the solution for 5 minutes before the addition of AcOH (1 equiv, 3.43 mmol, 0.2 mL) and 5% DeGussa Pd/C (one scoop). N_2 (g) was bubbled again for 5 minutes before shaking on Parr Shaker at 55 psi H_2 overnight. The reaction was filtered through celite and rotovapped to give the acetic acid salt of the desired product. The product was then partitioned between H_2O with NH_4OH and 20% isopropanol / chloroform, and extracted 3x with 20% isopropanol / chloroform to give the desired free-base.

The crude free-base was used to open the epoxide. The $M+H^+$ mass of the final product is 625.2.

EXAMPLE SP-143

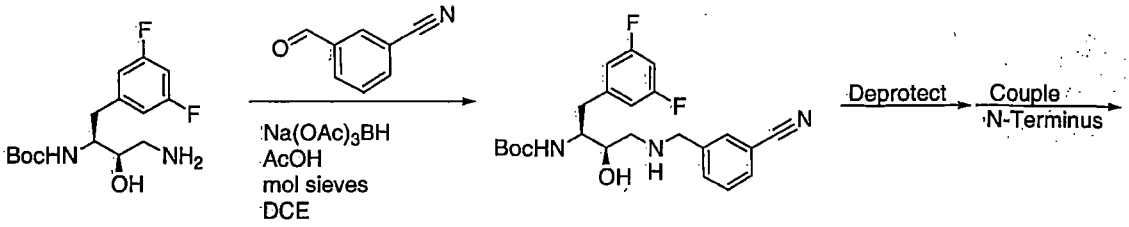


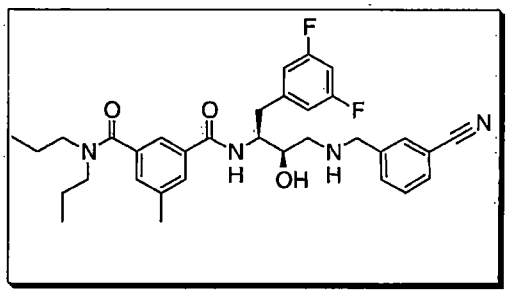
The aniline (1 equiv, 16.9 mmol, 2 g) was dissolved in pyridine and cooled to 0 °C before the addition of the sulfonyl chloride (1.5 equiv, 25.4 mmol, 2.91 g, 1.97 mL). Upon addition of the sulfonyl chloride, the reaction turned bright orange. The reaction was allowed to warm to room temperature overnight with stirring. After 12 hours, the reaction mixture was rotovapped, partitioned between CH_2Cl_2 and $NaHCO_3$ (aq), and extracted 3x with CH_2Cl_2. The combined organic extracts were washed with $KHSO_4$ (aq) and brine, dried over Na_2SO_4, filtered, and rotovapped to give the clean crude sulfonamide. (3.34 g, Quantitative)

The nitrile (1 equiv, 7.40 mmol, 1.45 g) was dissolved in methanol, and N_2 (g) was bubbled through the solution for 5 minutes before the addition of AcOH (1 equiv, 7.40, 0.42 mL) and 5% DeGussa Pd/C (one scoop). N_2 (g) was bubbled again for 5 minutes before shaking on Parr Shaker at 55 psi H_2 for 2 hours. The reaction was filtered through celite and rotovapped to give the acetic acid salt of the desired product. The product was then partitioned between H_2O with NH_4OH and 20% isopropanol / chloroform, and extracted 3x with 20% isopropanol / chloroform to give the desired free-base.

The crude free-base was used to open the epoxide. The $M+H^+$ mass of the final product is 645.2

EXAMPLE SP-144

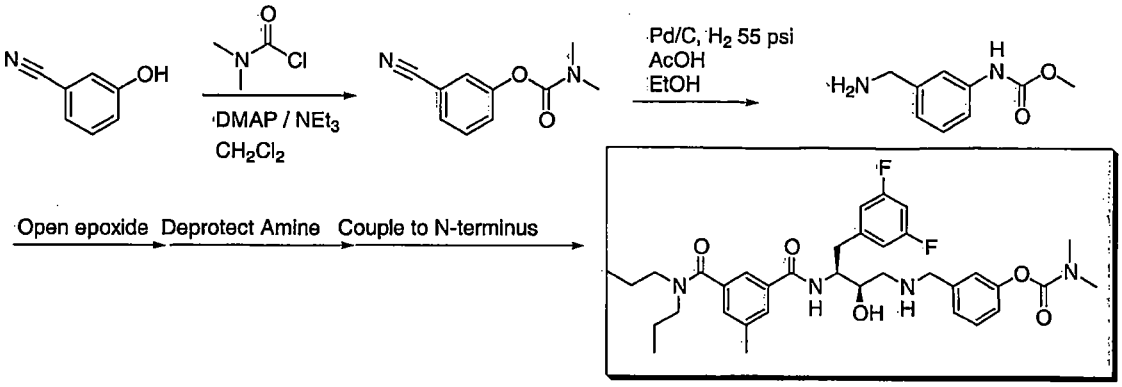




The aldehyde (1 equiv, 2.29 mmol, 0.3 g) and the amine (1.05 equiv, 2.40 mmol, 0.76 g) were dissolved in 1,2 dichloroethane (40 mL) and treated with molecular sieves (a small scoop) and a few drops of AcOH. The reaction was stirred for 1 h before adding $Na(OAc)_3BH$ (1.3 equiv, 2.98 mmol, 0.63 g). The reaction was stirred overnight at ambient temperature. After 12 h, the reaction mixture was filtered, and rotovapped. The residue was partitioned between EtOAc and H_2O, and the product was extracted 3x with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and rotovapped to give the clean crude desired amine. (Quantitative)

The crude material was deprotected with TFA and coupled to the N-terminus as usual. The $M+H^+$ mass of the final product is 577.2.

EXAMPLE SP-145

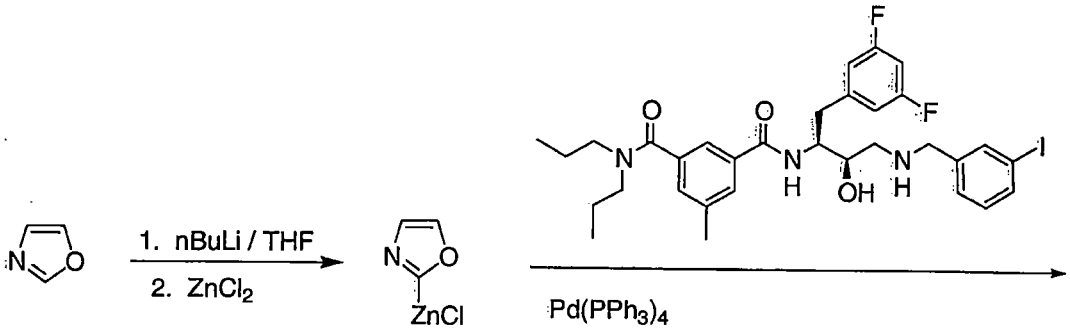


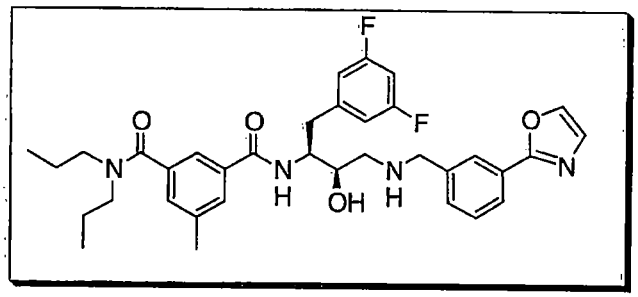
The phenol (1 equiv, 16.8 mmol, 2 g) was taken up in CH_2Cl_2, but did not dissolve, thus THF and acetone were added in a failed attempt to solubilize the phenol. The mixture was cooled to 0 °C before the addition of NEt_3 (1 equiv, 16.8 mmol, 1.7 g, 2.3 mL), DMAP (1 equiv, 16.8 mmol, 2.05 g), and dimethylcarbamyl chloride (1 equiv, 16.8 mmol, 1.81 g, 1.55 mL). Upon addition of NEt_3, the reagents dissolved. The reaction appeared to be complete after stirring for 2 hours, as judged by TLC. However, the reaction was stirred for 2 days. After 2 days, the reaction was partitioned between CH_2Cl_2 and $NaHCO_3$ (aq), and extracted 3x with CH_2Cl_2. The combined organic extracts were washed with 1 N HCl and brine, dried over Na_2SO_4, filtered, and rotovapped to afford the clean crude carbamate. (3.04 g, 95%)

The nitrile (1 equiv, 16.0 mmol, 3.04 g) was dissolved in ethanol, and N_2 (g) was bubbled through the solution for 5 minutes before the addition of 5% DeGussa Pd/C (one scoop). N_2 (g) was bubbled again for 5 minutes before shaking on Parr Shaker at 55 psi for 1 hour. The reaction was filtered through celite and rotovapped to give the desired free-base.

The crude free-base was used to open the epoxide. The $M+H^+$ mass of the final product is 639.3.

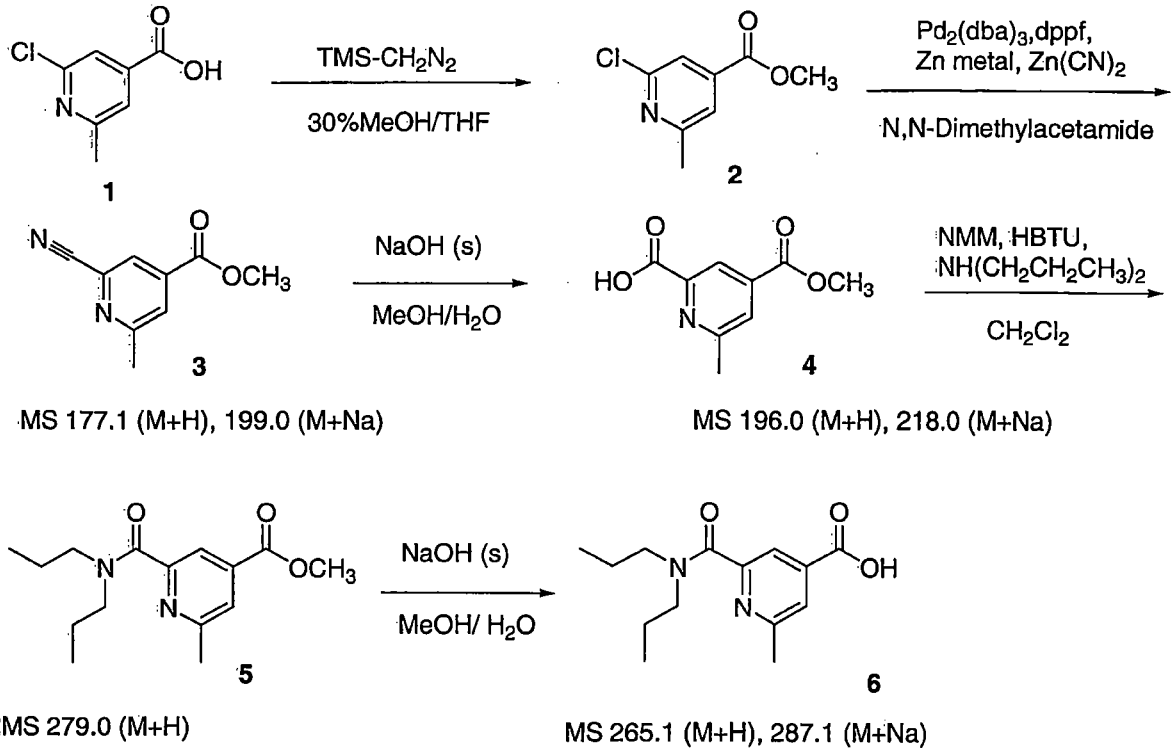
EXAMPLE SP-146





Oxazole (3.15 equiv, 1.89 mmol, 0.13 g) was weighed into an oven-dried round-bottom flask, dissolved in THF (3 mL), and cooled to -78 °C before the addition of a 1.6 M solution of nBuLi in hexanes (3.48 equiv, 2.09 mmol, 1.3 mL). After stirring for 30 minutes at -78 °C, a 1.0 M solution of $ZnCl_2$ in THF (9.06 equiv, 5.4 mmol, 5.4 mL) was added dropwise. At this point the stirring stopped due to increased viscosity or stickiness within the reaction vessel. This solution was warmed to 0 °C for 1 hour before the HCl salt of AN 104574-7 (1 equiv, 0.6 mmol, 0.429 g), along with $Pd(PPh_3)_4$ were added. This mixture was heated to reflux for 1 hour. The reaction was then partitioned between EtOAc and H_2O, extracted 3x with EtOAc, washed with brine, dried over Na_2SO_4, filtered and rotovapped. Chromatography on SiO_2 with 2 - 5% MeOH / CH_2Cl_2 with a few drops of NH_4OH yielded the clean desired product. (95%, 0.35 g, $M+H^+$ = 619.2)

EXAMPLE SP-147



2-Dipropylcarbamoyl-6-methyl-isonicotinic acid

A solution of 23.7 mmole (1.0eq.) of 2-chloro-6-methylisonicotinic acid in 32mL of 30%MeOH/THF was prepared. To the reaction mixture was added 30.0mmole (1.3eq) of (trimethylsilydiazo)methane dropwise. The reaction was complete after stirring at rt overnight. A few drops of glacial acetic acid were added to the reaction mixture prior to concentration by rotary evaporation to afford product **2**, quantitatively.

To a dried 100 mL round bottom flask was added 22.0 mmole (1.0eq.) of the methyl ester **2**, 0.45mmole (0.02eq.) tris(dibenzlideneacetone)dipalladium (0), 0.90 (0.04eq.) 1,1-bis(diphenylphosphine)ferrocene, 28.3mmole (0.13eq.) zinc metal dust and 10.7 (0.5eq) zinc cyanide. The reaction flask was flushed with nitrogen gas for 5 min and 45mL N,N-dimethylacetamide was added via syringe. The reaction was complete after refluxing while stirring vigorously for 4 h. The reaction mixture was diluted with EtOAc (50mL) and washed

with 2N NH_4OH (3 x 50mL) followed by sat. NaCl (50 mL). The combined organic extracts were dried over Na_2SO_4 and vacuum filtered. The filtrate was concentrated by rotary evaporation and purified via column chromatography Hex/EtOAc (8:2) to yield product **3**, 34% yield.

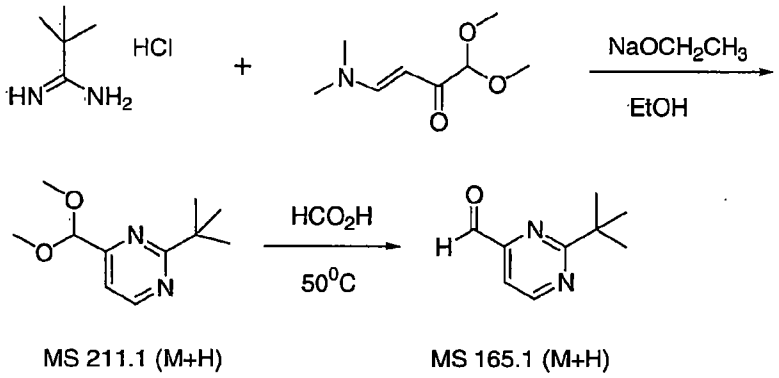
A solution of 1.2mmole (1.0eq.) of the nitrile **3** in 5 mL of methanol was prepared. To the reaction mixture was added 6.7mmole (5.7eq) of sodium hydroxide. After 1 h of stirring at rt, 5mL of H_2O were added to the reaction mixture. The reaction was complete after stirring for an additional 1.5h. The mixture was diluted with $CHCl_3$ and washed with 2NHCl. The organic extracts were collected and dried over Na_2SO_4 and vacuum filtered. The filtrate was concentrated by rotary evaporation to afford product **4**, 61% yield.

A solution of 0.7mmole (1.0 eq.) of the carboxylic acid **4** in 6mL of dichloromethane was prepared. To the reaction mixture was added 1.8mmole (2.6eq.) 4-methylmorpholine. The reaction flask was placed on ice to cool prior to addition of 0.8mmole (1.1eq.) HBTU and 0.8mmole (1.2eq.) diproplyamine. The reaction was complete after allowing to warm to rt overnight while stirring. The reaction mixture was diluted with EtOAc (25 mL) and washed with H_2O (2 x 25mL) followed by sat. $NaHCO_3$ (2 x 25mL). The combined organic extracts were dried over Na_2SO_4 and vacuum filtered. The filtrate was concentrated by rotary evaporation to afford product **5**, 64% yield.

A solution of 0.5 (1.0eq.) of the isophalate **5** in 2 mL of methanol was prepared. To the reaction mixture was added 4.5mmole (9.3eq) of sodium hydroxide. After 2 h of stirring at rt, 2mL of H_2O were added to the reaction mixture. The reaction was complete after stirring for an additional 1.5h. The mixture was diluted with EtOAc and washed with H_2O (2x) followed by sat. $NaHCO_3$ (2x). The aqueous extracts were collected and acidified with conc. HCl. A solution of $CHCl_3$/iPA (1:3) was utilized for extraction. The organic extracts were

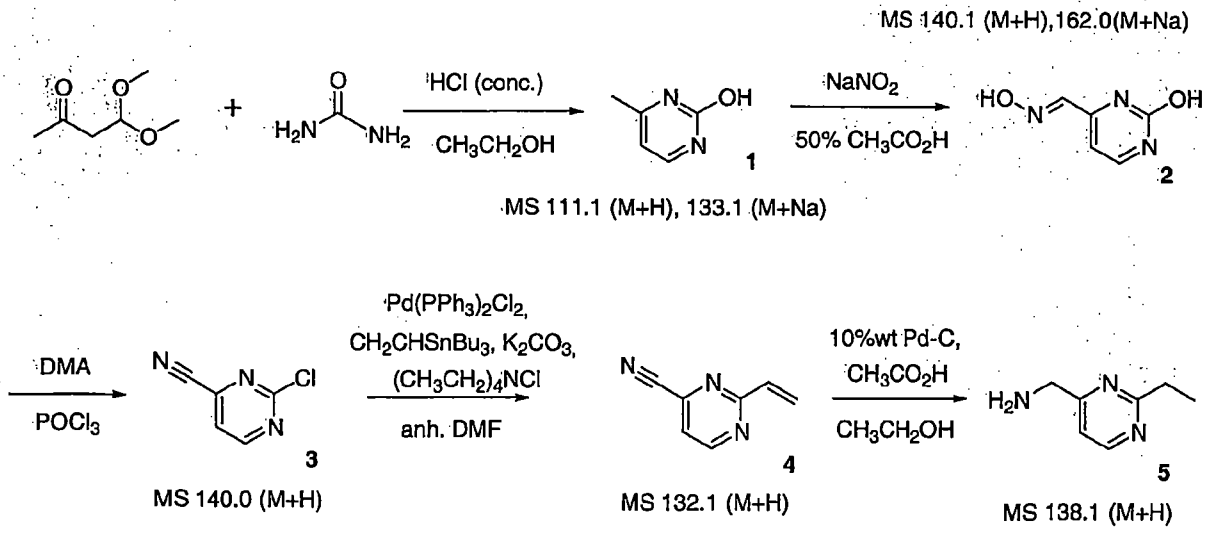
collected washed with sat. NaCl, dried over Na_2SO_4 and vacuum filtered. The filtrate was concentrated by rotary evaporation to afford product **6**.

EXAMPLE SP-148



Bredereck, H., Sell, R. and Effenberger, F.; *Chem. Ber.*; **1964**, 97, 3407.

EXAMPLE SP-149



(2-Ethyl-pyrimidin-4-yl)-methylamine

Experimental procedures were utilized in order to yield products **1** through **3** as described in the following references.

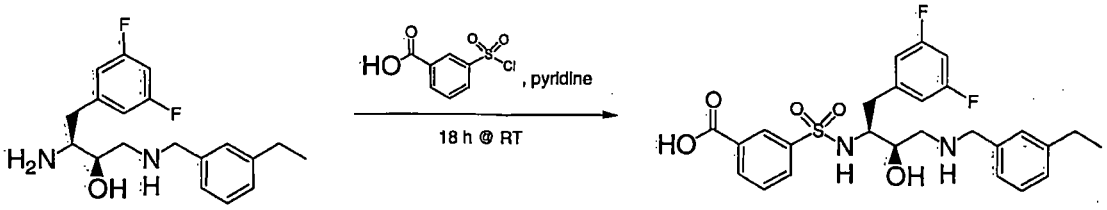
Burness, D.M.; *J. Org. Chem.*, **1956**,21,97.

Daves, G.D., O'Brien, D.E., Lewis, L. and Cheng, C.C.; *J. Heterocycl. Chem.*, **1963**, 1, 130.

Into a oven-dried 50 mL round bottom flask was added 3.6mmole (1.0eq.) of the halopyrimidine **3**, 5.4mmole (1.5eq.) tributyl(vinyl)tin, 0.09mmole (0.03eq.) bis(triphenylphosphine)palladium (II) chloride, 4.1mmole (1.1eq.) tetraethylammonium chloride, 3.8mmole (0.9eq.) potassium carbonate and 7.5 mL of dry DMF. The reaction was complete after refluxing under condenser with nitrogen inlet for 2 hrs. The reaction mixture was diluted with EtOAc (30 mL) and washed with H_2O (2 x 30 mL) followed by sat. NaCl (30 mL). The combined organic extracts were dried over Na_2SO_4 and vacuum filtered. The filtrate was concentrated by rotary evaporation, purified via column chromatography Hex/EtOAc (9:1) to yield product **4**,
42% yield.

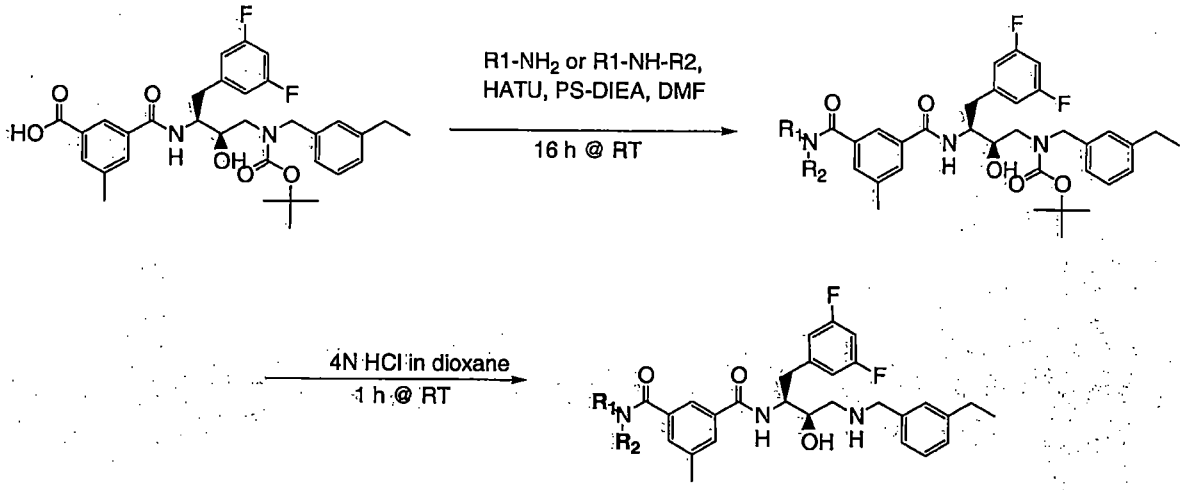
In a small vial, a solution of 1.53mmole (1.0eq.) of the styrene **4** was prepared by dissolving in a minimal amount of EtOH. To the reaction mixture was added 0.1 mL of glacial acetic acid followed by a catalytic amount of 10%wt palladium on carbon. The reaction was complete after placement on the hydrogentator for 30 min. at 50psi. The reaction mixture was vacuum filtered through Celite and rinsed with EtOAc. The filtrate was concentrated by rotary evaporation to afford product **5**.

EXAMPLE SP-150

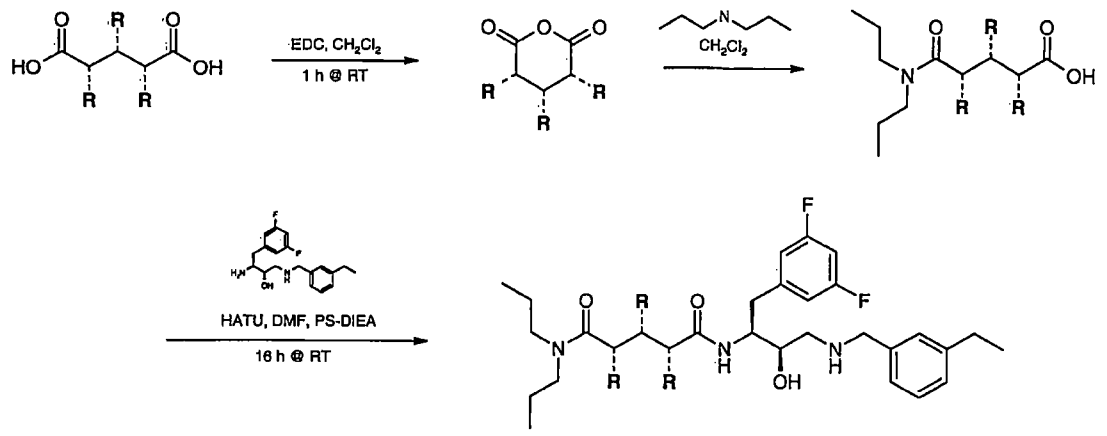


The starting diamine (~ 18 mgs, ~ 0.05 mmol) and 1 equiv. of sulfonyl chloride were dissolved in 1 ml of pyridine at -5.0 °C in a 1-dram vial. This mixture was allowed to react for 18 hours. After reaction time, the pyridine was dissolved and the product mixture was prepared for LC-MS analysis using a Hewlett-Packard 1050 Series HPLC coupled to a Thermo-Finnigan LCQ Deca MS. From the LC-MS results, the final product was purified using the Varian Pro Star Preparative HPLC.

EXAMPLE SP-151 **Synthesis of N-terminal dipropylamine replacement**

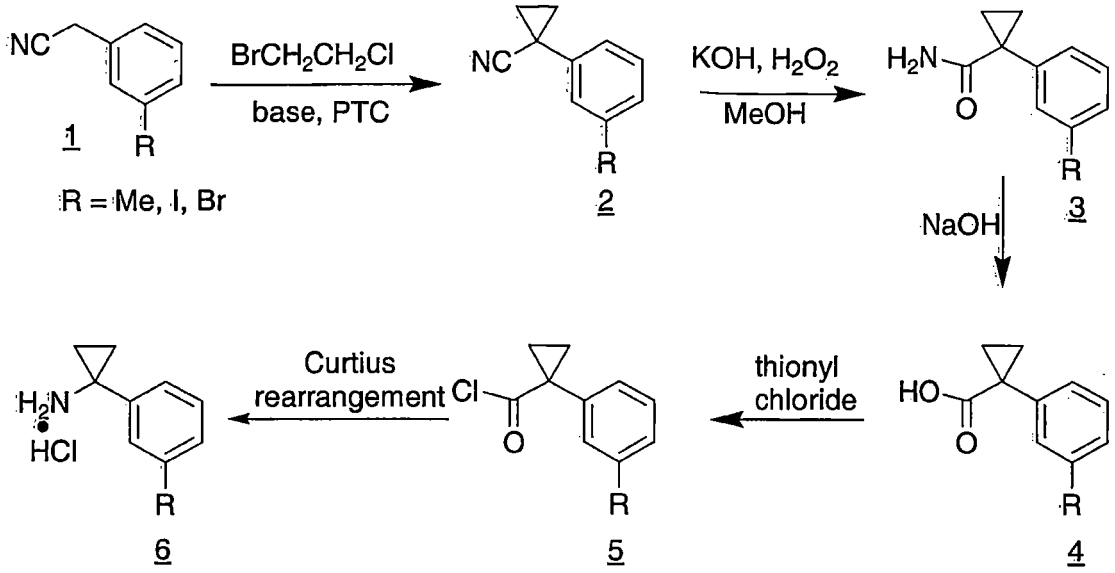


EXAMPLE SP-152 **Synthesis of N-terminal glutarates**



From the 11 compounds that were made in this library, 2 were made with the starting dicarboxylic acid and the other 9 were already in the glutaric anhydride form. To prevent the dicarboxylic acids from forming diamides, 0.1 mmol of each acid was reacted with 1 equiv. of EDC in 1 ml of dichloromethane for 1 hour at room temperature. With all of the starting materials in the glutaric anhydride form, 0.1 mmol of each glutaric anhydride was mixed with 0.1 mmol of dipropylamine in 1.5 ml of dichloromethane for 2 hours at room temperature. The resulting acids were then reacted with 1 equiv. of the HEA piece using 1.1 equiv. of HATU as the coupling agent. 3 equiv. of polystyrene-bound diisopropylethylamine was used as the base. These reactions were run in 1.5 ml of DMF for 4 hours at room temperature. The products were then purified via the Varian Pro Star Preparative HPLC.

EXAMPLE SP-153: Representative procedure of CHART Y(R=I)



Preparation of 1-arylcyclopropanecarbonitriles (2) (R = I)

Org. Prep. Proc. Inter. 1995, 27(3), 355-59

To a vigorously stirred mixture of the iodobenzyl cyanide 1 (3g, 12.35 mM), benzyltriethylammonium chloride (TEBAC, 100 mg) and 1-bromo-2-chloroethane (BCE, 15 mL), 50% aq. NaOH solution (20 mL) was added dropwise over 35 min. (temp. 50°C). After addition, the reaction was stirred at 50°C for additional 2 hrs, then at RT for 2 hrs. Added water to 100 mL total and extracted with dichloromethane (3 x 25 mL). Organic extracts were washed with water, 5% aq. HCl, and water, then dried over Na_2SO_4 and concentrated. Purified by Kugelrohr distillation. Yield 2 - 3.3 g (99%); MH+(CI) 269.9.

Preparation of amide 3. A mixture of 2 (13.3 mM), 25% aq. KOH (0.34 mL), 30% H_2O_2 (17.5 mL) and MeOH (100 mL) was heated at 55°C for 7 hrs. TLC showed no SM. The reaction mixture was concentrated and dried under vacuum. Yield 95%; MH+(CI) 288.0.

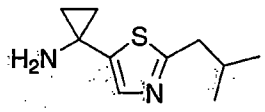
Hydrolysis of 3. An amide 3 (14 mM) was dissolved in a small amount of MeOH (5 mL) and 10% aq. NaOH solution (80 mL) and refluxed for 6 hrs. The mixture was cooled down and acidified with 15% HCl to pH~2. The solvent was partially

evaporated and white solid was collected by filtration. Yield of an acid 4 - 85%; MH+(CI) 288.9.

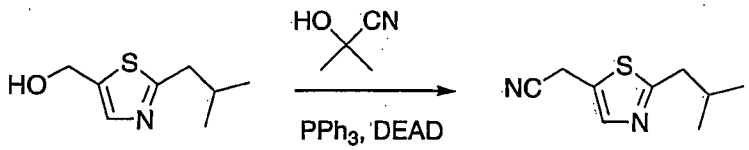
Preparation of acid chloride 5. The reaction mixture: acid 4 (8 mM) and thionyl chloride (2.0 g, 1.23 mL) in CH_2Cl_2 (10 mL) was heated o/n at 50°C (reflux). The next day a solvent was stripped on rotavapor and the residue was dried under vacuo. Used immediately without purification.

Curtius rearrangement. An acid chloride 5 (6.5 mM) was dissolved in acetone (15 mL), cooled to -10°C and treated with sodium azide (1.8 g in 5 mL of water). After stirring for 1 hr at -10°C the reaction mixture was poured into 100 mL of cold water and the azide was extracted into toluene. The toluene layer was washed with water and dried. The toluene solution was partially concentrated (to 15 mL) and the rest was carefully warmed to 100°C for 1 hr. Conc. HCl (8-10 mL) was added and the reaction mixture was refluxed for 15 min. with vigorous stirring. White crystals were decanted and dried under vacuo. Yield 84% of 6 (R = I); MH+(CI) 260.2.

EXAMPLE SP-154: Synthesis of 2-isobutyl-5-(1-

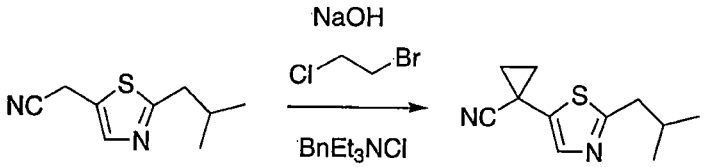


aminocycloprop-1-yl)thiazole:

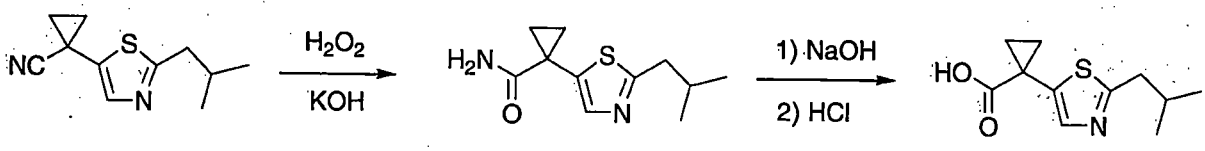


This procedure was adapted from: Wilk, BK. *Synth. Commun.* **1993**, *23*, 2481-4. To a solution of the thiazole methyl alcohol (753 mg, 4.4 mmol) and triphenylphosphine (1.74 g, 6.63 mmol) in dry THF (10 mL) at 0 °C was added diethyl azodicarboxylate

(DEAD, 1.0 mL, 6.4 mmol) dropwise with stirring. After 10 min, acetone cyanohydrin (Aldrich, 0.6 mL, 6.6 mmol) was added dropwise with stirring. The resulting solution was stirred at 0 °C for 10 min, then at rt for 3 h, whereupon the mixture was concentrated under reduced pressure, and the residue purified by flash chromatography (EtOAc/hexanes elution; product R_f = 0.73 in 60% EtOAc/hexanes) to give a yellow oil (516 mg, 65%) as product.



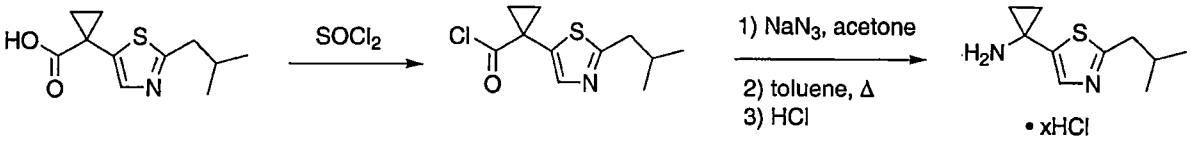
This procedure was adapted from: *Org. Prep. Proc. Int.* **1995**, *27*, 355-9. 50% Sodium hydroxide (aq, 5.0 mL total) was added to a solution of cyanide (516 mg, 2.9 mmol), 1-bromo-2-chloroethane (3.5 mL, 42 mmol), and benzyltriethylammonium chloride (25 mg, 0.09 mmol) at 50 °C. This was maintained at 50 °C for 2 h, then at rt for 2 h. Water was added such that the total volume was 20 mL, and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed (water, 1 N HCl, water), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAc/hexanes elution) to give the product as an oil (403 mg, 68%); MH+ (CI) 207.1.



This procedure was adapted from: *Org. Prep. Proc. Int.* **1995**, *27*, 355-9. Cyclopropylarylcyanide (403 mg, 1.96 mmol) was dissolved in MeOH (15 mL), and 30% hydrogen peroxide (2.7 mL) and 25% KOH (aq, 0.05 mL) were added at rt. The solution

was heated to 55 °C for 7 h. The reaction mixture was then concentrated in vacuo and stored in the freezer overnight. This crude product was used in the next reaction without further purification.

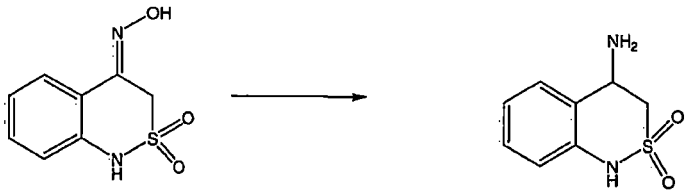
The crude amide was dissolved in minimal MeOH (1 mL), and 2.5 N NaOH (aq, 10 mL) was added. This suspension was heated to reflux (bath temp 105 °C) for 6 h, whereupon the mixture was cooled to 0 °C, and acidified to pH 3 using 3 N HCl (aq). This was partially concentrated , then extracted with $CHCl_3$ (3x). The combined extracts were dried (Na_2SO_4), filtered and concentrated to give a solid (189 mg, 43%); MH+(CI) 226.1.



The carboxylic acid (189 mg, 0.84 mmol) was dissolved in CH2Cl2 (5 mL) and thionyl chloride (0.2 mL, 2.7 mmol) was added at rt. This was heated to reflux (bath temp 55 °C) for 3.5 h, whereupon the mixture was concentrated under reduced pressure. The crude acid chloride was dissolved in acetone (4 mL), and a solution of sodium azide (270 mg, 4.2 mmol) in water (1 mL) was added at -15 °C. After 1 h at -15 °C, water (20 mL) was added, and the acyl azide was extracted into toluene (3x). The combined organic extracts were dried (Na_2SO_4), filtered and partially concentrated (to ca. 30 mL). The solution was then warmed to 100 °C for 1 h. Conc. HCl (aq, 2 mL) was then added, and the mixture was heated to reflux for 15 min. The mixture was cooled to 0 °C, basified with 10 N NaOH (aq), then extracted with $CHCl_3$ (3x). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give an oil (R_f = 0.37 in 5% MeOH/CH_2Cl_2; ninhydrin visualization); MH+ (CI) 197.1.

EXAMPLE SP-155 Procedure A: Synthesis of **2** :

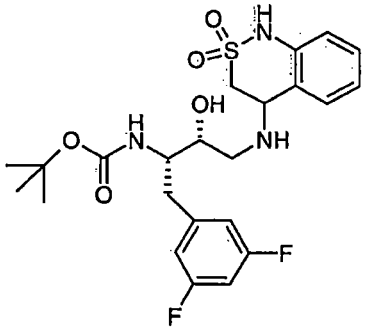
2,2-Dioxo-1,2,3,4-tetrahydro-2λ^6-benzo[*c*][1,2]thiazin-4-ylamine



1 2

A solution of 0.58 g (2.7 mmol) of oxime **1** (prepared according to *J. Heterocyclic. Chem.* **17**, 1281 (1980), the identical compound is described in this paper) in 13 ml of aqueous tetrahydrofurane (THF:H_2O, 10:1) was stirred under argon atmosphere. Aluminum amalgam (from 0.52 g, 19 mmol, 7eq. of Reynolds heavy-duty aluminum foil), prepared by sequential exposure (10-20 seconds each) of small strips to 1 N KOH, distilled water, 0.5% mercuric chloride, distilled water, and dry THF, was then added to the solution of **1** over a period of 3 hours. The reaction mixture was stirred overnight, then filtered on a bed of celite and the solvent evaporated to yield 510 mg of **2** (94%) as an orange oil that slowly solidified. mass spec (CI) (MH+): 199.1

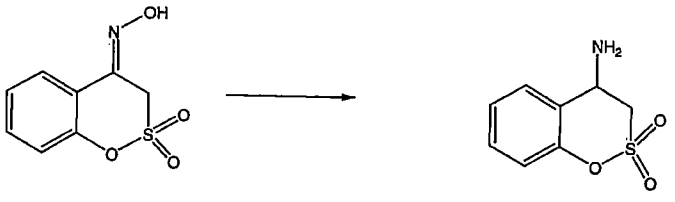
EXAMPLE SP-155A



The compound of Example SP-155 can be used to open the appropriate boc protected amino epoxide to generate the compound of Example SP-155A. This compound can then be

deprotected using methods well known in the art to generate the free amine, which can then be further manipulated.

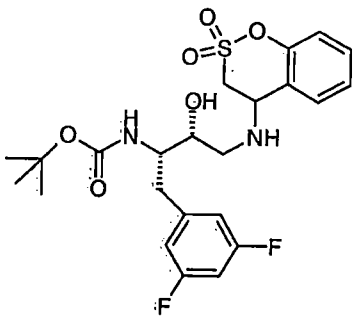
EXAMPLE SP-156: Procedure B: Synthesis of **4**, 2,2-Dioxo-3,4-dihydro-2*H*-2λ^6-benzo[*e*][1,2]oxathiin-4-ylamine



3 4

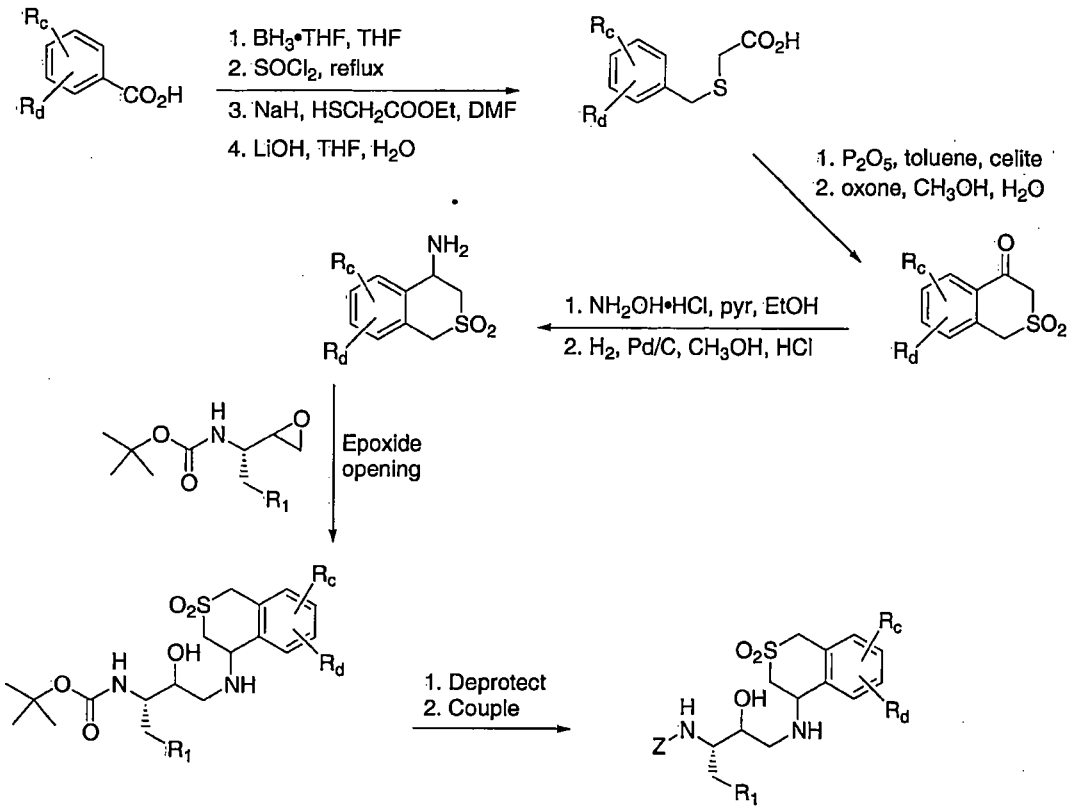
The amine **4** (mass spec (CI) (MH+): 200.0) was prepared according to the procedure **A** described above starting from 1H-2,1-Benzothiazin-4(3H)-one, oxime, 2,2-dioxide **3**.
Oxime **3** was obtained starting from commercially available 1,2-Benzoxathiin-4(3H)-one, 2,2-dioxide [49670-47-5].

EXAMPLE SP-156A:



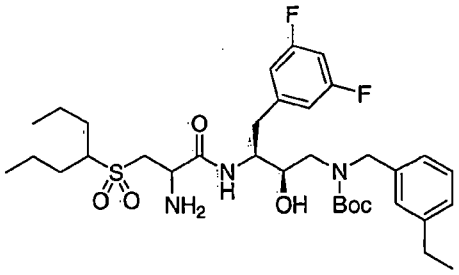
The compound of Example SP-156 can be used to open the appropriate boc protected amino epoxide to generate the compound of Example SP-156A. This compound can then be deprotected using methods well known in the art to generate the free amine, which can then be further manipulated.

EXAMPLE SP-156-B



Rc and Rd are independently H, halogen, alkoxy, or alkyl. R_1 is 3,5-difluorobenzene; Z is residue from a group that will couple to an amine, including, for example, carboxylic acid derivates (such as an isophthalamide), sulfonic acid derivatives (such as para-toluenesulfonic acid), haloalkane derivatives (such as iodopentane, and arylhaloalkyl derivatives (such as benzylbromide.)

EXAMPLE SP-157: Preparation of : *tert*-butyl (2R,3S)-4-(3,5-difluorophenyl)-2-hydroxy-3-({3-[(1-propylbutyl)sulfonyl]alanyl}amino)butyl(3-ethylbenzyl)carbamate



Part A.

A 250 ml round bottom flask equipped with magnetic stir bar and N_2 inlet was charged with 5.0 g (34 mmole) methyl 2-acetamidoacrylate, 4.6 g (34 mmole) 4-mercapto heptane in 50 ml methanol. The reaction vessel was charged with 3.6 g (36 mmole) triethylamine and stirred at room temperature for 45 minutes when HPLC indicated complete reaction. The reaction vessel was then treated with 47.2 g (77 mmole) Oxone. After 90 minutes HPLC indicated complete oxidation to the desired sulfone. The reaction was filtered and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water and the organic layer was washed with brine, dried over sodium sulfate, and concentrated *in vacuo* to 9.2 g (86 %) of methyl N-acetyl-3-[(1-propylbutyl)sulfonyl]alaninate as a colorless oil. M + H = 308 g/m.

Part B.

A 250 ml round bottom flask equipped with magnetic stir bar, reflux condenser, and N_2 inlet was charged with 9.2 g methyl N-acetyl-3-[(1-propylbutyl)sulfonyl]alaninate in 50 ml acetic acid and 50 ml conc. HCl. The solution was refluxed for 4 hours then concentrated *in vacuo*. The residue was chased with toluene (2X) then vacuum dried overnight to yield 7.8 g of the desired 3-[(1-propylbutyl)sulfonyl]alanine HCl salt.

Part C.

A 250 ml round bottom flask equipped with magnetic stir bar and N_2 inlet was charged with 7.8 g (27 mmole) 3-[(1-propylbutyl)sulfonyl]alanine and 7.4 g (30 mmole) N-Cbz succinamide in 100 ml methylene chloride. The reaction was cooled to 0 ^{0}C, and 6.9 g NMM was added dropwise. The reaction was allowed to warm to room temperature and stirred for 4 hours at which point HPLC analysis indicated complete reaction. The reaction was concentrated *in vacuo* and partitioned between ethyl acetate and 1 N HCl. The organic layer was washed with water, brine, dried over sodium sulfate, and concentrated *in vacuo* to give 11.4 g of N-[(benzyloxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]alanine that was used without further purification. M + H = 386.

Part D.

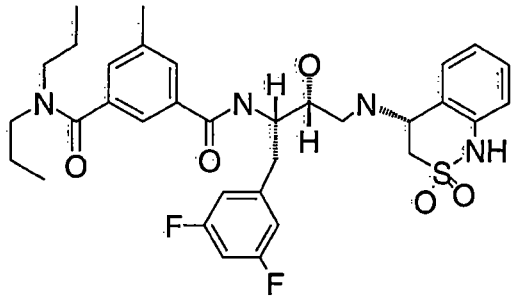
A 250 ml round bottom flask equipped with magnetic stir bar and N_2 inlet was charged with 4.0 g (10 mmole) N-[(benzyloxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]alanine and 1.2 g (12 mmole) (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride in 50 ml anhydrous methylene chloride. To the reaction mixture was added 5.6 ml (51 mmole) NMM, 1.7 g (13 mmole) hydroxybenzotriazole, and lastly 3.1 g (16 mmole) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After stirring at room temperature for 3 hours, HPLC analysis indicated complete reaction. The reaction was diluted with methylene chloride and washed with saturated sodium bicarbonate solution, 0.5 M citric acid, and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the N^2-[(benzyloxy)caronyl]-N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]alaninamide. A 50 ml round bottom flask equipped with magnetic stir bar and N_2

inlet was charged with the crude residue in anhydrous methylene chloride. The reaction was cooled to 0ºC and added 2.5 g (12 mmole) di-*tert*-butyl dicarbonate and 1.2 ml (11 mmole) *N*-methyl morpholine. The reaction was allowed to warm to room temperature and stirred for 18 hours at which point HPLC analysis indicated complete reaction. The reaction was diluted with methylene chloride and washed with saturated sodium bicarbonate solution, and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified on silica gel by flash chromatography using a gradient solvent of 5-40% ethyl acetate in hexane to give 3.4 g of N^2-[(benzyloxy-)caronyl]-N^1-{(1S,2R)- N-[(*t*-butyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide.
M+Na = 824.

Part E.

A Fisher-Porter bottle was charged with 3.4 g (4.2 mmole) of N^2-[(benzyloxy)-carbonyl]-N^1-{(1S,2R)- N-[(*t*-butyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]alaninamide in 50 ml methanol. After degassing with nitrogen, 1.6 g of 5% Pd/C (Degussa E101 50% water) was added. The reaction vessel was purged with 40 psi nitrogen (4X) then pressurized to 50 psi with hydrogen. After 15 minutes, HPLC analysis indicated complete reaction. The catalyst was removed by filtration through celite, and the filtrate concentrated *in vacuo* to give 2.4 g of N^1-{(1S,2R)- N-[(*t*-butyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alanine. M+H = 668.

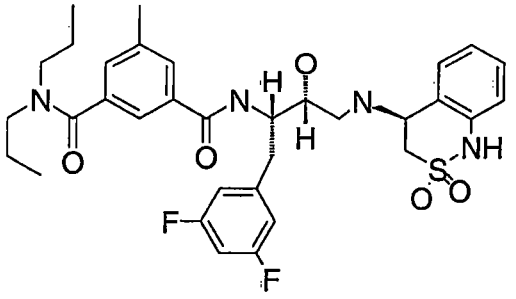
EXAMPLE SP-158



2,2-Dioxo-1,2,3,4-tetrahydro-2λ^6-benzo[*c*][1,2]thiazin-4-ylamine

2 was prepared according to procedure A of EXAMPLE SP-155. Also, epoxide opening with **2** (see procedure A of EXAMPLE SP-155) was achieved according to the procedure described in Bennett, Frank. *Synlett* **1993**, 703-704. Mass spec (CI) MH+ 643.7.

EXAMPLE SP-159



2,2-Dioxo-1,2,3,4-tetrahydro-2λ^6-benzo[*c*][1,2]thiazin-4-ylamine

2 was prepared according to procedure **A** in EXAMPLE SP-155. Also, epoxide opening with **2** (see procedure **A**) was achieved according to the procedure described in Bennett, Frank. *Synlett* **1993**, 703-704. Mass spec (CI) MH+ 643.7.

EXAMPLE SP-160

Synthesis of t-Boc-NH-di-F-Phe-Hydroxyethylamine(HEA)-O-Bn

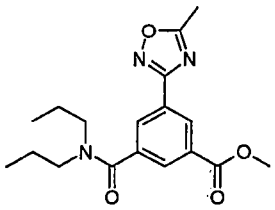
To 2.4g (15 mmole, 3 eq.)of O-benzylhydroxylamine hydrochloride in 20 ml of EtOAc was added 20 ml of 1N KOH with stirring. The organic layer extracted and dried, stripping of solvent and reconstituted with 20 ml of DCM, 1.5 g (5 mmole)of

erythro-di-F-Phe-epoxide and 0.62 g (1mmole, 0.2 eq.) of Ytterbium(III) trifluoromethanesulfonate was added at room temperature. The mixture was stirred overnight and worked up by 1N HCl, bicarb and brine washings, dried, stripping of solvent gave 1.23 g crude which was subject to column purification, it afforded 0.76 g(1.8 mmole, 36%) of the targeted compound as a pale white solid.

EXAMPLE SP-161

N^1-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(5-methyl-1,2,4-oxadiazol-3-yl)-N^3,N^3-dipropylisophthalamide hydrochloride

Step 1: Methyl 3-[(dipropylamino)carbonyl]-5-(5-methyl-1,2,4-oxadiazol-3-yl)benzoate



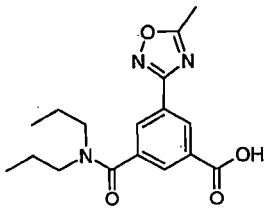
To a stirred solution of methyl 3-cyano-5-[(dipropylamino)carbonyl]benzoate prepared by the method in EXAMPLE S-2510 (2.3 g, 7.9 mmol) in methanol (26 mL) is added hydroxylamine hydrochloride (1.1 g, 16 mmol) and potassium carbonate (2.2 g, 16 mmol). The resulting reaction mixture is refluxed for 20 h, and then cooled to room temperature. The inorganic salts are filtered, and the filtrate is concentrated under reduced pressure to provide an amidoxime in quantitative yield.

To the amidoxime (1.3 g, 4 mmol), and EDC (1.5 g, 8 mmol) in 2-methoxyethyl ether (8 mL) is added acetic acid (0.21 mL, 4 mmol). The resulting reaction mixture is stirred for 24 h and then refluxed for 3 h. The reaction mixture is cooled to room temperature, diluted with ethyl acetate, washed with water, 1 N hydrochloric acid, saturated sodium bicarbonate,

and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 50% ethyl acetate hexanes) provides the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.18 (m, 1H), 8.11 (s, 1H), 3.91 (s, 3H), 3.43 (t, *J* = 7 Hz, 2H), 3.12 (t, *J* = 7 Hz, 2H), 2.63 (s, 3H), 1.66 (t, *J* = 7 Hz, 2H), 1.50 (t, *J* = 7 Hz, 2H), 0.95 (t, *J* = 7 Hz, 3H), 0.70 (t, *J* = 7 Hz, 3H).

Step 2

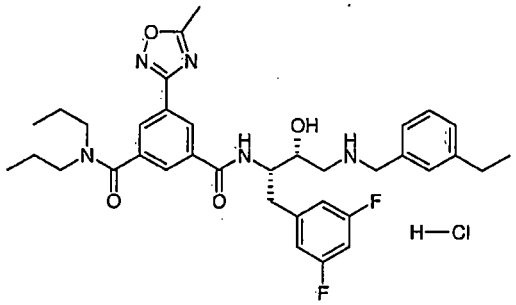
3-[(Dipropylamino)carbonyl]-5-(5-methyl-1,2,4-oxadiazol-3-yl)benzoic acid



A stirred solution of methyl 3-[(dipropylamino)carbonyl]-5-(5-methyl-1,2,4-oxadiazol-3-yl)benzoate (629 mg, 1.8 mmol) and lithium iodide (2.4 g, 18 mmol) in pyridine (7 ml) is refluxed for 18 h. The reaction mixture is cooled to room temperature and the solvent is concentrated under reduced pressure. The residue is dissolved in water, washed with ethyl acetate, the aqueous layer is acidified to pH 3 with 1 N hydrochloric acid and extracted with chloroform (3 x 100 mL). The organic layer is dried (sodium sulfate), filtered, and concentrated to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.11 (br s, 1H), 8.85 (t, *J* = 1 Hz, 1H), 8.31 (t, *J* = 1 Hz, 1H), 8.23 (t, *J* = 1 Hz, 1H), 3.51 (s, 2H), 3.19 (s, 2H), 2.72 (s, 3H), 1.73 (d, *J* = 7 Hz, 2H), 1.56 (d, *J* = 7 Hz, 2H), 1.01 (t, *J* = 7 Hz, 3H), 0.76 (t, *J* = 7 Hz, 3H).

Step 3

N^1-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(5-methyl-1,2,4-oxadiazol-3-yl)-N^3,N^3-dipropylisophthalamide hydrochloride



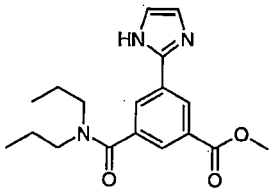
A solution of 3-[(dipropylamino)carbonyl]-5-(5-methyl-1,2,4-oxadiazol-3-yl)benzoic acid (209 mg, 0.63 mmol), HATU (359 mg, 0.95 mmol), HOBt (128 mg, 0.95 mmol), and diisopropylethylamine (165 □L, 0.95 mmol) is stirred in methylene chloride (2.0 mL) for 15 min. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method in EXAMPLE SP-272 (257 mg, 0.63 mmol) and diisopropylethylamine (165 □L, 0.95 mmol) in methylene chloride (2.0 mL) is added and the reaction mixture is stirred overnight. The reaction mixture is diluted with methylene chloride, washed with 1 N hydrochloric acid (25 mL), saturated sodium bicarbonate (25 mL), and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provides the title compound as the free base. The solid is dissolved in methanol (1 mL), and treated with hydrochloric acid (0.3 mL of a 1.0 M solution in diethyl ether, 0.3 mmol). The resulting precipitate is collected by filtration to provide the title compound. APCI MS *m/z* 648.4 $[M + H]^+$.

EXAMPLE SP-162

N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1H-imidazol-2-yl)-N^3,N^3-dipropylisophthalamide

Step 1

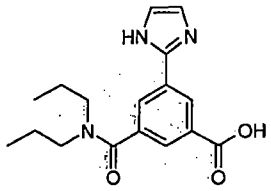
Methyl 3-[(dipropylamino)carbonyl]-5-(1H-imidazol-2-yl)benzoate



To a -70 °C stirred solution of 1-*tert*-butyldimethylsilylimidazole (602 mg, 3.3 mmol) in tetrahydrofuran (10 mL) is added *n*-butyllithium (1.6 M in hexanes, 2.3 mL, 3.63 mmol). After 30 min, zinc chloride (1 M in diethyl ether, 9.9 mL, 9.9 mmol) is added and the reaction mixture is warmed to 0 °C for 1 h. To this mixture is then added methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate prepared by the method in EXAMPLE SP-281, step2 (1.17 g, 3 mmol) followed by palladium(0) tetrakis(triphenylphosphine) (173 mg, 0.15 mmol). The reaction mixture is heated at reflux for 15 h. The reaction mixture is diluted with ethyl acetate (50 mL), washed with water, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 1-5% methanol/methylene chloride) provides the title compound in pure form. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.14 (s, 1H), 7.97 (s, 1H), 7.19 (s, 2H), 3.96 (s, 3H), 3.51 (m, 2H), 3.32 (m, 2H), 1.73 (m, 2H), 1.57 (m, 2H), 1.01 (m, 3H), 0.73 (m, 3H).

Step 2

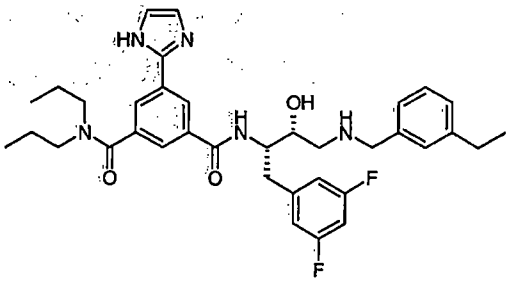
3-[(Dipropylamino)carbonyl]-5-(1H-imidazol-2-yl)benzoic acid



To a stirred solution of the ester from step 1 (260 mg, 0.79 mmol) in 2:1:1 tetrahydrofuran/methanol/water (8 mL) is added lithium hydroxide (140 mg, 3.3 mmol). The reaction mixture is stirred at room temperature for 2 h, and concentrated under reduced pressure. The residue is partitioned between water (10 mL) and diethyl ether (10 mL). The aqueous layer is acidified to pH 4 - 5 with 1 N hydrochloric acid and extracted with 3:1 chloroform/2-propanol (3 x 30 mL). The combined organic layers are dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide the title compound. ^{1}H NMR (300 MHz, CD_3OD) δ 8.64 (s, 1H), 8.10 (s, 1H), 8.01 (s, 1H), 7.28 (s, 2H), 3.52 (m, 2H), 3.26 (m, 2H), 1.75 (m, 2H), 1.59 (m, 2H), 1.02 (t, J = 7 Hz, 3H), 0.75 (t, J = 7 Hz, 3H).

