

NOVEL IMIDAZOLES

The present application claims priority under 35 U.S.C. section 119(e) to United States Provisional Applications Serial Numbers 60,563,124, filed April 16, 2004, and 60,600,705 filed August 11, 2004.

BACKGROUND OF THE INVENTION

High levels of blood cholesterol and blood lipids are conditions involved in the onset of atherosclerosis. The conversion of HMG-CoA to mevalonate is an early and rate-limiting step in the cholesterol biosynthetic pathway. This step is catalyzed by the enzyme HMG-CoA reductase. It is known that inhibitors of HMG-CoA reductase are effective in lowering the blood plasma level of low density lipoprotein cholesterol (LDL-C), in man. (cf. M.S. Brown and J.L. Goldstein, *New England Journal of Medicine*, 305, No. 9, 515-517 (1981)). It has been established that lowering LDL-C levels affords protection from coronary heart disease (cf. *Journal of the American Medical Association*, 251, No. 3, 351-374 (1984)).

Statins are collectively lipid lowering agents. Representative statins include atorvastatin, lovastatin, pravastatin, simvastatin and rosuvastatin. Atorvastatin and pharmaceutically acceptable salts thereof are selective, competitive inhibitors of HMG-CoA reductase. A number of patents have issued disclosing atorvastatin. These include: United States Patent Numbers 4,681,893; 5,273,995 and 5,969,156, which are incorporated herein by reference.

All statins interfere, to varying degrees, with the conversion of HMG-CoA to the cholesterol precursor mevalonate by HMG-CoA reductase. These drugs share many features, but also exhibit differences in pharmacologic attributes that may contribute to differences in clinical utility and effectiveness in modifying lipid risk factors for coronary heart disease. (Clin. Cardiol. Bol. 26 (Suppl. III), III-32-III-38 (2003)). Some of the desirable pharmacologic features with statin therapy include potent reversible inhibition of HMG-CoA reductase, the ability to produce large reductions in LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C), the ability to increase HDL cholesterol (HDL-C), tissue selectivity, optimal pharmacokinetics, availability of once a day dosing and a low potential for drug-drug interactions. Also desirable is the ability to lower circulating very-low-density-lipoprotein(VLDL) as well as the ability to lower triglyceride levels.

At the present time, the most potent statins display in vitro IC_{50} values, using purified human HMG-CoA reductase catalytic domain preparations, of between about 5.4 and about 8.0 nM. (*Am. J. Cardiol.* 2001; 87(suppl): 28B-32B; *Atheroscler Suppl.* 2002;2:33-37). Generally, the most potent LDL-C-lowering statins are also the most potent non-HDL-C-lowering statins. Thus, maximum inhibitory activity is desirable. With respect to HDL-C, the known statins generally produce only modest increases in HDL-C. Therefore, the ability to effect greater increases in HDL-C would be advantageous as well.

With respect to tissue selectivity, differences among statins in relative lipophilicity or hydrophilicity may influence drug kinetics and tissue selectivity. Relatively hydrophilic drugs may exhibit reduced access to nonhepatic cells as a result of low passive diffusion and increased relative hepatic cell uptake through selective organic ion transport. In addition, the relative water solubility of a drug may reduce the need for extensive cytochrome P450 (CYP) enzyme metabolism. Many drugs, including the known statins, are metabolized by the CYP3A4 enzyme system. (*Arch. Intern. Med.* 2000; 160:2273-2280; *J. Am. Pharm. Assoc.* 2000; 40:637-644). Thus, relative hydrophilicity is desirable with statin therapy.

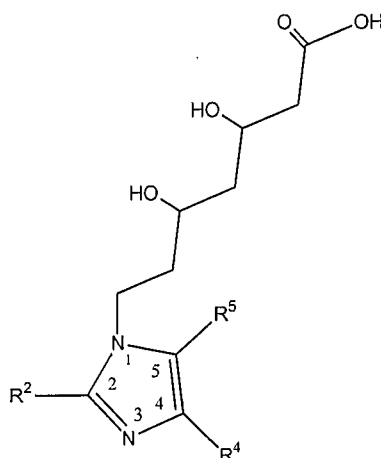
Two important pharmacokinetic variables for statins are bioavailability and elimination half-life. It would be advantageous to have a statin with limited systemic availability so as to minimize any potential risk of systemic adverse effects, while at the same time having enough systemic availability so that any pleiotropic effects can be observed in the vasculature with statin treatment. These pleiotropic effects include improving or restoring endothelial function, enhancing the stability of atherosclerotic plaques, reduction in blood plasma levels of certain markers of inflammation such as C-reactive protein, decreasing oxidative stress and reducing vascular inflammation. (*Arterioscler. Thromb. Vasc. Biol.* 2001; 21:1712-1719; *Heart Dis.* 5(1):2-7, 2003). Further, it would be advantageous to have a statin with a long enough elimination half-life to maximize effectiveness for lowering LDL-C.

Finally, it would be advantageous to have a statin that is either not metabolized or minimally metabolized by the CYP 3A4 systems so as to minimize any potential risk of drug-drug interactions when statins are given in combination with other drugs.

Accordingly, it would be most beneficial to provide a statin having a combination of desirable properties including high potency in inhibiting HMG-CoA reductase, the ability to produce large reductions in LDL-C and non-high density lipoprotein cholesterol, the ability to increase HDL cholesterol, selectivity of effect or uptake in hepatic cells, optimal systemic bioavailability, prolonged elimination half-life, and absence or minimal metabolism via the CYP3A4 system.

SUMMARY OF THE INVENTION

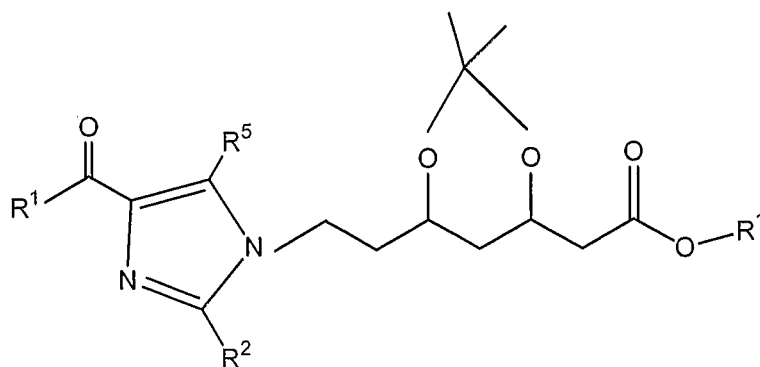
This invention provides a novel series of imidazoles. Compounds of the invention are potent inhibitors of cholesterol biosynthesis. Accordingly, the compounds find utility as therapeutic agents to treat hyperlipidemia, hypercholesterolemia, hypertriglyceridemia and atherosclerosis. More specifically, the present invention provides a compound having a Formula I,



Formula I

or a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug, wherein R^2 and R^5 are each independently H; halogen; C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted; R^4 is halogen; H; C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted; $-S(O)_nNR^6R^7$; $R^8S(O)_n$; $-(CH_2)_nNR^6R^7$; $-(CH_2)_nCOOR'$; $-(CH_2)_nC(O)NR^6R^7$; or $-(CH_2)_nCOR'$; R^6 and R^7 are each independently H; C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted with aryl, heteroaryl, lower alkyl, halogen, OR' , $-(CH_2)_nCOOR'$, $-(CH_2)_nCONR'R''$, $(CH_2)_nSO_2R'$, $SO_2NR'R''$ or CN; $-(CH_2)_nCOR'$, $-(CH_2)_nCOOR'$, $-(CH_2)_nCONR'R''$ or $-(CH_2)_nSO_2R'$; or N, R^6 and R^7 taken together form a 4-11 member ring optionally containing up to two heteroatoms selected from O, N and S, said ring being optionally substituted with aryl, aralkyl, heteroaryl, heteroaralkyl, C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, halogen, OR' , $-(CH_2)_nCOOR'$, $-(CH_2)_nCONR'R''$, $-(CH_2)_nSO_2R'$, $SO_2NR'R''$ or CN; R^8 is aryl, aralkyl, alkyl, heteroaryl, or heteroaralkyl; optionally substituted; R' and R'' are each independently H; C_1 - C_{12} alkyl, aryl or aralkyl; optionally substituted; and n is 0-2.

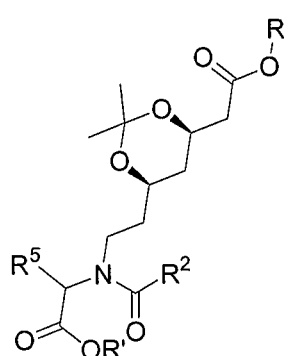
Further provided is a compound having a Formula:



or a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug, wherein R^2 and R^5 are each independently H; halogen;

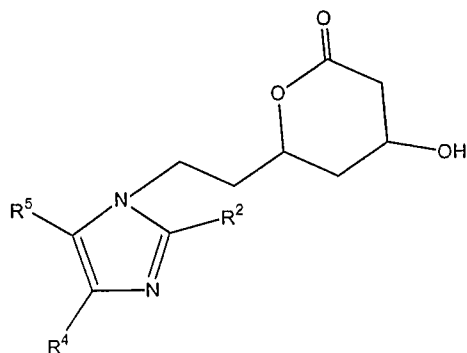
C₁-C₆ alkyl, C₃-C₈ cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted; and R¹ is H; OH; C₁-C₁₂ alkyl, aryl or aralkyl; optionally substituted; or NR⁶R⁷ wherein R⁶ and R⁷ are each independently H; C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted, or N, R⁶ and R⁷ taken together form a 4-11 member ring optionally containing up to two heteroatoms selected from O, N and S, said ring being optionally substituted with aryl, aralkyl, heteroaryl, heteroaralkyl, C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, halogen, OR', -(CH₂)_nCOOR', -(CH₂)_nCONR'R'', -(CH₂)_nSO₂R', SO₂NR'R'' or CN.

Further provided is a compound having a Formula



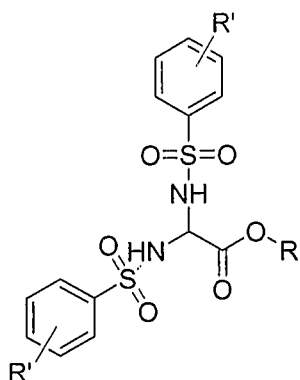
or a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R² and R⁵ are each independently H; halogen; C₁-C₆ alkyl, C₃-C₈ cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl, optionally substituted; and R' is H; C₁-C₁₂ alkyl, aryl or aralkyl; optionally substituted.

Further provided is a compound having a formula:



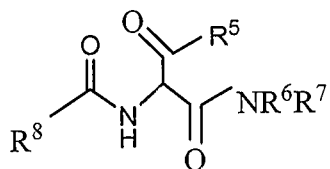
or a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug, wherein R², R⁴ and R⁵ are as defined above.

Further, the present invention provides a compound having a formula:



Wherein R' is H; C_1 - C_{12} alkyl, aryl or aralkyl; optionally substituted and R is H, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted.

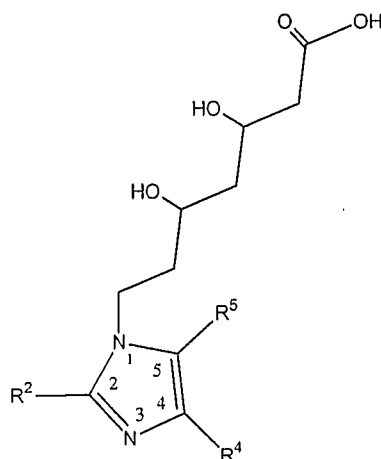
Further provided is a compound having a formula:



wherein R^5 is H; halogen; C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, aryl aralkyl, heteroaryl or heteroaralkyl; optionally substituted; R^6 and R^7 are each independently H, C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted; or N, R^6 and R^7 taken together form a 4-11 member ring optionally containing up to two heteroatoms selected from O, N and S, said ring being optionally substituted; with aryl, aralkyl, heteroaryl, heteroaralkyl, C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, halogen, OR' , $-(CH_2)_n COOR'$; $-(CH_2)_n CONR'R''$, $-(CH_2)_n SO_2R'$, $SO_2NR'R''$ or CN; and R^8 is aryl, aralkyl, alkyl, heteroaryl, or heteroaralkyl; optionally substituted.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a compound having a Formula I,



Formula I

or a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug, wherein R^2 , R^4 and R^5 are as defined above.

Further provided is the above-described compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R^5 is C_1 - C_6 alkyl or C_3 - C_8 cycloalkyl, optionally substituted. Further provided is the compound wherein R^5 is isopropyl or cyclopropyl.

Further provided is the compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R^2 is C_1 - C_6 alkyl or C_3 - C_8 cycloalkyl, optionally substituted. Further provided is the compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R^2 is isopropyl.

Further provided is the compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R^2 is aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted.

Further provided is the compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R^5 is aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted.

Further provided is the compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R^4 is $-(CH_2)_nC(O)NR^6R^7$.

Further provided is the compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R^6 and R^7 are each independently H; aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted with lower alkyl, halogen, OR' , $(CH_2)_nCOOR'$, $-(CH_2)_nCONR'R''$, $-(CH_2)_nSO_2R'$ or CN.

Further provided is the above-described compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R^2 is phenyl, optionally substituted with one or more halogen.

Further provided is the compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein one of R^6 and R^7 is aryl, optionally substituted; and the other one of R^6 and R^7 is H.

Further provided is the compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein one of R^6 and R^7 is phenyl, optionally substituted.

Further provided is the compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R^6 and R^7 are each independently H; C_1 - C_{10} alkyl, optionally substituted; or N, R^6 and R^7 taken together form a 4-11 member ring optionally containing up to two heteroatoms selected from O, N and S, said ring being optionally substituted.

Further provided is the above-described compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R^4 is $R^8 S(O)_n$.

Further provided is the compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R^8 is phenyl optionally substituted; and n is 2.

Further provided is the above-described compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R^4 is $-(CH_2)_nNR^6R^7$.

Further provided is the compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R^4 is $-(CH_2)_nCOOR'$ or $-(CH_2)_nCOR'$.

Further provided is the compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R^4 is halogen; H; C_1-C_6 alkyl or C_3-C_8 cycloalkyl; optionally substituted.

Further provided is the compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R^4 is aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted.

Further provided is a pharmaceutically acceptable salt of the above-described compound wherein the salt is a sodium salt.

Further provided is the above-described compound a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R^6 and R^7 are each independently H; $-(CH_2)_nCOR'$; $-(CH_2)_nCOOR'$; $-(CH_2)_nCONR'R''$ or $-(CH_2)_mSO_2R'$.

Further provided is the compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein one of R^6 and R^7 is phenyl, optionally substituted with one or more halogen.

Further provided is the compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein one of R^6 and R^7 is 4-fluorophenyl.

Further provided is the compound, a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein one of R^6 and R^7 is benzyl, optionally substituted with lower alkyl, halogen, OR' , $-(CH_2)_nCOOR'$, $-(CH_2)_nCONR'R''$, $(CH_2)_nSO_2R'$, $SO_2NR'R''$ or CN.

Further provided is a pharmaceutically acceptable ester of the above-described compound.

Further provided is a pharmaceutical composition comprising the above-described compound, the pharmaceutically acceptable salt, ester, amide or prodrug thereof, or the pharmaceutically acceptable salt of the prodrug; or a mixture thereof; and a pharmaceutically acceptable carrier, diluent, or vehicle.

Further provided is a method of inhibiting cholesterol biosynthesis in a mammal requiring inhibition comprising administering to the mammal a therapeutically effective amount of the above-described compound or the pharmaceutically acceptable salt, ester, amide or prodrug thereof, or the pharmaceutically acceptable salt of the prodrug.

Further provided is a method of lowering LDL cholesterol in a mammal.

Further provided is a method of raising HDL cholesterol in a mammal.

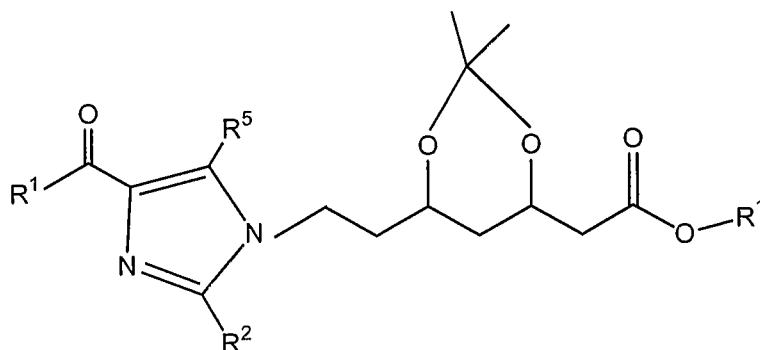
Further provided is a method of treating, preventing or controlling hyperlipidemia in a mammal.

Further provided is a method of treating, preventing or controlling hypercholesterolemia in a mammal.

Further provided is a method of treating, preventing or controlling hypertriglyceridemia in a mammal.

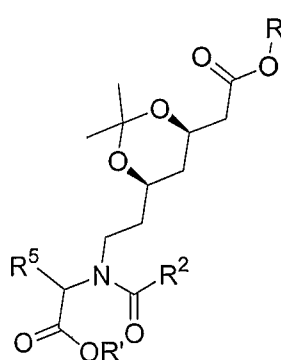
Further provided is a method of treating, preventing or controlling Alzheimer's disease, BPH, diabetes or osteoporosis in a mammal.

Further provided is a compound having a Formula:



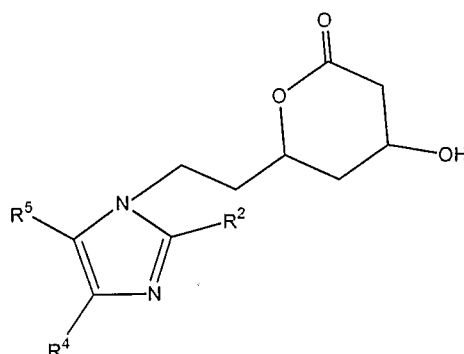
or a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug, wherein R¹, R² and R⁵ are as defined above.

Further provided is a compound having a Formula



or a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug wherein R², R⁵ and R' are as defined above.

Further provided is a compound having a Formula:

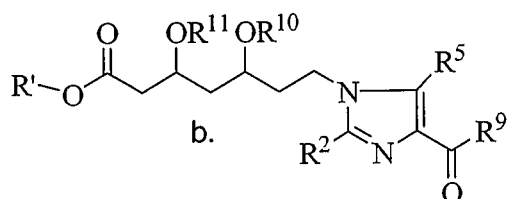


or a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug, wherein R^2 , R^4 and R^5 are as defined above.

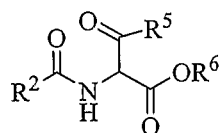
Further provided is the lactone form of a compound as described above, wherein R^2 is phenyl optionally substituted with one or more halogen, R^4 is $-(CH_2)_nC(O)NR^6R^7$, one of R^6 and R^7 is aralkyl, optionally substituted, and the other one of R^6 and R^7 is H; and R^5 is C_1 - C_6 alkyl or C_3 - C_8 cycloalkyl.

Further provided are racemic mixtures of all compounds described herein.

Further provided is a process for preparing a compound having a Formula b.



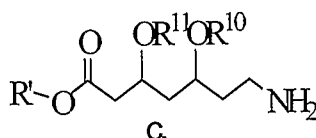
from a compound having a Formula a.



a.

comprising the following steps:

1.) Reacting the compound a. with a compound having a formula c.,



in a solvent; and

optionally reacting the compound a. with a compound NHR^6R^7 , in a solvent, prior to the first step; wherein R^2 and R^5 are each independently H; halogen; C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted;

R^9 is $-OR^6$ or $-NR^6R^7$;

R^6 is H; C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted with aryl, heteroaryl, lower alkyl, halogen, OR' , $-(CH_2)_nCOOR'$, $-(CH_2)_nCONR'R''$, $(CH_2)_nSO_2R'$, $SO_2NR'R''$ or CN;

R^7 is H; C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted with aryl, heteroaryl, lower alkyl, halogen, OR' ,

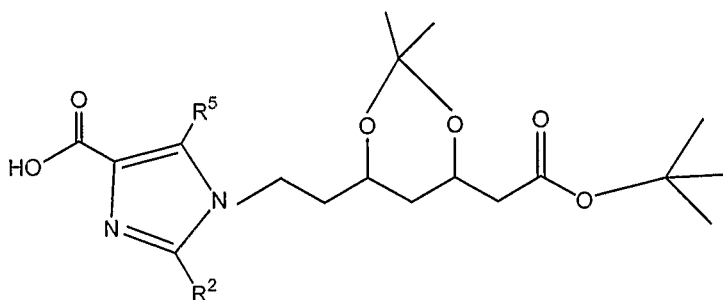
$-(CH_2)_nCOOR'$, $-(CH_2)_nCONR'R''$, $(CH_2)_nSO_2R'$, $SO_2NR'R''$ or CN; $-(CH_2)_nCOR'$, $-(CH_2)_nCOOR'$, $-(CH_2)_nCONR'R''$ or $-(CH_2)_nSO_2R'$; or

N, R^6 and R^7 taken together form a 4-11 member ring optionally containing up to two heteroatoms selected from O, N and S, said ring being optionally substituted with aryl, aralkyl, heteroaryl, heteroaralkyl, C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, halogen, OR' , $-(CH_2)_nCOOR'$, $-(CH_2)_nCONR'R''$, $-(CH_2)_nSO_2R'$, $SO_2NR'R''$ or CN;

R' and R'' are each independently H; C_1 - C_{12} alkyl, aryl or aralkyl; optionally substituted; n is 0-2;

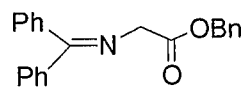
R^{10} and R^{11} are each independently C_1 - C_{10} alkyl, $C(O)R^7$, $-SiR^{12}R^{13}R^{14}$ or R^{10} and R^{11} taken together from isopropyl; and R^{12} , R^{13} and R^{14} are each independently C_1 - C_6 alkyl.

Further provided is a process for preparing a compound having a Formula:



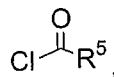
wherein R^1 , R^2 and R^5 are as defined above comprising the following steps:

1.) reacting a compound having a formula,



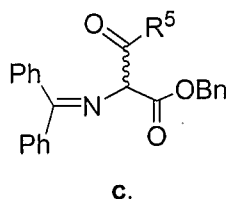
a.

wherein Ph is phenyl and Bn is benzyl, with a compound having a formula,



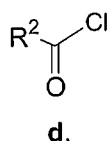
b.

wherein R^5 is as defined above, under basic conditions, to form a compound having a formula;

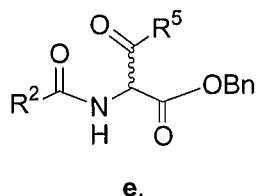


wherein R⁵ and Bn are as defined above;

2.) hydrolyzing the compound **c** and subsequently reacting the hydrolyzed compound **c** with a compound

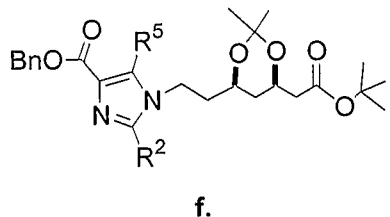


wherein R² is as defined above, under basic conditions, to form a compound



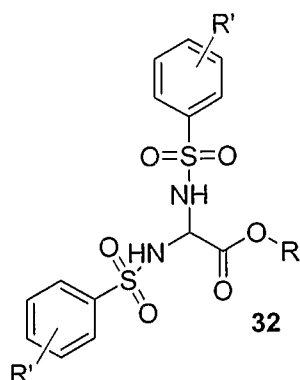
wherein R², R⁵ and Bn are as defined above;

3.) reacting the compound **e** with a compound having the formula $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O}-\text{C}(\text{CH}_3)_3$, to form a compound



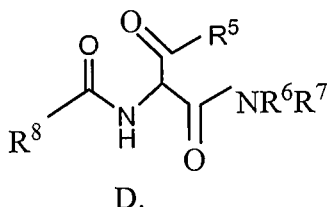
wherein Bn, R² and R⁵ are as defined above; and hydrogenolysing the compound **f** to form the compound.

Further, the present invention provides a compound having a formula:



Wherein R' and R are as defined above.

Further provided is a compound having a formula:



wherein R⁵, R⁶, R⁷ and R⁸ are as defined above.

The present invention further provides a compound of the Formula I selected from the group consisting of (3R,5R)-7-[4-Benzylcarbamoyl-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(2-methoxy-ethylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-phenylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[4-(1,3-Dihydro-isoindole-2-carbonyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[4-(Benzyl-ethyl-carbamoyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-[(pyridin-3-ylmethyl)-carbamoyl]-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(2-pyridin-3-yl-ethylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-((R)-2-phenyl-propylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[4-[2-(4-Chloro-phenyl)-3-hydroxy-propylcarbamoyl]-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-[2-(4-sulfamoyl-phenyl)-ethylcarbamoyl]-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-((S)-1-methyl-3-phenyl-propylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-{2-(4-fluoro-phenyl)-4-[2-(3-fluoro-phenyl)-ethylcarbamoyl]-5-isopropyl-imidazol-1-yl}-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-fluoro-phenyl)-4-((1S,2S)-2-hydroxy-1-methoxymethyl-2-phenyl-ethylcarbamoyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-{2-(4-fluoro-phenyl)-5-isopropyl-4-[2-(4-methoxy-phenyl)-ethylcarbamoyl]-imidazol-1-yl}-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-fluoro-phenyl)-4-((S)-1-hydroxymethyl-2-phenyl-ethylcarbamoyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-{2-(4-fluoro-phenyl)-4-[(1S,2S)-2-hydroxy-1-hydroxymethyl-2-(4-methylsulfanyl-phenyl)-ethylcarbamoyl]-5-isopropyl-imidazol-1-yl}-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[4-[2-(4-chloro-phenyl)-ethylcarbamoyl]-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-((S)-2-phenyl-propylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-{2-(4-fluoro-phenyl)-5-isopropyl-4-[2-(3-methoxy-phenyl)-ethylcarbamoyl]-imidazol-1-yl}-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-{2-(4-fluoro-phenyl)-4-[2-(4-fluoro-phenyl)-ethylcarbamoyl]-5-isopropyl-imidazol-1-yl}-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[4-[2-(3-chloro-phenyl)-ethylcarbamoyl]-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-(2-pyridin-4-yl-ethylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-fluoro-phenyl)-4-((1R,2R)-2-hydroxy-1-hydroxymethyl-2-phenyl-ethylcarbamoyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-benzylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-phenylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3S,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-(toluene-4-sulfonyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-ethyl-4-(4-fluorophenylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-propyl-4-phenylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-propyl-4-benzylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-propyl-4-phenethylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-propyl-4-(4-fluorophenylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-methyl-4-phenylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-methyl-4-benzylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-methyl-4-phenethylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[4-[(Biphenyl-3-yl)methyl]-carbamoyl]-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-phenethylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-methyl-4-(4-sulfamoyl-benzylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[4-benzylcarbamoyl-2-phenyl-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid; (3R,5R)-

7-[4-(3-Chloro-benzylcarbamoyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic

acid; (3R,5R)-7-[2-(4-Fluoro-phenyl)-4-(indan-1-ylcarbamoyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[4-Benzylcarbamoyl-5-cyclopropyl-2-(4-fluoro-phenyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic

acid; (3R,5R)-7-[5-Cyclopropyl-2-(4-fluoro-phenyl)-4-(4-methoxy-benzylcarbamoyl)-imidazol-1-yl]-3,5-

dihydroxy-heptanoic acid; and pharmaceutically acceptable salts, amides, esters and lactone forms

thereof.

The present invention further provides a compound of the Formula I, as described above, selected from the group consisting of (3R,5R)-7-[4-Benzylcarbamoyl-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid; pharmaceutically acceptable salts, amides, esters and lactone forms thereof.

The present invention further provides a combination of a compound of the Formula I as defined above, or a pharmaceutically acceptable salt, amide, ester or lactone thereof, and one or more additional pharmaceutically active agent.

The present invention further provides a pharmaceutical composition comprising a compound of Formula I as defined above or a combination as defined above, and a pharmaceutically acceptable carrier, diluent or vehicle.

Further, the present invention provides inter alia the following compounds: (3R, 5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(3-phenyl-pyrrolidine-1-carbonyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid; (3R,5R)-7-[4-(3-Benzenesulfonyl-pyrrolidine-1-carbonyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(4-sulfamoyl-benzylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid; and pharmaceutically acceptable salts, and lactone forms thereof.

Still further, the present invention provides inter alia the following compounds:

(3R,5R)-7-[5-cyclopropyl-4-[(3-fluorobenzyl)amino]carbonyl]-2-(4-fluorophenyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-[5-cyclopropyl-4-[(3,4-difluorobenzyl)amino]carbonyl]-2-(4-fluorophenyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-(5-cyclopropyl-2-(4-fluorophenyl)-4-[(3-methoxybenzyl)amino]carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-[5-cyclopropyl-4-[(3,4-dimethoxybenzyl)amino]carbonyl]-2-(4-fluorophenyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-[5-cyclopropyl-4-[(3-ethoxybenzyl)amino]carbonyl]-2-(4-fluorophenyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-(5-cyclopropyl-2-(4-fluorophenyl)-4-[(2-methoxybenzyl)amino]carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-(5-cyclopropyl-2-(4-fluorophenyl)-4-[(2-methylbenzyl)amino]carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-(5-cyclopropyl-2-(4-fluorophenyl)-4-[(3-methylbenzyl)amino]carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-(5-cyclopropyl-2-(4-fluorophenyl)-4-[(4-methylbenzyl)amino]carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-[4-[(4-cyanobenzyl)amino]carbonyl]-5-cyclopropyl-2-(4-fluorophenyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-[4-[(4-chlorobenzyl)amino]carbonyl]-5-cyclopropyl-2-(4-fluorophenyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-[4-[(3-cyanobenzyl)amino]carbonyl]-5-cyclopropyl-2-(4-fluorophenyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-[5-cyclopropyl-4-[(4-[(dimethylamino)carbonyl]benzyl)amino]carbonyl]-2-(4-fluorophenyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-[5-cyclopropyl-4-[(3-fluorobenzyl)(methyl)amino]carbonyl]-2-(4-fluorophenyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-[5-cyclopropyl-4-[(3,4-difluorobenzyl)(methyl)amino]carbonyl]-2-(4-fluorophenyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-[5-cyclopropyl-2-(4-fluorophenyl)-4-[(methyl[(1R)-1-phenylethyl]amino)carbonyl]-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-[4-[(cyclohexylmethyl)amino]carbonyl]-5-cyclopropyl-2-(4-fluorophenyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-[5-cyclopropyl-2-(4-fluorophenyl)-4-[(2-(4-methoxyphenyl)ethyl)amino]carbonyl]-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-[5-cyclopropyl-2-(4-fluorophenyl)-4-({[2-(3-fluorophenyl)ethyl]amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-(5-cyclopropyl-2-(4-fluorophenyl)-4-({[2-naphthylmethyl]amino}carbonyl)-1H-imidazol-1-yl)-3,5-dihydroxyheptanoic acid

(3R,5R)-7-[5-cyclopropyl-2-(4-fluorophenyl)-4-({[(6-phenylpyridin-3-yl)methyl]amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-[4-[(benzylamino)carbonyl]-2-(4-chlorophenyl)-5-cyclopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

(3R,5R)-7-[4-[(benzylamino)carbonyl]-5-cyclopropyl-2-(6-methylpyridin-3-yl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoic acid;

and pharmaceutically acceptable salts and lactone forms thereof.

The present invention further encompasses each of the title compounds set forth in the Examples herein.

The term "alkyl" as used herein refers to a straight or branched hydrocarbon of from 1 to 11 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, and the like. The alkyl group can also be substituted with one or more of the substituents selected from lower alkoxy, lower thioalkoxy, $-O(CH_2)_{0-2}CF_3$, -Oaryl, halogen, nitro, cyano, =O, =S, -OH, -SH, $-CF_3$, $-CO_2H$, $-CO_2C_1-C_6$ alkyl, $-NR'R''$, $NR'SO_2R''$, $NR'CONR'R''$, or $-CONR'R''$ where R' and R'' are independently H, alkyl, cycloalkyl, akenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or joined together to form a 4 to 7 member ring; or N, R' and R'' taken together form a 4-7 member ring. Useful alkyl groups have from 1 to 6 carbon atoms (C_1-C_6 alkyl).

The term "lower alkyl" as used herein refers to a subset of alkyl which means a straight or branched hydrocarbon radical having from 1 to 6 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, and the like. Optionally, lower alkyl is referred to as " C_1-C_6 alkyl."

The term "haloalkyl" as used herein refers to a lower alkyl radical, as defined above, bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl, trifluoromethyl, or 1,1,1-trifluoroethyl and the like. Haloalkyl can also include perfluoroalkyl wherein all hydrogens of a lower alkyl group are replaced with fluorine atoms.

The term "alkenyl" means a straight or branched unsaturated hydrocarbon radical from 2 to 12 carbon atoms and includes, for example, ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 3-methyl-3-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 3-heptenyl, 1-octenyl, 1-nonenyl, 1-decenyl, 1-undecenyl, 1-dodecenyl, and the like.

The term "alkynyl" means a straight or branched hydrocarbon radical of 2 to 12 carbon atoms having at least one triple bond and includes, for example, 3-propynyl, 1-butylnyl, 3-butylnyl, 1-pentylnyl, 3-pentylnyl, 3-methyl-3-butylnyl, 1-hexynyl, 3-hexynyl, 3-hexynyl, 3-heptynyl, 1-octynyl, 1-nonylnyl, 1-decynyl, 1-undecynyl, 1-dodecynyl, and the like.

The term "alkylene" as used herein refers to a divalent group derived from a straight or branched chain saturated hydrocarbon having from 1 to 10 carbon atoms by the removal of two hydrogen atoms, for example methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene, 2,2-dimethylpropylene, and the like. The alkylene groups of this invention can be optionally substituted with one or more of the substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, $-O(CH_2)_{0-2}CF_3$, halogen, nitro, cyano, $=O$, $=S$, $-OH$, $-SH$, $-CF_3$, $-CO_2H$, $-CO_2C_1-C_6$ alkyl, $NR'R''$, or $-CONR'R''$, where R' and R'' are independently H, alkyl, cycloalkyl, akenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or joined together to form a 4 to 7 member ring; or N , R' and R'' taken together form a 4-7 member ring. Useful alkylene groups have from 1 to 6 carbon atoms (C_1-C_6 alkylene).

The term "heteroatom" as used herein represents oxygen, nitrogen, or sulfur (O, N, or S) as well as sulfoxyl or sulfonyl (SO or SO_2) unless otherwise indicated.

The term "hydrocarbon chain" as used herein refers to a straight hydrocarbon of from 2 to 6 carbon atoms. The hydrocarbon chain is optionally substituted with one or more substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, $-O(CH_2)_{0-2}CF_3$, halogen, nitro, cyano, $=O$, $=S$, $-OH$, $-SH$, $-CF_3$, $-CO_2H$, $-CO_2C_1-C_6$ alkyl, $NR'R''$ or $-CONR'R''$, where R' and R'' are independently H, alkyl, cycloalkyl, akenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl or joined together to form a 4 to 7 member ring; or N , R' and R'' taken together form a 4-7 member ring.

The term "hydrocarbon-heteroatom chain" as used herein refers to a hydrocarbon chain wherein one or more carbon atoms are replaced with a heteroatom. The hydrocarbon-heteroatom chain is optionally substituted with one or more substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, $-O(CH_2)_{0-2}CF_3$, halogen, nitro, cyano, $=O$, $=S$, $-OH$, $-SH$, $-CF_3$, $-CO_2H$, $-CO_2C_1-C_6$ alkyl, $NR'R''$ or $-CONR'R''$, where R' and R'' are independently H, alkyl, cycloalkyl, akenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl or joined together to form a 4 to 7 member ring; or N , R' and R'' taken together form a 4-7 member ring.

The term "heteroalkylene" as used herein, refers to an alkylene radical as defined above that includes one or more heteroatoms such as oxygen, sulfur, or nitrogen (with valence completed by hydrogen or oxygen) in the carbon chain or terminating the carbon chain.

The terms "lower alkoxy" and "lower thioalkoxy" as used herein refers to O-alkyl or S-alkyl of from 1 to 6 carbon atoms as defined above for "lower alkyl."

The term "aryl" as used herein refers to an aromatic ring which is unsubstituted or optionally substituted by 1 to 4 substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, $-O(CH_2)_{0-2}CF_3$, $-Oaryl$, $-OSO_2R'$, nitro, cyano $-OH$, $-SH$, $-CF_3$, $-CO_2H$, $-CO_2C_1-C_6$ alkyl, $-NR'R''$, $NR'SO_2R''$, $NR'CONR'R''$, $-SO_{1-2}alkyl$, $SO_{1-2}aryl$, $SO_2NR'R''$, or $-CONR'R''$, where R' and R'' are independently H, alkyl, cycloalkyl, akenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl or joined together to form a 4 to 7 member ring; or N , R' and R'' taken together form a 4-7 member ring. Examples include, but are not limited to phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-chloro-3-methylphenyl, 2-chloro-4-methylphenyl,

2-chloro-5-methylphenyl, 3-chloro-2-methylphenyl, 3-chloro-4-methylphenyl, 4-chloro-2-methylphenyl, 4-chloro-3-methylphenyl, 5-chloro-2-methylphenyl, 2,3-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2,3-dimethylphenyl, 3,4-dimethylphenyl, or the like. Further, the term "aryl" means a cyclic or polycyclic aromatic ring having from 5 to 12 carbon atoms, and being unsubstituted or substituted with up to 4 of the substituent groups recited above for alkyl, alkenyl, and alkynyl.

The term aralkyl as used herein means aryl, as defined above, attached to an alkyl group, as defined above.

The term "heteroaryl" means an aromatic ring containing one or more heteroatom. The heteroaryl is optionally substituted with one or more groups enumerated for aryl. Examples of heteroaryl include, but are not limited to thienyl, furanyl, pyrrolyl, pyridyl, pyrimidyl, imidazolyl, pyrazinyl, oxazolyl, thiazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, isoquinolinyl, and quinazolinyl, and the like. Further, the term "heteroaryl" means an aromatic mono-, bi-, or polycyclic ring incorporating one or more (i.e. 1-4) heteroatoms selected from N, O, and S, which mono-, bi-, or polycyclic ring is optionally substituted with lower alkyl, lower alkoxy, lower thioalkoxy, $-O(CH_2)_{0-2}CF_3$, halogen, nitro, cyano, $-OH$, $-SH$, $-CF_3$, $-CO_2H$, $-CO_2C_1-C_6$ alkyl, $-NR'R''$, $-SO_2$ alkyl, SO_2 aryl, $SO_2NR'R''$, or $-CONR'R''$, where R' and R'' are independently H, alkyl, cycloalkyl, akenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl or joined together to form a 4 to 7 member ring; or N, R' and R'' taken together form a 4-7 member ring. Examples further include 1-, 2-, 4-, or 5-imidazolyl, 1-, 3-, 4-, or 5-pyrazolyl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 4-, or 5-oxazolyl, 3-, 4-, or 5-isoxazolyl, 1, 3-, or 5-triazolyl, 1-, 2-, or 3-tetrazolyl, 2-pyrazinyl, 2-, 4-, or 5-pyrimidinyl, 1- or 2-piperazinyl, 2-, 3-, or 4-morpholinyl. Examples of suitable bicyclic heteroaryl compounds include, but are not limited to indoliziny, isoindolyl, benzofuranyl, benzothienyl, benzoxazolyl, benzimidazolyl, quinolinyl, isoquinolinyl, quinazolinyl, 1-, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 1-, 2-, 3-, 5-, 6-, 7-, or 8-indoliziny, 1-, 2-, 3-, 4-, 5-, 6-, or 7-isoindolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzothienyl, 2-, 4-, 5-, 6-, or 7-benzoxazolyl, 1-, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, and 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl.

The term heteroaralkyl, as used herein, means heteroaryl, as defined above, attached to an alkyl group as defined above.

The term "heterocycle" means a saturated mono- or polycyclic (i.e. bicyclic) ring incorporating one or more (i.e. 1-4) heteroatoms selected from N, O, and S. It is understood that a heterocycle is optionally substituted with one or more of the substituents selected from lower alkoxy, lower thioalkoxy, $-O(CH_2)_{0-2}CF_3$, halogen, nitro, cyano, $=O$, $=S$, $-OH$, $-SH$, $-CF_3$, $-CO_2H$, $-CO_2C_1-C_6$ alkyl, $-NR'R''$ or $-CONR'R''$ where R' and R'' are independently H, alkyl, cycloalkyl, akenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or joined together to form a 4 to 7 member ring; or N, R' and R'' taken together form a 4-7 member ring. Useful alkyl groups have from 1 to 6 carbon atoms (C_1-C_6 alkyl). Examples of suitable monocyclic heterocycles include, but are not limited to piperidinyl, pyrrolidinyl, piperazinyl, azetidiny, aziridinyl, morpholinyl, thietanyl, oxetanyl.

The term "ring" as used herein includes heteroaryl, cycloalkyl or aryl and further includes fused, monocyclic and polycyclic permutations thereof.

The term "cycloalkyl" means a saturated hydrocarbon ring. Further, the term "cycloalkyl" means a hydrocarbon ring containing from 3 to 12 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, decalanyl, norpinanyl, or adamantyl. The cycloalkyl ring may be unsubstituted or substituted by 1 to 3 substituents selected from one or more of the substituents selected from lower alkoxy, lower thioalkoxy,

$-(CH_2)_{0-2}CF_3$, halogen, nitro, cyano, $=O$, $=S$, $-OH$, $-SH$, $-CF_3$, $-CO_2H$, $-CO_2C_1-C_6$ alkyl, $-NR'R''$ or $-CONR'R''$ where R' and R'' are independently H, alkyl, cycloalkyl, akenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or joined together to form a 4 to 7 member ring; or N, R' and R'' taken together form a 4-7 member ring. Useful alkyl groups have from 1 to 6 carbon atoms (C_1-C_6 alkyl),

wherein alkyl, aryl, and heteroaryl are as defined herein. Examples of substituted cycloalkyl groups include fluorocyclopropyl, 2-iodocyclobutyl, 2,3-dimethylcyclopentyl, 2,2-dimethoxycyclohexyl, and 3-phenylcyclopentyl.

The term "cycloalkenyl" means a cycloalkyl group having one or more carbon-carbon double bond. Example includes cyclobutene, cyclopentene, cyclohexene, cycloheptene, cyclobutadiene, cyclopentadiene, and the like.

The term "isomer" means "stereoisomer" and "geometric isomer" as defined below.

The term "stereoisomer" means compounds that possess one or more chiral centers and each center may exist in the R or S configuration. Stereoisomers includes all diastereomeric, enantiomeric and epimeric forms as well as racemates and mixtures thereof.

The term "geometric isomer" means compounds that may exist in cis, trans syn, anti, entgegen (E), and zusammen (Z) forms as well as mixtures thereof.

The symbol "=" means a double bond.

The symbol " $\cap$ " means a bond to a group wherein a 4 to 8 membered ring is formed. Typically this symbol will appear in pairs.

When a bond to a substituent is shown to cross the bond connecting 2 atoms in a ring, then such substituent may be bonded to any atom in the ring, provided the atom will accept the substituent without violating its valency. When there appears to be several atoms of the substituent that may bond to the ring atom, then it is the first atom of the listed substituent that is attached to the ring.

When a bond from a substituent is shown to cross the bond connecting 2 atoms in a ring of the substituent, then such substituent may be bonded from any atom in the ring which is available.

When a bond is represented by a line such as "----" this is meant to represent that the bond may be absent or present provided that the resultant compound is stable and of satisfactory valency. If an asymmetric carbon is created by such a bond, a particular stereochemistry is not to be implied.