Step 3

N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1H-imidazol-2-yl)-N^3,N^3-dipropylisophthalamide



To a stirred solution of 3-[(dipropylamino)carbonyl]-5-(1H-imidazol-2-yl)benzoic acid (250 mg, 0.79 mmol), diisopropylethylamine (103 mg, 0.8 mmol), and HBTU (330 mg, 0.87 mmol) in methylene chloride (5 mL) is added a mixture of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-

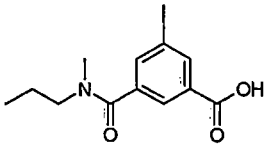
ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (322 mg, 0.79 mmol) and diisopropylethylamine (206 mg, 1.6 mmol) in methylene chloride (5 mL). The reaction mixture is stirred at room temperature for 4 h and concentrated under reduced pressure. The residue is diluted with ethyl acetate (20 mL), washed with saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5:95 methanol/methylene chloride) provides the title compound in pure form. APCI MS *m/z* 632.3 $[M + H]^+$.

EXAMPLE SP-163

N^1-{(1S,2R)-1-Benzyl-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-methyl-5-(1,3-oxazol-2-yl)-N^3-propylisophthalamide

Step 1

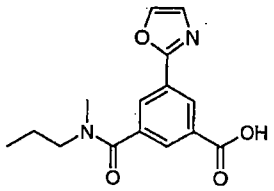
Methyl 3-iodo-5-{[methyl(propyl)amino]carbonyl}benzoate



To 3-iodo-5-(methoxycarbonyl)benzoic acid (1.0 g, 3.3 mmol), prepared as in EXAMPLE SP-281, step 1, and diisopropylethylamine (1.7 mL, 9.8 mmol) in DMF (10 mL) is added *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU, 1.5 g, 3.9 mmol) then *N*-methylpropylamine (503 µL, 4.9 mmol). The solution is stirred at room temperature 2 h. The solution is diluted in ethyl acetate and washed with water, saturated sodium bicarbonate, and brine. The organic layer is dried over sodium sulfate, filtered and concentrated under reduced pressure to give the title compound in crude form. This material is purified by flash chromatography (40% ethyl acetate/hexane) to give the purified title compound. MS (ESI) $[M+H^+]$ = 362.4.

Step 2

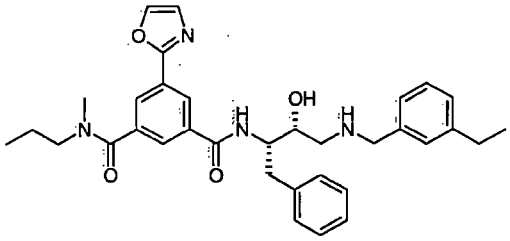
3-{[Methyl(propyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoic acid



To a -70 °C stirred solution of oxazole (330 mg, 4.8 mmol) in tetrahydrofuran (4 mL) is added *n*-butyllithium (1.6 M in hexanes, 3.3 mL, 5.3 mmol). After 30 min, zinc chloride (1 M in diethyl ether, 14.5 mL, 14.5 mmol) is added and the reaction mixture is warmed to 0 °C for 1 h. To this mixture is added a solution of methyl 3-iodo-5-{[methyl(propyl)amino]carbonyl}benzoate (1.6 g, 4.5 mmol) in anhydrous tetrahydrofuran (3 mL) followed by palladium(0) tetrakis(triphenylphosphine) (221 mg, 0.19 mmol). The reaction mixture is heated at reflux for 2 h. The reaction mixture is cooled, diluted with ethyl acetate, washed with water, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 60% ethyl acetate/hexane) provides a solid. The solid is redissolved in 1:1:1 tetrahydrofuran/methanol/water (9 mL), and lithium hydroxide monohydrate (311 mg, 7.4 mmol) is added and stirred 2 h at room temperature. The reaction is diluted in chloroform and washed with 1N hydrochloric acid (aq), water, and brine, dried (sodium sulfate), filtered and concentrated under reduced pressure to give the title compound. ESI MS *m/z* 287.3 $[M - H]^-$.

Step 3

N^1-{(1S,2R)-1-Benzyl-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-methyl-5-(1,3-oxazol-2-yl)-N^3-propylisophthalamide

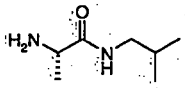


To 3-{[methyl(propyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoic acid (206 mg, 0.71 mmol) in DMF (5 mL) is added diisopropylethylamine (174 µL, 1.1 mmol), HATU (323 mg, 0.85 mmol), then (2R,3S)-3-amino-1-[(3-ethylbenzyl)amino]-4-phenylbutan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-272 (292 mg, 0.79 mmol). The reaction is stirred 4 h at room temperature. The reaction is partitioned between chloroform and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/chloroform) gives the title compound. ESI MS *m/z* 569.3 $[M + H]^+$.

EXAMPLE SP-164

Step 1

N^1- Isobutyl-L-alaninamide

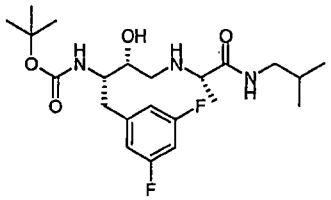


Boc-L-alanine (5.0 g, 26.4 mmol), isobutylamine (2.9 mL, 29.1 mmol), diisopropylethylamine (11.5 mL, 66 mmol), and HOBt (3.6 g, 26.4 mmol) in anhydrous DMF (15 mL) is stirred 15 min. EDC is added, and the reaction is stirred at room temperature 16 h. The reaction is diluted in ethyl acetate and washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. The residue is redissolved in 4N hydrochloric acid in dioxane (30 mL) and stirred for 2 h. The

solution is concentrated under reduced pressure, dissolved in chloroform and washed with 1 N NaOH (aq). The aqueous layer is extracted with chloroform, and the pooled organics are dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS *m/z* 145.2 $[M + H]^+$.

Step 2

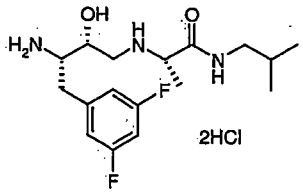
[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1-isobutylcarbamoyl-ethylamino)-propyl]-carbamic acid tert-butyl ester



N^1- Isobutyl-L-alaninamide (3.8 g, 26 mmol) and tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate prepared by the method in EXAMPLE S-3 (3.1 g, 10.4 mmol) in isopropanol (50 mL) are refluxed 4 h. The reaction is cooled and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/chloroform) gives the title compound. ESI MS *m/z* 444.1 $[M + H]^+$.

Step 3

N^2-[(2R,3S)-3-Amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]-N^1-isobutyl-L-alaninamide dihydrochloride

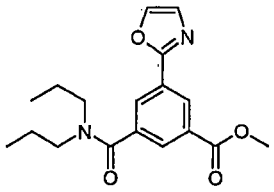


[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1-isobutylcarbamoyl-ethylamino)-propyl]-carbamic acid tert-butyl ester (2.7 g, 6 mmol) is dissolved in excess 4N hydrochloric acid in dioxane, and the reaction is stirred 2 h at room temperature. The solution is concentrated under reduced

pressure to give the title compound. ESI MS *m/z* 344.3 $[M + H]^+$.

Step 4

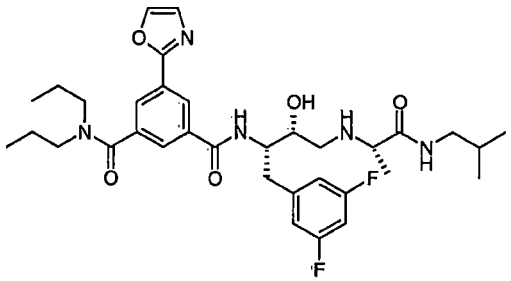
Methyl 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoate



3-[(Dipropylamino)carbonyl]-5-iodobenzoic acid (12 g, 32 mmol) is dissolved in 20% methanol/benzene (480 mL), and 2M trimethylsilyldiazomethane in hexane (19 mL, 38 mmol) is added slowly. Upon completion of the addition, the solution is concentrated under reduced pressure to give methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate for use without further purification in the following reaction. To a -70 °C stirred solution of oxazole (120 mg, 1.7 mmol) in tetrahydrofuran (4 mL) is added *n*-butyllithium (1.6 M in hexanes, 1.2 mL, 1.9 mmol). After 30 min, zinc chloride (1 M in diethyl ether, 5.2 mL, 5.2 mmol) is added and the reaction mixture is warmed to 0 °C for 1 h. To this mixture is added a solution of methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate (643 mg, 1.6 mmol) in anhydrous tetrahydrofuran (3 mL) followed by palladium(0) tetrakis(triphenylphosphine) (80 mg, 0.07 mmol). The reaction mixture is heated at reflux for 3 h. The reaction mixture is cooled, diluted with ethyl acetate, filtered, washed with saturated sodium bicarbonate, water, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 60% ethyl acetate/hexane) provides the title compound in pure form. ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.27 (s, 1H), 8.14 (s, 1H), 7.80 (s, 1H) 7.32 (s, 1H), 3.52 (t, 2H), 3.22 (t, 2H), 1.75 (m, 2H), 1.30 (m, 2H), 0.97 (t, 3H), 0.79 (t, 3H).

Step 5

N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1-isobutylcarbamoyl-ethylamino)-propyl]-5-oxazol-2-yl-N',N'-dipropyl-isophthalamide

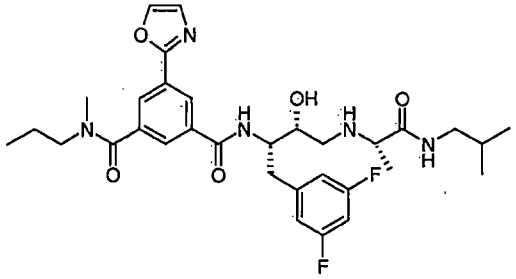


Methyl 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoate (430 mg, 1.3 mmol) is dissolved in 1:1:1 tetrahydrofuran/methanol/water (9 mL), and lithium hydroxide monohydrate (110 mg, 2.6 mmol) is added and stirred 2 h at room temperature. The reaction is concentrated under reduced pressure and chloroform is added. The solution is washed with 1N hydrochloric acid (aq). The aqueous layer is reextracted with chloroform, and the pooled organics are washed with brine. The solution is concentrated under reduced pressure.

To this residue redissolved in DMF (5 mL) is added diisopropylethylamine (438 µL, 2.52 mmol), HATU (289 mg, 0.76 mmol), then N^2-[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]-N^1-isobutyl-L-alaninamide dihydrochloride (288 mg, 0.69 mmol). The reaction is stirred 4 h at room temperature. The reaction is partitioned between chloroform and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/chloroform) gives the title compound. ESI MS *m/z* 642.3 $[M + H]^+$.

EXAMPLE SP-165

N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-(1-isobutylcarbamoyl-ethylamino)-propyl]-N'-methyl-5-oxazol-2-yl-N'-propyl-isophthalamide



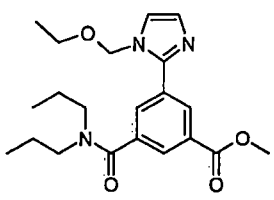
To 3-{[Methyl(propyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoic acid prepared by the method in EXAMPLE SP-163 in DMF (5 mL) is added diisopropylethylamine (361 µL, 2.1 mmol), HATU (237 mg, 0.62 mmol), then dihydrochloride prepared by the method of EXAMPLE SP-164 (237 mg, 0.57 mmol). The reaction is stirred 2 h at room temperature. The reaction is partitioned between chloroform and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/chloroform) gives the title compound. ESI MS *m/z* 614.4 $[M + H]^+$.

EXAMPLE SP-166

N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[1-(ethoxymethyl)-1H-imidazol-2-yl]-N^3,N^3-dipropylisophthalamide

Step 1

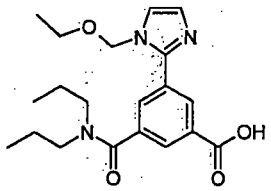
Methyl 3-[(dipropylamino)carbonyl]-5-[1-(ethoxymethyl)-1H-imidazol-2-yl]benzoate



To a -70 °C stirred solution of 1-ethoxylmethylimidazole (*J. Am. Chem. Soc.* **1978**, *100*, 3918) (420 mg, 3.3 mmol) in tetrahydrofuran (10 mL) is added *n*-butyllithium (1.6 M in hexanes, 2.3 mL, 3.6 mmol). After 30 min, zinc chloride (9.9 mL of a 1 M solution in diethyl ether, 9.9 mmol) is added and the reaction mixture is warmed to 0 °C for 1 h. To this mixture is then added methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate (1.17 g, 3 mmol) followed by palladium(0) tetrakis(triphenylphosphine) (173 mg, 0.15 mmol). The reaction mixture is heated at reflux for 2 h. The reaction mixture is diluted with ethyl acetate (50 mL), washed with water, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 1-5% methanol/methylene chloride) provides the title compound in pure form. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.10 (s, 1H), 8.03 (s, 1H), 8.19 (s, 2H), 5.28 (s, 2H), 3.95 (s, 3H), 3.59 (q, *J* = 7 Hz, 2H), 3.49 (m, 2H), 3.21 (m, 2H), 1.70 (m, 2H), 1.54 (m, 2H), 1.25 (t, *J* = 7 Hz, 3H), 0.99 (m, 3H), 0.75 (m, 3H).

Step 2

3-[(Dipropylamino)carbonyl]-5-[1-(ethoxymethyl)-1H-imidazol-2-yl]benzoic acid

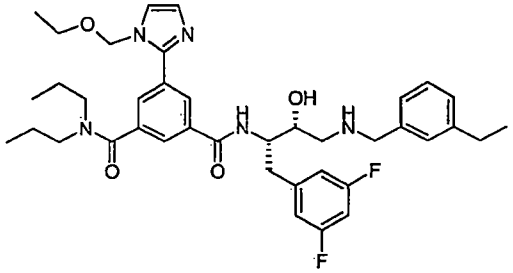


To a stirred solution of the ester from step 1 (756 mg, 1.95 mmol) in 2:1:1 tetrahydrofuran/methanol/water (12 mL) is added lithium hydroxide (170 mg, 4 mmol). The reaction mixture is stirred at room temperature for 42 h, and concentrated under reduced pressure. The residue is partitioned between water (10 mL) and chloroform (10 mL). The aqueous layer is acidified to pH 4 - 5 with 1 N hydrochloric

acid and extracted with 3:1 chloroform/2-propanol (3 x 30 mL). The combined organic layers are dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide the title compound. ^{1}H NMR (300 MHz, CD_3OD) δ 8.51 (s, 1H), 8.06 (s, 1H), 8.00 (s, 1H), 7.49 (s, 1H), 7.17 (s, 1H), 5.39 (s, 2H), 3.62 (q, J = 7 Hz, 2H), 3.51 (m, 2H), 3.27 (m, 2H), 1.72 (m, 2H), 1.59 (m, 2H), 1.21 (t, J = 7 Hz, 3H), 1.00 (m, 3H), 0.75 (m, 3H).

Step 3

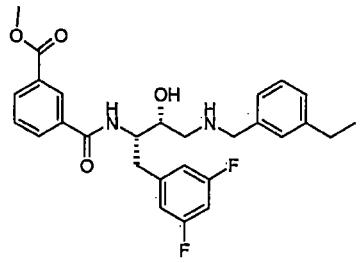
N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[1-(ethoxymethyl)-1H-imidazol-2-yl]-N^3,N^3-dipropylisophthalamide



To a stirred solution of 3-[(dipropylamino)carbonyl]-5-[1-(ethoxymethyl)-1H-imidazol-2-yl]benzoic acid (177 mg, 0.47 mmol), diisopropylethylamine (651 mg, 0.5 mmol), and HBTU (209 mg, 0.55 mmol) in methylene chloride (5 mL) is added a mixture of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (196 mg, 0.48 mmol) and diisopropylethylamine (130 mg, 1.0 mmol) in methylene chloride (5 mL). The reaction mixture is stirred at room temperature for 15 h and concentrated under reduced pressure. The residue is diluted with ethyl acetate (20 mL), washed with saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5:95 methanol/methylene chloride) provides the title compound. APCI MS m/z 690.3 $[M + H]^+$.

EXAMPLE SP-168

Methyl 3-[({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)carbonyl]benzoate

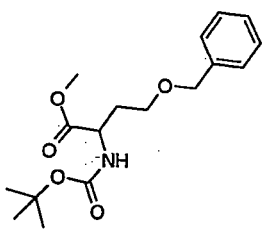


To methyl hydrogen isophthalate (1.0 g, 5.6 mmol) in DMF/chloroform (1:2, 15 mL) is added diisopropylethylamine (3.9 mL, 22 mmol), HATU (2.5 g, 6.7 mmol), then (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-272 (2.5 g, 6.1 mmol). The reaction is stirred 1 h at room temperature. The reaction is partitioned between ethyl acetate and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/chloroform) gives the title compound. ESI MS *m/z* 497.3 $[M + H]^+$.

EXAMPLE SP-169 N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[4-(2-hydroxyethyl)-1,3-oxazol-2-yl]benzamide

Step 1

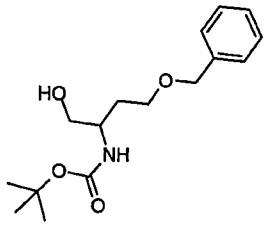
Methyl O-benzyl-N-(tert-butoxycarbonyl)homoserinate



To O-benzyl-N-(tert-butoxycarbonyl)homoserine (5.8 g, 18.9 mmol) in 20% methanol/benzene (72 mL) is added 2M trimethylsilyldiazomethane in hexane (12.3 mL, 24.5 mmol), and the reaction stirred at room temperature 1.5 h. The solution is concentrated under reduced pressure to give the title compound in pure form. ESI MS *m/z* 324.2 $[M + H]^+$.

Step 2

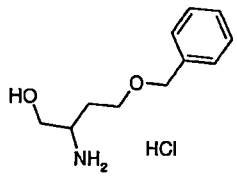
tert-Butyl 3-(benzyloxy)-1-(hydroxymethyl)propylcarbamate



To an ice-cold solution of methyl O-benzyl-N-(tert-butoxycarbonyl)homoserinate (6 g, 18.6 mmol) in absolute ethanol (100 mL) is added sodium borohydride (2.8 g, 74.2 mmol), and the reaction is refluxed 2 h. The solution is cooled, excess saturated potassium carbonate added, and stirred 16 h at room temperature. The ethanol is removed under reduced pressure, and the aqueous solution is extracted with chloroform. The organic layer is washed with saturated sodium bicarbonate, saturated sodium sulfate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS *m/z* 296.2 $[M + H]^+$.

Step 3

2-Amino-4-(benzyloxy)butan-1-ol hydrochloride

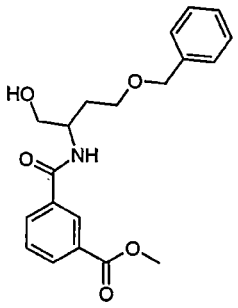


tert-Butyl 3-(benzyloxy)-1-(hydroxymethyl)propylcarbamate (5 g, 17 mmol) is dissolved in 4 N hydrochloric acid in

dioxane (21 mL) and stirred for 3 h at room temperature. The solution is concentrated under reduced pressure to give the title compound in pure form. ESI MS *m/z* 196.1 $[M + H]^+$.

Step 4

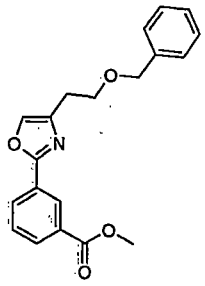
Methyl 3-({[3-(benzyloxy)-1-(hydroxymethyl)propyl]amino}carbonyl)benzoate



Methyl hydrogen isophthalate (1.5 g, 8.2 mmol), 2-amino-4-(benzyloxy)butan-1-ol hydrochloride (2 g, 8.6 mmol), diisopropylethylamine (4.2 mL, 24.7 mmol), and HATU (3.8 mg, 9.9 mmol), in DMF (15 mL) are stirred at room temperature 1 h. The reaction is diluted in ethyl acetate and washed with water, 1N hydrochloric acid (aq), saturated sodium bicarbonate, brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 4% methanol/chloroform) provides the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.18 (d, 1H, *J*= 7.9 Hz), 7.86 (d, 1H, *J*= 7.9 Hz), 7.43 (t, 1H, *J*= 7.6 Hz), 7.42-7.35 (m, 5 H), 4.59 (s, 2H), 4.33 (m, 1H), 3.96 (s, 3H), 3.88-3.72 (m, 4H), 3.53 (s, 1H), 2.08 (m, 2H).

Step 5

Methyl 3-{4-[2-(benzyloxy)ethyl]-1,3-oxazol-2-yl}benzoate

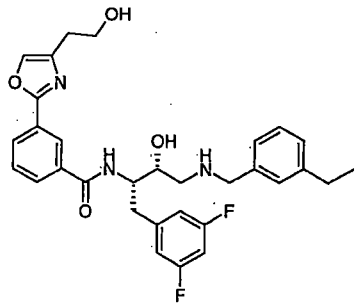


To methyl 3-({[3-(benzyloxy)-1-(hydroxymethyl)propyl]amino}carbonyl)benzoate (1.3 g, 3.6 mmol) in water-saturated methylene chloride (20 mL) is added sodium bromide (187 mg, 1.8 mmol) and water (2.75 mL), then TEMPO (6 mg, 0.04 mmol) with vigorous stirring. Sodium bicarbonate (115 mg) and 6% sodium hypochlorite (5 mL) is added and stirred 1 h. 6% sodium hypochlorite (1 mL) is added each hour for 3 h.

Excess saturated sodium thiosulfate is added and stirred 30 min. The mixture is partitioned, and the organic layer is washed with brine, dried (sodium sulfate), filtered and concentrated under reduced. The residue is dissolved in anhydrous tetrahydrofuran (4 mL), and (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt (670 mg, 2.8 mmol). The reaction is microwaved (100 W, 2 min) in a sealed vessel, cooled, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 40% ethyl acetate/hexanes) gives the title compound. ESI MS *m/z* 338.3 $[M + H]^+$.

Step 6

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[4-(2-hydroxyethyl)-1,3-oxazol-2-yl]benzamide



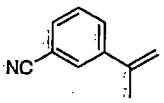
Methyl 3-{4-[2-(benzyloxy)ethyl]-1,3-oxazol-2-yl}benzoate (300 mg, 0.9 mmol), 20% palladium(II) hydroxide on carbon (65 mg), and cyclohexene (3 mL) in absolute ethanol (3 mL) are refluxed 1 h. The reaction is cooled, filtered through diatomaceous earth, and concentrated under reduced pressure. The residue is redissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL) is added lithium hydroxide (75 mg, 1.8 mmol). The reaction mixture is stirred at room temperature for 3 h, and concentrated under reduced pressure. The residue is dissolved in DMF (5 mL), and diisopropylethylamine (625 µL, 3.6 mmol), HATU (540 mg, 1.4 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method in EXAMPLE SP-272 (407 mg, 1 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with chloroform, washed with water, 1N hydrochloric acid (aq), saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/chloroform) provides the title compound. ESI MS *m/z* 550.3 $[M + H]^+$.

EXAMPLE SP-170

N^1-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-N^3,N^3-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide

Step 1

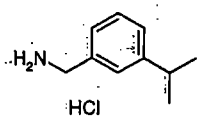
3-Isopropenylbenzonitrile



To a stirred solution of 3-cyanophenylboronic acid (10.0 g, 68.05 mmol) dissolved in DME (340 mL) is added 2-bromopropene (6.86 g, 56.7 mmol), and sodium carbonate (62.3 mL of a 2 M solution in water, 124.7 mmol). The reaction mixture is degassed for 20 min with nitrogen. Tetrakis(triphenylphosphine)palladium(0) (2.54 g, 2.2 mmol) is added, the reaction mixture degassed for 10 min, and heated at reflux overnight. The reaction mixture is cooled to room temperature and then partitioned between hexanes and water. The aqueous layer is extracted with hexanes (3 x 75 mL). The combined organic layers are washed with brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (9:1 hexanes/ethyl acetate) provides the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.96 (m, 1H), 7.85 (d, J = 8 Hz, 1H), 7.75 (d, J = 8 Hz, 1H), 7.56 (m, 1H) 5.58 (s, 1H), 5.23 (m, 1H), 2.13 (s, 3H).

Step 2

3-Isopropylbenzylamine hydrochloride

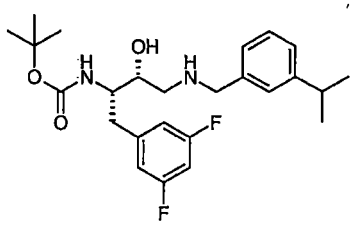


A solution of 3-isopropenylbenzonitrile (6.0 g, 41.9 mmol) and 10% Pd/C (600 mg) in ethanol (65 mL) and acetic acid (2.4 mL) is degassed with nitrogen for 15 min, and shaken under an atmosphere of hydrogen at 50 psi for 12 h. The reaction mixture is filtered through diatomaceous earth and concentrated under reduced pressure to provide an oil. The oil is dissolved in methanol (5 mL) and hydrochloric acid (15 mL of a 1 M solution in diethyl ether) is added. The

resulting precipitate is collected by filtration to provide the title compound. APCI MS *m/z* 149 $[M + H]^+$.

Step 3

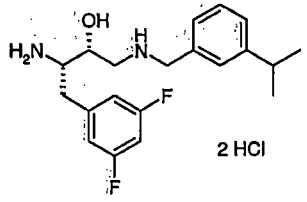
tert-Butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propylcarbamate



tert-Butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (2.0 g, 6.7 mmol) and 3-isopropylbenzylamine hydrochloride (2.5 g, 13.5 mmol) in isopropanol (60 mL) are refluxed 3 h. The reaction is cooled and stirred 16 h. The solution is concentrated under reduced pressure, redissolved in chloroform, washed with 1N hydrochloric acid, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered and concentrated under reduced pressure. Purification by flash chromatography (silica, 7% methanol/chloroform) gives the title compound in pure form. ESI MS *m/z* 449.3 $[M + H]^+$.

Step 4

(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-isopropylbenzyl)amino]butan-2-ol dihydrochloride

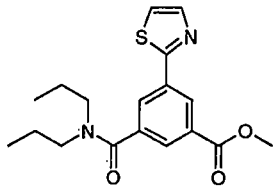


tert-Butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propylcarbamate (1.5 g, 3.3 mmol) is dissolved in 4 N hydrochloric acid in dioxane (20 mL), and the reaction is stirred at room temperature 3 h. The mixture is

concentrated under reduced pressure to afford the title compound. ESI MS *m/z* 349.2 $[M + H]^+$.

Step 5

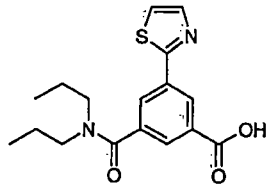
Methyl 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoate



To 0.5 M thiazole zinc bromide in tetrahydrofuran (45 mL) is added methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate (8.6 g, 21.4 mmol) in anhydrous tetrahydrofuran (130 mL) followed by palladium(0) tetrakis(triphenylphosphine) (2 g, 1.7 mmol). The reaction mixture is heated at reflux for 16 h. The reaction mixture is diluted with ethyl acetate (50 mL), washed with water, saturated sodium bicarbonate, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 35% ethyl acetate/hexanes) provides the title compound. ESI MS *m/z* 347.1 $[M + H]^+$.

Step 6

3-[(Dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoic acid

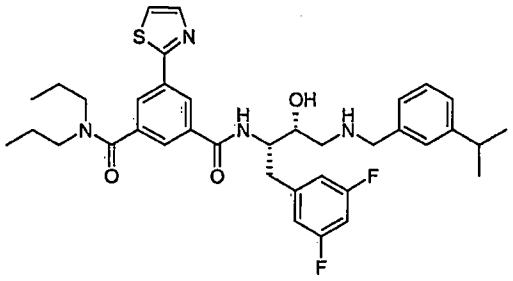


Methyl 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoate (4.4 g, 12.8 mmol) is dissolved in 1:1:1 tetrahydrofuran/methanol/water (60 mL), and lithium hydroxide monohydrate is added (1.1 g, 25.6 mmol). The reaction is stirred 15 min and is concentrated under reduced pressure. The residue is diluted in chloroform and washed with water,

brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS *m/z* 333.1 $[M + H]^+$.

Step 7

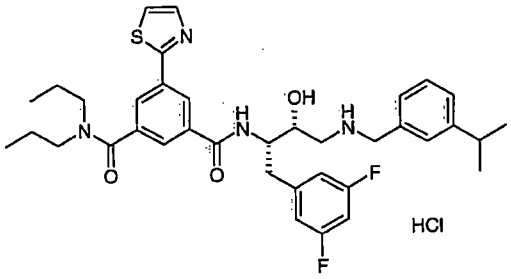
N^1-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-N^3,N^3-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide



3-[(Dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoic acid is dissolved in DMF (8 mL), and diisopropylethylamine (456 µL, 2.6 mmol), HATU (342 mg, 0.9 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-isopropylbenzyl)amino]butan-2-ol dihydrochloride (350 mg, 0.83 mmol) are added. The reaction stirred at room temperature 1 h. The reaction is partitioned between ethyl acetate and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (5 mL) and 1N hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 663.3 $[M + H]^+$.

EXAMPLE SP-171

N^1-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-N^3,N^3-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide hydrochloride



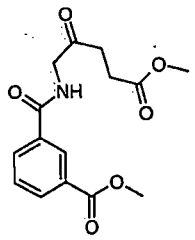
N^1-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-N^3,N^3-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide (180 mg, 0.27 mmol) is dissolved in diethyl ether (5 mL) and 1N hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 663.3 $[M + H]^+$.

EXAMPLE SP-172

Methyl 3-(2-{3-[({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)carbonyl]phenyl}-1,3-oxazol-5-yl)propanoate

Step 1

Methyl 3-{[(5-methoxy-2,5-dioxopentyl)amino]carbonyl}benzoate

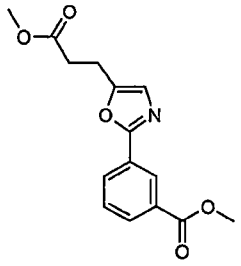


Methyl hydrogen isophthalate (1.8 g, 10.2 mmol) is dissolved in methylene chloride (10 mL) and DMF (10 mL), and diisopropylethylamine (4.4 mL, 25.5 mmol), HATU (4.6 g, 12.2 mmol), and 5-aminolevulinic acid methyl ester hydrochloride (2 g, 11.2 mmol) are added. The reaction stirred at room

temperature 1 h. The reaction is partitioned between ethyl acetate and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 4% methanol/chloroform) provides the title compound. ESI MS *m/z* 306.1 $[M - H]^-$.

Step 2

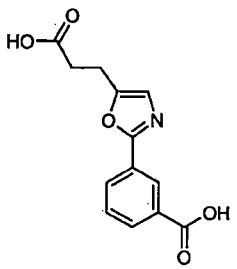
Methyl 3-[5-(3-methoxy-3-oxopropyl)-1,3-oxazol-2-yl]benzoate



Methyl 3-{[(5-methoxy-2,5-dioxopentyl)amino]carbonyl}benzoate (520 mg, 1.7 mmol) is dissolved in anhydrous tetrahydrofuran (4 mL), and (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt (810 mg, 3.4 mmol). The reaction is microwaved (100 W, 2 min) in a sealed vessel, cooled, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 40% ethyl acetate/hexanes) gives the title compound. ESI MS *m/z* 290.1 $[M + H]^+$.

Step 3

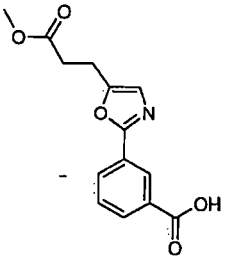
3-[5-(2-Carboxyethyl)-1,3-oxazol-2-yl]benzoic acid



To methyl 3-[5-(3-methoxy-3-oxopropyl)-1,3-oxazol-2-yl]benzoate (400 mg, 1.3 mmol) in 2:1:1 tetrahydrofuran/methanol/water (8 mL) is added lithium hydroxide monohydrate (112 mg, 2.7 mmol), and the reaction is stirred 2 h at room temperature. More lithium hydroxide monohydrate (225 mg, 5.4 mmol) is added and the reaction is stirred 16 h at room temperature. The reaction is treated with excess concentrated hydrochloric acid resulting in a precipitate. The precipitate is filtered to give the title compound. ESI MS *m/z* 260.1 $[M - H]^-$.

Step 4

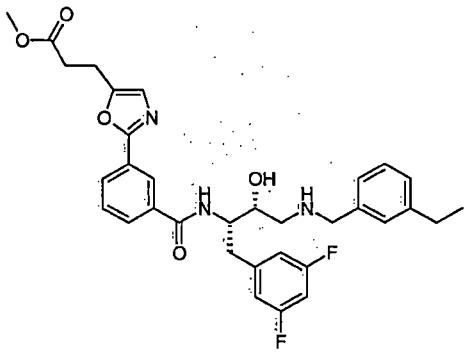
3-[5-(3-Methoxy-3-oxopropyl)-1,3-oxazol-2-yl]benzoic acid



To 3-[5-(2-carboxyethyl)-1,3-oxazol-2-yl]benzoic acid (317 mg, 1.2 mmol) in methanol (5 mL) is added thionyl chloride (4.4 µL, 0.06 mmol), and the reaction is stirred at room temperature 16 h. The solution is concentrated under reduced pressure to give the title compound. ESI MS *m/z* 274.1 $[M - H]^-$.

Step 5

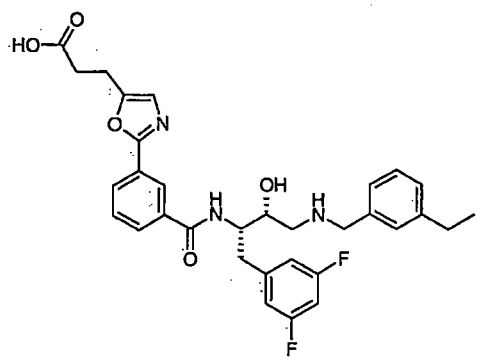
Methyl 3-(2-{3-[({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)carbonyl]phenyl}-1,3-oxazol-5-yl)propanoate



3-[5-(3-Methoxy-3-oxopropyl)-1,3-oxazol-2-yl]benzoic acid (285 mg, 1.0 mmol) is dissolved in methylene chloride (5 mL) and DMF (5 mL), and diisopropylethylamine (695 µL, 4.0 mmol), HATU (472 g, 1.2 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-272 (448 mg, 1.1 mmol) are added. The reaction stirred at room temperature 1 h. The reaction is partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/chloroform) provides the title compound. ESI MS *m/z* 591.9 $[M + H]^+$.

EXAMPLE SP-173

3-(2-{3-[({(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)carbonyl]phenyl}-1,3-oxazol-5-yl)propanoic acid



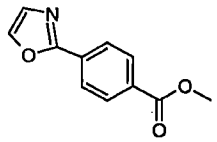
Methyl 3-(2-{3-[({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)carbonyl]phenyl}-1,3-oxazol-5-yl)propanoate (70 mg, 0.12 mmol) and lithium hydroxide monohydrate (10 mg, 0.24 mmol) in 2:1:1 tetrahydrofuran/methanol/water (6 mL) is stirred at room temperature 1.5 h. The reaction is concentrated under reduced pressure. The residue is washed with 1N hydrochloric acid (aq), then chloroform, and the solid is dried under reduced pressure to give the title compound. ESI MS *m/z* 578.2 $[M + H]^+$.

EXAMPLE SP-174

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(1,3-oxazol-2-yl)benzamide

Step 1

Methyl 4-(1,3-oxazol-2-yl)benzoate

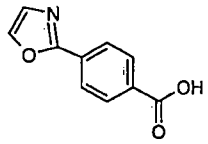


To a -70 °C, stirred solution of oxazole (190 □L, 3.8 mmol) in tetrahydrofuran (10 mL) is added *n*-butyl lithium (2.6 mL of a 1.6 M solution in hexanes, 4.2 mmol). After 30 min, zinc chloride (11.5 mL of a 1.0 M solution in diethyl ether, 11.5 mmol) is added. The reaction mixture is warmed to 0 °C and methyl 4-iodobenzoate (1 g, 3.8 mmol) and palladium(0) tetrakis(triphenylphosphine) (530 mg, 0.4 mmol) are added. The reaction mixture is heated at 70 °C for 20 h under argon, cooled to room temperature, and then partitioned between ethyl acetate and water. The organic layer is washed with water and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (3:1 hexanes/ethyl acetate) yields the title

compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 4H), 8.07-8.05 (m, 1H), 7.36-7.35 (m, 1H), 3.95 (s, 3H).

Step 2

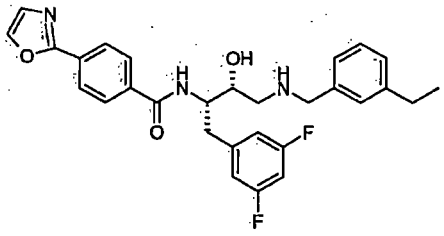
4-(1,3-Oxazol-2-yl)benzoic acid



To a stirred solution of methyl 4-(1,3-oxazol-2-yl)benzoate (690 mg, 3.4 mmol) in a mixture of 2:1:1 tetrahydrofuran/methanol/water (20 mL) is added lithium hydroxide (430 mg, 3 mmol). The reaction mixture is stirred at room temperature for 2 h. The solvent is removed under reduced pressure and the residue is partitioned between diethyl ether and water. The aqueous layer is acidified to pH 1 with 1 N hydrochloric acid and a precipitate is observed. The solid is collected by filtration to afford the title compound. ^{1}H NMR (300 MHz, CD_3OD) δ 8.14 (s, 4H), 8.05 (s, 1H), 7.36 (s, 1H).

Step 3

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(1,3-oxazol-2-yl)benzamide



To a solution of 4-(1,3-oxazol-2-yl)benzoic acid (105 mg, 0.6 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (220 mg, 0.6 mmol), and HATU (210 mg, 0.6 mmol) stirring in methylene chloride (5 mL) is added *N*,*N*-diisopropylethylamine (340 □L, 1.9 mmol). The reaction mixture is stirred at room

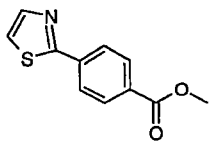
temperature for 18 h. The reaction mixture is partitioned between methylene chloride and water. The organic layer is washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford a crude solid. Purification by flash column chromatography (silica, gradient 96:4 to 93:7 methylene chloride/methanol) provided the title compound. ESI MS *m/z* 506.2 $[M + H]^+$.

EXAMPLE SP-173

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(1,3-thiazol-2-yl)benzamide

Step 1

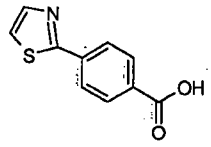
Methyl 4-(1,3-thiazol-2-yl)benzoate



To a -70 °C, stirred solution of thiazole (270 □L, 3.8 mmol) in tetrahydrofuran (10 mL) is added *n*-butyl lithium (2.6 mL of a 1.6 M solution in hexanes, 4.2 mmol). After 30 min, zinc chloride (11.4 mL of a 1.0 M solution in diethyl ether, 11.4 mmol) is added. The reaction mixture is warmed to 0 °C and methyl 4-iodobenzoate (1 g, 3.8 mmol) and palladium(0) tetrakis(triphenylphosphine) (530 mg, 0.4 mmol) are added. The reaction mixture is heated at 70 °C for 20 h under argon, cooled to room temperature, and then partitioned between ethyl acetate and water. The organic layer is washed with water, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (3:1 hexanes/ethyl acetate) yields the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14-8.03 (m, 4H), 7.93-7.92 (m, 1H), 7.42-7.41 (m, 1H), 3.95 (s, 3H).

Step 2

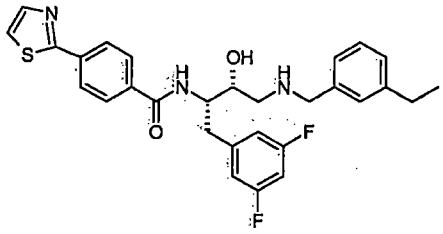
4-(1,3-Thiazol-2-yl)benzoic acid



To a stirred solution of methyl 4-(1,3-thiazol-2-yl)benzoate (560 mg, 2.6 mmol) in a mixture of 2:1:1 tetrahydrofuran/methanol/water (20 mL) is added lithium hydroxide (322 mg, 3 mmol). The reaction mixture is stirred at room temperature for 2 h. The solvent is removed under reduced pressure and the residue is partitioned between diethyl ether and water. The aqueous layer is acidified to pH 1 with 1 N hydrochloric acid and a precipitate is observed. The solid is collected by filtration to afford the title compound. ^{1}H NMR (300 MHz, CD_3OD) δ 8.14-8.05 (m, 4H), 7.95-7.93 (m, 1H), 7.71-7.69 (m, 1H).

Step 3

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(1,3-thiazol-2-yl)benzamide

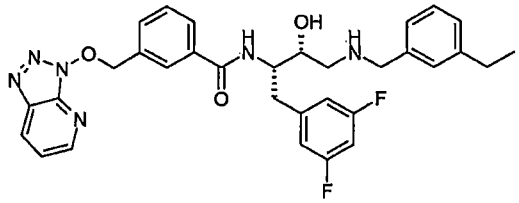


To a solution of 4-(1,3-thiazol-2-yl)benzoic acid (110 mg, 0.6 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (220 mg, 0.6 mmol), and HATU (210 mg, 0.6 mmol) stirring in methylene chloride (5 mL) is added *N,N*-diisopropylethylamine (340 □L, 1.9 mmol). The reaction mixture is stirred at room temperature for 18 h. The reaction mixture is partitioned between methylene chloride and water. The organic layer is washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash

column chromatography (silica, gradient 95:5 to 92:8 methylene chloride/methanol) provides the title compound. ESI MS *m/z* 522.2 $[M + H]^+$.

EXAMPLE SP-176

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)methyl]benzamide



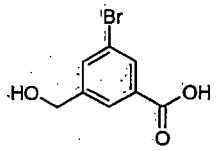
To 3-(bromomethyl)benzoic acid (200 mg, 0.93 mmol) and diisopropylethylamine (566 µL, 3.26 mmol) in DMF (5 mL) is added HATU (424 mg, 1.12 mmol), and the reaction is stirred 5 min. To the reaction is added (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method in EXAMPLE SP-272 (379 mg, 0.93 mmol), and the reaction stirred 30 min. The reaction mixture is diluted with methylene chloride, washed with 1 N hydrochloric acid (15 mL), saturated sodium bicarbonate (15 mL), and brine. The organic layer is then dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/chloroform) provides the title compound. ESI MS *m/z* 587.4 $[M + H]^+$.

EXAMPLE SP-177

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-3-{[(2-hydroxyethyl)(propyl)amino]methyl}-5-methylbenzamide dihydrochloride

Step 1

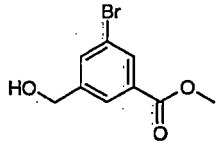
3-Bromo-5-(hydroxymethyl)benzoic acid



To an ice-cold solution of 3-bromo-5-(methoxycarbonyl)benzoic acid prepared by the method in Preparation 2 (10.3 g, 40 mmol) in anhydrous tetrahydrofuran (100 mL) is added lithium borohydride (12 g, 550 mmol) portion-wise. The reaction is stirred 4 h at this temperature. Absolute ethanol (20 mL) is added dropwise, and the reaction is stirred 1.5 h. The reaction is slowly poured on ice, and 10 % hydrochloric acid (aq) is added until gas evolution ceased. The aqueous layer is extracted with chloroform, and the organic layer is washed with brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS *m/z* 229, 231 [M - H]$^-$.

Step 2

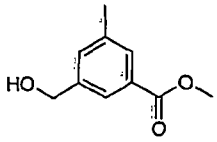
Methyl 3-bromo-5-(hydroxymethyl)benzoate



To 3-bromo-5-(hydroxymethyl)benzoic acid (7.0 g, 30 mmol) in 20% methanol/benzene (100 mL) is added trimethylsilyldiazomethane (2M in hexanes), and the reaction is stirred 16 h. The reaction is concentrated under reduced pressure to afford the title compound. ESI MS *m/z* 244.0 [M + H]$^+$.

Step 3

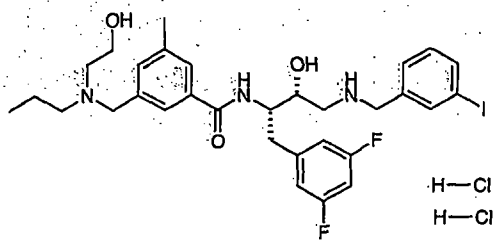
Methyl 3-(hydroxymethyl)-5-methylbenzoate



To a stirred solution of methyl 3-bromo-5-(hydroxymethyl)benzoate (3.0 g, 12.2 mmol) in dioxane (27 mL) is added cesium carbonate (4.0 g, 12.2 mmol), potassium carbonate (34 g, 24.4 mmol), and palladium(0) tetrakis(triphenylphosphine) (704 mg, 0.61 mmol), followed by trimethyl boroxine (1.7 mL, 12.2 mmol). The reaction mixture is refluxed for 5 h, cooled to room temperature, and then partitioned between water and ethyl acetate. The organic layer is washed with water, saturated sodium bicarbonate, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 20% ethyl acetate/hexanes) provides the title compound. ESI MS *m/z* 181.2 $[M + H]^+$.

Step 4

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-3-{[(2-hydroxyethyl)(propyl)amino]methyl}-5-methylbenzamide dihydrochloride

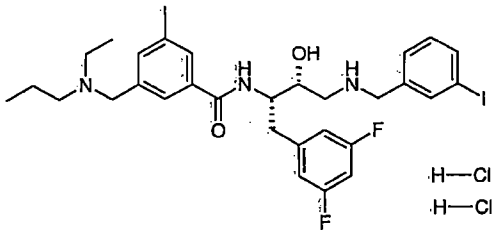


To a stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (1.25, 7 mmol) in methylene chloride (30 mL) at -30 °C is added methanesulfonyl chloride (752 µL, 9.7 mmol) followed by triethylamine (1.95 mL, 14 mmol). The reaction mixture is stirred for 15 min at 0 °C. The reaction is diluted in diethyl ether and washed with water and cold brine, dried (magnesium sulfate), filtered and concentrated under reduced

pressure to give an oil. The residue is redissolved in anhydrous methylene chloride (22 mL). From this stock solution, 2 mL is added to a solution of *N*-hydroxyethylpropylamine (115 µL, 1 mmol) in anhydrous methylene chloride (1 mL), and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 1:1:1 tetrahydrofuran/methanol/water (3 mL), and lithium hydroxide monohydrate is added (33 mg, 0.75 mmol). The reaction is stirred 2 h and is concentrated under reduced pressure. The residue is redissolved in DMF (3 mL), and diisopropylethylamine (261 µL, 1.5 mmol), HATU (214 mg, 0.56 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (189 mg, 0.37 mmol) are added. The reaction stirred at room temperature 16 h. Purification by flash column chromatography (silica, 8% methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 666.2 $[M + H]^+$.

EXAMPLE SP-178

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-3-{[ethyl(propyl)amino]methyl}-5-methylbenzamide dihydrochloride



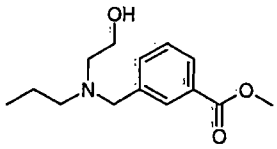
Analogous to the method described in EXAMPLE SP-177, Step 4, 2 mL of the stock solution is added to a solution of *N*-ethylpropylamine (143 μL, 1 mmol) in anhydrous methylene chloride (1 mL), and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 1:1:1 tetrahydrofuran/methanol/water (3 mL), and lithium hydroxide monohydrate is added (42 mg, 1 mmol). The reaction is stirred 2 h and is concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (265 μL, 1.5 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (252 mg, 0.5 mmol), and HATU (237 mg, 0.62 mmol) are added. The reaction stirred at room temperature 16 h. Purification by flash column chromatography (silica, 10% methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 650.2 $[M + H]^+$.

EXAMPLE SP-179

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-3-{[(2-hydroxyethyl)(propyl)amino]methyl}benzamide dihydrochloride

Step 1

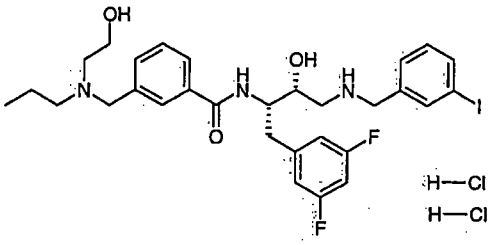
Methyl 3-{[(2-hydroxyethyl)(propyl)amino]methyl}benzoate



To 2-propylaminomethanol (505 μL, 4.4 mmol) in chloroform (20 mL) is added methyl bromomethylbenzoate (1 g, 4.4 mmol), and the reaction stirred at room temperature 16 h. The reaction is washed with saturated sodium bicarbonate and brine. The organic layer is then dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 80% ethyl acetate/hexanes) provides the title compound. ESI MS *m/z* 252.3 $[M + H]^+$.

Step 2

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-3-{[(2-hydroxyethyl)(propyl)amino]methyl}benzamide dihydrochloride

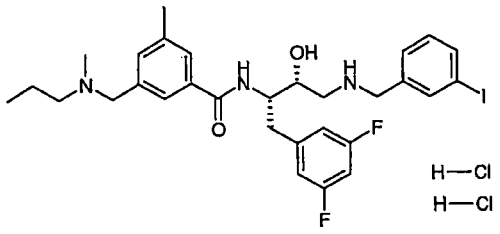


Methyl 3-{[(2-hydroxyethyl)(propyl)amino]methyl}benzoate (500 mg, 2 mmol) and lithium hydroxide monohydrate (170 mg, 4 mmol) are stirred in 2:1:1 tetrahydrofuran/methanol/water (4 mL) at room temperature for 16 h. The reaction is concentrated under reduced pressure and redissolved in DMF (15 mL). To this solution is added (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (1 g, 2 mmol), diisopropylethylamine (1.4 mL, 8 mmol), then HATU (1.1 g, 3 mmol), and the reaction stirred 2 h. Purification by flash column chromatography (silica, 10%

methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (5 mL) and 1N hydrochloric acid in diethyl ether (3 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 652.2 $[M + H]^+$.

EXAMPLE SP-180

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-3-methyl-5-{[methyl(propyl)amino]methyl}benzamide dihydrochloride

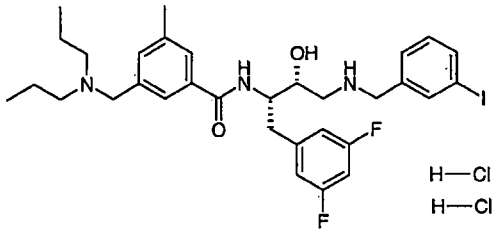


Analogous to the method described in EXAMPLE SP-177, Step 4, 2 mL of the stock solution is added to a solution of *N*-methylpropylamine (103 µL, 1 mmol) in anhydrous methylene chloride (1 mL), and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 1:1:1 tetrahydrofuran/methanol/water (3 mL), and lithium hydroxide monohydrate is added (33 mg, 0.75 mmol). The reaction is stirred 2 h and is concentrated under reduced pressure. The residue is redissolved in DMF (3 mL), and diisopropylethylamine (261 µL, 1.5 mmol), HATU (214 mg, 0.56 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (189 mg, 0.37 mmol) are added. The reaction stirred at room temperature 16 h. Purification by flash column chromatography (silica, 8%

methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 636.2 $[M + H]^+$.

EXAMPLE SP-181

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-3-[(dipropylamino)methyl]-5-methylbenzamide dihydrochloride

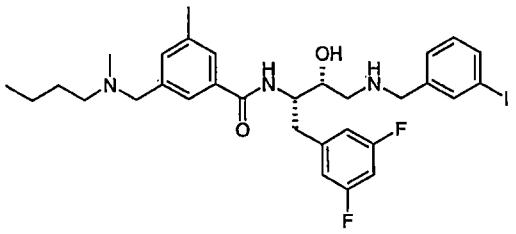


Analogous to the method described in EXAMPLE SP-177, Step 4, 2 mL of the stock solution is added to a solution of dipropylamine (137 µL, 1 mmol) in anhydrous methylene chloride (1 mL), and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 1:1:1 tetrahydrofuran/methanol/water (3 mL), and lithium hydroxide monohydrate is added (33 mg, 0.75 mmol). The reaction is stirred 2 h and is concentrated under reduced pressure. The residue is redissolved in DMF (3 mL), and diisopropylethylamine (261 µL, 1.5 mmol), HATU (214 mg, 0.56 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (189 mg, 0.37 mmol) are added. The reaction stirred at room temperature 16 h. Purification by flash column chromatography (silica, 8%

methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 664.2 $[M + H]^+$.

EXAMPLE SP-182

3-{[Butyl(methyl)amino]methyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-5-methylbenzamide dihydrochloride



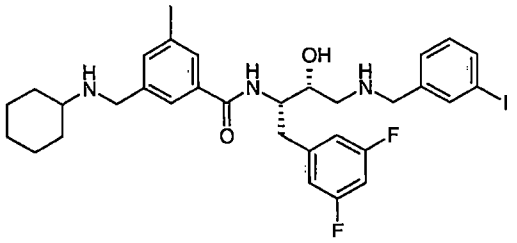
2 HCl

Analogous to the method described in EXAMPLE SP-177 Step 4, 2 mL of the stock solution is added to a solution of *N*-methylbutylamine (118 µL, 1 mmol) in anhydrous methylene chloride (1 mL), and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 1:1:1 tetrahydrofuran/methanol/water (3 mL), and lithium hydroxide monohydrate is added (33 mg, 0.75 mmol). The reaction is stirred 2 h and is concentrated under reduced pressure. The residue is redissolved in DMF (3 mL), and diisopropylethylamine (261 µL, 1.5 mmol), HATU (214 mg, 0.56 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (189 mg, 0.37 mmol) are added. The reaction stirred at room temperature 16

h. Purification by flash column chromatography (silica, 8% methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 650.2 $[M + H]^+$.

EXAMPLE SP-183

3-[(Cyclohexylamino)methyl]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-5-methylbenzamide dihydrochloride



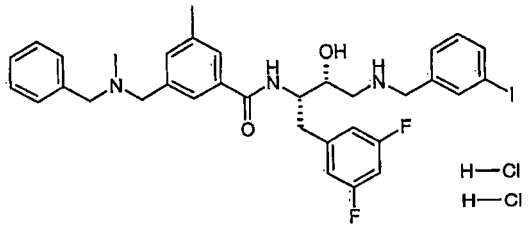
2 HCl

Analogous to the method described in EXAMPLE SP-177, Step 4, 2 mL of the stock solution is added to a solution of cyclohexylamine (114 µL, 1 mmol) in anhydrous methylene chloride (1 mL), and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 1:1:1 tetrahydrofuran/methanol/water (3 mL), and lithium hydroxide monohydrate is added (33 mg, 0.75 mmol). The reaction is stirred 2 h and is concentrated under reduced pressure. The residue is redissolved in DMF (3 mL), and diisopropylethylamine (261 µL, 1.5 mmol), HATU (214 mg, 0.56 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (189 mg, 0.37

mmol) are added. The reaction stirred at room temperature 16 h. Purification by flash column chromatography (silica, 8% methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 662.2 $[M + H]^+$.

EXAMPLE SP-184

3-{[benzyl(methyl)amino]methyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-5-methylbenzamide dihydrochloride



Analogous to the method described in EXAMPLE SP-177, a stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (1.0, 5.6 mmol) in methylene chloride (9 mL) at -30 °C is added methanesulfonyl chloride (600 µL, 7.8 mmol) followed by triethylamine (1.55 mL, 11 mmol). The reaction mixture is stirred for 1 h at 0 °C, then filtered. From this stock solution, 2 mL is added to a solution of *N*-methylbenzylamine (538 µL, 4.2 mmol) in anhydrous methylene chloride (1 mL), and the reaction mixture is stirred at room temperature for 16 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with saturated sodium bicarbonate and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (90 mg, 2 mmol). The reaction is stirred 16 h and is concentrated under

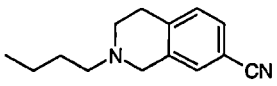
reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (695 µL, 4 mmol), HATU (570 mg, 1.5 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (505 mg, 1 mmol) are added. The reaction stirred at room temperature 16 h. Purification by flash column chromatography (silica, 7% methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 684.2 $[M + H]^+$.

EXAMPLE SP-185

2-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxamide dihydrochloride

Step 1

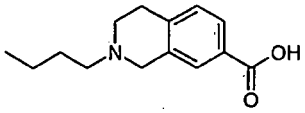
2-Butyl-1,2,3,4-tetrahydroisoquinoline-7-carbonitrile



To an ice-cold, stirred solution of 1,2,3,4-tetrahydroisoquinoline-7-carbonitrile (*J. Med. Chem.* **1997**, *40*, 3997) (485 mg, 3.1 mmol) and triethylamine (0.47 mL, 3.4 mmol) in methylene chloride (5 mL) is added DMAP (37 mg, 0.3 mmol) and bromobutane (0.5 mL, 4.6 mmol). The reaction mixture is stirred for 20 h, diluted with methylene chloride, washed with water, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 50% ethyl acetate/hexanes) affords the title compound. ESI MS *m/z* 215 $[M + H]^+$.

Step 2

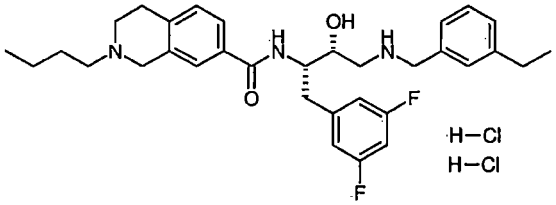
2-Butyl-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid



A sealed tube containing a solution of 2-butyl-1,2,3,4-tetrahydroisoquinoline-7-carbonitrile (480 mg, 2.2 mmol) in concentrated hydrochloric acid (10 mL) is stirred at 90 °C for 16 h. The reaction mixture is cooled to room temperature, concentrated ammonium hydroxide is added, and the precipitate formed is then collected by filtration to provide the title compound. ESI MS *m/z* 234 $[M + H]^+$.