As used herein, the following terms have the meanings given: RT or rt means room temperature. MP means melting point. MS means mass spectroscopy. TLC means thin layer chromatography. [S]at. means saturated. [C]onc. means concentrated. TBIA means [(4R,6R)-6-(2-Amino-ethyl)-2,2-dimethyl-

[1,3]dioxan-4-yl]-acetic acid tert-butyl ester. DCM means dichloromethane, which is used interchangeably with methylene chloride. NBS means *N*-Bromosuccinimide. "h" means hour. "v/v" means volume ratio or "volume per volume". "R_F" means retention factor. "Tf₂O" or "TfO" means triflic anhydride or C(F)₃S(O)₂OS(O)₂C(F)₃. Ac₂O means acetic anhydride. "[T]rifluorotol." Or "TFT" means trifluoro methyl-benzene. "DMF" means dimethylformamide. "DCE" means dichloroethane. "Bu" means butyl. "Me" means methyl. "Et" means ethyl. "DBU" means 1,8-Diazabicyclo-[5.4.0]undec-7-ene. "TBS" means "TBDMS" or tert-Butyldimethylsilyl. "DMSO" means dimethyl sulfoxide. "TBAF" means tetrabutylammonium fluoride. THF means tetrahydrofuran. n-BuLi or BuLi means n-butyl lithium. TFA means trifluoroacetic acid. i-Pr means isopropyl. [M]in means minutes. ml or mL means milliliter. "M" or "m" means molar. "Bn" means benzyl. "PyBOP" means bromo-tris-pyrrolidino-phosphonium hexafluorophosphate. "OtBu" means t-butoxy. "Ts" or "Tosyl" means p-toluenesulfonyl. "PS-DIEA" means polystyrene-bound diisopropylethylamine. "PS-NCO" means polystyrene-bound isocyanate resin. "Ph" means phenyl. As used herein, "hydrogenolysis" means the cleaving of a chemical bond by hydrogen. "EDCI" or "EDC" means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. "NMP" means 1-methyl-2-pyrrolidinone. "DPP" or "DPPA" means diphenyl phosphoryl azide. "HOBt" 1-hydroxybenzotriazole.

The term "patient" means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, and rabbits.

A "therapeutically effective amount" is an amount of a compound of the present invention that when administered to a patient ameliorates a symptom of hyperlipidemia, hypercholesterolemia, hypertriglyceridemia or atherosclerosis.

The terms pharmaceutically acceptable salt, ester, amide, lactone forms or prodrug as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "lactone form(s) thereof" means a six-membered ring lactone form of the compounds of the invention disclosed herein, as illustrated throughout the specification and claims. The term "a pharmaceutically acceptable salt" refers to the relatively non-toxic, inorganic and organic acid or base addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in its free form with a suitable organic or inorganic acid or base and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the

like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See, for example, Berge S.M., et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977;66:1-19, which is incorporated herein by reference.) The free base form may be regenerated by contacting the salt form with a base. While the free base may differ from the salt form in terms of physical properties, such as solubility, the salts are equivalent to their respective free bases for the purposes of the present invention.

Examples of pharmaceutically acceptable, non-toxic esters of the compounds of this invention include C₁-C₆ alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C₅-C₇ cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C₁-C₄ alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods.

Examples of pharmaceutically acceptable, non-toxic amides of the compounds of this invention include amides derived from ammonia, primary C₁-C₆ alkyl amines and secondary C₁-C₆ dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines, the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C₁-C₃ alkyl primary amines and C₁-C₂ dialkyl secondary amines are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

The use of prodrugs is contemplated by the present invention. "Prodrugs" are intended to include any covalently bonded carrier which releases the active parent drug according to Formula I *in vivo*. Further, the term "prodrug" refers to compounds that are transformed *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference. Examples of prodrugs include acetates, formates, benzoate derivatives of alcohols, and amines present in compounds of Formula I.

In some situations, compounds may exist as tautomers. All tautomers are included within Formula I and are provided by this invention.

Certain compounds of the present invention can exist in unsolvated form as well as solvated form including hydrated form. In general, the solvated form including hydrated form is equivalent to unsolvated form and is intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R or S configuration. The present invention includes all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Stereoisomers may be obtained, if desired, by methods known in the art as, for example, the separation of stereoisomers by chiral chromatographic columns and by chiral synthesis. Additionally, the compounds of the present

invention may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

The compounds of the present invention are suitable to be administered to a patient for the treatment, control, or prevention of, hypercholesteremia, hyperlipidemia, atherosclerosis and hypertriglyceridemia. The terms "treatment", "treating", "controlling", "preventing" and the like, refers to reversing, alleviating, or inhibiting the progress of the disease or condition to which such term applies, or one or more symptoms of such disease or condition. As used herein, these terms also encompass, depending on the condition of the patient, preventing the onset of a disease or condition or of symptoms associated with a disease or condition, including reducing the severity of a disease or condition or symptoms associated therewith prior to affliction with said disease or condition. Such prevention or reduction prior to affliction refers to administration of the compound of the invention to a subject that is not at the time of administration afflicted with the disease or condition. "Preventing" also encompasses preventing the recurrence of a disease or condition or of symptoms associated therewith. Accordingly, the compounds of the present invention can be administered to a patient alone or as part of a composition that contains other components such as excipients, diluents, and carriers, all of which are well-known in the art. The compositions can be administered to humans and animals either orally, rectally, parenterally (intravenously, intramuscularly, or subcutaneously), intracisternally, intravaginally, intraperitoneally, intravesically, locally (powders, ointments, or drops), or as a buccal or nasal spray.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid; (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (c) humectants, as

for example, glycerol; (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (e) solution retarders, as for example paraffin; (f) absorption accelerators, as for example, quaternary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well-known in the art. They may contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol, or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required.

Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 2,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is preferable. The specific dosage used, however, can vary. For example, the dosage can depend on a numbers of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well-known to those skilled in the art.

Combination Aspect of the Invention

The compounds of this invention may be used, either alone or in combination with the other pharmaceutical agents described herein, in the treatment of the following diseases/conditions: dyslipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, peripheral vascular disease, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, diabetes and vascular complications of diabetes, obesity, unstable angina pectoris, Alzheimer's Disease, BPH, osteoporosis, cerebrovascular disease, coronary artery disease, ventricular dysfunction, cardiac arrhythmia, pulmonary vascular disease, renal-vascular disease, renal disease, vascular hemostatic disease, autoimmune disorders, pulmonary disease, anti-oxidant disease, sexual dysfunction, cognitive dysfunction, cancer, organ transplant rejection, psoriasis, endometriosis, and macular degeneration.

The compounds of this invention may also be used in conjunction with other pharmaceutical agents (e.g., HDL-cholesterol raising agents, triglyceride lowering agents) for the treatment of the disease/conditions described herein. A combination aspect of this invention includes a pharmaceutical composition comprising a compound of this invention or its pharmaceutically acceptable salt and at least one other compound. For example, the compounds of this invention may be used in combination with cholesterol absorption inhibitors, MTP/Apo B secretion inhibitors, or other cholesterol modulating agents such as fibrates, niacin, ion-exchange resins, antioxidants, ACAT inhibitors, PPAR-activators, CETP inhibitors or bile acid sequestrants. In combination therapy treatment, both the compounds of this invention and the other drug therapies are administered to mammals by conventional methods. The following discussion more specifically describes the various combination aspects of this invention.

Any cholesterol absorption inhibitor can be used in a combination aspect of this invention. Such cholesterol absorption inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., J. Lipid Res. (1993) 34: 377-395). Cholesterol absorption inhibitors are known to those skilled in the art and are described, for example, in PCT WO 94/00480. An example of a recently approved cholesterol absorption inhibitor is ZETIATM.

Any cholesterol ester transfer protein ("CETP") inhibitor may be used in a combination aspect of this invention. The effect of a CETP inhibitor on lipoprotein profile is believed to be anti-atherogenic.

Such inhibition is readily determined by those skilled in the art by determining the amount of agent required to alter plasma lipid levels, for example HDL cholesterol levels, LDL cholesterol levels, VLDL cholesterol levels or triglycerides, in the plasma of certain mammals, (e.g., Crook et al. Arteriosclerosis 10, 625, 1990; U.S. Pat. No. 6,140,343). A variety of these compounds are described and referenced below, however other CETP inhibitors will be known to those skilled in the art. For example, U.S. Patent Nos. 6,197,786, 6,723,752 and 6,723,753 (the disclosures of each of which is incorporated herein by reference) disclose cholesteryl ester transfer protein inhibitors, pharmaceutical compositions containing such inhibitors and the use of such inhibitors to elevate certain plasma lipid levels, including high density lipoprotein-cholesterol and to lower certain other plasma lipid levels, such as LDL-cholesterol and triglycerides and accordingly to treat diseases which are exacerbated by low levels of HDL cholesterol and/or high levels of LDL-cholesterol and triglycerides, such as atherosclerosis and cardiovascular diseases in some mammals, including humans. Examples of useful CETP inhibitors include the following compounds: [2R, 4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3, 4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester, which is also known as TorcetrapibTM, and 3-[[3-(4-Chloro-3-ethyl-phenoxy)-phenyl]-[3-(1,1,2,2-tetrafluoro-ethoxy)-benzyl]-amino]-1,1,1-trifluoro-propan-2-ol. Many of the CETP inhibitors of this invention are poorly soluble and a dosage form that increases solubility facilitates the administration of such compounds. One such dosage form is a dosage form comprising (1) a solid amorphous dispersion comprising a cholesteryl ester transfer protein (CETP) inhibitor and an acidic concentration-enhancing polymer; and (2) an acid-sensitive HMG-CoA reductase inhibitor. This dosage form is more fully described in USSN 10/739,567 and entitled "Dosage Forms Comprising a CETP Inhibitor and an HMG-CoA Reductase Inhibitor", the specification of which is incorporated herein by reference.

Any compound that activates or otherwise interacts with a human peroxisome proliferator activated receptor ("PPAR") may be used in a combination aspect of this invention. Three mammalian peroxisome proliferator-activated receptors have been isolated and termed PPAR-alpha, PPAR-gamma, and PPAR-beta (also known as NUC1 or PPAR-delta). PPAR-gamma receptors are associated with regulation of insulin sensitivity and blood glucose levels. PPAR- α activators are associated with lowering plasma triglycerides and LDL cholesterol. PPAR- β activators have been reported to both increase HDL-C levels and to decrease LDL-C levels. Thus, activation of PPAR- β alone, or in combination with the simultaneous activation of PPAR- α and/or PPAR-gamma may be desirable in formulating a treatment for dyslipidemia in which HDL is increased and LDL lowered. PPAR-activation is readily determined by those skilled in the art by the standard assays (e.g. US 2003/0225158 and US 2004/0157885). A variety of these compounds are described and referenced below, however other PPAR-activator compounds will be known to those skilled in the art. The following patents and published patent applications, the disclosure of each of which is incorporated herein by reference, provides a sampling. US 2003/0225158 discloses compounds that alter PPAR activity and methods of using them as therapeutic agents for treating or preventing dyslipidemia, hypercholesterolemia, obesity, hyperglycemia, atherosclerosis and

hypertriglyceridemia. U.S. Pat. No. 6,710,063 discloses selective activators of PPAR delta. US 2003/0171377 discloses certain PPAR-activator compounds that are useful as anti-diabetic agents. US 2004/0157885 relates to PPAR agonists, in particular, certain PPAR α agonists, pharmaceutical compositions containing such agonists and the use of such agonists to treat atherosclerosis, hypercholesterolemia, hypertriglyceridemia, diabetes, obesity, osteoporosis and Syndrome X or metabolic syndrome.

Examples of useful PPAR-activator compounds include the following compounds: [5-Methoxy-2-methyl-4-(4'-trifluoromethyl-biphenyl-4-ylmethylsulfanyl)-phenoxy]-acetic acid; [5-Methoxy-2-methyl-4-(3'-trifluoromethyl-biphenyl-4-ylmethylsulfanyl)-phenoxy]-acetic acid;

[4-(4'-Fluoro-biphenyl-4-ylmethylsulfanyl)-5-methoxy-2-methyl-phenoxy]-acetic acid; {5-Methoxy-2-methyl-4-[4-(4-trifluoromethyl-benzoyloxy)-benzylsulfanyl]-phenoxy}-acetic acid; {5-Methoxy-2-methyl-4-[4-(5-trifluoromethyl-pyridin-2-yl)-benzylsulfanyl]-phenoxy}-acetic acid;

4-[4-[2-(3-Fluoro-phenyl)-vinyl]-benzylsulfanyl]-5-methoxy-2-methyl-phenoxy]-acetic acid; [5-Methoxy-2-methyl-4-(3-methyl-4'-trifluoromethyl-biphenyl-4-ylmethylsulfanyl)-phenoxy]-acetic acid; [5-Methoxy-2-methyl-4-(4'-trifluoromethyl-biphenyl-3-ylmethylsulfanyl)-phenoxy]-acetic acid;

{5-Methoxy-2-methyl-4-[2-(4-trifluoromethyl-benzoyloxy)-benzylsulfanyl]-phenoxy}acetic acid; 3-{5-[2-(5-Methyl-2-phenyl-oxazol-4-yl-ethoxy)-indol-1-yl]-propionic acid; 3-{4[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1H-indazol-1-yl}propanoic acid; 2-Methyl-2-{3-[(2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy)carbonyl]amino)methyl}phenoxy}propionic acid; 1-{3'-[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)-1,1'-biphenyl-3-yl]oxy}cyclobutanecarboxylic acid;

3-[3-(1-Carboxy-1-methyl-ethoxy)-phenyl]-piperidine-1-carboxylic acid 3-trifluoromethyl-benzyl ester; 2-{2-methyl-4-[(4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl)methyl]sulfanyl}phenoxy}acetic acid;

2-{2-methyl-4-[(4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-5-yl)methyl]sulfanyl}phenoxy}acetic acid;

methyl 2-{4-[(4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl)methyl]sulfanyl}phenoxy}acetate; 2-{4-[(4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl)methyl]sulfanyl}phenoxy}acetic acid; (E)-3-[2-methyl-4-{4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methoxy]phenyl]-2-propenoic acid;

2-{3-chloro-4-[(4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl)methyl]sulfanyl}phenyl}acetic acid; 2-{2-methyl-4-[(4-methyl-2-[3-fluoro-4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl)methyl]sulfanyl}phenoxy}acetic acid; and pharmaceutically acceptable salts thereof.

Any MTP/Apo B secretion (microsomal triglyceride transfer protein and/or apolipoprotein B secretion) inhibitor can be used in the combination aspect of the present invention. Such inhibition is readily determined by those skilled in the art according to standard assays (e.g., Wetterau, J. R. 1992; Science 258:999). A variety of these compounds are known to those skilled in the art, including imipramine (Bayer) and additional compounds such as those disclosed in WO 96/40640 and

WO 98/23593.

Any ACAT inhibitor can serve in the combination therapy aspect of the present invention. Such inhibition may be determined readily by one of skill in the art according to standard assays, such as the method of Heider et al. described in *Journal of Lipid Research*, 24:1127 (1983). A variety of these compounds are known to those skilled in the art, for example, U.S. Pat. No. 5,510,379 discloses certain carboxysulfonates, while WO 96/26948 and WO 96/10559 both disclose urea derivatives having ACAT inhibitory activity. Examples of ACAT inhibitors include compounds such as Avasimibe (Pfizer), CS-505 (Sankyo) and Eflucimibe (Eli Lilly and Pierre Fabre).

A lipase inhibitor can serve in the combination therapy aspect of the present invention. Such lipase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., *Methods Enzymol.* 286: 190-231). Pancreatic lipase mediates the metabolic cleavage of fatty acids from triglycerides at the 1- and 3-carbon positions. Because pancreatic lipase is the primary enzyme required for the absorption of dietary triglycerides, inhibitors have utility in the treatment of obesity and the other related conditions. Such pancreatic lipase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., *Methods Enzymol.* 286: 190-231). Gastric lipase is an immunologically distinct lipase that is responsible for approximately 10 to 40% of the digestion of dietary fats. Such gastric lipase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., *Methods Enzymol.* 286: 190-231).

A variety of gastric and/or pancreatic lipase inhibitors are known to one of ordinary skill in the art. Preferred lipase inhibitors are those inhibitors that are selected from the group consisting of lipstatin, tetrahydrolipstatin (orlistat), valilactone, esterastin, ebelactone A, and ebelactone B. The lipase inhibitor, N-3-trifluoromethylphenyl-N'-3-chloro-4'-trifluoromethylphenylurea, and the various urea derivatives related thereto, are disclosed in U.S. Pat. No. 4,405,644. The lipase inhibitor, esteracin, is disclosed in U.S. Pat. Nos. 4,189,438 and 4,242,453. The lipase inhibitor, cyclo-O,O'-[(1,6-hexanediyl)-bis-(iminocarbonyl)]dioxime, and the various bis(iminocarbonyl)dioximes related thereto may be prepared as described in Petersen et al., *Liebigs Annalen*, 562, 205-229 (1949). Lipstatin, (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecanoic acid lactone, and tetrahydrolipstatin (orlistat), (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone, and the variously substituted N-formylleucine derivatives and stereoisomers thereof, are disclosed in U.S. Pat. No. 4,598,089. Tetrahydrolipstatin may be prepared as described in, e.g., U.S. Pat. Nos. 5,274,143; 5,420,305; 5,540,917; and 5,643,874. The pancreatic lipase inhibitor, FL-386, 1-[4-(2-methylpropyl)cyclohexyl]-2-[(phenylsulfonyl)oxy]-ethanone, and the variously substituted sulfonate derivatives related thereto, are disclosed in U.S. Pat. No. 4,452,813. The pancreatic lipase inhibitor, WAY-121898, 4-phenoxyphenyl-4-methylpiperidin-1-yl-carboxylate, and the various carbamate esters and pharmaceutically acceptable salts related thereto, are disclosed in U.S. Pat. Nos. 5,512,565; 5,391,571 and 5,602,151. The pancreatic lipase inhibitor, valilactone, and a process for the preparation thereof by the microbial cultivation of Actinomycetes strain MG147-CF2, are disclosed in Kitahara, et al.,

J. Antibiotics, 40 (11), 1647-1650 (1987). The pancreatic lipase inhibitors, ebelactone A and ebelactone B, and a process for the preparation thereof by the microbial cultivation of Actinomycetes strain MG7-G1, are disclosed in Umezawa, et al., J. Antibiotics, 33, 1594-1596 (1980). The use of ebelactones A and B in the suppression of monoglyceride formation is disclosed in Japanese Kokai 08-143457, published Jun. 4, 1996.

Bile acid sequestrants, such as Welchol[®], Colestid[®], LoCholest[®], Questran[®] and fibric acid derivatives, such as Atromid[®], Lopid[®] and Tricor[®] may be used in a combination aspect of the invention.

Compounds of the present invention can be used with anti-diabetic compounds. Diabetes can be treated by administering to a patient having diabetes (especially Type II), insulin resistance, impaired glucose tolerance, or the like, or any of the diabetic complications such as neuropathy, nephropathy, retinopathy or cataracts, a therapeutically effective amount of a Formula I compound in combination with other agents (e.g., insulin) that can be used to treat diabetes. This includes the classes of anti-diabetic agents (and specific agents) described herein.

Any glycogen phosphorylase inhibitor can be used in combination with a Formula I compound of the present invention. The term glycogen phosphorylase inhibitor refers to compounds that inhibit the bioconversion of glycogen to glucose-1-phosphate which is catalyzed by the enzyme glycogen phosphorylase. Such glycogen phosphorylase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., J. Med. Chem. 41 (1998) 2934-2938). A variety of glycogen phosphorylase inhibitors are known to those skilled in the art including those described in WO 96/39384 and WO 96/39385.

Any aldose reductase inhibitor can be used in combination with a Formula I compound of the present invention. Aldose reductase inhibition is readily determined by those skilled in the art according to standard assays (e.g., J. Malone, Diabetes, 29:861-864 (1980). "Red Cell Sorbitol, an Indicator of Diabetic Control"). A variety of aldose reductase inhibitors are known to those skilled in the art.

Any sorbitol dehydrogenase inhibitor can be used in combination with a Formula I compound of the present invention. Such sorbitol dehydrogenase inhibitor activity is readily determined by those skilled in the art according to standard assays (e.g., Analyt. Biochem (2000) 280: 329-331). A variety of sorbitol dehydrogenase inhibitors are known, for example, U.S. Pat. Nos. 5,728,704 and 5,866,578 disclose compounds and a method for treating or preventing diabetic complications by inhibiting the enzyme sorbitol dehydrogenase.

Any glucosidase inhibitor can be used in combination with a Formula I compound of the present invention. Such glucosidase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Biochemistry (1969) 8: 4214).

A generally preferred glucosidase inhibitor includes an amylase inhibitor. An amylase inhibitor is a glucosidase inhibitor that inhibits the enzymatic degradation of starch or glycogen into maltose. Such amylase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Methods Enzymol. (1955) 1: 149). The inhibition of such enzymatic degradation is beneficial in

reducing amounts of bioavailable sugars, including glucose and maltose, and the concomitant deleterious conditions resulting therefrom.

A variety of glucosidase inhibitors are known to one of ordinary skill in the art and examples are provided below. Preferred glucosidase inhibitors are those inhibitors that are selected from the group consisting of acarbose, adiposine, voglibose, miglitol, emiglitate, camiglibose, tendamistate, trestatin, pradiamicin-Q and salbostatin. The glucosidase inhibitor, acarbose, and the various amino sugar derivatives related thereto are disclosed in U.S. Pat. Nos. 4,062,950 and 4,174,439 respectively. The glucosidase inhibitor, adiposine, is disclosed in U.S. Pat. No. 4,254,256. The glucosidase inhibitor, voglibose, 3,4-dideoxy-4-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-2-C-(hydroxymethyl)-D-epi-inositol, and the various N-substituted pseudo-aminosugars related thereto, are disclosed in U.S. Pat. No. 4,701,559. The glucosidase inhibitor, miglitol, (2R,3R,4R,5S)-1-(2-hydroxyethyl)-2-(hydroxymethyl)-3,4,5-piperidinetriol, and the various 3,4,5-trihydroxypiperidines related thereto, are disclosed in U.S. Pat. No. 4,639,436. The glucosidase inhibitor, emiglitate, ethyl p-[2-[(2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidino]ethoxy]-benzoate, the various derivatives related thereto and pharmaceutically acceptable acid addition salts thereof, are disclosed in U.S. Pat. No. 5,192,772. The glucosidase inhibitor, MDL-25637, 2,6-dideoxy-7-O-.beta.-D-glucopyranosyl-2,6-imino-D-glycero-L-gluco-heptitol, the various homodisaccharides related thereto and the pharmaceutically acceptable acid addition salts thereof, are disclosed in U.S. Pat. No. 4,634,765. The glucosidase inhibitor, camiglibose, methyl 6-deoxy-6-[(2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidino]-.alpha.-D-glucopyranoside sesquihydrate, the deoxy-nojirimycin derivatives related thereto, the various pharmaceutically acceptable salts thereof and synthetic methods for the preparation thereof, are disclosed in U.S. Pat. Nos. 5,157,116 and 5,504,078. The glycosidase inhibitor, salbostatin and the various pseudosaccharides related thereto, are disclosed in U.S. Pat. No. 5,091,524.

A variety of amylase inhibitors are known to one of ordinary skill in the art. The amylase inhibitor, tendamistat and the various cyclic peptides related thereto, are disclosed in U.S. Pat. No. 4,451,455. The amylase inhibitor AI-3688 and the various cyclic polypeptides related thereto are disclosed in U.S. Pat. No. 4,623,714. The amylase inhibitor, trestatin, consisting of a mixture of trestatin A, trestatin B and trestatin C and the various trehalose-containing aminosugars related thereto are disclosed in U.S. Pat. No. 4,273,765.

Additional anti-diabetic compounds, may be used in combination with a Formula I compound of the present invention, includes, for example, the following: biguanides (e.g., metformin), insulin secretagogues (e.g., sulfonylureas and glinides), glitazones, non-glitazone PPAR gamma agonists, PPAR.beta. agonists, inhibitors of DPP-IV, inhibitors of PDE5, inhibitors of GSK-3, glucagon antagonists, inhibitors of f-1,6-BPase (Metabasis/Sankyo), GLP-1/analogues (AC 2993, also known as exendin-4), insulin and insulin mimetics (Merck natural products). Other examples would include PKC-.beta. inhibitors and AGE breakers.

Compounds of the present invention can be used in combination with anti-obesity agents. Any anti-obesity agent can be used in such combinations and examples are provided herein. Such anti-obesity activity is readily determined by those skilled in the art according to standard assays known in the art. Suitable anti-obesity agents include phenylpropanolamine, ephedrine, pseudoephedrine, phentermine, beta sub.3 adrenergic receptor agonists, apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, MCR-4 agonists, cholecystokinin-A (CCK-A) agonists, monoamine reuptake inhibitors (e.g., sibutramine), sympathomimetic agents, serotonergic agents, cannabinoid receptor antagonists (e.g., rimonabant (SR-141,716A)), dopamine agonists (e.g., bromocriptine), melanocyte-stimulating hormone receptor analogs, 5HT2c agonists, melanin concentrating hormone antagonists, leptin (the OB protein), leptin analogs, leptin receptor agonists, galanin antagonists, lipase inhibitors (e.g., tetrahydrolipstatin, i.e. orlistat), bombesin agonists, anorectic agents (e.g., a bombesin agonist), Neuropeptide-Y antagonists, thyroxine, thyromimetic agents, dehydroepiandrosterones or analogs thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, urocortin binding protein antagonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors (e.g., Axokine.TM.), human agouti-related proteins (AGRP), ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, neuromedin U receptor agonists, and the like.

Any thyromimetic can be used in combination with compounds of the present invention. Such thyromimetic activity is readily determined by those skilled in the art according to standard assays (e.g., Atherosclerosis (1996) 126: 53-63). A variety of thyromimetic agents are known to those skilled in the art, for example those disclosed in U.S. Pat. Nos. 4,766,121; 4,826,876; 4,910,305; 5,061,798; 5,284,971; 5,401,772; 5,654,468; and 5,569,674. Other antiobesity agents include sibutramine which can be prepared as described in U.S. Pat. No. 4,929,629. and bromocriptine which can be prepared as described in U.S. Pat. Nos. 3,752,814 and 3,752,888.

Anti-resorptive agents (for example progestins, polyphosphonates, bisphosphonate(s), estrogen agonists/antagonists, estrogen, estrogen/progestin combinations, Premarin.RTM., estrone, estriol or 17.alpha.- or 17.beta.-ethynyl estradiol) may be used in conjunction with the compounds of Formula I of the present invention. Exemplary progestins are available from commercial sources and include: algestone acetophenide, altrenogest, amadinone acetate, anagestone acetate, chlormadinone acetate, cingestol, clogestone acetate, clomegestone acetate, delmadinone acetate, desogestrel, dimethisterone, dydrogesterone, ethynerone, ethynodiol diacetate, etonogestrel, fluogestone acetate, gestaclone, gestodene, gestonorone caproate, gestrinone, haloprogestosterone, hydroxyprogesterone caproate, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, melengestrol acetate, methynodiol diacetate, norethindrone, norethindrone acetate, norethynodrel, norgestimate, norgestomet, norgestrel, oxogestone phenpropionate, progesterone, quingestanol acetate, quingestrone, and tigestol. Preferred progestins are medroxyprogesterone, norethindrone and norethynodrel. Exemplary bone resorption inhibiting polyphosphonates include polyphosphonates of the type disclosed in U.S. Pat. No. 3,683,080, the disclosure of which is incorporated herein by reference. Preferred polyphosphonates are

geminal diphosphonates (also referred to as bis-phosphonates). Tiludronate disodium is an especially preferred polyphosphonate. Ibandronic acid is an especially preferred polyphosphonate. Alendronate and resindronate are especially preferred polyphosphonates. Zoledronic acid is an especially preferred polyphosphonate. Other preferred polyphosphonates are 6-amino-1-hydroxy-hexylidene-bisphosphonic acid and 1-hydroxy-3(methylpentylamino)-propylidene-bisphosphonic acid. The polyphosphonates may be administered in the form of the acid, or of a soluble alkali metal salt or alkaline earth metal salt.

Hydrolyzable esters of the polyphosphonates are likewise included. Specific examples include ethane-1-hydroxy 1,1-diphosphonic acid, methane diphosphonic acid, pentane-1-hydroxy-1, 1-diphosphonic acid, methane dichloro diphosphonic acid, methane hydroxy diphosphonic acid, ethane-1-amino-1, 1-diphosphonic acid, ethane-2-amino-1, 1-diphosphonic acid, propane-3-amino-1-hydroxy-1, 1-diphosphonic acid, propane-N, N-dimethyl-3-amino-1-hydroxy-1, 1-diphosphonic acid, propane-3,3-dimethyl-3-amino-1-hydroxy-1,1-diphosphonic acid, phenyl amino methane diphosphonic acid, N,N-dimethylamino methane diphosphonic acid, N(2-hydroxyethyl) amino methane diphosphonic acid, butane-4-amino-1-hydroxy-1,1-diphosphonic acid, pentane-5-amino-1-hydroxy-1,1-diphosphonic acid, hexane-6-amino-1-hydroxy-1,1-diphosphonic acid and pharmaceutically acceptable esters and salts thereof.

The compounds of this invention may be combined with a mammalian estrogen agonist/antagonist. Estrogen antagonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue, and blocking the actions of estrogen in one or more tissues. Such activities are readily determined by those skilled in the art of standard assays including estrogen receptor binding assays, standard bone histomorphometric and densitometer methods (Eriksen E. F. et al., *Bone Histomorphometry*, Raven Press, New York, 1994, pages 1-74; Grier S. J. et. al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, *Inv. Radiol.*, 1996, 31(1):50-62; Wahner H. W. and Fogelman I., The Evaluation of Osteoporosis: Dual Energy X-Ray Absorptiometry in Clinical Practice, Martin Dunitz Ltd., London 1994, pages 1-296). A variety of these compounds are described and referenced below.

Another preferred estrogen agonist/antagonist is 3-(4-(1,2-diphenyl-but-1-enyl)-phenyl)-acrylic acid, which is disclosed in Willson et al., *Endocrinology*, 1997, 138, 3901-3911. Another preferred estrogen agonist/antagonist is tamoxifen: (ethanamine,2-(-(4-(1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl, (Z)-2-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)) and related compounds which are disclosed in U.S. Pat. No. 4,536,516, the disclosure of which is incorporated herein by reference. Another related compound is 4-hydroxy tamoxifen, which is disclosed in U.S. Pat. No. 4,623,660, the disclosure of which is incorporated herein by reference.

A preferred estrogen agonist/antagonist is raloxifene: (methanone, (6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl)(4-(2-(1-piperidinyl)ethoxy)phenyl)-hydrochloride) which is disclosed in U.S. Pat. No. 4,418,068, the disclosure of which is incorporated herein by reference.

Another preferred estrogen agonist/antagonist is toremifene: (ethanamine, 2-(4-(4-chloro-1, 2-diphenyl-1-butenyl) phenoxy)-N, N-dimethyl-, (Z)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) which is disclosed in

U.S. Pat. No. 4,996,225, the disclosure of which is incorporated herein by reference. Another preferred estrogen agonist/antagonist is centchroman: 1-(2-((4-(methoxy-2, 2, dimethyl-3-phenyl-chroman-4-yl)-phenoxy)-ethyl)-p-yrrolidine, which is disclosed in U.S. Pat. No. 3,822,287, the disclosure of which is incorporated herein by reference. Also preferred is levormeloxifene. Another preferred estrogen agonist/antagonist is idoxifene: (E)-1-(2-(4-(1-(4-iodo-phenyl)-2-phenyl-but-1-enyl)-phenoxy)-ethyl)-pyrrolidinone, which is disclosed in U.S. Pat. No. 4,839,155, the disclosure of which is incorporated herein by reference.

Another preferred estrogen agonist/antagonist is 2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-benzo[b]thio-phen-6-ol which is disclosed in U.S. Pat. No. 5,488,058, the disclosure of which is incorporated herein by reference.

Another preferred estrogen agonist/antagonist is 6-(4-hydroxy-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-naphthalen-2-ol, which is disclosed in U.S. Pat. No. 5,484,795, the disclosure of which is incorporated herein by reference.

Another preferred estrogen agonist/antagonist is (4-(2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy)-phenyl)-(6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl)-methanone which is disclosed, along with methods of preparation, in PCT publication no. WO 95/10513 assigned to Pfizer Inc., the disclosure of which is incorporated herein by reference.

Other preferred estrogen agonist/antagonists include the compounds, TSE-424 (Wyeth-Ayerst Laboratories) and arazoxifene.

Other preferred estrogen agonist/antagonists include compounds as described in commonly assigned U.S. Pat. No. 5,552,412, the disclosure of which is incorporated herein by reference. Especially preferred compounds described therein are:

cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol (also known as lasofoxifene);

cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

cis-1-(6'-pyrrolidinoethoxy-3'-pyridyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene;

1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

is-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; and

1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline.

Other estrogen agonist/antagonists are described in U.S. Pat. No. 4,133,814 (the disclosure of which is incorporated herein by reference). U.S. Pat. No. 4,133,814 discloses derivatives of 2-phenyl-3-arylbenzothio-phenene and 2-phenyl-3-arylbenzothiophene-1-oxide.

Other anti-osteoporosis agents, which can be used in combination with a Formula I compound of the present invention, include, for example, the following: parathyroid hormone (PTH) (a bone anabolic agent); parathyroid hormone (PTH) secretagogues (see, e.g., U.S. Pat. No. 6,132,774), particularly calcium receptor antagonists; calcitonin; and vitamin D and vitamin D analogs.

Any compound that is an antihypertensive agent may be used in a combination aspect of this invention. Such compounds include amlodipine and related dihydropyridine compounds, calcium channel blockers, angiotensin converting enzyme inhibitors ("ACE-Inhibitors"), angiotensin-II receptor antagonists, beta-adrenergic receptor blockers and alpha-adrenergic receptor blockers. Such antihypertensive activity is determined by those skilled in the art according to standard tests (e.g. blood pressure measurements).

Amlodipine and related dihydropyridine compounds are disclosed in U.S. Pat. No. 4,572,909, which is incorporated herein by reference, as potent anti-ischemic and antihypertensive agents. U.S. Pat. No. 4,879,303, which is incorporated herein by reference, discloses amlodipine benzenesulfonate salt (also termed amlodipine besylate). Amlodipine and amlodipine besylate are potent and long lasting calcium channel blockers. As such, amlodipine, amlodipine besylate and other pharmaceutically acceptable acid addition salts of amlodipine have utility as antihypertensive agents and as antiischemic agents. Amlodipine and its pharmaceutically acceptable acid addition salts are also disclosed in U.S. Pat. No. 5,155,120 as having utility in the treatment of congestive heart failure. Amlodipine besylate is currently sold as Norvasc®.

Calcium channel blockers which are within the scope of a combination aspect of this invention include, but are not limited to: bepridil, which may be prepared as disclosed in U.S. Pat. No. 3,962, 238 or U.S. Reissue No. 30,577; clentiazem, which may be prepared as disclosed in U.S. Pat. No. 4,567,175; diltiazem, which may be prepared as disclosed in U.S. Pat. No. 3,562, fendiline, which may be prepared as disclosed in U.S. Pat. No. 3,262,977; gallopamil, which may be prepared as disclosed in U.S. Pat. No. 3,261,859; mibefradil, prenylamine, semotiadil, terodiline, verapamil, aranipine, barnidipine, benidipine, cilnidipine, efonidipine, elgodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, and perhexiline. The disclosures of all such U.S. Patents are incorporated herein by reference.

Angiotensin Converting Enzyme Inhibitors (ACE-Inhibitors) which are within the scope of this invention include, but are not limited to: alacepril, which may be prepared as disclosed in U.S. Pat. No. 4,248,883; benazepril, which may be prepared as disclosed in U.S. Pat. No. 4,410,520; captopril, ceronapril, delapril, enalapril, fosinopril, imadapril, lisinopril, moveltopril, perindopril, quinapril, ramipril, spirapril, temocapril, andtrandolapril,. The disclosures of all such U.S. patents are incorporated herein by reference.

Angiotensin-II receptor antagonists (A-II antagonists) which are within the scope of this invention include, but are not limited to: candesartan, which may be prepared as disclosed in U.S. Pat. No. 5,196,444; eprosartan, which may be prepared as disclosed in U.S. Pat. No. 5,185,351; irbesartan, losartan, and valsartan. The disclosures of all such U.S. patents are incorporated herein by reference.

Beta-adrenergic receptor blockers (beta- or beta. -blockers) which are within the scope of this invention include, but are not limited to: acebutolol, which may be prepared as disclosed in U.S. Pat. No. 3,857,952; alprenolol, amosulalol, which may be prepared as disclosed in U.S. Pat. No. 4,217,305;

arotinolol, atenolol, befunolol, betaxolol; The disclosures of all such U.S. patents are incorporated herein by reference.

Alpha-adrenergic receptor blockers (alpha- or .alpha.-blockers) which are within the scope of this invention include, but are not limited to: amosulalol, which may be prepared as disclosed in U.S. Pat. No. 4,217,307; arotinolol, which may be prepared as disclosed in U.S. Pat. No. 3,932,400; dapiprazole, doxazosin, fenspiride, indoramin, labetolol, naftopidil, nicergoline, prazosin, tamsulosin, tolazoline, trimazosin, and yohimbine, which may be isolated from natural sources according to methods well known to those skilled in the art. The disclosures of all such U.S. patents are incorporated herein by reference.

Any compound that is known to be useful in the treatment of Alzheimer's Disease may be used in a combination aspect of this invention. Such compounds include acetylcholine esterase inhibitors. Examples of known acetylcholine esterase inhibitors include donepezil (Aricept[®]), tacrine (Cognex[®]), rivastigmine (Exelon[®]) and galantamine (Remynil). Aricept[®] is disclosed in the following U.S. patents, all of which are fully incorporated herein by reference: 4,895,841, 5,985,864, 6,140,321, 6,245,911 and 6,372,760. Exelon[®] is disclosed in U.S. Patent Nos. 4,948,807 and 5,602,176 which are fully incorporated herein by reference. Cognex[®] is disclosed in U.S. Patent Nos. 4,631,286 and 4,816,456 (fully incorporated herein by reference). Remynil[®] is disclosed in U.S. Patent Nos. 4,663,318 and 6,099,863 which are fully incorporated herein by reference.

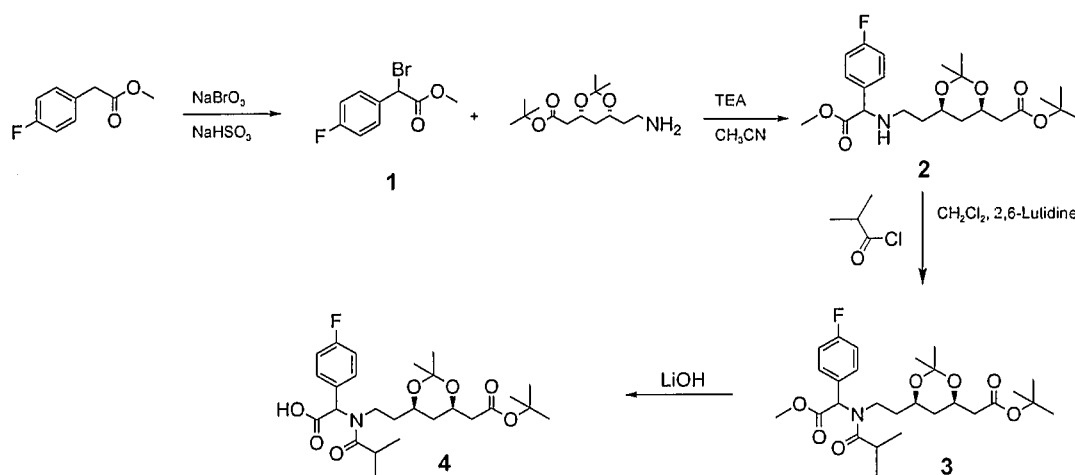
PREPARATION OF THE COMPOUNDS OF THE INVENTION

The present invention contains compounds that can be synthesized in a number of ways familiar to one skilled in organic synthesis. The compounds outlined herein can be synthesized according to the methods described below, along with methods typically used by a synthetic organic chemist, and combinations or variations of those methods, which are generally known to one skilled in the art of synthetic chemistry. The synthetic route of compounds in the present invention is not limited to the methods outlined below. One skilled in the art will be able to use the schemes below to synthesize compounds claimed in this invention. Individual compounds may require manipulation of the conditions in order to accommodate various functional groups. A variety of protecting groups known to one skilled in the art may be required. Purification, if necessary, may be accomplished on a silica gel column eluted with the appropriate organic solvent system. Also, reverse phase HPLC or recrystallization may be employed. The following non-limiting descriptions also demonstrate methods for the synthesis of compounds of the invention.

Schemes 1-3 relate to the preparation of compounds of the invention having a Formula I wherein R² is, for example, 4-fluorophenyl, R⁴ is, for example, benzyl amide, and R⁵ is, for example, isopropyl.

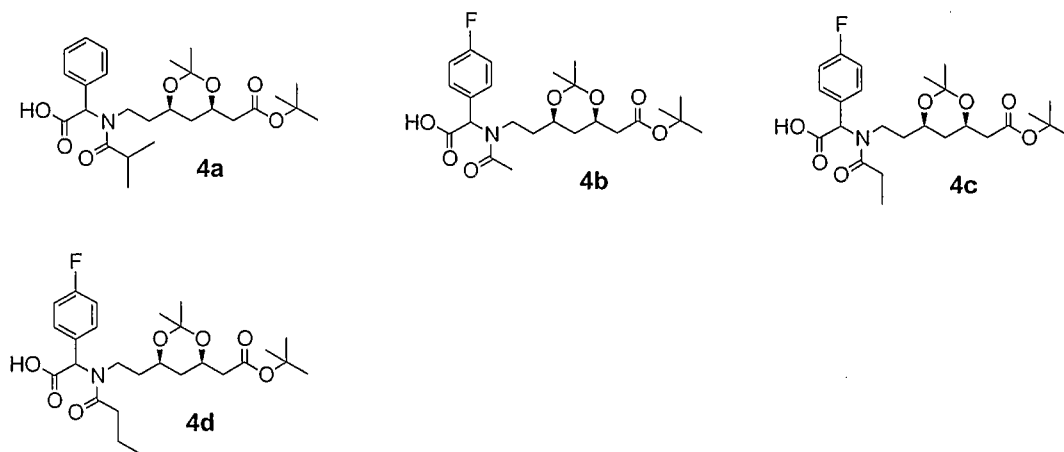
A general procedure for the preparation of the cycloaddition precursor **4** is illustrated in Scheme 1. The synthesis of **4** begins with a selective bromination of commercially available 4-fluorophenylacetic acid methyl ester via the method of Kikuchi, D. *et al* (*J. Org. Chem.*, **1998**, 63, 6023) to give racemic Bromo- (4-fluoro-phenyl)-acetic acid methyl ester **1**. Reaction of **1** with [(4R, 6R)-6-(2-Amino-ethyl)-2,2-

dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester (Baumann, Kelvin L.; Butler, Donald E.; Deering, Carl F.; Mennen, Kenneth E.; Millar, Alan; Nanninga, Thomas N.; Palmer, Charles W.; Roth, Bruce D.; *Tetrahedron Letters* (1992), 33(17), 2283) provides the amino ester **2** as a mixture of diastereomers. Acylation of **2** and saponification of the intermediate methyl ester **3** yields [2-((4R,6R)-6-tert-butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-isobutyryl-amino-(4-fluoro-phenyl)-acetic acid, **4**, which is isolated as a mixture of diastereomers.