Step 3

2-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxamide dihydrochloride

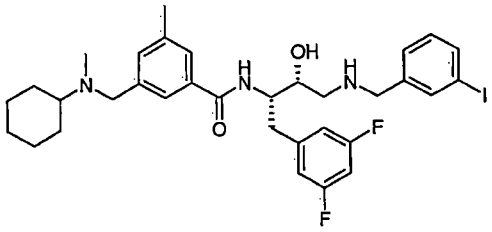


A solution of 2-butyl-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid (190 mg, 0.81 mmol), HATU (465 mg, 1.2 mmol), HOBt (162 mg, 1.2 mmol), and diisopropylethylamine (250 μL, 1.6 mmol) is stirred in methylene chloride (2.0 mL) for 15 min. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method in EXAMPLE SP-272 (332 mg, 0.81 mmol) and diisopropylethylamine (250 μL, 1.6 mmol) in methylene chloride (2.0 mL) is added, and the reaction mixture is stirred overnight. The reaction mixture is diluted with methylene chloride, washed with 1 N hydrochloric acid (15 mL), saturated sodium bicarbonate (15 mL), and brine. The organic layer is then dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provides the title compound as the free

base. The solid is dissolved in methanol (1 mL), and treated with hydrochloric acid (0.2 mL, 1.0 M diethyl ether, 0.2 mmol). The resulting precipitate was collected by filtration to provide the title compound. ESI MS *m/z* 550.3 $[M + H]^+$.

EXAMPLE SP-186

3-{[Cyclohexyl(methyl)amino]methyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-5-methylbenzamide dihydrochloride



2 HCl

Analogous to the method described in EXAMPLE SP-184, 2 mL of the stock solution is added to a solution of *N*-methylcyclohexylamine (545 μL, 4.2 mmol) in anhydrous methylene chloride (1 mL), and the reaction mixture is stirred at room temperature for 16 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with saturated sodium bicarbonate and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (60 mg, 1.4 mmol). The reaction is stirred 16 h and is concentrated under reduced pressure. The residue is redissolved in DMF (4 mL), and diisopropylethylamine (465 μL, 2.7 mmol), HATU (380 mg, 1 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (340 mg, 0.67 mmol) are added. The reaction stirred at room temperature 16 h. Purification by flash column chromatography (silica, 7%

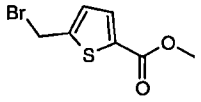
methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 676.2 $[M + H]^+$.

EXAMPLE SP-187

5-{[Butyl(methyl)amino]methyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}thiophene-2-carboxamide dihydrochloride

Step 1

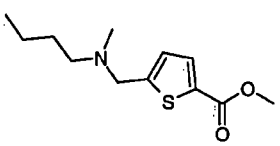
Methyl 5-(bromomethyl)thiophene-2-carboxylate



To an ice-cold solution of methyl 5-(hydroxymethyl)thiophene-2-carboxylate (375 mg, 2.17 mmol) in methylene chloride (9.0 mL) is added phosphorus tribromide (100 μL, 1.08 mmol) and the reaction mixture is stirred at 0 °C for 0.5 h. Saturated sodium bicarbonate (10 mL) is carefully added to the reaction mixture and the phases are separated. The organic phase is washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield the title compound in pure form. ESI MS *m/z* 235 $[M + H]^+$.

Step 2

Methyl 5-{[butyl(methyl)amino]methyl}thiophene-2-carboxylate

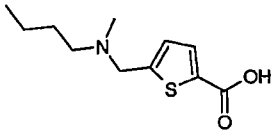


To a solution of methyl 5-(bromomethyl)thiophene-2-carboxylate (350 mg, 1.49 mmol) in dry acetone (6.0 mL) is added *N*-methylbutylamine (533 μL, 4.47 mmol) and the solution stirred at room temperature overnight. The reaction is then

concentrated under reduced pressure, redissolved in methylene chloride, washed with saturated sodium bicarbonate, water, and brine. The organic layer is then dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield the title compound in pure form. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 3 Hz, 1H), 6.88 (d, J = 3 Hz, 1H), 3.86 (s, 3H), 3.69 (s, 2H), 2.41-2.36 (m, 2H), 2.25 (s, 3H), 1.53-1.43 (m, 2H), 1.34-1.25 (m, 2H), 0.91 (t, J = 7 Hz, 3H).

Step 3

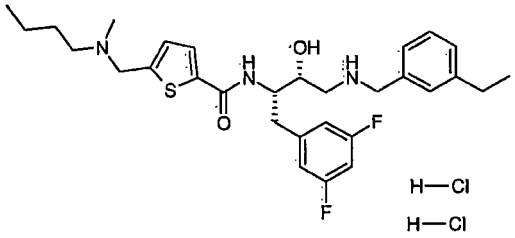
5-{[Butyl(methyl)amino]methyl}thiophene-2-carboxylic acid



To a solution of methyl 5-{[butyl(methyl)amino]methyl}thiophene-2-carboxylate (280 mg, 1.16 mmol) in 2:1:1 dioxane/methanol/water (8.0 mL) is added lithium hydroxide monohydrate (146 mg, 3.38 mmol) and the reaction mixture stirred at room temperature overnight. The reaction mixture is concentrated under reduced pressure and the solid residue partitioned between ethyl acetate and water The aqueous phase is acidified to pH 1with 1 N hydrochloric acid and extracted several times with 3:1 chloroform/2-propanol. The combined organic phase is washed with water, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide the title compound in pure form. ^{1}H NMR (300 MHz, CD_3OD) δ 7.75 (d, J = 4 Hz, 1H), 7.41 (d, J = 4 Hz, 1H), 4.63 (s, 2H), 3.20-3.14 (m, 2H), 2.85 (s, 3H), 1.82-1.72 (m, 2H), 1.42 (tq, J = 8, 7 Hz, 2H), 0.99 (t, J = 7 Hz, 3H).

Step 4

5-{[Butyl(methyl)amino]methyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}thiophene-2-carboxamide dihydrochloride



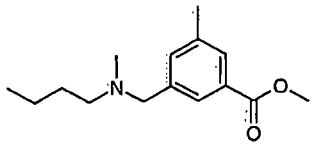
To a solution 5-{[butyl(methyl)amino]methyl}thiophene-2-carboxylic acid (171 mg, 0.75 mmol) and *N,N*-diisopropylethylamine (250 μL, 1.43 mmol) in methylene chloride (5.0 mL) is added HBTU (285 mg, 0.75 mmol) and the reaction stirred for 0.5 h. To this is added a solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method in EXAMPLE SP-272 (306 mg, 0.75 mmol) in methylene chloride (5.0 mL) containing *N,N*-diisopropylethylamine (250 μL, 1.43 mmol). The reaction mixture is then stirred at room temperature overnight. The reaction mixture is diluted with methylene chloride, washed with saturated sodium bicarbonate, and brine. The organic layer is then dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 95:5 chloroform/methanol) gives the title compound as the free base. The solid is dissolved in methanol (1 mL) and treated with hydrochloric acid (1.0 M diethyl ether). The resulting precipitate was collected by filtration to provide the title compound. ESI MS *m/z* 544.3 $[M + H]^+$.

EXAMPLE SP-188

3-{[Butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-methylbenzamide dihydrochloride

Step 1

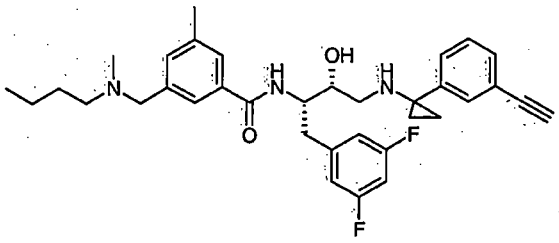
Methyl 3-{[butyl(methyl)amino]methyl}-5-methylbenzoate



To methyl 3-(hydroxymethyl)-5-methylbenzoate prepared by the method in EXAMPLE SP-177 (1.1 g, 6.1 mmol), in anhydrous methylene chloride (10 mL) is added methanesulfonyl chloride (663 μL, 8.6 mmol) at -30 °C, and the reaction is warmed to 0 °C. The reaction stirred 1 h, then filtered. The filtrate is added to *N*-methylbutylamine (2.1 mL, 18.3 mmol), and the reaction stirred at room temperature 16 h. The solution is concentrated under reduced pressure. Purification by flash chromatography affords the title compound in pure form. ESI MS *m/z* 250.2 $[M + H]^+$.

Step 2

3-{[Butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-methylbenzamide dihydrochloride



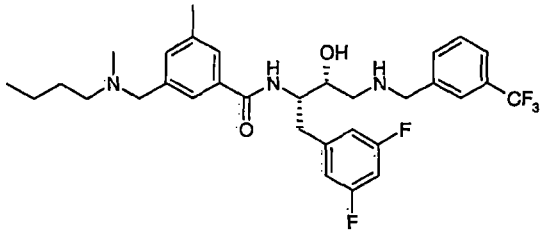
2 HCl

Methyl 3-{[butyl(methyl)amino]methyl}-5-methylbenzoate (122 mg, 0.49 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (41 mg, 1 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (350 μL, 2 mmol), HATU (240 mg, 0.63 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[1-(3-ethynylphenyl)cyclopropyl]amino}butan-2-ol dihydrochloride

prepared by the method in EXAMPLE SP-272 (215 mg, 0.5 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 574.3 $[M + H]^+$.

EXAMPLE SP-189

3-{[Butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-5-methylbenzamide dihydrochloride



2 HCl

Analogous to the method in EXAMPLE SP-188, methyl 3-{[butyl(methyl)amino]methyl}-5-methylbenzoate (112 mg, 0.45 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (38 mg, 0.9 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (350 µL, 2 mmol), HATU (240 mg, 0.63 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[1-(3-ethynylphenyl)cyclopropyl]amino}butan-2-ol dihydrochloride

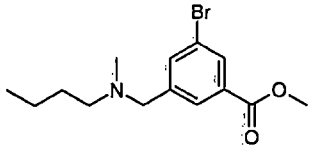
prepared by the method in EXAMPLE SP-272 (201 mg, 0.44 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 592.3 $[M + H]^+$.

EXAMPLE SP-190

3-Bromo-5-{[butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide dihydrochloride

Step 1

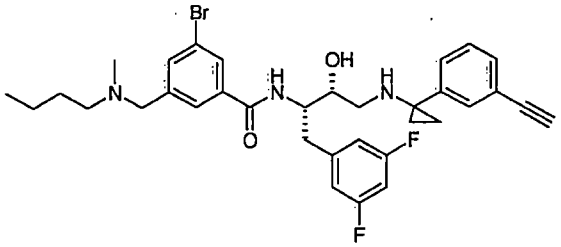
Methyl 3-bromo-5-{[butyl(methyl)amino]methyl}benzoate



To a solution of methyl 3-bromo-5-(hydroxymethyl)benzoate (4.1 g, 16.8 mmol) in anhydrous methylene chloride (35 mL) at -30 °C is added methanesulfonyl chloride (1.82 mL, 23.5 mmol) followed by triethylamine (4.7 mL, 33.6 mmol). The reaction mixture is stirred for 45 min at 0 °C, and then filtered. The filtrate is added to *N*-methylbutylamine (6 mL, 50.4 mmol) and stirred at room temperature for 16 h. The solution is concentrated under reduced pressure, and the residue is purified by flash column chromatography (silica, 8% ethyl acetate/hexanes) to give the title compound. ESI MS *m/z* 314.1 $[M + H]^+$.

Step 2

3-Bromo-5-{[butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide dihydrochloride

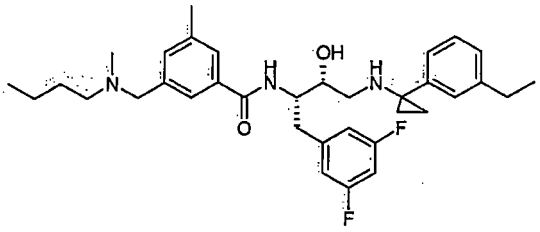


2 HCl

Methyl 3-bromo-5-{[butyl(methyl)amino]methyl}benzoate (113 mg, 0.36 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (30 mg, 0.72 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (250 µL, 1.44 mmol), HATU (170 mg, 0.45 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[1-(3-ethynylphenyl)cyclopropyl]amino}-3-methylbutan-2-ol dihydrochloride prepared as in EXAMPLE SP-264 (170 mg, 0.4 mmol) are added. The reaction stirred at room temperature 16 h. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 638.2 $[M + H]^+$.

EXAMPLE SP-191

3-{[Butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-methylbenzamide dihydrochloride

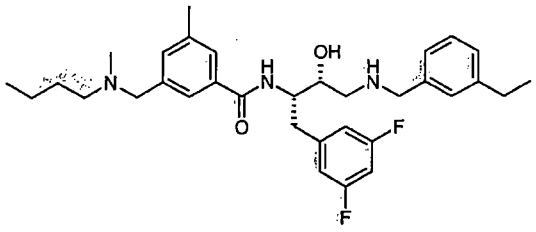


2 HCl

Analogous to the method in EXAMPLE SP-188, methyl 3-{[butyl(methyl)amino]methyl}-5-methylbenzoate (132 mg, 0.53 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (45 mg, 1.06 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (350 µL, 2 mmol), HATU (240 mg, 0.63 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[1-(3-ethylphenyl)cyclopropyl]amino}butan-2-ol prepared by the method in EXAMPLE SP-272 (191 mg, 0.5 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 578.4 $[M + H]^+$.

EXAMPLE SP-192

3-{[Butyl(methyl)amino]methyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylbenzamide dihydrochloride

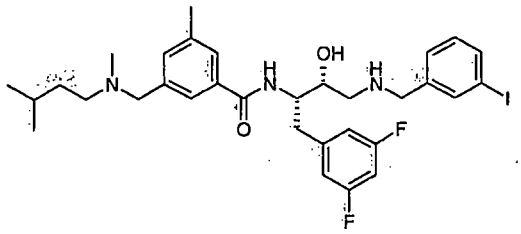


2 HCl

Analogous to the method in EXAMPLE SP-188, methyl 3-{[butyl(methyl)amino]methyl}-5-methylbenzoate (122 mg, 0.49 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (41 mg, 1.0 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (350 µL, 2 mmol), HATU (240 mg, 0.63 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method in EXAMPLE SP-272 (203 mg, 0.5 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 552.3 $[M + H]^+$.

EXAMPLE SP-193

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-3-{[isopentyl(methyl)amino]methyl}-5-methylbenzamide dihydrochloride



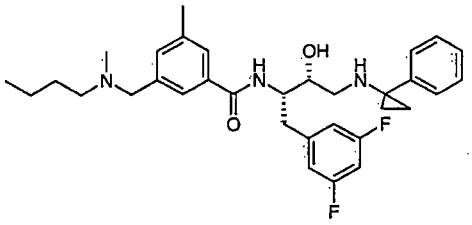
2 HCl

Analogous to the method described in EXAMPLE SP-184, 2 mL of the stock solution is added to a solution of *N*-isoamylmethylamine (526 µL, 4.2 mmol) in anhydrous methylene chloride (1 mL), and the reaction mixture is stirred at room temperature for 16 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with saturated sodium bicarbonate and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (42 mg, 1 mmol). The reaction is stirred 16 h and is concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (355 µL, 2 mmol), HATU (242 mg, 0.64 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (257 mg, 0.5 mmol) are added. The reaction stirred at room temperature 16 h. Purification by flash column chromatography (silica, 7% methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 664.2 $[M + H]^+$.

EXAMPLE SP-194

3-{[Butyl(methyl)amino]methyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1-

phenylcyclopropyl)amino]propyl}-5-methylbenzamide dihydrochloride

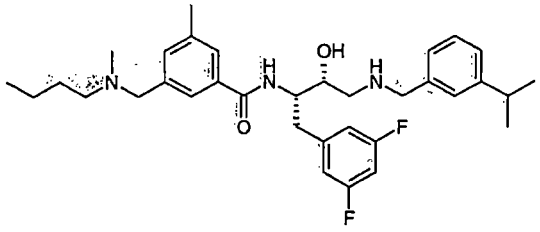


2 HCl

Analogous to the method in EXAMPLE SP-188, methyl 3-{[butyl(methyl)amino]methyl}-5-methylbenzoate (170 mg, 0.68 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (57 mg, 1.4 mmol), and the reaction stirred 2 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (3 mL), and diisopropylethylamine (472 µL, 2.7 mmol), HATU (322 mg, 0.85 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(1-phenylcyclopropyl)amino]butan-2-ol dihydrochloride prepared by the method in EXAMPLE S-XYZ (275 mg, 0.68 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 550.3 $[M + H]^+$.

EXAMPLE SP-195

3-{[Butyl(methyl)amino]methyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-5-methylbenzamide dihydrochloride



2 HCl

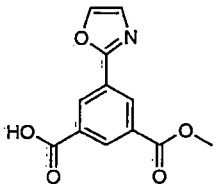
Analogous to the method in EXAMPLE SP-188, methyl 3-{[butyl(methyl)amino]methyl}-5-methylbenzoate (50 mg, 0.2 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (17 mg, 0.4 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (2 mL), and diisopropylethylamine (140 µL, 0.8 mmol), HATU (95 mg, 0.25 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-isopropylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method in EXAMPLE SP-170, Step 4 (85 mg, 0.2 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 566.3 $[M + H]^+$.

EXAMPLE SP-196

3-{[Butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)benzamide dihydrochloride

Step 1

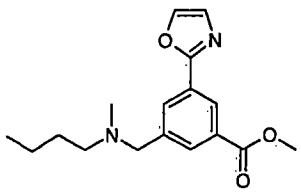
3-(Methoxycarbonyl)-5-(1,3-oxazol-2-yl)benzoic acid



To a -70 °C stirred solution of oxazole (432 mg, 6.3 mmol) in tetrahydrofuran (10 mL) is added *n*-butyllithium (2.5 M in hexanes, 2.75 mL, 6.9 mmol). After 30 min, zinc chloride (1 M in diethyl ether, 18.75 mL, 18.75 mmol) is added and the reaction mixture is warmed to 0 °C for 1 h. To this mixture is added a solution of 3-iodo-5-(methoxycarbonyl)benzoic acid prepared by the method in EXAMPLE SP-281, step 1 (1.8 g, 6 mmol) in anhydrous tetrahydrofuran (10 mL) followed by palladium(0) tetrakis(triphenylphosphine) (291 mg, 0.25 mmol). The reaction mixture is heated at reflux for 15 h. The reaction mixture is cooled, filtered through diatomaceous earth, diluted with ethyl acetate (50 mL), washed with water, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5% methanol/methylene chloride) provides the title compound in pure form. ESI MS *m/z* 246.1 $[M - H]^-$.

Step 2

Methyl 3-{[butyl(methyl)amino]methyl}-5-(1,3-oxazol-2-yl)benzoate

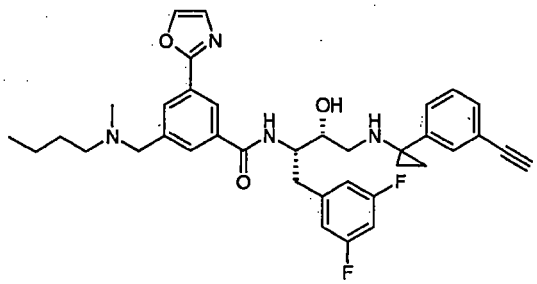


To an ice-cold solution of 3-(methoxycarbonyl)-5-(1,3-oxazol-2-yl)benzoic acid (340 mg, 1.4 mmol) in anhydrous tetrahydrofuran (10 mL) is added lithium borohydride (250 mg,

11 mmol) slowly. The reaction is stirred 30 min, then absolute ethanol (4 mL) is added, and the reaction is stirred 1 h. The solution is poured onto ice containing excess hydrochloric acid and extracted with ethyl acetate. The organic layer is washed with water, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. The residue is redissolved in 20% methanol/benzene (50 mL), and 2M trimethylsilyldiazomethane in hexane (0.9 mL, 1.8 mmol) is added. The reaction is stirred 2 h at room temperature, then concentrated under reduced pressure. The residue is redissolved in anhydrous methylene chloride (10 mL), cooled to -30 °C, then methanesulfonyl chloride (150 µL, 1.9 mmol) and triethylamine (380 µL, 2.7 mmol) are added. The reaction is stirred at 0 °C 15 min, then *N*-methylbutylamine (480 µL, 4 mmol) is added, and the reaction is stirred 16 h at room temperature. The solution is concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 40-100% ethyl acetate/hexane gradient) provides the title compound in pure form. ESI MS *m/z* 303.3 $[M + H]^+$.

Step 3

3-{[Butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)benzamide dihydrochloride



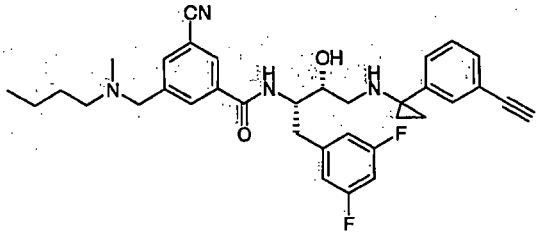
$\cdot 2\ HCl$

Methyl 3-{[butyl(methyl)amino]methyl}-5-(1,3-oxazol-2-yl)benzoate (30 mg, 0.1 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide

monohydrate is added (10 mg, 0.2 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (1 mL), and diisopropylethylamine (70 µL, 0.4 mmol), HATU (57 mg, 0.15 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[1-(3-ethynylphenyl)cyclopropyl]amino}butan-2-ol dihydrochloride (203 mg, 0.5 mmol) are added. The reaction stirred at room temperature 2 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9-10% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 627.3 $[M + H]^+$.

EXAMPLE SP-197

3-{[Butyl(methyl)amino]methyl}-5-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide dihydrochloride



2 HCl

3-Bromo-5-(methoxycarbonyl)benzoic acid (4 g, 15.4 mmol) and copper(I) cyanide (4.1 g, 89.5 mmol) in *N*-methylpyrrolidinone (20 mL) is heated at 175 °C for 4 h. The reaction is cooled, and water is added. The aqueous solution is extracted with methylene chloride, washed with 1N hydrochloric acid (aq), brine, dried (sodium sulfate),

filtered, and concentrated under reduced pressure. The residue is dissolved in tetrahydrofuran (20 mL), cooled in an ice bath, and lithium borohydride (475 mg, 22 mmol) is added slowly. The reaction stirred at this temperature 2 h. Absolute ethanol (4 mL) is added dropwise, and the reaction stirred 30 min. The mixture is poured on ice containing excess hydrochloric acid. After gas evolution ceases, the solution is extracted with methylene chloride and concentrated under reduced pressure.

The residue is dissolved in 20% methanol/benzene (20 mL), and 2M trimethylsilyldiazomethane in hexane (1.3 mL, 2.6 mmol) is added. The reaction stirred at room temperature 2 h and is concentrated under reduced pressure. The residue is then dissolved in anhydrous methylene chloride (10 mL), cooled to -30 °C, then methanesulfonyl chloride (216 µL, 2.8 mmol) and triethylamine (556 µL, 4 mmol) are added. The reaction is warmed to 0 °C and stirred 15 min, then filtered. The filtrate is added to N-methylbutylamine (5 mL) and stirred 16 h. The solution is concentrated under reduced pressure and purification by flash chromatography (silica gel, 40% ethyl acetate/hexane) gives an oil. The oil (107 mg) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (35 mg, 0.8 mmol), and the reaction stirred 1.5 h. The solution is concentrated under reduced pressure.

The residue is redissolved in DMF (3 mL), and diisopropylethylamine (280 µL, 1.6 mmol), HATU (230 mg, 0.6 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[1-(3-ethynylphenyl)cyclopropyl]amino}butan-2-ol dihydrochloride (206 mg, 0.5 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column

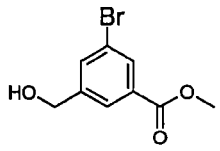
chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 585.3 $[M + H]^+$.

EXAMPLE SP-198

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2-furylmethyl)(methyl)amino]methyl}-5-methylbenzamide dihydrochloride

Step 1

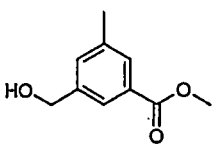
Methyl 3-bromo-5-(hydroxymethyl)benzoate



To an ice-cold, stirred solution of 3-bromo-5-(methoxycarbonyl)benzoic acid (5.0 g, 19.3 mmol) in tetrahydrofuran (77.2 mL) is added borane dimethyl sulfide complex (10.6 mL, 2.0 M tetrahydrofuran, 21.1 mmol). The reaction mixture is heated at 50 °C for 2 h. The reaction mixture is quenched with methanol (50 mL) and concentrated under reduced pressure. Purification by flash column chromatography (silica, 50% ethyl acetate/hexanes) affords the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.90 (s, 1H), 7.69 (s, 1H), 4.69 (s, 1H), 3.91 (s, 3H), 2.83 (br s, 1H).

Step 2

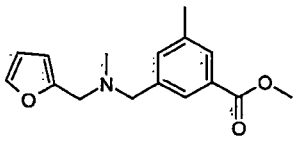
Methyl 3-(hydroxymethyl)-5-methylbenzoate



To a stirred solution of methyl 3-bromo-5-(hydroxymethyl)benzoate (4.53 g, 18.5 mmol) in dioxane (74 mL) is added cesium carbonate (6.0 g, 18.5 mmol), potassium carbonate (5.1 g, 37 mmol), and palladium(0) tetrakis(triphenylphosphine) (2.1 g, 1.85 mmol), followed by trimethyl boroxine (5.1 mL, 37 mmol). The reaction mixture is refluxed for 12 h, cooled to room temperature, and then partitioned between water and ethyl acetate. The organic layer is washed with water and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. The black oil is adsorbed onto silica gel followed by purification by flash column chromatography (silica, 25% ethyl acetate/hexanes) to provide the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.65 (s, 1H), 7.39 (s, 1H), 5.31 (br s, 1H), 4.53 (s, 1H), 3.84 (s, 3H), 2.36 (s, 3H).

Step 3

Methyl 3-{[(2-furylmethyl)(methyl)amino]methyl}-5-methylbenzoate

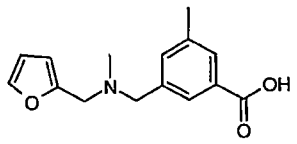


To an ice-cold, stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.1 mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 mmol). The reaction mixture is stirred for 15 min and filtered. *N*-Methylfurfurylamine (367 mg, 3.3 mmol) is added to the filtrate and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 50% ethyl

acetate/hexanes) provided the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 11 Hz, 2H), 3.79 (d, J = 6 Hz, 2H), 6.32 (d, J = 2 Hz, 1H), 6.21 (d, J = 3 Hz, 1H), 3.90 (s, 3H), 3.59 (s, 3H), 3.53 (s, 2H), 2.39 (s, 3H), 2.23 (s, 3H).

Step 4

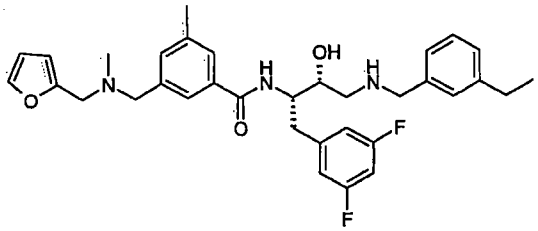
3-{[(2-Furylmethyl)(methyl)amino]methyl}-5-methylbenzoic acid



To a stirred solution of methyl 3-{[(2-furylmethyl)(methyl)amino]methyl}-5-methylbenzoate (180 mg, 0.66 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (277 mg, 6.6 mmol), and the reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound. ESI MS m/z 258 $[M + H]^+$.

Step 5

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2-furylmethyl)(methyl)amino]methyl}-5-methylbenzamide dihydrochloride



2 HCl

To a stirred solution of 3-{[(2-furylmethyl)(methyl)amino]methyl}-5-methylbenzoic acid (170 mg, 0.66 mmol) in methylene chloride (3 mL) is added HBTU (375 mg, 0.99 mmol), HOBt (134 mg, 0.99 mmol), and *N,N*-

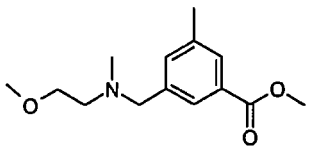
diisopropylethylamine (0.334 mL, 1.98 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method in EXAMPLE SP-272 (269 mg, 0.66 mmol), and the reaction mixture is stirred for 12 h at room temperature. The reaction mixture is diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 10% methanol/chloroform) affords the title compound as the free base. The compound is dissolved in methanol (2 mL), and to this solution is added hydrochloric acid (5 mL, 4 N dioxane, 20 mmol). The reaction mixture is stirred for 1 h at room temperature. The reaction mixture is then diluted with ethyl ether (10 mL). The precipitate that is formed is collected by filtration to provide the title compound. ESI MS *m/z* 576 $[M + H]^+$.

EXAMPLE SP-199

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2-methoxyethyl)(methyl)amino]methyl}-5-methylbenzamide dihydrochloride

Step 1

Methyl 3-{[(2-methoxyethyl)(methyl)amino]methyl}-5-methylbenzoate

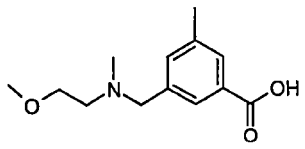


To an ice-cold stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.1 mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 mmol). The reaction mixture is stirred for 15 min and filtered. 2-Methoxy-*N*-methyleneamine (0.354 mL, 3.3 mmol) is

added to the filtrate, and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 50% ethyl acetate/hexanes) provided the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 5 Hz, 2H), 7.37 (s, 3H), 3.90 (s, 1H), 3.56 (s, 2H), 3.52 (t, J = 6 Hz, 2H), 3.34 (s, 3H), 2.61 (t, J = 6 Hz, 2H), 2.39 (s, 3H), 2.26 (s, 3H).

Step 2

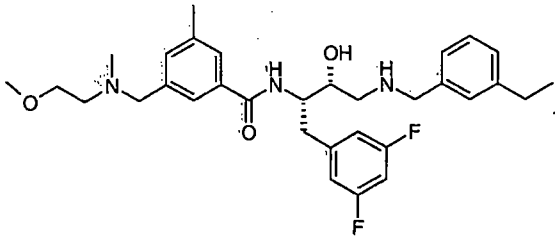
3-{[(2-Methoxyethyl)(methyl)amino]methyl}-5-methylbenzoic acid



To a stirred solution of methyl 3-{[(2-methoxyethyl)(methyl)amino]methyl}-5-methylbenzoate (180 mg, 0.72 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (302 mg, 7.2 mmol) and the reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound. ESI MS m/z 238 $[M + H]^+$.

Step 3

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2-methoxyethyl)(methyl)amino]methyl}-5-methylbenzamide dihydrochloride



2 HCl

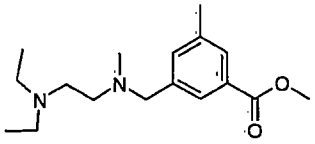
To a stirred solution of 3-{[(2-methoxyethyl)(methyl)amino]methyl}-5-methylbenzoic acid (140 mg, 0.56 mmol) in methylene chloride (3 mL) is added HBTU (318 mg, 0.84 mmol), HOBt (114 mg, 0.84 mmol), and *N,N*-diisopropylethylamine (0.284 mL, 1.68 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method in EXAMPLE SP-272 (228 mg, 0.56 mmol). The reaction mixture is stirred for 24 h at room temperature, diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 10% methanol/chloroform) affords the title compound as the free base. The compound is dissolved in methanol (2 mL), and to this solution is added hydrochloric acid (5 mL, 4 N dioxane, 20 mmol). The reaction mixture is stirred for 1 h at room temperature. The reaction mixture is then diluted with ethyl ether (10 mL). The precipitate that is formed is collected by filtration to provide the title compound. ESI MS *m/z* 554 $[M + H]^+$.

EXAMPLE SP-200

3-{[[2-(Diethylamino)ethyl](methyl)amino]methyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylbenzamide trihydrochloride

Step 1

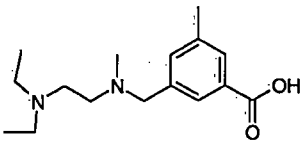
Methyl 3-{[[2-(diethylamino)ethyl](methyl)amino]methyl}-5-methylbenzoate



To an ice-cold, stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.19 mmol) and triethylamine (241 mg, 2.38 mmol) in methylene chloride (5 mL) is added methanesulfonyl chloride (191 mg, 1.67 mmol). The reaction mixture is stirred for 15 min, the precipitate that formed is removed by filtration, and *N,N*-diethyl-*N'*-methylethylenediamine (465 mg, 3.57 mmol) was added. The reaction mixture is stirred at room temperature for 2 h and then concentrated under reduced pressure. Purification by flash column chromatography (silica, 9:1 chloroform/methanol) gives the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 2H), 7.33 (s, 1H), 3.56 (s, 3H), 3.48 (s, 2H), 2.95 (m, 4H), 2.75 (m, 4H), 2.41 (s, 3H), 2.31 (s, 3H), 1.21 (m, 6H).

Step 2

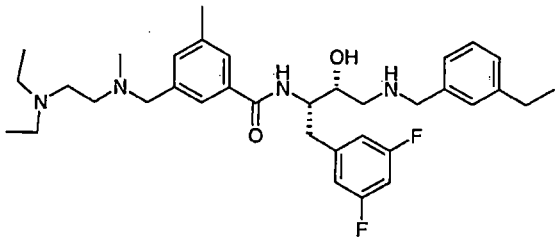
3-{[[2-(Diethylamino)ethyl](methyl)amino]methyl}-5-methylbenzoic acid



A mixture of methyl 3-{[[2-(diethylamino)ethyl](methyl)amino]methyl}-5-methylbenzoate (296 mg, 1.01 mmol) and 3:1:1 methanol/tetrahydrofuran/2 N sodium hydroxide (10 mL) is stirred overnight and then partitioned between ethyl acetate and water. The aqueous layer is acidified to pH 3 with 1 N hydrochloric acid and extracted with chloroform. The aqueous layer is concentrated under reduced pressure to give the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.99 (s, 1H), 7.82 (s, 1H), 7.80 (s, 1H), 4.56 (m, 2H), 4.31 (m, 2H), 3.98 (m, 2H), 3.17 (m, 4H), 2.51 (s, 3H), 2.50 (s, 3H), 1.27 (m, 6H).

Step 3

3-{[[2-(Diethylamino)ethyl](methyl)amino]methyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylbenzamide trihydrochloride

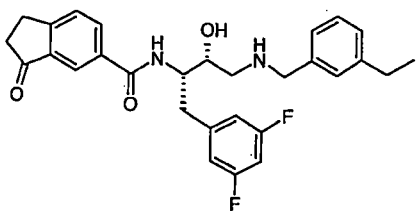


3 HCl

To a stirred solution of 3-{[[2-(diethylamino)ethyl](methyl)amino]methyl}-5-methylbenzoic acid (267 mg, 0.959 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (391 mg, 0.959 mmol), HOBt (129 mg, 0.959 mmol), and *N,N*-diisopropylethylamine (496 mg, 3.84 mmol) in methylene chloride (5 mL) is added EDC (331 mg, 1.73 mmol). The reaction mixture is stirred overnight and then partitioned between ethyl acetate and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9:1:1 methylene chloride/methanol/ammonium hydroxide) gives the title compound. ESI MS *m/z* 595.4 $[M + H]^+$.

EXAMPLE SP-201

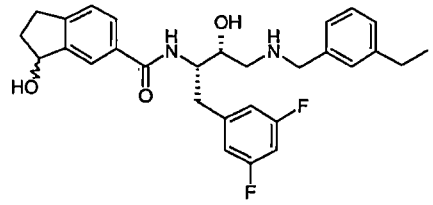
N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-oxoindane-5-carboxamide



To 3-oxoindane-5-carboxylic acid (2.0 g, 11.5 mmol) in DMF (10 mL) is added diisopropylethylamine (8 mL, 46 mmol), HATU (5.5 g, 14.4 mmol), then (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-272 (5.6 g, 13.8 mmol). The reaction is stirred 1 h at room temperature. The reaction was partitioned between ethyl acetate and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) gives the title compound. ESI MS *m/z* 493.2 $[M + H]^+$.

EXAMPLE SP-202

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-hydroxyindane-5-carboxamide



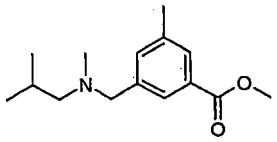
To an ice-cold solution of N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-oxoindane-5-carboxamide prepared by the method in EXAMPLE SP-201 (66 mg, 0.13 mmol) in methanol (3 mL) is added sodium borohydride (20 mg, 0.52 mmol). The reaction stirred at room temperature 3 h. The reaction is concentrated under reduced pressure, redissolved in water (3 mL) and partitioned into ethyl acetate. The organic layer is washed with water, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS *m/z* 495.2 $[M + H]^+$.

EXAMPLE SP-203

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[isobutyl(methyl)amino]methyl}-5-methylbenzamide hydrochloride

Step 1

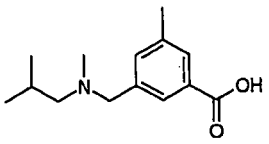
Methyl 3-{[isobutyl(methyl)amino]methyl}-5-methylbenzoate



To an ice-cold, stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.1 mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 mmol). The reaction mixture is stirred for 15 min and filtered. *N*-Methylisobutylamine (287 mg, 3.3 mmol) is added to the filtrate, and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 15% ethyl acetate/hexanes) provides the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.73 (s, 1H), 7.36 (s, 1H), 3.90 (s, 3H), 3.44 (s, 2H), 2.38 (s, 3H), 2.14 (s, 3H), 2.10 (d, J = 8 Hz, 2H), 1.81 (m, 1H), 0.90 (d, J = 7 Hz, 6H).

Step 2

3-{[Isobutyl(methyl)amino]methyl}-5-methylbenzoic acid

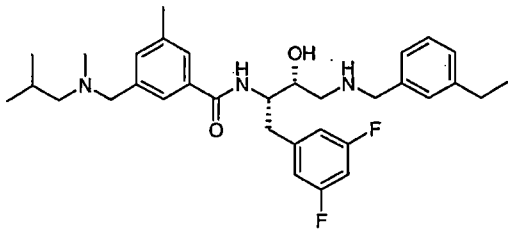


To a stirred solution of methyl 3-{[isobutyl(methyl)amino]methyl}-5-methylbenzoate (120 mg, 0.48 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (200 mg, 4.8 mmol), and the

reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound. ESI MS *m/z* 236 $[M + H]^+$.

Step 3

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[isobutyl(methyl)amino]methyl}-5-methylbenzamide hydrochloride



2 HCl

To a stirred solution of 3-{[isobutyl(methyl)amino]methyl}-5-methylbenzoic acid (110 mg, 0.48 mmol) in methylene chloride (3 mL) is added HBTU (273 mg, 0.72 mmol), HOBt (97 mg, 0.72 mmol), and *N,N*-diisopropylethylamine (0.243 mL, 1.44 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (196 mg, 0.48 mmol), and the reaction mixture is stirred for 12 h at room temperature. The reaction mixture is diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 10% methanol/chloroform) affords a clear oil, which is dissolved in methanol (2 mL). To this solution is added hydrochloric acid (5 mL, 4 N dioxane, 20 mmol), and the reaction mixture is stirred for 1 h at room temperature. The reaction mixture is then diluted with ethyl ether (10 mL). The precipitate that

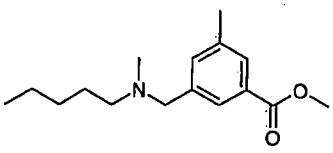
is formed is collected by filtration to provide the title compound. ESI MS *m/z* 552.5 $[M + H]^+$.

EXAMPLE SP-204

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-{[methyl(pentyl)amino]methyl}benzamide dihydrochloride

Step 1

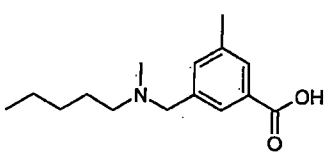
Methyl 3-methyl-5-{[methyl(pentyl)amino]methyl}benzoate



To an ice-cold, stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.1 mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 mmol). The reaction mixture is stirred for 15 min and filtered. *N*-Methylpentylamine (333 mg, 3.3 mmol) is added to the filtrate, and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 15% ethyl acetate/hexanes) provides the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 4 Hz, 2H), 7.36 (s, 1H), 3.90 (s, 3H), 3.47 (s, 2H), 3.13 (t, *J* = 9 Hz, 3H), 2.39 (s, 2H), 2.34 (d, *J* = 8 Hz, 2H), 2.18 (s, 3H), 1.45 (m, 5H), 1.32 (m, 2H).

Step 2

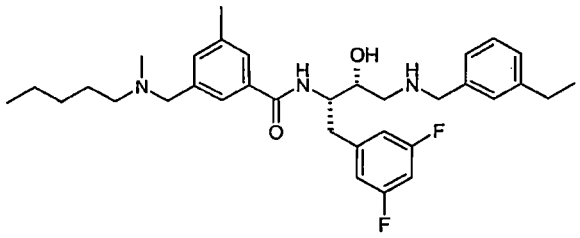
3-Methyl-5-{[methyl(pentyl)amino]methyl}benzoic acid



To a stirred solution of methyl 3-methyl-5-{[methyl(pentyl)amino]methyl}benzoate (120 mg, 0.46 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (191 mg, 4.6 mmol), and the reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound. ESI MS *m/z* 250 $[M + H]^+$.

Step 3

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-{[methyl(pentyl)amino]methyl}benzamide dihydrochloride



2 HCl

To a stirred solution of 3-methyl-5-{[methyl(pentyl)amino]methyl}benzoic acid (110 mg, 0.44 mmol) in methylene chloride (3 mL) is added HBTU (250 mg, 0.66 mmol), HOBt (90 mg, 0.66 mmol), and *N,N*-diisopropylethylamine (0.222 mL, 1.32 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (180 mg, 0.44 mmol), and the reaction mixture is stirred for 12 h at room temperature. The reaction mixture is diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 10% methanol/chloroform) affords a clear oil, which is dissolved in methanol (2 mL). To this solution is added hydrochloric

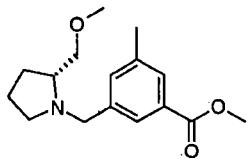
acid (5 mL, 4 N dioxane, 20 mmol), and the reaction mixture is stirred for 1 h at room temperature. The reaction mixture is then diluted with ethyl ether (10 mL). The precipitate that is formed is collected by filtration to provide the title compound. ESI MS *m/z* 566.5 $[M + H]^+$.

EXAMPLE SP-205

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzamide dihydrochloride

Step 1

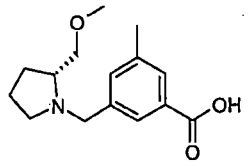
Methyl 3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoate



To an ice-cold, stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.1 mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 mmol). The reaction mixture is stirred for 15 min and filtered. (*R*)-2-(Methoxymethyl)pyrrolidine (380 mg, 3.3 mmol) is added to the filtrate, and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 50% ethyl acetate/hexanes) provides the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.73 (s, 1H), 7.37 (s, 1H), 4.11 (d, *J* = 13 Hz, 1H), 3.90 (d, *J* = 6 Hz, 2H), 3.41 (m, 2H), 3.34 (m, 3H), 2.89 (m, 1H), 2.71 (m, 1H), 2.38 (s, 3H), 2.19 (m, 1H), 1.93 (m, 2H), 1.54 (m, 3H).

Step 2

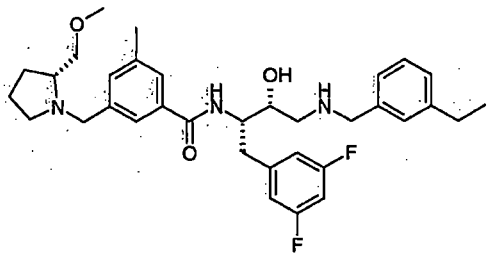
3-{[(2R)-2-(Methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoic acid



To a stirred solution of methyl 3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoate (120 mg, 0.43 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (180 mg, 4.3 mmol), and the reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound. ESI MS *m/z* 264 $[M + H]^+$.

Step 3

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzamide dihydrochloride



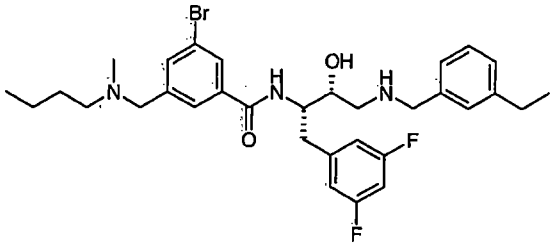
2 HCl

To a stirred solution of 3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoic acid (113 mg, 0.43 mmol) in methylene chloride (3 mL) is added HBTU (165 mg, 0.66 mmol), HOBt (89 mg, 0.66 mmol), and *N,N*-diisopropylethylamine (0.220 mL, 1.30 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE

SP-272 (175 mg, 0.43 mmol), and the reaction mixture is stirred for 12 h at room temperature. The reaction mixture is diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 10% methanol/chloroform) affords a clear oil, which was dissolved in methanol (2 mL). To this solution is added hydrochloric acid (5 mL, 4 N dioxane, 20 mmol), and the reaction mixture is stirred for 1 h at room temperature. The reaction mixture is then diluted with ethyl ether (10 mL). The precipitate that is formed is collected by filtration to provide the title compound. ESI MS *m/z* 580.4 $[M + H]^+$.

EXAMPLE SP-206

3-Bromo-5-{[butyl(methyl)amino]methyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide dihydrochloride



2 HCl

Methyl 3-bromo-5-{[butyl(methyl)amino]methyl}benzoate prepared by the method in EXAMPLE SP-190, Step 1 (170 mg, 0.54) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (45 mg, 1.1 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (375 µL, 2.16 mmol), HATU (256 mg, 0.68 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method in EXAMPLE SP-272 (265

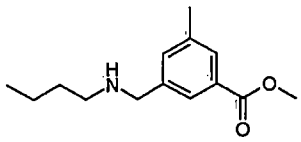
mg, 0.65 mmol) are added. The reaction stirred at room temperature 1 h. The reaction mixture is diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 616.2 $[M + H]^+$.

EXAMPLE SP-207

3-[(Butylamino)methyl]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylbenzamide dihydrochloride

Step 1

Methyl 3-[(butylamino)methyl]-5-methylbenzoate

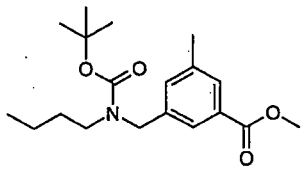


To an ice-cold, stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.1 mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 mmol). The reaction mixture is stirred for 15 min and filtered. Butylamine (0.543 mL, 5.5 mmol) is added to the filtrate, and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 89:10:1 chloroform/methanol/ammonium hydroxide) provides the title

compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.70 (s, 1H), 7.24 (br s, 1H), 4.42 (d, *J* = 9 Hz, 2H), 3.90 (s, 3H), 3.16 (m, 2H), 2.38 (s, 3H), 1.64 (s, 2H), 1.44 (m, 9H), 1.27 (m, 2H), 0.89 (t, *J* = 7 Hz, 3H).

Step 2

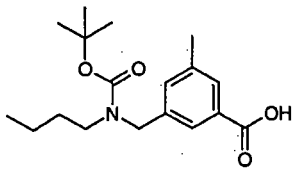
Methyl 3-{[(tert-butoxycarbonyl)(butyl)amino]methyl}-5-methylbenzoate



To a stirred solution of methyl 3-[(butylamino)methyl]-5-methylbenzoate (70 mg, 0.30 mmol) in methylene chloride is added triethylamine (0.046 mL, 0.33 mmol), and 4-dimethylaminopyridine (4.0 mg, 0.03 mmol) followed by di-*tert*-butyl-dicarbonate (72 mg, 0.30 mmol). The reaction mixture is stirred at room temperature for 24 h, diluted with methylene chloride, washed with 1 N hydrochloric acid, and brine. The organic solution is dried (magnesium sulfate), filtered, and concentrated under reduced pressure to afford the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.70 (s, 1H), 7.24 (br s, 1H), 4.42 (d, *J* = 9 Hz, 2H), 3.90 (s, 3H), 3.16 (m, 2H), 2.38 (s, 3H), 1.64 (s, 2H), 1.44 (m, 9H), 1.27 (m, 2H), 0.89 (t, *J* = 7 Hz, 3H).

Step 3

3-{[(tert-Butoxycarbonyl)(butyl)amino]methyl}-5-methylbenzoic acid

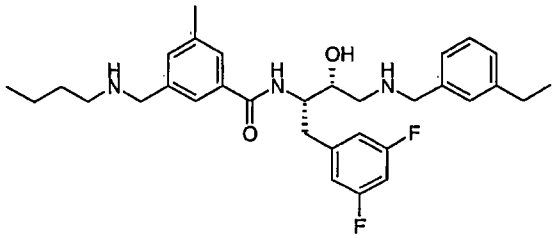


To a stirred solution of methyl 3-{[(tert-butoxycarbonyl)(butyl)amino]methyl}-5-methylbenzoate (70 mg,

0.21 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (88 mg, 2.1 mmol), and the reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound.

Step 4

3-[(Butylamino)methyl]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylbenzamide dihydrochloride



2 HCl

To a stirred solution of 3-{[(tert-butoxycarbonyl)(butyl)amino]methyl}-5-methylbenzoic acid (90 mg, 0.28 mmol) in methylene chloride (3 mL) is added HBTU (160 mg, 0.42 mmol), HOBt (57 mg, 0.42 mmol), and *N,N*-diisopropylethylamine (0.142 mL, 0.84 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (114 mg, 0.28 mmol), and the reaction mixture is stirred for 12 h at room temperature. The reaction mixture is diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 10% methanol/chloroform) affords a clear oil, which is dissolved in methanol (2 mL). To this solution is added hydrochloric acid (5 mL, 4 N dioxane, 20 mmol), and the reaction mixture is

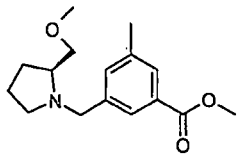
stirred for 1 h at room temperature. The reaction mixture is then diluted with ethyl ether (10 mL). The precipitate that is formed is collected by filtration to provide the title compound. ESI MS *m/z* 538.5 $[M + H]^+$.

EXAMPLE SP-208

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzamide dihydrochloride

Step 1

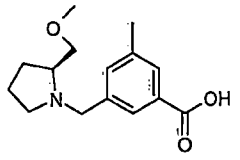
Methyl 3-{[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoate



To an ice-cold, stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.1 mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 mmol). The reaction mixture is stirred for 15 min and filtered. (*S*)-(+)-2-(Methoxymethyl)pyrrolidine (380 mg, 3.3 mmol) is added to the filtrate, and the reaction mixtire is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 15% ethyl acetate/hexanes) provides the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.73 (s, 1H), 7.37 (s, 1H), 4.12 (d, *J* = 17 Hz, 1H), 3.90 (s, 3H), 3.85 (m, 2H), 3.51 (m, 2H), 3.44 (m, 2H), 3.15 (s, 1H), 2.38 (s, 3H), 1.94 (m, 3H), 1.72 (m, 3H).

Step 2

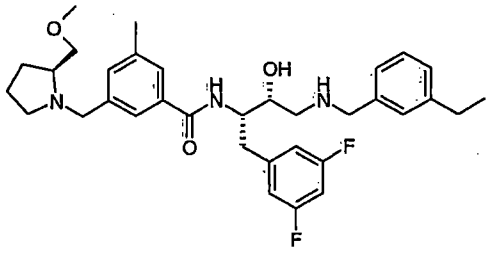
3-{[(2S)-2-(Methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoic acid



To a stirred solution of methyl 3-{[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoate (170 mg, 0.50 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (211 mg, 5.0 mmol), and the reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound. ESI MS *m/z* 264 $[M + H]^+$.

Step 3

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzamide dihydrochloride



2 HCl

To a stirred solution of 3-{[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoic acid (110 mg, 0.42 mmol) in methylene chloride (3 mL) is added HBTU (240 mg, 0.63 mmol), HOBt (85 mg, 0.63 mmol), and *N,N*-diisopropylethylamine (0.212 mL, 1.26 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (171 mg, 0.42 mmol). The reaction mixture is stirred

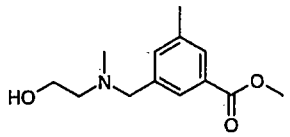
for 12 h at room temperature. The reaction mixture is diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 10% methanol/chloroform) affords a clear oil, which is dissolved in methanol (2 mL). To this solution is added hydrochloric acid (5 mL,4 N dioxane, 20 mmol), and the reaction mixture is stirred for 1 h at room temperature. The reaction mixture is then diluted with ethyl ether (10 mL). The precipitate that is formed was collected by filtration to provide the title compound. ESI MS *m/z* 580.4 $[M + H]^+$.

EXAMPLE SP-209

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2-hydroxyethyl)(methyl)amino]methyl}-5-methylbenzamide dihydrochloride

Step 1

Methyl 3-{[(2-hydroxyethyl)(methyl)amino]methyl}-5-methylbenzoate

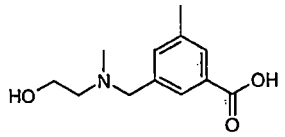


To an ice-cold stirred solution of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.1 mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 mmol). The reaction mixture is stirred for 15 min and filtered. 2-Methoxy-N-methyleneamine (0.354 mL, 3.3 mmol) is added to the filtrate and stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash

column chromatography (50% ethyl acetate/hexanes) provides the title compound. ESI MS *m/z* 238 $[M + H]^+$.

Step 2

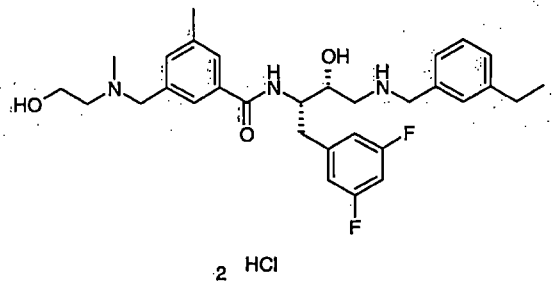
3-{[(2-Hydroxyethyl)(methyl)amino]methyl}-5-methylbenzoic acid



To a stirred solution of methyl 3-{[(2-hydroxyethyl)(methyl)amino]methyl}-5-methylbenzoate (180 mg, 0.72 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (302 mg, 7.2 mmol), and the reaction mixture is stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and concentrated under reduced pressure to provide the title compound. ESI MS *m/z* 224 $[M + H]^+$.

Step 3

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2-hydroxyethyl)(methyl)amino]methyl}-5-methylbenzamide dihydrochloride



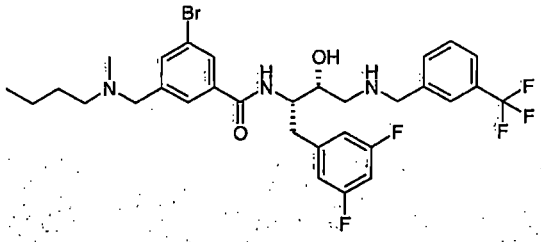
2 HCl

To a stirred solution of 3-{[(2-hydroxyethyl)(methyl)amino]methyl}-5-methylbenzoic acid (140 mg, 0.56 mmol) in methylene chloride (3 mL) is added HBTU (318 mg, 0.84 mmol), HOBt (114 mg, 0.84 mmol), and *N,N*-diisopropylethylamine (0.284 mL, 1.68 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-

ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (228 mg, 0.56 mmol). The reaction mixture is stirred for 24 h at room temperature, diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10% methanol/chloroform) affords a clear oil, which is dissolved in methanol (2 mL). To this is added hydrochloric acid (5 mL of a 4 N solution in dioxane, 20 mmol), and the reaction mixture is stirred for 1 h at room temperature. The reaction mixture is diluted with ethyl ether (10 mL). The precipitate that is formed is collected by filtration to provide the title compound. ESI MS *m/z* 540.4 $[M + H]^+$.

EXAMPLE SP-210

3-Bromo-5-{[butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)benzamide dihydrochloride



2 HCl

Methyl 3-bromo-5-{[butyl(methyl)amino]methyl}benzoate prepared by the method in EXAMPLE SP-190, Step 1 (200 mg, 0.64) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (60 mg, 1.3 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (445 µL, 2.6 mmol), HATU (304 mg, 0.8 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[3-(trifluoromethyl)benzyl]amino}butan-2-ol dihydrochloride

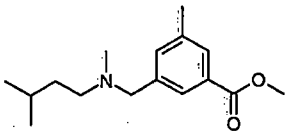
prepared by the method in EXAMPLE S-2511 (315 mg, 0.7 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, and saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 656.2 $[M + H]^+$.

EXAMPLE SP-211

N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-3-{[isopentyl(methyl)amino]methyl}-5-methylbenzamide dihydrochloride

Step 1

Methyl 3-{[isopentyl(methyl)amino]methyl}-5-methylbenzoate

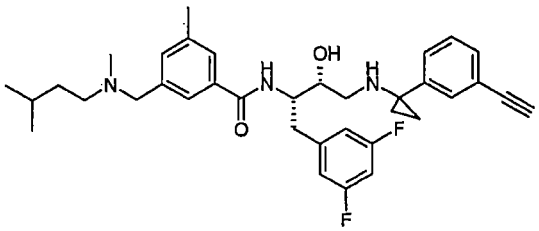


To methyl 3-(hydroxymethyl)-5-methylbenzoate prepared by the method in EXAMPLE SP-198, Step 2 in anhydrous methylene chloride at -30 °C is added methanesulfonyl chloride (601 µL, 7.8 mmol), then triethylamine (1.5 mL, 11.1 mmol), and the reaction is stirred at 0 °C 15 min. The resulting precipitate is filtered, and the filtrate is added to *N*-methylisoamylamine (2.1 mL, 16.7 mmol). The reaction stirred at room temperature 16 h. The solution is concentrated under reduced pressure, redissolved in ethyl acetate and washed with saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash

column chromatography (silica, 20% ethyl acetate/hexanes) provides the title compound. ESI MS *m/z* 264.2 $[M + H]^+$.

Step 2

N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-3-{[isopentyl(methyl)amino]methyl}-5-methylbenzamide dihydrochloride

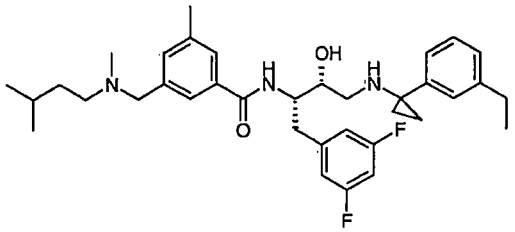


2 HCl

To methyl 3-{[isopentyl(methyl)amino]methyl}-5-methylbenzoate (250 mg, 0.95 mmol) in tetrahydrofuran/methanol/water (2:1:1, 8 mL) is added lithium hydroxide monohydrate (80 mg, 1.9 mmol), and the reaction is stirred at room temperature 16 h. The solution is concentrated under reduced pressure, redissolved in DMF (5 mL), and diisopropylethylamine (660 µL, 3.8 mmol), HATU (540 mg, 1.4 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[1-(3-ethynylphenyl)cyclopropyl]amino}-3-methylbutan-2-ol dihydrochloride (450 mg, 1.05 mmol) are added. The reaction stirred at room temperature 2 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 588.3 $[M + H]^+$.