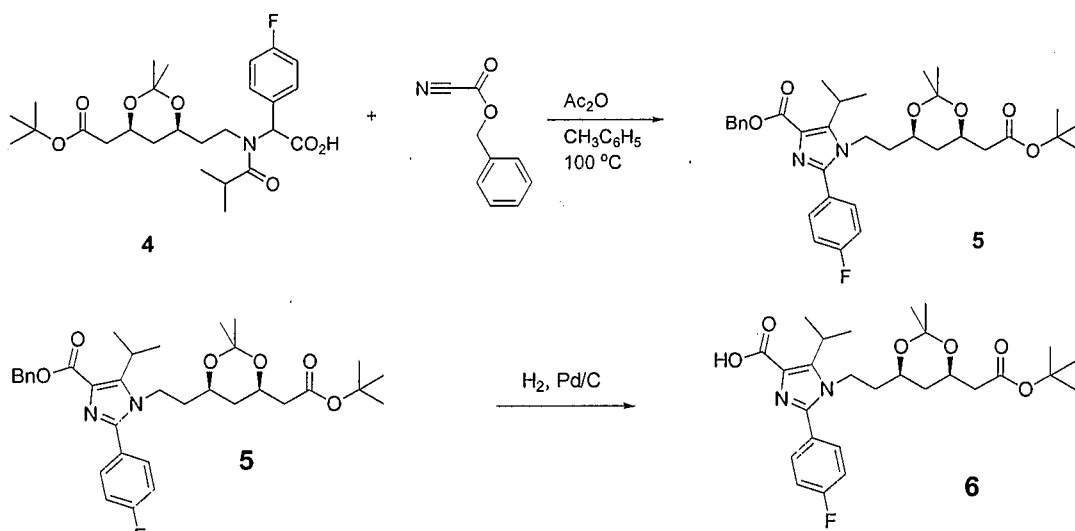


Scheme 1

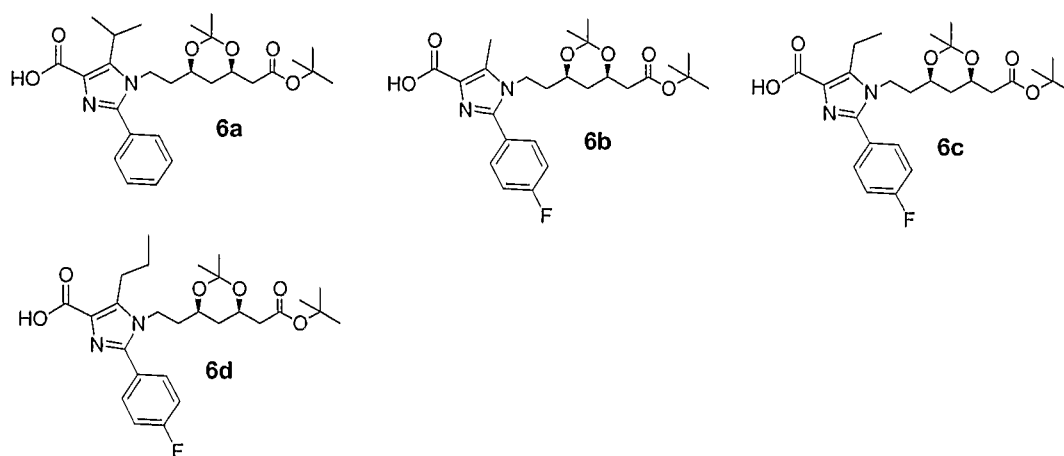
The following cycloaddition precursor compounds for example, may be prepared in a similar manner:



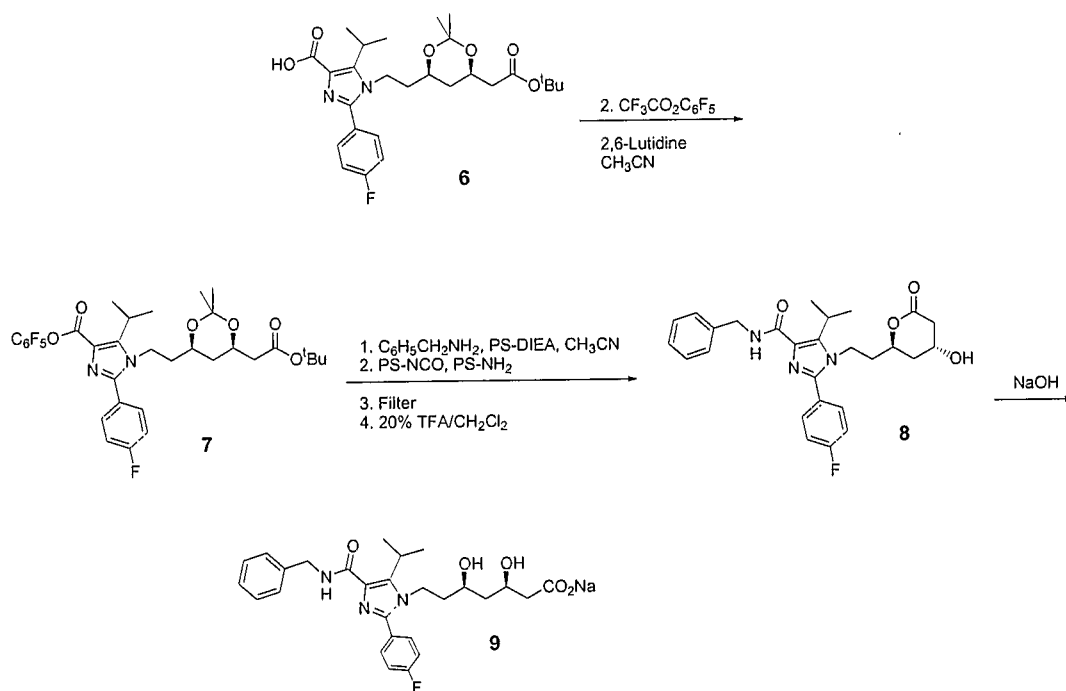
Scheme 2 illustrates the preparation of imidazole **5** and the imidazole-4-carboxylic acid **6**. Thus, in a manner similar to that described by R. Huisgen *et al* (Chem. Ber. 1971, 104, 1562), treatment of compound **4** with acetic anhydride in the presence benzyl cyanoformate gives the desired 1-[2-((4R,6R)-6-tert-butoxycarbonylmethyl-2,2-dimethyl [1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid benzyl ester **5**. Hydrogenolysis of **5** gives the free acid **6**.



The following compounds may be prepared as shown in Scheme 2, from which the corresponding free acids may also be prepared.

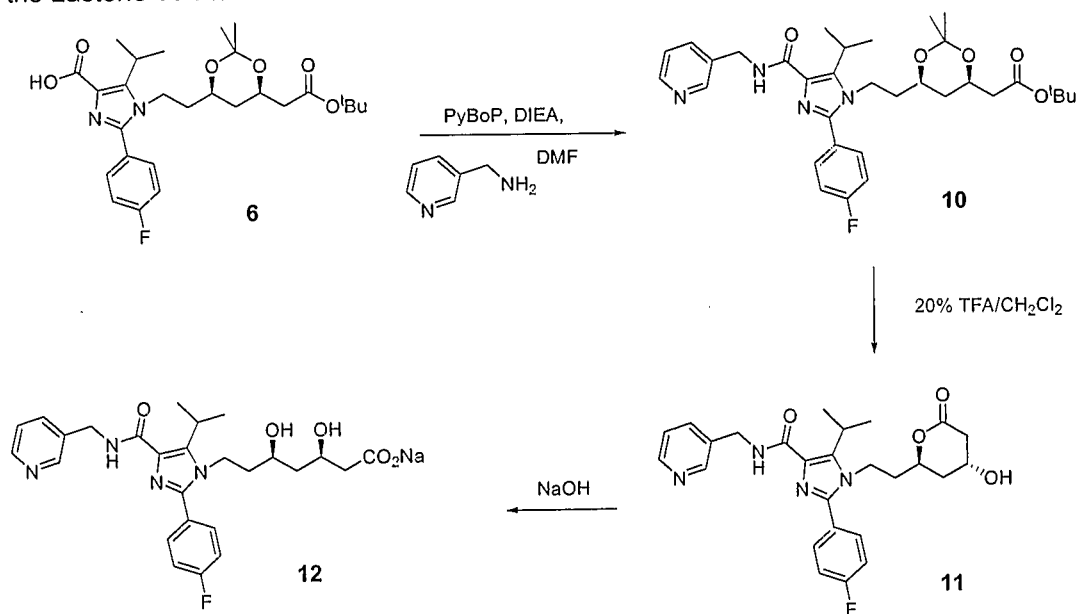


Scheme 3 illustrates the preparation of imidazole compound **9** from compound **6**. Thus, the free acid **6** is transformed to the pentafluorophenyl ester **7**. Reaction of compound **7** with benzyl amine and subsequent deprotection yields the lactone compound **8**. The lactone **8** is converted to **9** on treatment with sodium hydroxide.



Scheme 3

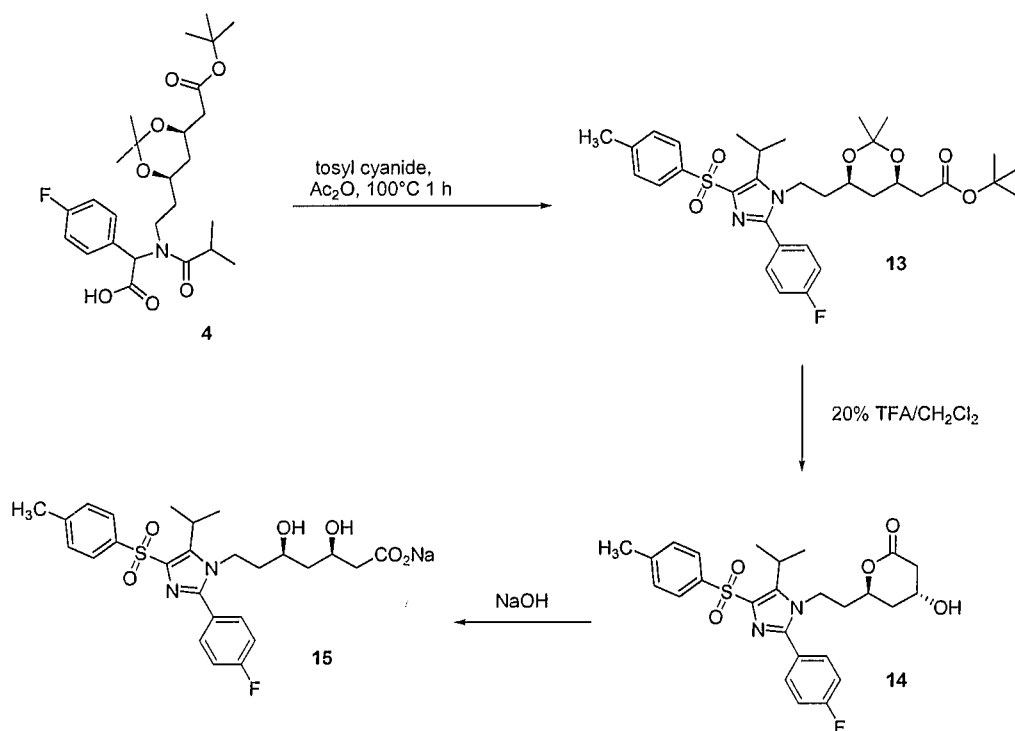
Scheme 4 illustrates an alternate preparation of compounds of the invention from the carboxylic acid **6**. Thus, *in situ* activation of **6** with PyBoP or EDCI/HOBt, or a similar activating agent, and treatment with 3-aminomethyl pyridine gives the amide **10**. Exposure of **10** to TFA provides the lactone **11** which is converted to **12** on treatment with base. Alternatively, the crude coupling product **10** may be converted to the Lactone **11** without isolation.



Scheme 4

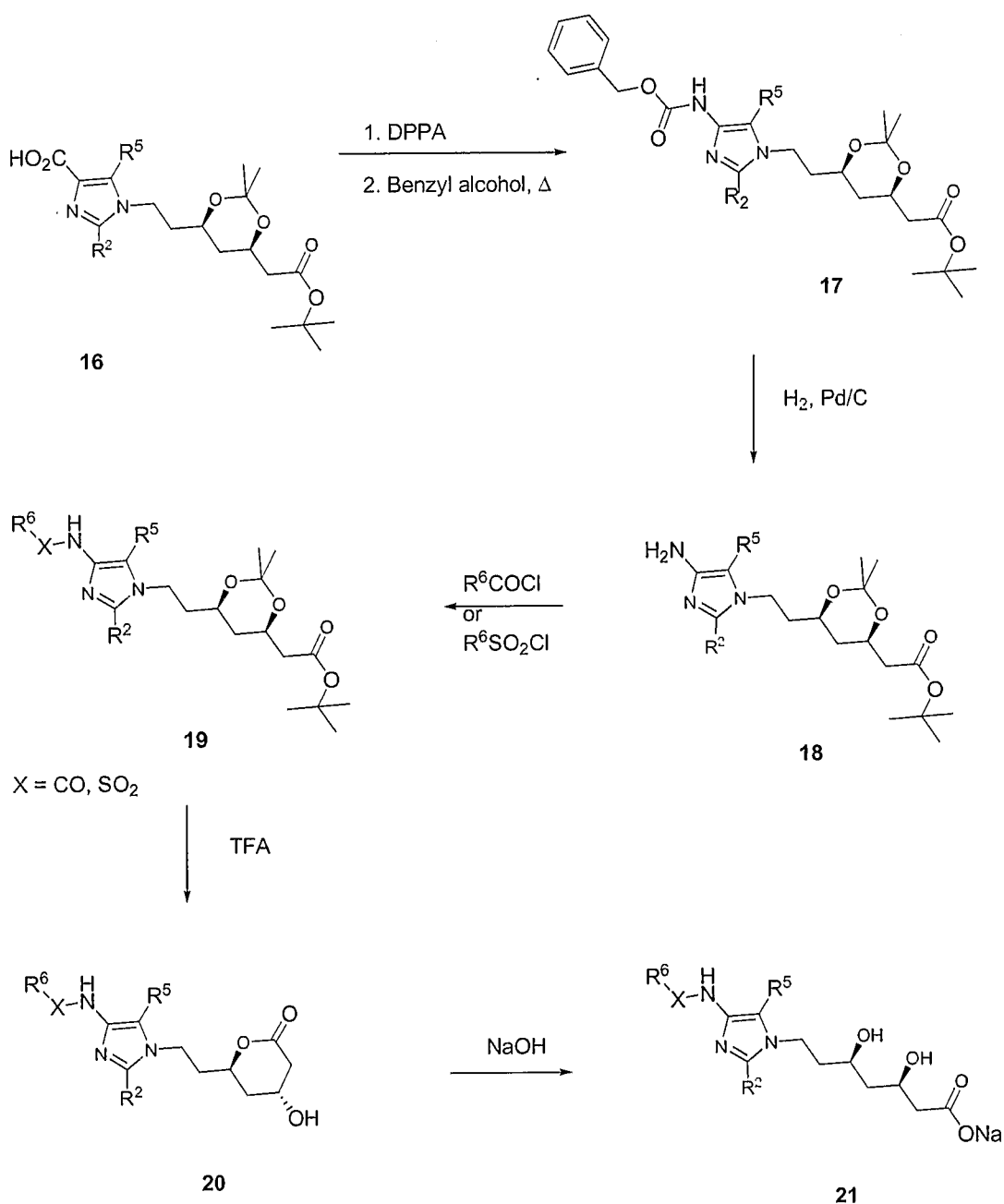
Scheme 5 illustrates the preparation of compounds of the invention having a Formula I wherein R^2 is, for example, 4-fluorophenyl, R^4 is a sulfone and R^5 is, for example, isopropyl.

Scheme 5 exemplifies the preparation of the sulfone **15** from the carboxylic acid **4**. Thus, reaction of compound **4** with commercially available tosyl cyanide yields the imidazole **13**. Exposure of **13** to TFA provides the lactone **14** which is converted to **15** on treatment with base.



Scheme 5

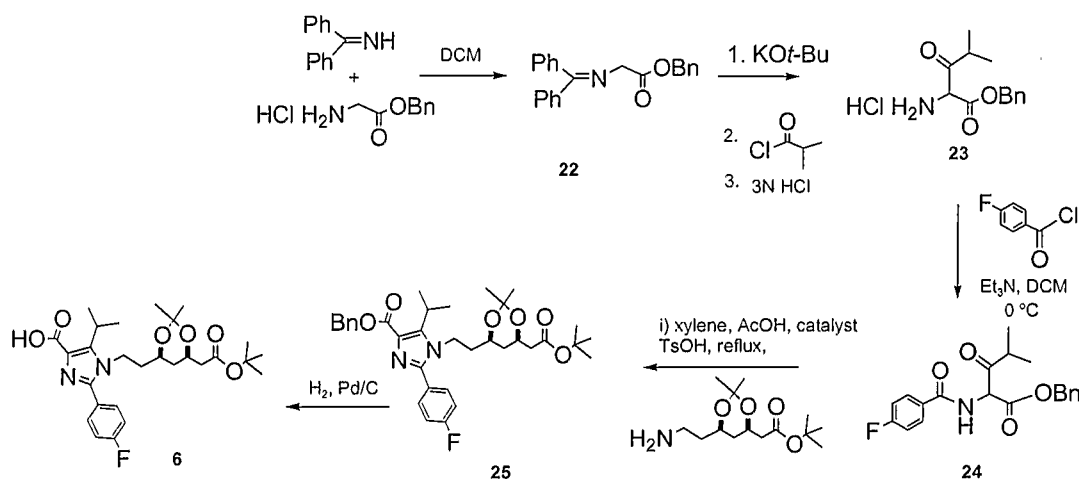
Scheme 6 illustrates a preparation of 4-aminoimidazoles **21** from the acid **16**, wherein R^2 , R^5 and R^6 are as defined *supra*. Thus, reaction of the acid **16** with diphenyl phosphoryl azide, (DPPA), in the presence of benzyl alcohol provides **17**. This compound is transformed to the aminoimidazole **18** by catalytic hydrogenation. Acylation or sulfonylation of **18** yields **19**. Exposure of **19** to TFA provides the lactone **20** which is converted to **21** on treatment with base.



Scheme 6

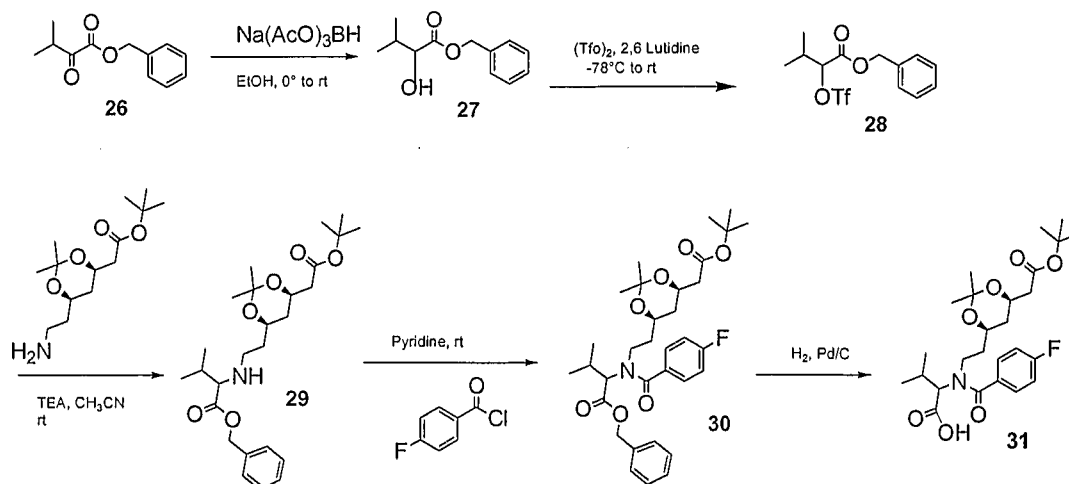
An alternate synthesis of 1-[2-((4R, 6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl [1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid **6** is illustrated in Scheme 7.

Thus, (benzhydrylidene-amino)-acetic acid benzyl ester **22**, prepared by the condensation of benzhydrylideneamine with glycine benzyl ester, is acylated with isobutyryl chloride according to the method of J. Singh *et al* (Tetrahedron Lett. **1993**, 34, 211). Subsequent hydrolysis gives **23**. A second acylation is accomplished by reacting the **23** with p-fluorobenzoyl chloride under basic condition to give **24**. Cyclodehydration of **24** with [(4R, 6R)-6-(2-Amino-ethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester yields the benzyl ester **25**. Hydrogenolysis of **25** yields the free acid **6**.



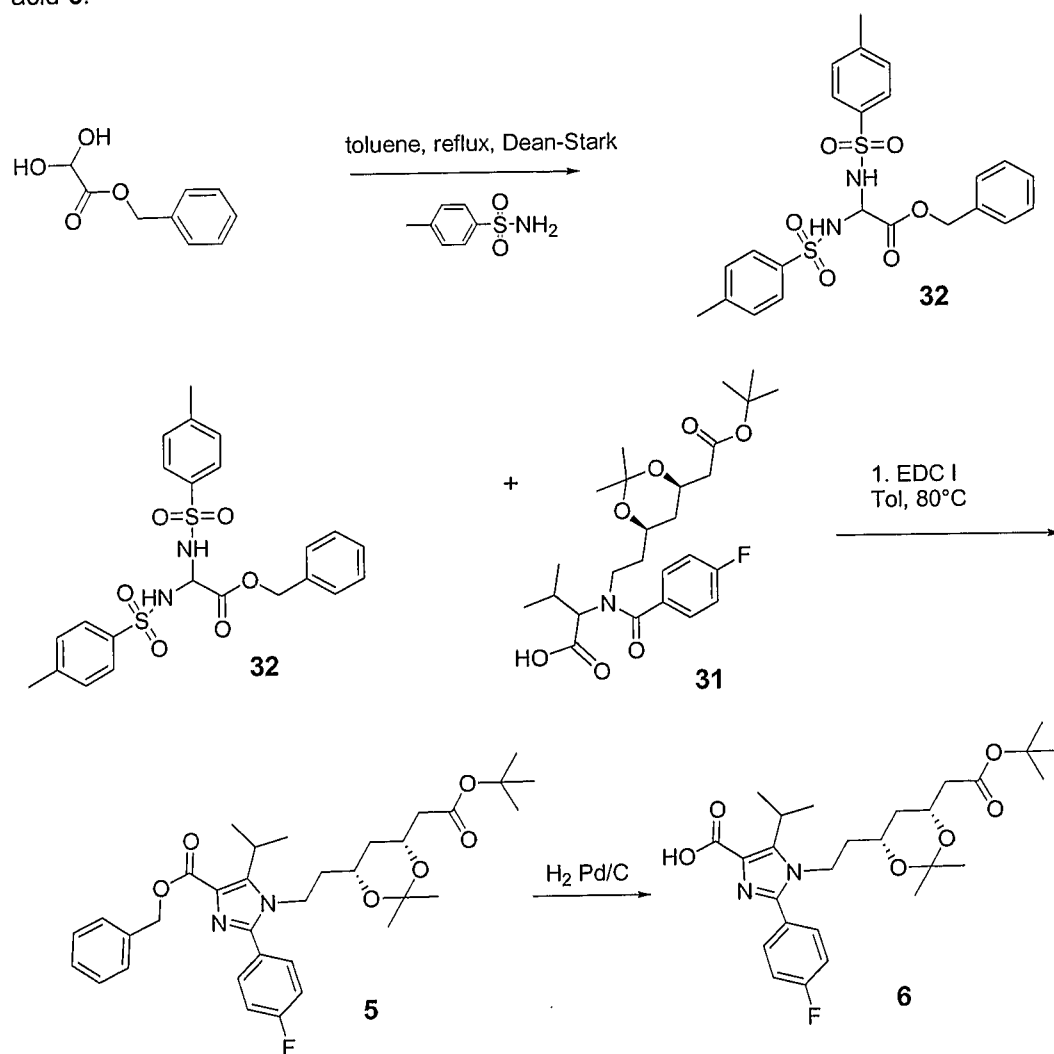
Scheme 7

Scheme 8 exemplifies the preparation of 2-[[2-((4R, 6R)-6-tert-Butoxycarbonylmethyl-2, 2-dimethyl [1,3] dioxan-4-yl)-ethyl]-(4-fluoro-benzoyl)-amino]-3-methyl-butyrac acid **31**. Thus, selective reduction of the benzyl ester **26**, prepared from commercially available sodium 3-methyl-2-oxo-butyrate according to the method of Manfred Hesse *et al* (Helvetica Chim. Acta, **2001**, 84, 3766), with sodium triacetoxyborohydride in ethanol at 0°C yields racemic 2-Hydroxy-3-methyl-butyrac acid benzyl ester **27**. Compound **27** is converted to the corresponding triflate **28** on treatment with triflic anhydride in the presence of 2,6-lutidine (Michael Walker, Tetrahedron, **1997**, 53, 14591). Reaction of **28** with [(4R, 6R)-6-(2-Amino-ethyl)-2,2-dimethyl-1,3]dioxan-4-yl]-acetic acid tert-butyl ester provides the amino ester **29** as a mixture of diastereomers which are not separated. Acylation of **29** and hydrogenolysis of the resulting benzyl ester **30** yields 2-[[2-((4R, 6R)-6-tert-Butoxycarbonylmethyl-2, 2-dimethyl [1,3] dioxan-4-yl)-ethyl]-(4-fluoro-benzoyl)-amino]-3-methyl-butyrac acid, **31**, as a mixture of diastereomers.



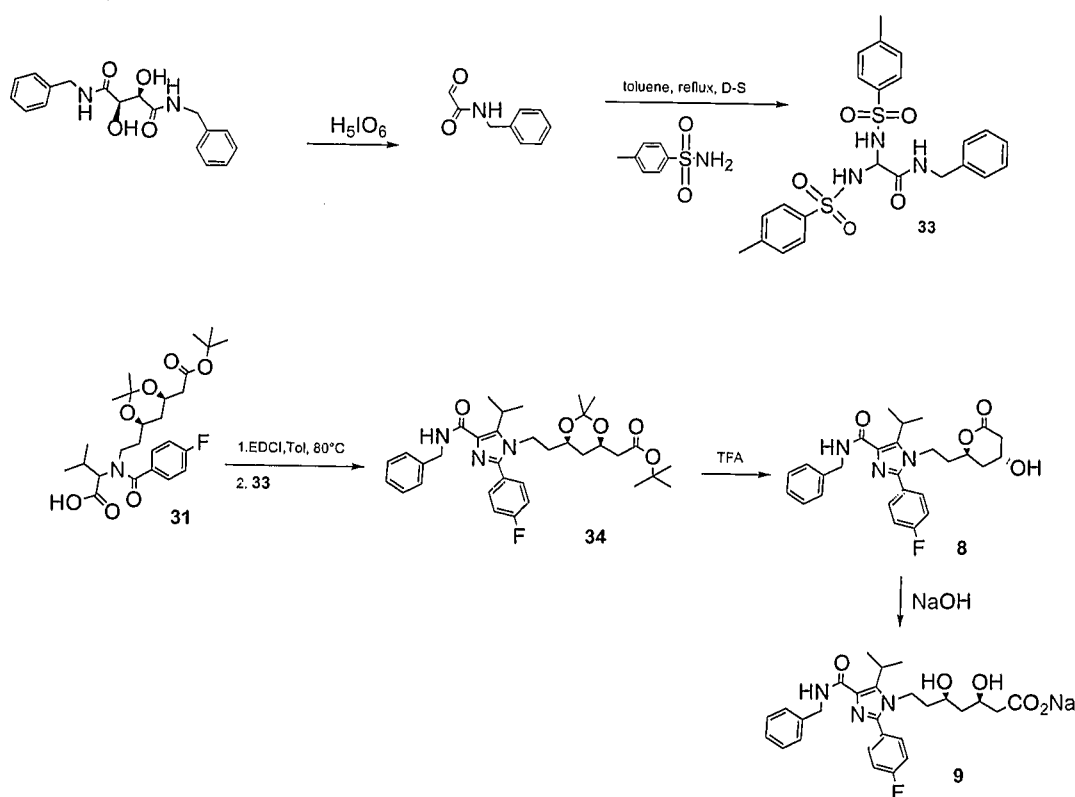
Scheme 8

Scheme 9 illustrates an alternate method for the preparation of 1-[2-((4R, 6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid **6**. Thus, reaction of **31** with Bis(toluene-4-sulfonyl amino) acetic acid benzyl ester **32**, prepared by condensation of benzyl glyoxalate hydrate with p-toluene sulfonamide, in the presence of EDCI yields 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid benzyl ester **5**. Hydrogenolysis of **5** gives the free acid **6**.



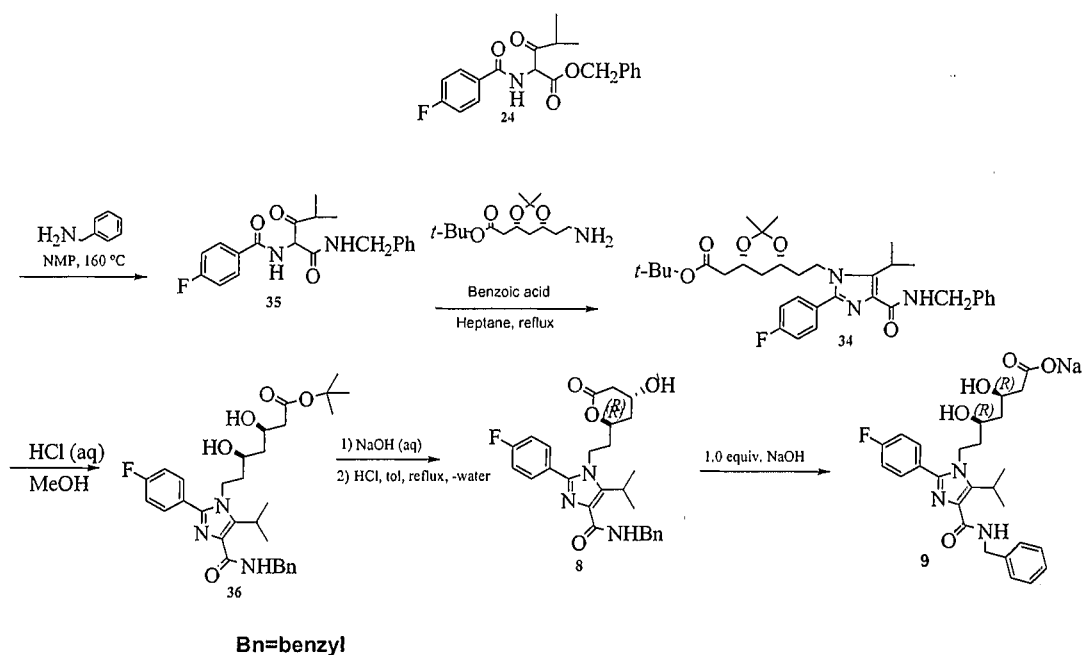
Scheme 9

Scheme 10 illustrates an alternate method for the preparation of the sodium salt of (3R,5R)-7-[4-Benzylcarbamoyl-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid **9**. Thus a reaction of **31** with Bis-(toluene-4-sulfonylamino)-acetic acid benzyl amide **33** in the presence of EDCI yields 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid benzyl amide **34**. Exposure of **34** to TFA provides the lactone **8** which is converted to **9** on treatment with base. The novel Bis-(toluene-4-sulfonylamino)-acetic acid benzyl amide **33** is prepared in two steps from commercially available N,N'-dibenzyl-oxalamide.



Scheme 10

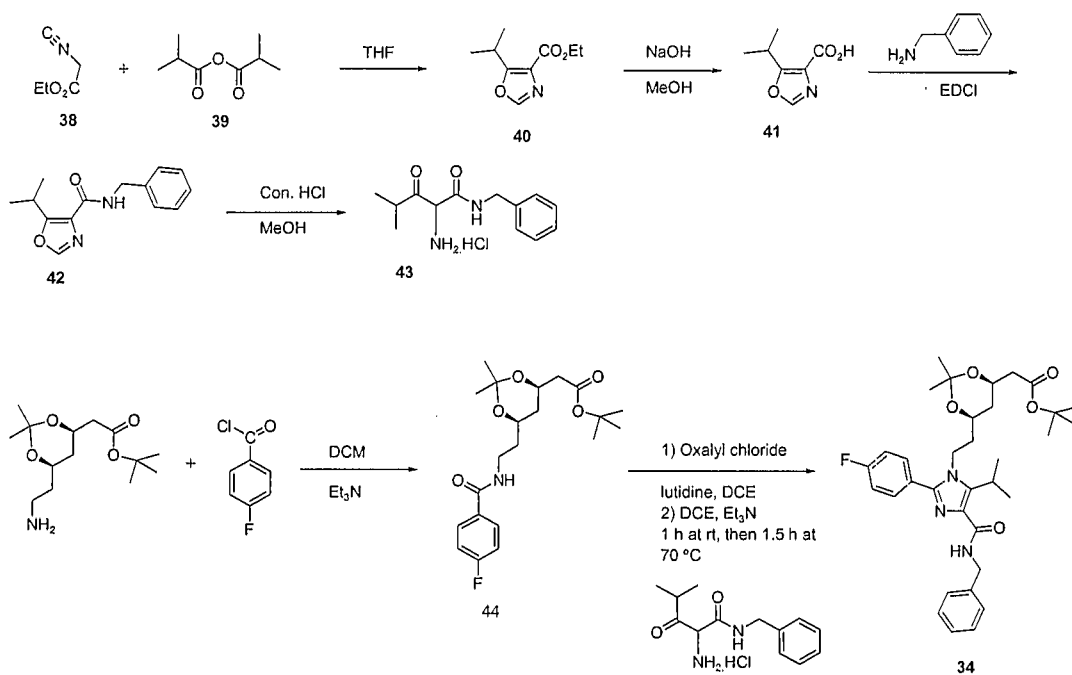
Scheme 11 illustrates an alternate method for the preparation of imidazole sodium salt **9** from ketoamide **24**. Trans-amidation of ketoamide **24** with benzylamine yields ketobenzamide **35**. Treatment of **35** with TBIA and benzoic acid or phenylacetic acid in refluxing heptane affords imidazole **34**. Acid-catalyzed removal of the acetal yields diol **36**, and subsequent hydroxide saponification, followed by acid-catalyzed condensation affords lactone **8**. Lactone **8** is converted to imidazole sodium salt **9** by treatment with aqueous sodium hydroxide. Alternatively, treatment of diol **36** with NaOH will give **9** directly. Recrystallization of crude sodium salt **9** affords material of high purity.



Scheme 11

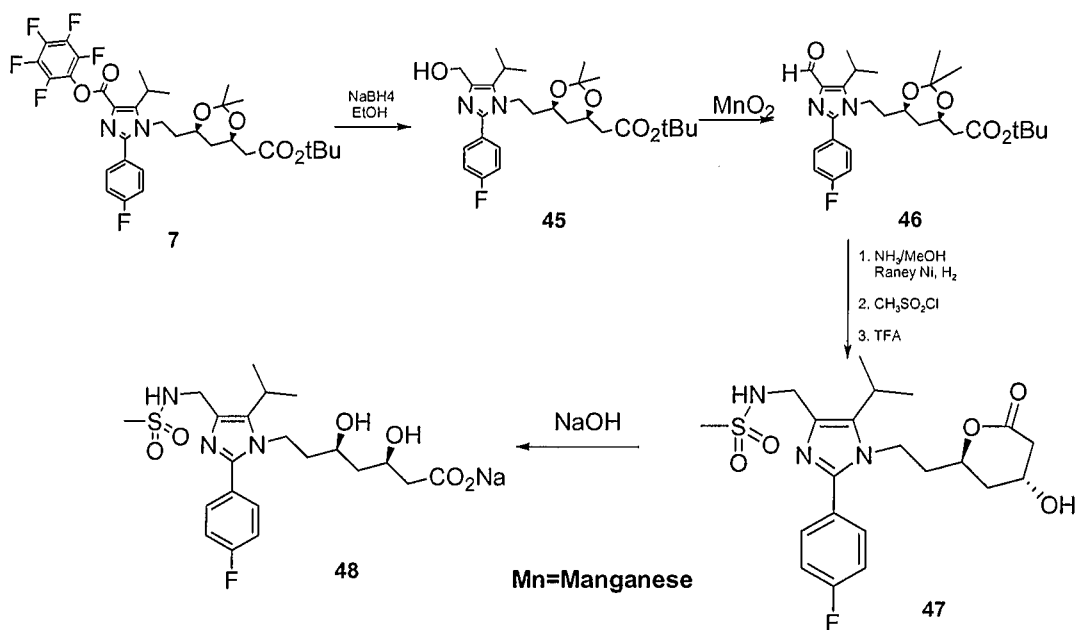
Scheme 12 illustrates an alternate method for the preparation of Imidazole 34.

As shown in Scheme 12, Compound 38 reacts with compound 39 to give compound 40 that is converted to acid 41. The acid 41 is coupled with an amine of choice under standard peptide bond formation reaction conditions to afford amide 42 that is subsequently converted to compound 43 in a salt form under acidic conditions. Compound 44 is derived from TBIA and an acid chloride of choice. Compound 44 is treated with oxalyl chloride in presence of a organic base such as 2,6-lutidine to form iminochloride in situ that reacts with compound 43 to give midazole 34.



Scheme 12

Scheme 13 shows the preparation of compound 48 from compound 7. Compound 7 is selectively reduced to the alcohol 45 on treatment with sodium borohydride. Manganese (IV) oxide oxidation of 45 gives the aldehyde 46. Reductive amination of 46 followed by sulfonylation and global provides the lactone 47, which is converted to 48 on treatment with sodium hydroxide.



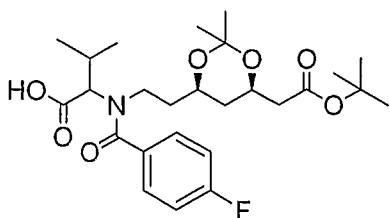
Scheme 13

EXAMPLES

The following non-limiting Examples show how to carry out the present invention. The synthetic route of compounds of the present invention is not limited to the methods outlined below. One skilled in the art will be able to use the schemes outlined below to synthesize various compounds claimed in this invention. Examples 1-3 illustrate preparations of useful intermediate compounds of the invention.

Example 1

2-[[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-(4-fluorobenzoyl)-amino]-3-methylbutyric acid

**Step A**2-Hydroxy-3-methylbutyric acid benzyl ester

A rt solution of 3-Methyl-2-oxo-butyric acid benzyl ester (20.0g, 97 mmol), prepared according to the method of M. Hesse *et al* (Helvetica Chimica Acta **2001**, 84, 3766), in abs. EtOH (400 mL) was treated

with sodium triacetoxyborohydride (25.0 g, 116 mmol) in portions over a period of 5 minutes. The reaction mixture became warm and the evolution of gas was noted. After stirring at rt for 12 h. The reaction mixture was concentrated to a slurry, diluted with water (300 mL), treated with sat. NaHCO_3 (pH ~ 9), and extracted (2X) with hexanes/EtOAc (150 mL, 3:1). The combined extracts were dried (Na_2SO_4) and concentrated to a colorless oil. Purification by flash chromatography [SiO_2 , EtOAc/hexanes 5-65%] provided the above named compound as a colorless liquid; yield: 17.7g (87%); ^1H NMR (400 MHz, CD_3CN): δ 0.83 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 2.03 (m, 1H), 3.22 (d, J = 6.1 Hz, 1H), 4.00 (dd, J = 6.2, 4.2 Hz, 1H) 5.15 (d, J = 12.2 Hz, 1H), 5.21 (d, J = 12.2 Hz, 1 H), 7.38 (m, 5 H).

Step B

3-Methyl-2-trifluoromethanesulfonyloxy-butyric acid benzyl ester

According to the method of M. Walker (Tetrahedron **1997**, 53, 14591), a solution of 2-Hydroxy-3-methyl-butyric acid benzyl ester (16.0g, 76.8 mmol) and 2,6-lutidine (10.74 mL, 92 mmol) in anhydrous CH_2Cl_2 (300 mL) was cooled to -78°C and treated with triflic anhydride, dropwise over a period of 5 minutes.

The golden yellow reaction mixture was stirred at -78°C for 30 min, then allowed to warm to rt. After stirring at rt for 1.5 h, the reaction mixture was poured into water (150 mL) and treated with 1M HCl (150 mL). The organic layer was separated, dried (Na_2SO_4) and concentrated to a yellow-brown oil.

Purification by flash chromatography [SiO_2 , EtOAc/hexanes 5-15%] provides the above named compound as a colorless liquid; yield: 25.3 g (96%); ^1H NMR (400 MHz, CD_3CN): δ 0.93 (d, J = 8 Hz, 3 H), 1.05 (d, J = 7.0 Hz, 3 H), 2.41 (m, 1 H), 5.22 (d, J = 3.9 Hz, 1 H), 5.26 (d, J = 12.2 Hz, 1 H), 5.29 (d, J = 12.2 Hz, 1 H), 7.41 (m, 5 H).

Step C

2-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethylamino]-3-methyl-butyric acid benzyl ester

A solution of [(4R,6R)-6-(2-Amino-ethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester (21.1 g, 77.1 mmol) and 3-Methyl-2-trifluoromethanesulfonyloxy-butyric acid benzyl ester (25 g, 73.5 mmol) in anhydrous acetonitrile was treated with TEA (12.3 mL, 88 mmol). The resulting mixture was allowed to stir at rt over the weekend (60 h). The reaction mixture was concentrated to a brown oil, poured into water (200 mL), made basic (pH >10) with 1 M NaOH, and extracted (2X) with hexane/EtOAc (1:1). The extracts were combined, washed with sat. NH_4Cl , dried (Na_2SO_4), and concentrated to a crude oil.

Purification by flash chromatography [SiO_2 , EtOAc/hexanes 5-60%] provided the above named compound as a mixture of diastereomers; yield: 30.6 g (89%); Low resolution mass spectroscopy (APCI) m/z 464 $[\text{M}+\text{H}]^+$.

Step D

2-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-[4-fluoro-benzoyl]-amino]-3-methyl-butyric acid benzyl ester

A solution of 2-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethylamino]-3-methyl-butyric acid benzyl ester (30 g, 64.7 mmol) in anhydrous pyridine was treated with and 4-

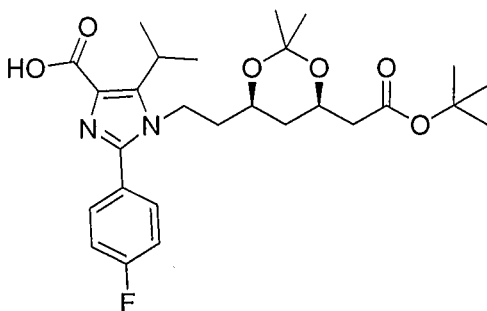
fluorobenzoyl chloride (8 mL, 67.9 mmol). The mixture becomes warm (36 °C). The reaction was allowed to stir at rt overnight then concentrated to a brown slurry, poured into water (250 mL), made basic (pH >10) with 1 M NaOH, and extracted (2X) with hexane/EtOAc (1:1). The extracts were combined, washed with sat. NH₄Cl, dried (Na₂SO₄), and concentrated to a crude oil. Purification by flash chromatography [SiO₂, EtOAc/hexanes 5-45%] provided the above named compound as a mixture of diastereomers; yield: 34.7 g (94%); Low resolution mass spectroscopy (APCI) *m/z* 496 [M+H]⁺ Analysis calculated for C₂₆H₃₈F₁N₁O₇: C, 63.01; H, 7.73; N, 2.83. Found: C, 62.81; H, 7.82; N, 2.78.

Step E

A solution of 2-[[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-(4-fluorobenzoyl)-amino]-3-methyl-butyric acid benzyl ester (34.0 g, 58.0 mmol) in THF (200 mL) was hydrogenated over 20 % Pd/C (2.0g) until the uptake of hydrogen ceased (10 h). The solution was filtered through celite and concentrated to give the title compound as a colorless foam; yield: 24.4g (84%); Low resolution mass spectroscopy (APCI) *m/z* 586 [M+H]⁺.

Example 2

1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid



Step A

Bromo-(4-fluoro-phenyl)-acetic acid methyl ester

According to the method of Y. Ishii *et al* (J. Org. Chem. **1998**, 63, 6023), a solution of (4-Fluoro-phenyl)-acetic acid methyl ester (25g, 0.15 mol) in ethyl acetate (300 mL) was added to an aqueous sodium bromate solution (67g ; 0.45 mol in 225 mL water). The biphasic mixture was treated with 1M NaHSO₃ (450 mL) and the reaction was allowed to stir at ambient temperature for 6 h. The phases were separated, the organic layer was washed with NaOH and Sat. NH₄Cl, dried (Na₂SO₄), and concentrated to give a yellow oil. Residual starting material was removed by vacuum distillation (75°C, < 0.1mm Hg); yield: 22.6g (62%); Low resolution mass spectroscopy (APCI) *m/z* 247/249 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃): δ 3.8 (s, 3 H), 5.3 (s, 1 H), 7.0 (t, *J* = 8.7 Hz, 2 H), 7.5 (m, 2 H).

Step B

[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethylamino]-(4-fluoro-phenyl)-acetic acid methyl ester

A solution of [(4R, 6R)-6-(2-Amino-ethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester (26.3g; 96mmol) and bromo-(4-fluoro-phenyl)-acetic acid methyl ester (22.6g; 92 mmol) in acetonitrile (200 mL) was treated with triethylamine (18.5g; 182 mmol). After 30 minutes a considerable precipitate was noted. The reaction was allowed to stir at rt overnight then filtered to remove the precipitate. The filtrate was concentrated to dryness. The residue was dissolved in EtOAc, washed with H₂O and brine, dried (MgSO₄), and concentrated to give a crude oil. The oil was triturated with hexanes to give a white solid which was collected by vacuum filtration and air dried; yield: 38.1 g (95%); Low resolution mass spectroscopy (APCI) *m/z* 440 [M+H]⁺.

Step C

{[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-isobutyryl-amino}-(4-fluoro-phenyl)-acetic acid methyl ester

A solution of [2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethylamino]-(4-fluoro-phenyl)-acetic acid methyl ester (10g; 23 mmol) and 2,6 lutidine (3.7g; 34 mmol) in CH₂Cl₂ (100 mL) was cooled to -78 °C and treated with isobutyryl chloride (2.46g 23.1 mmol). The reaction mixture was allowed to warm to rt and stirred overnight. The reaction was treated with 100 mL sat. aq. NaHCO₃ and the organic layer was separated, washed with 1 M HCl, and brine, dried (MgSO₄), and concentrated to a crude glass. Purification by flash chromatography (EtOAc/hexanes 0-60%) gave the above named compound as a yellow oil: yield 9.71 g (96%); Low resolution mass spectroscopy (APCI) *m/z* 510 [M+H]⁺.

Step D

{[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-isobutyryl-amino}-(4-fluoro-phenyl)-acetic acid

A solution of {[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-isobutyryl-amino}-(4-fluoro-phenyl)-acetic acid methyl ester (9.71g; 19.1 mmol) in THF: H₂O (150 mL, 2:1) was treated with solid LiOH (2g; 95 mmol) and the resulting mixture was stirred at rt overnight. The reaction mixture was diluted with H₂O and extracted with Hexanes-EtOAc (1:1). The aqueous layer was made acidic with 1 M HCl (pH ~4) and extracted with CH₂Cl₂. The organic layers were combined, dried (MgSO₄) and concentrated to dryness. The residue was concentrated from diethyl ether until a white solid is obtained. Yield: 9.0 g (95%); Low resolution mass spectroscopy (APCI) *m/z* 494 [M-H]⁻.

Step E

1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid benzyl ester

A solution of {[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-isobutyryl-amino}-(4-fluoro-phenyl)-acetic acid (800 mg, 1.6 mmol) and benzyl cyanofomate (520 mg, 3.2 mmol) in α,α,α-trifluorotoluene (5 mL) was treated with acetic anhydride (0.228 mL, 2.4 mmol). The resulting

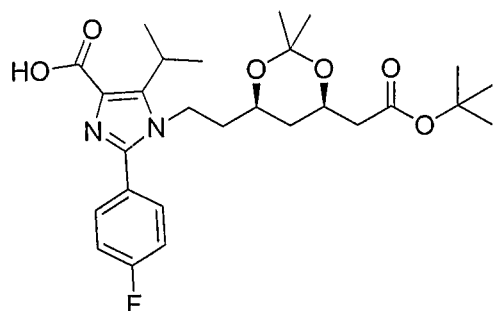
mixture was heated to reflux until TLC analysis indicated the absence of starting material (4 h). The reaction mixture was cooled to rt, concentrated to a light yellow oil, and partitioned between EtOAc and 1 M NaHCO₃. The organic layer was separated, dried (Na₂SO₄), and concentrated to an oil. Purification by flash chromatography (SiO₂, EtOAc/hexanes 10-75%) provided the desired product as an oil; yield: 293 mg (16%); Low resolution mass spectroscopy (APCI) m/z 595 [M+H]⁺.

Step F

A solution of 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid benzyl ester (14.84 g, 24.95 mmol) in THF (200 mL) was hydrogenated over 20 % Pd/C until the uptake of hydrogen ceased. The solution was filtered through celite and concentrated to give the title compound as a white foam; yield: 12.2 g (97%); Low resolution mass spectroscopy (APCI) m/z 505 [M+H]⁺; Anal. Calcd for C₂₇H₃₇FN₂O₆: C, 64.27; H, 7.39; N, 5.55. Found: C, 64.52; H, 7.53; N, 5.15.

Example 3

1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid



Step A

(Benzhydrylidene-amino)-acetic acid benzyl ester

Benzophenone imine (100.0 g, 496 mmol) and glycine benzylester hydrochloride (89.9g, 496 mmol) were combined in CH₂Cl₂ (250 mL) and the resulting mixture was stirred at ambient temperature for 24 h. The reaction mixture was filtered to remove precipitated NH₄Cl and the filtrate was concentrated under reduced pressure. The residue was taken up in EtOAc, washed with 1 M NaHCO₃, dried with (Na₂SO₄), and concentrated to give off-white solid. Recrystallization from hot EtOAc-hexane gives the desired product as colorless plates; Yield: 123.6g (76 %); Low resolution mass spectroscopy (APCI) m/z 330 [M+H]⁺; Anal. Calcd for C₂₂H₁₉N₁O₂: C, 80.22.; H, 5.81; N, 4.25. Found: C, 80.16.; H, 5.77; N, 4.22.

Step B

2-amino-4-methyl-3-oxo-pentenoic acid benzyl ester hydrochloride

A cooled (dry ice-acetone bath) solution of KOtBu (6.81 g, 60.7 mmole, 60.7 mL THF solution) in anhydrous THF (100 mL) was treated with (Benzhydrylidene-amino)-acetic acid benzyl ester (20.0 g, 60.7 mmole) as a solution in THF (10 mL). After 30 min., this mixture was added via cannula to a cooled (dry ice-acetone bath) solution of isobutyryl chloride (60.7 mmole, 6.41 mL) in THF (50 mL). The resulting

mixture was allowed to stir for 30 min, then quenched with 3N HCl solution (30 mL). The reaction mixture was warmed to rt and concentrated to dryness under reduced pressure. The residue was dissolved in water (20 mL) and extracted with ether (2 X 50 mL). The aqueous solution was concentrated to dryness under reduced pressure, concentrated twice from methanol, and re-dissolved residue in methanol. The insoluble salts were removed by filtration and the filtrate was concentrated to dryness. The residue was dissolved in THF (20 mL) and the above named compound was precipitated out upon addition of ether (50 mL); yield: ^1H NMR spectrum (400 MHz, CD_3OD) δ 7.30-7.37 (m, 5H), 5.18-5.29 (dd, J = 23.8, 12.2 Hz, 2H), 3.00-3.06 (m, 1H), 1.13 (d, J = 7.1 Hz, 3H), 1.00 (d, J = 6.9 Hz 3H); Low resolution mass spectroscopy (APCI) m/z 236 $[\text{M}+\text{H}]^+$.

Step C

2-(4-Fluoro-benzoylamino)-4-methyl-3-oxo-pentenoic acid benzyl ester

A solution of 2-amino-4-methyl-3-oxo-pentenoic acid benzyl ester hydrochloride (6.00 g, 22.1 mmole) in CH_2Cl_2 (50 mL), cooled in an ice-water bath, was treated sequentially with p-fluorobenzoyl chloride (1.1 equiv.), and TEA (2.2 equiv). After 2h the reaction mixture was diluted with EtOAc (25 mL) and washed sequentially with 1M HCl, 1 M NaHCO_3 , and water. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give a crude yellow liquid that solidifies on standing. Recrystallization from hot ether-hexanes gave the above named compound as a colorless solid; yield 5.8g (72 %); Low resolution mass spectroscopy (APCI) m/z 358 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ 7.81(dd, J = 7.0, 4.8 Hz, 2H), 7.38-7.29 (m, 5H), 7.09 dd, J = 8.5, 8.6 Hz, 2H), 5.60 (d, J = 6.5 Hz, 1H), 5.22 (dd, J = 21.2, 12.2 Hz, 2H), 3.00-3.07 (m, 1H), 1.20 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H).

Step D

1-[2-(6-tert-Butoxymethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid benzyl ester

A solution of 2-(4-Fluoro-benzoylamino)-4-methyl-3-oxo-pentenoic acid benzyl ester (1.50 g, 4.5 mmole), TBIA (1.5 equiv.), and acetic acid (glacial, 1.20 mL) acid in xylenes was warmed to 50 °C and treated with catalytic p-toluenesulfonic acid. The reaction mixture was heated to reflux for 24 h using a Dean-Stark trap charged with Na_2SO_4 . The reaction mixture was cooled and concentrated under reduced pressure to give a light-brown amorphous residue. This material was taken up in EtOAc (25 mL), washed with 1M HCl, NaHCO_3 , water, and brine, dried (MgSO_4), and concentrated under reduced pressure to give an amorphous material. Purification by flash chromatography (SiO_2 , EtOAc/hexanes 0-20%) gave the above named compound as a tan glass; Yield: 1.39 g (55.69 %); Low resolution mass spectroscopy (APCI) m/z 595 $[\text{M}+\text{H}]^+$.

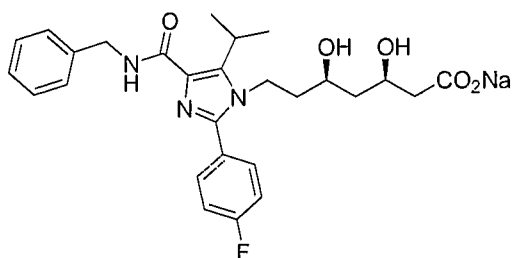
Step E

The title compound was prepared by following a process analogous to the one described in example 2, Step F

Example 4 and Example 4A exemplify the preparation of compounds of the invention wherein, for example, R² is 4-fluorophenyl, R⁴ is -(CH₂)_nC(O)NR⁶R⁷, R⁵ is isopropyl, one of R⁶ and R⁷ is H, the other one of R⁶ and R⁷ is aralkyl or heteroaryl, and n is 0.

Example 4

Sodium, (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-benzylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Step A

1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid pentafluorophenyl ester

An ice cold solution of 1-[2-((4R, 6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid (9.33g, 18.5 mmol) and 2,6-lutidine (3.96g, 37 mmol) in acetonitrile (50 mL) was treated with pentafluorophenyl trifluoroacetate (7.77g, 27.7 mmol). The resulting solution was stirred at rt for 2 h then treated with 1M HCl. The reaction mixture was diluted with water and EtOAc. The organic layer was separated, washed with sat. NaHCO₃, dried (Na₂SO₄), and concentrated to a crude oil. Purification by flash chromatography (EtOAc/hexanes 5-40%) provided the above named product as a yellow glass; yield: 4.5g (36%); Low resolution mass spectroscopy (APCI) *m/z* 671 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃): δ 1.19 (dd, *J* = 11.5, 24.2 Hz, 1 H), 1.30 (s, 3 H), 1.39 (s, 3 H), 1.41 (s, 9 H), 1.46 (d, *J* = 6.8 Hz, 3 H), 1.46 (d, *J* = 6.8 Hz, 3 H), 1.48 (partially obscured m, 1 H), 1.76 (m, 2 H), 2.25 (dd, *J* = 15.4, 6.3 Hz, 1 H), 2.40 (dd, *J* = 15.4, 6.8 Hz, 1 H), 3.38 (septet, *J* = 6.8 Hz, 1 H), 3.79 (m, 1 H), 3.95 (m, 1 H), 4.19 (m, 2H), 7.13 (m, 2 H), 7.56 (m, 2 H).

Step B

2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid benzylamide

A solution of 1-[2-((4R, 6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid pentafluorophenyl ester (1.0 mL, 0.298 mmol, 0.298 M in acetonitrile) was added to a screw-capped tube containing benzylamine (95 mg, 0.89 mmol) and resin bound DIEA (156 mg, loading 3.83 mmol/g) in acetonitrile (5 mL). The mixture was allowed to stir at rt overnight, then treated with polystyrene bound isocyanate (600 mg, loading 1.49 mmol/g) and allowed to stir at rt for 6hr. The spent resins were removed by filtration, rinsing with MeOH and acetonitrile, and the

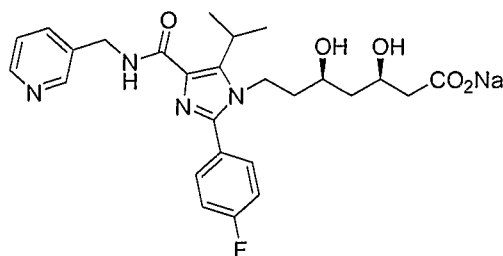
filtrate was concentrated to a crude oil. LC-MS is consistent with the desired amide (APCI) m/z 594 $[M+H]^+$. The crude amide was dissolved in CH_2Cl_2 (4 mL), treated with neat TFA (1.0 mL) and allowed to stir at rt for 30 min. The reaction mixture was concentrated to an oil, then partitioned between CH_2Cl_2 and water and carefully neutralized with 1 M $NaHCO_3$ (pH ~ 8). The organic layer was separated, dried (5
 0
 (Na₂SO₄), and concentrated to a crude glass. Purification by flash chromatography (SiO₂, EtOAc/hexanes 60-100% gave a yellow glass; yield: 75 mg (52%); Low resolution mass spectroscopy (APCI) m/z 480 $[M+H]^+$; ¹H NMR (400 MHz, CD₃CN) δ 7.96 (br t, 1H), 7.57 – 7.60 (m, 2H), 7.29-7.33 (m, 4H), 7.19-7.25 (m, 3H), 4.49-4.58 (m, 1H), 4.49 (d, J = 6.6 Hz, 2H), 4.02-4.23 (m, 3H), 3.36 (septet, J = 7.1 Hz, 1H), 3.29 (br s, 1H), 2.57 (dd, J = 4.8, 17.5 Hz, 1H), 2.38 (ddd, J = 1.7, 3.6, 17.5 Hz, 1H), 1.86-1.94 (m, 2H), 1.75-1.78 (m, 1H), 1.63 (ddd, J = 3.1, 11.3, 17.3 Hz, 1H), 1.46 (d, J = 7.1 Hz, 3H), 1.46 (d, J = 7.1 Hz, 3H).

Step C

A solution of the 2-(4-Fluoro-phenyl)-1-[2-((2R, 4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid benzylamide (75 mg, 0.15 mmol) in THF (4 mL) was treated with aqueous NaOH (1.53 mL, 1.02 eq) The reaction mixture was allowed to stir @ rt for 30 min at which time analysis by loop LC-MS indicated that the starting material was consumed. The sample was concentrated to ca. 0.5 mL, diluted with water (30 mL) and lyophilized to give a colorless powder; yield: 79 mg (97 %); Low resolution mass spectroscopy (APCI) m/z 498 $[M+H]^+$; Anal. Calcd for C₂₇H₃₁F₁N₃O₅Na₁/ 1.7H₂O: C, 58.94; H, 6.30; N, 7.64. Found: C, 58.84; H, 6.07; N, 7.34. ¹H NMR (400 MHz, DMSO-D₆) δ 1.23 (m, 1 H); 1.40 (m, 7 H); 1.57 (m, 1 H); 1.69 (m, 1 H); 1.78 (dd, J =15.14, 8.30 Hz, 1 H); 1.97 (dd, J =15.14, 4.15 Hz, 1 H); 3.35 (m partially obscured, 1 H); 3.67 (m, 2 H); 3.94 (m, 1 H); 4.08 (m, 1 H); 4.40 (d, J =6.35 Hz, 2 H); 4.94 (br s, 1 H); 7.21 (m, 1 H); 7.30 (m, 6 H); 7.50 (br s, 1 H); 7.64 (m, 2 H); 8.38 (br t, J =6.35 Hz, 1 H).

Example 4A

Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-phenylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Step A

[(4R,6R)-6-(2-{2-(4-Fluoro-phenyl)-5-isopropyl-4-[(pyridin-3-ylmethyl)-carbamoyl]-imidazol-1-yl}-ethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester

A solution of 1-{2-[(4R,6R)-6-tert-butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl]-ethyl}-2-(4-fluorophenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid (1.4g; 2.8 mmol) in CH₂Cl₂ was treated with PyBOP (1.44g, 2.8 mmol), diisopropylethylamine (0.72g, 5.5 mmol), and 3-aminomethylpyridine (0.6g, 5.5 mmol). The reaction was allowed to stir at rt for 2 hours. The reaction mixture was washed with H₂O, dried (MgSO₄), and concentrated to dryness. The residue was purified by flash chromatography (SiO₂; MeOH/EtOAc 0-10%) to give a white solid; yield: 500 mg (30%); Low resolution mass spectroscopy (APCI) *m/z* 595 [M+H]⁺.

Step B

2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (pyridin-3-ylmethyl)-amide

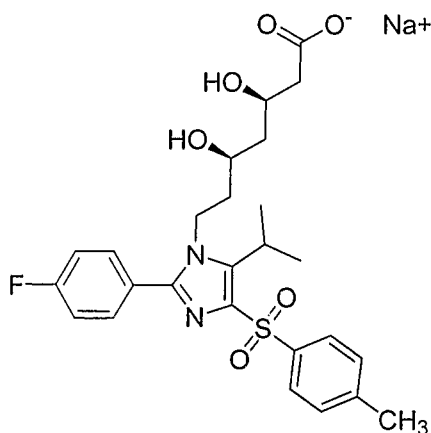
A solution of [(4R,6R)-6-(2-{2-(4-Fluoro-phenyl)-5-isopropyl-4-[(pyridin-3-ylmethyl)-carbamoyl]-imidazol-1-yl}-ethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester (500 mg, 0.8 mmol) in CH₂Cl₂ (4 mL) was treated with neat TFA (1 mL) and stirring was continued for 30 min. The reaction mixture was concentrated to dryness, then partitioned between CH₂Cl₂ and water and carefully neutralized with 1 M NaHCO₃ (pH ~ 8). The organic layer was separated, dried (Na₂SO₄), and concentrated to a crude glass. Purification by flash chromatography (SiO₂, MeOH/EtOAc 0-10%) gives the lactone as a colorless solid; yield: 116 mg (29%); Low resolution mass spectroscopy (APCI) *m/z* 481 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃): δ 1.43 (m, 6 H), 1.58 (m, 1 H), 1.76 (d, *J*=13.0 Hz, 2 H), 1.88 (m, 1 H), 2.56 (m, 1 H), 3.37 (m, 1 H), 4.06 (dq, *J*=7.3, 7.2 Hz, 2 H), 4.24 (m, 2 H), 4.56 (m, 3 H), 7.12 (t, *J*=8.4 Hz, 2 H), 7.21 (dd, *J*=7.6, 5.0 Hz, 1 H), 7.46 (dd, *J*=8.4, 5.3 Hz, 2 H), 7.66 (d, *J*=7.8 Hz, 1 H), 7.79 (t, *J*=6.1 Hz, 1 H), 8.40 (d, *J*=5.3 Hz, 1 H), 8.52 (s, 1 H).

Step C

The title compound was prepared by following a process analogous to the one described in example 4, Step C to give a colorless powder; yield: 102 mg (81 %); Low resolution mass spectroscopy (APCI) *m/z* 499 [M+H]⁺; Anal. Calculated for C₂₆H₃F₁N₄O₅Na₁·2.65H₂O: C, 54.95; H, 6.26; N, 9.86. Found C, 55.03; H, 6.20; N, 9.46.

Example 5

Sodium; (3S,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-(toluene-4-sulfonyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate

**Step A**

((4R,6R)-6-{2-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(toluene-4-sulfonyl)-imidazol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester

A solution of {[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-isobutyrylamino}-(4-fluoro-phenyl)-acetic acid (250 mg; 0.5 mmol) and acetic anhydride (155 mg; 1.5 mmol) in toluene (10 mL) was combined with *p*-toluenesulfonyl cyanide (90 mg; 0.5 mmol) and heated to reflux for 1 hour. After cooling to rt the reaction mixture was washed with sat. aq. NaHCO₃, dried (MgSO₄), and concentrated to dryness. Purification of the residue by MPLC (SiO₂ ; EtOAc/hexanes 0-60%) gave the above named compound as a yellow film; yield: 113 mg (36%); Low resolution mass spectroscopy (APCI) *m/z* 615 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 1.23 (d, *J*=23.44 Hz, 6 H), 1.30 (m, 6 H), 1.37 (s, 9 H), 1.44 (m, 2 H), 2.24 (m, 5 H), 2.98 (septet, *J* = 6.8 Hz, 1 H), 3.42 (q, *J*=7.1 Hz, 2 H), 3.57 (m, 1 H), 3.64 (m, 1 H), 3.80 (m, 1 H), 4.07 (m, 1 H), 7.10 (m, 4 H), 7.21 (m, 2 H), 7.60 (dt, *J*=8.36, 1.80 Hz, 2 H).

Step B

(4R,6R)-6-{2-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(toluene-4-sulfonyl)-imidazol-1-yl]-ethyl}-4-hydroxy-tetrahydro-pyran-2-one

Prepared in a manner analogous to Example 4A, step B to give a white solid; yield: 77 mg (87%); Low resolution mass spectroscopy (APCI) *m/z* 501 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 1.29 (m, 6 H), 1.49 (m, 1 H), 1.60 (m, 1 H), 1.69 (m, 1 H), 1.76 (m, 1 H), 2.34 (s, 3 H), 2.55 (d, *J*=3.78 Hz, 2 H), 3.01 (septet, *J* = 6.7 Hz, 1 H), 3.67 (d, *J*=2.93 Hz, 1 H), 3.80 (m, 1 H), 3.94 (m, 1 H), 4.08 (q, *J* = 7.1 Hz, 1 H), 4.30 (m, 1 H), 4.48 (m, 1 H), 7.10 (m, 2 H), 7.18 (m, 4 H), 7.54 (m, 2 H).

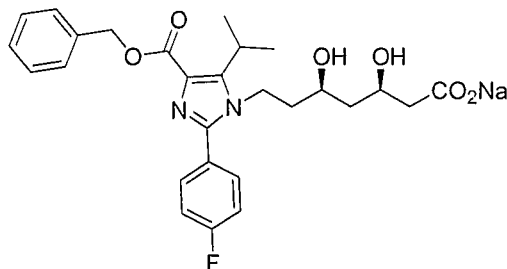
Step C

The title compound was prepared by following a process analogous to the one described in Examples 4, Step C, to give a colorless powder; yield: 66 mg (79%);

Low resolution mass spectroscopy (APCI) *m/z* 519 [M+H]⁺; Anal. Calculated for C₂₆H₂₉FN₂O₆SN_a · 1.55 H₂O; Theory: C, 54.93; H, 5.87; N, 4.93. Found C, 54.54; H, 5.52; N, 4.77.

Example 6

Sodium; (3R,5R)-7-[4-benzyloxycarbonyl-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate

**Step A**

2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid benzyl ester

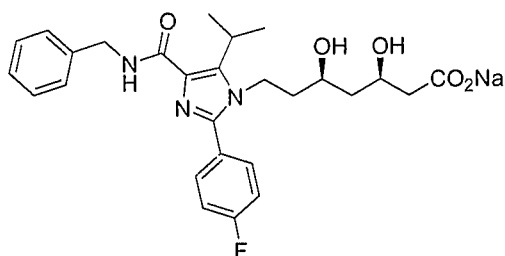
A solution of 1-[2-((4R, 6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid benzyl ester (40 mg, 0.067 mmol) was dissolved in CH₂Cl₂ (5 mL), treated with neat TFA (1.0 mL) and allowed to stir at rt for 30 min. The reaction mixture was concentrated to an oil, then partitioned between CH₂Cl₂ and water and carefully neutralized with 1 M NaHCO₃ (pH ~ 8). The organic layer was separated, dried (Na₂SO₄), and concentrated to a crude glass. Purification by flash chromatography (SiO₂, EtOAc/hexanes 60-100%) gives a colorless glass; yield: 30 mg (92%); Low resolution mass spectroscopy (APCI) *m/z* 481 [M+H]⁺; ¹H NMR (400 MHz, CD₃CN) δ 7.54 – 7.58 (m, 2H), 7.43-7.46 (m, 2H), 7.31-7.41 (m, 3H), 7.20-7.24 (m, 2H), 5.29 (s, 2H), 4.51 (ddd, *J* = 3.6, 7.8, 15.6 Hz 1H), 4.05-4.22 (m, 3H), 3.40 (septet, *J* = 7.1 Hz, 1H), 3.35 (br s, 1H), 2.57 (dd, *J* = 4.7, 17.4 Hz, 1H), 2.38 (ddd, *J* = 1.7, 3.4, 17.4 Hz, 1H), 1.86-1.93 (m, 2H), 1.69-1.75 (m, 1H), 1.61 (ddd, *J* = 2.9, 11.2, 14.1 Hz, 1H), 1.43 (d, *J* = 7.1 Hz, 3H), 1.43 (d, *J* = 7.1 Hz, 3H).

Step B

The title compound was prepared following a process analogous to the one described in Examples 4, Step C, to give a colorless powder; yield: 28 mg (90 %); Low resolution mass spectroscopy (APCI) *m/z* 49 [M+H]⁺; Anal. Calcd for C₂₇H₃₀F₁N₂Na₁O₆/1.3 H₂O: C, 59.62.; H, 6.04; N, 5.15. Found: C, 59.28; H, 5.65; N, 4.89.

Example 7

Sodium, (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-benzylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate

**Step A**N-Benzyl-2-oxo-acetamide

To a suspension of N, N'-dibenzyl-L-tartramide (3.07 g, 9.35 mmol) in THF (30 mL) was added periodic acid (2.13 g, 9.35 mmol) in two portions over 15 min. The mixture became slightly exothermic and slowly became homogeneous. After 1 hr, the solution was concentrated to give 5.0 g of a light orange foam, which was taken up in EtOAc, washed with saturated NaHCO₃ (2x), brine, dried over MgSO₄, and concentrated to give of a yellow foam which is a mixture of aldehyde and hydrate; yield: 2.90 g (95%); ¹H NMR (aldehyde) δ 9.34 (s, 1H), 7.40-7.20 (m, 5H), 4.51 (d, J = 6 Hz); low resolution mass spectroscopy (APCI) *m/z* 162 [M-H]⁻.

Step BN-Benzyl-2,2-bis-(toluene-4-sulfonylamino)-acetamide

To a solution of crude N-benzyl-2-oxo-acetamide (2.80 g, 17.2 mmol) in toluene (40 mL) was added p-toluenesulfonamide (2.94 g, 17.2 mmol). The mixture was heated in an oil bath and initially became homogeneous, then a large amount of white precipitate formed before oil bath temp reached 100°C. The mixture was heated at reflux for 1 hr with a Dean Stark trap. The mixture was cooled and filtered to afford N-benzyl-2, 2-bis-(toluene-4-sulfonylamino)-acetamide as an off-white solid; yield: 3.68 g (88%); low resolution mass spectroscopy (APCI) *m/z* 486 [M-H]⁻; Anal. Calcd. for C₂₃H₂₅N₃O₅S₂: C, 56.66; H, 5.17; N, 8.62. Found: C, 56.85; H, 5.01; N, 8.58.

Step C(6-{2-[4-Benzylcarbamoyl-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester

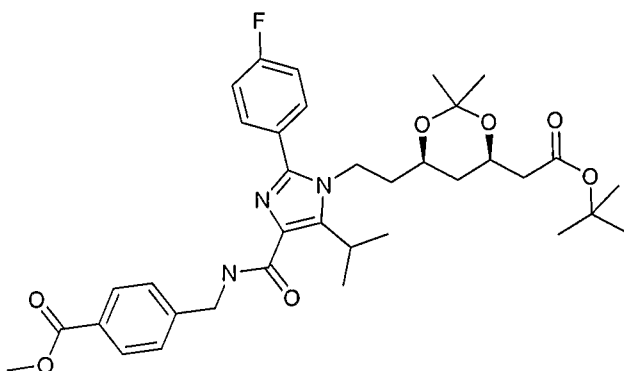
To a solution of acid 2-[[2-((4R, 6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-(4-fluoro-benzoyl)-amino]-3-methyl-butyric acid (0.30 g, 0.605 mmol) in toluene (5 mL) was added EDC (0.128 g, 0.67 mmol) followed by N-benzyl-2,2-bis-(toluene-4-sulfonylamino)-acetamide 0.44 g, 0.91 mmol). The suspension was heated at 80-90°C for 90 min. Additional EDC (45 mg, 0.4 eq) and bis-sulfonamide (0.15 g, 0.5 eq) were added and heating was continued for 3 hr. The mixture was cooled and filtered, washing with EtOAc. The filtrate was diluted with EtOAc, washed with sat. NaHCO₃, brine, dried over MgSO₄, and concentrated to give 0.49 g of a yellow foam. Flash chromatography (30-40% EtOAc/hexane) gave the title compound product as a white foam; yield: 0.13 g (36%); low resolution mass spectroscopy (APCI) *m/z* 594 [M+H]⁺.

Step D

The title compound is prepared by a process analogous to that described in Example 4A, Steps B and C. Following a reaction scheme analogous to Examples 4 and 4A, a variety of esters, lactones and salts were prepared having the following variations on R², R⁴ and R⁵ (Examples 8-93). Such representative compounds follow along with characterizing data.

Example 8

4-({[1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carbonyl
]-amino}-methyl)-benzoic acid methyl ester

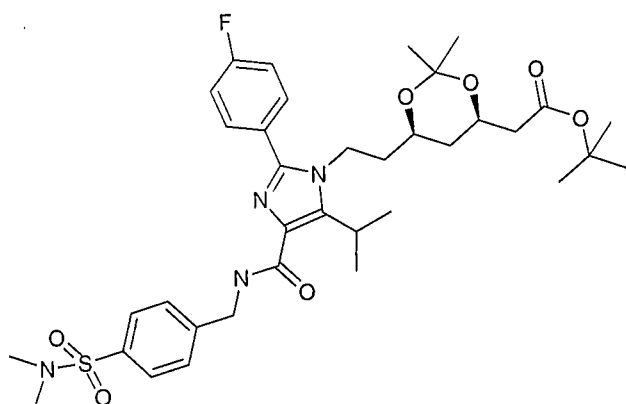


Obtain 255mg (39%) as a white solid.

Low resolution mass spectroscopy (APCI) m/z 652 $[M+H]^+$. ¹H NMR (400 MHz, CDCl₃) δ 1.31 (s, 3 H) 1.35 (s, 3 H) 1.43 (s, 9 H) 1.46 (m, 2 H) 1.51 (dd, $J=7.02, 3.36$ Hz, 6 H) 1.76 (m, 2 H) 2.33 (m, 2 H) 3.42 (sept, $J=21.4, 14.3, 7.3$ Hz, 1 H) 3.79 (m, 1 H) 3.88 (s, 3 H) 3.94 (m, 1 H) 4.18 (m, 2 H) 4.63 (d, $J=6.23$ Hz, 2 H) 7.13 (t, $J=8.67$ Hz, 2 H) 7.40 (d, $J=8.42$ Hz, 2 H) 7.55 (dd, $J=8.85, 531$ Hz, 2 H) 7.80 (s, 1 H) 7.97 (m, 2 H).

Example 9

((4R,6R)-6-{2-[4-(4-Dimethylsulfamoyl-benzylcarbamoyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester



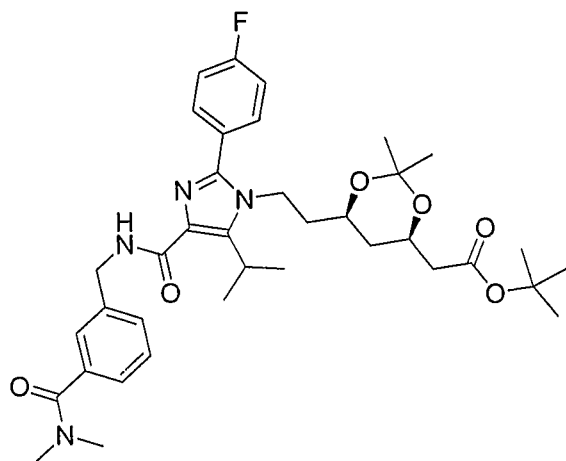
Obtain 220mg (44%) as a white solid.

Low resolution mass spectroscopy (APCI) m/z 701 $[M-H]^+$.

1H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 3 H) 1.35 (s, 3 H) 1.43 (s, 9 H) 1.47 (m, 2 H) 1.51 (dd, $J=7.1$, 3.3 Hz, 6 H) 1.76 (m, 2 H) 2.33 (m, 2 H) 2.67 (s, 6 H) 3.43 (sept, $J=13.9$, 6.9, 6.8 Hz, 1 H) 3.80 (m, 1 H) 3.94 (m, 1 H) 4.20 (m, 2 H) 4.66 (d, $J=6.35$ Hz, 2 H) 7.15 (t, $J=8.6$ Hz, 2 H) 7.51 (d, $J=8.4$ Hz, 2 H) 7.56 (dd, $J=8.6$, 5.4 Hz, 2 H) 7.71 (m, 2 H) 7.90 (s, 1 H).

Example 10

((4R,6R)-6-{2-[4-(3-Dimethylcarbamoyl-benzylcarbamoyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester

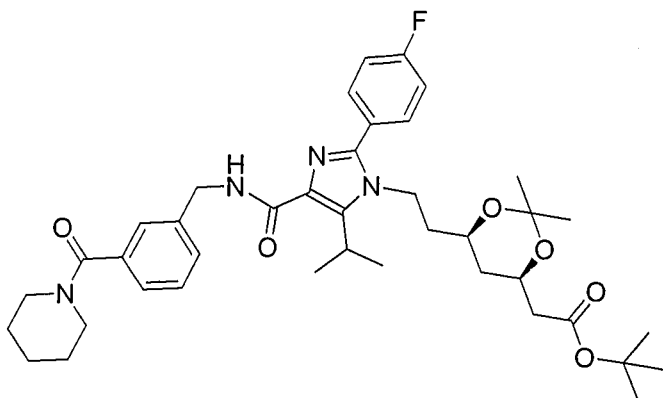


Obtain 143 mg (22%) as a white solid.

Low resolution mass spectroscopy (APCI) m/z 665 $[M-H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 1.13 (q, $J=11.80$ Hz, 1 H) 1.31 (s, 3 H) 1.34 (s, 3 H) 1.42 (s, 9 H) 1.50 (dd, $J=7.0$, 3.5 Hz, 6 H) 1.74 (m, 2 H) 2.25 (dd, $J=15.3$, 6.3 Hz, 1 H) 2.40 (m, 1 H) 3.03 (m, 7 H) 3.42 (sept, $J=20.8$, 13.8, 6.8 Hz, 1 H) 3.79 (m, 1 H) 3.93 (m, 1 H) 4.18 (m, 2 H) 4.59 (d, $J=6.2$ Hz, 2 H) 7.12 (m, 2 H) 7.33 (m, 3 H) 7.54 (m, 2 H) 7.92 (m, 1 H) 10.03 (s, 1 H).

Example 11

[(4R,6R)-6-(2-{2-(4-Fluoro-phenyl)-5-isopropyl-4-[3-(piperidine-1-carbonyl)-benzylcarbamoyl]-imidazol-1-yl}-ethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester

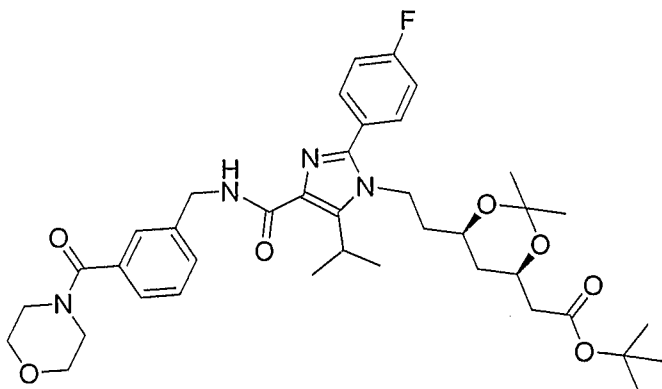


Obtain 124 mg (18%) as a white solid.

Low resolution mass spectroscopy (APCI) m/z 705 $[M-H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 1.15 (m, 2 H) 1.31 (s, 3 H) 1.35 (s, 3 H) 1.43 (s, 9 H) 1.51 (dd, $J=7.1, 3.5$ Hz, 6 H) 1.56 (s, 2 H) 1.64 (s, 4 H) 1.75 (m, 2 H) 2.25 (dd, $J=15.4, 6.2$ Hz, 1 H) 2.40 (m, 1 H) 3.31 (s, 2 H) 3.42 (sept, $J=14.1, 6.9$ Hz, 1 H) 3.67 (s, 2 H) 3.79 (m, 1 H) 3.93 (m, 1 H) 4.19 (m, 2 H) 4.60 (d, $J=6.3$ Hz, 2 H) 7.16 (m, 2 H) 7.35 (m, 4 H) 7.55 (m, 2 H) 7.75 (s, 1 H).

Example 12

[(4R,6R)-6-(2-{2-(4-Fluoro-phenyl)-5-isopropyl-4-[3-(morpholine-4-carbonyl)-benzylcarbamoyl]-imidazol-1-yl}-ethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester

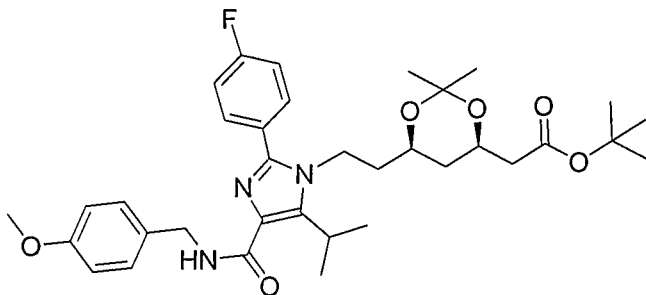


Obtain 116mg (17%) as a white solid.

Low resolution mass spectroscopy (APCI) m/z 707 $[M-H]^+$. 1H MR (400 MHz, $CDCl_3$) δ ppm 1.16 (m, 2 H) 1.31 (s, 3 H) 1.35 (s, 3 H) 1.44 (m, 10 H) 1.50 (dd, $J=7.1, 3.4$ Hz, 6 H) 1.56 (s, 2 H) 1.76 (m, 2 H) 2.25 (m, $J=15.4, 6.3$ Hz, 1 H) 2.40 (m, $J=15.4, 6.9$ Hz, 1 H) 3.40 (m, $J=20.9, 13.4, 6.9$ Hz, 1 H) 3.60 (s, 2 H) 3.72 (s, 2 H) 3.79 (m, 2 H) 3.93 (m, 1 H) 4.18 (m, 2 H) 4.60 (d, $J=6.2$ Hz, 2 H) 7.14 (m, 2 H) 7.27 (t, $J=1.5$ Hz, 1 H) 7.34 (m, 1 H) 7.40 (m, 2 H) 7.54 (m, 2 H) 7.76 (s, 1 H)

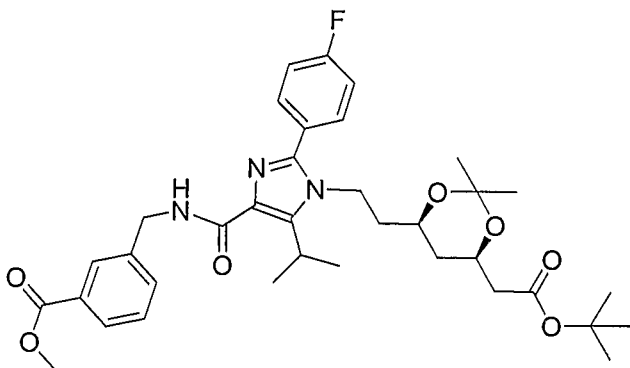
Example 13

((4R,6R)-6-{2-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(4-methoxy-benzylcarbamoyl)-imidazol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester



Obtain 472mg (76%) as a white solid.

Low resolution mass spectroscopy (APCI) m/z 624 $[M-H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ ppm 1.12 (m, 1 H) 1.30 (s, 3 H) 1.34 (s, 3 H) 1.45 (m, 10 H) 1.51 (dd, $J=7.1, 3.5$ Hz, 6 H) 1.73 (m, 2 H) 2.24 (dd, $J=15.4, 6.3$ Hz, 1 H) 2.39 (m, $J=15.3, 6.8$ Hz, 1 H) 3.43 (m, $J=21.1, 15.1, 7.0$ Hz, 1 H) 3.76 (s, 3 H) 3.79 (m, 1 H) 3.92 (m, 1 H) 4.15 (m, 2 H) 4.50 (d, $J=6.0$ Hz, 2 H) 6.82 (m, 2 H) 7.11 (m, 2 H) 7.26 (m, 2 H) 7.52 (m, 2 H) 7.62 (t, $J=5.9$ Hz, 1 H).

Example 14

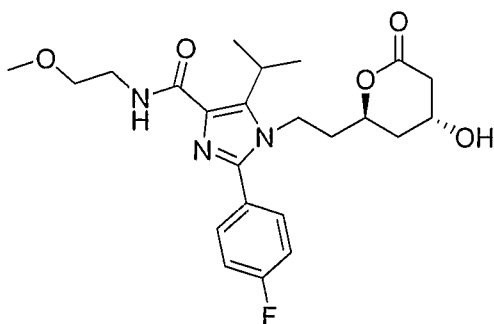
3-({[1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carbonyl]-amino}-methyl)-benzoic acid methyl ester

Obtain 107mg (8%) as a white solid.

Low resolution mass spectroscopy (APCI) m/z 652 $[M-H]^+$. 1H NMR (400 MHz, CD_3OD) δ ppm 1.01 (m, 1 H) 1.19 (s, 3 H) 1.30 (s, 3 H) 1.36 (m, 10 H) 1.43 (dd, $J=7.0, 1.4$ Hz, 6 H) 1.64 (m, 2 H) 1.74 (m, 1 H) 2.20 (m, $J=15.1, 7.8$ Hz, 1 H) 3.40 (m, $J=20.3, 13.3, 3.5$ Hz, 1 H) 3.79 (m, 1 H) 3.82 (s, 3 H) 4.01 (m, 1 H) 4.17 (m, 2 H) 4.52 (s, 2 H) 7.18 (m, 2 H) 7.37 (t, $J=7.7$ Hz, 1 H) 7.57 (m, 3 H) 7.84 (m, 1 H) 7.96 (t, $J=1.0$ Hz, 1 H).

Example 15

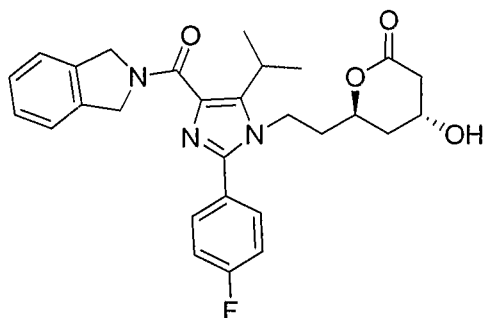
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (2-methoxy-ethyl)-amide



Low resolution mass spectroscopy (APCI) m/z 448 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN): δ 7.57 – 7.62 (m, 3H), 7.21-7.27 (m, 2H), 4.53 (ddd, J = 3.6, 8.0, 15.6 Hz 1H), 4.05-4.21 (m, 3H), 3.47 (m, 4H), 3.36 (septet, J = 7.1 Hz, 1H), 3.32 (br s, 1H), 3.31 (s, 3H), 2.58 (dd, J = 4.6, 17.3 Hz, 1H), 2.38 (ddd, J = 1.8, 3.5, 17.3 Hz, 1H), 1.86-1.93 (m, 2H), 1.72-1.79 (m, 1H), 1.67 (ddd, J = 3.1, 11.3, 17.3 Hz, 1H), 1.47 (d, J = 7.1 Hz, 3H), 1.46 (d, J = 7.1 Hz, 3H).

Example 16

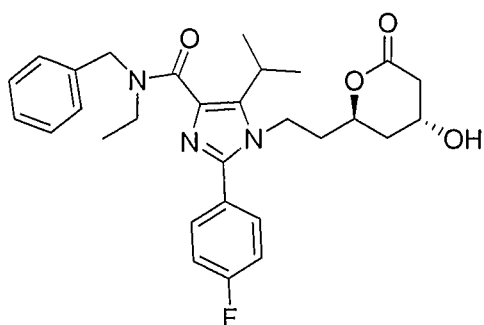
(4R,6R)-6-{2-[4-(1,3-Dihydro-isoindole-2-carbonyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-ethyl}-4-hydroxy-tetrahydro-pyran-2-one



Low resolution mass spectroscopy (APCI) m/z 492 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN): δ 7.64 – 7.68 (m, 2H), 7.21-7.38 (m, 6H), 5.05 (s, 2H), 4.87 (s, 2H), 4.53 (ddd, J = 3.9, 7.8, 15.6 Hz 1H), 4.05-4.28 (m, 3H), 3.41 (br s, 1H), 3.24 (septet, J = 7.1 Hz, 1H), 2.58 (dd, J = 4.6, 17.6 Hz, 1H), 2.41 (ddd, J = 1.4, 3.4, 17.3 Hz, 1H), 1.83-1.93 (m, 2H), 1.72-1.79 (m, 1H), 1.64 (ddd, J = 3.2, 11.5, 14.4 Hz, 1H), 1.39 (apparent d, J = 7.1 Hz, 6H).