EXAMPLE SP-212

N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-3-{[isopentyl(methyl)amino]methyl}-5-methylbenzamide dihydrochloride



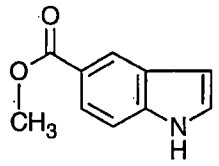
2 HCl

To methyl 3-{[isopentyl(methyl)amino]methyl}-5-methylbenzoate prepared by the method in EXAMPLE SP-211, Step 1 (160 mg, 0.61 mmol) in tetrahydrofuran/methanol/water (2:1:1, 8 mL) is added lithium hydroxide monohydrate (51 mg, 1.2 mmol), and the reaction is stirred at room temperature 16 h. The solution is concentrated under reduced pressure, redissolved in DMF (5 mL), and diisopropylethylamine (424 µL, 2.4 mmol), HATU (290 mg, 0.8 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[1-(3-ethylphenyl)cyclopropyl]amino}-3-methylbutan-2-ol dihydrochloride prepared by the method in EXAMPLE SP-272 (291 mg, 0.7 mmol) are added. The reaction stirred at room temperature 2 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 592.3 $[M + H]^+$.

EXAMPLE SP-213

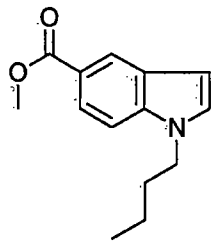
1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide

Step 1: Methyl 1H-indole-5-carboxylate



To a mixture of indole-5-carboxylic acid (3.0 g) and triethylamine (1.9 g) in dry THF (100 mL) was added 1,1-carbonyldiimidazole (3.08 g). The mixture was stirred for 30 minutes at room temperature, at which time methanol (25 mL) was added. The mixture was stirred at room temperature for 1 h, partitioned between water and ethyl acetate. The layers were separated and the organic layer washed twice with water, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Column chromatography on silica gel (200 mL) using CH_2Cl_2 as eluent to give 0.794 g of the title compound: ^1H NMR ($CDCl_3$) δ 3.93, 6.66, 7.28, 7.41, 7.91, 8.34, 8.42.

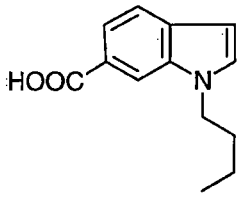
Step 2: Methyl 1-butyl-1H-indole-5-carboxylate



To a mixture of methyl 1H-indole-5-carboxylate (6.0 g) in methylsulfoxide (30 mL) was added potassium t-butoxide (3.88 g). The mixture was stirred at room temperature for 10 minutes at which time 1-iodobutane (1.8 mL) was added. The mixture was stirred at room temperature for 5 h then partitioned between water and methylene chloride. The layers

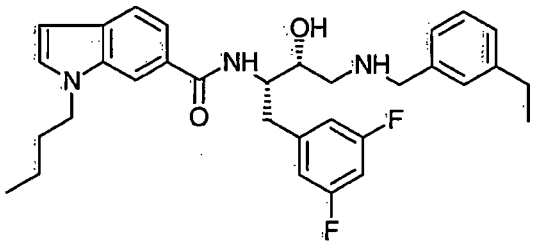
were separated and the organic layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 10% ethyl acetate in hexanes as eluent to give 6.18 g of the title compound: ^{1}H NMR ($CDCl_3$) δ 0.923, 1.38, 1.83, 3.9, 4.14, 6.58, 7.15, 7.34, 7.9, 8.39.

Step 3: 1-Butyl-1H-indole-6-carboxylic acid



To a mixture of 1-butyl-1H-indole-6-carboxylic acid (0.52 g) in methanol (25.0 mL) and water (5.0 mL) was added lithium hydroxide monohydrate (2.0 g). The mixture was heated to 60 °C for 6 h, cooled to room temperature, poured into 1N HCl (50mL) and extracted into ethyl acetate. The ethyl acetate extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 0.496 g (72%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J = 7.3 Hz, 3 H), 1.4 (m, 2 H), 1.9 (m, 2 H), 4.2 (m, 2 H), 6.57 (ss, J = 2.6 Hz, 1 H), 7.31 (ss, J = 3.1 Hz, 1 H), 7.68 (d, J = 8.4 Hz, 1 H), 7.89 (dd, J = 1.4, 8.4 Hz, 1 H), 8.24 (s, 1 H).

Step 4: 1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide



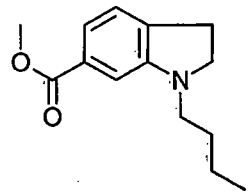
To a mixture of 1-butyl-1H-indole-6-carboxylic acid (0.278 g) in methylene chloride (10 mL) was added triethylamine (0.129 g), HOBT (0.175 g) and, HATU (0.486 g).

The mixture was stirred at room temperature for 30 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.408 g) was added. The resulting mixture was stirred at room temperature for 18 h then partitioned between water and methylene chloride. The layers were separated and the organic layer washed with water followed by brine and dried over anhydrous magnesium sulfate. Column chromatography on silica gel (100 mL) using 3% methanol in methylene chloride as eluent to give 0.256 g of the title compound: MS (ESI+) for $C_{32}H_{37}F_2N_3O_2$ *m/z* 542.2 (M+H).

EXAMPLE SP-201

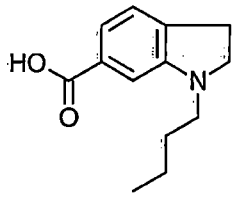
1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}indoline-6-carboxamide hydrochloride

Step 1: Methyl 1-butylindoline-6-carboxylate



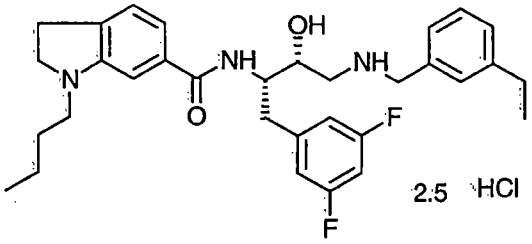
To a mixture of methyl 1-butyl-1H-indole-6-carboxylate, (2.1 g) in glacial acetic acid (25 mL) was added sodium cyanoborohydride (2.28 g). The mixture was heated at 40 °C for 3 h then cooled to room temperature, partitioned between water and ethyl acetate and the layers were separated. The organic layer was washed three times with brine, dried over anhydrous sodium sulfate and concentrated to give 1.64 g of the title compound: ^{1}H NMR ($CDCl_3$) δ 0.969, 1.43, 1.59, 2.99, 3.1, 3.4, 3.88, 7.07, 7.34.

Step 2: 1-Butylindoline-6-carboxylic acid



To a mixture of Methyl 1-butylindoline-6-carboxylate (1.6 g) in methanol (20 mL) was added 1N NaOH (5.0 mL). The mixture was heated at 60 °C for 2 h then cooled to room temperature, poured into 1N HCl and extracted into ethyl acetate. The ethyl acetate extract was dried over anhydrous magnesium sulfate and concentrated to give 1.16 gof the title compound: ^{1}H NMR ($CDCl_3$) δ 0.974, 1.43, 1.60, 3.01, 3.11, 3.42, 7.1, 7.43.

Step 3: 1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}indoline-6-carboxamide hydrochloride



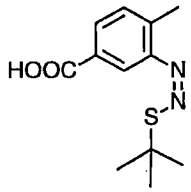
To a mixture of 1-butylindoline-6-carboxylic acid (0.2 g) in methylene chloride was added triethylamine (0.0.27 g), HOBT (0.125 g) and, HATU (0.347 g). The mixture was stirred at 40 °C for 15 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.346 g) was added. The resulting mixture was stirred at 40 °C for 5 h then partitioned between water and methylene chloride. The layers were separated and the organic layer washed with water followed by brine and dried over anhydrous magnesium sulfate. Column chromatography on silica gel (100 mL) using 5% methanol

in methylene chloride as eluent to give 0.100 g of the title compound: MS (ESI+) for $C_{32}H_{39}F_2N_3O_2$ *m/z* 535.9 $(M+H)^+$.

EXAMPLE SP-215

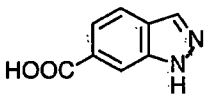
1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indazole-6-carboxamide

Step 1: 3-[(E)-(Tert-butylthio)diazenyl]-4-methylbenzoic acid



To a mixture of 3-amino-4-methyl benzoic acid (5.0 g) in water (50 mL) was added concentrated hydrochloric acid (15 mL). The mixture was chilled to 0 °C in an ice/acetone bath. Sodium nitrite (2.28 g) was dissolved in water (10 mL) and slowly added to the mixture at 0 °C. The pH was adjusted to 6 with saturated sodium acetate and 2-methyl-2-propanethiol (1.8 mL) was added. The mixture was stirred for 1 h and the resulting solids were collected by filtration, washed with water and dried under reduced pressure to give 5.7 g of the title compound: ^{1}H NMR ($CDCl_3$) δ 1.61, 2.20, 7.38, 7.55, 9.67.

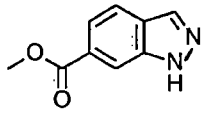
Step 2: 1H-Indazole-6-carboxylic acid



To a mixture of 3-[(E)-(tert-butylthio)diazenyl]-4-methylbenzoic acid (5.7 g) in nitrogen degassed methylsulfoxide (90 mL) was added potassium t-butoxide (25.0 g). The mixture was stirred at room temperature for 24 h then poured onto ice and acidified to pH 4 with concentrated hydrochloric acid. The mixture was extracted with diethyl

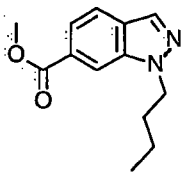
ether and the organic layer washed with brine. The organic layer was dried over anhydrous magnesium sulfate and decolorizing carbon then concentrated under reduced pressure to give 1.2 gof the title compound: ^{1}H NMR ($CDCl_3$) δ 0.963, 1.36, 1.95, 4.48, 7.81, 7.88, 8.08, 8.29.

Step 3: Methyl 1H-indazole-6-carboxylate



To a mixture of 1H-indazole-6-carboxylic acid (1.0 g) in methylene chloride (15 mL) was added EDC (1.8 g), HOBT (1.27 g), and triethylamine (1.29 mL). The mixture was heated to 40 °C for 30 minutes at which time methanol (10.0 mL) was added. The mixture was stirred at 40 °C for 18 h. The mixture was removed from heat, cooled to room temperature and poured into methylene chloride. The mixture was washed twice with water then brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 0.955 g of the title compound: ^{1}H NMR ($CDCl_3$) δ 3.98, 7.81, 7.86, 8.16, 8.29, 10.6.

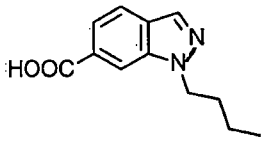
Step 4: Methyl 1-butyl-1H-indazole-6-carboxylate



To a mixture of methyl 1H-indazole-6-carboxylate (0.95 g) in DMF (10 mL) was added 60% NaH (0.216 g). The mixture was heated to 60 °C and 1-iodobutane (0.61 mL) was added. The mixture was heated at 60 °C for 72 h and 1-iodobutane (0.61 mL) was added every 24 h. The mixture was removed from heat and cooled to room temperature and partitioned between water and ethyl acetate. The layers were separated and the organic

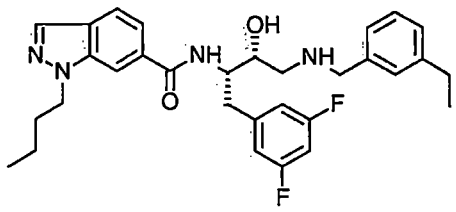
layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 5% ethyl acetate in hexanes as eluent to give 0.356 g of the title compound: ^{1}H NMR ($CDCl_3$) δ 0.938, 1.34, 1.92, 3.97, 4.43, 7.73, 7.79, 8.03, 8.18.

Step 5: 1-Butyl-1H-indazole-6-carboxylic acid



To a mixture of methyl 1-butyl-1H-indazole-6-carboxylate (0.356 g) in methanol (10 mL) was added saturated sodium bicarbonate (5 mL). The mixture was heated at 60 °C for 2 h at which time 1N NaOH (5 mL) was added and the mixture heated to 80°C for 18 h. The mixture was cooled to room temperature, poured into 1N HCl (50 mL), and extracted with ethyl acetate. The ethyl acetate extract dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 0.310 g of the title compound: ^{1}H NMR ($CDCl_3$) δ 0.964, 1.96, 4.48, 7.81, 7.89, 8.29, 8.46.

Step 6: 1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indazole-6-carboxamide



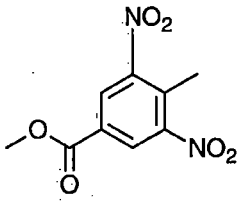
To a mixture of 1-butyl-1H-indazole-6-carboxylic acid (0.2 g) in methylene chloride (20 mL) was added triethylamine (0.182 g), HOBT (126 g), and HATU (0.348 g). The mixture was

stirred at 40 °C for 10 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.35 g) was added. The mixture was stirred at 40 °C for 3 h then poured into methylene chloride (50 mL), washed with water then brine, dried over anhydrous magnesium sulfate and concentrated under vacuum. Column chromatography on silica gel (100 mL) using 5% methanol in methylene chloride as eluent to give 0.2 g of the title compound: MS (ESI+) for $C_{31}H_{36}F_2N_4O_2$ *m/z* 534.9 $(M+H)^+$.

EXAMPLE SP-216

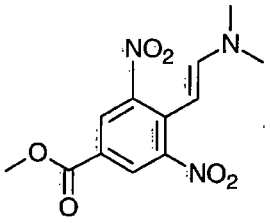
1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[methyl(methylsulfonyl)amino]-1H-indole-6-carboxamide

Step 1: Methyl 4-methyl-3,5-dinitrobenzoate



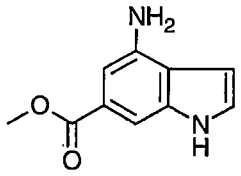
To a mixture of 3,5 dinitrotoluic acid (16 g) in methanol (10 mL) was added sulfuric acid (15 mL). The mixture was heated to 75 °C for 72 h, removed from heat and cooled to room temperature. The solvents were removed under pressure and the residue was partitioned between water and ethyl acetate. The layers were separated and the organic layer washed with 2 N NaOH followed by water. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to give 16.28 g (96%) of the title compound: ^1H NMR ($CDCl_3$) δ 2.65 (s, 3 H), 4.02 (s, 3 H), 8.61 (s, 2 H

Step 2: Methyl 4-[(E)-2-(dimethylamino)ethenyl]-3,5-dinitrobenzoate



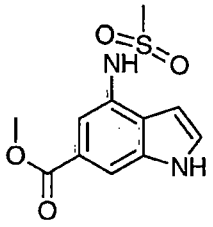
To a mixture of methyl 4-methyl-3,5-dinitrobenzoate (5.6 g) in toluene (20 mL) was added dimethylformamide dimethyl acetal (4.17 g) and 5-sulfo salycylic acid hydrate (0.1 g). The mixture was heated to 110 °C for 19 h, removed from heat and cooled to room temperature. The solvents were removed under reduced pressure at which time hexanes was added to the residue and the residue was filtered to give 6.85 g of the title compound: ^{1}H NMR ($CDCl_3$) δ 2.97, 3.96, 5.54, 6.74, 8.33.

Step3: Methyl 4-amino-1H-indole-6-carboxylate



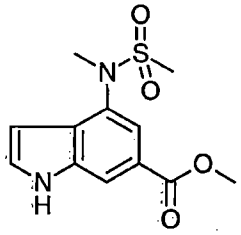
To a mixture of methyl 4-[(E)-2-(dimethylamino)ethenyl]-3,5-dinitrobenzoate (19.3 g) in ethyl acetate (200 mL) was added 5% palladium on carbon (1.5 g). The mixture was placed under 45 PSI H_2 and shaken overnight. The mixture was filtered through celite and concentrated. The residue was dissolved in CH_2Cl_2 to which was added ((1:1) H_2O:conc. HCl (250 mL)). The resulting solids were collected by filtration, dissolved in ethyl acetate and washed with 2N NaOH. The ethyl acetate layer with anhydrous magnesium sulfate, filtered and concentrated to give 7.4 g if the title compound: ^{1}H NMR ($CDCl_3$) δ 3.91, 4.01, 6.51, 7.09, 7.27, 8.40.

Step 4: Methyl 4-[(methylsulfonyl)amino]-1H-indole-6-carboxylate



To a mixture of methyl 4-amino-1H-indole-6-carboxylate (1.0 g) in DMF (10 mL) was added 4-dimethylaminopyridine (1.46 g) and methanesulfonyl chloride (0.6 g). The mixture was heated to 60 °C for 3 h, cooled to room temperature, and partitioned between water and ethyl acetate. The layers were separated and the organic layer washed three times with brine, dried over anhydrous sodium sulfate and concentrated to give 0.71 g of the title compound: ^{1}H NMR ($CDCl_3$) δ 3.02, 3.94, 6.69, 7.42, 7.81, 8.04.

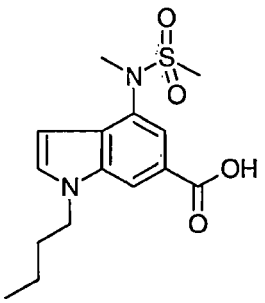
Step 5: Methyl 4-[methyl(methylsulfonyl)amino]-1H-indole-6-carboxylate



To a mixture of Methyl 4-[(methylsulfonyl)amino]-1H-indole-6-carboxylate (0.6 g) in THF (10 mL) was added potassium carbonate (0.309 g) and iodomethane (0.63 mL). The mixture was stirred at room temperature for 4 h then heated to 40 °C overnight. Iodomethane (0.3 mL) was added and the mixture heated an additional 3 h. The mixture was cooled to room temperature, partitioned between water and diethyl ether, dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in ether and decolorizing carbon (2 g) was added and the mixture refluxed for 5 minutes then filtered through celite while hot. The ether was removed under reduced

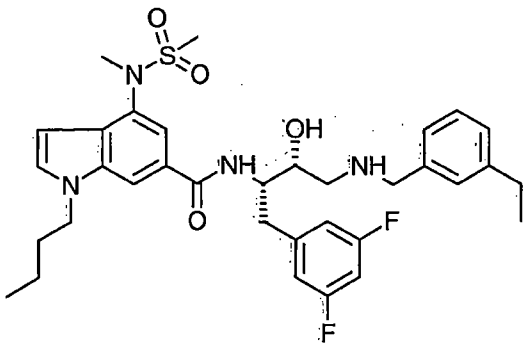
pressure to give 0.437 g of the title compound: MS (ESI+) for C12 H14 N2 O4 S1 *m/z* 321.1 (M+K).

Step 6: 1-Butyl-4-[methyl(methylsulfonyl)amino]-1H-indole-6-carboxylic acid



To a mixture of methyl 4-[methyl(methylsulfonyl)amino]-1H-indole-6-carboxylate (0.437 g) in DMF(15 mL) was added potassium hydroxide (0.087 g) and iodobutane (0.34 mL). The mixture was heated to 70 °C for 6 h. then stirred at room temperature for 72 h. The mixture was partitioned between water and ethyl acetate, the layers were separated and the organic layer washed three times with water. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was dissolved in methanol (5 mL) to which was added 1N NaOH (2 mL) and the mixture heated to 50 °C for 1 h. The mixture was cooled to room temperature and poured into water and washed with ether. The aqueous layer was acidified to pH 4 with 1N HCl and the product extracted into ethyl acetate which was dried over anhydrous sodium sulfate, filtered and concentrated to dryness to give 0.377 g of the title compound: ^{1}H NMR ($CDCl_3$) δ 0.973, 1.38, 1.87, 3.01, 3.45, 4.21, 6.71, 7.36, 7.82, 8.18.

Step 7: 1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[methyl(methylsulfonyl)amino]-1H-indole-6-carboxamide

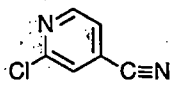


To a mixture of 1-Butyl-4-[methyl(methylsulfonyl)amino]-1H-indole-6-carboxylic acid (0.2g) in methylene chloride (15 mL) was added triethylamine (0.156 g), HOBT (0.105 g), and HATU (0.293 g). The mixture was stirred at 39 °C for 10 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.293 g) was added. The mixture was stirred at 40 °C for 4 h then poured into methylene chloride (50 mL), washed with water followed by brine then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 5% methanol in methylene chloride as eluent to give 0.21 g of the title compound: MS (ESI+) for $C_{34}H_{42}F_2N_4O_4S_1$ *m/z* 640.8 (M+H).

EXAMPLE SP-217

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)isonicotinamide hydrochloride

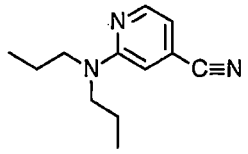
Step 1: 2-Chloroisonicotinonitrile



4-cyanopyridine-N-oxide (10.0 g) was added to phosphorus oxychloride (85 mL) and heated to 110 °C for 2.5 h. The mixture was cooled to room temperature and the excess phosphorus oxychloride removed under reduced pressure. The residue was dissolved in water and made basic with concentrated ammonia. The product was extracted into

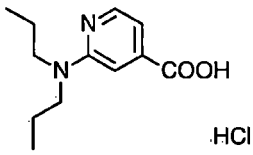
methylene chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using methylene chloride as eluent to give 7.19 g of the title compound: ^{1}H NMR ($CDCl_3$) δ 7.48, 7.6, 8.6.

Step 2: 2-(Dipropylamino)isonicotinonitrile



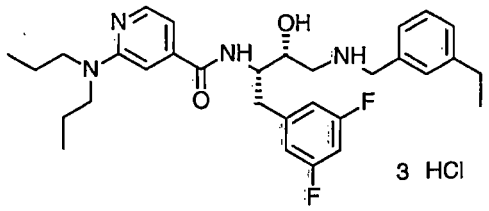
2-Chloroisonicotinonitrile (1.0 g) and dipropylamine (10 mL) were placed in a sealed heavy wall tube and heated to 100 °C for 18 h. The mixture was removed from heat and cooled to room temperature. The dipropylamine was removed under reduced pressure and the residue chromatographed on silica gel using 2% ethyl acetate in hexanes as eluent to give 1.06 g of the title compound: MS (ESI+) for $C_{12}H_{17}N_3$ *m/z* 204.1 $(M+H)^+$.

Step 3: 2-(Dipropylamino)isonicotinic acid hydrochloride



2-(Dipropylamino)isonicotinonitrile (1.0 g) was dissolved in concentrated hydrochloric acid (30 mL) and heated at 65 °C for 3 h. The solvents were removed under reduced pressure to give 1.27 g of the title compound: MS (ESI+) for $C_{13}H_{20}N_2O_2$ *m/z* 237.3 $(M+H)^+$.

Step 4: N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)isonicotinamide hydrochloride

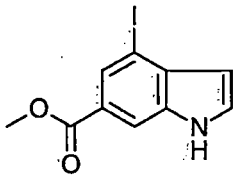


To a mixture of 2-(Dipropylamino)isonicotinic acid hydrochloride (0.2g) in methylene chloride (15 mL) was added triethylamine (0.195 g), HOBT (0.105 g), and HATU (0.293 g). The mixture was stirred at 39 °C for 10 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.285 g) was added. The mixture was stirred at 40 °C for 4 h then poured into methylene chloride (50 mL), washed with water then brine, dried over anhydrous magnesium sulfate and concentrated under vacuum. Column chromatography on silica gel (100 mL) using 5% methanol in methylene chloride as eluent and conversion to the hydrochloride salt gave 0.105 g of the title compound: MS (ESI+) for $C_{31}H_{40}F_2N_4O_2$ *m/z* 539.3 $(M+H)^+$.

EXAMPLE SP-218

1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(1,3-oxazol-2-yl)-1H-indole-6-carboxamide

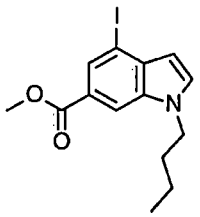
Step 1: Methyl 4-iodo-1H-indole-6-carboxylate



To a mixture of methyl 4-amino-1H-indole-6-carboxylate (EXAMPLE SP-216, step 3) (3.2 g) in water (50 mL) was added concentrated hydrochloric acid (5 mL). The mixture was chilled to below 5 °C with the addition of ice. To this was added sodium nitrite (1.16 g) dissolved in water (10 mL). The

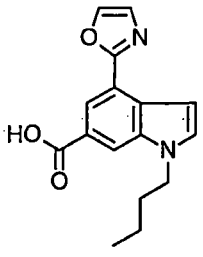
mixture was stirred chilled for 1 h followed by addition of sodium iodide (3 g) in water (20 mL). The mixture was stirred for 30 minutes, filtered and the solids collected by filtration were washed with water and dried at 50 °C. The solids turned black and gas evolved rapidly upon drying. Column chromatography on silica gel (200 mL) using 20 % hexanes in CH_2Cl_2 as eluent to give 0.82 g of the title compound: ^{1}H NMR ($CDCl_3$) δ 3.94, 6.55, 7.43, 8.14, 8.22, 8.62.

Step 2: Methyl 1-butyl-4-iodo-1H-indole-6-carboxylate



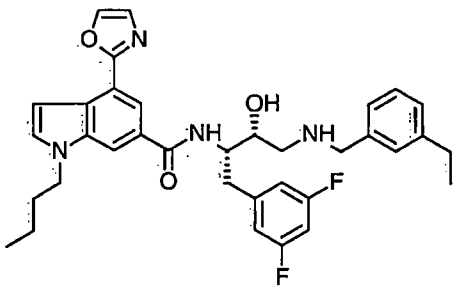
To a mixture of methyl 4-iodo-1H-indole-6-carboxylate (1.0 g) in DMF (10 mL) was added potassium hydroxide (0.392 g) and 1-iodobutane (0.8 mL). The mixture was heated to 80 °C for 18 h. The mixture was cooled to room temperature and partitioned between water and ethyl acetate. The layers were separated and the organic layer washed twice with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 20% ethyl acetate in hexanes as eluent to give 0.73 g of the title compound: ^{1}H NMR ($CDCl_3$) δ 0.940, 1.32, 1.81, 3.95, 4.15, 6.45, 7.31, 8.09, 8.18.

Step 3: 1-Butyl-4-(1,3-oxazol-2-yl)-1H-indole-6-carboxylic acid



To a -72 °C solution of oxazole (0.069 g) in dry THF (20 mL) was added dropwise 1.6 M N-butyl lithium (0.68 mL). The mixture was stirred at -72 °C for 30 minutes at which time 1.0 M zinc chloride (3.3 mL) was added. The mixture was allowed to warm to 0 °C at which time methyl 1-butyl-4-iodo-1H-indole-6-carboxylate (0.37 g) and tetrakis triphenylphosphine palladium (0) (0.07 g) were added and the mixture heated to 85 °C. The mixture was heated at 85 °C for 20 h then cooled to room temperature and partitioned between water and ethyl acetate. The layers were separated and the organic layer washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Column chromatography was performed on silica gel (100 mL) using 20% ethyl acetate in hexanes as eluent. The residue was dissolved in methanol (10 mL) and 1N NaOH (3 mL) and heated at 60 °C for 2 h. The mixture was acidified to pH 4 with 1N HCl and extracted with ethyl acetate. The ethyl acetate extracts were dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure to give 0.2 g of the title compound: MS (ESI+) for $C_{16}H_{16}N_2O_3$ *m/z* 283.16 $(M+H)^+$.

Step 4: 1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(1,3-oxazol-2-yl)-1H-indole-6-carboxamide



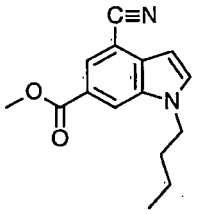
To a mixture of 1-butyl-4-(1,3-oxazol-2-yl)-1H-indole-6-carboxylic acid (0.2g) in methylene chloride (20 mL) was added 1,1-carbonyldiimidazole (0.114 g). The mixture was stirred at room temperature for 1 h at which time (2R,3S)-3-amino-4-(3,5-

difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.265 g) dissolved in methylene chloride (10 mL) was added. The mixture was stirred at room temperature for 18 h then poured into methylene chloride (50 mL), washed with water followed by brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 65% methylene chloride, 30 % hexanes, and 5% methanol as eluent to give 0.0985 g of the title compound: MS (ESI+) for $C_{35}H_{38}F_2N_4O_3$ *m/z* 601.99 $(M+H)^+$.

EXAMPLE SP-219

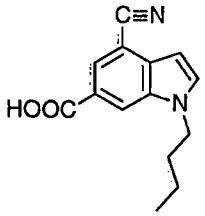
1-Butyl-4-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide

Step 1: Methyl 1-butyl-4-cyano-1H-indole-6-carboxylate



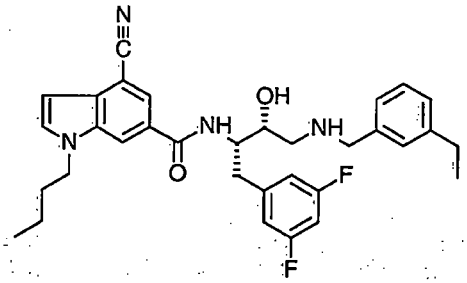
To a mixture of methyl 1-butyl-4-iodo-1H-indole-6-carboxylate (EXAMPLE SP-218, Step 4) (1.47 g) in N-methyl pyrrolidinone (15 mL) was added copper (I) cyanide (1.1 g). The mixture was heated to 150 °C for 6 h, removed from heat and cooled to room temperature. The mixture was partitioned between water and ethyl acetate and the layers were separated. The organic layer was washed three times with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 20% ethyl acetate as eluent to give 0.5 g of the title compound: ^1H NMR ($CDCl_3$) δ 0.955, 1.32, 1.85, 3.98, 4.23, 6.76, 7.43, 8.16, 8.30.

Step 2: 1-Butyl-4-cyano-1H-indole-6-carboxylic acid



To a mixture of methyl 1-butyl-4-cyano-1H-indole-6-carboxylate (10.5 g) in methanol (15 mL) was added 1N NaOH (3.0 mL). The mixture was heated at 40 °C for 2 h then cooled to room temperature. The mixture was poured into 1N HCl and extracted into ethyl acetate. The ethyl acetate extract was dried over anhydrous magnesium sulfate and concentrated to give 0.45 g of the title compound: ^{1}H NMR ($CDCl_3$) δ 0.973, 1.38, 1.88, 4.27, 6.79, 7.48, 8.24, 8.38.

Step 3: 1-Butyl-4-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide



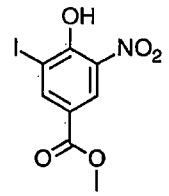
To a mixture of 1-butyl-4-cyano-1H-indole-6-carboxylic acid (0.29 g) in methylene chloride (10 mL) was added 1,1-carbonyldiimidazole (0.194 g) and triethylamine (0.267 g). The mixture was stirred at room temperature for 45 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.5 g) dissolved in methylene chloride (10 mL) was added. The mixture was stirred at room temperature for 18 h then poured into methylene chloride (50 mL), washed with water followed by brine, dried over anhydrous magnesium sulfate and concentrated under vacuum. Column chromatography on silica gel (100 mL) using 5% methanol in

methylene chloride as eluent to give 0.47 g of the title compound: MS (ESI+) for $C_{33}H_{36}F_2N_4O_2$ *m/z* 559.0 $(M+H)^+$.

EXAMPLE SP-220

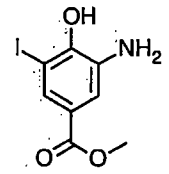
4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

Step 1: Methyl 4-hydroxy-3-iodo-5-nitrobenzoate



To a solution of methyl 4-hydroxy-3-nitrobenzoate (2.0 g) in acetic acid (15 mL) was added iodine monochloride (1.65 mg) in acetic acid, and the mixture was stirred at 100 °C for 1.5 h. After cooling to room temperature, the mixture was poured into water (200mL), and stirred for 30 min. The mixture was filtered and washed with water and hexanes. The yellow powder was collected by filtration and dried in vacuum oven overnight to give 2.99 g of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.68, 8.81, 8.72, 3.96.

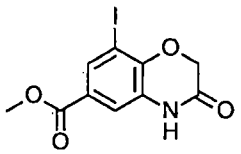
Step 2: Methyl 3-amino-4-hydroxy-5-iodobenzoate



To a mixture of methyl 4-hydroxy-3-iodo-5-nitrobenzoate (2.99 g) in ethanol (40 mL) was added tin (II) chloride (10 g) portion wise. After stirring for 1 h at reflux, the mixture was cooled to 0 °C and quenched by saturated potassium carbonate (100 mL). The mixture was filtered through

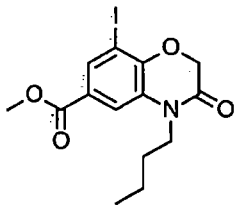
diatomaceous earth and the filtrate was extracted with ethyl acetate (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 2.5 g of the title compound: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.50, 7.24, 3.75.

Step 3: Methyl 8-iodo-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate



To an ice-cold, stirred solution of Methyl 3-amino-4-hydroxy-5-iodobenzoate (2.3 g) and sodium bicarbonate (1.5 g) in 1:1 isobutyl methyl ketone/water (80 mL) was added chloroacetyl chloride (1.1 g), and the reaction mixture was stirred for 1 h. The mixture was warmed to room temperature and heated at reflux for 18 h. After overnight, a beige solid formed. The mixture was filtered, and washed with water and hexanes to give 2.4 g of the title compound: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.98, 7.89, 7.47, 4.79, 3.82.

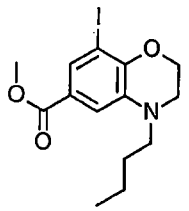
Step 4: Methyl 4-butyl-8-iodo-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate



To a solution of Methyl 8-iodo-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (2.64 g) and potassium carbonate (5 g) in DMSO (20 mL) was added bromobutane (5 g), and the reaction mixture was stirred for 1 h at 80 °C. The mixture was cooled to room temperature, diluted with 1:1 ethyl

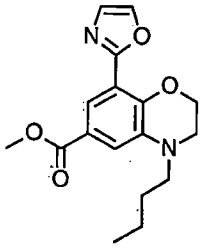
acetate/hexanes (100 mL) and water (160 mL), and separated. The organic layer was washed with water, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:10 ethyl acetate/hexanes) afforded 2.24 g of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13, 7.63, 4.74, 3.96, 3.92, 1.64, 1.42, 0.97.

Step 5: Methyl 4-butyl-8-iodo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate



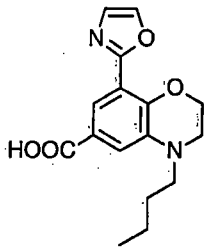
A solution of Methyl 4-butyl-8-iodo-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (680 mg) and 9-BBN (900 mg) in tetrahydrofuran (30 mL) was heated at reflux for 1.5 h. The mixture was cooled to room temperature, ethanolamine (0.22 mL) was added, and the resulting solution was concentrated under reduced pressure. The residue was washed with hexanes, filtered, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (silica, 10% ethyl acetate/hexanes) afforded 600 mg of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75, 7.28, 4.34, 3.86, 3.36, 3.28, 1.58, 1.40, 0.96.

Step 6: Methyl 4-butyl-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate



To a -70 °C solution of oxazole (227 mg) in tetrahydrofuran (10 mL) was added *n*-butyllithium (2.5 M in hexanes, 2 mL). After stirred at -70 °C for 30 min, zinc chloride (1 M in ethyl ether, 13 mL) was added. The mixture was warmed to 0 °C for 1 h. To this mixture was then added ethyl 4-butyl-8-iodo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (600 mg, 1.6 mmol) in THF (5 mL) followed by tetrakis triphenylphosphine palladium (0) (115 mg). The mixture was heated at reflux for 3 h, diluted with ethyl acetate (300 mL) and washed with water followed by brine. The organic solution was dried (sodium sulfate) and concentrated under reduced pressure. Purification by silica gel plug (1:1 acetate/hexanes) provided 363 mg of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96, 7.73, 7.40, 7.28, 4.44, 3.90, 3.43, 3.34, 1.61, 1.41, 0.98.

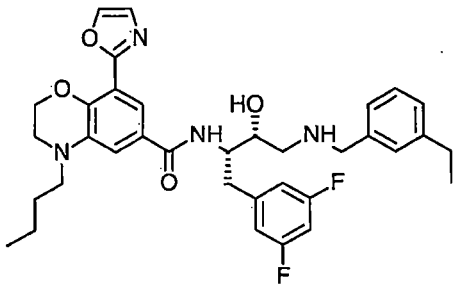
Step 7: 4-Butyl-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylic acid



To a stirred solution of Methyl 4-butyl-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (474 mg) in methanol (20 mL) was added potassium hydroxide (15 mL of a 1.0 M solution in water). The mixture was stirred at room temperature overnight then concentrated under reduced pressure. The residue was diluted with water and washed with ethyl acetate. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with chloroform (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 450 mg of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$)

δ 11.60, 8.08, 7.74, 7.46, 7.37, 4.46, 3.43, 3.34, 1.62, 1.41, 0.98.

Step 8: 4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

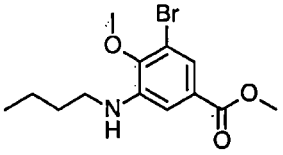


A solution of 4-Butyl-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylic acid (450 mg, HBTU (853 mg), and diisopropylethylamine (580 mg) was stirred in methylene chloride (15 mL) for 15 min. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (606 mg) in methylene chloride (7 mL) was added and the reaction mixture was stirred overnight. The mixture was filtered with methylene chloride, dried (magnesium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided 400 mg of the title compound: ESI MS *m/z* 619 $[M + H]^+$.

EXAMPLE SP-221

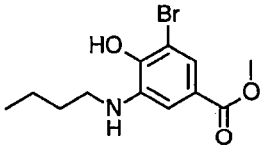
4-Butyl-8-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

Step 1: Methyl 3-bromo-5-(butylamino)-4-methoxybenzoate



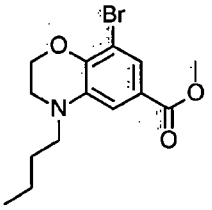
To a stirred solution of $Pd(OAc)_2$ (144 mg), BINAP (1.2 g), and cesium carbonate (8.4 g) in toluene (100 mL) was added butylamine (1.6 mL), and the mixture was heated at 80 °C for 15 min. A solution methyl 3,5-dibromo-4-methoxybenzoate (4.2 g) in toluene (30 mL) was added dropwise over 20 min. The mixture was refluxed overnight. The mixture was cooled to room temperature, filtered through diatomaceous earth, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 ethyl acetate/hexanes) provided 3.5 g of the title compound: ^1H NMR (300 MHz, $CDCl_3$) δ 7.52, 7.19, 3.90, 3.88, 3.18, 1.66, 1.46, 0.97.

Step 2: Methyl 3-bromo-5-(butylamino)-4-hydroxybenzoate



To a -78 °C solution of the Methyl 3-bromo-5-(butylamino)-4-methoxybenzoate (520 mg) in methylene chloride (10 mL) was added BBr_3 (8 ml of 1.0 M solution in methylene chloride) dropwise and the reaction mixture was stirred for 18 h. The mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride and saturated sodium bicarbonate was added. The mixture was cooled to 0 °C and methanol was added dropwise. After stirring for 30 min, the mixture was stirred at room temperature for 1 h. The solvent was removed, and the residue dissolved in methylene chloride, washed with water, saturated sodium bicarbonate (15 mL), and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:20, ethyl acetate/hexanes) provided 440 mg of the title compound: ^1H NMR (300 MHz, $CDCl_3$) δ 7.52, 7.19, 3.88, 3.18, 1.65, 1.46, 0.97.

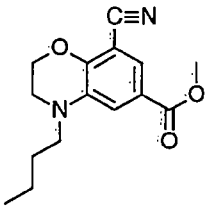
Step 3: Methyl 8-bromo-4-butyl-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate



To an ice-cold, stirred solution of Methyl 3-bromo-5-(butylamino)-4-hydroxybenzoate (440 mg) and sodium bicarbonate (280 mg) in 1:1 isobutyl methyl ketone/water (10 mL) was added chloroacetyl chloride (226 mg). The mixture was stirred for 1 h, warmed to room temperature, and heated at reflux for 14 h. The mixture was cooled to room temperature, diluted with chloroform, and the layer separated. The organic layer was washed with water, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to give a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94, 7.62, 4.76, 3.98, 3.93, 1.65, 1.43, 0.97, which was used in the next step without further purification or characterization.

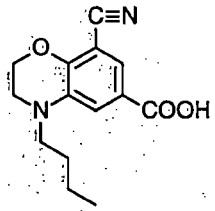
Step 4: A solution of the amide from step 3 and 9-BBN (780 mg) in tetrahydrofuran (10 mL) was heated at reflux for 1.5 h. The mixture was cooled to room temperature, ethanolamine (0.2 mL) was added, and the resulting solution was concentrated under reduced pressure. The residue was washed with hexanes, filtered, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (silica, 10% ethyl acetate/hexanes) afforded (330 mg, over 2 steps) of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55, 7.27, 4.36, 3.87, 3.37, 3.30, 1.60, 1.41, 0.97.

Step 5: Methyl 4-butyl-8-cyano-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate



To a flask containing methyl 8-bromo-4-butyl-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (0.33 g) was added NMP (7 mL), followed by copper cyanide (0.18 g). The mixture was then heated to 175 °C and stirred overnight. The resulting mixture was cooled to room temperature and poured into 1 N hydrochloric acid. The acidic aqueous layer was extracted with ethyl acetate, washed with 1 N hydrochloric acid (15 mL), saturated sodium bicarbonate (15 mL), and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 ethyl acetate/hexanes) provided 184 mg of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55, 7.43, 4.41, 3.89, 3.39, 3.31, 1.58, 1.40, 0.97.

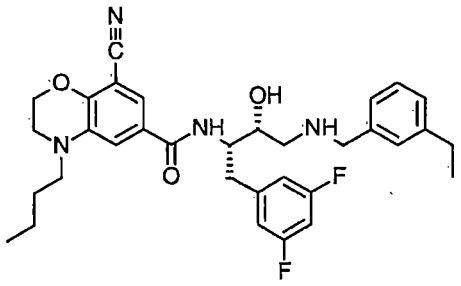
Step 6: 4-Butyl-8-cyano-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylic acid



To a stirred solution of Methyl 4-butyl-8-cyano-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (184 mg) in methanol (3 mL) was added potassium hydroxide (7 mL of a 1.0 M solution in water). The mixture was stirred at room temperature overnight then concentrated under reduced pressure. The residue was diluted with water and washed with ethyl acetate. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with chloroform (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and

concentrated under reduced pressure to give 154 mg of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62, 7.46, 4.44, 3.41, 3.33, 1.60, 1.41, 0.98.

Step 7: 4-Butyl-8-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

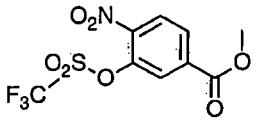


A solution of 4-Butyl-8-cyano-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylic acid (129 mg), HBTU (284 mg), and diisopropylethylamine (0.26 mL) was stirred in methylene chloride (6 mL) for 15 min. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (204 mg) in methylene chloride (4 mL) was added and the reaction mixture was stirred overnight. The mixture was diluted with methylene chloride, washed with 1 N hydrochloric acid (15 mL), saturated sodium bicarbonate (15 mL), and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided 20 mg of the title compound: ESI MS *m/z* 577 $[M + H]^+$.

EXAMPLE SP-222

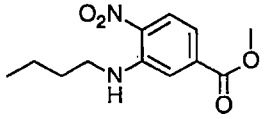
4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(methylsulfonyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide

Step 1: Methyl 4-nitro-3-{[(trifluoromethyl)sulfonyl]oxy}benzoate



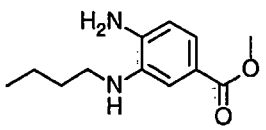
To an ice-cold, stirred solution of methyl 3-hydroxy-4-nitrobenzoate (1.5 g) and triethylamine (1.1 mL) in methylene chloride (15 mL) was added trifluoromethane sulfonic anhydride (1.4 mL), and the reaction mixture was stirred for 30 min. The mixture was diluted with methylene chloride, washed with saturated sodium bicarbonate, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure provided 2.4 g of the title compound: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.47, 8.27, 8.15, 3.99.

Step 2: Methyl 3-(butylamino)-4-nitrobenzoate



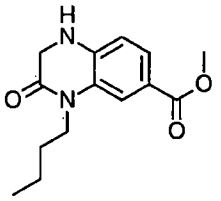
To a stirred solution of $Pd_2(dba)_3$ (139 mg), BINAP (284 mg), and cesium carbonate (2.0 g) in toluene (50 mL) was added butylamine (0.45 mL), and the reaction mixture was heated at 80 °C for 15 min. A solution of methyl 4-nitro-3-{[(trifluoromethyl)sulfonyl]oxy}benzoate (1.0 g) in toluene (15 mL) was added dropwise over 1 h. The mixture was cooled to room temperature, filtered through diatomaceous earth, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 3:1 ethyl acetate/hexanes) provided 670 mg of the title compound as a yellow oil: ESI MS *m/z* 550 $[M + H]^+$.

Step 3: Methyl 4-amino-3-(butylamino)benzoate



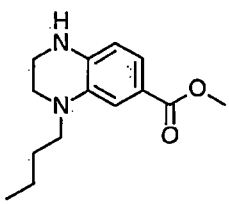
A solution of methyl 3-(butylamino)-4-nitrobenzoate (1.1 g) and 10% Pd/C (110 mg) in methanol (20 mL) was shaken under an atmosphere of hydrogen at 50 psi for 2 h. The mixture was filtered through diatomaceous earth, and concentrated under reduced pressure to provide 940 mg of the title compound: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.13, 6.94, 6.52, 3.72, 3.02, 1.60, 1.42, 0.93.

Step 4: Methyl 4-butyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylate



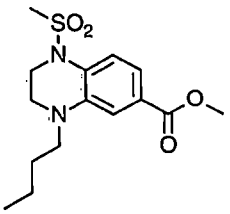
To an ice-cold, stirred solution of methyl 4-amino-3-(butylamino)benzoate (950 mg) and sodium bicarbonate (862 mg) in 1:1 isobutyl methyl ketone/water (20 mL) was added chloroacetyl chloride (0.41 mL), and the mixture was stirred for 1 h. The mixture was warmed to room temperature and refluxed for 14 h. The mixture was cooled to room temperature, diluted with chloroform, and separated. The organic layer was washed with water, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) afforded 850 mg of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89, 7.72, 6.80, 3.97, 3.88, 3.30-3.25, 1.68-1.58, 1.47-1.35, 0.94-0.88.

Step 5: Methyl 4-butyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylate



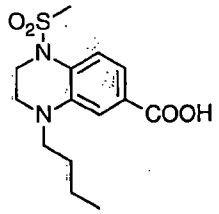
To an ice-cold, stirred solution of methyl 4-butyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylate (840 mg) in tetrahydrofuran (32 mL) was added borane dimethylsulfide complex (3.2 mL, 2.0 M tetrahydrofuran) and the resulting mixture was refluxed for 24 h. The mixture was cooled to room temperature, quenched with methanol, and the solvent was removed under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided 364 mg of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27, 7.22, 6.41, 3.84, 3.47-3.45, 3.32-3.23, 1.60-1.58, 1.42-1.37, 0.99-0.94.

Step 6: Methyl 4-butyl-1-(methylsulfonyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxylate



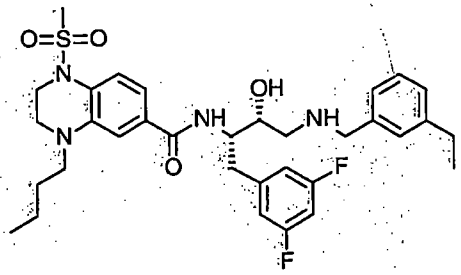
To an ice-cold, stirred solution of methyl 4-butyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylate (180 mg) and triethylamine (62 μL) in methylene chloride (2 mL) was added methanesulfonyl chloride (101 μL) and the mixture was stirred for 1 h. The mixture was warmed to room temperature, diluted with methylene chloride, washed with washed with 1 N hydrochloric acid, and brine. The organic layer was then dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:3 ethyl acetate/hexanes) provided 150 mg of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57, 7.41, 7.32, 3.90, 3.84, 3.45, 3.38, 1.61, 1.41, 0.98.

Step 7: 4-Butyl-1-(methylsulfonyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid



To a stirred solution of methyl 4-butyl-1-(methylsulfonyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxylate (144 mg) in methanol (1.3 mL) was added 1 M potassium hydroxide (13 mL). The mixture was stirred at room temperature for 48 h and concentrated under reduced pressure. The residue was diluted with water and washed with ethyl acetate. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with chloroform (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 99 mg of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43, 7.39, 7.24, 3.77, 3.39, 3.32, 1.56, 1.33, 0.90.

Step 8: 4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(methylsulfonyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide



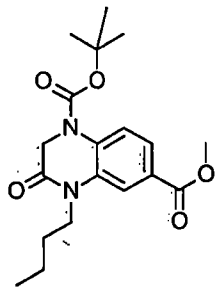
A solution of 4-butyl-1-(methylsulfonyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid (99 mg), HATU (181 mg), HOBt (64 mg), and diisopropylethylamine (100 μL) was stirred in methylene chloride (1.0 mL) for 15 min. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (129 mg) and diisopropylethylamine (100 μL) in methylene chloride (1.0 mL) was added and the mixture was stirred overnight. The mixture

was diluted with methylene chloride, washed with 1 N hydrochloric acid (10 mL), saturated sodium bicarbonate (10 mL), and brine. The organic layer was then dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided a clear solid. The solid was dissolved in methanol (1 mL), and treated with hydrochloric acid (0.5 mL, 1.0 M diethyl ether). The resulting precipitate was collected by filtration to provide 90 mg of the title compound: ESI MS *m/z* 629 $[M + H]^+$.

EXAMPLE SP-223

4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroquinoxaline-6-carboxamide hydrochloride

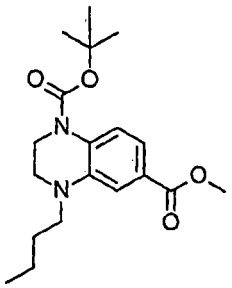
Step 1: 1-Tert-butyl 6-methyl 4-butyl-3-oxo-3,4-dihydroquinoxaline-1,6(2H)-dicarboxylate



To an ice-cold, stirred solution of methyl 4-butyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylate (1.1 g), and triethylamine (0.9 mL) in methylene chloride (10 mL) was added DMAP (51.3 mg) and di-*tert*-butyl dicarbonate (1.4 g), and the resulting mixture was stirred for 4 d. The mixture was diluted with methylene chloride, washed with water, and brine. The organic layer was then dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl

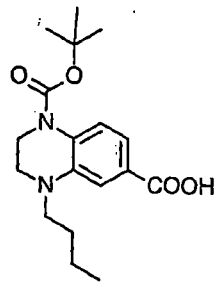
acetate/hexanes) provided 440 mg of the title compound: ESI MS *m/z* 363 $[M + H]^+$.

Step 2: 1-Tert-butyl 6-methyl 4-butyl-3,4-dihydroquinoxaline-1,6(2H)-dicarboxylate



A solution of 1-tert-butyl 6-methyl 4-butyl-3-oxo-3,4-dihydroquinoxaline-1,6(2H)-dicarboxylate (440 mg) and 9-BBN dimer (600 mg) in tetrahydrofuran (10 mL) was heated at 65 °C for 10 h. The mixture was cooled to room temperature, ethanolamine (0.15 mL) was added and the resulting solution was concentrated under reduced pressure. The residue was washed with hexanes, filtered, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 ethyl acetate/hexanes) afforded 158 mg of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50, 7.34, 7.28, 3.88, 3.77, 3.38-3.30, 1.65-1.51, 1.42-1.34, 0.99-0.94.

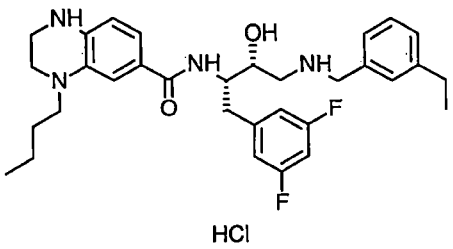
Step 3: 1-(Tert-butoxycarbonyl)-4-butyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid



To a stirred solution of 1-tert-butyl 6-methyl 4-butyl-3,4-dihydroquinoxaline-1,6(2H)-dicarboxylate (158 mg) in

methanol (1.4 mL) was added 1 M potassium hydroxide (1.4 mL). The mixture was stirred at 40 °C for 12 h and then concentrated under reduced pressure. The residue was diluted with water and washed with ethyl acetate. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with chloroform (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 120 mg of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55, 7.40, 7.37, 3.79, 3.38, 3.34, 1.60, 1.53, 1.39, 0.97.

Step 4: 4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroquinoxaline-6-carboxamide hydrochloride



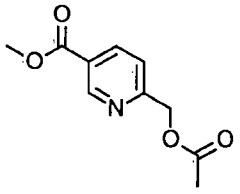
A solution of 1-(tert-butoxycarbonyl)-4-butyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid (120 mg), HBTU (204 g), and diisopropylethylamine (100 μL) was stirred in methylene chloride (2.0 mL) for 15 min. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (146 mg) and diisopropylethylamine (100 μL) in methylene chloride (2.0 mL) was added and the mixture was stirred overnight. The mixture was diluted with methylene chloride, washed with 1 N hydrochloric acid (10 mL), saturated sodium bicarbonate (10 mL), and brine. The organic layer was then dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided a clear solid. The solid was dissolved in methanol (1 mL), and treated with hydrochloric

acid (0.5 mL, 1.0 M diethyl ether, 0.5 mmol). The resulting precipitate was collected by filtration to provide 45 mg of the title compound: ESI MS *m/z* 551 $[M + H]^+$.

EXAMPLE SP-224

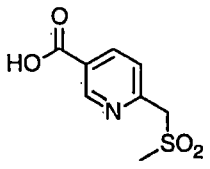
N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-[(methylsulfonyl)methyl]nicotinamide

Step 1: Methyl 6-[(acetyloxy)methyl]nicotinate



To a solution of methyl 6-methylnicotinate (6.05 g) in methylene chloride (100 mL) was added *m*-chloroperbenzoic acid (77%, 13.5 g). The reaction mixture was stirred at room temperature for 2 h and then diluted with chloroform (100 mL). The mixture was washed successively with aqueous sodium sulfite, saturated sodium bicarbonate, and brine. The organic later was then dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 6.21 g of methyl 6-methylnicotinate 1-oxide. A solution of methyl 6-methylnicotinate 1-oxide (4.35 g) in acetic anhydride (50 mL) was heated at 120 °C for 2 h and then concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 1:2 to 3:5 ethyl acetate/hexanes) provided 3.3 g of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18, 8.31, 7.44, 5.29, 3.96, 2.19.

Step 3: 6-[(Methylsulfonyl)methyl]nicotinic acid



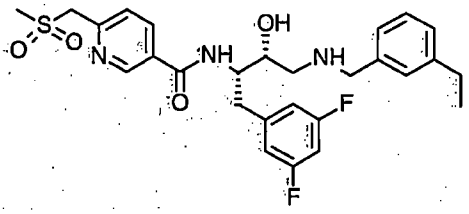
To a solution of methyl 6-[(acetyloxy)methyl]nicotinate (3.0 g) in dry methanol (100 mL) was added potassium carbonate (4.56 g). The mixture was stirred at room temperature for 2 h and then diluted with methylene chloride (200 mL) and water (200 mL). The organic layer was washed with brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 1.70 g of the alcohol. This material was used without further purification. To an ice-cold solution of methyl 6-(hydroxymethyl)nicotinate (1.6 g) in methylene chloride (40 mL) was added diisopropylethylamine (1.5 g) followed by methanesulfonyl chloride (1.21 g). The mixture was stirred at room temperature for 1 h and then diluted with methylene chloride (100 mL). The mixture was washed successively with 0.5 N potassium hydrogen sulfate, water, and brine. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide mesylate 2.34 g. This mesylate was used without further purification.

To a solution of methyl 6-{[(methylsulfonyl)oxy]methyl}nicotinate (2.34 g) in *N,N*-dimethylformamide (10 mL) was added sodium thiomethoxide (850 mg). The mixture was stirred at 50 °C for 15 h. The mixture was diluted with ethyl acetate (100 mL) and washed successively with water, saturated sodium bicarbonate, and brine. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 1.61 g of the methyl thioether. This material was used without further purification. To an ice-cold solution of methyl 6-[(methylthio)methyl]nicotinate (1.61 g) in methanol (35 mL) was added a solution of oxone (7.52 g) in water (35 mL). The resulting slurry was stirred at room temperature for 2 h. The resulting mixture was diluted with water (50 mL), and extracted with chloroform (3 x 100 mL). The combined organic extracts were washed with brine, dried (sodium

sulfate), filtered, and concentrated under reduced pressure to provide 1.77 g of the methyl sulfone, which was used without further purification.

To a stirred solution of methyl 6-[(methylsulfonyl)methyl]nicotinate (800 mg) in 1:1:1 tetrahydrofuran/methanol/water (30 mL) was added lithium hydroxide (440 mg). The mixture was stirred at room temperature for 1 h, and concentrated under reduced pressure. The residue was partitioned between water (10 mL) and chloroform (10 mL). The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with 3:1 chloroform/2-propanol (3 x 30 mL). The combined organic layers were dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 700 mg of the title compound: ^{1}H NMR (300 MHz, CD_3OD) δ 9.07, 8.33, 7.65, 4.77, 3.06.

Step 4: N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-[(methylsulfonyl)methyl]nicotinamide



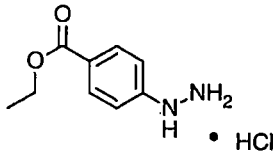
To a stirred solution of 6-[(methylsulfonyl)methyl]nicotinic acid (181 mg), diisopropylethylamine (116 mg), and HBTU (341 mg) in methylene chloride (5 mL) was added a mixture of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (326 mg) and *N,N*-diisopropylethylamine (233 mg) in methylene chloride (5 mL). The mixture was stirred at room temperature for 15 h and concentrated under reduced pressure. The residue was diluted with ethyl acetate (50 mL), washed with saturated sodium bicarbonate, and brine, dried (sodium sulfate),

filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5:95 to 10:90 methanol/methylene chloride) provided 165 mg of the title compound: ESI MS *m/z* 532 $[M + H]^+$.

EXAMPLE SP-225

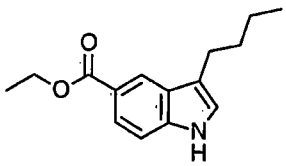
3-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-methyl-1H-indole-5-carboxamide

Step 1: Ethyl 4-hydrazinobenzoate hydrochloride



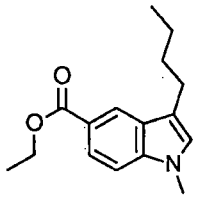
To a 0 °C mixture of 4-ethylaminobenzoate (10.0 g) in water (56 mL) and concentrated hydrochloric acid (20 mL) was added portion wise a solution of sodium nitrite (4.25 g) in water (20 mL). The mixture was stirred at 0 °C for 15 minutes at which time the mixture was poured into a solution of tin (II) chloride (50 gm) in water (34 mL). The resulting mixture was removed from the ice bath and allowed to slowly come to room temperature over 1 h at which time the resulting solids were collected by filtration and washed with chilled concentrated hydrochloric acid (30 mL) followed by ether. The solids were dried under vacuum to give 13 g of the title compound: ^{1}H NMR (DMSO-d_6) δ 1.29, 4.25, 7.03, 7.85, 9.0, 9.06, 10.6.