Example 17

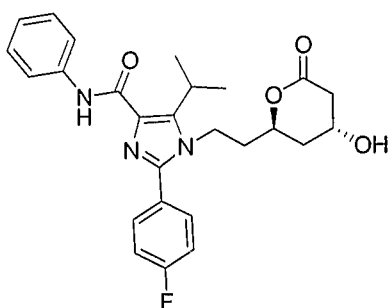
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid benzyl-ethyl-amide



Low resolution mass spectroscopy (APCI) m/z 508 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ 7.53 – 7.63 (m, 2H), 7.16-7.59 (m, 7H), 4.69 (s, 2H), 4.50 (ddd, $J = 3.9, 7.8, 15.6$ Hz 1H), 4.00-4.24 (m, 3H), 3.4 (m, 2H), 3.12 (m, 1H), 2.56 (apparent dt, $J = 4.4, 17.6$ Hz, 1H), 2.38 (m, 1H), 1.80-1.93 (m, 2H), 1.54-1.76 (m, 2H), 1.34 (apparent t, $J = 6.4$ Hz, 6H), 1.13 (apparent dt, $J = 7.1, 13.9$ Hz, 3H).

Example 18

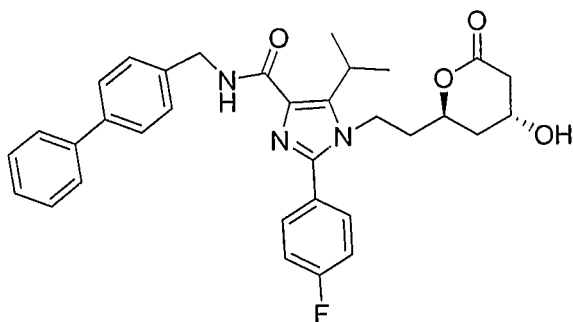
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid phenylamide



Low resolution mass spectroscopy (APCI) m/z 466 $[M+H]^+$.

Example 19

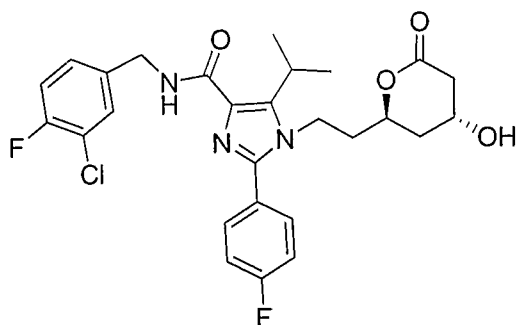
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl))-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (biphenyl-4-ylmethyl)-amide



Low resolution mass spectroscopy (APCI) m/z 556 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ 8.02 (br t, $J = 6.3$ Hz, 1H), 7.56 – 7.63 (m, 6H), 7.31-7.45 (m, 5H), 7.24-7.19 (m, 2H), 4.50-4.54 (m, 3H), 4.05-7.25 (m, 3H), 3.36 (septet, $J = 7.1$ Hz, 1H), 3.30 (obscured br s, 1H), 2.58 (dd, $J = 4.6, 17.3$ Hz, 1H), 2.39 (ddd, $J = 1.7, 3.4, 17.3$ Hz, 1H), 1.83-1.93 (m, 2H), 1.72-1.79 (m, 1H), 1.63 (ddd, $J = 3.2, 11.2, 14.4$ Hz, 1H), 1.47 (d, $J = 7.1$ Hz, 3H), 1.47 (d, $J = 7.1$ Hz, 3H).

Example 20

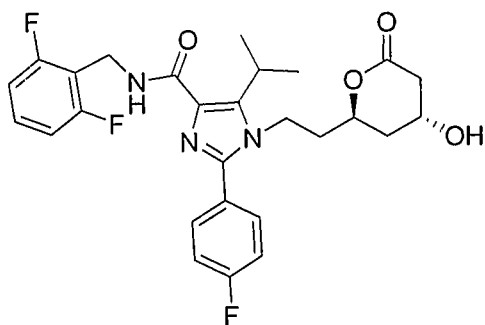
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl))-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 3-chloro-4-fluoro-benzylamide



Low resolution mass spectroscopy (APCI) m/z 532 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ 8.04 (br t, $J = 6.3$ Hz, 1H), 7.56 – 7.61 (m, 2H), 7.41 (dd, $J = 2.2, 7.3$ Hz, 1H), 7.15-7.29 (m, 4H), 4.53 (ddd, $J = 3.4, 7.8, 15.6$ Hz, 1H), 4.44 (d, $J = 6.4$ Hz, 2H), 4.05-4.25 (m, 3H), 3.35 (septet, $J = 7.1$ Hz, 1H), 3.28 (br s, 1H), 2.58 (dd, $J = 4.6, 17.3$ Hz, 1H), 2.39 (ddd, $J = 1.7, 3.4, 17.3$ Hz, 1H), 1.83-1.93 (m, 2H), 1.72-1.79 (m, 1H), 1.63 (ddd, $J = 3.2, 11.2, 14.4$ Hz, 1H), 1.45 (d, $J = 7.1$ Hz, 3H), 1.45 (d, $J = 7.1$ Hz, 3H).

Example 21

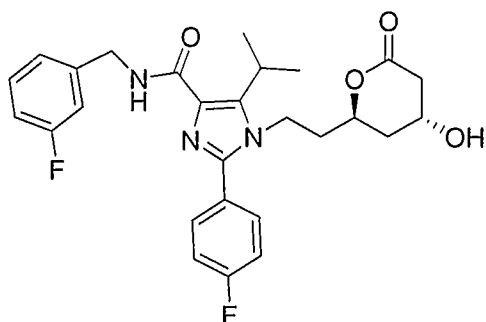
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl))-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 2,6-difluoro-benzylamide



Low resolution mass spectroscopy (APCI) m/z 516 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ 7.81 (br t, $J = 5.7$ Hz, 1H), 7.54 – 7.61 (m, 2H), 7.41 (dd, $J = 2.2, 7.3$ Hz, 1H), 7.15-7.29 (m, 4H), 4.59 (d, $J = 6.1$ Hz, 2H), 4.51 (ddd, $J = 3.9, 7.6, 15.6$ Hz, 1H), 4.05-4.25 (m, 3H), 3.33 (septet, $J = 7.1$ Hz, 1H), 3.28 (br s, 1H), 2.56 (dd, $J = 4.6, 17.3$ Hz, 1H), 2.38 (ddd, $J = 1.4, 3.4, 17.3$ Hz, 1H), 1.83-1.93 (m, 2H), 1.71-1.79 (m, 1H), 1.62 (ddd, $J = 3.2, 11.2, 14.4$ Hz, 1H), 1.44 (d, $J = 7.1$ Hz, 3H), 1.44 (d, $J = 7.1$ Hz, 3H).

Example 22

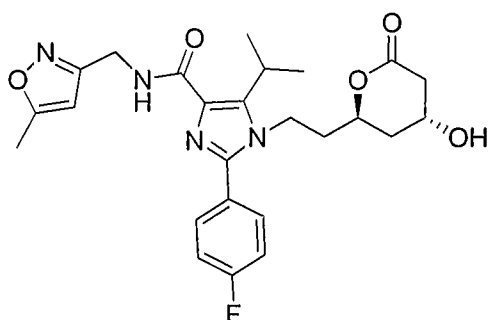
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl))-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 3-fluoro-benzylamide



Low resolution mass spectroscopy (APCI) m/z 498 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ 8.02 (br t, J = 5.7 Hz, 1H), 7.58 – 7.61 (m, 2H), 7.33 (ddd, J = 6.1, 7.8, 13.9 Hz, 1H), 7.20-7.24 (m, 2H), 7.12-7.18 (m, 1H), 7.04-7.09 (m, 1H), 6.97-7.05 (m, 1H), 4.53 (ddd, J = 3.9, 7.6, 15.6 Hz 1H), 4.49 (d, J = 6.6 Hz, 2H), 4.05-4.25 (m, 3H), 3.35 (septet, J = 7.1 Hz, 1H), 3.28 (br s, 1H), 2.58 (dd, J = 4.6, 17.3 Hz, 1H), 2.41 (ddd, J = 1.4, 3.4, 17.3 Hz, 1H), 1.83-1.93 (m, 2H), 1.71-1.79 (m, 1H), 1.63 (ddd, J = 3.2, 11.2, 14.4 Hz, 1H), 1.46 (d, J = 7.1 Hz, 3H), 1.46 (d, J = 7.1 Hz, 3H).

Example 23

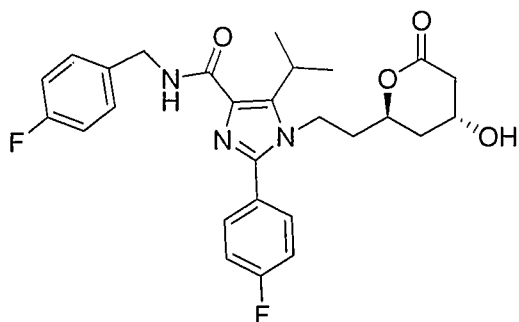
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl)-5-isopropyl-1H-imidazole-4-carboxylic acid (5-methyl-isoxazol-3-ylmethyl)-amide



Low resolution mass spectroscopy (APCI) m/z 485 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ 7.95 (br t, J = 5.9 Hz, 1H), 7.56 – 7.61 (m, 2H), 7.19-7.25 (m, 2H), 6.03 (m, 1H), 4.53 (ddd, J = 2.9, 8.0, 15.8 Hz 1H), 4.48 (d, J = 6.1 Hz, 2H), 4.05-4.25 (m, 3H), 3.35 (septet, J = 7.1 Hz, 1H), 3.28 (br s, 1H), 2.58 (dd, J = 4.7, 17.4 Hz, 1H), 2.41 (ddd, J = 1.7, 3.7, 17.5 Hz, 1H), 2.35 (s, 3H), 1.83-1.93 (m, 2H), 1.71-1.79 (m, 1H), 1.63 (ddd, J = 3.2, 11.5, 14.4 Hz, 1H), 1.46 (d, J = 7.1 Hz, 3H), 1.46 (d, J = 7.1 Hz, 3H).

Example 24

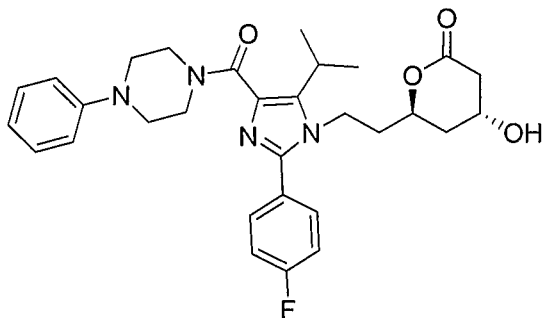
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl))-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 4-fluoro-benzylamide



Low resolution mass spectroscopy (APCI) m/z 498 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ 7.97 (br t, J = 6.4 Hz, 1H), 7.55 – 7.61 (m, 2H), 7.31-7.38 (m, 2H), 7.18-7.26 (m, 2H), 7.04-7.09 (m, 2H), 4.53 (ddd, J = 4.2, 7.6, 15.6 Hz 1H), 4.46 (d, J = 6.4 Hz, 2H), 4.05-4.25 (m, 3H), 3.35 (septet, J = 7.1 Hz, 1H), 3.28 (br s, 1H), 2.57 (dd, J = 4.6, 17.6 Hz, 1H), 2.41 (ddd, J = 1.7, 3.4, 17.3 Hz, 1H), 1.83-1.93 (m, 2H), 1.71-1.79 (m, 1H), 1.63 (ddd, J = 3.2, 11.2, 17.3 Hz, 1H), 1.46 (d, J = 7.1 Hz, 3H), 1.46 (d, J = 7.1 Hz, 3H).

Example 25

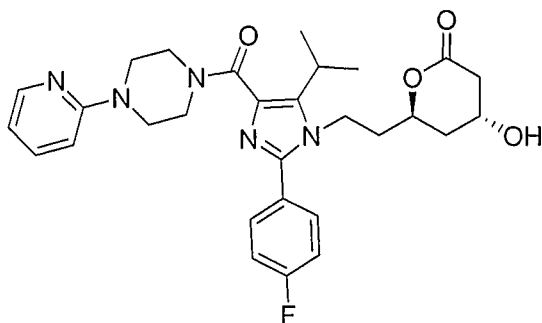
6-{2-[2-((2R,4R)-(4-Fluorophenyl)-5-isopropyl-4-(4-phenyl-piperazine-1-carbonyl)-imidazol-1-yl)-ethyl]-4-hydroxy-tetrahydro-pyran-2-one



Low resolution mass spectroscopy (APCI) m/z 535 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN): δ 1.36 (apparent d, J =6.8 Hz, 6 H), 1.63 (ddd, J =14.2, 11.2, 3.0 Hz, 1 H), 1.73 (m, 1 H), 1.91 (m, 2 H), 2.40 (ddd, J =17.4, 3.5, 1.7 Hz, 1 H), 2.58 (dd, J =17.3, 4.6 Hz, 1 H), 3.13 (m, 3 H), 3.19 (d, J =10.0 Hz, 2 H), 3.46 (s, 1 H), 3.72 (m, 2 H), 3.82 (m, 2 H), 4.10 (m, 1 H), 4.19 (m, 2 H), 4.51 (ddd, J =15.5, 7.8, 3.7 Hz, 1 H), 6.85 (m, 1 H), 6.96 (m, 2 H), 7.24 (m, 4 H), 7.62 (m, 2 H).

Example 26

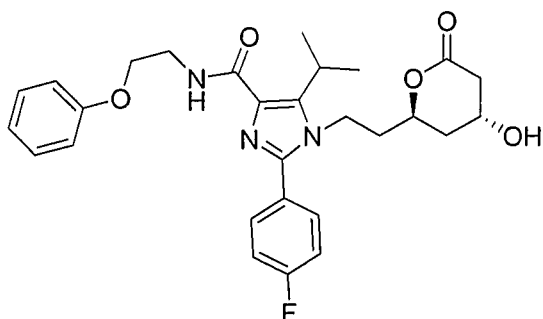
6-{2-[2-((4R,6R)-(4-Fluorophenyl)-5-isopropyl-4-(4-pyridin-2-yl-piperazine-1-carbonyl)-imidazol-1-yl)-ethyl]-4-hydroxy-tetrahydro-pyran-2-one



Low resolution mass spectroscopy (APCI) m/z 536 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN): δ 1.36 (apparent d, $J=7.0$ Hz, 6 H), 1.63 (ddd, $J=14.2, 11.2, 3.0$ Hz, 1 H), 1.74 (m, 1 H), 1.90 (m, 2 H), 2.40 (ddd, $J=17.5, 3.6, 1.5$ Hz, 1 H), 2.58 (dd, $J=17.3, 4.6$ Hz, 1 H), 3.14 (septet, $J=7.0$ Hz, 1 H), 3.49 (m, 3 H), 3.58 (m, 2 H), 3.68 (m, 2 H), 3.78 (m, 2 H), 4.10 (m, 1 H), 4.19 (m, 2 H), 4.51 (ddd, $J=15.3, 7.6, 3.7$ Hz, 1 H), 6.65 (ddd, $J=7.1, 4.9, 0.8$ Hz, 1 H), 6.75 (m, 1 H), 7.23 (m, 2 H), 7.53 (ddd, $J=8.7, 7.0, 2.0$ Hz, 1 H), 7.63 (m, 2 H), 8.13 (ddd, $J=4.8, 1.9, 0.7$ Hz, 1 H).

Example 27

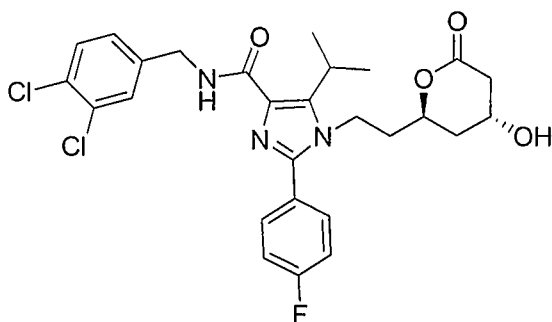
2-(4-Fluoro-phenyl)-1-[2-((4R,6R)(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (2-phenoxy-ethyl)-amide



Low resolution mass spectroscopy (APCI) m/z 510 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN): δ 1.48 (d, $J=7.0$ Hz, 3 H), 1.48 (d, $J=7.0$ Hz, 3 H), 1.64 (ddd, $J=14.2, 11.2, 3.0$ Hz, 1 H), 1.75 (m, 1 H), 1.89 (m, 2 H), 2.40 (ddd, $J=17.5, 3.6, 1.7$ Hz, 1 H), 2.59 (dd, $J=17.5, 4.6$ Hz, 1 H), 3.37 (septet, $J=7.0$ Hz, 1 H), 3.37 (br s, 1 H), 3.70 (q, $J=5.8$ Hz, 2 H), 4.14 (m, 5 H), 4.53 (ddd, $J=15.5, 7.8, 3.6$ Hz, 1 H), 6.94 (m, 3 H), 7.26 (m, 4 H), 7.60 (m, 2 H), 7.75 (t, $J=5.86$ Hz, 1 H).

Example 28

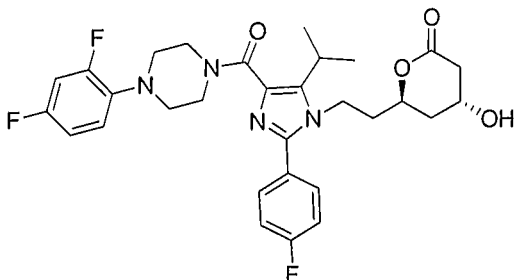
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 3,4-dichloro-benzylamide



Low resolution mass spectroscopy (APCI) m/z 548/550/552 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN): δ 1.45 (d, $J = 7.0$ Hz, 3 H), 1.47 (d, $J = 7.0$ Hz, 3 H), 1.65 (ddd, $J=14.2, 11.2, 3.0$ Hz, 1 H), 1.76 (m, 1 H), 1.93 (m, 3 H), 2.40 (ddd, $J = 17.4, 3.5, 1.7$ Hz, 1 H), 2.59 (dd, $J=17.5, 4.64$ Hz, 1 H), 3.36 (septet, $J = 7.0$ Hz, 1 H), 4.11 (m, 1 H), 4.18 (m, 2 H), 4.45 (d, $J=6.3$ Hz, 2 H), 4.54 (ddd, $J = 15.5, 7.8, 3.6$ Hz, 1 H), 7.23 (m, 3 H), 7.45 (m, 2 H), 7.60 (m, 2 H), 8.09 (t, $J=6.3$ Hz, 1 H).

Example 29

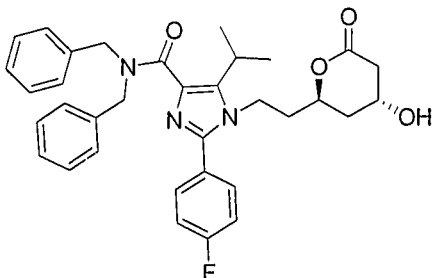
(4R,6R)-6-{2-[4-[4-(2,4-Difluoro-phenyl)-piperazine-1-carbonyl]-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-ethyl}-4-hydroxy-tetrahydro-pyran-2-one



Low resolution mass spectroscopy (APCI) m/z 571 $[M+H]^+$ 1H NMR (400 MHz, CD_3CN): δ 1.36 (d, $J = 7.0$ Hz, 3 H), 1.36 (d, $J = 7.0$ Hz, 3 H), 1.62 (ddd, $J=14.2, 11.23, 3.0$ Hz, 1 H), 1.73 (m, 1 H), 1.88 (m, 2 H), 2.39 (ddd, $J=17.4, 3.5, 1.7$ Hz, 1 H), 2.57 (dd, $J=17.5, 4.6$ Hz, 1 H), 2.95 (m, 2 H), 3.02 (m, 2 H), 3.13 (septet, $J=7.0$ Hz, 1 H), 3.71 (m, 2 H), 3.82 (m, 2H), 4.12 (m, 3 H), 4.50 (ddd, $J=15.3, 7.8, 3.6$ Hz, 1 H) 6.90 (m, 2 H) 7.03 (td, $J=9.2, 5.8$ Hz, 1 H), 7.22 (m, 2 H) 7.61 (m, 2 H).

Example 30

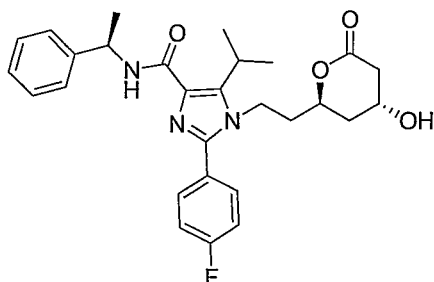
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid dibenzylamide



Low resolution mass spectroscopy (APCI) m/z 570 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN): δ ppm 1.35 (d, $J = 7.0$ Hz, 3 H), 1.35 (d, $J = 7.0$ Hz, 3 H), 1.61 (ddd, $J=14.2, 11.1, 3.1$ Hz, 1 H), 1.72 (m, 1 H), 1.86 (m, 2 H), 2.38 (ddd, $J=17.5, 3.6, 1.5$ Hz, 1 H), 2.57 (dd, $J=17.3, 4.6$ Hz, 1 H), 3.14 (septet, $J=7.0$ Hz, 1 H), 3.35 (br s, 1H), 4.13 (m, 3 H), 4.51 (m, $J=7.8, 7.7, 7.7, 3.7$ Hz, 1 H), 4.61 (s, 2 H), 4.74 (s, 2 H), 7.27 (m, 12 H), 7.59 (m, 2 H).

Example 31

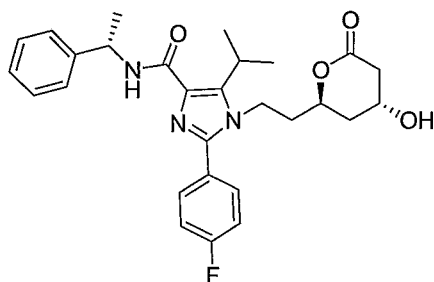
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid ((R)-1-phenyl-ethyl)-amide



Low resolution mass spectroscopy (APCI) m/z 494 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ ppm 1.42 (d, $J=6.8$ Hz, 3 H), 1.46 (d, $J=7.0$ Hz, 3 H), 1.50 (d, $J=7.0$ Hz, 3 H), 1.64 (ddd, $J=14.2$, 11.3, 3.1 Hz, 1 H), 1.75 (m, $J=14.2$, 3.6, 3.6, 1.9 Hz, 1 H), 1.90 (m, 2 H), 2.40 (ddd, $J=17.5$, 3.6, 1.7 Hz, 1 H), 2.58 (dd, $J=17.3$, 4.6 Hz, 1 H), 3.34 (septet, $J=7.0$ Hz, 1 H), 3.34 (obscured br s, 1H), 4.14 (m, 3 H), 4.53 (ddd, $J=15.6$, 7.8, 3.6 Hz, 1 H), 5.15 (m, 1 H), 7.24 (m, 3 H), 7.35 (m, 4 H), 7.62 (m, 2 H), 7.80 (d, $J=8.3$ Hz, 1 H).

Example 32

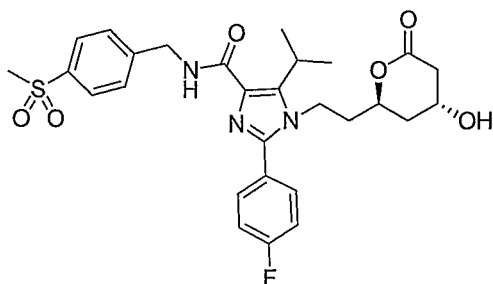
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid ((S)-1-phenyl-ethyl)-amide



Low resolution mass spectroscopy (APCI) m/z 494 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN): δ ppm 1.4 (d, $J=7.1$ Hz, 3 H), 1.5 (d, $J=7.1$ Hz, 3 H), 1.5 (d, $J=7.1$ Hz, 3 H), 1.6 (ddd, $J=14.3$, 11.4, 3.2 Hz, 1 H), 1.7 (m, $J=14.3$, 3.6, 3.6, 1.7 Hz, 1 H), 1.9 (m, 2 H), 2.4 (ddd, $J=17.5$, 3.5, 1.7 Hz, 1 H), 2.6 (dd, $J=17.3$, 4.6 Hz, 1 H), 3.3 (septet, $J=7.0$ Hz, 1 H), 4.1 (m, 3 H), 4.5 (ddd, $J=15.6$, 7.8, 3.7 Hz, 1 H), 5.1 (m, 1 H), 7.2 (m, 3 H), 7.3 (m, 4 H), 7.6 (m, 2 H), 7.8 (br d, $J=8.3$ Hz, 1 H).

Example 33

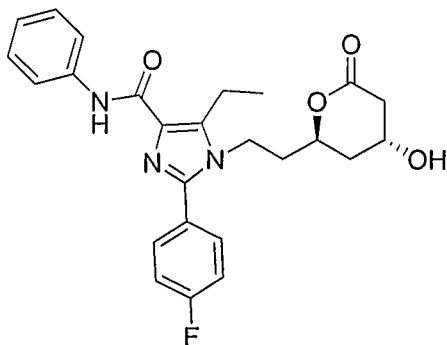
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 4-methanesulfonyl-benzylamide



Low resolution mass spectroscopy (APCI) m/z 558 $[M+H]^+$.

Example 34

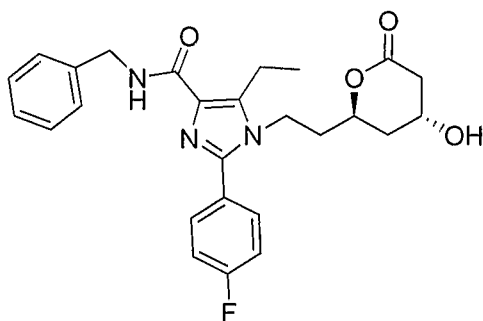
5-Ethyl-2-(4-fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-1H-imidazole-4-carboxylic acid phenylamide



Low resolution mass spectroscopy (APCI) m/z 452 $[M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, $J=7.51$ Hz, 3 H), 1.46 (m, 1 H), 1.64 (m, 1 H), 1.86 (m, 2 H), 2.39 (t, 1 H), 2.62 (m, 2 H), 3.15 (m, 1 H), 3.47 (q, $J=6.9$ Hz, 2 H), 4.13 (m, 1 H), 4.32 (m, 1 H), 4.58 (m, 1 H), 7.08 (m, 1 H), 7.19 (m, 2 H), 7.32 (m, 1 H), 7.39 (m, 1 H), 7.57 (m, 2 H), 7.68 (m, 2 H), 9.11 (s, 1 H).

Example 35

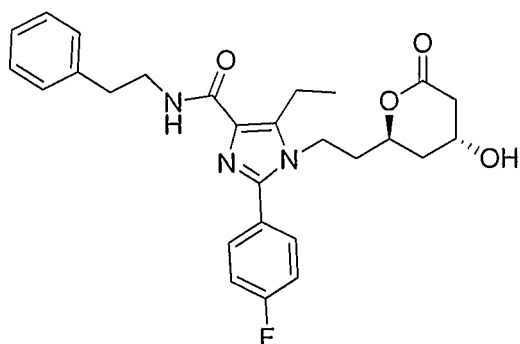
5-Ethyl-2-(4-fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-1H-imidazole-4-carboxylic acid benzylamide



1H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, $J=6.6$ Hz, 4 H), 1.30 (t, $J=7.5$ Hz, 1 H), 1.44 (m, 1 H), 1.74 (m, 4 H), 2.60 (m, 2 H), 3.12 (m, 1 H), 3.45 (m, 1 H), 3.73 (s, 2 H), 4.22 (m, 1 H), 4.52 (m, 1 H), 7.06 (m, 2 H), 7.17 (m, 1 H), 7.28 (m, 2 H), 7.34 (m, 2 H), 7.56 (m, 2 H), 8.19 (t, $J=7.93$ Hz, 1 H).

Example 36

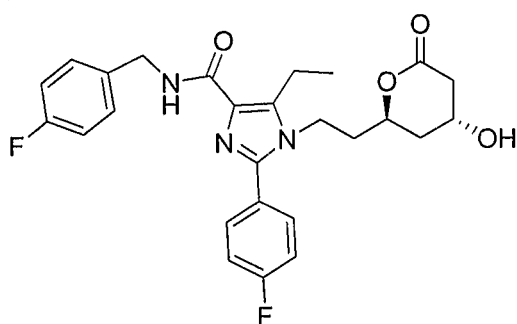
5-Ethyl-2-(4-fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-1H-imidazole-4-carboxylic acid phenethyl-amide



^1H NMR (400 MHz, CDCl_3) δ 1.41 (d, $J=6.59$ Hz, 3 H), 1.46 (m, 4 H), 1.63 (m, 1 H), 1.84 (m, 2 H), 2.60 (m, 2 H), 2.89 (m, 1 H), 3.13 (m, 2 H), 3.62 (m, 1 H), 3.70 (m, 1 H), 4.11 (m, 1 H), 4.29 (m, 1 H), 4.56 (m, 1 H), 7.20 (m, 4 H), 7.29 (m, 2 H), 7.38 (m, 1 H), 7.53 (m, 2 H).

5 Example 37

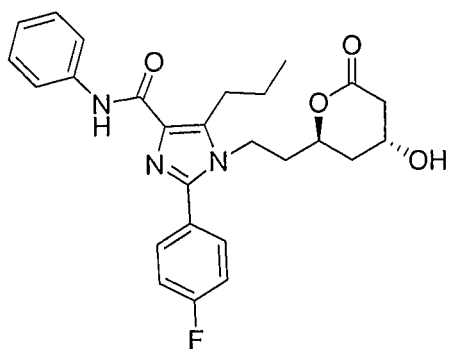
5-Ethyl-2-(4-fluorophenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-1H-imidazole-4-carboxylic acid 4-fluorobenzylamide



Low resolution mass spectroscopy (APCI) m/z 484 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 1.30 (t, $J=7.50$ Hz, 2 H), 1.44 (m, 4 H), 1.62 (m, 1 H), 1.85 (m, 2 H), 2.60 (m, 1 H), 3.13 (m, 2 H), 3.69 (m, 1 H), 4.11 (m, 1 H), 4.26 (m, 1 H), 4.34 (m, 1 H), 4.53 (d, $J=6.10$ Hz, 2 H), 6.98 (m, 2 H), 7.17 (m, 2 H), 7.31 (m, 2 H), 7.53 (m, 2 H), 7.62 (t, $J=4.70$ Hz, 1 H).

Example 38

2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-propyl-1H-imidazole-4-carboxylic acid phenylamide

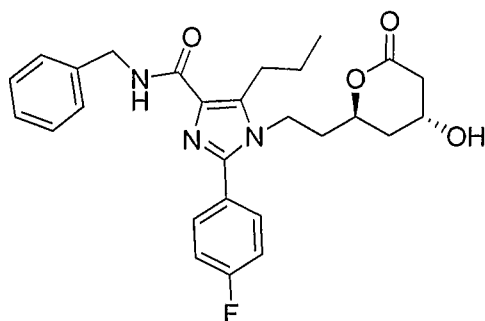


Low resolution mass spectroscopy (APCI) m/z 466 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 1.06 (t, $J=7.32$ Hz, 3 H), 1.62 (m, 2 H), 1.77 (m, 3 H), 1.89 (m, $J=14.29, 9.45, 9.45, 4.76$ Hz, 1 H), 2.19 (s, 1 H), 2.59 (m,

2 H), 3.08 (dd, $J=9.09, 6.65$ Hz, 2 H), 4.11 (m, 1 H), 4.29 (m, 2 H), 4.56 (m, $J=11.76, 9.29, 3.02, 3.02$ Hz, 1 H), 7.07 (t, $J=7.44$ Hz, 1 H), 7.21 (t, $J=8.66$ Hz, 2 H), 7.32 (m, 2 H), 7.58 (dd, $J=8.91, 5.25$ Hz, 2 H), 7.66 (d, $J=8.66$ Hz, 2 H), 9.10 (s, 1 H).

Example 39

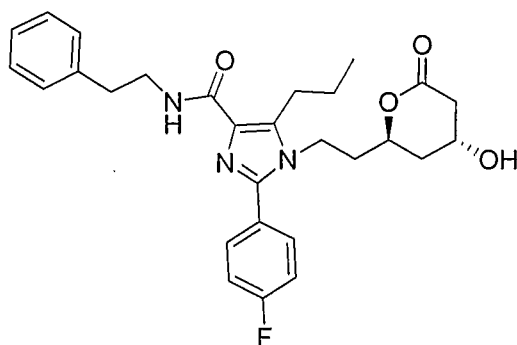
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-propyl-1H-imidazole-4-carboxylic acid benzylamide



Low resolution mass spectroscopy (APCI) m/z 480 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, $J = 7.32$ Hz, 3 H), 1.59 (m, 1 H), 1.73 (m, 4 H), 1.86 (m, 1 H), 2.36 (s, 1 H), 2.57 (m, 2 H), 3.05 (m, 2 H), 4.06 (m, 1 H), 4.26 (m, 2 H), 4.52 (m, 1 H), 4.57 (d, $J = 6.1$ Hz, 2 H), 7.15 (t, $J = 8.7$ Hz, 2 H), 7.22 (m, 1 H), 7.29 (m, 2 H), 7.32 (m, 2 H), 7.53 (m, 2 H).

Example 40

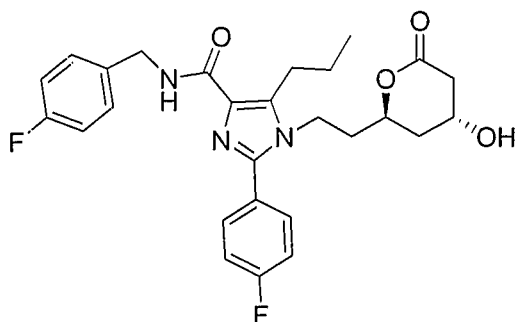
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-propyl-1H-imidazole-4-carboxylic acid phenethyl-amide



Low resolution mass spectroscopy (APCI) m/z 494 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, $J=7.32$ Hz, 3 H), 1.60 (m, 1 H), 1.69 (m, 3 H), 1.78 (m, 1 H), 1.87 (m, 1 H), 2.33 (s, 1 H), 2.60 (m, 2 H), 2.89 (m, 2 H), 3.04 (m, 2 H), 3.62 (m, 2 H), 4.09 (m, 1 H), 4.25 (m, 1 H), 4.32 (m, 1 H), 4.55 (m, 1 H), 7.17 (m, 2 H), 7.22 (m, 2 H), 7.29 (m, 2 H), 7.33 (t, $J=6.16$ Hz, 1 H), 7.53 (m, 2 H).

Example 41

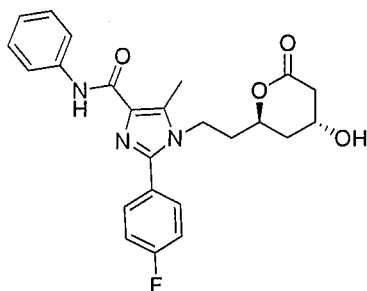
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-propyl-1H-imidazole-4-carboxylic acid 4-fluoro-benzylamide



Low resolution mass spectroscopy (APCI) m/z 498 $[M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, $J=7.32$ Hz, 2 H), 1.69 (m, 4 H), 1.87 (m, 1 H), 2.59 (m, 2 H), 3.06 (m, 2 H), 3.39 (s, 1 H), 4.11 (m, 1 H), 4.25 (m, 1 H), 4.31 (m, 2 H), 4.53 (d, $J=5.98$ Hz, 2 H), 6.98 (m, 2 H), 7.17 (m, 2 H), 7.30 (m, 2 H), 7.53 (m, 2 H), 7.71 (t, $J=5.98$ Hz, 2 H), 7.94 (s, 1 H).

Example 42

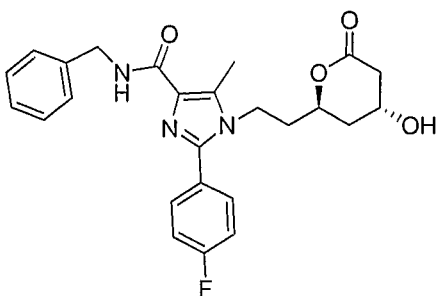
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-methyl-1H-imidazole-4-carboxylic acid phenylamide



Low resolution mass spectroscopy (APCI) m/z 438 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 1.39 (m, 1 H), 1.62 (m, 1 H), 1.87 (m, 2 H), 2.00 (s, 1 H), 2.58 (m, 1 H), 2.68 (s, 3 H), 3.32 (m, 1 H), 3.66 (m, 1 H), 4.08 (m, 1 H), 4.21 (m, 1 H), 4.31 (m, 1 H), 4.56 (m, 1 H), 7.05 (m, 1 H), 7.16 (m, 2 H), 7.30 (m, 2 H), 7.53 (m, 2 H), 7.63 (d, $J=7.57$ Hz, 2 H).

Example 43

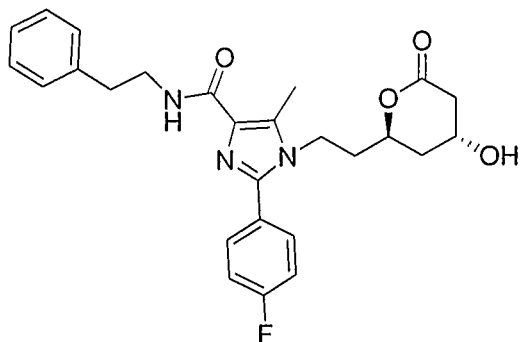
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-methyl-1H-imidazole-4-carboxylic acid benzylamide



Low resolution mass spectroscopy (APCI) m/z 452 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 1.63 (m, 1 H), 1.85 (m, 3 H), 2.59 (m, 2 H), 2.68 (s, 3 H), 3.11 (m, 1 H), 4.10 (m, 1 H), 4.23 (m, 1 H), 4.32 (m, 1 H), 4.55 (m, 2 H), 7.19 (m, 2 H), 7.31 (m, 3 H), 7.51 (m, 2 H), 7.65 (t, $J=5.86$ Hz, 2 H).

Example 44

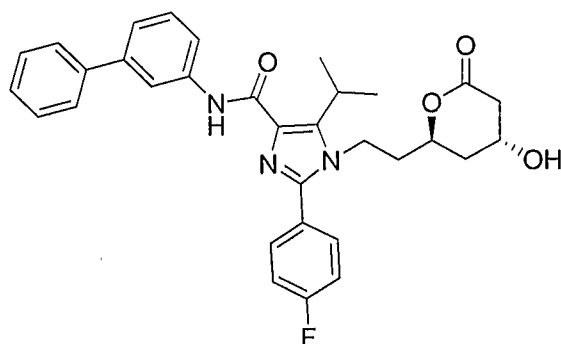
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-methyl-1H-imidazole-4-carboxylic acid phenethyl-amide



Low resolution mass spectroscopy (APCI) m/z 466 $[M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ 1.41 (m, 2 H), 1.63 (m, 1 H), 1.82 (m, 2 H), 1.91 (m, 1 H), 2.61 (m, 4 H), 2.89 (m, 1 H), 3.11 (td, $J=6.65, 3.66$ Hz, 1 H), 3.61 (m, 1 H), 3.68 (m, 1 H), 4.10 (m, 1 H), 4.23 (m, 1 H), 4.33 (m, 1 H), 4.57 (m, 1 H), 7.19 (m, 4 H), 7.28 (m, 2 H), 7.43 (t, $J = 6.16$ Hz, 1 H), 7.52 (m, 2 H), 10.04 (s, 1 H).

Example 45

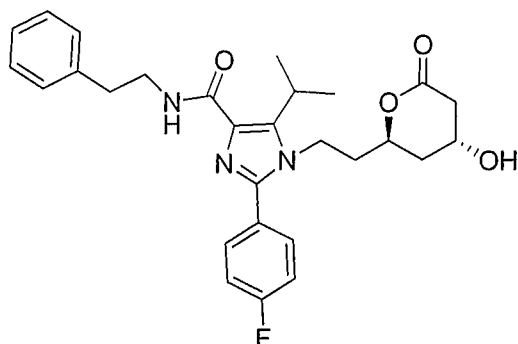
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (biphenyl-3-ylmethyl)-amide



Low resolution mass spectroscopy (APCI) m/z 556 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 1.53 (d, $J=7.02$, Hz, 3 H), 1.53 (d, $J=7.02$, Hz, 3 H), 1.65 (m, 1 H), 1.74 (s, 1 H), 1.80 (m, 2 H), 1.92 (m, 1 H), 2.61 (m, 2 H), 2.98 (m, 1 H), 4.11 (m, 1 H), 4.22 (m, 1 H), 4.33 (m, 1 H), 4.58 (m, 1 H), 4.64 (d, $J=5.86$ Hz, 2 H), 7.16 (m, 2 H), 7.37 (m, 4 H), 7.48 (m, 4 H), 7.57 (m, 1 H), 7.80 (s, 1 H).

Example 46

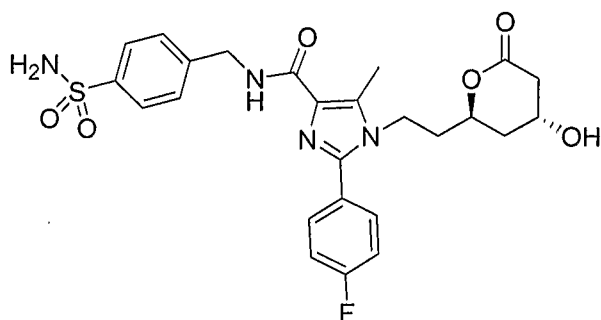
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid phenethyl-amide



Low resolution mass spectroscopy (APCI) m/z 494 $[M+H]^+$.

Example 47

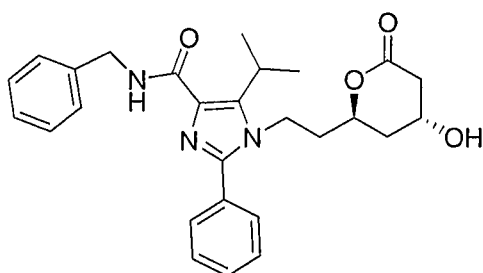
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-methyl-1H-imidazole-4-
carboxylic acid 4-sulfamoyl-benzylamide



Low resolution mass spectroscopy (APCI) m/z 531 $[M+H]^+$.

Example 48

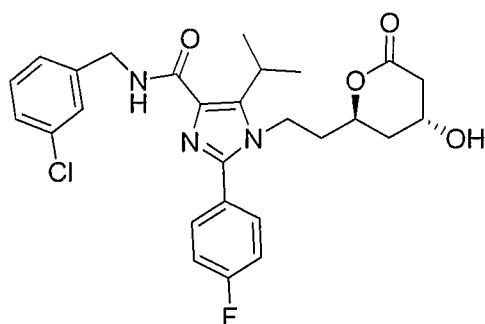
1-[2-((2R,4R)-4-Hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-2-phenyl-1H-imidazole-4-
carboxylic acid benzylamide



Low resolution mass spectroscopy (APCI) m/z 462 $[M+H]^+$.

Example 49

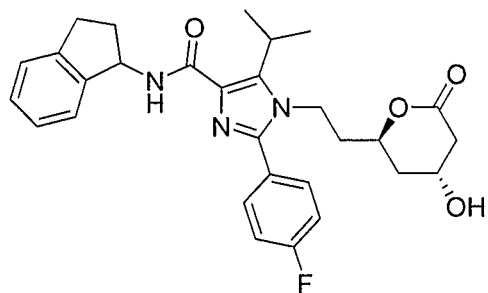
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-
4-carboxylic acid 3-chloro-benzylamide



Low resolution mass spectroscopy (APCI) m/z 514 $[M+H]^+$.

Example 50

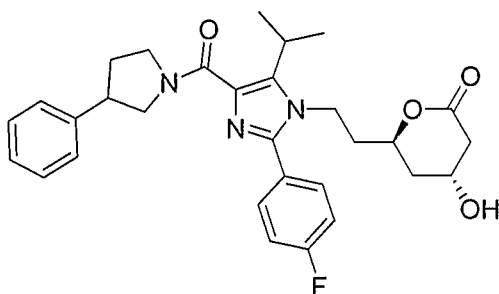
2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid indan-1-ylamide



Low resolution mass spectroscopy (APCI) m/z 506 $[M+H]^+$.

Example 51

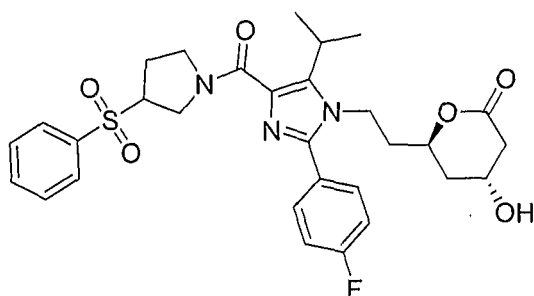
(4R,6R)-6-{2-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(3-phenyl-pyrrolidine-1-carbonyl)-imidazol-1-yl]-ethyl}-4-hydroxy-tetrahydro-pyran-2-one



Low resolution mass spectroscopy (APCI) m/z 520 $[M+H]^+$.

Example 52

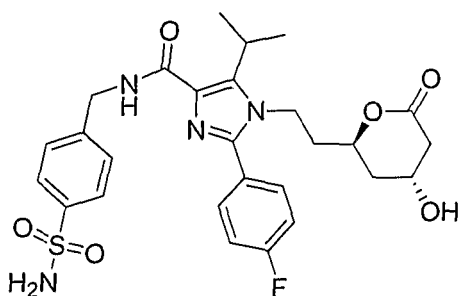
(4R,6R)-6-{2-[4-(3-Benzenesulfonyl-pyrrolidine-1-carbonyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-ethyl}-4-hydroxy-tetrahydro-pyran-2-one



Low resolution mass spectroscopy (APCI) m/z 584 $[M+H]^+$.

Example 53

2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 4-sulfamoyl-benzylamide

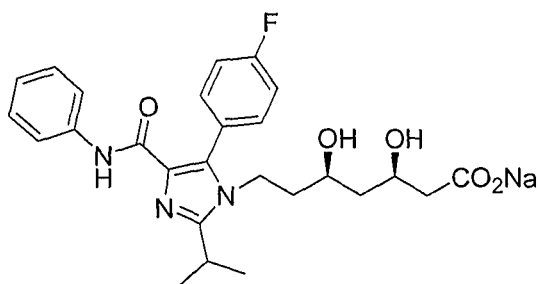


Low resolution mass spectroscopy (APCI) m/z 559 $[M+H]^+$.

Following a scheme analogous to that described in Example 9, Step C a variety of sodium salts were prepared from the corresponding lactones having the following variations on R^2 , R^4 and R^5

Example 54

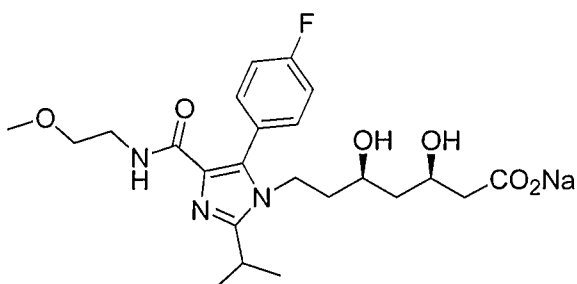
Sodium; (3R,5R)-7-[5-(4-Fluoro-phenyl)-2-isopropyl-4-phenylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 482 $[M-H]^-$; Anal. Calcd for $C_{26}H_{29}F_1N_3Na_1O_6$ / 0.5 H_2O / 1.0 NaOH: C, 56.32.; H, 5.63; N, 7.58. Found: C, 56.64; H, 5.38; N, 7.41.

Example 55

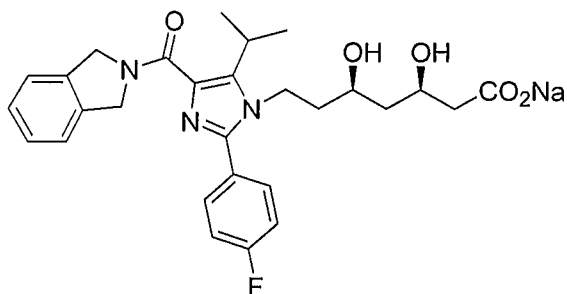
Sodium, (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(2-methoxy-ethylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate acid



Low resolution mass spectroscopy (APCI) m/z 464 $[M-H]^-$; Anal. Calcd for $C_{23}H_{31}F_1N_3Na_1O_6 / 0.5 H_2O$: C, 55.64.; H, 6.50; N, 8.46. Found: C, 55.86; H, 6.55; N, 8.33.

Example 56

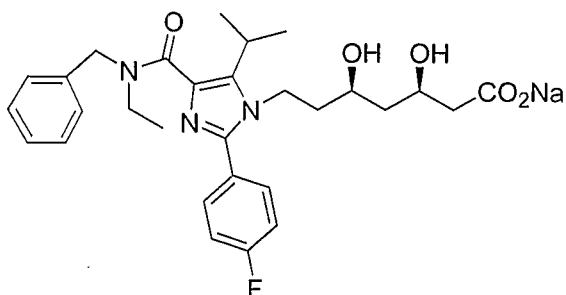
5 (3R,5R)-7-[4-(1,3-Dihydro-isoindole-2-carbonyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 508 $[M-H]^-$; Anal. Calcd for $C_{28}H_{31}F_1N_3Na_1O_5 / 2.1 H_2O$: C, 59.06.; H, 6.23; N, 7.38. Found: C, 58.81; H, 6.09; N, 7.18

Example 57

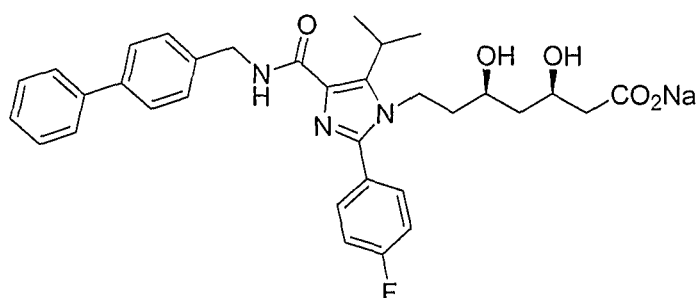
0 Sodium; (3R,5R)-7-[4-(Benzyl-ethyl-carbamoyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



5 Low resolution mass spectroscopy (APCI) m/z 524 $[M-H]^-$; Anal. Calcd for $C_{29}H_{35}F_1N_3Na_1O_5 / 1.0 H_2O$: C, 61.58.; H, 6.59; N, 7.43. Found: C, 61.20.; H, 6.55; N, 7.23.

Example 58

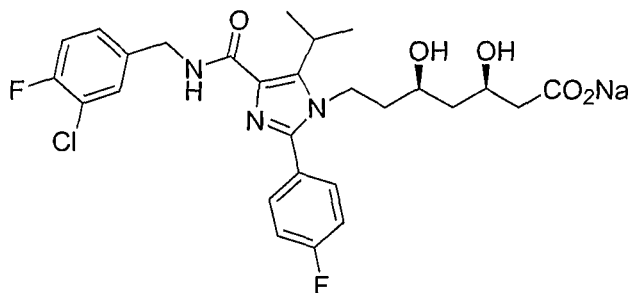
Sodium; (3R,5R)-7-[4-[(Biphenyl-4-ylmethyl)-carbamoyl]-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 572 $[M-H]^-$; Anal. Calcd for $C_{33}H_{35}F_1N_3Na_1O_5 / 1.7 H_2O$: C, 63.29.; H, 6.18; N, 6.71. Found: C, 63.16.; H, 6.11; N, 6.49.

Example 59

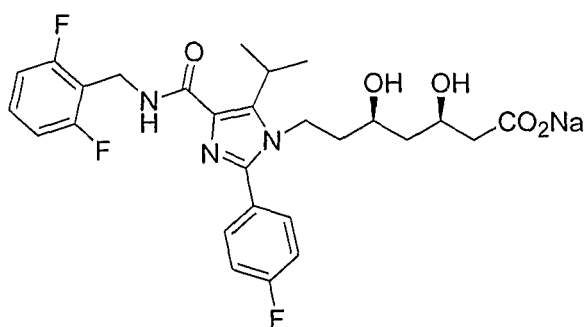
5 Sodium; (3R,5R)-7-[4-(3-Chloro-4-fluoro-benzylcarbamoyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 548 $[M-H]^-$; Anal. Calcd for $C_{27}H_{29}Cl_1F_2N_3Na_1O_5 / 1.3 H_2O$: C, 54.47.; H, 5.35; N, 7.06. Found: C, 54.57.; H, 5.18; N, 6.85.

Example 60

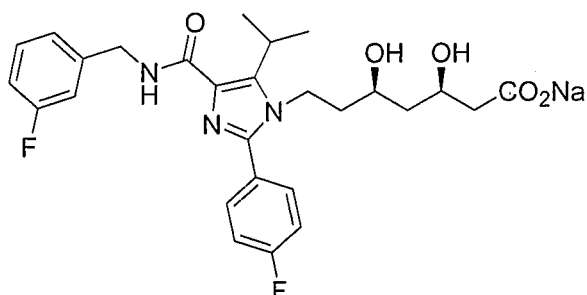
10 Sodium; (3R,5R)-7-[4-(2,6-Difluoro-benzylcarbamoyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



15 Low resolution mass spectroscopy (APCI) m/z 532 $[M-H]^-$; Anal. Calcd for $C_{27}H_{29}F_3N_3Na_1O_5 / 1.0 H_2O$: C, 56.54.; H, 5.45; N, 7.33. Found: C, 56.21.; H, 5.42; N, 7.10.

Example 61

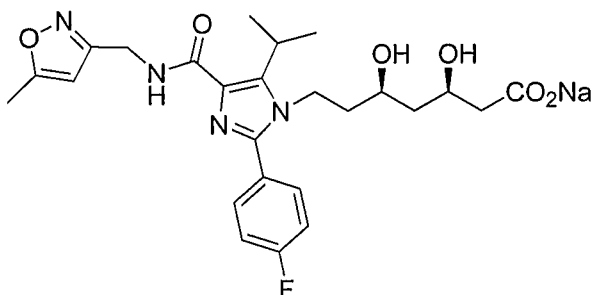
Sodium; (3R,5R)-7-[4-(3-Fluoro-benzylcarbamoyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 514 $[M-H]^-$; Anal. Calcd for $C_{27}H_{30}F_2N_3Na_1O_5$ / 1.0 H_2O : C, 58.37.; H, 5.81; N, 7.56. Found: C, 58.47.; H, 5.76; N, 7.31.

Example 62

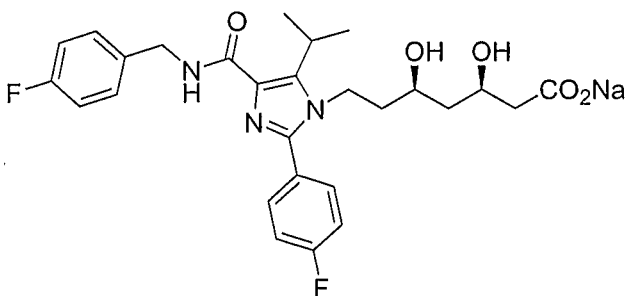
Sodium; (3R,5R)-7-{2-(4-Fluoro-phenyl)-5-isopropyl-4-[(5-methyl-isoxazol-3-ylmethyl)-carbamoyl]-imidazol-1-yl}-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 501 $[M-H]^-$; Anal. Calcd for $C_{25}H_{30}F_1N_4Na_1O_6$ / 2.0 H_2O : C, 53.57.; H, 6.11; N, 10.00. Found: C, 53.17.; H, 5.82; N, 9.71.

Example 63

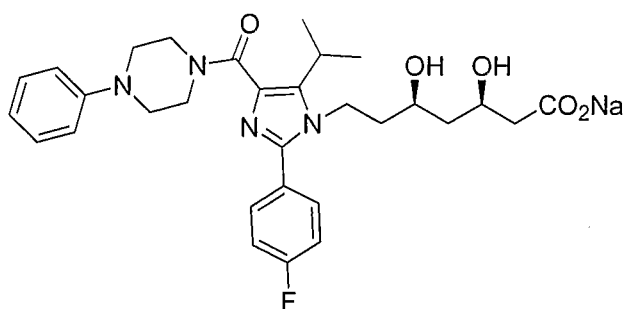
Sodium; (3R,5R)-7-[4-(4-Fluoro-benzylcarbamoyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 514 $[M-H]^-$; Anal. Calcd for $C_{27}H_{30}F_2N_3Na_1O_5$ / 1.3 H_2O : C, 57.81.; H, 5.86; N, 7.49. Found: C, 57.81.; H, 5.70; N, 7.24.

Example 64

Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(4-phenyl-piperazine-1-carbonyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate



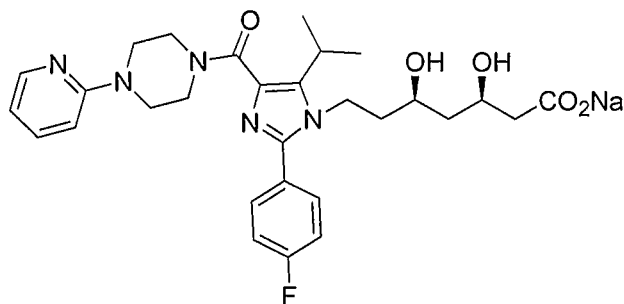
Low resolution mass spectroscopy (APCI) m/z 551 [M-H]⁻; Anal. Calcd for C₃₀H₃₆F₁N₄Na₁O₅ / 3.5 H₂O: C, 56.51.; H, 6.80; N, 8.79. Found: C, 56.54.; H, 6.66; N, 8.47.

Example 65

5 There is no Example 65

Example 66

Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(4-pyridin-2-yl-piperazine-1-carbonyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate

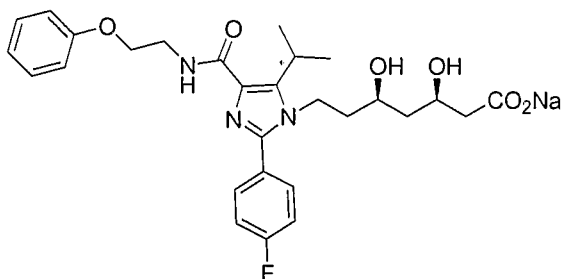


0 Low resolution mass spectroscopy (APCI) m/z 552 [M-H]⁻; Anal. Calcd for C₂₉H₃₅F₁N₅Na₁O₅ / 3.0 H₂O / 0.10 NaOH: C, 54.97.; H, 6.54; N, 11.05. Found: C, 54.81.; H, 6.53; N, 10.76.

Example 67

Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(2-phenoxy-ethylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate

5

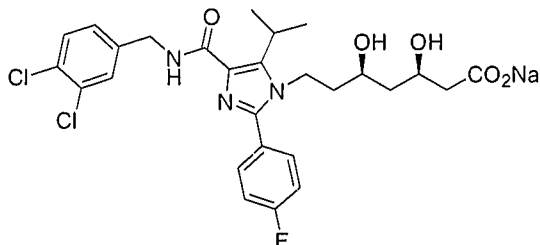


Low resolution mass spectroscopy (APCI) m/z 526 [M-H]⁻; Anal. Calcd for C₂₈H₃₃F₁N₃Na₁O₆ / 3.0 H₂O: C, 55.71.; H, 6.51; N, 6.96. Found: C, 55.41.; H, 6.39; N, 6.62.

)

Example 68

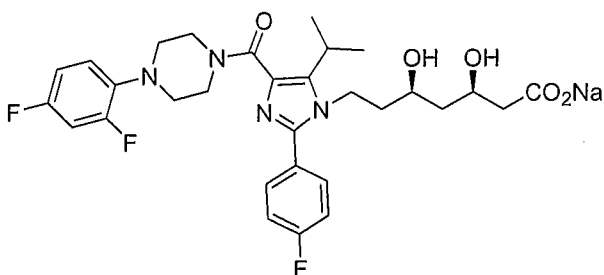
Sodium; (3R,5R)-7-[4-(3,4-Dichloro-benzylcarbamoyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 564/566 $[M-H]^-$; Anal. Calcd for $C_{27}H_{29}Cl_2F_1N_3Na_1O_5$ / 3.0 H_2O / 0.10 NaOH: C, 50.16.; H, 5.47; N, 6.50. Found: C, 50.11.; H, 5.07; N, 6.15.

Example 69

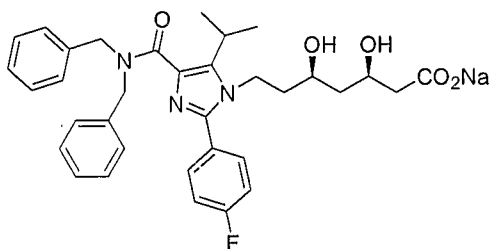
Sodium; (3R,5R)-7-[4-[4-(2,4-Difluoro-phenyl)-piperazine-1-carbonyl]-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 587 $[M-H]^-$.

Example 70

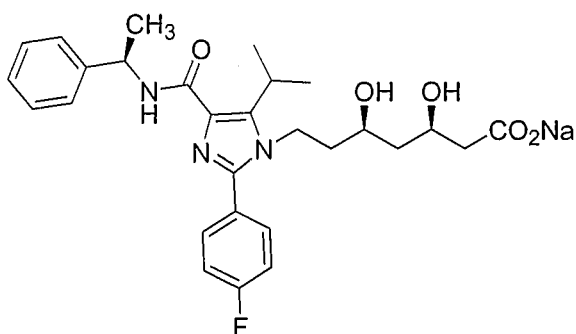
Sodium; (3R,5R)-7-[4-Dibenzylcarbamoyl-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 586 $[M-H]^-$; Anal. Calcd for $C_{34}H_{37}F_1N_3Na_1O_5$ / 2.8 H_2O : C, 61.86.; H, 6.50; N, 6.37. Found: C, 61.91.; H, 6.14; N, 6.20.

Example 71

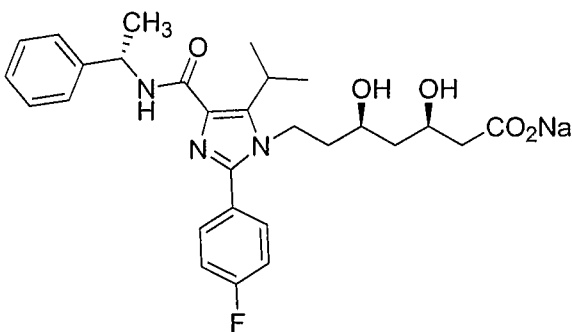
Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-((R)-1-phenyl-ethylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 510 $[M-H]^-$; $C_{28}H_{33}F_1N_3Na_1O$ / 2.8 H_2O / 0.15 NaOH: C, 57.88; H, 6.55; N, 7.23. Found: C, 57.88.; H, 6.16; N, 6.92

Example 72

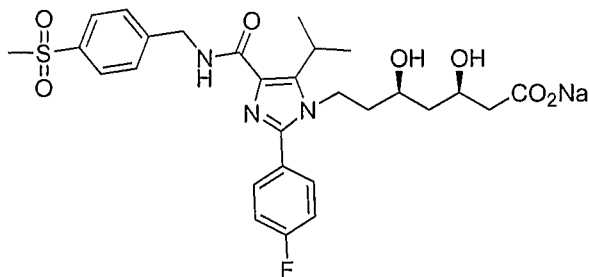
5 Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-((S)-1-phenyl-ethylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 510 $[M-H]^-$; $C_{28}H_{33}F_1N_3Na_1O_5$ / 2.7 H_2O / 0.30 NaOH: C, 56.60; H, 6.56; N, 7.07. Found: C, 56.55.; H, 6.19; N, 6.68.

Example 73

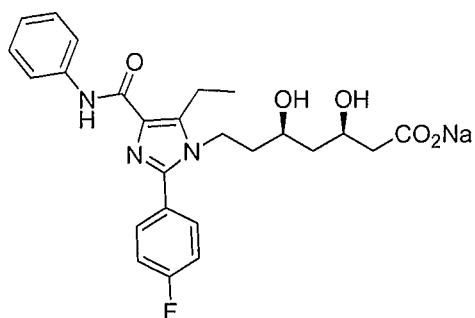
0 Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(4-methanesulfonyl-benzylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate



5 Low resolution mass spectroscopy (APCI) m/z 576 $[M+H]^+$; $C_{28}H_{33}F_1N_3Na_1O_7S_1$ / 3.0 H_2O : C, 51.61; H, 6.03; N, 6.45. Found: C, 51.46.; H, 5.70; N, 6.27.

Example 74

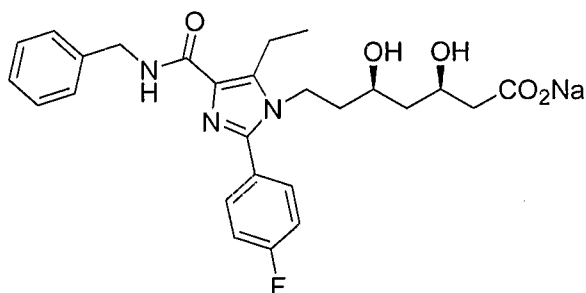
Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-ethyl-4-phenylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 470 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 1.23 (t, $J=7.3$ Hz, 3 H) 1.41 (m, 2 H) 1.54 (m, 1 H) 1.67 (m, 1 H) 1.84 (dd, $J=15.0, 8.3$ Hz, 1 H) 2.02 (dd, $J=15.0, 3.9$ Hz, 1 H) 3.05 (m, 2 H), 3.59 (m, 1 H), 3.69 (m, 1 H), 4.00 (m, 1 H), 4.15 (m, 1 H), 4.91 (s, 1 H), 6.98 (m, 2 H), 7.37 (m, 4 H), 7.75 (m, 3 H), 9.64 (s, 1 H).

Example 75

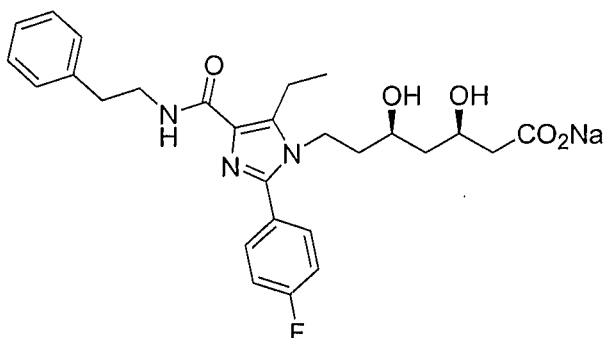
Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-ethyl-4-benzylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 482 $[M-H]^-$;

Example 76

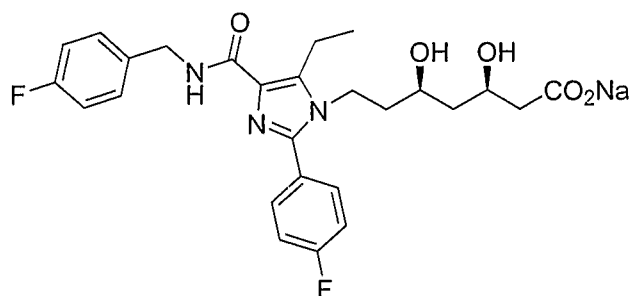
Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-ethyl-4-phenethylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 498 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 1.16 (t, $J=7.3$ Hz, 3 H), 1.23 (m, 1 H), 1.51 (m, 1 H), 1.63 (m, 1 H), 1.74 (m, 1 H), 1.81 (dd, $J=15.0, 8.2$ Hz, 1 H), 2.00 (dd, $J=14.9, 4.2$ Hz, 1 H), 2.80 (m, 2 H), 3.00 (m, 2 H), 3.43 (m, 2 H), 3.57 (m, 1 H), 3.67 (m, 1 H), 3.95 (m, 1 H), 4.09 (m, 1 H), 4.68 (s, 1 H), 7.20 (m, 3 H), 7.30 (m, 4 H), 7.66 (m, 2 H), 7.87 (t, $J=5.9$ Hz, 1 H).

Example 77

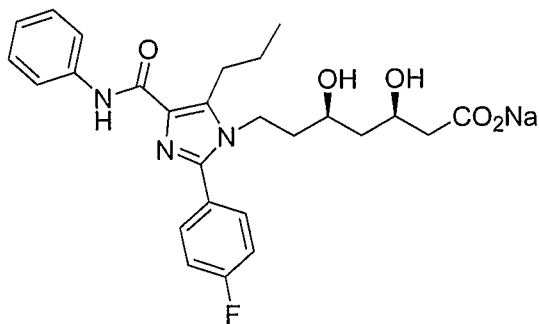
Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-ethyl-4-(4-fluorobenzylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 502 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 1.16 (t, $J=7.3$ Hz, 1 H), 1.23 (m, 1 H), 1.39 (m, 2 H), 1.51 (m, 1 H), 1.63 (m, 1 H), 1.75 (m, 1 H), 1.83 (dd, $J=15.1, 8.3$ Hz, 1 H), 2.01 (dd, $J=15.0, 4.0$ Hz, 1 H), 3.00 (m, 2 H), 3.58 (m, 1 H), 3.68 (m, 1 H), 3.95 (m, 1 H), 4.10 (m, 1 H), 4.37 (d, $J=6.3$ Hz, 2 H), 4.88 (s, 1 H), 7.11 (m, 2 H), 7.31 (m, 4 H), 7.68 (m, 2 H), 8.41 (t, $J=6.4$ Hz, 1 H).

Example 78

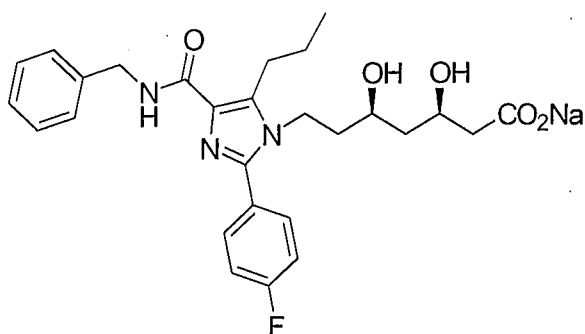
Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-propyl-4-phenylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 484 $[M+H]^+$; Anal. Calculated for $C_{26}H_{29}FN_3O_5Na$ / 2.83 H_2O : C, 56.11; H, 6.28; N, 7.55. Found C, 56.50; H, 5.94; N, 7.15.

Example 79

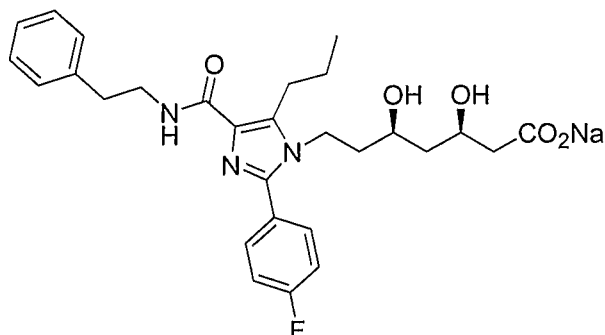
Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-propyl-4-benzylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 498 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 0.93 (t, $J=7.3$ Hz, 2 H), 1.18 (m, 1 H), 1.36 (m, 1 H), 1.53 (m, 4 H), 1.73 (dd, $J=14.8, 8.1$ Hz, 1 H), 1.93 (dd, $J=14.8, 4.1$ Hz, 1 H), 2.96 (m, 2 H), 3.28 (s, 1 H), 3.56 (m, 1 H), 3.65 (m, 1 H), 3.95 (m, 1 H), 4.09 (m, 1 H), 4.39 (d, $J=6.3$ Hz, 2 H), 4.94 (s, 1 H), 7.20 (m, 1 H), 7.30 (m, 5 H), 7.68 (m, 3 H), 8.35 (t, $J=6.3$ Hz, 1 H).

Example 80

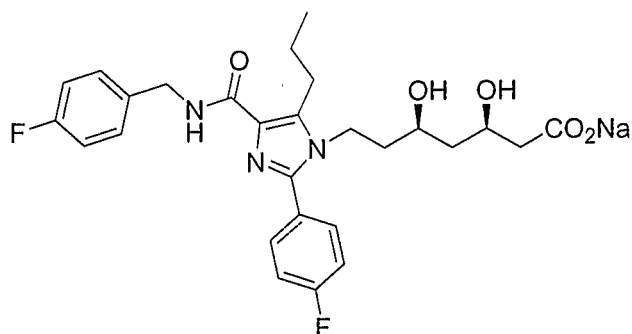
Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-propyl-4-phenethylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 512 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 0.94 (t, $J=7.3$ Hz, 2 H), 1.18 (m, 1 H), 1.36 (m, 1 H), 1.53 (m, 4 H), 1.74 (dd, $J=14.9, 8.2$ Hz, 1 H), 1.94 (dd, $J=14.8, 4.0$ Hz, 1 H), 2.79 (m, 2 H), 2.96 (m, 2 H), 3.29 (s, 1 H), 3.43 (m, 2 H), 3.56 (m, 1 H), 3.64 (m, 1 H), 3.94 (m, 1 H), 4.08 (m, 1 H), 4.93 (s, 1 H), 7.19 (m, 3 H), 7.29 (m, 4 H), 7.67 (m, 2 H), 7.87 (t, $J=6.1$ Hz, 1 H).

Example 81

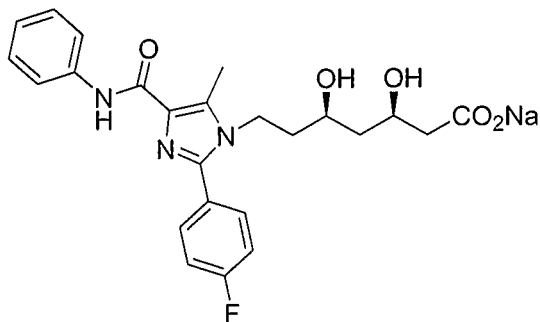
Sodium; (3R, 5R)-7-[2-(4-Fluoro-phenyl)-5-methyl-4-(4-fluorophenylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate



J = Low resolution mass spectroscopy (APCI) m/z 516 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 0.93 (t, 7.3 Hz, 3 H), 1.18 (m, 1 H), 1.36 (m, 1 H), 1.53 (m, 4 H), 1.73 (dd, J =15., 8.1 Hz, 1 H), 1.93 (dd, J =14.8, 4.0 Hz, 1 H), 2.9 (m, 2 H), 3.2 (s, 1 H), 3.56 (s, 1 H), 3.63 (m, 1 H), 3.95 (m, 1 H), 4.09 (m, 1 H), 4.36 (d, J =6.3 Hz, 2 H), 4.93 (s, 1 H), 7.11 (m, 2 H), 7.31 (m, 4 H), 7.67 (m, 2 H), 8.40 (t, J =6.4 Hz, 1 H)

Example 82

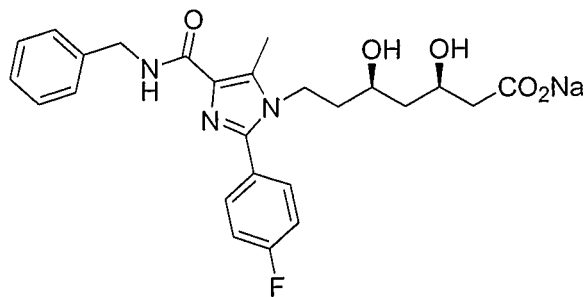
Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-methyl-4-phenylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 456 $[M+H]^+$;

Example 83

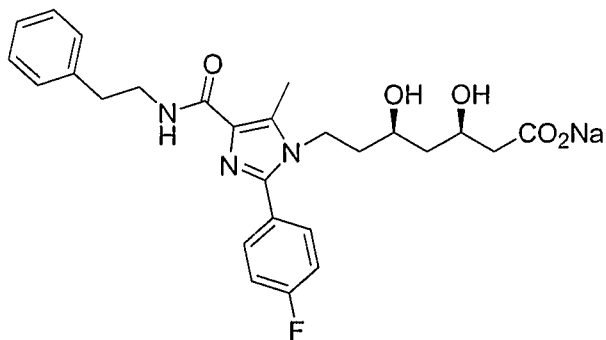
Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-methyl-4-benzylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 470 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 1.22 (m, 1 H), 1.39 (m, 1 H), 1.54 (m, 1 H), 1.73 (m, 1 H), 1.94 (dd, J =14.9, 3.9 Hz, 1 H), 2.56 (s, 3 H), 3.00 (m, 1 H), 3.28 (s, 1 H), 3.57 (m, 1 H), 3.66 (m, 1 H), 3.94 (m, 1 H), 4.06 (m, 1 H), 4.39 (d, J =6.2 Hz, 2 H), 4.94 (s, 1 H), 7.20 m, 1 H), 7.30 (m, 4 H), 7.67 (m, 2 H), 7.79 (s, 1 H), 8.36 (t, J =6.3 Hz, 1 H).

Example 84

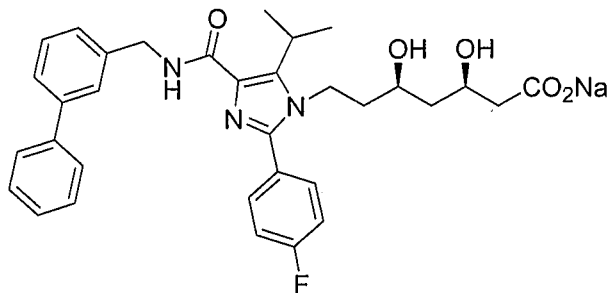
Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-methyl-4-phenethylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 484 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 1.17 (m, 1 H), 1.34 (m, 1 H), 1.49 (m, 1 H), 1.68 (m, 1 H), 1.89 (dd, $J=15.0, 4.0$ Hz, 1 H), 2.51 (s, 3 H), 2.75 (m, 2 H), 2.96 (m, 2 H), 3.38 (m, 2 H), 3.52 (m, 1 H), 3.61 (m, 1 H), 3.89 (m, 1 H), 4.01 (m, 1 H), 4.89 (s, 1 H), 7.15 (m, 3 H), 7.26 (m, 4 H), 7.61 (m, 2 H), 7.83 (t, $J=6.1$ Hz, 1 H).

Example 85

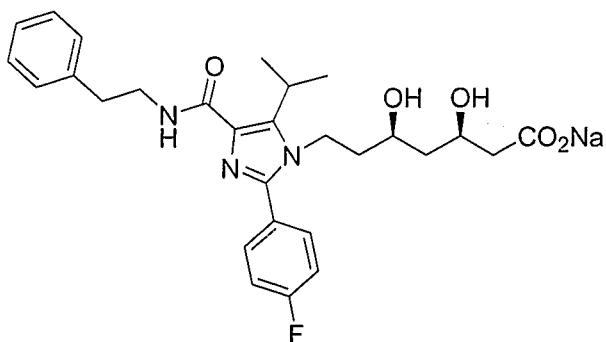
Sodium; (3R,5R)-7-[4-[(Biphenyl-3-yl)methyl]-carbamoyl]-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Anal. Calculated for $C_{33}H_{35}FN_3O_5Na \cdot 8.48 H_2O$: C, 52.96; H, 7.00; N, 5.61. Found C, 52.57; H, 7.06; N, 5.53.

Example 86

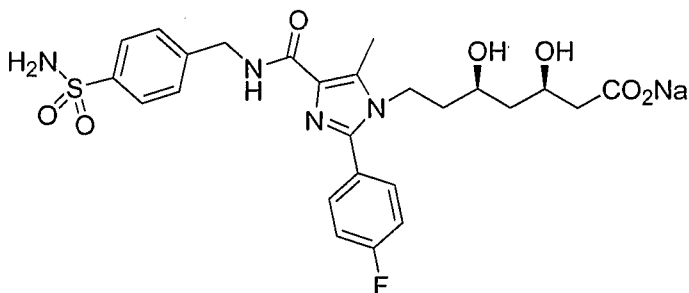
Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-phenethylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



MS($C_{28}H_{34}FN_3O_5$) sought 510; found 413,497 Anal. Calculated for $C_{28}H_{33}FN_3O_5Na \cdot 23.5 H_2O$: C, 35.14; H, 8.43; N, 4.39. Found C, 35.13; H, 3.65; N, 2.97.

Example 87

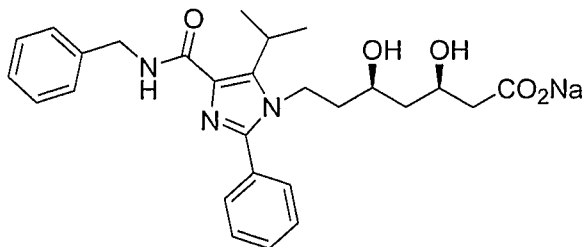
Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-methyl-4-(4-sulfamoyl-benzylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 549 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 1.17 (m, 1 H), 1.34 (m, 3 H), 1.49 (m, 1 H), 1.63 (m, 1 H), 1.70 (dd, $J=15.0, 8.3$ Hz, 1 H), 1.90 (dd, $J=14.7, 4.0$ Hz, 1 H), 2.51 (s, 3 H), 3.24 (s, 1 H), 3.52 (m, 1 H), 3.62 (m, 1 H), 3.90 (m, 1 H), 4.02 (m, 1 H), 4.40 (d, $J=6.4$ Hz, 2 H), 4.89 (s, 1 H), 7.22 (s, 1 H), 7.27 (m, 1 H), 7.40 (m, 2 H), 7.63 (m, 2 H), 7.70 (m, 2 H), 8.49 (t, $J=6.2$ Hz, 1 H).

Example 88

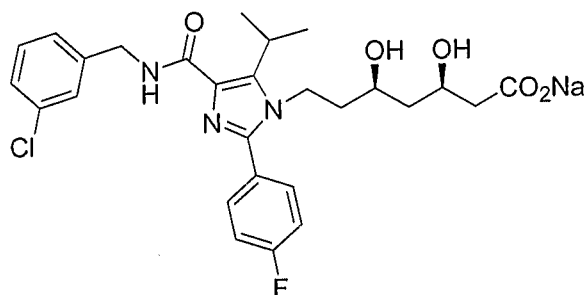
Sodium; (3R,5R)-7-[4-benzylcarbamoyl-2-phenyl-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 480 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 1.24 (m, 2 H), 1.40 (m, 6 H), 1.58 (m, 1 H), 1.70 (m, 1 H), 1.80 (dd, $J=15.0, 8.3$ Hz, 1 H), 1.98 (dd, $J=15.1, 4.0$ Hz, 1 H), 3.29 (s, 1 H), 3.37 (m, 1 H), 3.62 (m, 1 H), 3.69 (m, 1 H), 3.96 (m, 1 H), 4.12 (m, 1 H), 4.41 (d, $J=6.3$ Hz, 2 H), 4.92 (s, 1 H), 7.20 (m, 1 H), 7.29 (m, 4 H), 7.47 (m, 3 H), 7.59 (m, 2 H), 8.37 (t, $J=6.4$ Hz, 1 H).

Example 89

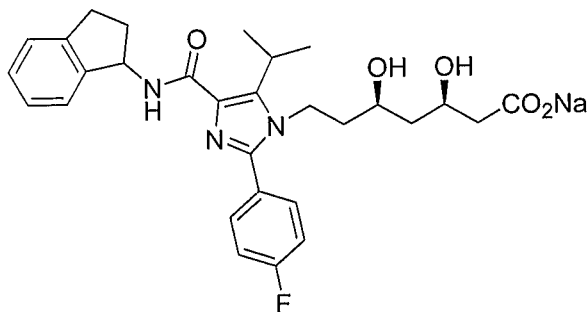
Sodium; (3R,5R)-7-[4-(3-Chloro-benzylcarbamoyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 532 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 0.97 (t, J = 7.5 Hz, 1 H), 1.18 (m, 1 H), 1.35 (m, 6 H), 1.63 (m, 1 H), 1.72 (dd, J = 14.9, 8.1 Hz, 1 H), 1.92 (dd, J = 14.8, 4.0 Hz, 1 H), 3.25 (m, 1 H), 3.33 (m, 2 H), 3.56 (m, 1 H), 3.63 (m, 1 H), 3.91 (m, 1 H), 4.06 (m, 1 H), 4.35 (d, J = 6.4 Hz, 2 H), 4.91 (s, 1 H), 7.22 (m, 2 H), 7.28 (m, 4 H), 7.61 (m, 2 H), 8.49 (t, J = 6.4 Hz, 1 H).

Example 90

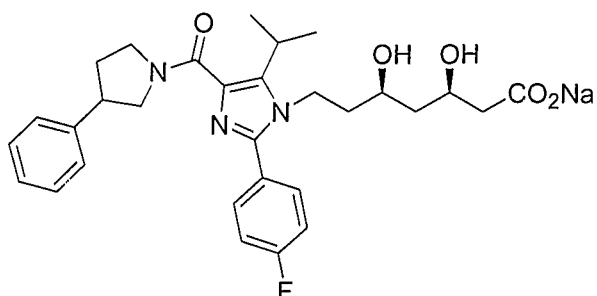
Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-4-(indan-1-ylcarbamoyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 524 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 1.02 (m, 1 H), 1.12 (m, 1 H), 1.24 (m, 1 H), 1.37 (m, 1 H), 1.45 (m, 6 H), 1.69 (m, 1 H), 1.78 (dd, J = 14.8, 8.1 Hz, 1 H), 1.97 (J = 14.8, 3.9 Hz, 1 H), 2.41 (m, 1 H), 2.90 (m, 1 H), 3.39 (m, 2 H), 3.61 (m, 1 H), 3.68 (m, 1 H), 3.96 (m, 1 H), 4.09 (m, 1 H), 4.94 (s, 1 H), 5.41 (m, 2 H), 7.17 (m, 2 H), 7.29 (m, 3 H), 7.48 (s, 1 H), 7.64 (m, 2 H), 7.90 (d, J = 8.9 Hz, 1 H).

Example 91

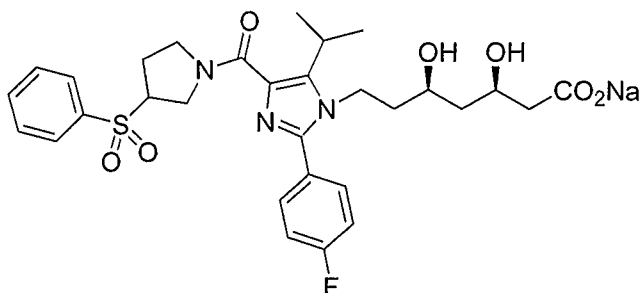
Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(3-phenyl-pyrrolidine-1-carbonyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 538 $[M+H]^+$;

Example 92

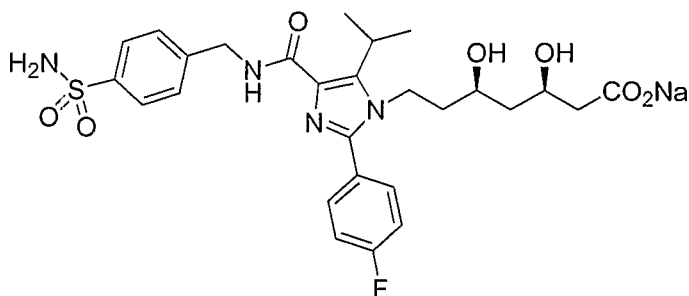
5 Sodium; (3R,5R)-7-[4-(3-Benzenesulfonyl-pyrrolidine-1-carbonyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Low resolution mass spectroscopy (APCI) m/z 602 $[M+H]^+$; Anal. Calculated for $C_{30}H_{35}FN_3O_7S$ Na·0.85 H_2O : C, 56.39; H, 5.79; N, 6.58. Found C, 56.39; H, 5.65; N, 6.36.

0 Example 93

Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(4-sulfamoyl-benzylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate

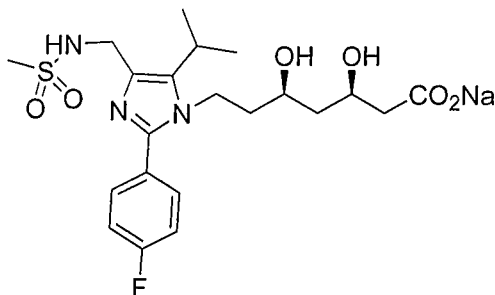


5 Low resolution mass spectroscopy (APCI) m/z 577 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ
 1.00 (m, 3 H), 1.23 (m, 2 H), 1.39 (m, 6 H), 1.55 (m, 1 H), 1.55 (m, 1 H), 1.68 (m, 1 H), 1.77 (dd, $J=15.0$,
 8.2 Hz, 1 H), 1.97 (dd, $J=14.8$, 4.0 Hz, 1 H), 3.62 (m, 1 H), 3.68 (m, 1 H), 3.95 (m, 1 H), 4.10 (m, 1 H),
 4.46 (d, $J=6.4$ Hz, 1 H), 4.94 (s, 1 H), 7.12 (s, 1 H), 7.31 (m, 1 H), 7.45 (m, 1 H), 7.53 (s, 1 H), 7.66 (m, 2
 H), 7.74 (m, 2 H), 8.55 (t, $J=6.2$ Hz, 1 H).