Step 2: Ethyl 3-butyl-1H-indole-5-carboxylate



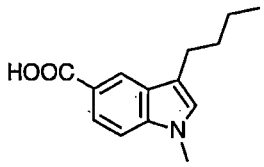
To a mixture of ethyl 4-hydrazinobenzoate hydrochloride (10 gm) in ethanol: water (5:1 100 mL) was added hexanal (4.62 gm). The mixture was refluxed at 100 °C for 3 h. The solvents were removed and toluene (100 mL) and p-toluene sulfonic acid (0.1 g) were added. The mixture was refluxed at 120 °C for 18 h, cooled to room temperature and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 90:9:1 (hexanes: methylene chloride: ethyl acetate) as eluent to give 0.8 g of the title compound: ^{1}H NMR ($CDCl_3$) δ 0.957, 1.44, 1.72, 2.78, 4.40, 7.02, 7.34, 7.90, 8.13, 8.38.

Step 3: Ethyl 3-butyl-1-methyl-1H-indole-5-carboxylate



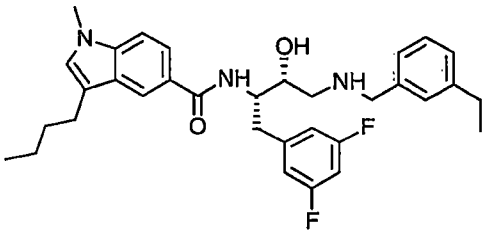
To a mixture of ethyl 3-butyl-1H-indole-5-carboxylate (0.6 g) in methylsulfoxide (10 mL) was added potassium t-butoxide (0.29 g) and iodomethane (2.0 mL). The mixture was stirred at 50 °C for 18 H, at which time the mixture was pored into water (50 mL). The solution was extracted with ethyl acetate and the organic extracts washed three times with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 5% ethyl acetate in hexanes as eluent to give 0.294 g of the title compound: ^{1}H NMR ($CDCl_3$) δ 0.953, 1.44, 1.69, 2.77, 3.76, 4.40, 6.87, 7.26, 7.91, 8.35.

Step 4: 3-Butyl-1-methyl-1H-indole-5-carboxylic acid



To a mixture of ethyl 3-butyl-1-methyl-1H-indole-5-carboxylate (0.294 g) in methanol (20 mL) was added 1N NaOH (10 mL). The mixture was stirred at 50 °C for 18 h, cooled to room temperature and poured into 1N HCl (50 mL). The mixture was extracted with ethyl acetate and the ethyl acetate extract was dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure to give 0.234 g (89%) of the title compound: ^{1}H NMR (CD_3OD) δ 0.965, 1.42, 1.69, 2.76, 3.77, 7.02, 7.35, 7.84, 8.29.

Step 5: 3-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-methyl-1H-indole-5-carboxamide

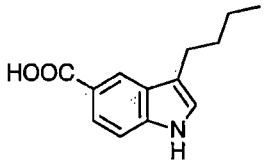


To a mixture of 3-Butyl-1-methyl-1H-indole-5-carboxylic acid (0.15 g) in methylene chloride (5 mL) and tetrahydrofuran (10 mL) was added 1,1-carbonyldiimidazole (0.105 g). The mixture was stirred at 40 °C at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.2 g) in methylene chloride (5 mL) was added. The mixture was stirred at 40 °C for 18 h then poured into methylene chloride (50 mL). The mixture was washed with water then brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 85:10:5 (methylene chloride: hexanes: methanol) as eluent to give 0.102 g of the title compound: MS (ESI+) for $C_{33}H_{39}F_2N_3O_2$ *m/z* 547.9 $(M+H)^+$.

EXAMPLE SP-226

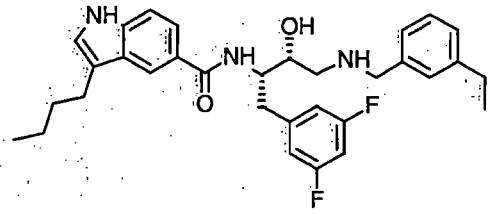
3-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-5-carboxamide

Step 1: 3-Butyl-1H-indole-5-carboxylic acid



To a mixture of Ethyl 3-butyl-1H-indole-5-carboxylate, EXAMPLE SP-225, step2, (0.4 g) in methanol (15 mL) was added 1N NaOH (5 mL). The mixture was stirred at 50 °C for 18 h, cooled to room temperature and poured into 1N HCl (50 mL). The mixture was extracted with ethyl acetate. The ethyl acetate extract was dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure to give 0.145 g of the title compound: MS (ESI+) for $C_{13}H_{15}N_1O_2$ *m/z* 216.12 $(M+H)^+$.

Step 2: 3-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-5-carboxamide



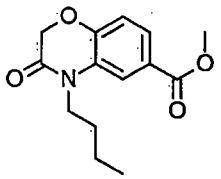
To a mixture of 3-Butyl-1H-indole-5-carboxylic acid (0.145g) in methylene chloride (15 mL) was added triethylamine (0.068 g), and HATU (0.255 g). The mixture was stirred at room temperature for 15 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.224 g) was added. The mixture was stirred at room temperature for 72 h then poured into methylene chloride (50 mL), washed with water then saturated sodium bicarbonate, dried over anhydrous magnesium sulfate and concentrated under

vacuum. Column chromatography on silica gel (100 mL) using 5% methanol in methylene chloride with 0.15% HOAc as eluent to give 0.247 g of the title compound: MS (ESI+) for $C_{32}H_{37}F_2N_3O_2$ *m/z* 534.3 $(M+H)^+$.

EXAMPLE SP-227

4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

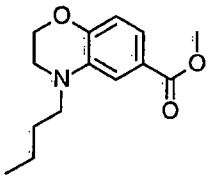
Step 1: Methyl 4-butyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate



To an ice-cold, stirred solution of methyl 3-amino-4-hydroxybenzoate (3.0 g) and sodium bicarbonate (3.3 g) in 1:1 isobutyl methyl ketone/water (40 mL) was added chloroacetyl chloride (1.7 mL), and the mixture was stirred for 1 h. The mixture was warmed to room temperature and refluxed for 14 h, cooled to room temperature, diluted with chloroform, and separated. The organic layer was washed with water, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) afforded a phenoxazine 3.2 g as a white solid, which was used without further purification or characterization. To a solution of phenoxazine from step 1 (700 mg) and potassium carbonate (934 mg) in methanol (8 mL) was added bromobutane (1.8 mL), and the mixture was refluxed for 6 d. The mixture was cooled to room temperature, concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and water. The organic layer washed with brine, dried (magnesium sulfate),

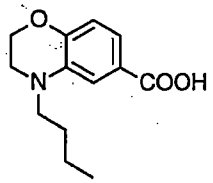
filtered, and concentrated under reduced pressure to afforded 800 mg of the title compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.68, 7.02-6.99, 4.66, 4.00-3.92, 1.69-1.64, 1.46-1.38, 1.01-0.95.

Step 2: Methyl 4-butyl-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate



A solution of methyl 4-butyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (800 mg) and 9-BBN (1.6 g) in tetrahydrofuran (13 mL) was refluxed for 1.5 h. The mixture was cooled to room temperature, ethanolamine (0.4 mL) was added, and the resulting solution was concentrated under reduced pressure. The residue was washed with hexanes, filtered, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (silica, 25% ethyl acetate/hexanes) afforded 607 mg of the title compound: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.21, 7.16, 6.75, 4.24-4.21, 3.78, 3.34-3.24, 1.55-1.47, 1.38-1.30, 0.95-0.90.

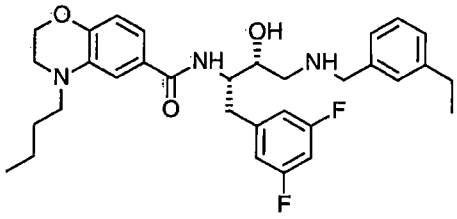
Step 3: 4-Butyl-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylic acid



To a stirred solution of methyl 4-butyl-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (412 mg) in methanol (5 mL) was added 1 M potassium hydroxide (17 mL). The mixture was stirred at room temperature for 5 h and concentrated under reduced pressure. The residue was diluted with water and

washed with ethyl acetate. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with chloroform (4 x 50 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 384 mg of the title compound: ESI MS *m/z* 236 $[M + H]^+$.

Step 4: 4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

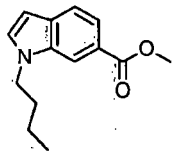


A solution of 4-Butyl-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylic acid (43 mg), HATU (104 mg), HOBt (37 mg), and diisopropylethylamine (47 □L) was stirred in methylene chloride (1.0 mL) for 15 min. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (62 mg) and diisopropylethylamine (47 □L) in methylene chloride (1.0 mL) was added and the reaction mixture was stirred overnight. The mixture was diluted with methylene chloride, washed with 1 N hydrochloric acid (15 mL), saturated sodium bicarbonate (15 mL), and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided 15 mg of the title compound: APCI MS *m/z* 552 $[M + H]^+$.

EXAMPLE SP-228

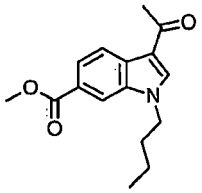
3-acetyl-1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide

Step 1. Methyl 1-butyl-1H-indole-6-carboxylate



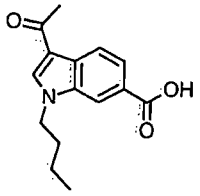
Methyl 1H-indole-6-carboxylate (4.17g) was dissolved in DMSO (30 mL), and potassium *tert*-butoxide (2.93 g) was added. The mixture was stirred for ten min at room temperature. Iodobutane (3.0 mL) was added. The mixture was allowed to stir for three additional hours. The mixture was partitioned between ethyl acetate and water and brine, dried over sodium sulfate, filtered, and concentrated to give methyl 1-butyl-1H-indole-6-carboxylate (4.53 g). MS (ESI+) for $C_{14}H_{17}NO_2+H_1$ *m/z* 232.12 $(M+H)^+$.

Step 2. Methyl 3-acetyl-1-butyl-1H-indole-6-carboxylate



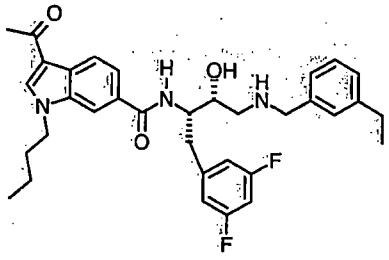
Methyl 1-butyl-1H-indole-6-carboxylate (4.53 g) was dissolved in dichloromethane (25ml). The mixture was cooled to 0 °C. Diethyl aluminum chloride was added dropwise (29.5 mL) and the mixture was allowed to stir at 0 °C for 30 min. A solution of dichloromethane (25 mL) and acetyl chloride (2.1 mL) was added dropwise, and the mixture was stirred for 2 h at 0 °C. The mixture was then partitioned between dichloromethane, water, and brine, dried over sodium sulfate, filtered, and concentrated. The concentrate was chromatographed on silica gel using ethyl acetate/heptane (40/60) to give methyl 3-acetyl-1-butyl-1H-indole-6-carboxylate (3.38 g). MS (ESI+) for $C_{16}H_{19}N_1O_3+H_1$ *m/z* 274.14 $(M+H)^+$.

Step 3. 3-acetyl-1-butyl-1H-indole-6-carboxylic acid



Methyl 3-acetyl-1-butyl-1H-indole-6-carboxylate (2.00 g) was dissolved in methanol (100mL). Sodium hydroxide (1N) was added until the mixture became slightly cloudy. Methanol was again added (20 mL) until the solution was clear. Sodium hydroxide was again added until the mixture was slightly cloudy. The mixture was allowed to stir at room temperature overnight. The solution was concentrated to half its original volume and hydrochloric acid (2N) was added until the aqueous layer indicated a pH of about one. The mixture was extracted with dichloromethane and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The resulting material was chromatographed on silica gel using MeOH/heptane/dichloromethane (4/20/76) to give 3-acetyl-1-butyl-1H-indole-6-carboxylic acid (1.60 g). MS (ESI+) for $C_{15}H_{17}N_1O_3+H_1$ *m/z* 260.13 $(M+H)^+$.

Step 4. 3-acetyl-1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide



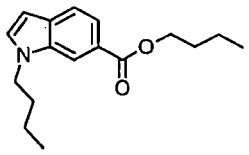
3-Acetyl-1-butyl-1H-indole-6-carboxylic acid (0.322 g) was dissolved in dichloromethane (15 mL). 1,1'-Carbonyldiimidazole was added (0.171 g). The mixture was stirred for 2 h and then a mixture of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.250 g) in dichloromethane (15 mL) was added. After stirring

overnight, the mixture was partitioned between dichloromethane, water, and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel using MeOH/ dichloromethane (4/96) to give 3-acetyl-1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide (0.335 g). MS (ESI+) for $C_{34}H_{39}F_2N_3O_3+H_1$ *m/z* 576.30 $(M+H)^+$.

EXAMPLE SP-229

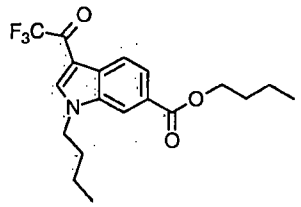
1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(trifluoroacetyl)-1H-indole-6-carboxamide

Step 1. Butyl 1-butyl-1H-indole-6-carboxylate



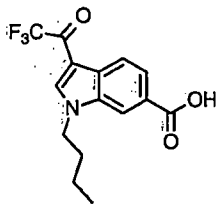
1-Butyl-1H-indole-6-carboxylic acid (0.450 g) was dissolved in dimethyl sulfoxide (10mL). Potassium *tert*-butoxide (0.317 g) was added and the mixture was stirred for 10 min at room temperature. Iodobutane (0.33 mL) was added and the mixture was allowed to stir at room temperature for 6 h. Water was then added and the mixture was partioned between ethyl acetate, water, and brine, and dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography using heptane/dichloromethane (30/70) gave butyl 1-butyl-1H-indole-6-carboxylate (0.429 g). MS (ESI+) for $C_{17}H_{23}NO_2 + H_1$ *m/z* 274.20 $(M+H)^+$.

Step 2. Butyl 1-butyl-3-(trifluoroacetyl)-1H-indole-6-carboxylate



Boron trifluoride-methyl sulfide complex (0.238 g) was dissolved in dichloromethane (10 mL). The solution was cooled to -78 °C and a solution of trifluoroacetic anhydride (0.384 g) in dichloromethane (2 mL) was added. The mixture was stirred at -78 °C for 10 min, at which time a solution of butyl 1-butyl-1H-indole-6-carboxylate (0.250 g) in dichloromethane (3 mL) was added. The mixture was allowed to stir at -78 °C for 15 min and then allowed to warm to room temperature overnight. The mixture was then poured into aqueous sodium bicarbonate and extracted with dichloromethane. The organic layer was dried over sodium sulfate, filtered, and concentrated and the resulting material was chromatographed on silica gel using ethyl acetate/heptane (20/80) to give butyl 1-butyl-3-(trifluoroacetyl)-1H-indole-6-carboxylate (0.302 g). MS (ESI+) for $C_{19}H_{22}F_3N_1O_3+H_1$ *m/z* 370.16 $(M+H)^+$.

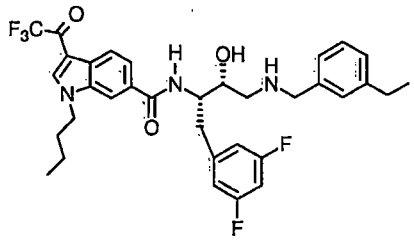
Step 3. 1-butyl-3-(trifluoroacetyl)-1H-indole-6-carboxylic acid



Butyl 1-butyl-3-(trifluoroacetyl)-1H-indole-6-carboxylate (0.277 g), $LiOH•H_2O$ (0.040 g), THF (1.5 mL), water (0.5 mL), and methanol (0.5 mL) were stirred overnight at room temperature. The solvents were then removed under reduced pressure and HCl (2N, 0.5mL) was added to the residue. The residue was extracted with ethyl acetate, dried over magnesium sulfate, filtered, and concentrated. Chromatography on silica

gel using methanol/dichloromethane (6/94) gave 1-butyl-3-(trifluoroacetyl)-1H-indole-6-carboxylic acid (0.166 g). MS (ESI+) for $C_{15}H_{14}F_3N_1O_3+H_1$ *m/z* 314.10 $(M+H)^+$.

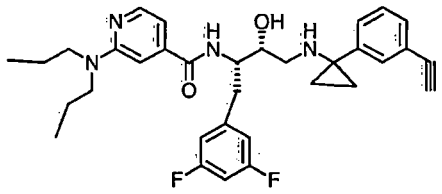
Step 4. 1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(trifluoroacetyl)-1H-indole-6-carboxamide



1-Butyl-3-(trifluoroacetyl)-1H-indole-6-carboxylic acid (0.141 g) was dissolved in dichloromethane (10 mL). 1,1'-Carbonyldiimidazole (0.080 g) was added and the mixture was stirred at room temperature for 2 h. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.166 g) in dichloromethane was added and the mixture was allowed to stir overnight at room temperature. The mixture was then partitioned between dichloromethane and water, dried over sodium sulfate, filtered, and concentrated. Chromatography on silica gel using methanol/ethyl acetate/heptane /dichloromethane (3/10/10/77 to 6/10/10/74) gave 1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(trifluoroacetyl)-1H-indole-6-carboxamide (0.155 g). MS (ESI+) for $C_{34}H_{36}F_5N_3O_3+H_1$ *m/z* 630.28 $(M+H)^+$.

EXAMPLE SP-230

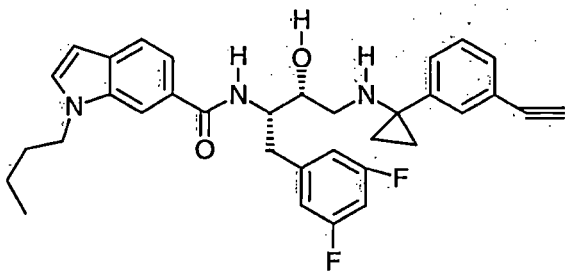
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-2-(dipropylamino)isonicotinamide



2-(Dipropylamino)isonicotinic acid (0.206 g) was dissolved in dichloromethane (10 mL). 1,1'-Carbonyldiimidazole was added (0.142 g) and the mixture was stirred for 2 h at room temperature, at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[1-(3-ethynylphenyl)cyclopropyl]amino}butan-2-ol (0.284 g) in dichloromethane was added. The mixture was allowed to stir overnight and then was partitioned between dichloromethane, water, and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The concentrate was chromatographed on silica gel using methanol/dichloromethane (4/96) to give N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-2-(dipropylamino)isonicotinamide (0.268g). MS (ESI+) for $C_{33}H_{38}F_2N_4O_2+H_1$ *m/z* 561.30 $(M+H)^+$.

EXAMPLE SP-231

1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-1H-indole-6-carboxamide



In the same manner as for N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-2-(dipropylamino)isonicotinamide, 1-butyl-1H-indole-6-carboxylic acid (0.119 g) gave 1-butyl-N-((1S,2R)-1-

(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-1H-indole-6-carboxamide (0.076g). MS (ESI+) for $C_{34}H_{35}F_2N_3O_2+H_1$ *m/z* 556.28 $(M+H)^+$.

EXAMPLE SP-231

3-(allylthio)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide

Step 1. 3-(Allylthio)benzoic acid

3-Thiobenzoic acid (Aldrich, 4.3g, 28mmol) was dissolved in THF (100mL), cooled to 0°C, and treated with KO-tBu (6.3g, 56mmol), followed by allyl bromide (2.4mL, 28mmol). The solvent was removed from the reaction mixture and the residue was partitioned between 3M HCl and EtOAc. The organic layer was separated, dried ($MgSO_4$) and concentrated to give the title compound (5.3g). (LRMS (M-H) m/z 193.2)

Step 2. 3-(allylthio)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide

3-(Allylthio)benzoic acid (717mg, 3.69mmol), (2R,3R)-3-amino-4-(3,5-difluorophenyl)-1-{[1-(3-ethylphenyl)cyclopropyl]amino}butan-2-ol (247mg, 0.685mmol), and HATU (Aldrich, 2.1g, 5.54mmol) were dissolved in dichloromethane (35mL), at ambient temperature, and treated with diisopropylethylamine (1.6mL, 9.225mmol). Upon completion, the reaction mixture was concentrated and chromatographed (SiO2, 2:1 to 1:1 Hexanes: EtOAc) to give the desired compound (650mg). (LRMS (M+H) m/z =537.8)

EXAMPLE SP-232

3-(allylsulfinyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide

3-(allylthio)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide (325mg, 0.606mmol) was dissolved in CH_2Cl_2 (10mL) and AcOH (1mL)and treated with mCPBA (104mg, 0.606mmol). The reaction mixture was stirred for 2.5h, at which time more mCPBA (20mg, 0.11mmol) was added and stirring continued for 30 min. more. The organic layer was diluted with Et_2O and washed with 15% sodium thiosulfite solution. The organic was washed with brine, then dried ($MgSO_4$) and concentrated to give an oil, which was chromatographed with 25% to 50%EtOAc in hexanes to give the title compound. (LRMS (M+H) m/z 553.8)

EXAMPLE SP-233

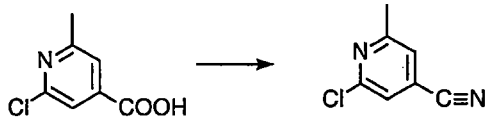
3-(allylsulfonyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide

3-(allylthio)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide (245mg, 0.456mmol) was dissolved in MeOH:H_2O (9:1, 6mL) and treated with oxone (561mg, 0.913mmol). When the reaction was complete, the mixture was concentrated to 0.5x volume and poured onto EtOAc. This was washed with a 15% sodium thiosulfite solution, dried ($MgSO_4$) and concentrated to give the title compound. (LRMS (M+H) m/z 569.8)

EXAMPLE SP-234

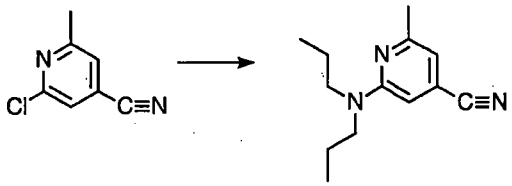
N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylisonicotinamide

Step 1. 2-chloro-6-methylisonicotinonitrile



Using the method of Org. Prep. Proceed. Intern. (1982) 396, 2-chloro-6-methylisonicotinic acid (0.405 g, 2.36 mmol) was converted to 2-chloro-6-methylisonicotinonitrile (0.241 g).

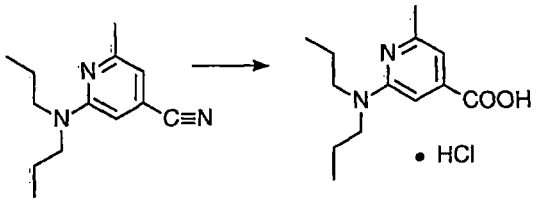
Step 2. 2-(dipropylamino)-6-methylisonicotinonitrile



To 2-chloro-6-methylisonicotinonitrile (0.230 g, 1.51 mmol) was added di-n-propylamine (5 mL). The mixture was heated at 80 °C in a sealed, thick-walled glass vessel for 12 h and then at room temperature for 17 h. Excess di-n-

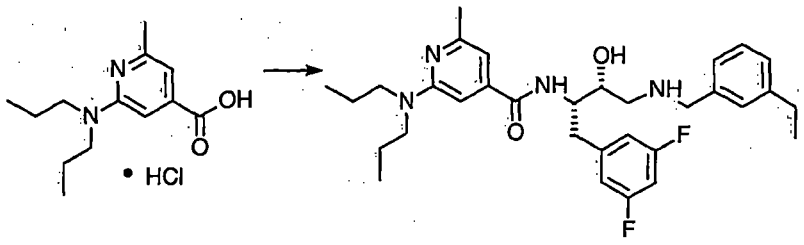
propylamine was removed under reduced pressure and the residue was partitioned between dichloromethane and aq. sodium bicarbonate. After drying over sodium sulfate and concentration, the residue was chromatographed on silica gel using ethyl acetate-hexane (10/90) to give 0.14 g of 2-chloro-6-methylisonicotinonitrile and 0.059 g of 2-(dipropylamino)-6-methylisonicotinonitrile. Using the above conditions, 2-chloro-6-methylisonicotinonitrile (0.14 g) was converted to an additional 0.043 g of 2-(dipropylamino)-6-methylisonicotinonitrile.

Step 3. 2-(dipropylamino)-6-methylisonicotinic acid hydrochloride



To 2-(dipropylamino)-6-methylisonicotinonitrile (0.094 g, 0.433 mmol) was added 4N HCl (2 mL) and THF (1 mL). The mixture was stirred at 100 °C (THF allowed to distill off) for 12 h, then the aqueous layer was removed under reduced pressure and using a toluene azeotrope to give 2-(dipropylamino)-6-methylisonicotinic acid hydrochloride, which was used without further purification in the next step.

Step 4. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylisonicotinamide



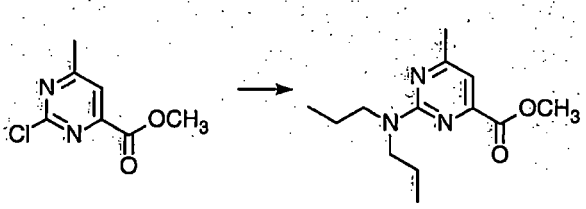
To 2-(dipropylamino)-6-methylisonicotinic acid hydrochloride (approx. 0.4 mmol) in THF (3 mL) was added

triethylamine (0.17 mL), followed by dichloromethane (2 mL) and then CDI (0.071 g, 0.44 mmol). After stirring for 1 h, a mixture of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (0.163 g, 0.400 mmol), triethylamine (0.11 mL), and dichloromethane (approx. 2 mL) was added to the CDI mixture. The mixture was allowed to stir overnight, after which an additional 0.12 mL of triethylamine and 0.045 g of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride was added. After stirring for several more hours, the mixture was partitioned between dichloromethane and aq. sodium bicarbonate. The organic layer was dried with sodium sulfate, concentrated, and the residue was chromatographed on silica gel using MeOH-dichloromethane (5/95) to give 0.04 g of the title compound.

EXAMPLE SP-235

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide

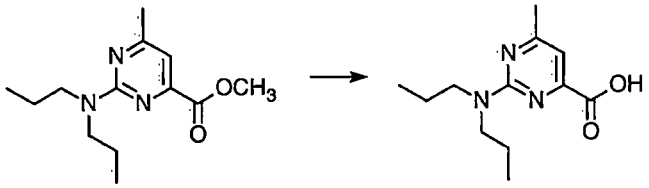
Step 1. methyl 2-(dipropylamino)-6-methylpyrimidine-4-carboxylate



A mixture of methyl 2-chloro-6-methylpyrimidine-4-carboxylate (0.411 g, 2.20 mmol), di-n-propylamine (0.668 g, 6.60 mmol), triethylamine (0.267 g, 2.64 mmol), and THF (5 ml) was stirred at room temperature for 55 min and then at reflux for 1.3 h, at which time is was cooled and partitioned between ethyl acetate and a mixture of brine and aq. sodium bicarbonate. The organic layer was dried over magnesium

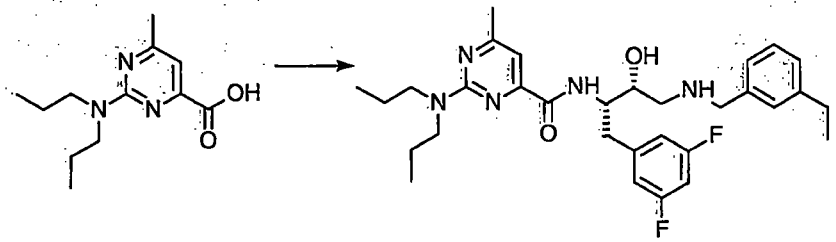
sulfate and concentrated and then chromatographed on silica gel using ethyl acetate-hexane (90/10) to give methyl 2-(dipropylamino)-6-methylpyrimidine-4-carboxylate (0.457 g) as a pale yellow liquid.

Step 2. 35137-ret-135 2-(dipropylamino)-6-methylpyrimidine-4-carboxylic acid



To methyl 2-(dipropylamino)-6-methylpyrimidine-4-carboxylate (0.450 g, 1.79 mmol) in MeOH (2 mL), water (1 mL), and THF (1 mL) was added lithium hydroxide monohydrate (0.113 g, 2.68 mmol). The mixture was stirred at room temperature for 1 h and then MeOH and THF were removed under reduced pressure. The pH of the residue was adjusted to approximately 5 and the resulting mixture was extracted with dichloromethane, dried over sodium sulfate, and concentrated to give 2-(dipropylamino)-6-methylpyrimidine-4-carboxylic acid (0.351 g) as a yellow solid.

Step 3. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide



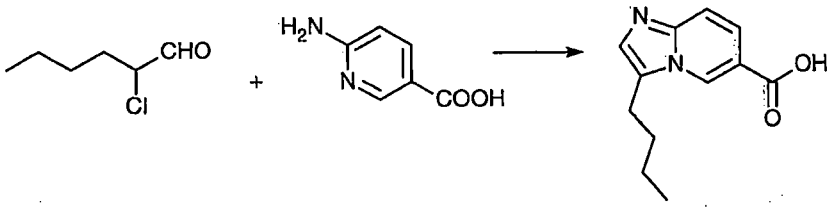
To 2-(dipropylamino)-6-methylpyrimidine-4-carboxylic acid (0.101 g, 0.426 mmol) in THF (0.5 mL) was added 1,1'-carbonyldiimidazole (CDI) (0.076 g, 0.468 mmol). After 50 min the CDI mixture was added to a mixture of (2R,3S)-3-amino-4-

(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (0.173 g, 0.425 mmol) and triethylamine (0.18 mL, 1.28 mmol) in THF (6 mL) and dichloromethane (2 mL). After stirring overnight, the solvents were removed under reduced pressure and the residue was partitioned between dichloromethane, aq. sodium bicarbonate, and aq. sodium bicarbonate-brine mixture. The organic layer was dried over sodium sulfate, concentrated, and the residue was chromatographed on silica gel using MeOH-dichloromethane (5/95) to give 0.199 g of the title compound as a solid.

EXAMPLE SP-236

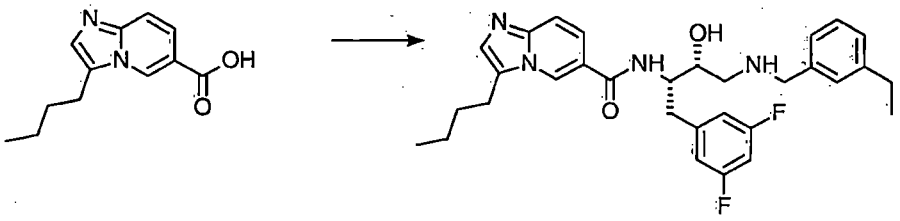
3-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}imidazo[1,2-a]pyridine-6-carboxamide

Step 1. 3-butylimidazo[1,2-a]pyridine-6-carboxylic acid



To hexanal (1.02 g, 10.2 mmol) in 15 mL of isopropyl alcohol-water (4:1 v/v) was added $CuCl_2$ (1.37 g, 10.2 mmol). The mixture was heated at 80 °C for 2.5 h, then cooled. The solids were removed by filtration and the filtrate was added to 6-aminonicotinic acid (1.35 g, 10 mmol). The mixture was stirred overnight at room temperature, then heated at reflux 32 h. After cooling, the solvents were removed under reduced pressure and MeOH was added to the residue. The resulting solid was removed by filtration and the filtrate was concentrated to dryness. MeOH was again added, and the resulting solid removed by filtration. After concentration of the filtrate, the residue was chromatographed on silica gel using MeOH-dichloromethane (33/67) to give 0.26 g of 3-butylimidazo[1,2-a]pyridine-6-carboxylic acid.

3-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}imidazo[1,2-a]pyridine-6-carboxamide

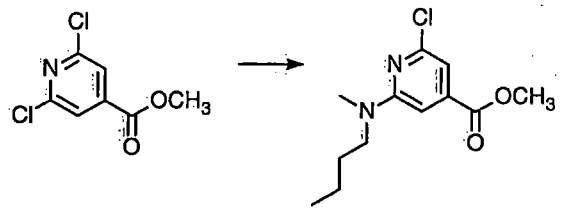


Step 2. In the same manner as for N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide {EXAMPLE S-SP-235}, Step 3, 3-butylimidazo[1,2-a]pyridine-6-carboxylic acid (0.16 g) was converted to 0.30 g of the title compound.

EXAMPLE SP-237

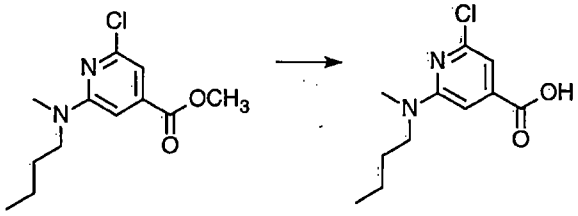
2-[butyl(methyl)amino]-6-chloro-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isonicotinamide

Step 1. methyl 2-[butyl(methyl)amino]-6-chloroisonicotinate



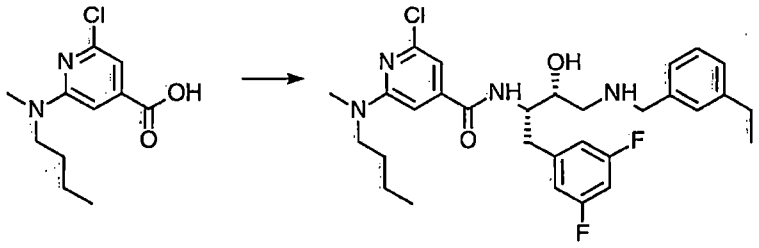
In the same manner as for N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylisonicotinamide {EXAMPLE SP-234, Step 2,} methyl 2,6-dichloroisonicotinate (1.0 g) was converted to methyl 2-[butyl(methyl)amino]-6-chloroisonicotinate (0.87 g).

Step 2. 2-[butyl(methyl)amino]-6-chloroisonicotinic acid



In the same manner as for N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide {EXAMPLE S-2435}, Step 2, methyl 2-[butyl(methyl)amino]-6-chloroisonicotinate (0.17 g) was converted to 2-[butyl(methyl)amino]-6-chloroisonicotinic acid (0.15 g).

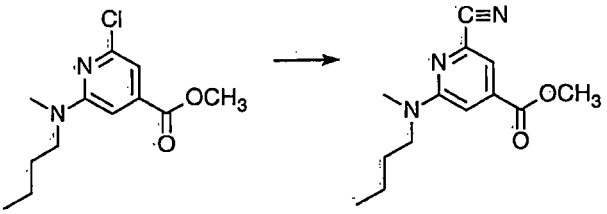
Step 3. 2-[butyl(methyl)amino]-6-chloro-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isonicotinamide



In the same manner as for N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide {EXAMPLE S-2435}, Step 3, 2-[butyl(methyl)amino]-6-chloroisonicotinic acid (0.15 g) was converted to 0.13 g of the title compound.

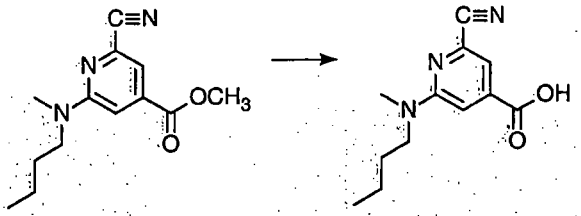
EXAMPLE SP-238
2-[butyl(methyl)amino]-6-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isonicotinamide

Step 1. methyl 2-[butyl(methyl)amino]-6-cyanoisonicotinate



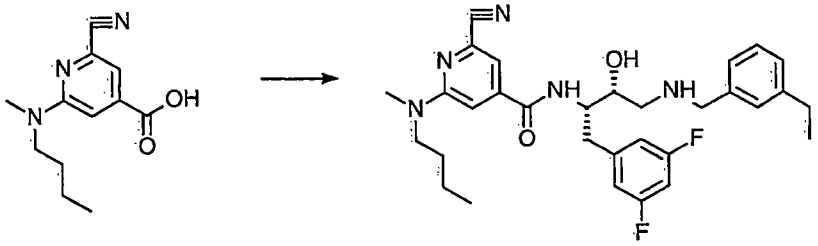
A flask containing methyl 2-[butyl(methyl)amino]-6-chloroisonicotinate (0.306 g, 1.19 mmol), zinc cyanide (0.0839 g, 0.714 mmol), Pd_2dba_3 (0.0218 g, 0.024 mmol), dppf (0.0264 g, 0.048 mmol), and zinc dust (0.0093 g, 0.143 g) was flushed with nitrogen. N-Methylpyrrolidinone (2 mL) was added and the mixture was heated at 120 °C for 2 h, at which time it was cooled and partitioned between ethyl acetate and aq. ammonium hydroxide and brine. The organic layer was dried over magnesium sulfate and concentrated, followed by silica get chromatography using ethyl acetate-hexane (10/90) to give 0.161 g of methyl 2-[butyl(methyl)amino]-6-cyanoisonicotinate.

Step 2. 2-[butyl(methyl)amino]-6-cyanoisonicotinic acid



In the same manner as for N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide {EXAMPLE S-2435}, Step 2 ,methyl 2-[butyl(methyl)amino]-6-cyanoisonicotinate (0.157 g) was converted to 2-[butyl(methyl)amino]-6-cyanoisonicotinic acid (0.151 g).

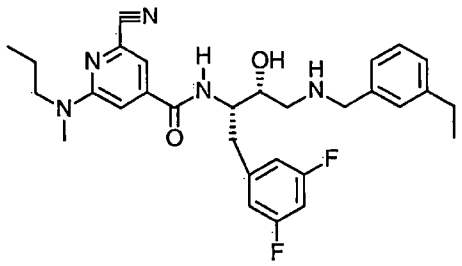
Step 3. 2-[butyl(methyl)amino]-6-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isonicotinamide



In the same manner as for N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide {EXAMPLE S-2435}, Step 3, 2-[butyl(methyl)amino]-6-cyanoisonicotinic acid (0.135 g) was converted to the title compound (0.223 g).

EXAMPLE SP-239

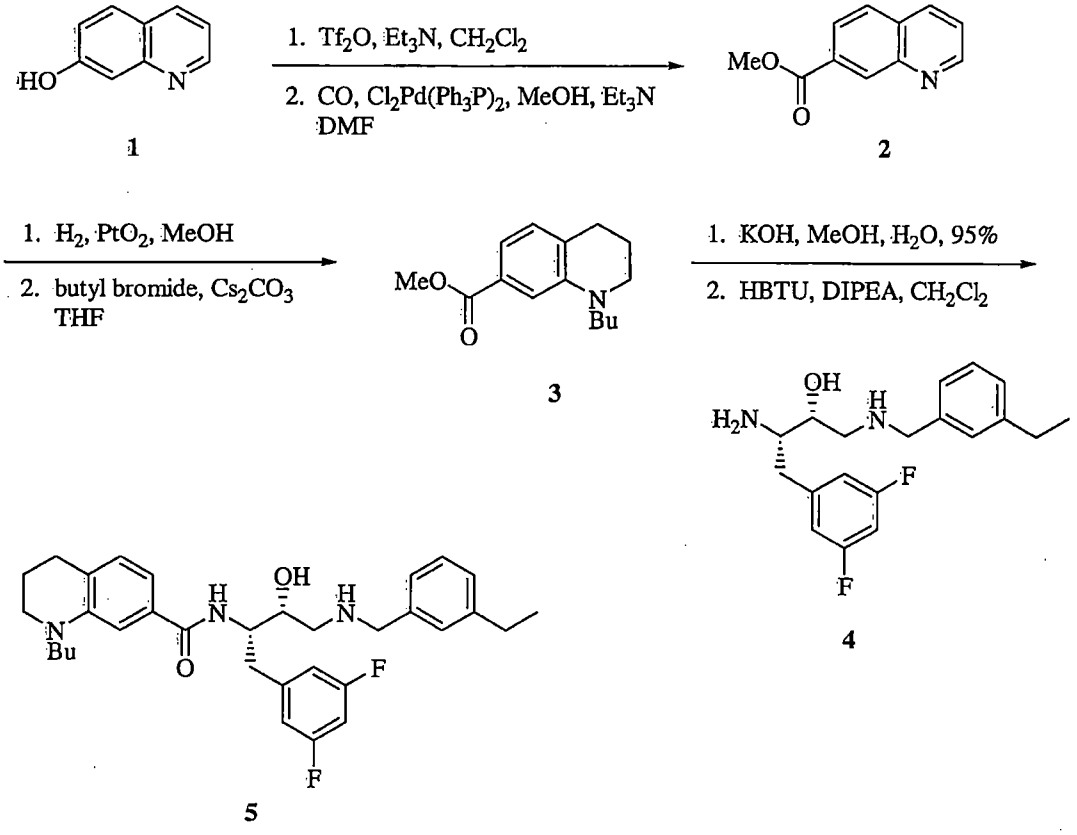
2-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-[methyl(propyl)amino]isonicotinamide



In the same manner as for N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide {EXAMPLE S-2435}, Step 3, 2-cyano-6-[methyl(propyl)amino]isonicotinic acid (0.13 g) gave 0.23 g of the title compound.

EXAMPLE SP-240

Reaction scheme for the preparation of 1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroquinoline-7-carboxamide



1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroquinoline-7-carboxamide

Step 1: To an ice-cold, stirred solution of quinolin-7-ol (1.0 g, 6.9 mmol) and triethylamine (1.0 mL, 7.6 mmol) in methylene chloride (14 mL) was added trifluoromethane sulfonic anhydride (1.3 mL, 7.6 mmol), and the mixture was stirred for 30 min. The mixture was diluted with methylene chloride, washed with saturated sodium bicarbonate, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure provided quinolin-7-yl trifluoroacetate (1.5 g): ESI MS *m/z* 278 $[M + H]^+$.

Step 2: To a stirred solution of quinolin-7-yl trifluoroacetate (750 mg, 2.7 mmol), $PdCl_2(Ph_3P)$ (95 mg, 0.14 mmol), and triethylamine (1.2 mL, 8.4 mmol) in 1:2 DMF/MeOH

(39 mL) was degassed and sparged with CO, and the mixture was heated at 60 °C for 48 h. The mixture was cooled to room temperature, filtered through diatomaceous earth, and concentrated under reduced pressure. The residue was diluted with a 5% solution of LiCl, and washed with $CHCl_3$ (3 x 250 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 3:1 ethyl acetate/hexanes) provided methyl quinoline-7-carboxylate (185 mg): ESI MS *m/z* 188 $[M + H]^+$.

Step 3: A solution of methyl quinoline-7-carboxylate (185 mg, 1.0 mmol) and PtO_2 (20 mg) in methanol (10 mL) was shaken under an atmosphere of hydrogen for 2 h. The reaction mixture was filtered through diatomaceous earth, and concentrated under reduced pressure to provide methyl 1,2,3,4-tetrahydroquinoline-7-carboxylate (189 mg): ESI MS *m/z* 192 $[M + H]^+$.

Step 4: To a stirred solution of methyl 1,2,3,4-tetrahydroquinoline-7-carboxylate (180 mg, 0.94 mmol) and cesium bicarbonate (1.5 g, 4.7 mmol) in THF (2 mL) was added *n*-butyl bromide (1.0 mL, 9.4 mmol), and the reaction mixture was heated at reflux for 48 h. The reaction mixture was cooled to room temperature, and diluted with EtOAc. The organic layer was washed with water, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:3 ethyl acetate/hexanes) afforded methyl 1-butyl-1,2,3,4-tetrahydroquinoline-7-carboxylate (156 mg): ESI MS *m/z* 248 $[M + H]^+$.

Step 5: To a stirred solution of methyl 1-butyl-1,2,3,4-tetrahydroquinoline-7-carboxylate (156 mg, 0.63 mmol) in

methanol (1.3 mL) was added potassium hydroxide (6.3 mL of a 1 M solution in water, 6.3 mmol). The reaction mixture was stirred at room temperature for 48 h and concentrated under reduced pressure. The residue was diluted with water and washed with ethyl acetate. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with chloroform (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) afforded 1-butyl-1,2,3,4-tetrahydroquinoline-7-carboxylic acid (139 mg): ESI MS *m/z* 234 $[M + H]^+$.

Step 6: A solution of 1-butyl-1,2,3,4-tetrahydroquinoline-7-carboxylic acid (134 mg, 0.57 mmol), HBTU (327 mg, 0.86 mmol), and diisopropylethylamine (150 µL, 0.86 mmol) was stirred in methylene chloride (3.0 mL) for 15 min. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (EXAMPLE SP-272) (234 mg, 0.57 mmol) and diisopropylethylamine (150 µL, 0.86 mmol) in methylene chloride (3.0 mL) was added and the reaction mixture was stirred overnight. The reaction mixture was diluted with methylene chloride, washed with 1 N hydrochloric acid (10 mL), saturated sodium bicarbonate (10 mL), and brine. The organic layer was then dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided 1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroquinoline-7-carboxamide (130 mg): ESI MS *m/z* 550 $[M + H]^+$

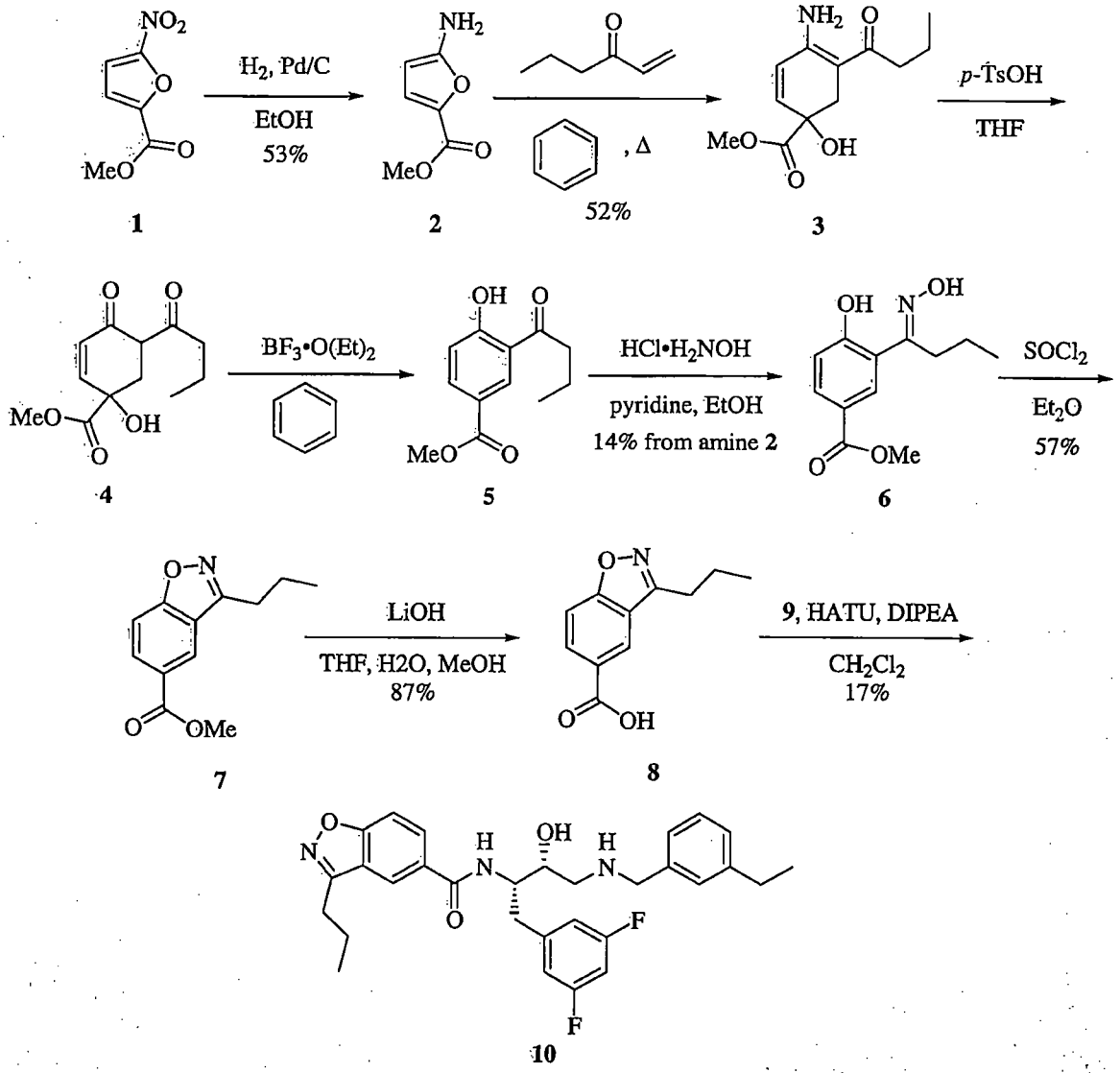
EXAMPLE SP-241

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-propyl-1,2-benzisoxazole-5-carboxamide

General Synthesis of Benzisoxazole

Furan **1** was hydrogenated to afford amine **2**. Diels-Alder reaction of amine **2** and 1-hexen-3-one afforded ketone **3**.[1] Ketone **3** was then treated with *p*-toluenesulfonic acid to afford diketone **4**. Diketone **4** was rearomatized with boron trifluoride to give phenol **5**. Phenol **5** was then converted to oxime **6** with hydroxylamine. Oxime **6** was cyclized with thionyl chloride to afford methyl ester **7**.[2] Methyl ester **7** was then saponified to acid **8**. Coupling of acid **8** and amine **9** in the presence of HATU, provided benzoxazole **10**.

Reaction scheme



N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-propyl-1,2-benzisoxazole-5-carboxamide

Step 1: A mixture of methyl 5-nitro-2-furoate (13 g, 76 mmol) and 10% Pd/C (1.3 g) in ethanol (150 mL) was shaken under an atmosphere of hydrogen at 40 psi for 18 h. The reaction mixture was filtered through diatomaceous earth and concentrated under reduced pressure to afford a crude oil. Purification by flash column chromatography (silica, 1:1 hexanes/ethyl acetate) provided methyl 5-amino-2-furoate (5.6 g): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11-7.10 (m, 1H), 5.31-5.29 (m, 1H), 4.31 (br s, 2H), 3.84 (s, 3H).

Step 2: A stirred solution of methyl 5-amino-2-furoate (1.4 g, 10 mmol) and 1-hexen-3-one (7 mL, 60 mmol) in benzene (50 mL) was heated to reflux for 2 h. The reaction mixture was concentrated under reduced pressure to afford a crude oil. Purification by flash column chromatography (silica, 2:1 hexanes/ethyl acetate) provided methyl 4-amino-5-butyryl-1-hydroxycyclohexa-2,4-diene-1-carboxylate (1.25 g): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.26-6.23 (m, 1H), 6.09-6.05 (m, 1H), 3.80 (s, 3H), 3.02-2.96 (m, 1H), 2.89-2.84 (m, 1H), 2.42-2.37 (m, 2H), 1.64-1.57 (m, 2H), 0.96-0.88 (m, 3H).

Step 3: To a stirred solution of methyl 4-amino-5-butyryl-1-hydroxycyclohexa-2,4-diene-1-carboxylate (1.25 g, 5.2 mmol) in a 1:1 mixture of water/tetrahydrofuran (10 mL) was added *p*-toluenesulfonic acid monohydrate (1.1 g, 5.8 mmol). The reaction mixture was stirred for 18 h and then partitioned between dichloromethane and water. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford methyl 5-butyryl-1-hydroxy-4-oxocyclohex-2-ene-1-carboxylate which was used without further purification or characterization.

Step 4: To a stirred solution of methyl 5-butyryl-1-hydroxy-4-oxocyclohex-2-ene-1-carboxylate in benzene was added $BF_3 \cdot O(Et)_2$ (1.3 mL, 10 mmol). The mixture was stirred for 0.25 h and then quenched with saturated sodium bicarbonate followed by extraction with dichloromethane. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford methyl 3-butyryl-4-hydroxybenzoate which was used without further purification or characterization.

Step 5: A stirred solution of methyl 3-butyryl-4-hydroxybenzoate, pyridine (3.7 mL, 46 mmol), and hydroxylamine

hydrochloride (3.55 g, 51 mmol) in ethanol (30 mL) was heated reflux for 2 h. The mixture was concentrated under reduced pressure and partitioned between water and ethyl acetate. The organic layer was washed with 1 N hydrochloric acid, saturated sodium bicarbonate, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford a crude oil. Purification by flash column chromatography (silica, 10:1 hexanes/ethyl acetate) provided methyl 4-hydroxy-3-[(1E)-N-hydroxybutanimidoyl]benzoate (170 mg): ^{1}H NMR (500 MHz, CD_3OD): δ 8.30-8.28 (m, 1H), 7.85-7.82 (m, 1H), 6.92-6.89 (m, 1H), 3.88 (s, 3H), 2.87-2.84 (m, 2H), 1.67-1.60 (m, 2H), 1.05-1.00 (m, 3H).

Step 6: To an ice-cold stirred solution of methyl 4-hydroxy-3-[(1E)-N-hydroxybutanimidoyl]benzoate (170 mg, 0.7 mmol) in diethyl ether (5 mL) was added a mixture of thionyl chloride (60 μL, 0.8 mmol) and pyridine (580 μL, 7.2 mmol) in diethyl ether (5 mL). After 2.5 h the mixture was poured over ice-water and acidified to pH = 1 with 1 N hydrochloric acid. The mixture was then partitioned between water and ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford a crude oil. Purification by flash column chromatography (silica, 10:1 hexanes/ethyl acetate) provided methyl 3-propyl-1,2-benzisoxazole-5-carboxylate (90 mg): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36-8.35 (m, 1H), 8.07-8.04 (m, 1H), 7.52-7.49 (m, 1H), 3.95 (s, 3H), 2.96-2.91 (m, 2H), 2.00-1.87 (m, 2H), 1.09-1.04 (m, 3H).

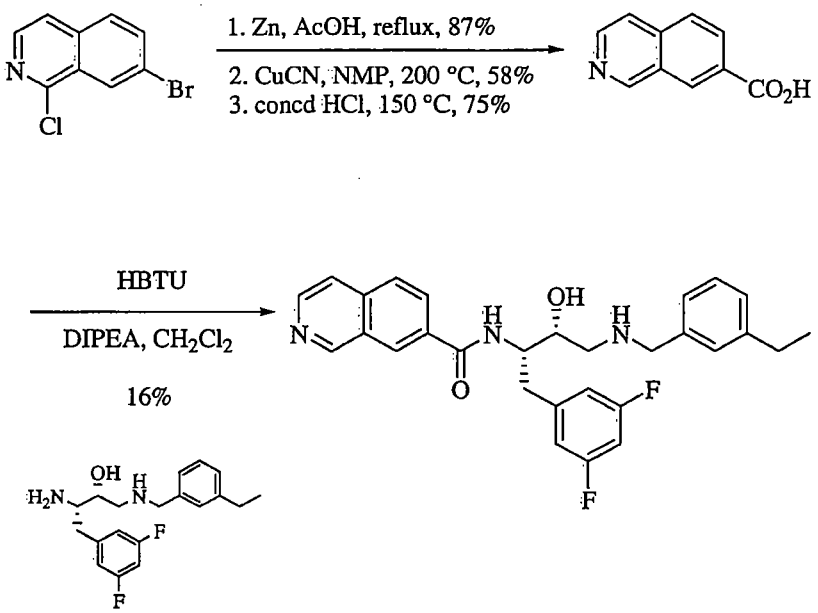
Step 7: To a solution of methyl 3-propyl-1,2-benzisoxazole-5-carboxylate (90 mg, 0.4 mmol) in a 2:1:1 mixture of tetrahydrofuran, water, and methanol (4 mL) was added lithium hydroxide (50 mg, 1.2 mmol) and the resulting reaction mixture

stirred at room temperature for 2.5 h. The reaction mixture was concentrated under reduced pressure, and partitioned between water and ethyl ether. The aqueous layer was washed twice with ether and acidified to pH 1 with 6 M hydrochloric acid. The resulting aqueous layer was extracted with ethyl acetate, dried (sodium sulfate), and concentrated under reduced pressure to afford 3-propyl-1,2-benzisoxazole-5-carboxylic acid (73 mg): ^{1}H NMR (300 MHz, CD_3OD): δ 8.28-8.27 (m, 1H), 8.09-8.06 (m, 1H), 7.64-7.61 (m, 1H), 2.99-2.94 (m, 2H), 1.96-1.86 (m, 2H), 1.08-1.02 (m, 3H).

Step 8: To a stirred solution of 3-propyl-1,2-benzisoxazole-5-carboxylic acid (70 mg, 0.3 mmol) and HATU (130 mg, 0.3 mmol) in methylene chloride (5 mL) was added *N,N*-diisopropylethylamine (110 µL, 0.6 mmol). In a separate flask, *N,N*-diisopropylethylamine (110 µL, 0.6 mmol) was added to (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (EXA xxx) (140 mg, 0.3 mmol) in methylene chloride (2 mL). This solution was added to the above solution containing the acid and the resulting reaction mixture was stirred at room temperature for 18 h. The reaction mixture was partitioned between methylene chloride and water. The organic layer was washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford a crude oil. Purification by flash column chromatography (silica, gradient 97:3 to 94:6 methylene chloride/methanol) provided N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-propyl-1,2-benzisoxazole-5-carboxamide (30 mg). ESI-MS *m/z* 522 $[M + H]^+$

EXAMPLE SP-242

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isoquinoline-7-carboxamide dihydrochloride



Step 1: A solution of 7-bromo-1-chloroisoquinoline (2.50 g, 10.3 mmol) and activated zinc (1.40 g, 21.65 mmol) in acetic acid (20 mL) was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 7-bromoisoquinoline (1.86 g): ESI MS *m/z* 208 $[M + H]^+$.

Step 2: A solution of 7-bromoisoquinoline (1.80 g, 8.65 mmol) and cuprous cyanide (1.16 g, 12.97 mmol) in *N*-methyl pyrrolidinone (17 mL) was heated to 200 °C for 2 h. The reaction mixture was cooled to room temperature and partitioned between ethyl acetate and water. The aqueous phase was back-extracted with additional ethyl acetate and the combined organic layers were washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield 7-cyano-isoquinoline (770 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.70 (d, *J* = 5 Hz, 1H),

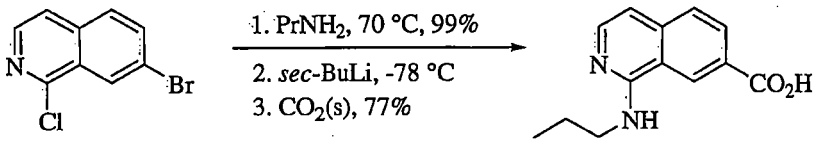
8.40 (s, 1H), 7.95 (d, J = 8 .Hz, 1H), 7.84 (d, J = 8 Hz, 1H), 7.73 (d, J = 5 Hz, 1H); ESI MS m/z 155 $[M + H]^+$.