0

Example 94

Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(methanesulfonylamino-methyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate

**Step A**

((4R,6R)-6-{2-[2-(4-Fluoro-phenyl)-4-hydroxymethyl-5-isopropyl-imidazol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester

A solution of 1-[2-((4R, 6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid pentafluorophenyl ester (4.0 g, 6.7 mmol) in absolute EtOH (120 mL) was carefully treated with excess NaBH₄ (2.5 g, 67 mmol) in portions over a period of 5 min. The reaction mixture was allowed to stir at ambient temperature for 48h. The reaction mixture was carefully treated with neat HOAc (2 mL) and allowed to stir for 5 min. The mixture was concentrated to a crude oil and partitioned between EtOAc/1 M NaOH. The organic layer was separated, washed (sat. NH₄Cl), dried (Na₂SO₄), and concentrated to a colorless oil. TLC analysis indicated one major component (R_f = 0.17, (EtOAc, UV & KMnO₄). Purification by flash chromatography (SiO₂, MeOH/EtOAc 5%) gave the desired product as a colorless foam; Yield: 2.03g (61%); Low resolution mass spectroscopy (APCI) *m/z* 491 [M+H]⁺; Anal. Calcd. For C₂₇H₃₉F₁N₂O₅: C, 66.10; H, 8.01; N, 5.71. Found: C, 65.78; H, 8.01; N, 5.53.

Step B

((4R,6R)-6-{2-[2-(4-Fluoro-phenyl)-4-formyl-5-isopropyl-imidazol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester

A solution of ((4R,6R)-6-{2-[2-(4-Fluoro-phenyl)-4-hydroxymethyl-5-isopropyl-imidazol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester (6.0 g, 12 mmol) in anhydrous CH₂Cl₂ (60 mL) was treated with excess Manganese (IV) oxide (11 g, 122 mmol). The heterogenous reaction mixture was vigorously stirred at rt under a nitrogen atmosphere overnight. TLC analysis (EtOAc, 100%) indicates complete consumption of the starting material (R_f = 0.17) and a new non polar component (R_f = 0.70). The reaction mixture was filtered through celite, concentrated to a colorless glass and dried under high vacuum to give the desired product; yield: 5.82g (97%); Low resolution mass spectroscopy (APCI) *m/z* 490 [M+H]⁺; Anal. Calcd. For C₂₇H₃₇F₁N₂O₅: C, 66.37; H, 7.63; N, 5.73. Found: C, 66.42; H, 7.83; N, 5.73.

Step C

N-{2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazol-4-ylmethyl}-methanesulfonamide.

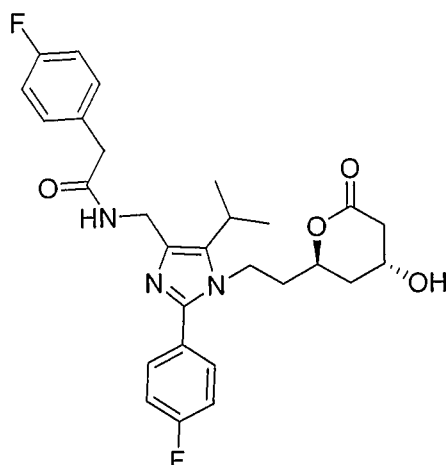
A solution of ((4R, 6R)-6-{2-[2-(4-Fluoro-phenyl)-4-formyl-5-isopropyl-imidazol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester (1.5g, mmol) in methanol (50 mL) saturated with ammonia was hydrogenated over Raney Nickel (0.5 g). The mixture was filtered through celite and concentrated to give crude ((4R, 6R)-6-{2-[4-Aminomethyl-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester as a glass; Low resolution mass spectroscopy (APCI) m/z 491 $[M+H]^+$. A portion of this material (300 mg, 0.61 mmol) was dissolved in THF (5 mL) and treated sequentially with 2,6-lutidine (98 mg, 0.91 mmol) and neat methanesulfonyl chloride (77 mg, 0.67 mmol). The resulting mixture was allowed to stir at rt overnight. The reaction mixture was concentrated to an oil and partitioned between EtOAc and sat. NaHCO_3 . The organic layer was separated, washed with sat. NH_4Cl , dried (Na_2SO_4), and concentrated to give ((4R,6R)-6-{2-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(methanesulfonylamino-methyl)-imidazol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester as a crude solid; Low resolution mass spectroscopy (APCI) m/z 568 $[M+H]^+$. The crude amide was taken up in CH_2Cl_2 (4 mL) and treated with neat TFA (1 mL). The reaction mixture was allowed to stir at rt for 120 min then diluted with trifluoromethylbenzene (5 mL) and concentrated to a crude oil. The oil was partitioned between EtOAc and water. The aqueous layer was carefully adjusted to pH ~8 by the addition of sat. NaHCO_3 and the organic layer was separated, washed with sat. NH_4Cl , dried (Na_2SO_4), and concentrated to a crude solid. Purification by flash chromatography [SiO_2 , MeOH/EtOAc 0-10%] provided the desired lactone a cream colored solid that was placed under high vacuum (overnight); yield: 63mg (22 %); Low resolution mass spectroscopy (APCI) m/z 454 $[M+H]^+$; Anal. Calcd. For $\text{C}_{21}\text{H}_{28}\text{F}_1\text{N}_3\text{O}_5\text{S}_1$ 0.2 $\text{C}_4\text{H}_8\text{O}_2$: C, 55.57; H, 6.33; N, 8.92. Found: C, 55.76; H, 6.22; N, 8.77.

Step D

A solution of N-{2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazol-4-ylmethyl}-methanesulfonamide (58 mg, 0.12 mmol) in THF (5 mL) was treated with aqueous NaOH (1.12 mL, 0.12 mmol, 0.114M). The reaction was allowed to stir at rt and monitored by HPLC for the consumption of SM. The sample was concentrated to approximately 2 mL total volume, then diluted with water (5 mL) and lyophilized to give a colorless powder; Yield: 63 mg (100%); Low resolution mass spectroscopy (APCI) m/z 472 $[M+H]^+$; Anal. Calcd. For $\text{C}_{21}\text{H}_{29}\text{F}_1\text{N}_3\text{Na}_1\text{O}_6\text{S}_1$ 1.5 H_2O : C, 48.45; H, 6.20; N, 8.07. Found: C, 48.44; H, 6.13; N, 7.92.

Example 95

2-(4-Fluoro-phenyl)-N-{2-(4-fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazol-4-ylmethyl}-acetamide



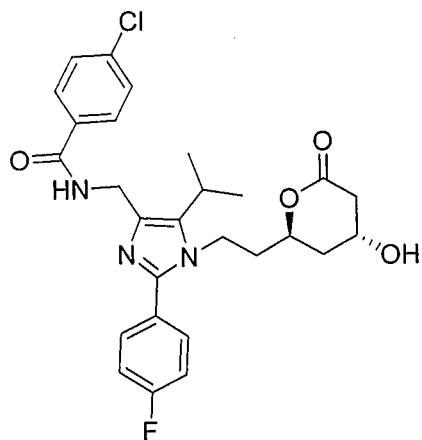
Starting from ((4R, 6R)-6-{2-[2-(4-Fluoro-phenyl)-4-formyl-5-isopropyl-imidazol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester, this compound was prepared in a manner similar to that described for Example 94,

Step C.

Low resolution mass spectroscopy (APCI) m/z 512 $[M+H]^+$;

Example 96

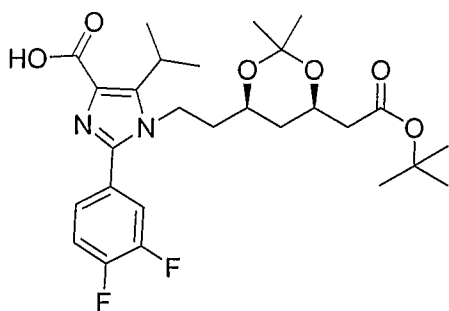
4-Chloro-N-[2-(4-fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazol-4-ylmethyl]-benzamide



Starting from ((4R, 6R)-6-{2-[2-(4-Fluoro-phenyl)-4-formyl-5-isopropyl-imidazol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester, this compound was prepared in a manner similar to that described for Example 94, Step C. Low resolution mass spectroscopy (APCI) m/z 514 $[M+H]^+$; Anal. Calcd. For $C_{27}H_{29}ClF_1N_3O_4$: C, 63.09; H, 5.69; N, 8.18. Found: C, 62.96; H, 5.66; N, 8.17.

Example 97

1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl)-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(3,4-difluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid

**Step A**2-(3,4-Difluoro-benzoylamino)-4-methyl-3-oxo-pentanoic acid benzyl ester

Starting from 2-Amino-4-methyl-3-oxo-pentanoic acid benzyl ester hydrochloride, the above named compound was prepared by following a process analogous to the one described in Example 3, Step C. Recrystallization from hot MTBE-hexanes gives the desired product as a colorless solid. Yield (84%); Low resolution mass spectroscopy (APCI) m/z 376 $[M+H]^+$; Anal. Calcd. For $C_{20}H_{19}F_2N_1O_4$: C, 64.00; H, 5.10; N, 3.73. Found: C, 64.01, H, 5.01; N, 3.75.

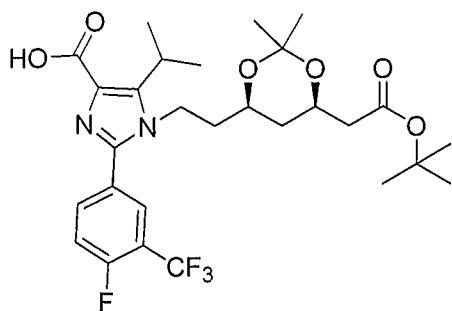
Step B1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(3,4-difluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid benzyl ester

Starting from 2-(3,4-Difluoro-benzoylamino)-4-methyl-3-oxo-pentanoic acid benzyl ester (3.0g, 8.0 mmol) the above named compound was prepared by following a process analogous to the one described in Example 3, Step D. Purification by flash chromatography (SiO_2 , EtOAc/Hexanes 10-50 %) gave the desired product as an amber glass. Yield: 2.2g (44%); Low resolution mass spectroscopy (APCI) m/z 613 $[M+H]^+$; Anal. Calcd. For $C_{27}H_{37}F_2N_2O_6$: C, 66.65; H, 6.91; N, 4.57. Found: C, 66.41, H, 6.93; N, 4.23.

Step C

Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(3,4-difluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid benzyl ester (2.1 g, 3.4 mmol), the title compound was prepared by following a process analogous to the one described in Example 2, Step F. Yield: 2.2g (44%); Low resolution mass spectroscopy (APCI) m/z 523 $[M+H]^+$; Anal. Calcd. For $C_{27}H_{36}F_2N_2O_6$: C, 62.06; H, 6.94; N, 5.36. Found: C, 62.44; H, 7.02; N, 5.09.

Example 981-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-3-trifluoromethyl-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid

**Step A**2-(4-fluoro-3-trifluoromethyl-benzoylamino)-4-methyl-3-oxo-pentanoic acid benzyl ester

Starting from 2-Amino-4-methyl-3-oxo-pentanoic acid benzyl ester hydrochloride the above named compound was prepared by following a process analogous to the one described in Example 3, Step C. Recrystallization from hot MTBE-hexanes gives the desired product as a colorless solid. Yield: (48%); Low resolution mass spectroscopy (APCI) m/z 426 $[M+H]^+$; Anal. Calcd. For $C_{21}H_{19}F_4N_1O_4$: C, 59.30; H, 4.50; N, 3.29. Found: C, 59.00; H, 4.41; N, 3.36.

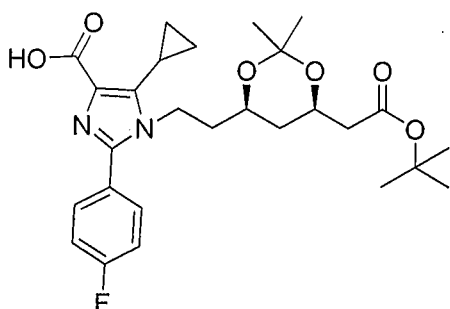
Step B1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-3-trifluoromethyl-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid benzyl ester

Starting with 2-(4-fluoro-3-trifluoromethyl-benzoylamino)-4-methyl-3-oxo-pentanoic acid benzyl ester (3.5 g, 8.2 mmol) the above named compound was prepared by following a process analogous to the one described in Example 3, Step D. Purification by flash chromatography (SiO_2 , EtOAc/Hexanes 25-40 %) gave the desired product as a colorless foam. Yield: 3.3 g (61%); Low resolution mass spectroscopy (APCI) m/z 663 $[M+H]^+$; Anal. Calcd. For $C_{35}H_{42}F_4N_2O_6$: C, 63.43; H, 6.39; N, 4.23. Found: C, 63.42; H, 6.39; N, 4.13.

Step C

Starting with 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-3-trifluoromethyl-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid benzyl ester (3.2 g, 4.8 mmol), the title compound was prepared by following a process analogous to the one described in Example 2, Step F. Yield: 2.6g (94%); Low resolution mass spectroscopy (APCI) m/z 573 $[M+H]^+$; Anal. Calcd. For $C_{27}H_{36}F_2N_2O_6$: C, 58.73; H, 6.34; N, 4.89. Found: C, 58.82; H, 6.37; N, 4.69.

Example 991-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-5-cyclopropyl-2-(4-fluoro-phenyl)-1H-imidazole-4-carboxylic acid

**Step A**3-Cyclopropyl-2-(4-fluorobenzoylamino)-3-oxo-propionic acid benzyl ester

A 500 mL round-bottomed flask was charged with potassium *tert*-butoxide (9.4 g, 83 mmol) and THF (150 mL). The solution was cooled, under nitrogen, in an ice-brine bath and treated with a solution of (Benzhydrylidene-amino)-acetic acid benzyl ester (25.0 g, 79.5 mmol) in THF (150 mL). The red-orange solution was stirred for 1 h at 0 °C and then cannulated into a -78 °C solution of cyclopropanecarbonyl chloride (8.33g, 79.7 mmol) in THF (400 mL). The resulting mixture was stirred for 2 h at -78 °C, then quenched with 3M HCl (75 mL, 225 mmol). The cold bath was removed and the reaction mixture was allowed to stand overnight. The reaction mixture was concentrated in vacuo to produce an oily yellow residue. The residue was dissolved in water (200 mL) and extracted with hexanes (2 x 100 mL). The aqueous layer was adjusted to pH >8 by the careful addition of solid NaHCO₃. EtOAc was added (300 mL), the biphasic mixture was cooled in an ice-brine bath, and the cooled mixture was treated with 4-fluorobenzoyl chloride (12.6g, 79.7 mmol). The reaction mixture was allowed to warm to rt and left to stand overnight. The organic layer was separated, washed with 1 M HCl and sat. NH₄Cl, dried (Na₂SO₄), and concentrated to a crude oil that solidified on standing. The crude product was recrystallized from a minimum of hot 95% EtOH to give colorless needles that were collected by vacuum filtration. The purified material was dried *in vacuo*.

Yield: 14.2g (52%); mp = 94.5-96 °C; Low resolution mass spectroscopy (APCI) *m/z* 354[M+H]⁺; Anal. Calcd. For C₂₀H₁₈F₁N₁O₄. Theory: C, 67.67; H, 5.11; N, 3.94. Found: C, 67.48; H, 5.12; N, 3.90.

Step B1-[2-((4R,6R)-6-*tert*-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-cyclopropyl-1H-imidazole-4-carboxylic acid benzyl ester

A mixture of 3-Cyclopropyl-2-(4-fluorobenzoylamino)-3-oxo-propionic acid benzyl ester (6.0 g, 17 mmol), [(4R,6R)-6-(2-Amino-ethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid *tert*-butyl ester (TBIA) (9.2 g, 33.8 mmol), benzoic acid (6.19 g, 50.7 mmol), and *p*-toluenesulfonic acid (0.29 g, 1.7 mmol) in *n*-heptane (150 mL) was heated to reflux for 65 h with the removal of water (Dean-Stark trap). The reaction mixture was cooled, diluted with EtOAc (100 mL), and washed with 1M NaOH (2 X 150 mL) and sat NH₄Cl, dried (Na₂SO₄) and concentrated to a yellow-brown oil. Purification by flash chromatography [SiO₂, Ethyl Acetate/hexanes 10-50%] provides the desired product as a yellow glass that was dried under high

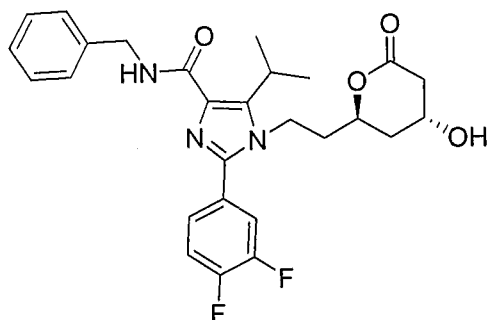
vacuum. Yield: 2.1 g (21 %); Low resolution mass spectroscopy (APCI) m/z 593 $[M+H]^+$; Anal. Calcd. For $C_{34}H_{41}F_1N_2O_6$: C, 68.90; H, 6.97; N, 4.73. Found: C, 68.66; H, 7.01; N, 4.64.

Step C

Starting with 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluorophenyl)-5-cyclopropyl-1H-imidazole-4-carboxylic acid benzyl ester (2.0 g, 3.4 mmol), the title compound was prepared by following a process analogous to the one described in Example 2, Step F. Yield: 1.69 g (99%); Low resolution mass spectroscopy (APCI) m/z 503 $[M+H]^+$; Anal. Calcd. For $C_{27}H_{35}F_1N_2O_6$: C, 64.53; H, 7.02; N, 5.57. Found: C, 63.99; H, 7.38; N, 5.25.

Example 100

2-(3,4-Difluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid benzylamide

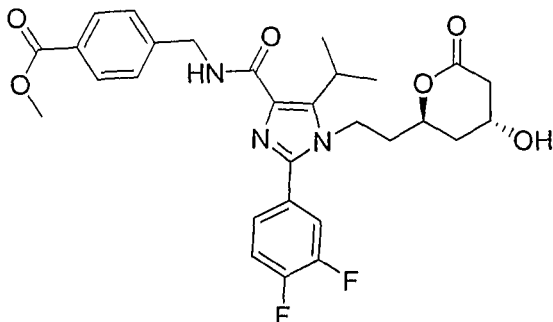


A rt solution 1-[2-((4R, 6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(3,4-difluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid (522 mg, 1.0 mmol) in dry DMF (20 mL) was treated with EDCI (290 mg, 1.5 mmol) and HOBt (200 mg, 1.5 mmol). After stirring for 20 min, neat benzyl amine (128 mg, 1.2 mmol) was added and the reaction was allowed to stir at rt overnight. An LC-MS analysis of the crude reaction mixture indicates a mass corresponding to the expected product $[M+H]^+ = 612$. The reaction mixture was poured into water (150 mL) and extracted with EtOAc (3X). The extracts were combined, washed with water (2X) and sat. NH_4Cl (2X), dried (Na_2SO_4) and concentrated to a colorless foam. The crude amide was taken up in CH_2Cl_2 (20 mL), treated with neat TFA (5 mL), and allowed to stir at rt for 30 min at which time an LC-MS analysis indicated no remaining SM and a new mass corresponding to the expected lactone $[M+H]^+ = 498$. The reaction mixture was concentrated to dryness and residue was partitioned between EtOAc and 1 M $NaHCO_3$ (pH ~ 8). The organic layer was separated, washed with sat. NH_4Cl , dried (Na_2SO_4), and concentrated to an oil.

Purification by flash chromatography (silica, EtOAc/hexanes 50-100%) provides the lactone as a colorless glass. Yield: 302 mg (61%); Low resolution mass spectroscopy (APCI) m/z 498 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ 1.44 (d, $J=1.46$ Hz, 3 H), 1.46 (d, $J=1.46$ Hz, 3 H), 1.63 (ddd, $J=14.40, 11.23, 3.17$ Hz, 1 H), 1.74 (m, 1 H), 1.88 (m, 2 H), 2.38 (ddd, $J=17.58, 3.66, 1.71$ Hz, 1 H), 2.56 (dd, $J=17.58, 4.64$ Hz, 1 H), 3.27 (d, $J=3.17$ Hz, 1 H), 3.35 (m, 1 H), 4.16 (m, 3 H), 4.50 (m, 3 H), 7.30 (m, 7 H), 7.50 (m, 1 H), 7.95 (br t, $J=6.35$ Hz, 1 H).

Example 101

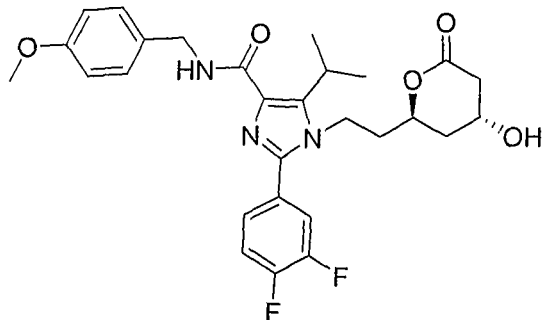
4-[(2-(3,4-Difluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carbonyl)-amino)-methyl]-benzoic acid methyl ester



Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(3,4-difluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid (522 mg, 1.0 mmol) the title compound was prepared in a manner similar to that described for Example 100. Yield: 332 mg (59%); Low resolution mass spectroscopy (APCI) m/z 556 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ 1.45 (d, $J=1.71$ Hz, 3 H), 1.46 (d, $J=1.46$ Hz, 3 H), 1.65 (ddd, $J=14.40, 11.47, 3.17$ Hz, 1 H), 1.76 (m, 1 H), 1.90 (m, 2 H), 2.39 (ddd, $J=17.58, 3.42, 1.71$ Hz, 1 H), 2.58 (dd, $J=17.33, 4.39$ Hz, 1 H), 3.26 (d, $J=2.93$ Hz, 1 H), 3.36 (m, 1 H), 3.85 (s, 3 H), 4.17 (m, 3 H), 4.51 (m, 1 H), 4.56 (d, $J=6.35$ Hz, 2 H), 7.39 (m, 4 H), 7.52 (m, 1 H), 7.94 (m, 2 H), 8.06 (br t, 1 H).

Example 102

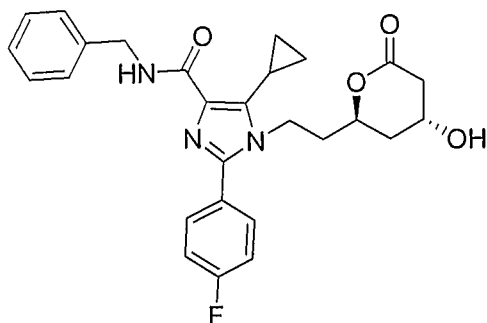
2-(3,4-Difluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 4-methoxy-benzylamide



Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(3,4-difluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid (522 mg, 1.0 mmol) the title compound was prepared in a manner similar to that described for Example 100. Yield: 335mg (63%); Low resolution mass spectroscopy (APCI) m/z 528 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ 1.45 (d, $J=1.46$ Hz, 3 H), 1.47 (d, $J=1.46$ Hz, 3 H), 1.64 (ddd, $J=14.40, 11.23, 2.93$ Hz, 1 H), 1.75 (m, 1 H), 1.88 (m, 2 H), 2.39 (ddd, $J=17.33, 3.42, 1.46$ Hz, 1 H), 2.57 (dd, $J=17.58, 4.64$ Hz, 1 H), 3.28 (d, $J=3.17$ Hz, 1 H), 3.36 (m, 1 H), 3.75 (m, 3 H), 4.17 (m, 3 H), 4.41 (d, $J=6.35$ Hz, 2 H), 4.51 (ddd, $J=15.87, 8.06, 3.91$ Hz, 1 H), 6.87 (m, 2 H), 7.25 (m, 2 H), 7.37 (m, 2 H), 7.50 (m, 1 H), 7.89 (br t, $J=6.35$ Hz, 1 H).

Example 103

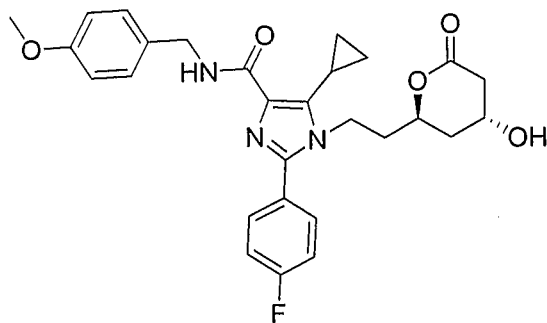
5-Cyclopropyl-2-(4-fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-1H-imidazole-4-carboxylic acid benzylamide



Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-5-cyclopropyl-2-(4-fluoro-phenyl)-1H-imidazole-4-carboxylic acid (4.85 g, 9.65 mmol) the title compound was prepared in a manner similar to that described for Example 100. Yield: 2.11 g (42%); Low resolution mass spectroscopy (APCI) m/z 478 $[M+H]^+$; Anal. Calcd. For $C_{27}H_{28}F_1N_3O_2/0.40 C_4H_8O_2$: C, 66.99; H, 6.13; N, 8.19. Found: C, 66.63; H, 6.10; N, 8.22.

Example 104

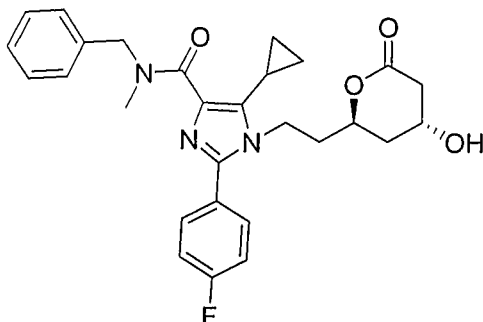
5-Cyclopropyl-2-(4-fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-1H-imidazole-4-carboxylic acid 4-methoxybenzylamide



Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-5-cyclopropyl-2-(4-fluoro-phenyl)-1H-imidazole-4-carboxylic acid (500 mg, 1.0 mmol) the title compound was prepared in a manner similar to that described for Example 100. Yield: 243 mg (48%); Low resolution mass spectroscopy (APCI) m/z 508 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ 0.97 (m, 2 H), 1.06 (m, 2 H), 1.63 (ddd, $J=14.40, 11.23, 3.17$ Hz, 1 H), 1.76 (m, 2 H), 1.94 (obscured m, 2 H), 2.39 (ddd, $J=17.57, 3.66, 1.71$ Hz, 1 H), 2.57 (dd, $J=17.33, 4.64$ Hz, 1 H), 3.26 (d, $J=2.44$ Hz, 1 H), 3.75 (s, 3 H), 4.16 (m, $J=2.44$ Hz, 1 H), 4.29 (m, 2 H), 4.40 (d, $J=6.34$ Hz, 2 H), 4.50 (m, 1 H), 6.87 (m, 2 H), 7.23 (m, 4 H), 7.60 (m, 2 H), 7.76 (br t, $J=5.86$ Hz, 1 H).

Example 105

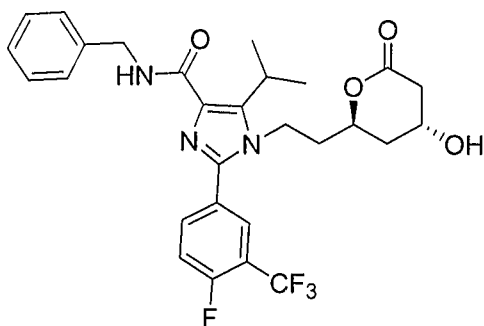
5-Cyclopropyl-2-(4-fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-1H-imidazole-4-carboxylic acid benzyl-methyl-amide



Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-5-cyclopropyl-2-(4-fluoro-phenyl)-1H-imidazole-4-carboxylic acid (700 mg, 1.39 mmol) the title compound was prepared in a manner similar to that described for Example 100. Yield: 298 mg (43%); Low resolution mass spectroscopy (APCI) m/z 492 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ 0.66 (m, 2 H), 0.94 (m, 2 H), 1.72 (m, 3 H), 1.97 (m, 2 H), 2.40 (m, 1 H), 2.58 (ddd, $J=17.34, 4.64, 3.17$ Hz, 1 H), 2.93 (d, $J=5.37$ Hz, 3 H), 3.32 (br t, $J=3.42$ Hz, 1 H), 4.24 (m, 3 H), 4.55 (m, 1 H), 4.68 (d, $J=7.33$ Hz, 2 H), 7.25 (m, 5 H), 7.39 (d, $J=4.15$ Hz, 2 H), 7.62 (m, 2 H).

Example 106

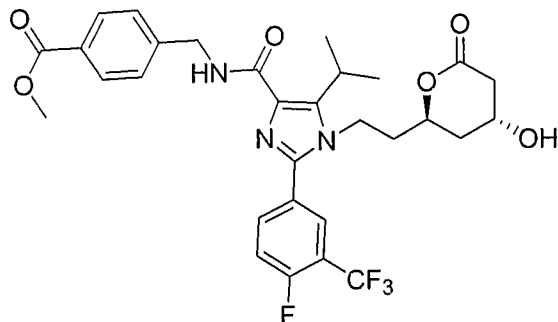
2-(4-Fluoro-3-trifluoromethyl-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid benzylamide



Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-3-trifluoromethyl-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid (500 mg, 0.87 mmol) this compound was prepared in a manner similar to that described for Example 100. Yield: 167 mg (35%); Low resolution mass spectroscopy (APCI) m/z 548 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ 1.46 (d, $J=1.46$ Hz, 3 H), 1.48 (d, $J=1.71$ Hz, 3 H), 1.63 (ddd, $J=14.40, 11.47, 2.93$ Hz, 1 H), 1.75 (m, 2 H), 1.90 (m, 1 H), 2.38 (ddd, $J=17.58, 3.42, 1.71$ Hz, 1 H), 2.56 (dd, $J=17.58, 4.64$ Hz, 1 H), 3.32 (m, 1 H), 3.37 (m, 1 H), 4.18 (m, 3 H), 4.49 (m, 3 H), 7.23 (m, 1 H), 7.30 (m, 4 H), 7.42 (m, 1 H), 7.86 (m, 1 H), 7.91 (m, 1 H), 8.01 (t, $J=6.35$ Hz, 1 H).

Example 107

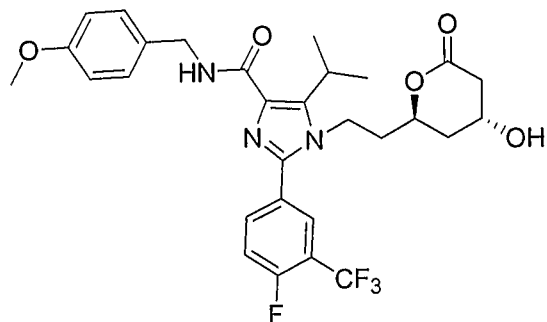
4-[(2-(4-Fluoro-3-trifluoromethyl-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carbonyl)-amino)-methyl]-benzoic acid methyl ester



Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-3-trifluoromethyl-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid (500 mg, 0.87 mmol) this compound was prepared in a manner similar to that described for Example 100. Yield: 186 mg (35%); Low resolution mass spectroscopy (APCI) m/z 606 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ 1.45 (d, $J=2.20$ Hz, 3 H), 1.47 (d, $J=2.20$ Hz, 3 H), 1.64 (ddd, $J=14.16$, 11.23, 2.93 Hz, 1 H), 1.75 (d, 1 H), 1.90 (m, 2 H), 2.38 (ddd, $J=17.58$, 3.42, 1.71 Hz, 1 H), 2.56 (dd, $J=17.33$, 4.39 Hz, 1 H), 3.36 (m, 2 H), 3.83 (s, 3 H), 4.18 (m, 3 H), 4.50 (m, 3 H), 7.39 (m, 3 H), 7.86 (ddd, $J=7.32$, 4.88, 1.95 Hz, 1 H), 7.90 (m, 3 H), 8.19 (t, $J=6.35$ Hz, 1 H).

Example 108

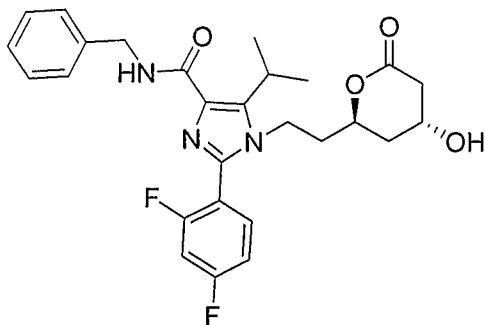
2-(4-Fluoro-3-trifluoromethyl-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 4-methoxy-benzylamide



Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-3-trifluoromethyl-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid (500 mg, 0.87 mmol) this compound was prepared in a manner similar to that described for Example 100. Yield: 239 mg (47%); Low resolution mass spectroscopy (APCI) m/z 578 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ 1.46 (d, $J=1.71$ Hz, 3 H), 1.48 (d, $J=1.71$ Hz, 3 H), 1.63 (ddd, $J=14.28$, 11.35, 2.93 Hz, 1 H), 1.74 (m, 1 H), 1.89 (m, 2 H), 2.38 (ddd, $J=17.58$, 3.42, 1.71 Hz, 1 H), 3.35 (m, 1 H), 3.40 (d, $J=3.17$ Hz, 1 H), 3.74 (s, 3 H), 4.16 (m, 3 H), 4.40 (d, $J=6.35$ Hz, 2 H), 4.49 (m, 1 H), 6.84 (m, 2 H), 7.22 (m, 2 H), 7.41 (dd, $J=10.25$, 8.79 Hz, 1 H), 7.85 (m, 1 H), 7.90 (dd, $J=6.84$, 2.20 Hz, 1 H), 7.97 (t, $J=6.23$ Hz, 1 H).

Example 109

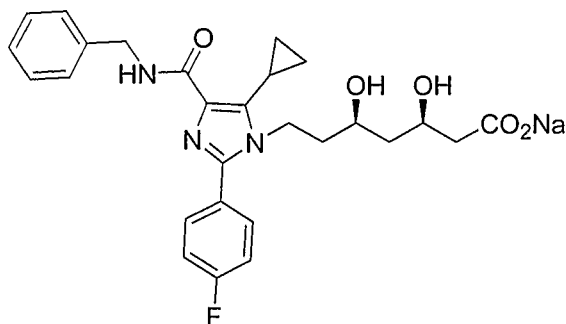
2-(2,4-Difluoro-phenyl)-5-isopropyl-1-[2-((S)-6-oxo-3,6-dihydro-2H-pyran-2-yl)-ethyl]-1H-imidazole-4-carboxylic acid benzylamide



Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(2,4-difluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid (234 mg, 0.44 mmol) this compound was prepared in a manner similar to that described for Example 100. Yield: 121 mg (54%); Low resolution mass spectroscopy (APCI) m/z 498 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ ppm (d, $J=7.08$ Hz, 6 H), 1.59 (ddd, $J=14.28, 11.35, 3.17$ Hz, 1 H), 1.70 (m, $J=14.31, 3.59, 3.59, 1.95$ Hz, 1 H), 1.82 (m, 2 H), 2.37 (ddd, $J=17.46, 3.54, 1.46$ Hz, 1 H), 2.55 (dd, $J=17.33, 4.64$ Hz, 1 H), 3.12 (s, 1 H), 3.39 (m, 1 H), 4.04 (m, 2 H), 4.14 (m, 1 H), 4.44 (m, 1 H), 4.50 (d, $J=6.35$ Hz, 2 H), 7.10 (m, 2 H), 7.24 (m, 1 H), 7.32 (m, 4 H), 7.48 (m, 1 H), 7.90 (br t, $J=6.10$ Hz, 1 H).

Example 110

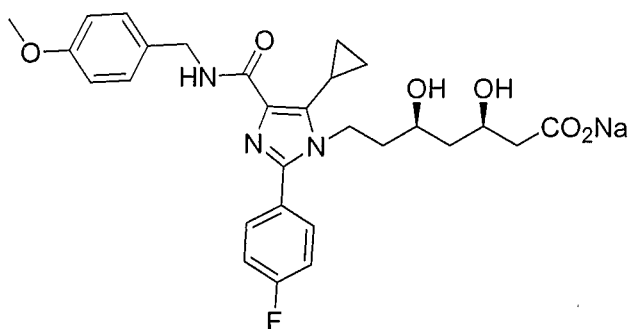
Sodium; (3R,5R)-7-[4-Benzylcarbamoyl-5-cyclopropyl-2-(4-fluoro-phenyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Starting from 5-Cyclopropyl-2-(4-fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-1H-imidazole-4-carboxylic acid benzylamide (1.52 g, 3.18 mmol) the title compound was prepared in a manner similar to that described for Example 4, step C. Yield: 1.69g (100%); Low resolution mass spectroscopy (APCI) m/z 496 $[M+H]^+$; Anal. Calcd. For $C_{27}H_{29}F_1N_3Na_1O_5/1.4H_2O$: C, 59.75; H, 5.91; N, 7.74. Found: C, 59.75; H, 5.75; N, 7.65.

Example 111

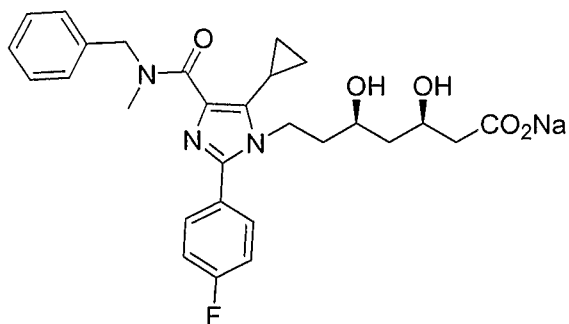
Sodium; (3R,5R)-7-[5-Cyclopropyl-2-(4-fluoro-phenyl)-4-(4-methoxy-benzylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Starting from 5-Cyclopropyl-2-(4-fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-1H-imidazole-4-carboxylic acid 4-methoxybenzylamide (1.66 g, 3.28 mmol) the title compound was prepared in a manner similar to that described for Example 4, step C. Yield: 1.79 g (99%); Low resolution mass spectroscopy (APCI) m/z 526 $[M+H]^+$; Anal Calcd. For $C_{26}H_{31}F_1N_3Na_1O_6/0.9 H_2O$: C, 59.65; H, 5.86; N, 7.45. Found: C, 59.69; H, 5.79; N, 7.40.

Example 112

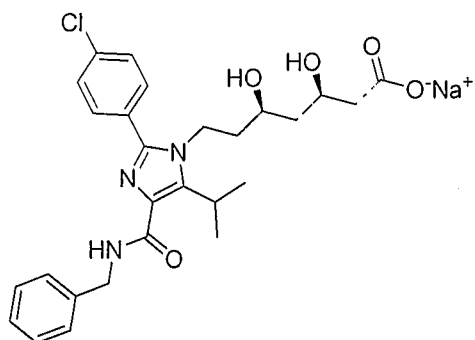
Sodium; (3R,5R)-7-[4-(Benzyl-methyl-carbamoyl)-5-cyclopropyl-2-(4-fluoro-phenyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Starting from 5-Cyclopropyl-2-(4-fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-1H-imidazole-4-carboxylic acid benzyl-methyl-amide (288 mg, 0.58 mmol) the title compound was prepared in a manner similar to that described for Example 4, step C. Yield: 305 mg (97%); Low resolution mass spectroscopy (APCI) m/z 510 $[M+H]^+$; Anal. Calcd. For $C_{28}H_{31}F_1N_3Na_1O_5/1.9H_2O$: C, 59.44; H, 6.20; N, 7.43. Found: C, 59.43; H, 5.93; N, 7.39.

Example 113

Sodium; (3R,5R)-7-[4-benzylcarbamoyl-2-(4-chloro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate

**Step A**(Benzhydrylidene-amino)-acetic acid methyl ester

Combined benzophenone imine (51 g, 273 mmol, Aldrich Chemical Co.), glycine methylester hydrochloride (35 g, 279 mmol, Aldrich Chemical Co.) and dichloromethane (340 ml) in a 500 ml round bottom flask under argon atmosphere. Stirred mixture 72 hours at rt. Removed solids by vacuum filtration, washing with diethyl ether. Concentrated solution to a pale yellow oil under reduced pressure. Diluted oil with diethyl ether (250 ml), washed twice with water, dried over sodium sulfate, filtered and concentrated to a pale yellow syrup. Product precipitates under vacuum drying to yield 64.9 g pale yellow prismatic crystals. MS (APCI) m/z 254 $[M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ ppm 3.73 (s, 3H), 4.21 (s, 2H), 7.17 (m, 2H), 7.29-7.51 (m, 6H), 7.66 (m, 2H).

Step B2-(4-Chloro-benzoylamino)-4-methyl-3-oxo-pentanoic acid methyl ester

To a 3-neck round bottom flask (equipped with overhead stirrer, N_2 line and thermocouple) charged with potassium tert-butoxide (124 ml, 1.0 M in THF, Aldrich Chemical Co.) at $-30^\circ C$ was added (Benzhydrylidene-amino)-acetic acid methyl ester (21 g, 82.9 mmol). The reaction mixture was stirred at $-30^\circ C$ for 30 minutes under nitrogen positive pressure, then isobutyryl chloride (9.9 g, 91.2 mmol in 20 ml THF) was added via pressure equalizing addition funnel, dropwise, over 30 minutes. The reaction was stirred another 1 hour at the cold temperature then quenched with HCl (55 ml, 3.0 M). The precipitated yellow slurry was stirred 15 minutes, then concentrated under reduced pressure to a minimum volume. The residue was diluted with water (30 ml) and this mixture washed twice with diethyl ether (150 ml). The aqueous phase was returned to the 3-neck reaction flask, cooled to $2^\circ C$ and made basic (pH 9) by slow addition of neat sodium bicarbonate. Added ethyl acetate (150 ml), equilibrated mixture to $2^\circ C$ with stirring, then added 4-Chlorobenzoyl chloride (15.4 g, 87.1 mmol in 5 ml THF) via pressure equalizing funnel to maintain temperature below $5^\circ C$. After 40 minutes stirring, warmed mixture to rt and transferred to a separation funnel. Removed aqueous phase and discarded. Washed organic phase with water, brine, dried over sodium sulfate, filtered and concentrated to a yellow powder. Purification by flash chromatography (SiO_2 , 15%-60% ethyl acetate in hexanes) yielded 12.05 g fluffy white powder as desired product. MS (APCI) m/z 298 $[M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ ppm 1.14 (d, $J = 6.8$ Hz, 3H), 1.24 (d, $J = 7.1$ Hz, 3H), 3.13 (septet, $J = 6.8$ Hz, 1H), 3.83 (s, 3H), 5.58 (d, $J = 6.8$ Hz, 1H), 7.42 (m, 2H), 7.78 (m, 2H), 8.01 (m, partially exchanged H).

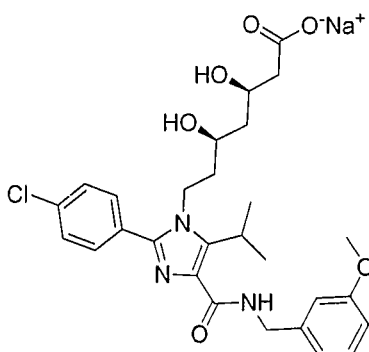
Step CN-(1-Benzylcarbamoyl-3-methyl-2-oxo-butyl)-4-chloro-benzamide

To a solution of 2-(4-Chloro-benzoylamino)-4-methyl-3-oxo-pentanoic acid methyl ester (12.0 g, 40.3 mmol) in N-Methylpyrrolidinone (70 ml) was added benzylamine (4.8 g, 44.3 mmol) and a catalytic amount of p-Toluenesulfonic acid. The mixture was stirred and heated to 160C for 2 hours, then cooled and poured into chilled water (500 ml). The resultant slurry was extracted twice with ethyl acetate (150 ml). The organic phase was washed twice with 5% HCl solution, once with saturated sodium bicarbonate solution, once with brine, dried over sodium sulfate, filtered and concentrated to an off-white powder. The powder was dried overnight in vacuum oven at 40C to a stable weight of 10.3 g of desired product and ester. (APCI) m/z 371 [M-H].