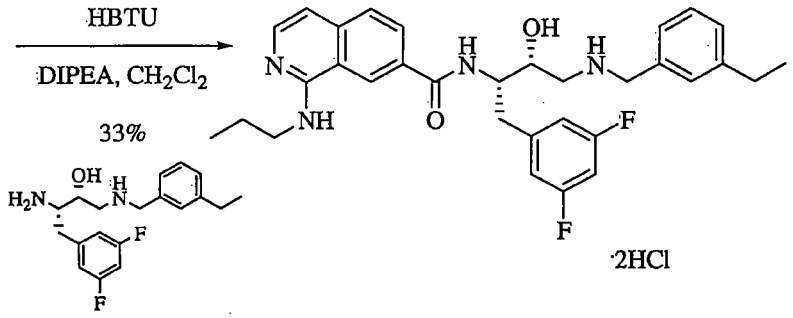
Step 3: A solution of 7-cyanoisoquinoline (770 mg, 5.0 mmol) in concentrated hydrochloric acid (25 mL) was heated in a sealed tube to 150 °C for 18 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in water (10 mL) and neutralized to pH 7.0 with concentrated ammonium hydroxide. The solution was vacuum filtered and the filtrate concentrated under reduced pressure to provide isoquinoline-7-carboxylic acid (640 mg): ESI MS m/z 174 $[M + H]^+$.

Step 4: To a stirred solution of isoquinoline-7-carboxylic acid (200 mg, 1.15 mmol) and *N*,*N*-diisopropyl ethylamine (1.20 mL, 6.88 mmol) in methylene chloride (14.0 mL) was added HBTU (438 mg, 1.15 mmol) and the reaction stirred for 0.5 h. (2R,3S)-3-Amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (470 mg, 1.15 mmol) was added in one portion and the reaction mixture was stirred under nitrogen for 18 h. The reaction mixture was then diluted with additional methylene chloride and washed with saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 0-5% methanol/methylene chloride) gave N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isoquinoline-7-carboxamide (100 mg) which was characterized as its bis-HCl salt: mp 142-143 °C; ESI MS m/z 490 $[M + H]^+$

EXAMPLE SP-243

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(propylamino)isoquinoline-7-carboxamide dihydrochloride





Step 1: A solution of 7-bromo-1-chloroisoquinoline in propylamine (15.0 mL) was heated at 70 °C in a sealed tube overnight. The reaction mixture was concentrated under reduced pressure, then dissolved in chloroform and washed with saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield 7-bromo-2-(*N*-propylamino)isoquinoline (820 mg): ESI MS *m/z* 266 $[M + H]^+$.

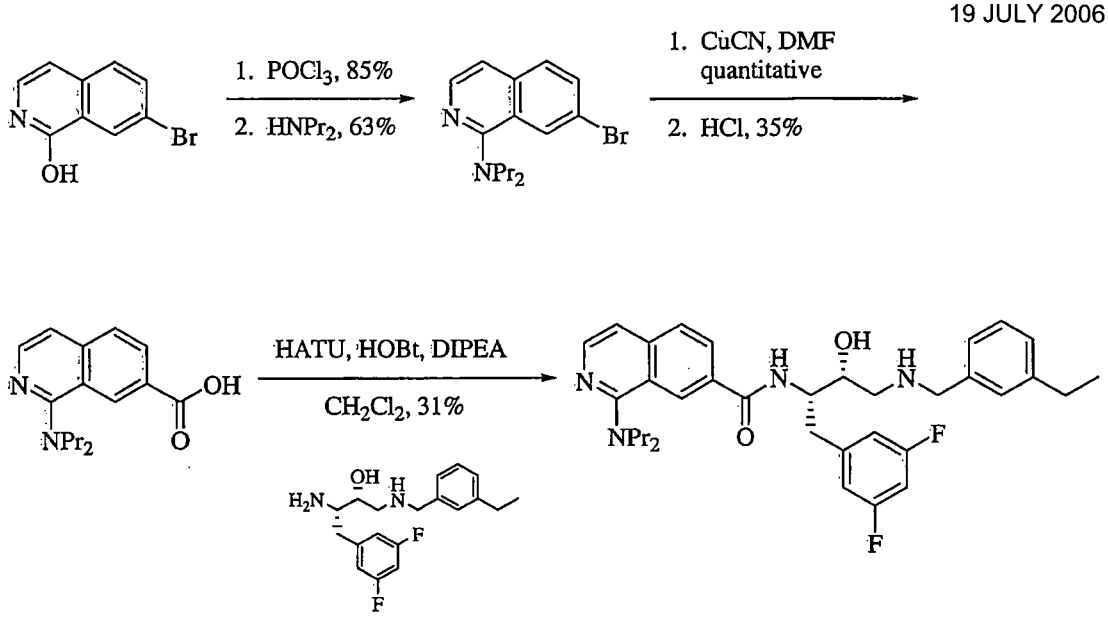
Step 2: A solution of 7-bromo-2-(*N*-propylamino)isoquinoline (200 mg, 0.754 mmol) in anhydrous diethyl ether (1.0 mL) was cooled to -65 °C. To this solution *sec*-butyllithium was added dropwise (1.30 mL of a 1.3 M solution in cyclohexane, 1.69 mmol) and the reaction mixture stirred at -60 °C for 10 min. The reaction mixture was quenched by addition of pulverized dry ice (CO_2) and the reaction allowed to slowly warm to room temperature over 1 h. The resulting solution was acidified

with 1 N hydrochloric acid and the reaction mixture extracted with ethyl acetate (3 x 15 mL). The combined organic phase was washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a brown solid. Purification by flash column chromatography (silica, 66:20:10:4 ethyl acetate/chloroform/methanol/concentrated ammonium hydroxide) gave 1-(propylamino)isoquinoline-7-carboxylic acid (133 mg): ESI MS *m/z* 231 $[M + H]^+$.

Step 3: To a stirred solution of 1-(propylamino)isoquinoline-7-carboxylic acid (81 mg, 0.396 mmol) and *N*,*N*-diisopropyl ethylamine (3.75 μL, 2.16 mmol) in methylene chloride (5.0 mL) was added HBTU (152 mg, 0.396 mmol) and the reaction stirred for 0.5 h. (2R,3S)-3-Amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (150 mg, 0.36 mmol) was added in one portion and the reaction mixture was stirred under nitrogen for 18 h. The reaction mixture was then diluted with additional methylene chloride and washed with saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 0-5% methanol/methylene chloride) gave N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(propylamino)isoquinoline-7-carboxamide (67 mg) which was characterized as its bis-HCl salt: mp 262 °C dec; ESI MS *m/z* 547 $[M + H]^+$

EXAMPLE SP-244

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(dipropylamino)isoquinoline-7-carboxamide



Step 1: A solution of 7-bromoisoquinolin-1-ol (2.5 g, 11.1 mmol) and $POCl_3$ (10.4 mL, 111 mmol) was stirred at 70 °C for 2.5 h. The reaction mixture was cooled to room temperature, poured into ice water, and the solution was stirred overnight. The aqueous mixture was diluted with chloroform, washed with a saturated solution of $NaHCO_3$, saturated NaCl, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 7-bromo-1-chloroisoquinoline (2.3 g): ^1H NMR (300 MHz, DMSO-d_6) δ 8.39-8.36 (m, 2H), 8.09-8.02 (m, 2H), 7.95 (d, J = 6 Hz, 1H).

Step 2: A solution of 7-bromo-1-chloroisoquinoline from step 1 (500 mg, 2.1 mmol) and dipropylamine (2.8 mL, 21 mmol) was heated at 150 °C in a sealed tube for 2 d. The reaction mixture was cooled, and the solvent was removed under reduced pressure to provide 7-bromo-N,N-dipropylisoquinolin-1-amine (400 mg): ^1H NMR (300 MHz, DMSO-d_6) δ 8.55 (s, 1H), 7.90 (d, J = 6 Hz, 1H), 7.75-7.64 (m, 2H), 6.87 (d, J = 6 Hz, 1H), 3.42 (q, J = 7 Hz, 4H), 1.65 (q, J = 7 Hz, 4H), 0.94 (t, J = 7 Hz, 6H).

Step 3: A solution of 7-bromo-N,N-dipropylisoquinolin-1-amine (350 mg, 1.1 mmol) and CuCN (204 mg, 2.2 mmol) in *N,N*-dimethylformamide (2 mL) was stirred at reflux for 24 h. The reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to provide 1-(dipropylamino)isoquinoline-7-carbonitrile (279 mg, which was used without any further characterization.

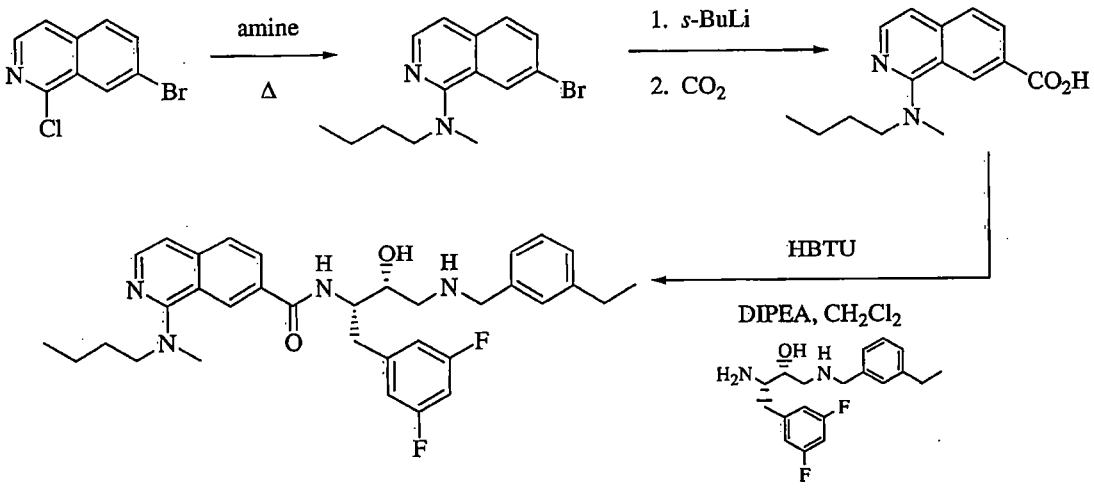
Step 4: A solution of 1-(dipropylamino)isoquinoline-7-carbonitrile from step 3 (279 mg, 1.1 mmol) in concentrated hydrochloric acid (4 mL) was heated at 150 °C in a sealed tube for 14 h. The reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was dissolved in a 25% ammonium hydroxide/water solution and stirred for 1 h. The solution was acidified to pH 4 with concentrated hydrochloric acid, and extracted with chloroform (3 x 50 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide 1-(dipropylamino)isoquinoline-7-carboxylic acid (104 mg): ESI MS *m/z* 273 $[M + H]^+$.

Step 5: To a stirred solution of 1-(dipropylamino)isoquinoline-7-carboxylic acid (103 mg, 0.38 mmol), (2R,3S)-3-Amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (154 mg, 0.38 mmol), HOBt (77 mg, 0.57 mmol), and DIPEA (0.2 mL, 1.1 mmol) in methylene chloride (4 mL) was added HATU (216 mg, 0.57 mmol). The reaction mixture was stirred overnight and then partitioned between methylene chloride and 1 N hydrochloric acid. The organic layer was washed with saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and

concentrated under reduced pressure. Purification by flash column chromatography (silica, 9:1 chloroform/methanol) gave N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(dipropylamino)isoquinoline-7-carboxamide (70 mg): mp: 142-151 °C; APCI MS *m/z* 589 $[M + H]^+$

EXAMPLE SP-244

1-[butyl(methyl)amino]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isoquinoline-7-carboxamide



Step 1: A solution of 7-bromo-1-chloroisoquinoline (750 mg, 3.09 mmol) in *N*-methylbutylamine (7.0 mL) was heated at 65 °C in a sealed tube for 18 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with chloroform and washed with saturated sodium bicarbonate, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a brown oil. Purification by flash column chromatography (silica, 3:1 hexanes/diethyl ether) provided 7-bromo-N-butyl-N-methylisoquinolin-1-amine (730 mg): ESI MS *m/z* 293 $[M + H]^+$.

Step 2: To a -60 °C solution of 7-bromo-N-butyl-N-methylisoquinolin-1-amine (230 mg, 0.78 mmol) in diethyl ether

was added *sec*-butyllithium (1.00 mL of a 1.3 M solution in cyclohexanes, 1.30 mmol). The solution was stirred at -60 °C for 20 min then excess dry ice (CO_2) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was then acidified with 1 N hydrochloric acid and extracted with ethyl acetate. The aqueous phase was concentrated under reduced pressure to yield a yellow oil. Purification by flash column chromatography (silica, 50:30:15:5 ethyl acetate/chloroform/methanol/ammonium hydroxide) provided 1-[butyl(methyl)amino]isoquinoline-7-carboxylic acid (90 mg): ESI MS *m/z* 259 $[M + H]^+$.

Step 3: To a solution of 1-[butyl(methyl)amino]isoquinoline-7-carboxylic acid (130 mg, 0.5 mmol) and *N,N*-diisopropylethylamine (525 µL, 3.0 mmol) in methylene chloride (6.25 mL) was added HBTU (190 mg, 0.5 mmol) and the reaction mixture was stirred for 0.5 h. (2R,3S)-3-Amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (174 mg, 0.42 mmol) was added in one portion and the reaction mixture was stirred at room temperature 18 h. The reaction mixture was diluted with methylene chloride and washed with saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 1-5% methanol in chloroform) gave 1-[butyl(methyl)amino]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isoquinoline-7-carboxamide
(101 mg): mp 120-121 °C; ESI MS *m/z* 575 $[M + H]^+$

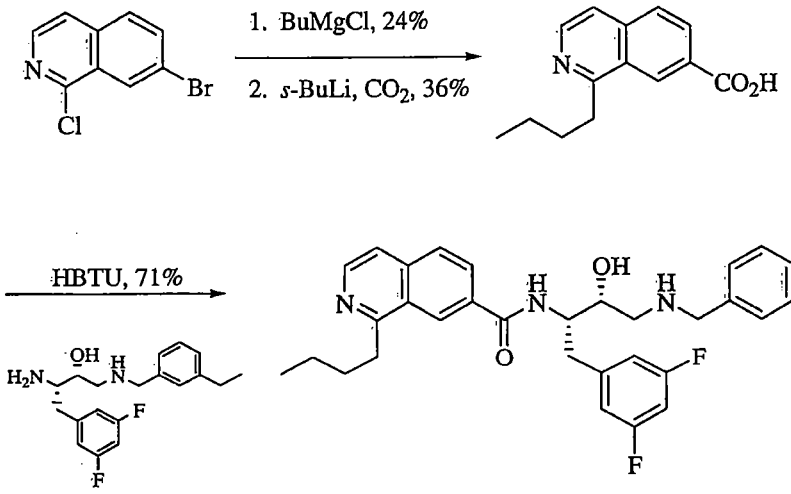
EXAMPLE SP-244

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-[methyl(propyl)amino]isoquinoline-7-carboxamide

was prepared in a manner similar to that outlined above for 1-[butyl(methyl)amino]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2hydroxypropyl}isoquinoline-7-carboxamide. ESI MS *m/z* 561 $[M + H]^+$

EXAMPLE SP-245

1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isoquinoline-7-carboxamide



Step 1: To a refluxing solution of 7-bromo-1-chloroisoquinoline (4.85 g, 23.28 mmol) in diethyl ether (75 mL) was added butylmagnesium chloride (17.8 mL, 2.0 M ether, 35.6 mmol) and the reaction maintained at reflux for 2 h. The reaction mixture was cooled to room temperature, carefully diluted with an equal volume of ethyl acetate, washed with saturated sodium bicarbonate, water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give an brown oil. Purification by flash column chromatography (silica, 1-10% ether/hexanes) gave the desired 7-bromo-1-butylisoquinoline (1.50 g): ESI MS *m/z* 264 $[M + H]^+$.

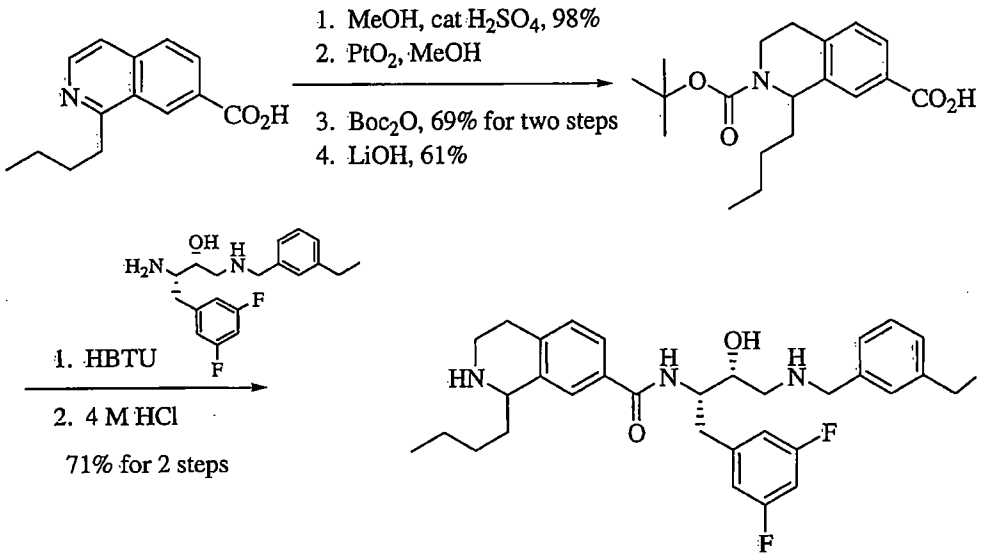
Step 2: To a -60 °C solution of 7-bromo-1-butylisoquinoline prepared in step 1 (940 mg, 3.55 mmol) in diethyl ether (15

mL) was added *sec*-butyl lithium (3.0 mL, 1.3 M cyclohexanes, 3.90 mmol) to yield a dark green solution. The reaction mixture was stirred at -60 °C for an additional 15 minutes at which time carbon dioxide gas was bubbled through the solution for 20 minutes with the aid of a gas dispersion tube. The resulting solution was then allowed to warm to room temperature and concentrated under reduced pressure to yield a pink solid. The residue was partitioned between ethyl acetate and water and then acidified to pH 7 with 1 N hydrochloric acid. The aqueous phase was extracted again with ethyl acetate and the combined organic phases were washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated to yield 1-butylisoquinoline-7-carboxylic acid (299 mg). ESI MS *m/z* 230 $[M + H]^+$.

Step 3: To a solution of 1-butylisoquinoline-7-carboxylic acid (79 mg, 0.26 mmol) and *N,N*-diisopropylethylamine (150 µL, 0.86 mmol) in methylene chloride (1.8 mL) was added HBTU (100 mg, 0.264 mmol) and the reaction mixture stirred for 0.5 h. To this was added a solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (107 mg, 0.264 mmol) in methylene chloride (1.8 mL) containing *N,N*-diisopropylethylamine (150 µL, 0.86 mmol). The reaction mixture was then stirred at room temperature overnight. The reaction mixture was diluted with methylene chloride, washed with saturated sodium bicarbonate, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 93:7 chloroform/methanol) gave 1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isoquinoline-7-carboxamide (103 mg): mp 109-110 °C; ESI MS *m/z* 546 $[M + H]^+$.

EXAMPLE SP-246

1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxamide



Step 1: A solution of 1-butylisoquinoline-7-carboxylic acid (325 mg, 1.41 mmol) in methanol (25 mL) containing concentrated sulfuric acid (800 µL) was refluxed overnight. The reaction mixture was then concentrated under reduced pressure, diluted with methylene chloride, washed with water, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated to yield methyl 1-butylisoquinoline-7-carboxylate (350 mg): ESI MS *m/z* 244 $[M + H]^+$;

Step 2: To a solution of methyl 1-butylisoquinoline-7-carboxylate prepared in step 1 (350 mg, 1.44 mmol) in methanol (6.0 mL) was added platinum(IV) oxide (35 mg) and the reaction mixture stirred under one atmosphere of hydrogen at room temperature overnight. The reaction mixture was concentrated under reduced pressure and redissolved in methylene chloride (15 mL). To this solution was added di-*tert*-butyl dicarbonate

(350 mg, 1.6 mmol), triethylamine (500 µL, 3.11 mmol), 4-dimethylaminopyridine (20 mg, 0.16 mmol), and the reaction mixture stirred at room temperature for 4 h. The reaction mixture was then diluted with methylene chloride, washed with saturated sodium bicarbonate, water, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a colorless oil. Purification by flash column chromatography (silica, 85:15 hexanes/ethyl acetate) yielded 2-tert-butyl 7-methyl 1-butyl-3,4-dihydroisoquinoline-2,7(1H)-dicarboxylate (347 mg)1: ESI MS *m/z* 248 $[M + H]^+$.

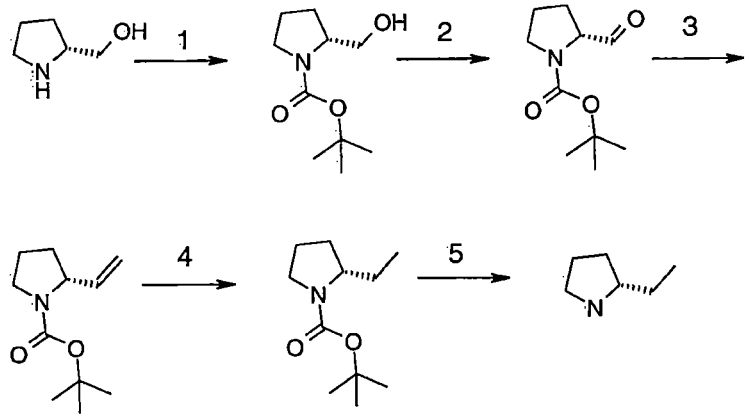
Step 3: To a solution of 2-tert-butyl 7-methyl 1-butyl-3,4-dihydroisoquinoline-2,7(1H)-dicarboxylate prepared in step 2 (347 mg, 1.0 mmol) in 2:1:1 dioxane/methanol/water (6.6 mL) was added lithium hydroxide monohydrate (125 mg, 3.0 mmol) and the reaction mixture stirred 24 h at room temperature. The reaction mixture was concentrated under reduced pressure and the solid residue partitioned between ethyl acetate and water. The aqueous phase was acidified with 1 N hydrochloric acid to pH 1 and extracted several times with 3:1 chloroform/2-propanol. The combined organic phases were washed with water and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 2-(tert-butoxycarbonyl)-1-butyl-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid (205 mg). ESI MS *m/z* 332 $[M - H]^-$.

Step 4: To a solution of 2-(tert-butoxycarbonyl)-1-butyl-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid (205 mg, 0.61 mmol) and *N,N*-diisopropylethylamine (150 µL, 0.86 mmol) in methylene chloride (4.0 mL) was added HBTU (233 mg, 0.61 mmol) and the reaction mixture stirred for 0.5 h. To this was added a solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-

ethylbenzyl)amino]butan-2-ol (250 mg, 0.61 mmol) in methylene chloride (4.0 mL) containing *N,N*-diisopropylethylamine (150 µL, 0.86 mmol). The reaction mixture was then stirred at room temperature overnight. The reaction mixture was diluted with methylene chloride, washed with saturated sodium bicarbonate, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 95:5 chloroform/methanol) gave the desired amide product. The amide was then dissolved in dioxane (5.0 mL) to which was added hydrochloric acid (20 mL, 4.0 M dioxanes, 80 mmol) and the reaction mixture stirred overnight. The reaction mixture was then concentrated to dryness and purified by flash column chromatography (silica, 90:6:3:1 ethyl acetate/chloroform/methanol/ammonium hydroxide) to yield a colorless oil. The oil was partitioned between 3:1 chloroform/2-propanol, washed with water, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated to yield a white solid. The solid was dried under high vacuum at 45 °C in the presence of P_2O_5 to yield 1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxamide(140 mg) characterized as a mixture of diastereomers: mp 121-124 °C; ESI MS *m/z* 550 $[M + H]^+$.

EXAMPLE SP-247

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2S)-2-ethylpyrrolidin-1-yl]carbonyl}-5-methylbenzamide hydrochloride



Step 1: Di-*tert*-butyl-dicarbonate (10.8 g, 49 mmol) was added to an ice-cold solution of R-pyrrolidinemethanol (5.0 g, 49 mmol) and triethylamine (7.6 mL, 55 mmol) in 125 mL of CH_2Cl_2. The resultant solution was warmed to ambient temperature and stirred overnight. The reaction solution was then concentrated, diluted with EtOAc, washed 2X with 1 M KH_2PO_4 and 2X with brine, dried over Na_2SO_4, filtered, and concentrated to afford *tert*-butyl (2R)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (9.9 g).

Step 2: Oxalyl chloride (9.0 mL, 100 mmol) was added to a solution of DMSO (10.5 mL, 150 mmol) in 80 mL of CH_2Cl_2 at -78 °C, under a nitrogen atmosphere. The solution was stirred for 20 min at -78 °C, *tert*-butyl (2R)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (9.9 g, 49 mmol) was added, and the resultant solution stirred at -78 °C for 20 min. Triethylamine (28 mL, 200 mmol) was added to the reaction solution, the dry ice-acetone bath was removed, and the resultant solution was allowed to stir for two hours, slowly warming to ambient temperature. The reaction solution was quenched with brine, the phases were separated, and the organic phase was washed with 1 M KH_2PO_4 and saturated $NaHCO_3$. The organic solution was then dried over Na_2SO_4, filtered, and concentrated to an orange oil. This oil was then dissolved in heptane, filtered through

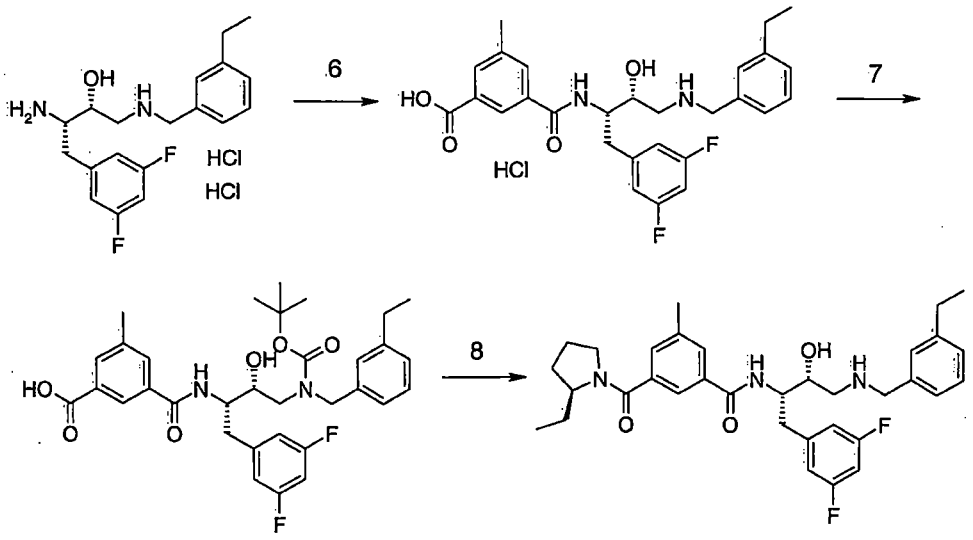
a plug of silica gel eluting with heptane, and the filtrate was concentrated to yield *tert*-butyl (2R)-2-formylpyrrolidine-1-carboxylate (7.87 g).

Step 3: n-Butyl lithium (1.6 M in hexanes) (27 mL, 43 mmol) was added to ice-cold hexamethyldisilazane (9.2 mL, 44 mmol) under a nitrogen atmosphere. The solution was stirred for 10 min and was then added to a suspension of methyl(triphenylphosphonium)bromide (15.5 g, 43 mmol) in 100 mL of THF at ambient temperature. After stirring for 1 h, the mixture was cooled to -78 °C and a solution of *tert*-butyl (2R)-2-formylpyrrolidine-1-carboxylate (7.9 g, 40 mmol) in 50 mL of THF was added. The cold bath was removed and the mixture stirred overnight at ambient temperature. The reaction mixture was then quenched with saturated NH_4Cl, the phases were separated, and the organic phase was washed with saturated NH_4Cl, brine, dried over Na_2SO_4, filtered, and concentrated to give an orange oil. The oil was purified on a Biotage 40M column eluting with heptane to give *tert*-butyl (2R)-2-vinylpyrrolidine-1-carboxylate (5.0 g).

Step 4: To a suspension of palladium (II) hydroxide on activated carbon (20% by wt, 1.2 g) in 10 mL of ethanol was added *tert*-butyl (2R)-2-vinylpyrrolidine-1-carboxylate (2.0 g, 10 mmol) as a solution in 15 mL of ethanol and the mixture was placed under 12 psi of H_2 on a parr hydrogenator overnight. The resultant mixture was then filtered and concentrated to give *tert*-butyl (2S)-2-ethylpyrrolidine-1-carboxylate (1.5 g).

Step 5: To a solution of *tert*-butyl (2S)-2-ethylpyrrolidine-1-carboxylate (1.0 g, 5.0 mmol) in 10 mL of dioxane was added 8 mL of 6N HCl and the resultant solution stirred overnight at ambient temperature. The reaction solution was then

concentrated, turned basic with solid KOH, and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to give (2S)-2-ethylpyrrolidine hydrochloride (0.30 g).



Step 6: A solution of 3-(methoxycarbonyl)-5-methylbenzoic acid (0.48 g, 2.5 mmol), HATU (1.0 g, 2.6 mmol), and HOAt (0.37 g, 2.7 mmol) in 10 mL of dry DMF was stirred for an hour over ice, under a nitrogen atmosphere prior to the addition of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (1.0 g, 2.5 mmol) and DIPEA (1.8 mL, 10 mmol). The solution was stirred overnight at ambient temperature. The reaction solution was then quenched with 1 M HCl, diluted with EtOAc, and the phases were separated. The organic phase was washed with 1 M HCl, the combined acid washings were back-extracted with EtOAc, and the organic phases combined. The combined organic phases were then washed with saturated $NaHCO_3$, brine and dried over Na_2SO_4 The mixture was filtered and concentrated to give the coupled product as an orange oil. This oil was dissolved in 35 mL of MeOH and solid $LiOH{\cdot}H_2O$ (0.6 g, 14 mmol) was added with 2 mL of water. The mixture was stirred overnight at ambient

temperature. The solution was concentrated, diluted with water, neutralized with 1 M HCl, and concentrated. The resulting oily residue was purified on a Biotage 40S column eluting with 5% MeOH in CH_2Cl_2 to give a colorless oil. This was dissolved in 10 mL of MeOH and 3 mL of 1 M HCl in ether was added. The solution was concentrated and the residue triturated with heptane to give 3-[({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)carbonyl]-5-methylbenzoic acid hydrochloride (0.65 g).

Step 7: To a solution of 3-[({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)carbonyl]-5-methylbenzoic acid hydrochloride (0.50 g, 0.94 mmol) and di-tert-butyldicarbonate (0.20 g, 0.92 mmol) in 10 mL of methanol and 10 mL of CH_2Cl_2 was added triethylamine (0.40 mL, 2.9 mmol). The solution was stirred for 2.5 hours at ambient temperature, at which time it was concentrated, partitioned between EtOAc and 1 M KH_2PO_4, and the phases were separated. The organic phase was washed with M KH_2PO_4, dried over Na_2SO_4, filtered, concentrated, and triturated with heptane to give 3-({[(1S,2R)-3-[(tert-butoxycarbonyl)(3-ethylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]amino}carbonyl)-5-methylbenzoic acid (0.50 g).

Step 8: A solution of 3-({[(1S,2R)-3-[(tert-butoxycarbonyl)(3-ethylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]amino}carbonyl)-5-methylbenzoic acid (0.30 g, 0.50 mmol), HATU (0.19 g, 0.50 mmol) and HOAt (0.07 g, 0.51 mmol) in 5 mL of dry DMF under a nitrogen atmosphere was stirred for 15 minutes. A solution of (2S)-2-ethylpyrrolidine hydrochloride (0.05 g, 0.50 mmol) and DIPEA (0.35 mL, 2.0 mmol) in 5 mL of DMF was added. The solution was stirred overnight at ambient temperature. It was then quenched with 1

M HCl, diluted with EtOAc, and the phases were separated. The organic phase was washed with 1 M HCl, saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated to give an orange-brown oil. This oil was purified on a Biotage 40S column eluting with 200 mL of CH_2Cl_2, then 3% MeOH in CH_2Cl_2. The yellow oil obtained was dissolved in 4 mL of CH_2Cl_2 and 4 mL of TFA was added. After stirring for two hours at ambient temperature the reaction solution was concentrated and the residue was purified by reverse phase prep hplc using a 1-inch Kromasil c18 column to give the product as the formic acid salt. This was then converted to the HCl salt by the addition of 2 mL of 1 M HCl in ether. Upon concentration and trituration with heptane N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2S)-2-ethylpyrrolidin-1-yl]carbonyl}-5-methylbenzamide hydrochloride was obtained (0.010 g). MS *m/z* 579.0 [M + H].

EXAMPLE SP-248

The following compounds,

3-{[(2S)-2-butylpyrrolidin-1-yl]carbonyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylbenzamide, MS *m/z* 606.4 [M + H];

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-{[(2S)-2-propylpyrrolidin-1-yl]carbonyl}benzamide formic acid salt, MS *m/z* 638.6 [M + H];

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2R)-2-(2-methoxyethyl)pyrrolidin-1-yl]carbonyl}-5-methylbenzamide, MS *m/z* 608.6[M + H]; and

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2S)-2-ethylpyrrolidin-1-yl]carbonyl}-5-methylbenzamide

hydrochloride; were prepared in a manner similar to that outlined above for EXAMPLE SP-247.

EXAMPLE SP-249

The following compounds;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-methylbenzamide hydrochloride, MS *m/z* 608.3 [M + H];

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-methylbenzamide hydrochloride, MS *m/z* 590.3 [M + H]; and

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-methylbenzamide hydrochloride, MS *m/z* 620.3 [M + H]; were also prepared using the methods disclosed herein.

EXAMPLE SP-250

Preparation of: N-[(1S,2R)-3-{[1-(3-bromophenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide:

Step 1: A stirred solution of N-{(1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiran-2-yl]ethyl}acetamide (4.96 g) and 1-(3-bromophenyl)cyclopropylamine (8.6 g) in 60 mL of *i*-PrOH was heated to 75 °C for 3 h. The cooled solution was evaporated and the residue re-dissolved in ethyl acetate (200 mL). The organic layer was washed with 10 % aqueous HCl (25 mL x 2). The aqueous washings were extracted once with EtOAc (75 mL) and the combined organic layers washed with a saturated solution of NaCl (100 mL). The organic layers were then dried

over Na_2SO_4 and evaporated to yield a residue that was purified by column chromatography to give 5.0 g of tert-butyl (1S,2R)-3-{[1-(3-bromophenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate.

Step 2: To a suspension of tert-butyl (1S,2R)-3-{[1-(3-bromophenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (1.3 g) in 5.0 mL of dichloromethane was added 5.0 mL of trifluoroacetic acid at 23 °C. After stirring for 1 h, 10.0 mL of toluene was added and the solution evaporated. The resulting residue was re-dissolved in toluene and the solution evaporated. This procedure was repeated once more. After drying under high vacuum for 2 h, the residue was suspended in dichloromethane (10.0 mL) and triethylamine (0.5 g) and acetylimidazole (0.3 g) were added. The solution was stirred for 4 h and concentrated under reduced pressure. The residue was purified by column chromatography to yield 0.90 g of the title compound. ES+ found ($M+H^+$): 455.

EXAMPLE SP-251

Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3'-methoxy-1,1'-biphenyl-3-yl)cyclopropyl]amino}propyl)acetamide:

To a solution of N-[(1S,2R)-3-{[1-(3-bromophenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide (0.030 g) in DMF (0.75 mL) was added 3-methoxyphenylboronic acid (0.030 g), Cs_2CO_3 (0.085 g) and $Pd(Ph_3P)_4$. The mixture was heated for 12 h at 90 °C. The cooled solution was diluted with EtOAc (15 mL) and washed with brine (10 mL x 2). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The

resulting residue was purified by column chromatography to give 0.010 g of the title compound. ES+ found ($M+H^+$): 481.

EXAMPLE SP-251

N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-[3'-(hydroxymethyl)-1,1'-biphenyl-3-yl]cyclopropyl}amino)propyl]acetamide, was prepared by the method of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3'-methoxy-1,1'-biphenyl-3-yl)cyclopropyl]amino}propyl)acetamide step 1, using 3-(hydroxymethyl)phenylboronic acid (0.036 g) to give 0.008 g of the title compound. ES+ found ($M+H^+$): 481.

EXAMPLE SP-252A

N-[(1S,2R)-3-{[1-(2'-acetyl-1,1'-biphenyl-3-yl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide was prepared by the method of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3'-methoxy-1,1'-biphenyl-3-yl)cyclopropyl]amino}propyl)acetamide step 1, using 2-acetylphenylboronic acid (0.032 g) to give 0.012 g of the title compound. ES+ found ($M+H^+$): 493.

EXAMPLE SP-252B

N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-({1-[3-(5-formylthien-2-yl)phenyl]cyclopropyl}amino)-2-hydroxypropyl]acetamide was prepared by the method of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3'-methoxy-1,1'-biphenyl-3-yl)cyclopropyl]amino}propyl)acetamide step 1, using 5-formylthien-2-ylboronic acid (0.030 g) to give 0.005 g of the title compound. ES+ found ($M+H^+$): 484.

EXAMPLES 2453A to 2453D

EXAMPLE SP-253A

N^1-{(1S,2R)-1-(cyclopentylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^3,N^3-dipropylisophthalamide hydrochloride;

EXAMPLE SP-253B

N^1-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclopentylmethyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide hydrochloride;

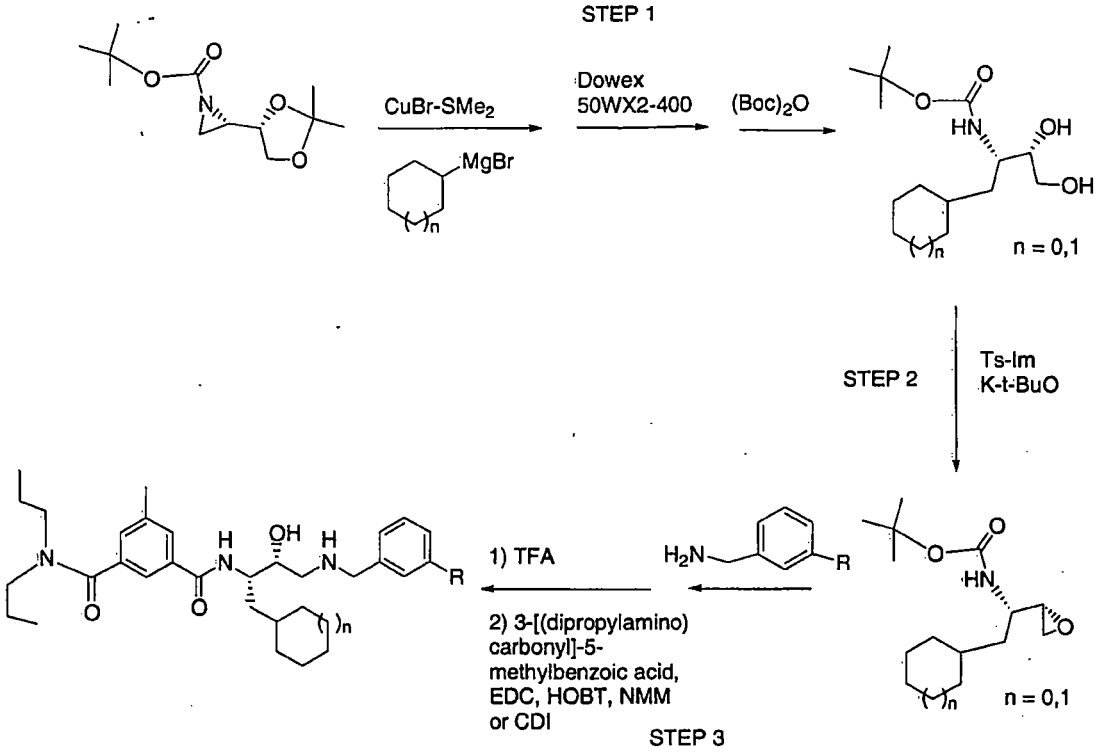
EXAMPLE SP-253C

N^1-{(1S,2R)-1-(cyclohexylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^3,N^3-dipropylisophthalamide hydrochloride;

EXAMPLE SP-253D

N^1-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclohexylmethyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide hydrochloride;

EXAMPLE SP-254A



N^1-{(1S,2R)-1-(cyclopentylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^3,N^3-dipropylisophthalamide hydrochloride (EXAMPLE SP-254) and N^1-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclopentylmethyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide hydrochloride (EXAMPLE SP-255)

Step 1: Cyclopentyl magnesium bromide (8 mL of 2M ethereal solution) was added to cuprous bromide/dimethylsulfide complex (0.33 g, 1.6 mmol) in 10 mL of dry THF cooled to - 25°C under nitrogen. After 20 min, a solution of tert-butyl (2R)-2-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]aziridine-1-carboxylate (1.95 g, 8 mmol) in 4 mL of dry THF was introduced. The mixture was allowed to warm to ambient temperature overnight. It was quenched with saturated aqueous NH_4Cl and extracted with ethyl ether. The organic phase was washed with aqueous saturated NH_4Cl, 1 N $NaHCO_3$, and brine. It was dried over anhydrous Na_2SO_4 and concentrated to 2.38 g of a solid. This material was dissolved in 70 mL of methanol, 12 g of Dowex 50WX2-400 was

added, and the mixture was refluxed for 2 h. The mixture was filtered, washing with methanol and dichloromethane. A clean receiver was attached, and the resin was washed with 100 mL of 1:1 concentrated NH_4OH: ethanol. The filtrate was concentrated to 1.16 g of tan crystals. The crystals were dissolved in 30 mL of dry THF, and 1.5 g (6.9 mmol) of di-t-butyldicarbonate was introduced. The mixture was stirred under nitrogen overnight. It was concentrated, extracted with ether and the ether was washed with several portions of water and brine. Drying over Na_2SO_4 and concentration afforded 1.8 g (6.7 mmol, 84% from tert-butyl (2R)-2-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]aziridine-1-carboxylate) of tert-butyl (1S,2S)-1-[cyclopentylmethy]-2,3-dihydroxypropylcarbamate: ^1H NMR ($CDCl_3$) δ 4.5 (d, 1 H, NH), 3.7 (m, 1 H), 3.6-3.49 (m, 2 H), 3.36 (m, 1 H), 3.26 (t, 1 H, OH), 2.76 (d, 1 H, OH), 1.45 (s, 9 H), 1.88-1.36 (m, 9 H), 1.17-1.08 (m, 2 H).

Step 2: Toluenesulfonyl imidazole (Ts-Im, 2.22 g, 10 mmol) was added to tert-butyl (1S,2S)-1-[cyclopentylmethy]-2,3-dihydroxypropylcarbamate (1.8 g, 6.7 mmol) in 15 mL of dry THF under nitrogen, cooled in an ice bath. To this was added 13.4 mL (13.4 mmol) of a 1M solution of potassium-t-butoxide in THF over 8 min. After 5 min, the ice bath was removed and the orange mixture was stirred for 3 h. It was quenched with 1 N KH_2PO_4 and diluted with ether. The organic phase was washed with 1 N KH_2PO_4, water, and brine. The solution was dried over Na_2SO_4, concentrated, and chromatographed over silica gel, eluting with 5% dichloromethane, 15% ethyl acetate, and 80% heptane. Fraction 4 afforded 900 mg of a 2:1 mixture of tert-butyl (1S)-2-(cyclopentyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate and a side product. Fraction 5 afforded 230 mg of tert-butyl (1S)-2-(cyclopentyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate: ^1H NMR ($CDCl_3$) δ 4.56 (d, 1 H), 3.45 (m, 1 H), 2.85 (m, 1 H), 2.75 (m,

2 H), 1.91 (m, 1 H), 1.8 (m, 2 H), 1.6-1.4 (m, 6 H), 1.44 (s, 9 H), 1.13-1.07 (m, 2 H).

EXAMPLE SP-254B

N^1-{(1S,2R)-1-(cyclopentylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^3,N^3-dipropylisophthalamide hydrochloride

Step 3: To tert-butyl (1S)-2-(cyclopentyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (230 mg, 0.9 mmol) was added 260 mg (1.9 mmol) of m-ethylbenzylamine in 5 mL of isopropanol. The mixture was refluxed for 1.5 h under nitrogen, the solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate. It was washed three times with small portions of 10% HCl, and the aqueous phases were back-extracted with ethyl acetate. The combined organic phases were washed with 1 N $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was partially purified by forming the HCl salt, triturating with pentane, and then neutralizing to the free base (290 mg, 0.74 mmol). To this was added 2 mL of trifluoroacetic acid (TFA) and 2 mL of dichloromethane, and the mixture was stirred under nitrogen for 30 min. It was concentrated to an oil which was dissolved in 2 mL of dry THF and neutralized with 0.2 mL of 4-methyl morpholine. To this mixture was added a solution of 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid (0.2 g, 0.76 mmol) and carbonyldiimidazole (CDI, 0.13 g, 0.8 mmol) in 3 mL of dry THF, which had been stirring together for 35 min. The reaction was stirred under nitrogen overnight. To the mixture was added 1 N KH_2PO_4 and ethyl acetate. The organic phase was washed with 1 N KH_2PO_4, 1 N $NaHCO_3$ (2X) and brine, dried over Na_2SO_4, and concentrated. Chromatography over silica gel, eluting with 6% methanol (containing 1% NH_4OH) in dichloromethane afforded 109 mg (0.19 mmol) of N^1-{(1S,2R)-1-(cyclopentylmethyl)-3-[(3-

ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^3,N^3-dipropylisophthalamide hydrochloride (EXAMPLE SP-254) after formation of the salt with ethereal HCl: CI MS *m/z* 536 $[M+H]^+$.

EXAMPLE SP-255

N^1-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclopentylmethyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide hydrochloride

Step 3: The fraction containing tert-butyl (1S)-2-(cyclopentyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (*ca.* 2 mmol) and a side product, described in the above example, was reacted with m-bromobenzylamine (10 mmol) in 12 mL of isopropanol at reflux for 3 h. The solvent was removed and the residue was dissolved in ethyl acetate. This was washed with several portions of 10% HCl, 1 N $NaHCO_3$, and brine, dried (Na_2SO_4), concentrated. Chromatography on silica gel, eluting with dichloromethane, then up to 2% of methanol (containing 1% NH_4OH) in dichloromethane afforded 523 mg (1.19 mmol, 60% based on epoxide) of the oily addition product. This material (0.31 g, 0.7 mmol) was dissolved in 2 mL of dichloromethane, and 1 mL of TFA was added. After 1 h it was concentrated, dissolved in ethyl acetate, neutralized with 1 N $NaHCO_3$, washed with brine, and concentrated to the free base. To this was added 4 mL of dry THF and a pre-mixed (for 2 h) solution of 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid (190 mg, 0.72 mmol) and CDI (120 mg, 0.74 mmol) in 3 mL of dry THF.
After 2 days the reaction was quenched with 1 N KH_2PO_4 and dissolved in ethyl acetate.
The organic phase was washed with 1 N KH_2PO_4, 1 N $NaHCO_3$ (2X) and brine, dried over Na_2SO_4, and concentrated. Chromatography over silica gel, eluting with 5% methanol (containing 1% NH_4OH) in dichloromethane afforded 184 mg (0.29 mmol) of N^1-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclopentylmethyl)-2-

hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide hydrochloride EXAMPLE SP-255 as a white solid after formation of the salt with ethereal HCl: CI MS *m/z* 586 $[M+H]^+$.

N^1-{(1S,2R)-1-(cyclohexylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^3,N^3-dipropylisophthalamide hydrochloride (EXAMPLE SP-256) and N^1-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclohexylmethyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide hydrochloride (EXAMPLE SP-257)

Step 1: Cyclohexyl magnesium bromide was prepared by adding cyclohexyl bromide (2.46 mL, 20 mmol) to magnesium turnings (0.97 g, 40 mmol) in dry THF (20 mL) and refluxing for 1.5 h. Following the procedures described in step 1 for the previous EXAMPLE S-tert-butyl (1S,2S)-1-[cyclohexylmethy]-2,3-dihydroxypropylcarbamate was obtained as 1.66 g (5.8 mmol, 70% from tert-butyl (2R)-2-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]aziridine-1-carboxylate) of a slightly yellow oil which solidified on standing: ^{1}H NMR ($CDCl_3$) δ 4.43 (d, 1 H, NH), 3.69 (m, 1 H), 3.59 (m, 2 H), 3.32 (m, 1 H), 3.24 (t, 1 H, OH), 2.70 (d, 1 H, OH), 1.45 (s, 9 H), 1.8-1.13 (m, 11 H), 1.01 (m, 1 H), 0.87 (m, 1 H).

Step 2: tert-Butyl (1S,2S)-1-[cyclohexylmethy]-2,3-dihydroxypropylcarbamate (1.6 g, 5.5 mmol) was reacted with Ts-Im (1.5 g, 6.75 mmol) and potassium t-butoxide (11 mL of a 1 M solution in THF) in 20 mL of dry THF according to the procedure described in step 2 for the preceding example. Chromatography on silica gel, eluting with 5% dichloromethane and 5%, increasing to 15% ethyl acetate in heptane afforded 456 mg 1.7 mmol, of tert-butyl (1S)-2-(cyclohexyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate: ^{1}H NMR ($CDCl_3$) δ 4.41 (m, 1 H),

3.55 (m, 1 H), 2.84 (m, 1 H), 2.75 (m, 2 H), 1.8-1.6 (m, 4 H), 1.45 (s, 9 H), 1.4-1.1 (m, 7 H), 0.98 (m, 1 H), 0.86 (m, 1H).

EXAMPLE SP-256

N^1-{(1S,2R)-1-(cyclohexylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^3,N^3-dipropylisophthalamide hydrochloride

Step 3: tert-Butyl (1S)-2-(cyclohexyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (225 mg, 0.84 mmol) was refluxed with m-ethyl benzylamine (254 mg, 1.9 mmol) in 5 mL of isopropanol under nitrogen for 1.5 h, the solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate. It was washed three times with small portions of 10% HCl, and the aqueous phases were back-extracted with ethyl acetate. The combined organic phases were washed with 1 N $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The resulting oil (300 mg) was dissolved in 2 mL of dichloromethane and 2 mL of TFA and stirred for 30 min. It was concentrated, and by weight determined to contain 4 eq. of TFA. This was dissolved in 2 mL of dry THF, and 0.4 mL (3.6 mmol) of 4-methyl morpholine was added. This was cooled to - 30°C, and a mixture of 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid (238 mg, 0.9 mmol) and CDI (165 mg, 1 mmol) in 3 mL of dry THF, which had previously been stirred together for 1 h at room temperature, was added. The mixture was allowed to warm to ambient temperature. After 3 days the reaction was quenched with 1 N KH_2PO_4 and dissolved in ethyl acetate. The organic phase was washed with 1 N KH_2PO_4, 1 N $NaHCO_3$ (2X) and brine, dried over Na_2SO_4, and concentrated. Chromatography over silica gel, eluting with 4% to 10% methanol (containing 1% NH_4OH) in dichloromethane afforded 124 mg (0.21 mmol) of N^1-{(1S,2R)-1-(cyclohexylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N^3,N^3-dipropylisophthalamide hydrochloride (EXAMPLE

SP-256) as a white solid after formation of the salt with ethereal HCl: CI MS *m/z* 550 $[M+H]^+$.

EXAMPLE SP-257

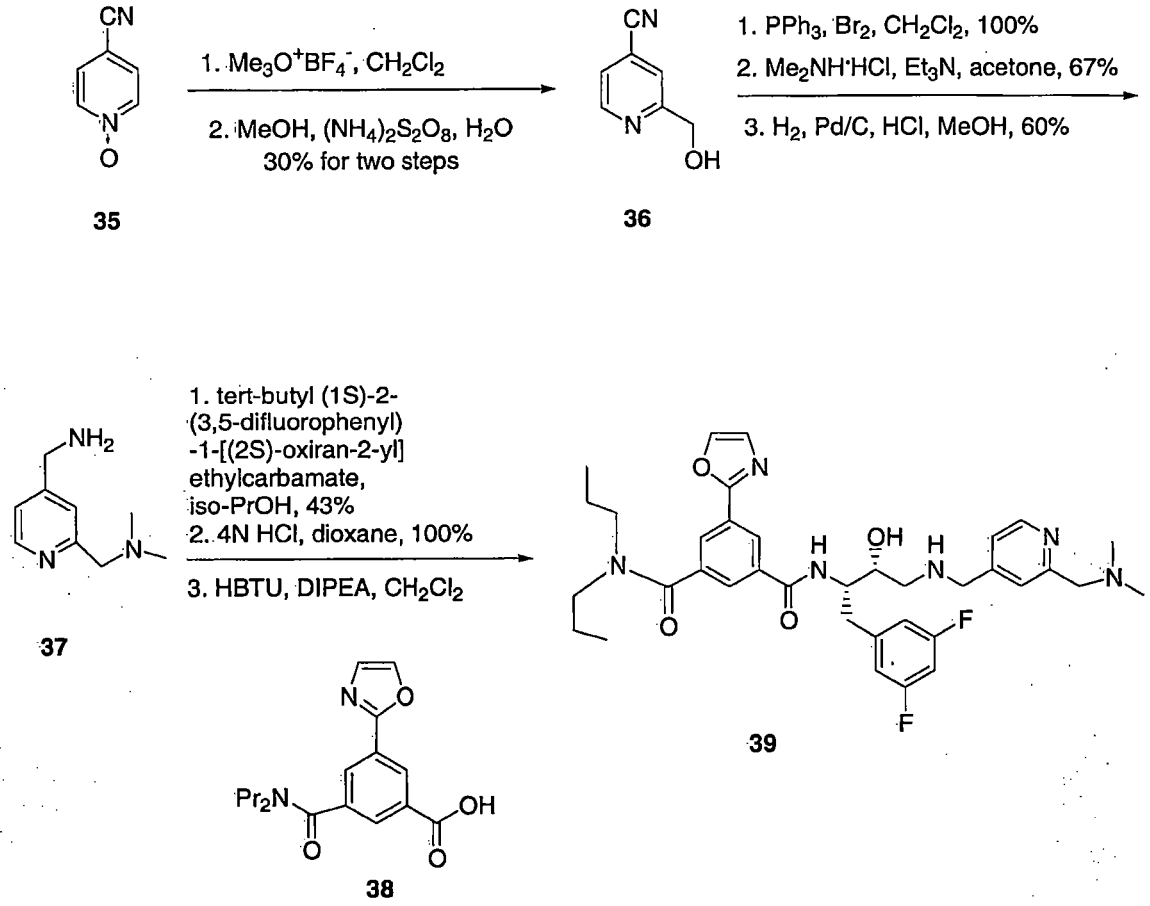
N^1-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclohexylmethyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide hydrochloride

Step 3: tert-Butyl (1S)-2-(cyclohexyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (225 mg, 0.84 mmol) was refluxed with m-bromobenzylamine (380 mg, 2.0 mmol) in 7 mL of isopropanol under nitrogen for 2 h, the solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate. It was washed three times with small portions of 10% HCl, and the aqueous phases were back-extracted with ethyl acetate. The combined organic phases were washed with 1 N $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The resulting oil (356 mg) was dissolved in 3 mL of dichloromethane and 2 mL of TFA and stirred for 1.5 h. It was concentrated, and by weight determined to contain 3 eq. of TFA. To this was added 2 mL of dry dimethylformamide (DMF) and 0.35 mL (3.2 mmol) of 4-methyl morpholine. To this was added a pre-mixed solution of 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid (240 mg, 0.9 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 190 mg, 1 mmol), and 1-hydroxybenzotriazole hydrate (HOBT, 135 mg, 1 mmol) in 3 mL of dry DMF, which had been stirring together for 1.5 h. . After 3 days the reaction was quenched with 1 N KH_2PO_4 and dissolved in ethyl acetate. The organic phase was washed with 1 N KH_2PO_4, 1 N $NaHCO_3$ (2X) and brine, dried over Na_2SO_4, and concentrated. Chromatography over silica gel, eluting with 5% methanol (containing 1% NH_4OH) in dichloromethane afforded 208 mg (0.32 mmol) of N^1-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclohexylmethyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-

dipropylisophthalamide hydrochloride (EXAMPLE SP-257) after formation of the salt with ethereal HCl: CI MS *m/z* 600 $[M+H]^+$.

EXAMPLE SP-258

Synthesis of N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[({2-[(dimethylamino)methyl]pyridin-4-yl}methyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide



Step 1: Trimethyloxonium tetrafluoroborate (2.46 g, 16.7 mmol) was added dropwise at room temperature to a solution of 4-cyanopyridine *N*-oxide (compound **35**, above) (2.0 g, 16.7 mmol) in methylene chloride (260 mL) and the reaction mixture stirred at room temperature overnight. The reaction was concentrated under reduced pressure to give the desired 4-cyanopyridinum *N*-methoxy tetrafluoroborate: ^1H NMR (300 MHz,

DMSO-d_6) δ 9.80 (d, J = 6.0 Hz, 2H), 8.87 (d, J = 6.0 Hz, 2H), 4.48 (s, 3H).

Step 2: An aqueous solution of ammonium persulfate (8.3 mL, 8.3 mmol) was added to a refluxing solution of the N-methoxypyridinium salt prepared in step 1 was dissolved in methanol (200 mL). After stirring for 0.5 h, additional 1 M ammonium persulfate was added (4.2 mL, 4.2 mmol) and the reaction mixture was heated at reflux overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between methylene chloride and saturated sodium bicarbonate. The organic layer was separated and washed with water, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a white solid. Purification by flash column chromatography (silica, 98:2 methylene chloride/methanol) gave 4-cyano-2-hydroxymethylpyridine (36) as a white solid (670 mg, 30%): 1H NMR (300 MHz, CDCl3) δ 8.75 (d, J = 5.0 Hz, 1H), 7.59 (d, J = 0.5 Hz, 1H), 7.46 (dd, J = 5.3, 0.5 Hz, 1H), 4.85 (d, J = 5.3 Hz, 2H), 3.25 (t, J = 5.3 Hz, 1H).

Step 3: Bromine (1.07 mL, 20.8 mmol) was added slowly at 0 °C to a solution of triphenylphosphine (5.53 g, 21.1 mmol) in methylene chloride (97 mL). The solution was warmed to room temperature and a white precipitate was observed. 4-Cyano-2-hydroxymethylpyridine **36** (2.61 g, 19.5 mmol) in methylene chloride (20 mL) was added dropwise and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between water and methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a white solid. Purification by flash column chromatography (silica, 99:1 methylene

chloride/methanol) gave 4-cyano-2-bromomethylpyridine (3.95 g), which was used immediately in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, J = 5.0 Hz, 1H), 7.7 (s, 1H), 7.46 (dd, J = 5.0, 1.3 Hz, 1H), 4.58 (s, 2H).

Step 4: Dimethylamine hydrochloride (4.78 g, 58.6 mmol) was added to a solution of 4-cyano-2-bromomethylpyridine (3.95 g, 19.5 mmol) and triethylamine (13.58 mL, 97.7 mmol) in acetone (40 mL). The reaction mixture was stirred overnight at room temperature in a sealed tube. The reaction mixture was concentrated under reduced pressure and partitioned between methylene chloride and saturated sodium bicarbonate. The organic layer was separated and washed with water, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 99:1 methylene chloride/methanol) gave the desired 4-cyano-2-(dimethylamino)methylpyridine (2.10 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, J = 5.0 Hz, 1H), 7.71 (s, 1H), 7.41 (dd, J = 5.0, 1.2 Hz, 1H), 3.65 (s, 2H), 2.31 (s, 6H); ESI MS m/z 162 $[M + H]^+$.

Step 5: A mixture of 4-cyano-2-(dimethylamino)methylpyridine (800 mg, 4.97 mmol), palladium (80 mg, 10% Pd/C) and concentrated hydrochloric acid (3 mL) in methanol (30 mL) was shaken under 60 psi of hydrogen overnight. The reaction mixture was filtered through diatomaceous earth and the filter cake rinsed with water and methanol. The filtrate was concentrated under reduced pressure and the residue partitioned between water and methylene chloride. The aqueous layer was made alkaline with 1 N sodium hydroxide and extracted with methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate),

filtered, and concentrated under reduced pressure to give an orange oil. Purification by flash column chromatography (97:3 2-propanol/ammonium hydroxide) gave 4-aminomethyl-2-(dimethylamino) methylpyridine **37** (492 mg): ^{1}H NMR (500 Hz, $CDCl_3$) δ 8.50 (d, J = 5.1 Hz, 1H), 7.37 (s, 1H), 7.15 (d, J = 5.1 Hz, 1H), 3.91 (s, 2H), 3.58 (s, 2H), 2.30 (s, 6H); ESI MS m/z 166 $[M + H]^+$.

Step 6: A mixture of 4-aminomethyl-2-(dimethylamino) methylpyridine **37** (490 mg, 2.98 mmol) and tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiran-2-yl] ethylcarbamate (892 mg, 2.98 mmol) in 2-propanol (20 mL) was heated at reflux overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (99:1 2-propanol/ammonium hydroxide) to give product (590 mg): ESI MS m/z 465 $[M + H]^+$.

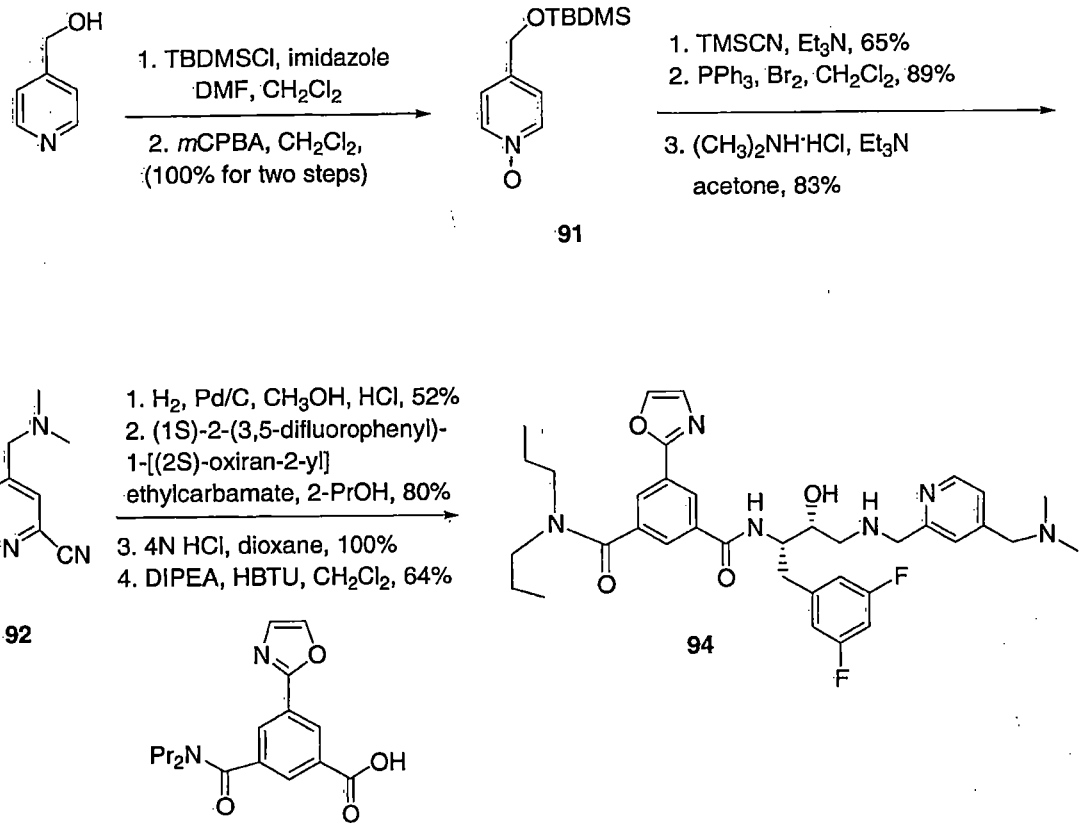
Step 7: Hydrogen chloride (6.3 mL of a 4 N solution in dioxane, 25 mmol) was added at room temperature to a solution of the yellow solid prepared in step 6 (590 mg, 1.26 mmol) in dioxane (6.3 mL) and the reaction mixture stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure and the residue dissolved in methylene chloride containing *N,N*-diisopropylethylamine (3 mL). The organic phase was washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the product (523 mg): ESI MS m/z 365 $[M + H]^+$

Step 8: A solution of 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid **38** (120 mg, 0.38 mmol) in methylene chloride (3.8 mL) containing *N,N*-diisopropylethylamine (132 µL, 0.76 mmol) and HBTU (151 mg, 0.40 mmol) was stirred at

room temperature for 0.5 h. To the above solution was added a solution of the orange oil from step 7 (207 mg, 0.57 mmol) in methylene chloride (3.8 mL) containing *N,N*-diisopropylethylamine (132 µL, 0.76 mmol) and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then diluted with additional methylene chloride and washed with saturated sodium bicarbonate and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield an oily residue. Purification by flash column chromatography (silica, 90:10 methylene chloride/methanol) gave N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[({2-(dimethylamino) methyl]pyridin-4-yl}methyl)amino]-2-hydroxypropyl} -5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide (178 mg): mp 63-66 °C; ESI MS *m/z* 663 $[M + H]^+$.

EXAMPLE SP-259

Synthesis of N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[({4-[(dimethylamino)methyl] pyridin-2-yl}methyl)amino]-2-hydroxypropyl} -5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide, compound 94 in scheme 23, below



Synthesis of 2-cyano-4-(dimethylamino)methylpyridine (92)

Step 1: A mixture of 4-(hydroxymethyl)pyridine (17.4 g, 159 mmol), *t*-butyldimethylsilyl chloride (26.36 g, 174.88 mmol), and imidazole (13.31 g, 195.5 mmol) in *N*,*N*-dimethyformamide (200 mL) and methylene chloride (20 mL) was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and then partitioned between water and a mixture of ethyl acetate and hexanes (1:1). The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give an oil (35.62 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J = 6 Hz, 2H), 7.13 (d, J = 6 Hz, 2H), 4.63 (s, 2H), 0.84 (s, 9H), 0.05 (s, 6H).

Step 2: To a stirred solution of the oil from step 1 (35.62 g, 159 mmol) in dry methylene chloride (470 mL) was added 3-

choloroperoxybenzoic acid (47.03 g, 172.57 mmol). The reaction mixture was stirred at room temperature overnight and then partitioned between water and methylene chloride. The organic layer was washed with saturated sodium sulfite, saturated sodium bicarbonate, 1 N sodium hydroxide, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 4-(*t*-butyldimethylsilyloxy)methylpyridine *N*-oxide **91** (37.8 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 6 Hz, 2H), 7.13 (d, *J* = 6 Hz, 2H), 4.59 (s, 2H), 0.83 (s, 9H), 0.05 (s, 6H).

Step 3: A mixture of 4-(*t*-butyldimethylsilyloxy)methylpyridine *N*-oxide **91** (30 g, 125 mmol), triethylamine (40 mL), and trimethylsilylcyanide (44 mL, 360 mmol) was refluxed overnight. The black solution was cooled to room temperature and concentrated under reduced pressure to give a black gum. Purification by flash column chromatography (silica, 10:90 ethyl acetate/hexanes) gave an oil (20.3 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5 Hz, 1H), 7.55 (s, 1H), 7.34 (d, *J* = 5 Hz, 1H), 4.66 (s, 2H), 0.83 (s, 9H), 0.05 (s, 6H).

Step 4: Bromine (1.97 mL, 38.74 mmol) was added slowly at 0 °C to a solution of triphenylphosphine (10.29 g, 39.28 mmol) in methylene chloride (200 mL). The solution was warmed to room temperature and a white precipitate was observed. The brown oil from step 3 (9.0 g, 36.27 mmol) in methylene chloride (50 mL) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between water and methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a brown solid. Purification by flash column chromatography (silica, 17:83 ethyl acetate/hexanes) gave a white solid (6.20

g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, *J* = 3 Hz, 1H), 7.73 (s, 1H), 7.55 (dd, *J* = 6, 3 Hz, 1H), 4.42 (s, 2H).

Step 5: To a stirred solution of the solid from step 4 (9.1 g, 46.44 mmol) in acetone (90 mL) was added dimethylamine hydrochloride (11.36 g, 139.3 mmol) and trimethylamine (38.73 mL, 278.6 mmol). The reaction mixture was stirred overnight in a sealed bottle. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in water, made alkaline with 1 N sodium hydroxide to pH 10 and extracted with methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 2-cyano-4-(dimethylamino)methylpyridine **92** (6.2 g): ESI MS *m/z* 162 $[M + H]^+$.

EXAMPLE SP-260

N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[({4-[(dimethylamino)methyl]pyridin-2-yl}methyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide

Step 1: A mixture of 2-cyano-4-(dimethylamino)methylpyridine **92** (2.0 g, 12.4 mmol), 10% Pd/C (200 mg) and concentrated hydrochloric acid (8 mL) in methanol (180 mL) was shaken under 60 psi hydrogen overnight. The reaction mixture was filtered through diatomaceous earth and repeatedly washed with water and methanol. Methanol was removed under reduced pressure and the residue partitioned between water and methylene chloride. The aqueous layer was made alkaline with 1 N sodium hydroxide and extracted with methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give an oil (1.07 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, *J* = 5 Hz, 1H),

7.25 (s, 1H), 7.13 (d, J = 5 Hz, 1H), 3.98 (s, 2H), 3.42 (s, 2H), 2.26 (s, 6H); ESI MS *m/z* 166 $[M + H]^+$.

Step 2: A mixture of the orange oil from step 1 (500 mg, 3.03 mmol) and tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (907 mg, 3.03 mmol) in 2-propanol (20 mL) was refluxed overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica, 1:99 ammonium hydroxide/2-propanol) to give a solid (1.13 g): ESI MS *m/z* 465 $[M + H]^+$.

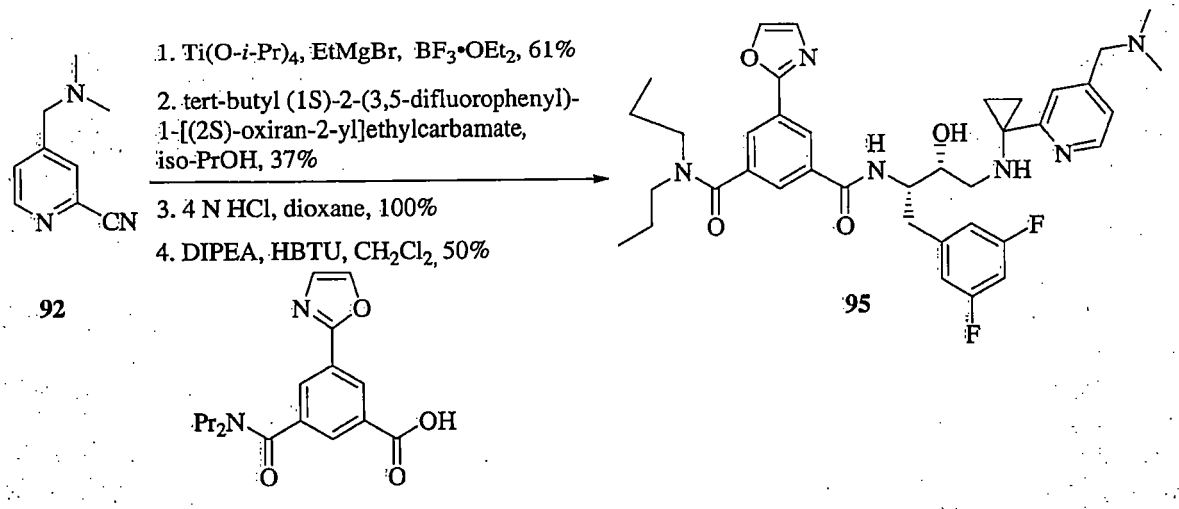
Step 3: The yellow solid from step 2 (400 mg, 0.86 mmol) was dissolved in dioxane (4.3 mL) and hydrogen chloride (4.3 mL, 4 M dioxane, 17.22 mmol) was added. The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure and methylene chloride and *N,N*-diisopropylethylamine (3 mL) were added. The organic phase was washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give an oil (365 mg): ESI MS *m/z* 365 $[M + H]^+$

Step 4: To a stirred solution of 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid **93** (173.6 mg, 0.55 mmol) and *N,N*-diisopropyl ethylamine (191 µL, 1.10 mmol) in methylene chloride (6.0 mL) was added HBTU (218.62 mg, 0.58 mmol) and the reaction mixture stirred for 0.5 h. To the above solution was added a solution of the orange oil from step 3 (300 mg, 0.823 mmol) and *N,N*-diisopropylethylamine (191 µL, 1.10 mmol) in methylene chloride (6.0 mL), and the reaction mixture was stirred under nitrogen for 18 h. The reaction mixture was then diluted with additional methylene chloride and washed with saturated sodium bicarbonate, 0.5 N hydrochloric acid,

and saturated sodium chloride,. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield an oily residue. Purification by flash column chromatography (silica, 10:90 methanol/methylene chloride) gave N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[({4-[(dimethylamino)methyl] pyridin-2-yl}methyl)amino]-2-hydroxypropyl} -5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide **(94)** (233 mg): mp 65-68 °C; ESI MS *m/z* 663 $[M + H]^+$

EXAMPLE SP-261

Synthesis of N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(1-{4-[(dimethylamino)methyl] pyridin-2-yl}cyclopropyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide



Step 1: To a solution of 2-cyano-4-(dimethylamino)methylpyridine **92** (prepared as in EXAMPLE SP-259) (500 mg, 3.10 mmol) in tetrahydrofuran (10 mL) was added titanium(IV) isopropoxide (1.01 mL, 3.41 mmol) and ethylmagnesium bromide (6.20 mL, 1 N THF, 6.20 mmol). After stirring for 0.5 h, boron trifluoride diethyl etherate (786 µL, 6.20 mmol) was added in one portion. The reaction mixture was stirred for 1 h at room temperature and 1 N sodium hydroxide was added to adjust the mixture to pH 9-10. The

white solid generated was removed by filtration and the filtrate was partitioned between water and methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a yellow oil. Purification by flash column chromatography (silica, 1:99 to 3:97 ammonium hydroxide/2-propanol) gave an oil (360 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 6, 5 Hz, 1H), 3.41 (s, 2H), 7.02 (dd, *J* = 6, 5 Hz, 1H), 3.98 (s, 2H), 3.42 (s, 2H), 2.25 (s, 6H), 2.08 (s, 2H), 1.31-1.27 (m, 2H), 1.15-1.11 (m, 2H); ESI MS *m/z* 192 $[M + H]^+$.

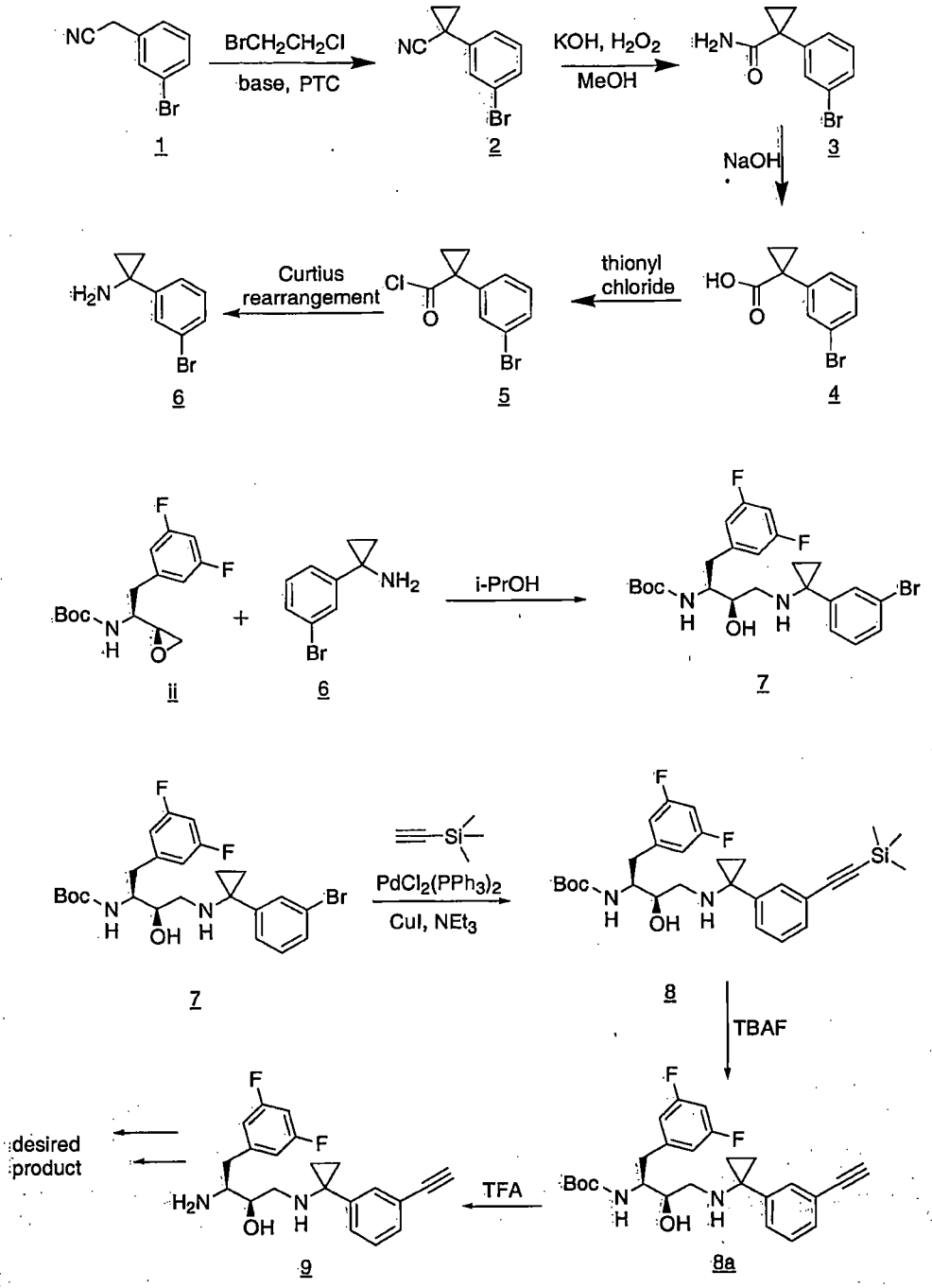
Step 2: A mixture of the oil from step 1 (350 mg, 1.83 mmol) and tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (496.8 mg, 1.66 mmol) in 2-propanol (13 mL) was refluxed overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica, 1:99 ammonium hydroxide/2-propanol) to give a solid (300 mg): ESI MS *m/z* 491 $[M + H]^+$.

Step 3: To a stirred solution of the solid from step 2 (300 mg, 0.61 mmol) in dioxane (6.0 mL) was added hydrochloric acid (6.0 mL, 4 N dioxane, 24.40 mmol). The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure and methylene chloride and *N,N*-diisopropylethylamine (3 mL) were added. The organic layer was washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give an oil (269 mg): ESI MS *m/z* 391 $[M + H]^+$.

Step 4: To a stirred solution of 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid **93** (prepared as in EXAMPLE S-

2364, step 5) (124.3 mg, 0.39 mmol) and *N,N*-diisopropyl ethylamine (139 µL, 0.79 mmol) in methylene chloride (3.0 mL) was added HBTU (156.5 mg, 0.41 mmol) and the reaction mixture stirred for 0.5 h. To the above solution was added a solution of the orange oil from step 3 (269.6 mg, 0.823 mmol) and *N,N*-diisopropylethylamine (139 µL, 0.79 mmol) in methylene chloride (3.0 mL), and the reaction mixture was stirred under nitrogen for 18 h. The reaction mixture was then diluted with additional methylene chloride and washed with saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield an oily residue. Purification by flash column chromatography (silica, 10:90 methanol/methylene chloride) gave N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(1-{4-[(dimethylamino)methyl] pyridin-2-yl}cyclopropyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide **(95)** (134 mg): mp 70-72 °C; ESI MS *m/z* 689 $[M + H]^+$.

EXAMPLE SP-262



Preparation of bromo-cyclopropyl cyanide **2** (modification of procedure from Org. Prep. & Proc. Int., 1995, 27(3), 355)

A mixture of 1-bromo-2-chloroethane (BCE; 120 ml), 3-bromobenzyl cyanide (25 g) and benzyl-triethylammonium chloride (TEBAC, 1.1 g) was stirred at 40°C while base (50% NaOH, 120 g) was added dropwise over 20 min. Temperature has risen to ~80°C within first 15 min. Very vigorous mechanical

stirring was continued while temperature slowly dropped to 50°C (over the next 3 hr). The mixture was deep red at this stage. After 3 hr there was no starting material (TLC). The reaction mixture was cooled down to RT, water (100 ml) was added and stirred for 5 min. Organic layer was separated and aqueous was extracted with dichloromethane (3 x). Combined organic layers were washed with water and dil. aq. HCl. Solution was dried using $MgSO_4$, filtered and concentrated yielding deep yellow oil (126 g; still contains some BCE). Product was purified by a high vacuum fractionation using short-path set-up and single receiver. Collected fraction with bp 108-115°C / 0.1-0.05 mmHg as a heavy oily liquid 26.6 g (94%). After cooling to RT this liquid solidified.

Preparation of bromoamide **3**

Bromocyanide **2** (5.9 g; 26.6 mmol) was dissolved in methanol (150 ml). To this solution while stirring KOH (25% aq soln., 0.68 ml) and hydrogen peroxide (30%, 35 ml) was added and the reaction mixture was heated at 55°C for 5 hr. At that time there was no starting material (TLC). Mixture was evaporated yielding solid residue (7.1 g; contains KOH).

Preparation of bromoacid **4**

Crude bromoamide 3 from previous reaction was slurried in methanol (10 ml) and NaOH (10% aq, 150 ml) was added. Reaction mixture was refluxed 4.5 hr (TLC control). The mixture was cooled to RT, acidified with 15% HCl (to pH 2) and concentrated. Precipitated white solid was collected by filtration. Yield 6.8 g.

Preparation of acid chloride **5** (slight modification of procedure from Synlett 1999, 11, 1763)

Thionyl chloride (2.73 ml) and benzotriazole (4.47 g) were dissolved in dry dichloromethane (25 ml). Crude bromoacid **4** (6.8 g) was dissolved in dichloromethane (120 ml) and to this stirred solution the prepared above thionyl chloride solution (22.2 ml; 1.25 eq) was added portionwise over a few minutes. Before the addition was complete, benzotriazole hydrochloride started separating out as a white solid. The reaction mixture was stirred for additional 15 min and at the end the solids were filtered off. Filtrate was stirred with anhydrous $MgSO_4$ (2 g) to destroy an excess of reagent. The solids were filtered off and filtrate was evaporated and dried under high vacuum for 1 hr to give viscous amber oil. Yield 6.6 g.

Preparation of bromoamine **6**

Crude acid chloride **5** was dissolved in dry acetone (40 ml), cooled to -10°C and treated with sodium azide (4 g in 15 ml of waterl). After stirring for 1 hr at -10°C a mixture was allowed to warm to 0°C and was poured into cold water (300 ml). Azide was extracted into smallest possible amount of toluene (ca. 40 ml). The toluene layer was washed with water and dried. Solids were filtered off and resulting solution was stirred and heated cautiously at 100°C for 1 hr. Conc. HCl (~ 25 ml) was added through condenser and mixture was refluxed for 15 min. On cooling white crystalline material precipitated and was filtered off. Filtrate was slightly concentrated, cooled down and additional portion of precipitate was collected. Combined solids were dried to give 4.1 g of bromo-cyclopropylamine **6** as hydrochloride salt.

Preparation of compound **7**

Crude bromoamine hydrochloride **6** (2 g; 8 mmol) was dissolved in sat. aq Na_2CO_3 (20 ml) and extracted with dichloromethane (5 x 10 ml). Combined extracts were dried, evaporated and kept overnight under vacuum. Yield of bromoamine **6** (1.68 g, 7.92 mmol). This amine was dissolved in isopropanol (20 ml) and epoxide (ii; 2.36 g, 7.92 mmol) was added. A mixture was stirred in a sealed tube at 80°C until starting epoxide was not detected by TLC (2-6 hr). Reaction mixture was cooled and solvent was evaporated to give, after drying under vacuum, white solid (3.9 g, 82 % pure).

Preparation of compound **8**

Crude BOC bromide **7** (3.9 g; 7.0 mmol; 1 eq) was dissolved in triethylamine (20 ml) and $PdCl_2(PPh_3)_2$ (0.196 g, 0.28 mmol; 0.04 eq) and CuI (0.068 g; 0.36 mmol; 0.05 eq) were added. Upon addition of CuI a reaction mixture turned yellow then changed color slowly to green. The reaction mixture was heated to reflux, at which point it turned orange-brown. Trimethylsilyl acetylene (0.82 g, 1.2 ml, 8.2 mmol, 1.2 eq) was added via syringe. A black precipitate formed immediately. The reaction mixture was refluxed for 3 hr under nitrogen, then it was cooled to RT before partitioning between aq. sat. Na_2CO_3 and ethyl acetate. Organic layer was separated and aqueous was extracted with ethyl acetate (3 x 25 ml). Combined extracts were washed with brine, dried and evaporated. The crude product was contaminated by acetylene derived from bromoamine 6.

Preparation of BOC-acetylene **8a**

To a solution of crude silyl-protected acetylene **8** (from previous reaction) in THF (5 ml) the tetrabutylammonium fluoride (1M in THF, 8 ml) was added. Mixture was stirred for

1 hr at RT, solvent was evaporated, residue was dissolved in ether (30 ml), washed with brine, dried and concentrated. Crude product was purified by flash chromatography on silica gel using ethyl acetate/hexane (2:3) mixture to give purified BOC-acetylene **8a** (1.54 g, 43% from **6**).

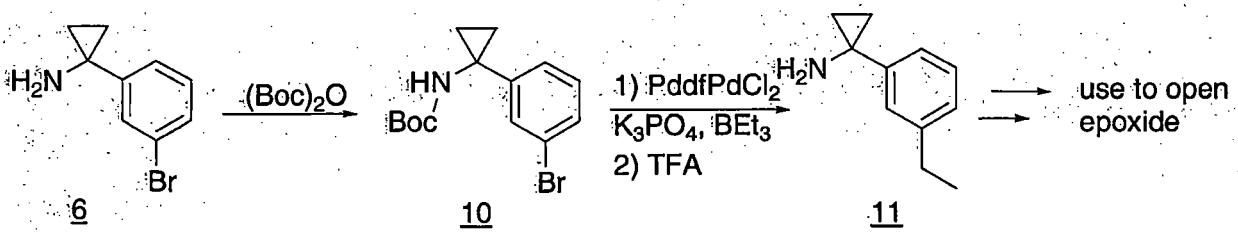
Preparation of 9:

1-(3,5-difluorobenzyl)-3-[1-(3-ethynylphenyl)cyclopropylamino)]-2-hydroxypropyl amine dihydrochloride

[1-(3,5-difluorobenzyl)-3-[1-(3-ethynylphenyl)cyclopropylamino]-2-hydroxypropyl]-carbamic acid tert-butyl ester (2.34 g, 5.13 mmol) was treated with 4N HCl in dioxane (15.8 mL, 63.3. mmol). The resulting heterogeneous mixture was treated with methanol (10 mL) whereupon it became homogeneous over 30 min.. The volatiles were evaporated *in vacuo*. Dioxane (20 mL) was added and the mixture was evaporated *in vacuo* to produce a white solid (2.33 g, 106%).

EXAMPLE SP-263

Preparation of cyclopropyl m-ethylbenzylamine (11)



6 10 11

Preparation of **10.**

1-(3-Bromo-phenyl)-cyclopropylamine 6 (25 g, 112 mmol), triethylamine(21.7g, 2170 mmol) were mixed together in CH_2Cl_2 (300 mL). The solution was cooled to 0 °C and boc anhydride (25.07 g, 115 mmol) added in 4 equal portions at 15 minute

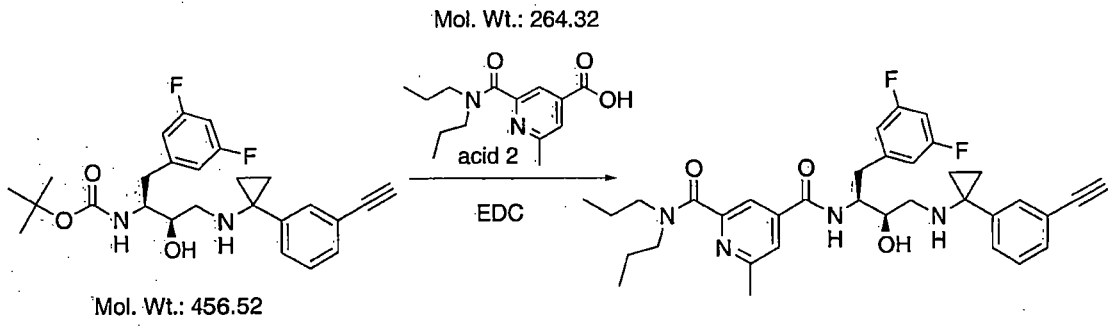
intervals. (Gas evolution noted after each addition). Mixture stirred for 30 minutes and then an additional 5 grams of boc anhyrdide was added to drive reaction to completion (GC/MS). Solution worked up with 1 N HCl (2X 100 mL), saturated aq. sodium bicarbonate (2 X 100 mL), and dried over sodium sulfate. Solvent was removed at reduced pressure and product was isolated by crystallization from cold hexanes (about 150 mL). Obtained 20.6 grams of white solid. Reduced volume of hexanes to about 75 ml and second crop was obtained (9.2 g)

Preparation of **11**.

The Boc-bromobenzyl amine 10 (26.8 g, 94.03 mmol), and PddfPdCl$_2$ (816 mg, 0.38 mmol, 0.004 eq) were mixed together in anhydrous THF (300 mL) and aqueous K_3PO_4 (100 mL of 2.0 M). To this red solution was added triethylborane (100 ml of 1.0 M in THF, 100 mmol). The solution turned black and was refluxed for 4 hours. GC/MS indicated the reaction was complete. The solution was poured into a separatory funnel and the aqueous layer separated. The organic layer was collected and solvent removed to a volume of 100 mL. Ethyl acetate/ hexanes (300 mL of 1:1) were added and the solution was extracted with 1N HCl (1X100 mL), sodium bicarbonate (2X 100 mL) and brine (1X100 mL). The solution was dried over sodium sulfate and vacuum filtered through a bed of silica gel (125 ml of silica). The solvent was removed at reduced pressure to afford 20.6 grams of 11 as light yellow oil.

EXAMPLE SP-264

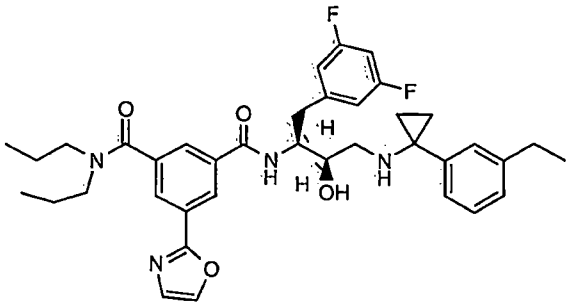
Preparation of 6-Methyl-pyridine-2,4-dicarboxylic acid 4-({1-(3,5-difluoro-benzyl)-3-[1-(3-ethynyl-phenyl)-cyclopropylamino]-2-hydroxy-propyl}-amide) 2-dipropylamide



The Boc protected amine (prepared as in EXAMPLE SP-262) (0.912 g, 2 mM) was treated with 50% TFA in CH_2Cl_2 (1 hr, RT). Solvents were removed under reduced pressure to form an oil. Added toluene and evaporated; repeated stripping with toluene. After this operation and keeping residue under high vacuum for 1 hr off-white solid was obtained (free amine, most likely as a TFA salt). This amine was dissolved in CH_2Cl_2 (10 mL, slurry), added acid 2 (0.528 g; 2 mM), HOBt (0.297 g; 2.2 mM) and EDC (0.423 g; 2.2 mM). When EDC was added slurry rapidly became clear solution. At the end an excess of NEt_3 (2 mL) was added and a reaction mixture was stirred o/n at RT. The next day solvent was stripped and EtOAc solution was washed with aq. saturated solution of Na_2CO_3 (3x), brine, dried and concentrated. Initially purified by flash chromatography on Biotage (eluted with 20% hexane and 80% EtOAc). Final purification was done by HPLC. The TFA salt was converted into HCl mono salt by addition of 1.25M solution of HCl in MeOH (1.6 mL). Yield 0.971 g (76%).

EXAMPLE SP-265

N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide;



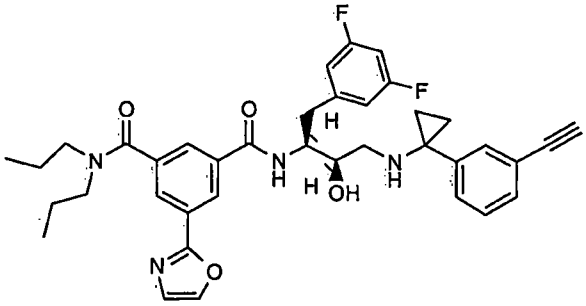
The above identified compound is prepared essentially using the procedure described in EXAMPLE SP-264.

M+ 659.3.

Carbon NMR ($CDCl_3$): 11.00, 11.56, 11.78, 15.37, 20.80, 21.90, 28.71, 35.28, 44.45, 47.26, 49.97, 51.16, 53.75, 69.43, 77.12, 102.12, 112.02, 112.34, 126.23, 126.94, 127.29, 128.01, 128.68, 129.20, 129.51, 133.90, 134.70, 137.56, 139.59, 142.15, 145.53, 160.26, 161.43, 164.73, 166.98, 170.42.

EXAMPLE SP-266

N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide



The above identified compound is prepared essentially using the procedure described in EXAMPLE SP-264.

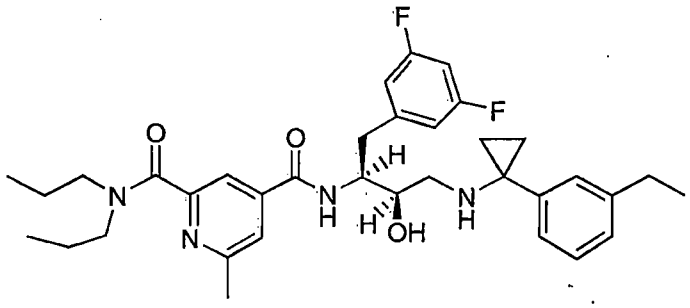
M+ 655.3.

Carbon NMR ($CDCl_3$): 11.01, 11.47, 11.58, 11.98, 20.82, 21.91, 35.22, 43.94, 47.28, 50.09, 51.17, 53.77, 69.49, 77.11, 78.63, 82.55, 102.17, 112.05, 123.22, 126.23, 126.82, 128.07, 128.76,

129.49, 130.68, 133.33, 134.50, 137.57, 139.61, 142.17, 160.23, 161.27, 164.56, 167.04, 170.44.

EXAMPLE SP-267

N^4-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-6-methyl-N^2,N^2-dipropylpyridine-2,4-dicarboxamide



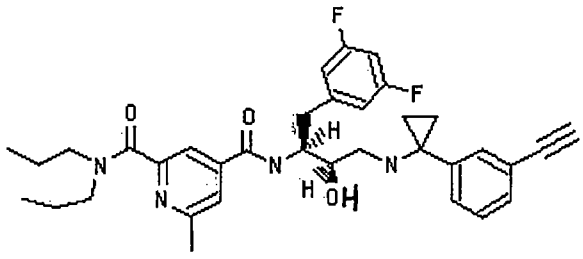
The above identified compound is prepared essentially using the procedure described in EXAMPLE SP-264.

M+ 607.3

Carbon NMR ($CDCl_3$): 10.96, 11.06, 11.53, 12.09, 15.43, 20.73, 21.90, 23.96, 28.75, 33.93, 44.32, 47.82, 49.60, 50.90, 53.98, 68.65, 77.11, 101.98, 112.064, 112.39, 117.03, 122.12, 127.25, 129.23, 129.49, 134.06, 142.21, 145.61, 153.63, 158.94, 161.19, 161.36, 164.48, 164.65, 165.65, 169.06.

EXAMPLE SP-268

N^4-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-6-methyl-N^2,N^2-dipropylpyridine-2,4-dicarboxamide



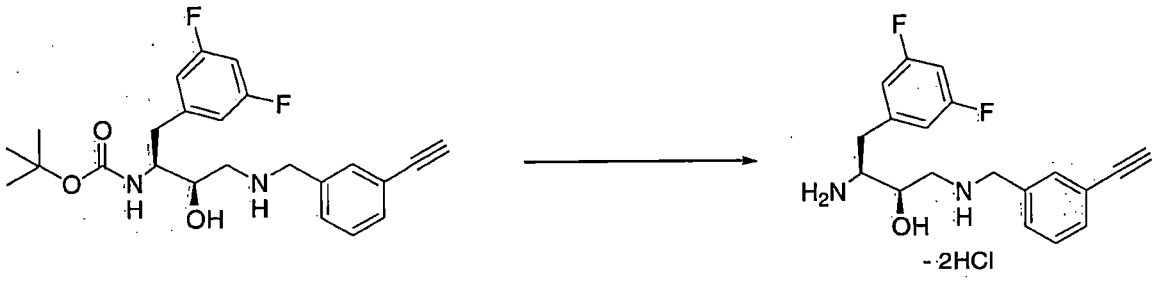
The above identified compound is prepared essentially using the procedure described in EXAMPLE SP-264.

M+ 603.3.

Carbon NMR ($CDCl_3$): 10.99, 11.58, 12.29, 20.75, 21.92, 24.03, 33.98, 43.91, 47.91, 49.83, 50.96, 53.95, 68.74, 77.13, 78.72, 82.57, 102.08, 112.08, 112.41, 117.63, 122.16, 123.32, 129.51, 130.66, 133.37, 133.55, 134.63, 142.28, 153.56, 158.96, 161.20, 161.37, 164.66, 165.80.

EXAMPLE SP-269

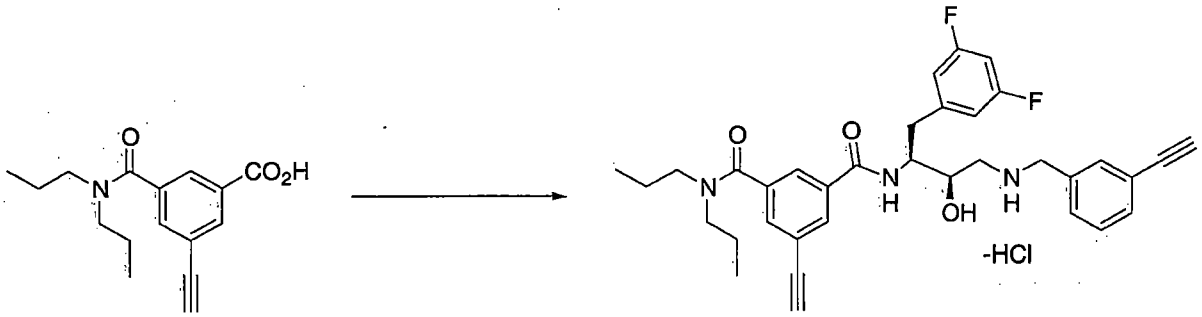
Preparation of 1-(3,5-difluorobenzyl)-3-(3-ethynyl)benzylamino)-2-hydroxypropyl amine dihydrochloride



[1-(3,5-difluorobenzyl)-3-(3-ethynylbenzylamino)-2-hydroxypropyl]-carbamic acid tert-butyl ester (2.73 g, 6.33 mmol) was treated with 4N HCl in dioxane (15.8 mL, 63.3. mmol). The mixture became homogeneous after 5 min and then deposited a precipitate. Diethyl ether (15 mL) was added to aid stirring and the mixture was stirred for 2 h. The volatiles were evaporated *in vacuo*. Dioxane (20 mL) was added and the mixture was evaporated *in vacuo* to produce a white solid (2.67 g, 104%).

EXAMPLE SP-270

N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-5-ethynyl-N^3,N^3-dipropylisophthalamide



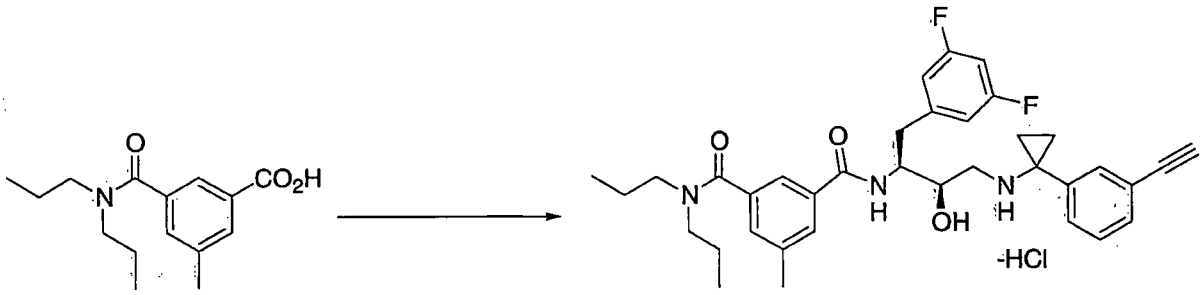
5-Ethynyl-N,N-dipropyl-*iso*-phthalamic acid (1.73 g, 6.32 mmol) was dissolved in anhydrous DMF (20 ml) under nitrogen. 1-Hydroxybenzotriazole (1.28 g, 9.48 mmol) and 1-(3-dimethylaminopropy)-3-ethylcarbodiimidehydrochloride (1.70 g, 8.85 mmol)) were added in succession. This mixture was stirred for 30 min at RT until homogeneous and then was added in one portion to a rapidly-stirred slurry of amine dihydrochloride (2.67, 6.32 mmol) and N-methylmorpholine (2.78 mL, 2.56 g, 25.3 mmol) in DMF (25mL). The resulting mixture was stirred for 2 h before diluting with saturated aq sodium bicarbonate (200 mL). The mixture was extracted with ethyl acetate (3 X 100 mL) and the combined organic extracts were washed with saturated aq sodium bicarbonate (100 mL), water (2 X 100 mL), and brine (100 mL), dried (sodium sulfate), filtered and evaporated *in vacuo* to give an oil (3.7 g). The product was purified using flash column chromatography on silica gel (Flash 65i cartridge, eluting with 1L 100% ethyl acetate, then 4L 95:5 ethyl acetate/methanol) to yield a pale yellow oil (2.74 g, 74%). LC-MS (m/e): 586 (M+1); 100% (254 nm). The ELN 152006 free base was dissolved in ethanol (25 mL) and treated with 4N HCl in dioxane (2.0 mL). The resulting mixture was evaporated *in vacuo* to remove volatiles, re-dissolved in 1:1 ethanol/water (25 mL) and evaporated *in vacuo*. The resulting solid was slurried in diethyl ether (50 mL), filtered and washed with diethyl ether to produce an off-white solid which

was vacuumed dried to constant weight (2 d) to yield the desired product (2.43 g).

Analysis: for $C_{35}H_{37}F_2N_3O_3$ +HCl: calcd.: C, 67.57; H, 6.16; N, 6.75; Cl, 5.50; found: C, 67.21; H, 6.04; N, 6.55; Cl, 5.71.

EXAMPLE SP-271

Preparation of N^1-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-methyl-N^3,N^3-dipropylisophthalamide

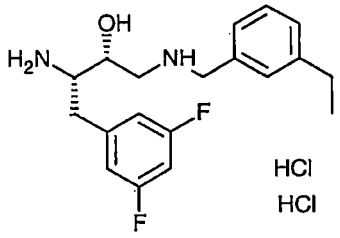


5-Methyl-N,N-dipropyl-*iso*-phthalamic acid (1.35 g, 5.13 mmol, was dissolved in anhydrous DMF (15 ml) under nitrogen. 1-Hydroxybenzotriazole (1.04 g, 7.69 mmol) and 1-(3-dimethylaminopropy)-3-ethylcarbodiimide hydrochloride (1.38 g, 7.18 mmol)) were added in succession. This mixture was stirred for 30 min at RT until homogeneous and then was added in one portion to a rapidly-stirred slurry of amine dihydrochloride (2.23 g, 5.13 mmol) and N-methylmorpholine (2.25 mL, 2.07 g, 20.5 mmol) in DMF (20 mL). The resulting mixture was stirred for 3.5 h before diluting with saturated aq sodium bicarbonate (150 mL). The mixture was extracted with ethyl acetate (3 X 100 mL) and the combined organic extracts were washed with saturated aq sodium bicarbonate (100 mL), water (2 X 100 mL), and brine (100 mL), dried (sodium sulfate), filtered and evaporated *in vacuo* to give an oil (3.0 g). The product was purified using flash column chromatography on silica gel (Flash 65i cartridge, eluting with 2.8L 1:1 ethyl acetate/hexane, 2.5L 2:1 ethyl acetate/hexane, then 2L 100%

ethyl acetate) to yield a clear oil (2.34 g, 76%). LC-MS (m/e): 602 (M+1); 100% (254 nm). The ELN 152227 free base was dissolved in ethanol (25 mL) and treated with 4N HCl in dioxane (2.0 mL). The resulting mixture was evaporated *in vacuo* to remove volatiles, re-dissolved ethanol (25 mL) and evaporated *in vacuo*. The resulting solid was slurried in diethyl ether (50 mL) and filtered to produce a hygroscopic solid which was lyophilized to yield ELN 152227-3 (1.93 g). Analysis: for $C_{36}H_{41}F_2N_3O_3$ +HCl + 0.8 H_2O: calcd.: C, 66.26; H, 6.73; N, 6.44; Cl, 5.43; found: C, 67.21; H 6.40; N, 6.42; Cl, 5.34.

EXAMPLE SP-272

Preparation of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride

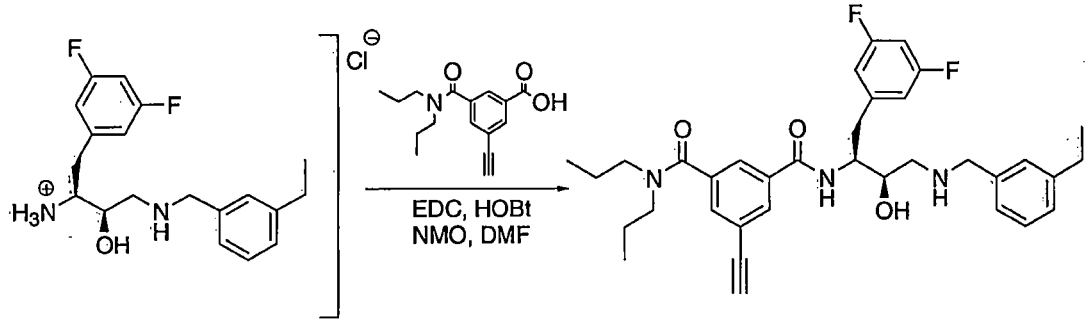


The slurry of [1-(3,5-difluorobenzyl)-3-(3-ethylbenzylamino)-2-hydroxypropyl]-carbamic acid tert-butyl ester (5.25 g, 0.012 m) in anhydrous dioxane (20 ml) was stirred (magnetic bar) at RT under nitrogen atmosphere in an 250 ml round-bottom flask, immersed in a cold water bath. The solution of hydrogen chloride in dioxane (4M, 32 ml) was added in one portion. The reaction mixture, initially homogenous, became a thick slurry within ca. 20 min. Mixture was stirred for 70 min, and was monitored by the TLC (silica gel plates, 5 x 10 cm, eluted with ethyl acetate - methanol 95:5 mixture). Ethyl ether (100 ml) was added, precipitated product was filtered off and rinsed with ether (2 x 50 ml). The filter cake was air-dried for 1 hour then placed in an vacuum oven at

35 °C and the oven evacuated (5 torr). Product was dried to constant mass for 7 hours. Yield was 5.24 g. LC-MS (m/e): 335 (M+1); purity: 100% (254 nm).

EXAMPLE SP-273

N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-ethynyl-N^3,N^3-dipropylisophthalamide



The 5-ethynyl-N,N-dipropyl-*iso*-phthalamic acid (1.64 g, 0.006m) was dissolved in anhydrous DMF (30 ml) in an round-bottom flask (50 ml) equipped with magnetic stirring bar. Flask was flushed with nitrogen and HOBt (1.23 g, 0.009m, 1.5 eq), followed by EDC (1.63 g, 0.0084m, 1.4 eq) were added. This mixture was stirred for 45 min at RT and then was added in one portion to the stirred solution of amine hydrochloride (2.45 g, 0.006m) in anhydrous DMF (30 ml) and NMO (5.0 g, 0.05m, 8.5 eq). The resulted heterogeneous mixture was vigorously stirred under nitrogen at RT for 2 hr. During that time all solids gradually dissolved, mixture remained however cloudy. Reaction progress was monitored by TLC (silica gel plates, 5 x 10 cm, eluted with ethyl acetate-methanol 95:5 mixture). Product was isolated by diluting reaction mixture with sat. aq. sodium bicarbonate (250 ml) and extraction with ethyl acetate (3 x 150 ml). Combined extracts were washed with brine and dried over magnesium sulfate. Solution was filtered and evaporated, yield of crude product was 4.6 g (yellow oil). Product was purified using flash column chromatography on silica gel (Flash 65i cartridge, applied in dichloromethane

solution and eluted with ethyl acetate-methanol 93:7 mixture). Fractions containing product were combined and evaporated to give pale yellow oil, 2.7 g. LC-MS (m/e): 590 (M+1); 100% (254 nm). Purified product was treated with ethanolic hydrogen chloride (1.05 eq), filtered and lyophilized. Yield of final hydrochloride salt was 2.4 g. LC-MS (m/e) 590 (M+1); purity: 100% (254 nm), 100% (280 nm).

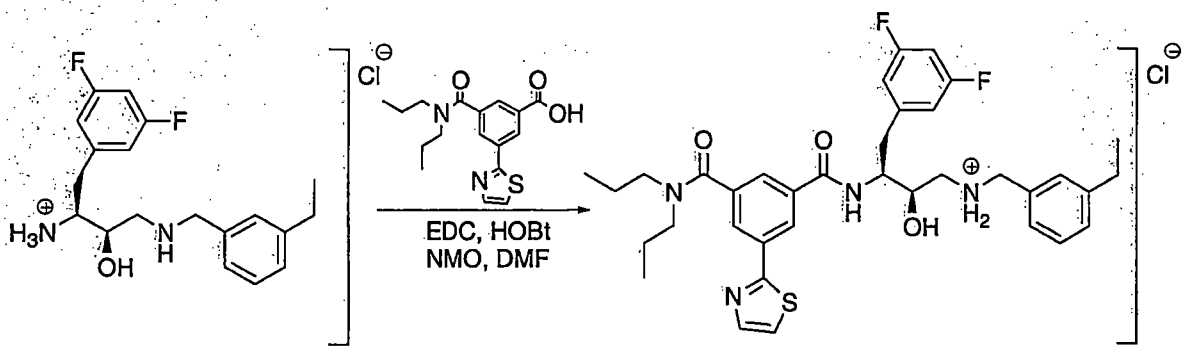
^{1}H-NMR (MeOH-*d4*): δ 0.70 (t, 3H), 1.01 (t, 3H), 1.23 (t, 3H), 1.53(m, 2H), 1.73 (m, 2H), 2.67 (q, 2H), 2.87 (m, 1H), 3.05-3.35 (m, 8H), 4.00 (s, 1H), 4.01 (m, 1H), 4.25 (m, 3H), 4.91 (s), 6.77 (m, 1H), 6.91 (d, 2H), 7.29-7.38 (m, 4H), 7.56 (d, 2H), 7.79 (s, 1H).

^{13}C-NMR: (MeOH-*d4*): 9.73, 10.17, 20.17, 21.33, 46.51-48.32, 49.27, 50.71, 54.04, 68.75, 79.79, 80.94, 101.17 (t), 111.56 (d), 123.26, 124.83, 127.00, 128.73, 129.23, 130.53, 130.95, 132.15, 134.29, 137.46, 142.69, 142.81, 145.17, 161.28 (d), 164.40 (d), 167.13, 170.28.

Analysis: for $C_{35}H_{42}ClF_2N_3O_3$ x 0.5 H_2O calcd.: C, 66.18; H, 6.82; N, 6.62; Cl, 5.58; found: C, 66.07; H 6.85; N, 6.79; Cl, 5.17.

EXAMPLE SP-274

Preparation of N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide



The N,N-dipropyl-5-thiazol-2-yl-*iso*-phthalamic acid (1.99 g, 0.006m) was dissolved in anhydrous DMF (30 ml) in an round-

bottom flask (50 ml) equipped with magnetic stirring bar. Flask was flushed with nitrogen and HOBt (1.24 g, 0.009m, 1.5 eq), followed by EDC (1.63 g, 0.0084m, 1.4 eq) were added. This mixture was stirred for 45 min at RT and then was added in one portion to the stirred solution of amine hydrochloride (2.45 g, 0.006m) in anhydrous DMF (30 ml) and NMO (5.0 g, 0.05m, 8.5 eq). The resulted heterogeneous mixture was vigorously stirred under nitrogen at RT for 2 hr. During that time all solids gradually dissolved, mixture remained however slightly cloudy. Reaction progress was monitored by TLC (silica gel plates, 5 x 10 cm, eluted with ethyl acetate-methanol 95:5 mixture). Product was isolated by diluting reaction mixture with sat. aq. sodium bicarbonate (250 ml) and extraction with ethyl acetate (3 x 150 ml). Combined extracts were washed with brine and dried over magnesium sulfate. Solution was filtered and evaporated, yield of crude product was 4.2 g (pale yellow oil). Product was purified using flash column chromatography on silica gel (Flash 65i cartridge, applied in dichloromethane solution and eluted with ethyl acetate-methanol 9:1 mixture). Fractions containing product were combined and evaporated to give pale yellow oil, 2.75 g. LC-MS (m/e): 649 (M+1); purity: 100% (254 nm). Purified product was treated with ethanolic hydrogen chloride (1.05 eq) and lyophilized (added ethanol to improve solubility before filtration). Yield of final hydrochloride salt was 2.6 g.

LC-MS (m/e): 649 (M+1); purity: 100% (254 nm).

^{1}H-NMR (MeOH-*d4*): δ 0.74 (t, 3H), 1.04 (t, 3H), 1.20 (t, 3H), 1.58 (m, 2H), 1.77 (m, 2H), 2.64 (q, 2H), 2.92 (m, 1H), 3.10-3.55 (m, 9H), 4.04 (m, 1H), 4.26 (m, 2H), 4.90 (s), 6.77 (m, 1H), 6.96 (d, 2H), 7.23-7.38 (m, 4H), 7.68 (t, 1H), 7.73 (d, 1H), 7.96 (d, 1H), 8.11 (t, 1H), 8.28 (t, 1H).

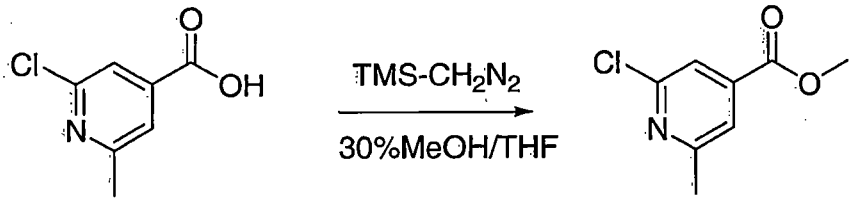
^{13}C-NMR: (MeOH-*d4*): 9.76, 10.19, 14.75, 20.21, 21.39, 28.10, 35.38, 46.60-48.31, 50.75, 54.12, 68.78, 101.22 (t), 111.53 (d), 120.48, 125.65, 126.12, 126.97, 128.70, 129.218, 130.56,

133.96, 134.97, 138.00, 142.84, 143.53, 145.16, 161.31 (d), 164.52 (d), 165.96, 167.36, 170.47.

Analysis: for $C_{36}H_{43}ClF_2N_4O_3S$ x 0.5 H_2O calcd.: C, 62.28; H, 6.39; N, 8.07; Cl, 5.11; found: C, 62.42; H 6.24; N, 8.03; Cl, 5.10.

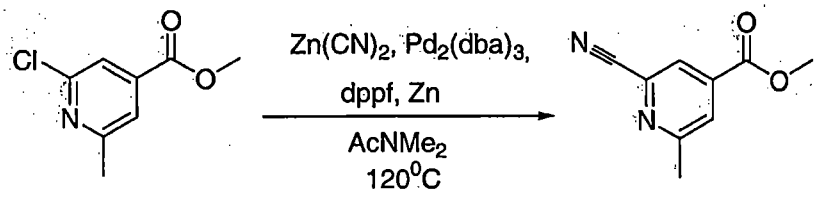
EXAMPLE SP-275

2-Dipropylcarbamoyl-6-methyl-isonicotinic acid



Commercially available, 2-chloro-methylisotinic acid (4.07g, 23.72 mmol) was dissolved in a 30%MeOH/ THF solution (32 ml). (Trimethylsilyl)diazomethane (2.0 M solution in hexanes) was added dropwise. Bubbling was observed and more reagent was added until bubbling ceased (15mL). The reaction mixture was allowed to stir overnight at room temp. Prior to evaporation of solvent, glacial acetic acid was added to the reaction flask dropwise in order to rid of excess amine.

EXAMPLE SP-276

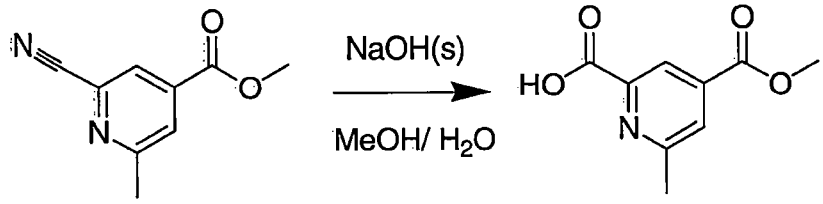


Reference: Fuqiang, J. and Confalone, N. Tet. Lett., 41, 2000, 3271-3273

Into a R.B flask equipped with a stir bar was added the methylated intermediate, tri(dibenzlideneacetone)dipalladium

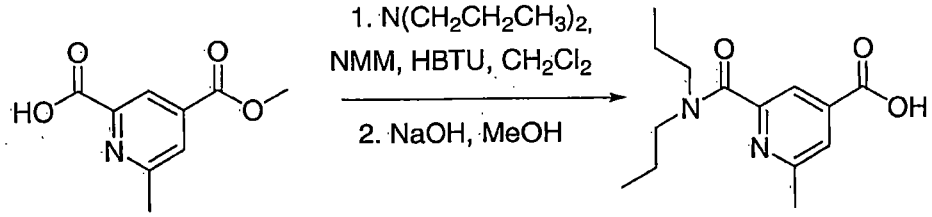
(0), 1,1-bis(diphenylphosphine), zinc metal dust and zinc cyanide. The flask was flushed with nitrogen gas for approx. 5 min. N,N-dimethylacetamide was added via syringe. The reaction mixture was refluxed in an oil bath set at 120°C with a condenser under nitrogen atmosphere. Stir vigorously. After 4 h, the reaction mixture was partitioned between ethyl acetate (50 ml) and 2N NH_4OH (50 ml) Repeat washing with 2N NH_4OH (2 x 50 ml) followed by brine (50 ml). Organic phases were collected and dried over Na_2SO_4, filtered and evaporated. Purification by column chromatography was performed with eluting solvent (80:20;Hex/EtOac).

EXAMPLE SP-277



Dissolve nitrile intermediate (0.206g, 1.170 mmol) in methanol (5 ml). Add sodium hydroxide (0.267g, 6.675 mmol) and continue to stir at room temp. After 90 min add water (5 ml) and continue to stir for an additional 90 min. Partition between chloroform and 2 N HCl (aq). Add NaCl(s) to aqueous phase in order to saturate. Continue extraction with isopropanol:chloroform (1:3). Collect organic phases, dry over $NaSO_4$, filter and evaporate.

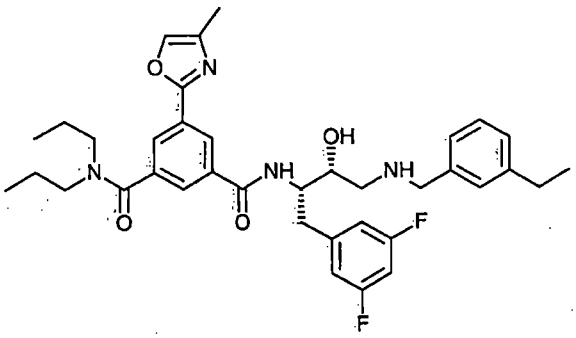
EXAMPLE SP-278



Anhydrous dichloromethane was added to the hydrolyzed intermediate (0.136, 0.697 mmol) followed by 4-methylmorpholine. The flask was placed on an ice bath to cool prior to addition of HBTU and dipropylamine. The mixture was allowed to warm to room temp. over night under nitrogen atmosphere. Partition reaction mixture between ethyl acetate (25 ml) and water (25 ml). Wash with water followed by sat. $NaHCO_3$ (2 x 25 ml). Organic phase was collected, dried over Na_2SO_4, filtered and evaporated.

EXAMPLE SP-279

N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(4-methyl-1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide



Step 1: A stirred solution of methyl 3-(aminocarbonyl)-5-[(dipropylamino)carbonyl]benzoate (200 mg, 0.65 mmol) chloroacetone (10 mL, 93 mmol) and potassium carbonate (90 mg, 0.65 mmol) was refluxed for 18 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with 2 N sodium hydroxide (2 x 50 mL), and saturated sodium

chloride, dried (magnesium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided methyl 3-[(dipropylamino)carbonyl]-5-(4-methyl-1,3-oxazol-2-yl)benzoate (119 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, J = 1 Hz, 1H), 8.20 (d, J = 1 Hz, 1H), 8.09 (d, J = 1 Hz, 1H), 7.48 (s, 1H), 3.96 (s, 3H), 3.46 (d, J = 7 Hz, 2H), 3.16 (t, J = 7 Hz, 2H), 2.26 (s, 3H), 1.71 (d, J = 7 Hz, 2H), 1.54 (d, J = 7 Hz, 2H), 1.00 (t, J = 7 Hz, 3H), 0.74 (t, J = 7 Hz, 3H); ESI MS m/z 345 $[M + H]^+$.

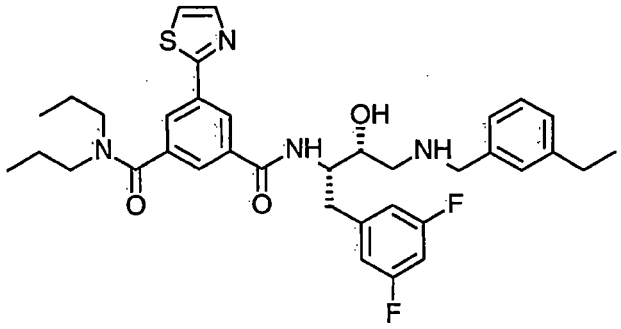
Step 2: A solution of methyl 3-[(dipropylamino)carbonyl]-5-(4-methyl-1,3-oxazol-2-yl)benzoate (118 mg, 0.34 mmol) in methanol (1 mL) and potassium hydroxide (1 mL of a 1.0 M solution in water, 1 mmol) was stirred at room temperature for 45 min. The solvent was removed under reduced pressure, the residue was dissolved in water, extracted with ethyl acetate, the aqueous layer was acidified to pH 4 with 1 N hydrochloric acid, extracted with chloroform (3 x 100 mL), and the combined organics were concentrated under reduced pressure to afford 3-[(dipropylamino)carbonyl]-5-(4-methyl-1,3-oxazol-2-yl)benzoic acid (110 mg): ^{1}H NMR (300 MHz, CD_3OD) δ 8.66 (d, J = 1 Hz, 1H), 8.17 (d, J = 1 Hz, 1H), 8.07 (d, J = 1 Hz, 1H), 7.75 (d, J = 1 Hz, 1H), 3.51 (t, J = 7 Hz, 2H), 3.25 (t, J = 7 Hz, 2H), 2.23 (s, 3H), 1.74 (d, J = 7 Hz, 2H), 1.60 (d, J = 7 Hz, 2H), 1.01 (t, J = 7 Hz, 3H), 0.76 (t, J = 7 Hz, 3H).

Step 3: A solution of 3-[(dipropylamino)carbonyl]-5-(4-methyl-1,3-oxazol-2-yl)benzoic acid (77.5 mg, 0.23 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (96 mg, 0.23 mmol), HOBt (32 mg, 0.23 mmol), and *N*-methylmorpholine (83 µL, 0.75 mmol) was stirred in dimethylformamide (2 mL) for 15 min. EDC (73 mg, 0.42 mmol) was added and the reaction mixture was stirred overnight. The

reaction mixture was diluted with water, and extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with 1 N hydrochloric acid (25 mL), saturated sodium bicarbonate (25 mL), saturated sodium chloride, dried (sodium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(4-methyl-1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide (40 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (br s, 1H, -NH), 8.17 (s, 1H), 8.05 (s, 1H), 7.52 (s, 1H), 7.38 (s, 1H), 7.24-7.08 (m, 5H), 7.02 (d, *J* = 8 Hz, 2H), 6.61 (t, *J* = 8 Hz, 1H), 4.27 (br s, 1H), 3.93 (d, *J* = 4 Hz, 1H), 3.85 (s, 2H), 3.54 (br s, 2H), 3.43 (br s, 2H), 2.84 (d, *J* = 5 Hz, 2H), 2.63 (q, *J* = 8 Hz, 2H), 2.18 (s, 3H), 1.74 (t, *J* = 5 Hz, 2H), 1.41 (d, *J* = 7 Hz, 2H), 1.22 (t, *J* = 8 Hz, 3H), 1.03 (t, *J* = 7 Hz, 3H), 0.64 (t, *J* = 7 Hz, 3H); ESI MS *m/z* 647 $[M + H]^+$

EXAMPLE SP-280

N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide



Step 1: To a -78 °C solution of thiazole (1.2 g) in THF (25 mL) was added n-butyl lithium (1.6 M in hexanes, 10 mL). The mixture was stirred for 30 min and then allowed to warm to 0 °C

in an ice/water bath. Zinc chloride (1M in ethyl ether, 40 mL) was added and the mixture was stirred for 1 h, at which time methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate (5.1 g) in THF (20 mL) was added, followed by $Pd(PPh_3)_4$ (palladium tetrakis triphenylphosphine) (0.68 g). The mixture was then heated at 80 °C for 2 h, at which time it was allowed to cool and partitioned between ethyl acetate and water. The organic layers were washed with brine, dried (magnesium sulfate), and concentrated. The residue was chromatographed on silica gel using ethyl acetate/heptane (50/50) to give 4.5 g of methyl 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoate.

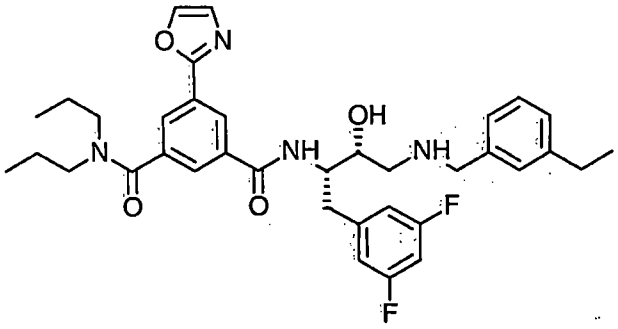
Step 2: Methyl 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoate (4.5 g) was dissolved in THF (20 mL), methanol (20 mL), and water (20 mL). Lithium hydroxide monohydrate (1.1 g) was added and the mixture was stirred at room temperature for 1.5 h, at which time the organic solvents were removed under reduced pressure. Some ethyl acetate and water were added and the pH was adjusted to about 0 with aq. HCl. The mixture was extracted with ethyl acetate and the organic layers were washed with brine, dried (magnesium sulfate), and concentrated to give 3.8 g of 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoic acid

Step 3: A solution of 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoic acid (156 mg, 0.47 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (191 mg, 0.47 mmol), HOBt (64 mg, 0.47 mmol), and *N*-methylmorpholine (200 µL, 1.5 mmol) was stirred in dimethylformamide (2 mL) for 15 min. EDC (145 mg, 0.84 mmol) was added and the reaction mixture was stirred overnight. The reaction mixture was diluted with water, and extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with 1 N hydrochloric acid (25 mL), saturated sodium bicarbonate

(25 mL), saturated sodium chloride, dried (sodium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3,N^3-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide (33 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (br s, 1H, -NH), 8.15 (br s, 1H), 7.94 (br s, 1H), 7.80 (d, *J* = 3 Hz, 1H), 7.51 (br s, 1H), 7.34 (d, *J* = 3 Hz, 1H), 7.27-7.24 (m, 1H), 7.21-7.18 (m, 2H), 7.11-7.10 (m, 1H), 7.00 (br s, 1H), 6.62-6.58 (m, 1H), 4.23 (d, *J* = 5 Hz, 1H), 3.91-3.85 (m, 3H), 3.57 (br s, 2H), 3.31 (br s, 2H), 3.05 (d, *J* = 5 Hz, 4H), 2.83 (d, , *J* = 6 Hz, 2H), 2.64 (q, *J* = 8 Hz, 2H), 1.75 (br s, 2H), 1.44 (t, *J* = 7 Hz, 2H), 1.22 (t, *J* = 8 Hz, 3H) 1.04 (t, *J* = 7 Hz, 3H), 0.65 (t, *J* = 7 Hz, 3H); ESI MS *m/z* 649 $[M + H]^+$;

EXAMPLE SP-281

N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide



Step 1. To an ice-cold, stirred solution of 3-amino-5-(methoxycarbonyl)benzoic acid (5.19 g, 26.59 mmol) in a 2 N hydrochloric acid (156 mL) was added a solution of sodium nitrite (1.84 g, 26.67 mmol) in water (10.8 mL). This mixture was then added dropwise to an ice-cold, stirred solution of potassium iodide (8.84 g, 53.25 mmol) in water (26.2 mL).

After stirring for 35 min, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with 5% aqueous sodium thiosulfate, and saturated sodium chloride, dried (sodium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 50:50:2 hexanes/ethyl acetate/acetic acid) afforded 3-iodo-5-(methoxycarbonyl)benzoic acid (4.48 g): ^{1}H NMR (500 MHz, DMSO-d_6): δ13.49 (br s, 1H), 8.45-8.38 (m, 3H), 3.83 (s, 3H); ESI-MS (*m/z*): 305 $[M + H]^+$.

Step 2: To a mixture of 3-iodo-5-(methoxycarbonyl)benzoic acid (65.8 g, 0.215 mol), triethylamine (52.2 g, 0.516 mol), and dipropylamine (23.9 g, 0.237 mol) in methylene chloride (950 mL) was added 2-chloro-1-methylpyridinium iodide (65.9 g, 0.258 mol). The reaction mixture was stirred at room temperature for 15 h and then concentrated under reduced pressure. Purification by silica gel plug (3:1 hexanes/ethyl acetate) provided methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate (66.8 g): ^{1}NMR (300 MHz, CDCl3) δ 8.39 (s, 1H), 7.98 (s, 1H), 7.88 (s, 1H), 3.93 (s, 3H), 3.45 (m, 2H), 3.14 (m, 2H), 1.69 (m, 2H), 1.54 (m, 2H), 0.98 (m, 3H), 0.77 (m, 3H).

Step 3: A stirred solution of 2-triethylstannyloxazole (Chem. Mater. 1994, 6, 1023)(1.5 g, 5.5 mmol) and methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate (1.8 g, 4.6 mmol) in dimethylformamide (12 mL) was degassed under reduced pressure for 15 min and purged with argon. Palladium(0) tetrakis(triphenylphosphine) (158 mg, 0.14 mmol) was added and the reaction mixture was degassed under reduced pressure for 15 min and then purged with argon. The reaction mixture was heated at reflux for 2 d, cooled to room temperature, diluted with ethyl acetate, washed with water (3 x 50 mL), dried

(sodium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided methyl 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoate (423 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.23 (s, 1H), 8.11 (s, 1H), 7.76 (s, 1H), 7.28 (s, 1H), 3.97 (s, 3H), 3.49 (br s, 2H), 3.18 (br s, 2H), 1.72 (d, *J* = 7 Hz, 2H), 1.55 (d, *J* = 7 Hz, 2H), 1.00 (t, *J* = 7 Hz, 3H), 0.75 (t, *J* = 7 Hz, 3H).

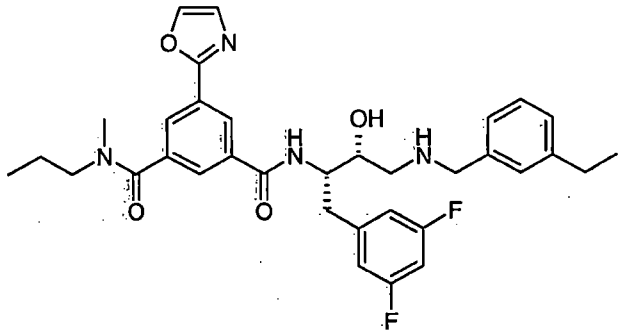
Step 4: A solution of methyl 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoate (315 mg, 0.95 mmol) in methanol (3 mL) and potassium hydroxide (3 mL of a 1.0 M solution in water, 3 mmol) was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, the residue was dissolved in water, and extracted with ethyl acetate. The aqueous layer was acidified to pH 3 with 1 M hydrochloric acid, extracted with chloroform (3 x 100 mL), and the combined organic layers were concentrated under reduced pressure to afford 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid (265 mg): ^{1}H NMR (300 MHz, CD_3OD) δ 8.71 (s, 1H), 8.08 (s, 2H), 8.05 (s, 1H), 7.34 (s, 1H), 3.52 (t, *J* = 8 Hz, 2H), 3.26 (t, *J* = 8 Hz, 2H), 1.75 (q, *J* = 8 Hz, 2H), 1.59 (q, *J* = 8 Hz, 2H), 1.02 (t, *J* = 8 Hz, 3H), 0.74 (t, *J* = 8 Hz, 3H).

Step 5: A solution of 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid (133 mg, 0.42 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (171 mg, 0.42 mmol), HOBt (57 mg, 0.42 mmol), and *N*-methylmorpholine (148 µL, 1.3 mmol) was stirred in dimethylformamide (2 mL) for 15 min. EDC (130 mg, 0.75 mmol) was added and the reaction mixture was stirred overnight. The reaction mixture was diluted with water, and extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with 1 M hydrochloric acid (25 mL), saturated sodium bicarbonate

(25 mL), saturated sodium chloride, dried (sodium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide (62 mg): mp 65-67 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (br s, 1H), 8.15 (s, 2H), 7.69 (s, 1H), 7.60 (s, 1H), 7.25 (t, *J* = 8 Hz, 1H), 7.19-7.17 (m, 3H), 7.10 (d, *J* = 8 Hz, 1H), 6.96 (d, *J* = 8 Hz, 2H), 6.60 (t, *J* = 8 Hz, 1H), 4.27 (d, *J* = 8 Hz, 1H), 3.88-3.80 (m, 3H), 3.53 (br s, 2H), 3.44 (br s, 2H), 3.09-3.01 (m, 4H), 2.85-2.82 (m, 2H), 2.62 (t, *J* = 8 Hz, 2H), 1.74 (br s, 2H), 1.45 (br s, 2H), 1.21 (t, *J* = 8 Hz, 3H), 1.03 (t, *J* = 7 Hz, 3H), 0.66 (t, *J* = 7 Hz, 3H); APCI MS *m/z* 633 $[M + H]^+$

EXAMPLE SP-281

N^1-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-methyl-5-(1,3-oxazol-2-yl)-N^3-propylisophthalamide



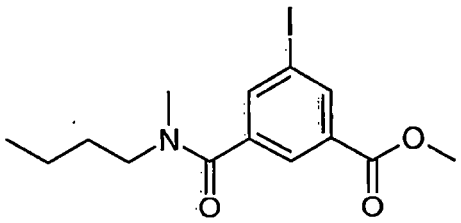
To 3-{[Methyl(propyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoic acid (350 mg, 1.2 mmol) in DMF (5 mL) is added diisopropylethylamine (835 µL, 4.8 mmol), HATU (554 mg, 1.5 mmol), then (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-272 (488 mg, 1.2 mmol). The reaction is stirred for 16 h at room temperature. The reaction is

partitioned between chloroform and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9% methanol/chloroform) gives the title compound. ESI MS *m/z* 605.3 $[M + H]^+$.

EXAMPLE SP-282

Step 1

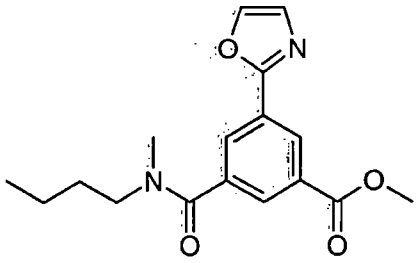
Methyl 3-{[butyl(methyl)amino]carbonyl}-5-iodobenzoate



3-Iodo-5-(methoxycarbonyl)benzoic acid (1 g, 3.3 mmol) is dissolved in DMF (10 mL), and diisopropylethylamine (1.7 mL, 9.8 mmol), HATU (1.5 g, 3.9 mmol), and *N*-methylbutylamine (581 µL, 4.9 mmol) are added. The reaction stirred at room temperature 2 h. The reaction is partitioned between ethyl acetate and water. The organic layer is washed with saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 40% ethyl acetate/hexane) provides the title compound. ESI MS *m/z* 376.1 $[M + H]^+$.

Step 2

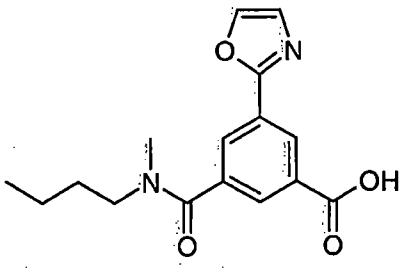
Methyl 3-{[butyl(methyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoate



To a -70 °C stirred solution of oxazole (167 mg, 2.4 mmol) in tetrahydrofuran (4 mL) is added *n*-butyllithium (1.6 M in hexanes, 1.7 mL, 2.7 mmol). After 30 min, zinc chloride (1 M in diethyl ether, 7.3 mL, 7.3 mmol) is added and the reaction mixture is warmed to 0 °C for 1 h. To this mixture is added a solution of methyl 3-{[butyl(methyl)amino]carbonyl}-5-iodobenzoate (864 mg, 2.3 mmol) in anhydrous tetrahydrofuran (3 mL) followed by palladium(0) tetrakis(triphenylphosphine) (112 mg, 0.10 mmol). The reaction mixture is heated at reflux for 1.5 h. The reaction mixture is cooled, diluted with ethyl acetate, washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 60% ethyl acetate/hexane) provides the title compound. ESI MS *m/z* 317.1 $[M + H]^+$.

Step 3

3-{[Butyl(methyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoic acid

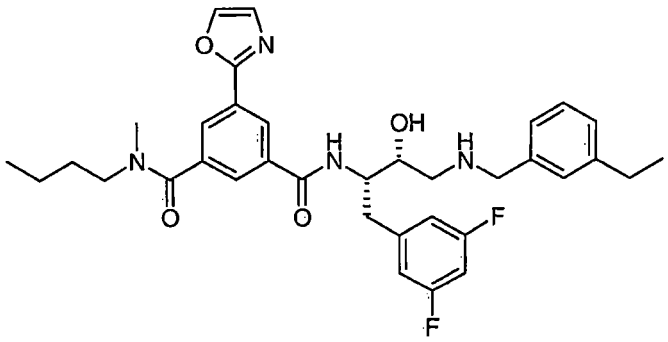


To methyl 3-{[butyl(methyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoate (660 mg, 2.1 mmol) in tetrahydrofuran/methanol/water (1:1:1, 9 mL) is added lithium hydroxide monohydrate (175 mg, 4.2 mmol), and the reaction is

stirred at room temperature 16 h. The solution is diluted in chloroform and washed with water and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS *m/z* 301.1 $[M - H]^-$.

Step 4

N^1-butyl-N^3-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^1-methyl-5-(1,3-oxazol-2-yl)isophthalamide



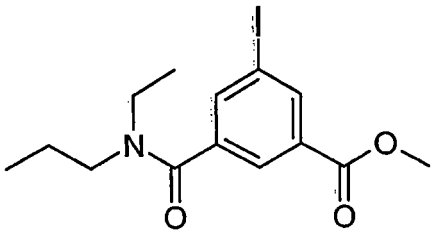
3-{[Butyl(methyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoic acid (237 mg, 0.78 mmol) is dissolved in DMF (5 mL), and diisopropylethylamine (546 µL, 3.1 mmol), HATU (358 mg, 0.94 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-272 (319 mg, 0.78 mmol) are added. The reaction stirred at room temperature 5 h. The reaction mixture is diluted with chloroform, washed with water, 1N hydrochloric acid (aq), saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9% methanol/methylene chloride) provides the title compound. ESI MS *m/z* 619.3 $[M + H]^+$.

EXAMPLE SP-283

N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-ethyl-5-(1,3-oxazol-2-yl)-N^3-propylisophthalamide

Step 1

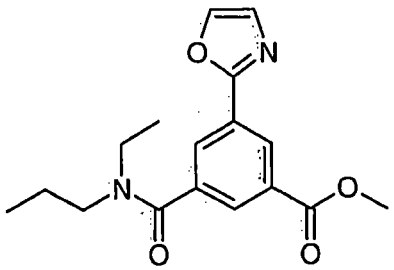
Methyl 3-{[ethyl(propyl)amino]carbonyl}-5-iodobenzoate



3-Iodo-5-(methoxycarbonyl)benzoic acid (1 g, 3.3 mmol) is dissolved in DMF (10 mL), and diisopropylethylamine (1.7 mL, 9.8 mmol), HATU (1.5 g, 3.9 mmol), and *N*-ethylpropylamine (572 µL, 4.9 mmol) are added. The reaction stirred at room temperature 16 h. The reaction is partitioned between ethyl acetate and water. The organic layer is washed with saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 40% ethyl acetate/hexane) provides the title compound. ESI MS *m/z* 376.1 $[M + H]^+$.

Step 2

Methyl 3-{[ethyl(propyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoate

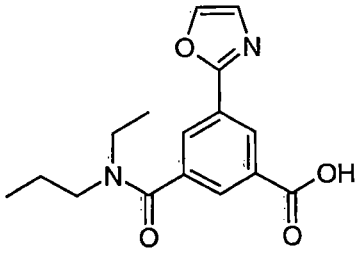


To a -70 °C stirred solution of oxazole (106 mg, 1.5 mmol) in tetrahydrofuran (4 mL) is added *n*-butyllithium (1.6 M in hexanes, 1.0 mL, 1.7 mmol). After 30 min, zinc chloride (1 M

in diethyl ether, 4.6 mL, 4.6 mmol) is added and the reaction mixture is warmed to 0 °C for 1 h. To this mixture is added a solution of methyl 3-{[ethyl(propyl)amino]carbonyl}-5-iodobenzoate (535 mg, 1.45 mmol) in anhydrous tetrahydrofuran (1.8 mL) followed by palladium(0) tetrakis(triphenylphosphine) (120 mg, 0.10 mmol). The reaction mixture is heated at reflux for 2 h. The reaction mixture is cooled, diluted with ethyl acetate, washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 60% ethyl acetate/hexane) provides the title compound. ESI MS *m/z* 317.1 $[M + H]^+$.

Step 3

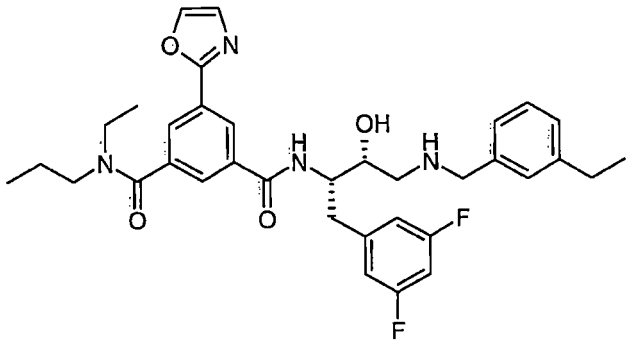
3-{[Ethyl(propyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoic acid



To methyl 3-{[ethyl(propyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoate (375 mg, 1.2 mmol) in tetrahydrofuran/methanol/water (1:1:1, 9 mL) is added lithium hydroxide monohydrate (100 mg, 2.4 mmol), and the reaction is stirred at room temperature 16 h. The solution is diluted in chloroform and washed with water and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS *m/z* 301.1 $[M - H]^-$.

Step 4

N^1-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-ethyl-5-(1,3-oxazol-2-yl)-N^3-propylisophthalamide



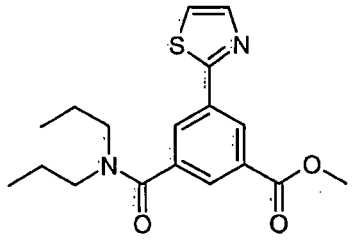
3-{[Ethyl(propyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoic acid (290 mg, 0.96 mmol) is dissolved in DMF (5 mL), and diisopropylethylamine (668 µL, 3.8 mmol), HATU (438 mg, 1.15 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-272 (391 mg, 0.96 mmol) are added. The reaction stirred at room temperature 5 h. The reaction mixture is diluted with chloroform, washed with water, 1N hydrochloric acid (aq), saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9% methanol/methylene chloride) provides the title compound. ESI MS *m/z* 619.3 $[M + H]^+$.

EXAMPLE SP-284

N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-N^3,N^3-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide

Step 1

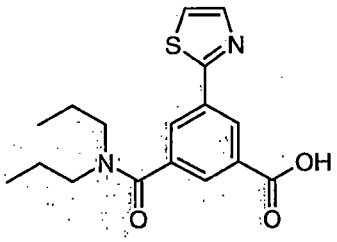
Methyl 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoate



To 0.5M thiazole zinc bromide (45 mL) is added methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate (8.6 g, 21.4 mmol) in THF (130 mL), then palladium(0) tetrakis(triphenylphosphine) (2 g, 1.7 mmol) are added. The reaction mixture is heated at reflux for 16 h, cooled to room temperature, and then filtered. The solution is washed with water, saturated sodium bicarbonate, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (35% ethyl acetate/hexane) yields the title compound. ESI MS *m/z* 347.1 $[M + H]^+$.

Step 2

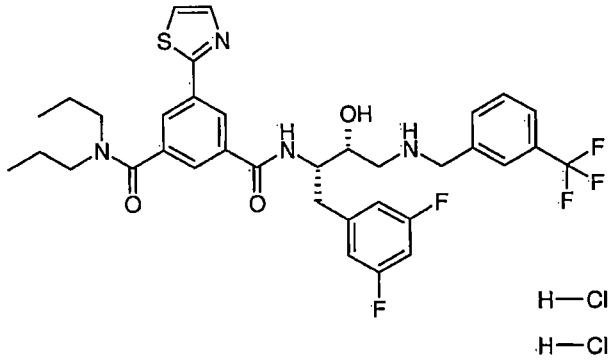
3-[(Dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoic acid



Methyl 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoate (4.4 g, 12.8 mmol) is dissolved in 1:1:1 tetrahydrofuran/methanol/water (60 mL), and lithium hydroxide monohydrate is added (1.1 g, 25.6 mmol), and the reaction stirred 15 min. The solution is concentrated under reduced pressure and diluted in chloroform. The solution is washed with water and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS *m/z* 333.1 $[M + H]^+$.

Step 3

N^1-((1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-N^3,N^3-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide dihydrochloride

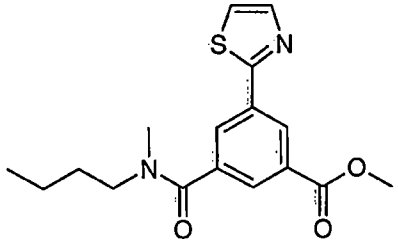


3-[(Dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoic acid is dissolved in DMF (10 mL), and diisopropylethylamine (364 µL, 2.1 mmol), HATU (237 mg, 0.62 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[3-(trifluoromethyl)benzyl]amino}butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-311 (250 mg, 0.52 mmol) are added. The reaction stirred at room temperature 4 h. The reaction mixture is diluted with chloroform, washed with water, saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 689.3 $[M + H]^+$.

EXAMPLE SP-285

Step 1

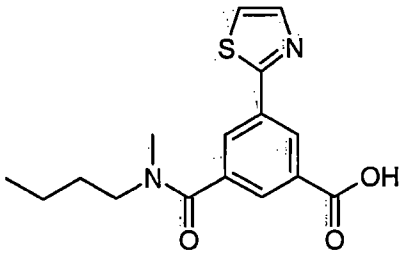
3-{[Butyl(methyl)amino]carbonyl}-5-(1,3-thiazol-2-yl)benzoic acid



To 0.5M thiazole zinc bromide (4.5 mL) is added methyl 3-{[butyl(methyl)amino]carbonyl}-5-iodobenzoate (700 mg, 1.9 mmol) in THF (5 mL), then palladium(0) tetrakis(triphenylphosphine) (175 mg, 0.15 mmol) are added. The reaction mixture is heated at reflux for 16 h, cooled to room temperature, and then filtered. The solution is washed with water, saturated sodium bicarbonate, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (35% ethyl acetate/hexane) yields the title compound. ESI MS *m/z* 333.1 $[M + H]^+$.

Step 2

3-{[Butyl(methyl)amino]carbonyl}-5-(1,3-thiazol-2-yl)benzoic acid

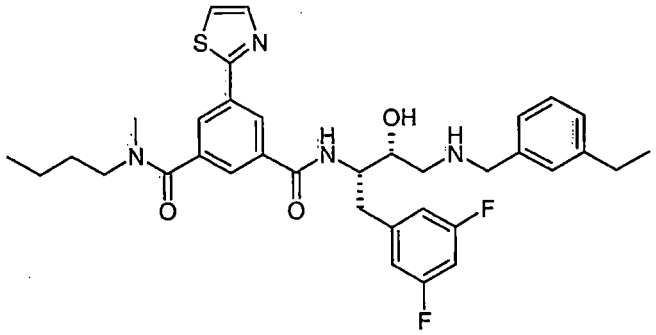


3-{[Butyl(methyl)amino]carbonyl}-5-(1,3-thiazol-2-yl)benzoic acid (410 mg, 1.23 mmol) is dissolved in 1:1:1 tetrahydrofuran/methanol/water (9 mL), and lithium hydroxide monohydrate is added (103 mg, 2.5 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced

pressure and diluted in ethyl acetate. The solution is washed with water and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS *m/z* 319.1 $[M + H]^+$.

Step 3

N^1-Butyl-N^3-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^1-methyl-5-(1,3-thiazol-2-yl)isophthalamide

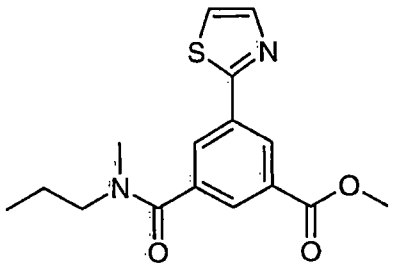


3-{[Butyl(methyl)amino]carbonyl}-5-(1,3-thiazol-2-yl)benzoic acid (125 mg, 0.39 mmol) is dissolved in DMF (3 mL), and diisopropylethylamine (271 µL, 1.6 mmol), HATU (178 mg, 0.47 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[3-(trifluoromethyl)benzyl]amino}butan-2-ol dihydrochloride (176 mg, 0.43 mmol) are added. The reaction stirred at room temperature 4 h. The reaction mixture is diluted with chloroform, washed with water, saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS *m/z* 635.3 $[M + H]^+$.

EXAMPLE SP-286

Step 1

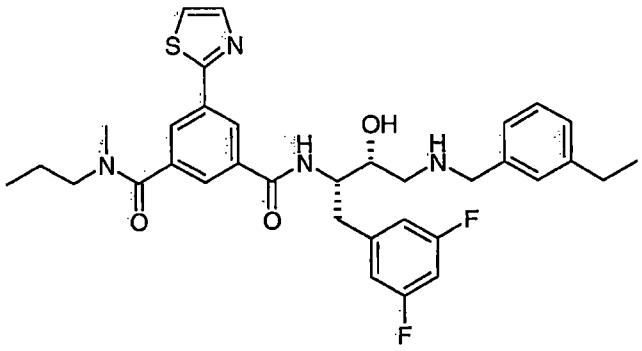
Methyl 3-{[methyl(propyl)amino]carbonyl}-5-(1,3-thiazol-2-yl)benzoate



To 0.5M thiazole zinc bromide (4.1 mL) is added methyl 3-iodo-5-{[methyl(propyl)amino]carbonyl}benzoate (616 mg, 1.7 mmol) in THF (5 mL), then palladium(0) tetrakis(triphenylphosphine) (158 mg, 0.14 mmol) are added. The reaction mixture is heated at reflux for 16 h, cooled to room temperature, and then filtered. The solution is washed with water, saturated sodium bicarbonate, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (35% ethyl acetate/hexane) yields the title compound. ESI MS *m/z* 319.1 $[M + H]^+$.

Step 2

N^1-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N^3-methyl-5-(1,3-thiazol-2-yl)-N^3-propylisophthalamide



Methyl 3-{[methyl(propyl)amino]carbonyl}-5-(1,3-thiazol-2-yl)benzoate (390 mg, 1.22 mmol) is dissolved in 1:1:1 tetrahydrofuran/methanol/water (9 mL), and lithium hydroxide monohydrate is added (103 mg, 2.4 mmol), and the reaction stirred 2 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (355 μL, 2.0 mmol), HATU (230 mg, 0.61 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-272 (206 mg, 0.51 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9% methanol/methylene chloride) provides the title compound. ESI MS *m/z* 621.3 $[M + H]^+$.

EXAMPLE SP-287

{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-dipropyl-5-pyridin-4-ylisophthalamide dihydrochloride

Step 1: To a stirred solution of borate ester methyl 3-[(dipropylamino)carbonyl]-5-(3,3,4,4-tetramethylborolan-1-yl)benzoate dissolved in 1,4-dioxane (9.3 mL) was added sodium carbonate (2 mL of a 2 M solution in water, 4 mmol), 4-bromopyridine hydrochloride (250 mg, 1.3 mmol), and the reaction mixture was degassed for 15 min. The reaction mixture was flushed with argon and heated to reflux overnight. The reaction mixture was cooled to room temperature, diluted with water, extracted with ethyl acetate (3 x 50 mL), dried (magnesium sulfate), filtered, and concentrated under reduced

pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided methyl 3-[(dipropylamino)carbonyl]-5-pyridin-4-ylbenzoate (240 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, J = 7 Hz, 2H), 8.10 (t, J = 3 Hz, 1H), 8.04 (t, J = 3 Hz, 1H), 7.97 (t, J = 3 Hz, 1H), 7.48 (d, J = 6 Hz, 2H), 3.45 (m, 2H), 3.16 (m, 2H), 2.09 (s, 3H), 1.69 (m, 2H), 1.54 (m, 2H), 0.94 (m, 3H), 0.74 (m, 3H).

Step 2: To a stirred solution of 1-methyl 3-[(dipropylamino)carbonyl]-5-pyridin-4-ylbenzoate (240 mg, 0.7 mmol) in methanol (1.5 mL), tetrahydrofuran (0.7 mL), and water (0.7 mL) was added lithium hydroxide (58 mg, 1.4 mmol). The reaction mixture was stirred for 4 h, and concentrated under reduced pressure. The residue was dissolved in water, and extracted with ethyl acetate (3 x 75 mL). The aqueous layer was acidified to pH 5 with 1 N hydrochloric acid and extracted with chloroform (4 x 50 mL). The combined organic extracts were dried (magnesium sulfate), filtered, and concentrated under reduced pressure to provide a pyridine (160 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (d, J = 5 Hz, 2H), 8.45 (s, 1H), 8.19 (s, 1H), 7.89 (s, 1H), 7.69 (d, J = 6 Hz, 2H), 3.50 (d, J = 7 Hz, 2H), 1.74 (d, J = 7 Hz, 2H), 1.02 (m, 3H), 0.78 (m, 3H).

Step 3: To a stirred solution of pyridine from step 3 (160 mg, 0.49 mmol) in dichloromethane (1.96 mL) was added DIPEA (190 mg, 1.47 mmol), HATU (278 mg, 0.73 mmol), and HOBt (99 mg, 0.73 mmol), followed by amine **2** (200 mg, 0.49 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was partitioned between dichloromethane and water. The organic layer was washed with saturated sodium bicarbonate, saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. The resulting oil was dissolved in a minimal amount of

methanol, and precipitated with hydrochloric acid (10 mL of a 1 M solution in diethyl ether, 10 mmol). The precipitate was filtered, washed with diethyl ether, and dried under vacuum to afford the title compound (100 mg): mp 166-169 °C; APCI MS *m/z* 643 $[M + H]^+$.

EXAMPLE SP-288

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(methylsulfonyl)methyl]piperidine-1-carboxamide:

Step 1: To an ice-cold, stirred solution of acid 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (1.0 g, 4.4 mmol) in tetrahydrofuran (11 mL) was added borane-dimethylsulfide complex (3.4 mL of a 2.0 M solution in tetrahydrofuran, 6.8 mmol). After 2 h, the reaction mixture was quenched with methanol, and concentrated under reduced pressure to provide an alcohol (939 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (br s, 2H), 3.50 (t, *J* = 6 Hz, 2H), 2.68 (d, *J* = 12 Hz, 2H), 1.74-1.65 (m, 3H), 1.45 (s, 9H), 1.31 (t, *J* = 7 Hz, 1H), 1.14 (dd, *J* = 12, 4 Hz, 2H).

Step 2: To an ice-cold, stirred solution of the alcohol from step 1 (450 mg, 2.1 mmol) and triethylamine (0.32 mL, 2.3 mmol) in tetrahydrofuran (6 mL) was added methanesulfonyl chloride (0.18 mL, 2.3 mmol). The reaction mixture was stirred for 5 min and then sodium iodide (375 mg, 2.3 mmol) was added. The reaction mixture was warmed to room temperature and filtered. To the collected filtrate was added sodium thiomethoxide (161 mg, 2.3 mmol) and the reaction mixture was heated at reflux for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with water, and saturated sodium chloride, dried

(sodium sulfate), filtered, and concentrated under reduced pressure to provide tert-butyl 4-[(methylthio)methyl]piperidine-1-carboxylate (430 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (t, J = 7 Hz, 2H), 2.69 (t, J = 12 Hz, 2H), 2.42 (d, J = 7 Hz, 2H), 2.10 (s, 3H), 1.83-1.78 (m, 2H), 1.66-1.59 (m, 2H), 1.45 (s, 9H), 1.26-1.06 (m, 2H).

Step 3: A solution of sulfide from step 2 (420 mg, 1.7 mmol), hydrogen peroxide (11 mL of a 30% solution in water, 170 mmol), and sodium bicarbonate (143 mg, 1.7 mmol) in acetone (10 mL) was stirred for 18 h. The reaction mixture was washed with 1.3 N sodium hydroxide, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to provide a sulfone (390 mg): ^{1}H NMR (300 MHz, $CDCl_3$) □ 4.11 (t, J = 7 Hz, 2H), 2.94 (s, 3H), 2.81-2.73 (m, 2H), 2.35-2.20 (m, 2H), 1.96-1.91 (m, 2H), 1.45 (s, 9H), 1.38-1.23 (m, 3H).

Step 4: A solution of sulfone from step 3 (390 mg, 1.4 mmol) and hydrochloric acid (4 mL of a 4 M solution in dioxane, 14 mmol) was stirred for 18 h. The resulting precipitate was collected by filtration to provide tert-butyl 4-[(methylsulfonyl)methyl]piperidine-1-carboxylate (220 mg): ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.94 (br s, 1H), 8.70 (br s, 1H), 3.24-3.15 (m, 4H), 3.00 (s, 3H), 2.89 (q, J = 7 Hz, 2H), 2.29-2.18 (m, 1H), 1.97 (d, J = 13 Hz, 2H), 1.57-1.43 (m, 2H).

Step 5: To an ice-cold, stirred solution of triphosgene (108 mg, 0.36 mmol) and diisopropylethylamine (0.6 mL, 3.3 mmol) in methylene chloride (2.0 mL) was added amino sulfone from step 4 (210 mg, 0.98 mmol) in methylene chloride (3.5 mL) dropwise. After 5 min a solution of dihydrochloride of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (401 mg, 0.98 mmol) was added and the reaction mixture was warmed

until the solution became homogeneous. The reaction mixture was diluted with methylene chloride, washed with 1 N hydrochloric acid (25 mL), saturated sodium bicarbonate (25 mL), and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 15:85 methanol/chloroform) provided a clear solid. The solid was dissolved in methanol (1 mL), and treated with hydrochloric acid (0.3 mL of a 1.0 M solution in diethyl ether, 0.3 mmol). The resulting precipitate was collected by filtration to provide the title compound (38 mg): mp 130-134 °C; APCI MS *m/z* 538 $[M + H]^+$.

EXAMPLE SP-289

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(methylsulfonyl)methyl]cyclohexane carboxamide

Step 1: To a stirred solution of dimethyl cyclohexane-1,4-dicarboxylate (10.2 g, 51 mmol) in a mixture of 2:1:1 tetrahydrofuran/methanol/water (52 mL) was added lithium hydroxide (2.13 g, 51 mmol). The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was partitioned between diethyl ether and water. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid, and the precipitate collected, and dried under vacuum to afford 4-(methoxycarbonyl)cyclohexanecarboxylic acid (7.4 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.33-2.27 (m, 2H), 2.11-2.06 (m, 4H), 1.50-1.43 (m, 4H).

Step 2: To an ice-cold, stirred solution of acid (3.2 g, 17 mmol) in tetrahydrofuran (40 mL) was added borane-dimethyl

sulfide complex (12 mL, 22 mmol). The reaction mixture was heated at 70 °C for 2 h and a 1:1 mixture of acetic acid/water (10 mL) added. The resulting mixture was concentrated. Purification by flash column chromatography (silica, 1:1 hexanes/ethyl acetate) provided methyl 4 (hydroxymethyl)cyclohexanecarboxylate (1.26 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.48-3.46 (m, 2H), 2.26-2.15 (m, 1H), 2.05-1.85 (m, 4H), 1.52-1.42 (m, 3H), 1.02-0.97 (m, 2H).

Step 3: To an ice-cold, stirred solution of the alcohol (365 mg, 2.12 mmol) and triethylamine (440 µL, 4.8 mmol) in methylene chloride (5 mL) was added mesyl chloride (200 µL, 2.6 mmol). The reaction mixture was stirred for 20 min and then partitioned between methylene chloride and water. The organic layer was washed with 1 M hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), and concentrated under reduced pressure to afford a the desired mesylate, which was carried on without purification or characterization.

Step 4: To a stirred solution of the mesylate from step 3 (2.12 mmol) in tetrahydrofuran (5 mL) was added sodium iodide (640 mg, 4.3 mmol). The reaction mixture was heated to 60 °C for 5 h and then filtered. The reaction mixture was concentrated under reduced pressure, and carried on without purification or characterization.

Step 5: To a stirred solution of the iodide from step 4 (2.12 mmol) in a mixture of *N*,*N*-dimethylformamide (10 mL) and tetrahydrofuran (1 mL) was added sodium thiomethoxide (450 mg, 6.4 mmol). The reaction mixture was heated at 70 °C for 15 h. The reaction mixture was allowed to cool to room temperature, the solvents were removed, and the residue was partitioned between ether and water. The aqueous layer was acidified to

pH 1 with 1 N hydrochloric acid, extracted with ethyl acetate, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford methyl 4-[(methylthio)methyl]cyclohexanecarboxylate (230 mg): ^{1}H NMR (300 MHz, CD_3OD) δ 2.40-2.37 (m, 2H), 2.22-2.05 (m, 1H), 2.05 (s, 3H), 2.02-1.93 (m, 4H), 1.48-1.38 (m, 3H), 1.03-0.95 (m, 2H).

Step 6: To a stirred solution of the methyl sulfide (240 mg, 1.3 mmol) in sodium hydroxide solution (3.5 mL, 0.5 M solution) was added sodium bicarbonate (870 mg, 10.3 mmol) and acetone (1 mL) followed by the addition of a solution of oxone (1.0 g, 1.7 mmol) in 0.0004 M EDTA (4 mL). The reaction mixture was stirred at room temperature for 2 h and then quenched with sodium bisulfite. The reaction mixture was acidified with hydrochloric acid and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide acid 4-[(methylthio)methyl]cyclohexanecarboxylic acid (240 mg): ^{1}H NMR (300 MHz, CD_3OD) δ 3.06-3.04 (m, 2H), 2.96 (s, 3H), 2.28-2.20 (m, 1H), 2.08-1.98 (m, 5H), 1.50-1.40 (m, 2H), 1.21-1.16 (m, 2H).

Step 7: To a stirred solution of the acid (120 mg, 0.6 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (230 mg, 0.6 mmol), and HATU (210 mg, 0.6 mmol) in methylene chloride (5 mL) was added *N,N*-diisopropylethylamine (340 µL, 1.93 mmol). The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was partitioned between methylene chloride and water. The organic layer was washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford a crude oil. Purification by flash column

chromatography (silica, gradient 95:5 to 93:7 methylene chloride/methanol) provided the title compound (35 mg): mp 178-180 ºC; ESI MS *m/z* 537 $[M + H]^+$.

EXAMPLE SP-290

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-piperidin-4-yl-N\(u)3\(d),N\(u)3\(d)-dipropylisophthalamide

Step 1: To a -70 °C stirred solution of N-Boc-piperidone (500 mg, 2.5 mmol) in tetrahydrofuran (11 mL) was added lithium diisopropylamine (1.37 mL of a 2 M solution in tetrahydrofuran, 2.75 mmol). The reaction mixture was stirred for 2 h, warmed to 0 °C, and *N*-phenyltriflamide (955 mg, 2.67 mmol) was added. The solution was allowed to warm to room temperature and was stirred for 12 h. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography (3:1 hexanes/ethyl acetate) afforded tert-butyl 4-{[(trifluoromethyl)sulfonyl]oxy}-3,6-dihydropyridine-1(2H)-carboxylate (240 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (s, 1H), 4.05 (m, 2H), 3.63 (m, 2H), 2.45 (m, 2H), 1.48 (s, 9H).

Step 2: To a stirred solution of the triflate (240 mg, 0.72 mmol) and borate ester methyl 3-[(dipropylamino)carbonyl]-5-(3,3,4,4-tetramethylborolan-1-yl)benzoate (280 mg, 0.72 mmol) in dioxane (3 mL) was added sodium carbonate (1.1 mL of a 2 M solution in water, 2.16 mmol). The reaction mixture was flushed with argon, palladium(0) tetrakis(triphenylphosphine) (34 mg, 0.03 mmol) was added, and the reaction mixture was heated at reflux for 12 h. The reaction mixture was cooled to room temperature, filtered through diatomaceous earth, dried (magnesium sulfate), filtered, and concentrated under reduced

pressure. Purification by flash column chromatography (90:10 chloroform/methanol) afforded an acid (160 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.95 (s, 1H), 7.58 (s, 1H), 6.15 (br s, 1H), 4.10 (s, 2H), 3.65 (m, 2H), 3.48 (m, 2H), 3.16 (s, 2H), 2.54 (s, 2H), 1.70 (s, 2H), 1.50 (s, 9H), 1.25 (m, 2H), 0.99 (s, 3H), 0.76 (s, 3H).

Step 3: A solution of the acid from step 2 (160 mg, 0.37 mmol) and 10% Pd/C (25 mg) in ethanol (10 mL) was degassed with nitrogen for 15 min, and shaken under an atmosphere of hydrogen at 50 psi for 12 h. The reaction mixture was filtered through diatomaceous earth, and concentrated under reduced pressure to give acid 3-[1-(tert-butoxycarbonyl)piperidin-4-yl]-5-[(dipropylamino)carbonyl]benzoic acid (121 mg), which was carried on without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 12 Hz, 2H), 7.44 (s, 1H), 4.27 (br s, 2H), 3.43 (m, 2H), 3.14 (m, 2H), 2.78 (m, 4H), 1.84 (m, 3H), 1.63 (m, 6H), 1.49 (s, 9H), 1.23 (m, 3H), 0.86 (m, 3H), 0.75 (m, 3H).

Step 4: To a stirred solution of the acid (120 mg, 0.28 mmol) in methylene chloride (2 mL) was added *N,N*-diisopropylethylamine (0.141 mL, 0.84 mmol), HOBt (56 mg, 0.42 mmol), and HATU (160 mg, 0.42 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (114 mg, 0.28 mmol). The reaction mixture was stirred for 16 h at room temperature. The reaction mixture was diluted with methylene chloride (25 mL), washed with water, saturated sodium bicarbonate, and saturated sodium chloride, and dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (93:7 chloroform/methanol) afforded a piperidine (90 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 7.14 (m,

4H), 6.79 (m, 2H), 6.64 (m, 1H), 4.29 (m, 3H), 3.68 (m, 4H), 3.47 (m, 2H), 3.02 (m, 4H), 2.77 (m, 5H), 2.66 (m, 2H), 1.71 (m, 8H), 1.48 (s, 9H), 1.24 (m, 5H), 0.99 (m, 3H), 0.73 (m, 3H).

Step 5: A solution of piperidine from step 4 (90 mg, 0.12 mmol) and hydrochloric acid (0.3 mL of a 4.0 M solution in dioxane, 1.2 mmol) was stirred for 30 min at room temperature. The reaction mixture was concentrated under reduced pressure, washed with ether (50 mL), and filtered. Purification by flash column chromatography (89:10:1 chloroform/methanol/ammonium hydroxide) afforded the title compound (35 mg): mp 84-87 °C; ESI MS *m/z* 649 $[M + H]^+$.

EXAMPLE SP-291

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-(1,3-oxazol-2-yl)benzamide hydrochloride

Step 1: To an ice-cold, stirred solution of acid 3-(methoxycarbonyl)-5-nitrobenzoic acid (24.6 g, 0.11 mol) in tetrahydrofuran (200 mL) was added borane-dimethylsulfide complex (82 mL of a 2.0 M solution in tetrahydrofuran, 0.16 mol) and the reaction mixture was heated at reflux for 24 h. The reaction mixture was cooled to room temperature, quenched with methanol, and the solvent was removed under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided an alcohol (16 g): ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.51 (d, J = 1 Hz, 1H), 8.42 (s, 1H), 8.32 (s, 1H), 5.69 (t, J = 6 Hz, 1H), 4.70 (d, J = 6 Hz, 2H), 3.93 (s, 3H).

Step 2: To an ice-cold, stirred solution of the alcohol from step 1 (6.6 g, 32 mmol) in methylene chloride was added phosphorus tribromide (1.5 mL, 16 mmol) and the reaction mixture was stirred for 40 min. The reaction mixture was diluted with methylene chloride, washed with saturated sodium bicarbonate, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to give a bromide (8.1 g): ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.79 (t, J = 2 Hz, 1H), 8.45 (t, J = 2 Hz, 1H), 8.39 (d, J = 2 Hz, 1H), 4.57 (s, 2H), 4.00 (s, 3H).

Step 3: A solution of bromide from step 2 (8.1 g, 32 mmol) and 10% Pd/C (1.0 g) in 13:4:1 methanol/ethyl acetate/acetic acid (90 mL) was shaken under an atmosphere of hydrogen at 45 psi for 24 h. The reaction mixture was filtered through diatomaceous earth, and concentrated under reduced pressure to provide 1 methyl 3-amino-5-methylbenzoate (2.8 g): ESI MS m/z 166 $[M + H]^+$.

Step 4: To an ice-cold, stirred solution of the aniline (2.8 g, 17 mmol) in 2 N hydrochloric acid (48 mL) was added a solution of sodium nitrite (1.2 g, 17 mmol) in water (10 mL), and the reaction mixture was stirred for 30 min. This reaction mixture was added to an ice-cold, stirred solution of potassium iodide (5.6 g, 34 mmol) and copper(I) iodide (1.6 g, 8.6 mmol) in water (10 mL). The reaction mixture was warmed to room temperature over 2 h and then diluted with ethyl acetate. The organic layer was washed with a 10% solution of sodium thiosulfate, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 ethyl acetate/hexanes) provided an iodide (1.4 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.80 (d, J = 1 Hz, 1H), 7.72 (d, J = 1 Hz, 1H), 3.90 (s, 3H), 2.35 (s, 3H).

Step 5: To a -70 °C stirred solution of oxazole (174 mg, 2.5 mmol) in tetrahydrofuran (5 mL) was added *n*-butyllithium (1.7 mL of a 1.6 M solution in hexanes, 2.8 mmol). After 30 min, zinc chloride (7.5 mL of a 1 M solution in diethyl ether, 7.5 mmol) was added and the reaction mixture was warmed to 0 °C for 1 h. To this mixture was then added iodide from step 4 (695 mg, 2.5 mmol) followed by palladium(0) tetrakis-(triphenylphosphine) (145 mg, 0.13 mmol). The reaction mixture was heated at reflux for 16 h. The reaction mixture was cooled, and diluted with ethyl acetate (50 mL). The organic layer was washed with water, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided an oxazole (330 mg): ^{1}H NMR (300 MHz, CD_3OD) δ 8.45 (s, 1H), 8.08 (d, J = 1 Hz, 1H), 8.01 (s, 1H), 7.97 (d, J = 1 Hz, 1H), 7.32 (s, 1H), 3.95 (s, 3H), 2.48 (s, 3H); ESI MS *m/z* 218 $[M + H]^+$.

Step 6: To a stirred solution of the ester from step 5 (384 mg, 1.7 mmol) in methanol (5 mL) was added potassium hydroxide (15 mL of a 1.0 M solution in water, 15 mmol). The reaction mixture was stirred at room temperature for 2 h and concentrated under reduced pressure. The residue was diluted with water and washed with ethyl acetate. The aqueous layer was acidified to pH 5 with 1 N hydrochloric acid and extracted with chloroform (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to give an acid (358 mg): ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.2 (br s, 1H), 8.32 (s, 1H), 8.20 (s, 1H), 8.03 (s, 1H), 7.93 (s, 1H), 7.42 (s, 1H), 2.45 (s, 3H).

Step 7: A solution of the acid from step 6 (358 mg, 1.8 mmol), HATU (1.0 g, 2.6 mmol), HOBt (357 mg, 2.6 mmol), and diisopropylethylamine (500 µL, 2.6 mmol) was stirred in methylene chloride (2.0 mL) for 15 min. A solution of dihydrochloride of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (718 mg, 1.8 mmol) and diisopropylethylamine (500 µL, 2.6 mmol) in methylene chloride (2.0 mL) was added and the reaction mixture was stirred overnight. The reaction mixture was diluted with methylene chloride, washed with 1 N hydrochloric acid (20 mL), saturated sodium bicarbonate (20 mL), and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided a clear solid. The solid was dissolved in methanol (2 mL), and treated with hydrochloric acid (0.5 mL of a 1.0 M solution in diethyl ether, 0.5 mmol). The resulting precipitate was collected by filtration to provide the title compound (250 mg): mp 105-107 °C; APCI MS *m/z* 520 $[M + H]^+$.

EXAMPLE SP-292

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(methylsulfonyl)methyl]thiophene-2-carboxamide

Step 1: To a solution of acid 5-(methoxycarbonyl)thiophene-2-carboxylic acid (1.00 g, 5.37 mmol) in tetrahydrofuran (21.5 mL) was added borane-dimethylsulfide complex (3.0 mL of a 2.0 M soltion in tetrahydrofuran, 6.00 mmol). The reaction mixture was heated at reflux for 24 h and then carefully quenched with anhydrous methanol (1.0 mL) and cooled to room temperature. The reaction mixture was acidified with 1 N hydrochloric acid and extracted with ethyl acetate. The

combined organic phases were washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated to yield the desired alcohol (820 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 4 Hz, 1H), 6.96 (d, J = 4 Hz, 1H), 4.83 (s, 2H), 3.87 (s, 3H).

Step 2: To a 0 °C solution of the alcohol prepared in step 1 (805 mg, 4.67) in tetrahydrofuran (31 mL) containing triethylamine (790 µL, 5.61 mmol) and dimethylaminopyridine (6 mg) was added methanesulfonyl chloride (400 µL, 5.14 mmol) and the reaction mixture was stirred for 0.5 h. The reaction mixture was filtered and the filtrate concentrated under reduced pressure to provide the crude mesylate, which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (m, 1H), 7.18 (m, 1H), 5.39 (s, 2H), 3.90 (s, 3H), 2.97 (s, 3H).

Step 3: To the mesylate prepared in step 2 in *N,N*-dimethylformamide (10 mL) was added sodium thiomethoxide (516 mg, 7.0 mmol) and the reaction mixture was warmed to 50 °C for 18 h. The reaction was diluted with water (200 mL) and extracted with chloroform (4 x 25 mL). The combined organic phases were washed with 5% lithium chloride, water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the desired sulfide (760 mg) which was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 4 Hz, 1H), 6.93 (d, J = 4 Hz, 1H), 3.89 (m, 5H), 2.08 (s, 3H).

Step 4: To a 0 °C solution of the sulfide prepared in step 3 (760 mg, 3.75 mmol) in chloroform (6.25 mL) was added 70% *m*-CPBA (2.31 g, 9.37 mmol) and the reaction stirred at 0 °C for 2.5 h. The reaction mixture was then diluted with chloroform and washed with 1 N sodium hydroxide, water, and saturated