Step DSodium; (3R,5R)-7-[4-benzylcarbamoyl-2-(4-chloro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate

To a solution of N-(1-Benzylcarbamoyl-3-methyl-2-oxo-butyl)-4-chloro-benzamide (9.9 g, 26.7 mmol) in n-heptane (80 ml), was added [(4R,6R)-6-(2-Amino-ethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester (15 g, 53 mmol in 20 ml heptane), benzoic acid (9.8 g, 80 mmol) and a catalytic amount of p-toluenesulfonic acid. Attached Dean-Stark trap filled with heptane, condenser, nitrogen gas line and heated stirring mixture to reflux overnight. Cooled mixture to rt and concentrated under reduced pressure to a slurry. Dissolved mixture in ethyl acetate (100 ml), washed with saturated sodium bicarbonate solution (2 x 100 ml), water (3 x 100 ml), brine, dried over sodium sulfate, filtered and concentrated to a red-orange glass. Purified by flash chromatography (SiO₂, 10%-50% ethyl acetate in hexanes) to recover 4.8 g yellow glass as the protected imidazole amide. Dissolved glass in dichloromethane 25% trifluoroacetic acid (30 ml) and stirred at rt for 1.6 hours, then quenched and made basic with 1 M NaOH solution (pH 11). Concentrated product mixture to a minimum volume and purified by reverse phase (hemi-spherical C18, 100- 80% water/3% n-propanol in acetonitrile) and lyophilized to recover 1.92 g off-white powder as desired product. MS (APCI) m/z 514 [M+H]⁺; Anal. Calcd. for C₂₇H₃₁ClN₃NaO₅/1.0 H₂O: C, 58.53; H, 6.00; N, 7.58. Found: C, 58.49; H, 6.17; N, 7.40.

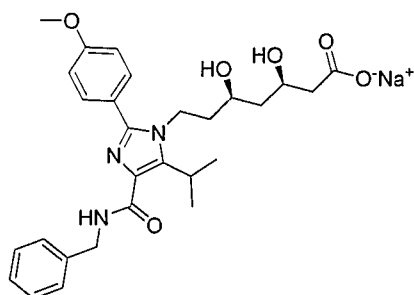
Example 114Sodium; (3R,5R)-7-[2-(4-chloro-phenyl)-5-isopropyl-4-(3-methoxy-benzylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Starting from 2-(4-Chloro-benzoylamino)-4-methyl-3-oxo-pentanoic acid methyl ester this compound was made in a similar manner as described for example 113_ (Steps C and D). MS (APCI) m/z 544 $[M+H]^+$; Anal. Calcd. for $C_{28}H_{33}ClN_3NaO_6/1.15 H_2O$: C, 57.32; H, 6.06; N, 7.16. Found: C, 57.22; H, 5.88; N, 7.01.

5 Example 115

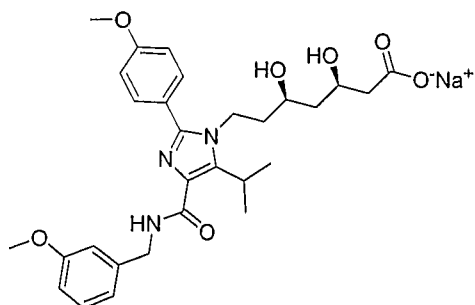
Sodium; (3R,5R)-7-[4-benzylcarbamoyl-5-isopropyl-2-(4-methoxy-phenyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate



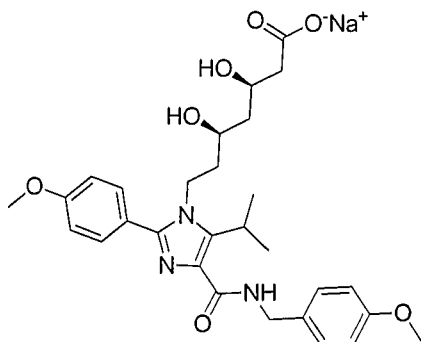
Starting from (Benzhydrylidene-amino)-acetic acid benzyl ester this compound was prepared in a similar manner as described for Example 113 (Steps B, C and D). MS (APCI) m/z 510 $[M+H]^+$; Anal. Calcd. for $C_{28}H_{34}N_3NaO_6/1.95 H_2O$: C, 59.34; H, 6.74; N, 7.41. Found: C, 59.36; H, 6.62; N, 7.33.

0 Example 116

Sodium; (3R,5R)-3,5-dihydroxy-7-[5-isopropyl-4-(3-methoxy-benzylcarbamoyl)-2-(4-methoxy-phenyl)-imidazol-1-yl]-heptanoate



Starting from (Benzhydrylidene-amino)-acetic acid benzyl ester, this compound was prepared in a similar manner as described for Example 113 (Steps B, C and D). MS (APCI) m/z 540 $[M+H]^+$; Anal. Calcd. for $C_{29}H_{36}N_3NaO_7/1.35 H_2O$: C, 59.45; H, 6.66; N, 7.17. Found: C, 59.37; H, 6.72; N, 7.16.

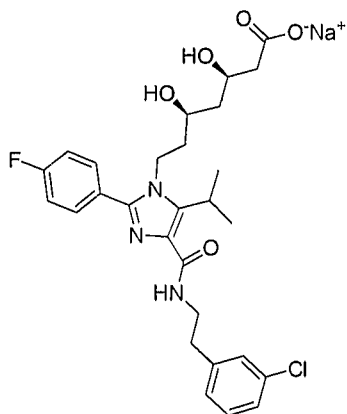
Example 117

Sodium;(3R,5R)-3,5-dihydroxy-7-[5-isopropyl-4-(4-methoxy-benzylcarbamoyl)-2-(4-methoxy-phenyl)-imidazol-1-yl]-heptanoate

Starting from (Benzhydrylidene-amino)-acetic acid methyl ester, this compound was prepared in a similar manner as described for Example 113 (Steps B, C and D). MS (APCI) m/z 540 $[M+H]^+$; Anal. Calcd. for $C_{29}H_{36}N_3NaO_7/1.30 H_2O$: C, 59.54; H, 6.65; N, 7.18. Found: C, 59.60; H, 6.74; N, 7.14.

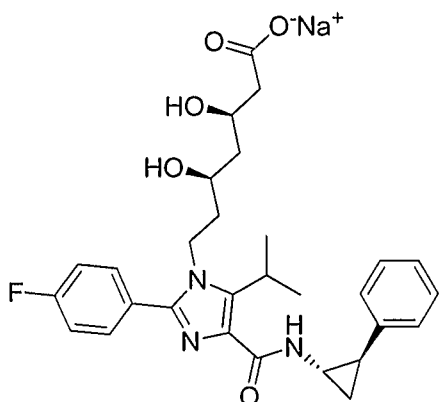
Example 118

Sodium;(3R,5R)-7-[4-[2-(3-chloro-phenyl)-ethylcarbamoyl]-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



A solution of 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid (300 mg, 0.59 mmol), EDCI (170 mg, 0.89 mmol), and HOBt-monohydrate (140 mg, 0.89 mmol), in dichloromethane (2 ml) was stirred at rt for 30 minutes. 2-(3-Chloro-phenyl)-ethylamine (102 mg, 0.66 mmol) was added and the resultant mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with saturated sodium bicarbonate and brine, dried (Na_2SO_4), filtered and concentrated to a yellow glass. The crude glass was dissolved in a 30% trifluoroacetic acid/ CH_2Cl_2 solution (4 ml) and stirred 1 hour. The reaction

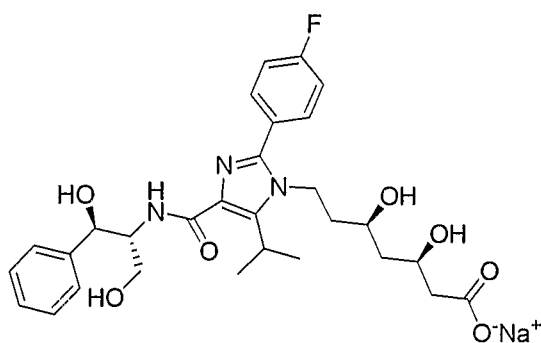
mixture was chilled (ice bath) diluted with water, made basic by the addition of 1 M NaOH, and concentrated under reduced pressure to a minimum volume. Purification by column chromatography (C18, CH₃CN/water, 0 to 80% (3% *n*-propanol)) and lyophilization gave the desired product as an off-white powder: Yield 233 mg ; MS (APCI) *m/z* 546 [M+H]⁺; Anal. Calcd. for C₂₈H₃₂Cl₁F₁N₃Na₁O₅/1.0 H₂O: C, 57.30; H, 5.71; N, 7.22. Found: C, 57.39; H, 5.85; N, 7.17.



Example 119

Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-((1S,2R)-2-phenylcyclopropylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxyheptanoate

Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for Example 118. MS (APCI) *m/z* 524 [M+H]⁺; Anal. Calcd. for C₂₉H₃₃F₁N₃Na₁O₅/1.2 H₂O: C, 61.41; H, 6.29; N, 7.41. Found: C, 61.20; H, 5.92; N, 7.44.



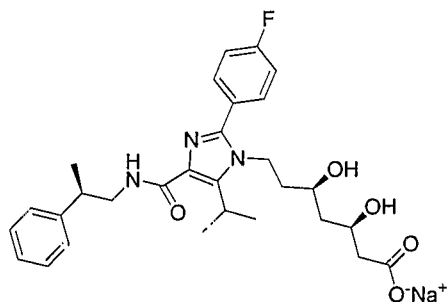
Example 120

Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-4-((1R,2R)-2-hydroxy-1-hydroxymethyl-2-phenylethylcarbamoyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxyheptanoate

Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for Example 118. MS (APCI) *m/z* 558 [M+H]⁺; ¹H NMR (400 MHz, Methanol-D₄)

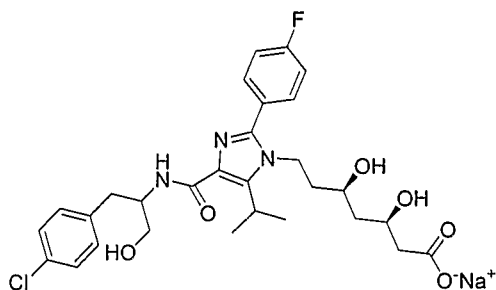
δ ppm 1.26 (d, *J* = 7.1 Hz, 3H), 1.35 (d, *J* = 7.1 Hz, 3H), 1.40 (dt, partially obscured, *J* = 9.4, 4.9 Hz, 1H), 1.51 (dt, *J* = 13.9, 8.1 Hz, 1H), 1.62 (m, 1H), 1.73 (m, 1H), 2.16 (dd, *J* = 15.1, 7.3 Hz, 1H), 2.22 (dd, *J* =

14.9, 5.4 Hz, 1H), 3.30 (septet, partially obscured, $J = 7.1$ Hz, 1H), 3.50 (dd, $J = 11.0, 5.6$ Hz, 1H), 3.66 (m, 2H), 3.93 (m, 2H), 4.13 (m, 2H), 4.93 (d, $J = 4.2$ Hz, 1H), 7.12 (m, 1H), 7.19 (m, 4H), 7.34 (m, 2H), 7.56 (m, 2H).

Example 121

Sodium; (3R,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-((R)-2-phenyl-propylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate

Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for Example 118. MS (APCI) m/z 526 $[M+H]^+$; Anal. Calcd. for $C_{29}H_{35}F_1N_3Na_1O_5/1.70$ H_2O : C, 60.24; H, 6.69; N, 7.27. Found: C, 60.00; H, 6.38; N, 7.15.

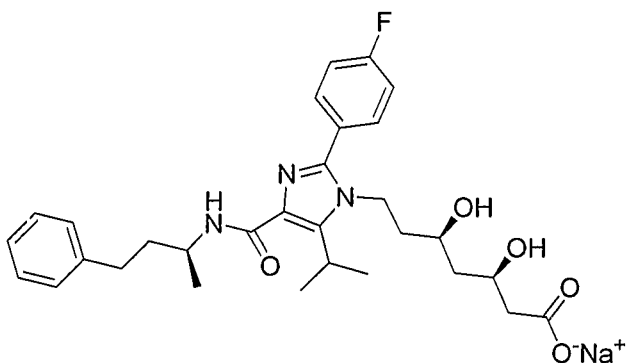
Example 122

Sodium; (3R,5R)-7-[4-[2-(4-chloro-phenyl)-1-hydroxymethyl-ethylcarbamoyl]-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate

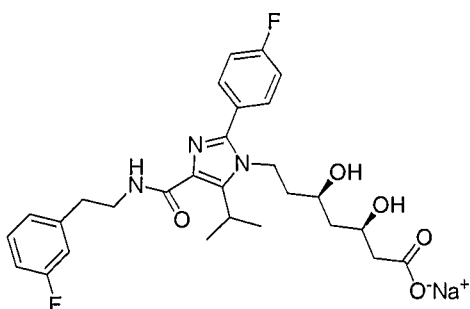
Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for Example 118. MS (APCI) m/z 576 $[M+H]^+$; Anal. Calcd. for $C_{29}H_{34}Cl_1F_1N_3Na_1O_6/1.34$ H_2O : C, 55.98; H, 5.94; N, 6.75. Found: C, 55.59; H, 5.94; N, 6.68.

Example 123

Sodium; (3R,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-((S)-1-methyl-3-phenyl-propylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for Example 118. MS (APCI) m/z 540 $[M+H]^+$; 1H NMR (400 MHz, Methanol-D₄) δ ppm 1.15 (d, J = 6.6 Hz, 3H), 1.39 (t, J = 4.9 Hz, 1H), 1.43 (dd, J = 6.8, 2.0 Hz, 6H), 1.51 (dt, J = 13.9, 8.2 Hz, 1H), 1.63 (m, 1H), 1.75 (m, 3H), 2.16 (dd, J = 15.2, 7.3 Hz, 1H), 2.22 (dd, J = 14.9, 5.1 Hz, 1H), 2.60 (m, 2H), 3.39 (septet, J = 7.1 Hz, 1H), 3.66 (m, 1H), 3.93 (m, 3H), 4.14 (ddd, J = 14.7, 11.1, 5.3 Hz, 1H), 7.01-7.23 (m, 7H), 7.55 (m, 2H).

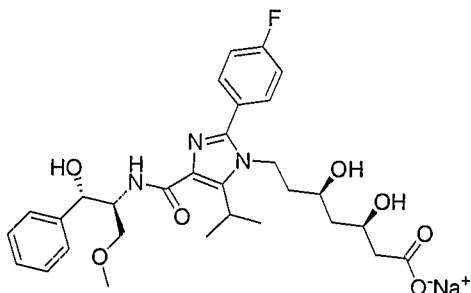
Example 124

Sodium; (3R,5R)-7-[2-(4-fluoro-phenyl)-4-[2-(3-fluoro-phenyl)-ethylcarbamoyl]-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate

Starting from 1-[2-((4R, 6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for Example 118 MS (APCI) m/z 530 $[M+H]^+$; 1H NMR (400 MHz, Methanol-D₄) δ ppm 1.39 (d, J = 7.1, Hz, 3H), 1.40 (d, J = 7.1, Hz, 3H), 1.42 (t, partially obscured, J = 4.9 Hz, 1H), 1.51 (dt, J = 13.9, 8.3 Hz, 1H), 1.62 (m, 1H), 1.74 (m, 1H), 2.16 (dd, J = 15.1, 7.3 Hz, 1H), 2.22 (dd, J = 15.1, 5.4 Hz, 1H), 2.81 (t, J = 7.3 Hz, 2H), 3.35 (septet, J = 6.8 Hz, 1H), 3.48 (t, J = 7.3 Hz, 2H), 3.66 (m, 1H), 3.93 (m, 2H),

4.13 (ddd, $J = 14.8, 11.1, 5.1$ Hz, 1H), 6.83 (td, $J = 8.6, 1.8$ Hz, 1H), 6.94 (dt, $J = 10.1, 1.9$ Hz, 1H), 7.00 (d, $J = 7.6$ Hz, 1H), 7.13-7.23 (m, 3H), 7.49-7.57 (m, 2H).

Example 125



Sodium; (3R,5R)-7-[2-(4-fluoro-phenyl)-4-((1S,2S)-2-hydroxy-1-methoxymethyl-2-phenyl-ethylcarbamoyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate

Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for Example 118 MS (APCI) m/z 572 $[M+H]^+$; 1H NMR (400 MHz, Methanol-D4)

δ ppm 1.30 (d, $J = 6.8$ Hz, 3H), 1.38 (d, $J = 6.8$ Hz, 3H), 1.43 (dt, $J = 13.9, 4.8$ Hz, 1H), 1.53 (dt, $J = 13.9, 8.1$ Hz, 1H), 1.64 (m, 1H), 1.76 (m, 1H), 2.18 (dd, $J = 15.1, 7.3$ Hz, 1H), 2.24 (dd, $J = 15.1, 5.4$ Hz, 1H), 3.28 (m, 4H), 3.32 (septet, partially obscured, $J = 6.8$ Hz, 1H), 3.53 (dd, $J = 9.5, 6.6$ Hz, 1H), 3.68 (m, 1H), 3.89-4.02 (m, 2H), 4.15 (m, 1H), 4.26 (td, $J = 6.0, 5.1, 4.8$ Hz, 1H), 4.90 (d, $J = 4.4$ Hz, 1H), 7.12-7.25 (m, 5H), 7.34 (apparent d, $J = 7.3$ Hz, 2H), 7.58 (m, 2H).

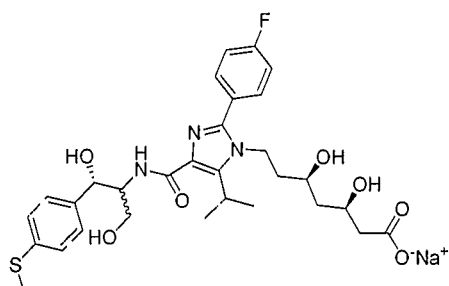
Example 126

Sodium; (3R,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-[2-(4-methoxy-phenyl)-ethylcarbamoyl]-imidazol-1-yl]-3,5-dihydroxy-heptanoate

Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for Example 118. MS (APCI) m/z 542 $[M+H]^+$; 1H NMR (400 MHz, Methanol-D4) δ ppm 1.40 (d, $J = 7.1$ Hz, 6H), 1.14 (m, partially obscured, 1H), 1.51 (dt, $J = 13.9, 8.1$ Hz, 1H), 1.64 (m, 1H), 1.73 (m, 1H), 2.16 (dd, $J = 15.1, 7.3$ Hz, 1H), 2.22 (dd, $J = 14.9, 5.1$ Hz, 1H), 2.72 (t, $J = 7.3$ Hz, 2H), 3.36 (septet, partially obscured, $J = 6.8$ Hz, 1H), 3.43 (t, $J = 7.4$ Hz, 2H), 3.66 (m, 4H), 3.91 (m, partially obscured, 1H), 3.98 (dd, $J = 10.7, 5.1$ Hz, 1H), 4.13 (ddd, $J = 16.1, 11.5, 5.1$ Hz, 1H), 6.75 (m, 2H), 7.1 (m, 2H), 7.17 (m, 2H), 7.52 (m, 2H).

Example 127

Sodium; (3R,5R)-7-[2-(4-fluoro-phenyl)-4-[(S)-2-hydroxy-1-hydroxymethyl-2-(4-methylsulfonyl-phenyl)-ethylcarbamoyl]-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate

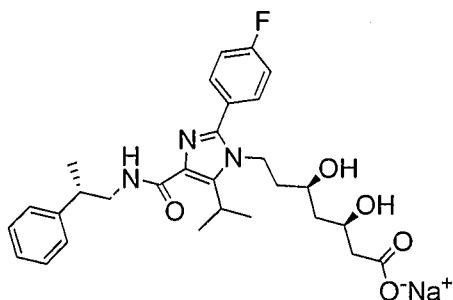


Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for Example 118. MS (APCI) m/z 604 $[M+H]^+$; 1H NMR (400 MHz, Methanol-D₄)

δ ppm 1.25 (dd, $J = 6.8, 4.9$ Hz, 3H), 1.36 (dd, $J = 7.1, 2.7$ Hz, 3H), 1.41 (m, 1H), 1.51 (m, 1H), 1.62 (m, 1H), 1.74 (m, 1H), 2.16 (ddd, $J = 15.1, 7.5, 1.6$ Hz, 1H), 2.22 (ddd, $J = 15.2, 5.4, 2.1$ Hz, 1H), 2.35 (d, $J = 2.9$ Hz, 3H), 3.29 (m, partially obscured, 1H), 3.52 (dd, $J = 11.1, 5.5$ Hz, 0.66H), 3.60 (dd, $J = 11.5, 4.2$ Hz, 0.33H), 3.68 (dd, partially obscured, $J = 11.2, 6.6$ Hz, 0.66H), 3.65 (m, obscured, 1H), 3.77 (dd, $J = 11.5, 5.9$ Hz, 0.33H), 3.87-4.01 (m, 2H), 4.07-4.21 (m, 2H), 4.91 (d, $J = 3.7$ Hz, 1H), 7.12 (m, 2H), 7.19 (m, 2H), 7.28 (m, 2H), 7.55 (m, 2H).

Example 128

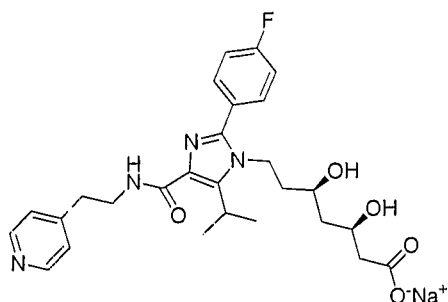
Sodium; (3R,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-((S)-2-phenyl-propylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for PF-02309081-02. MS (APCI) m/z 526 $[M+H]^+$; 1H NMR (400 MHz, Methanol-D₄) δ ppm 1.22 (d, $J = 6.8$ Hz, 3H), 1.36-1.44 (m, 7H), 1.51 (dt, $J = 13.9, 8.1$ Hz, 1H), 1.61 (m, 1H), 1.72 (m, 1H), 2.16 (dd, $J = 14.9, 7.3$ Hz, 1H), 2.22 (dd, $J = 15.1, 5.4$ Hz, 1H), 2.95 (sextet, $J = 7.1$ Hz, 1H), 3.28-3.50 (m, 3H), 3.65 (m, 1H), 3.91 (m, 1H), 3.97 (dd, $J = 10.9, 5.3$ Hz, 1H), 4.12 (ddd, $J = 14.8, 11.1, 5.1$ Hz, 1H), 7.06-7.25 (m, 7H), 7.50 (m, 2H), 7.63 (t, $J = 6.0$ Hz, partially exchanged amide H).

Example 129

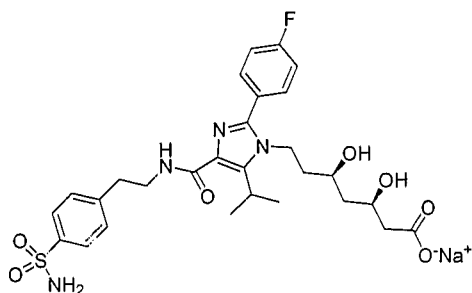
Sodium; (3R,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-(2-pyridin-4-yl-ethylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for Example 118. MS (APCI) m/z 513 $[M+H]^+$; Anal. Calcd. for $C_{27}H_{32}F_1N_4Na_1O_5/1.6 H_2O$: , 57.56; H, 6.30; N, 9.94. Found: C, 57.49; H, 6.00; N, 9.84.

Example 130

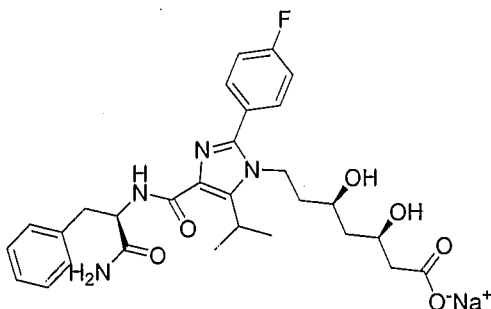
Sodium; (3R,5R)-7-{2-(4-fluoro-phenyl)-5-isopropyl-4-[2-(4-sulfamoyl-phenyl)-ethylcarbamoyl]-imidazol-1-yl}-3,5-dihydroxy-heptanoate



Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for Example 118. MS (APCI)⁺ m/z 591 $[M+H]^+$; ¹H NMR (400 MHz, Methanol-D₄) δ ppm 1.40 (d, J = 7.1 Hz, 3H), 1.40 (d, J = 7.1 Hz, 3H), 1.41 (m, partially obscured, 1H), 1.51 (dt, J = 13.8, 8.1 Hz, 1H), 1.62 (m, 1H), 1.74 (m, 1H), 2.16 (dd, J = 15.0, 7.3 Hz, 1H), 2.22 (dd, J = 15.0, 5.4 Hz, 1H), 2.88 (t, J = 7.3 Hz, 2H), 3.36 (septet, J = 7.1 Hz, 1H), 3.51 (t, J = 7.3 Hz, 2H), 3.66 (m, 1H), 3.91 (m, 1H), 3.98 (apparent dd, J = 10.9, 5.0 Hz, 1H), 4.13 (apparent ddd, J = 15.1, 11.2, 5.1 Hz, 1H), 7.17 (apparent t, J = 8.7 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.53 (m 2H), 7.74 (apparent d, J = 8.3 Hz, 2H).

Example 131

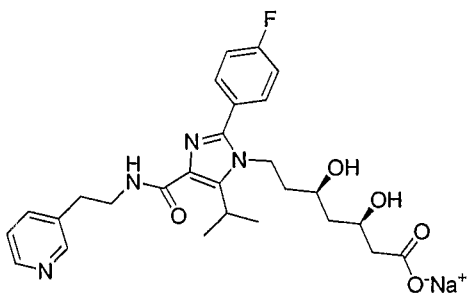
Sodium; (3R,5R)-7-[4-((R)-1-carbamoyl-2-phenyl-ethylcarbamoyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for Example 118. MS (APCI) m/z 555 $[M+H]^+$; Anal. Calcd. for $C_{29}H_{34}F_4N_4Na_1O_6/2.8 H_2O$: C, 55.55; H, 6.37; N, 8.94. Found: C, 55.20; H, 6.29; N, 8.77.

Example 132

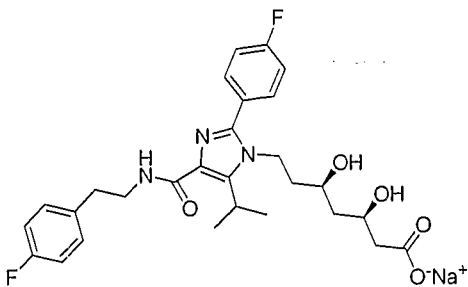
Sodium; (3R,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-(2-pyridin-3-yl-ethylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for Example 118. MS (APCI) m/z 513 $[M+H]^+$; Anal. Calcd. for $C_{27}H_{32}F_4N_4Na_1O_5/1.0 H_2O$: C, 58.69; H, 6.20; N, 10.14. Found: C, 58.46; H, 6.28; N, 10.00.

Example 133

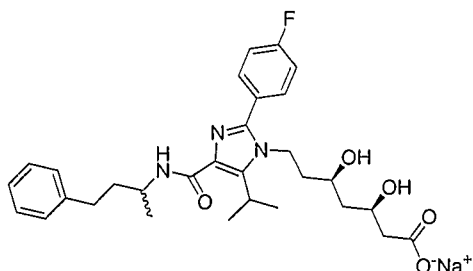
Sodium; (3R,5R)-7-[2-(4-fluoro-phenyl)-4-[2-(4-fluoro-phenyl)-ethylcarbamoyl]-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for Example 118. MS (APCI) m/z 530 $[M+H]^+$; Anal. Calcd. for

$C_{28}H_{32}F_2N_3Na_1O_5/0.95 H_2O$: C, 59.14; H, 6.01; N, 7.39. Found: C, 58.97; H, 5.90; N, 7.30.

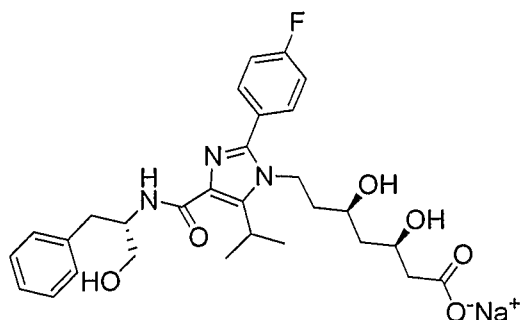
Example 134



Sodium; (3R,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-(1-methyl-3-phenyl-propylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoate

Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for Example 118. MS (APCI) m/z 540 $[M+H]^+$; Anal. Calcd. for $C_{30}H_{37}F_1N_3Na_1O_5/1.85 H_2O$: C, 60.56; H, 6.90; N, 7.06. Found: C, 60.43; H, 6.97; N, 7.00.

Example 135

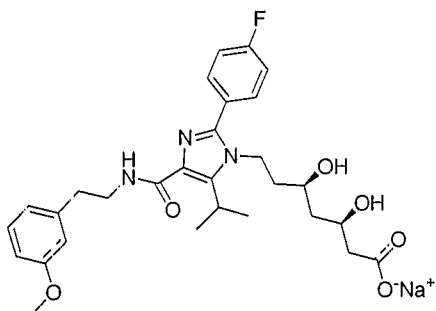


Sodium; (3R,5R)-7-[4-((S)-1-benzyl-2-hydroxy-ethylcarbamoyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate

Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for Example 118. MS (APCI) m/z 542 $[M+H]^+$; 1H NMR (400 MHz, Methanol-D₄) δ ppm 1.32 (d, $J = 7.1$ Hz, 3H), 1.38 (d, $J = 7.1$ Hz, 3H), 1.40 (m, partially obscured, 1H), 1.51 (dt, $J = 13.9, 8.2$ Hz, 1H), 1.61 (m, 1H), 1.72 (m, 1H), 2.16 (dd, $J = 15.1, 7.3$ Hz, 1H), 2.22 (dd, $J = 15.1, 5.1$ Hz, 1H), 2.78 (dd, $J = 13.7, 7.6$ Hz, 1H), 2.88 (dd, $J = 13.4, 6.8$ Hz, 1H), 3.33 (septet, $J = 7.1$ Hz, 1H), 3.51 (d, $J = 4.9$ Hz, 2H), 3.65 (m, 1H), 3.92 (m, 1H), 3.98 (dd, $J = 10.7, 5.4$ Hz, 1H), 4.11 (dd, $J = 11.0, 4.9$ Hz, 1H), 4.17 (m, 1H), 7.10 (m, 1H), 7.19 (m, 6H), 7.56 (m, 2H).

Example 136

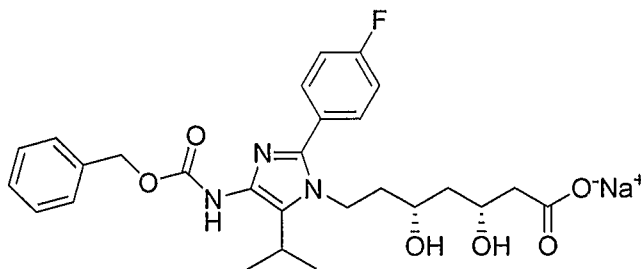
Sodium; (3R,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-[2-(3-methoxy-phenyl)-ethylcarbamoyl]-imidazol-1-yl]-3,5-dihydroxy-heptanoate



Starting from 1-[2-((4R,6R)-6-tert-Butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazole-4-carboxylic acid, this compound was prepared in a similar fashion as described for Example 118. MS (APCI) m/z 542 $[M+H]^+$; 1H NMR (400 MHz, Methanol-D₄) δ ppm 1.39 (d, $J = 7.1$ Hz, 3H), 1.39 (d, $J = 7.1$ Hz, 3H), 1.40 (m, partially obscured, 1H), 1.51 (dt, $J = 14.0, 8.2$ Hz, 1H), 1.61 (m, 1H), 1.73 (m, 1H), 2.15 (dd, $J = 15.1, 7.8$, 1H), 2.22 (dd, $J = 15.1, 5.1$, 1H), 2.75 (t, apparent, $J = 7.6$ Hz, 2H), 3.35 (septet, $J = 7.1$ Hz, 1H), 3.46 (dd, $J = 8.1, 6.8$ Hz, 2H), 3.64 (s, 3H), 3.66 (m, 1H), 3.91 (m, 1H), 3.97 (dd, $J = 11.0, 5.4$ Hz, 1H), 4.12 (ddd, $J = 14.6, 11.0, 4.9$ Hz, 1H), 6.65 (ddd, $J = 8.3, 2.7, 1.0$ Hz, 1H), 6.74 (m, 2H), 7.09 (m, 1H), 7.16 (m, 2H), 7.51 (m, 2H).

Example 137

Sodium; (3R,5R)-7-[4-benzyloxycarbonylamino-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate sodium salt



Step A

(4R,6R)-(6-{2-[4-benzyloxycarbonylamino-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester

To a solution of (4R,6R)-1-[2-(6-tert-butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-2-(4-fluoro-phenyl)-5-isopropyl-1H-imidazol-4-carboxylic acid (5.0 g, 9.9 mmol) (Example 2) in 125 mL of toluene was added diphenylphosphoryl azide (DPPA) (2.4 mL, 3.0 g, 11 mmol), followed by triethylamine (2.2 mL, 1.6 g, 7.2 mmol). The reaction mixture was refluxed for 3 hrs and then cooled to room temperature. Benzyl alcohol (1.5 mL, 1.6 g, 15 mmol) was added and then the reaction mixture was stirred for 3 days. The reaction mixture was evaporated to give a brown oil, which was purified by flash chromatography (silica gel, 60% ethyl acetate in hexane, gradient elution) to provide 0.78 g (32% chr) of

the desired product as a tan tacky solid: MS(APCI⁺) *m/z* 610; ¹H NMR (400 MHz DMSO-*d*₆) δ 8.60, 7.10-7.70, 5.05, 3.75-4.10, 2.90, 2.10-2.30, 0.95-1.70.

Step B

(4,6)-{2-(4-Fluoro-phenyl)-1-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazol-4-yl}-carbamic acid benzyl ester

To a solution of (4R,6R)-(6-{2-[4-benzyloxycarbonylamino-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester (0.49 g, 0.80 mmoles) in 20 mL of dichloromethane was added 5 mL of trifluoroacetic acid (7.5 g, 65 mmoles). The reaction mixture was stirred at room temperature for 1.5 hrs. The reaction mixture was diluted with 200 mL of dichloromethane and 100 mL of saturated sodium bicarbonate solution. Solid sodium bicarbonate was added to pH=9. The organic layer was separated, dried (sodium sulfate), filtered, and then the filtrate was evaporated to afford a light-yellow foamy solid. Purification by flash chromatography (silica gel, 95% ethyl acetate in methanol) gave 269 mg (68%) of the desired product as a light yellow foamy solid: mp 86-90 °C; MS(APCI⁺) *m/z* 496.

Step C

(3R,5R)-7-[4-benzyloxycarbonylamino-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate sodium salt

To a solution of (4R,6R)-{2-(4-fluoro-phenyl)-1-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazol-4-yl}-carbamic acid benzyl ester (0.24 g, 0.47 mmoles) in 6 mL of methanol was added 0.51 mL of a 1.028 N aqueous solution of NaOH (0.02 g, 0.52 mmoles). The reaction mixture was stirred at room temperature for 3 hrs and then evaporated in *vacuo* to give a yellow oil, which was triturated in 50 mL of anhydrous diethyl ether at room temperature for 18 hrs. The mixture was filtered to collect a solid, which was rinsed with anhydrous diethyl ether and then dried to provide 198 mg (78%) of the desired product as an off-white solid: MS(APCI⁺) *m/z* 514; ¹H NMR (400 MHz DMSO-*d*₆) δ 8.65, 7.20-7.60, 5.05, 4.90, 3.80-4.10, 3.50-3.70, 2.90, 1.1-1.95

Examples 138-423 are tabulated in the following Table I, (Lactones) and Table II (salts). The NMR data for each of the compounds of the following examples is consistent with its molecular structure.

TABLE I

Example #	Lactone (IUPAC)	Lactone LC-MS (APCI) [M+H] ⁺
138	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid benzylamide	480
139	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (pyridin-3-ylmethyl)-amide	481
140	2-(4-Fluoro-phenyl)-1-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid benzyl-methyl-amide	494
141	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 2,3-dichloro-benzylamide	550
142	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 3-methoxy-benzylamide	510
143	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (2'-fluoro-biphenyl-3-ylmethyl)-amide	574.2
144	2-(4-Fluoro-phenyl)-1-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid benzyl-isopropyl-amide	523
145	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (6-phenyl-pyridin-3-ylmethyl)-amide	557
146	2-(4-Fluoro-phenyl)-1-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid benzyl-propyl-amide	522
147	2-(4-Fluoro-phenyl)-1-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (1,5-dimethyl-1H-pyrazol-3-ylmethyl)-amide	498
148	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-	586

	carboxylic acid (3'-hydroxymethyl-biphenyl-3-ylmethyl)-amide	
149	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 3-pyridin-3-yl-benzylamide	557
150	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (6-o-tolyl-pyridin-3-ylmethyl)-amide	571
151	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid [(S)-1-(4-bromo-phenyl)-ethyl]-amide	572
152	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid [(R)-1-(4-bromo-phenyl)-ethyl]-amide	572
153	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid ((R)-1-p-tolyl-ethyl)-amide	508
154	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid ((S)-1-p-tolyl-ethyl)-amide	508
155	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid [(R)-1-(4-methoxy-phenyl)-ethyl]-amide	524
156	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid [(S)-1-(4-methoxy-phenyl)-ethyl]-amide	524
157	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid [(R)-1-(3-methoxy-phenyl)-ethyl]-amide	524
158	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid [(S)-1-(3-methoxy-phenyl)-ethyl]-amide	524
159	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (2'-methyl-biphenyl-3-ylmethyl)-amide	570
160	3'-[[(2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-	614

	carbonyl)-amino)-methyl]-biphenyl-3-carboxylic acid methyl ester	
161	2-(4-Fluoro-phenyl)-1-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid methyl-pyridin-2-ylmethyl-amide	495
162	2-(4-Fluoro-phenyl)-1-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid methyl-pyridin-3-ylmethyl-amide	495
163	2-(4-Fluoro-phenyl)-1-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid methyl-pyridin-4-ylmethyl-amide	495
164	3-{5-[(2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carbonyl)-amino)-methyl]-pyridin-2-yl}-benzoic acid ethyl ester	629
165	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (2'-methoxy-biphenyl-3-ylmethyl)-amide	557
166	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	508
167	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid ((R)-1-phenyl-propyl)-amide	508
168	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (2-phenyl-pyridin-4-ylmethyl)-amide	557
169	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid ((S)-2-hydroxy-1-phenyl-ethyl)-amide	510
170	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid methyl-((R)-1-phenyl-ethyl)-amide	508
171	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (4-chloro-benzyl)	528

	-methyl-amide	
172	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid ((R)-2-hydroxy-1-phenyl-ethyl)-amide	510
173	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (3-chloro-benzyl)-methyl-amide	528
174	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (2-chloro-benzyl)-methyl-amide	528
175	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid methyl-((S)-1-phenyl-ethyl)-amide	508
176	(4R,6R)-6-{2-[4-(3,4-Dihydro-2H-quinoline-1-carbonyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-ethyl}-4-hydroxy-tetrahydro-pyran-2-one	506
177	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 2,4-difluoro-benzylamide	516
178	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 2-chloro-6-methyl-benzylamide	528
179	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (1-methyl-1-phenyl-ethyl)-amide	508
180	(4R,6R)-6-{2-[4-(3,4-Dihydro-1H-isoquinoline-2-carbonyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-ethyl}-4-hydroxy-tetrahydro-pyran-2-one	506
181	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid [2-(2-fluoro-phenyl)-pyridin-4-ylmethyl]-amide	575

182	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 3,4-difluoro-benzylamide	516
183	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (2'-methoxy-biphenyl-4-ylmethyl)-amide	586
184	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 2-trifluoromethyl-benzylamide	548
185	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 2-fluoro-benzylamide	498
186	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (2'-methyl-biphenyl-4-ylmethyl)-amide	570
187	2-(4-Fluoro-phenyl)-1-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (5-methyl-pyrazin-2-ylmethyl)-amide	496
188	2-(4-Fluoro-phenyl)-1-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (1H-benzoimidazol-2-ylmethyl)-amide	520
189	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid benzhydryl-methyl-amide	570
190	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (4-fluoro-benzyl)-methyl-amide	512
191	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid [6-(4-methoxy-phenyl)-pyridin-3-ylmethyl]-amide	587
192	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-	508

	carboxylic acid ((R)-2-phenyl-propyl)-amide	
193	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid [2-(4-chloro-phenyl)-1-hydroxymethyl-ethyl]-amide	558
194	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid ((S)-1-methyl-3-phenyl-propyl)-amide	522
195	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (pyridin-2-ylmethyl)-amide	481
196	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (4-trifluoromethyl-pyridin-2-ylmethyl)-amide	549
197	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (1-pyridin-3-yl-ethyl)-amide	495
198	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 4-methyl-benzylamide	494
199	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 4-chloro-benzylamide	514
200	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (biphenyl-2-ylmethyl)-amide	556
201	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid [2-(4-methoxy-phenyl)-ethyl]-amide	524
202	2-(4-Fluoro-phenyl)-1-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (2-amino-2-phenyl-ethyl)-amide	509
203	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (2'-fluoro-biphenyl-4-ylmethyl)-amide	574
204	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-	524

	carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide	
205	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 4-tert-butyl-benzylamide	536
206	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 3-carbamoyl-benzylamide	523
207	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 3-methanesulfonyl-benzylamide	558
208	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid ((S)-2-phenyl-propyl)-amide	508
209	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid [6-(3-acetyl-phenyl)-pyridin-3-ylmethyl]-amide	599
210	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 2-methyl-benzylamide	494
211	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (2-hydroxy-benzyl)-methyl-amide	510
212	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (2-fluoro-benzyl)-methyl-amide	512
213	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid methyl-naphthalen-1-ylmethyl-amide	544
214	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid methyl-naphthalen-1-ylmethyl-amide	510

	l)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 2-methoxy-benzylamide	
215	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid [2-(3-fluoro-phenyl)-ethyl]-amide	512
216	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (1S,2S)-2-hydroxy-1-methoxymethyl-2-phenyl-ethyl)-amide	554
217	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 4-morpholin-4-ylmethyl-benzylamide	579
218	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (6-methoxy-biphenyl-3-ylmethyl)-amide	586
219	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (3,2'-difluoro-biphenyl-4-ylmethyl)-amide	592
220	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 4-bromo-2-fluoro-benzylamide	576
221	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (3-fluoro-2'-methyl-biphenyl-4-yl)-amide	574
222	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 4-trifluoromethyl-benzylamide	548
223	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (3,4-dichloro-benzyl)-methyl-amide	562
224	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-	524

	carboxylic acid [2-(3-methoxy-phenyl)-ethyl]-amide	
225	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (3-fluoro-3'-methoxy-biphenyl-4-ylmethyl)-amide	604
226	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 2-chloro-benzylamide	514
227	4-[(2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carbonyl)-amino)-methyl]-benzoic acid methyl ester	538
228	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid [(1S,2S)-2-hydroxy-1-hydroxymethyl-2-(4-methylsulfanyl-phenyl)-ethyl]-amide	586
229	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid ((S)-1-benzyl-2-hydroxy-ethyl)-amide	524
230	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (2-pyridin-3-yl-ethyl)-amide	495
231	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (2,4-difluoro-benzyl)-methyl-amide	530
232	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 3-methyl-benzylamide.	494
233	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 3-methoxy-4-methyl-benzylamide	524
234	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid methyl-(4-methyl-benzyl)-amide	508
235	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-	551

	carboxylic acid 4-dimethylcarbamoyl-benzylamide	
236	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 3-chloro-4-methyl-benzylamide	
237	4-[(2-(4-Fluoro-3-trifluoromethyl-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carbonyl)-amino)-methyl]-benzoic acid methyl ester	606
238	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 4-pyridin-2-yl-benzylamide	557
239	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (2-phenyl-pyridin-3-ylmethyl)-amide	557
240	(4R,6R)-6-{2-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(2-phenyl-pyrrolidine-1-carbonyl)-imidazol-1-yl]-ethyl}-4-hydroxy-tetrahydro-pyran-2-one	520
241	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (4-methoxy-benzyl)-methyl-amide	524
242	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (3-fluoro-benzyl)-methyl-amide	512
243	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (3-methoxy-benzyl)-methyl-amide	524
244	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid [(S)-1-(3-methoxy-phenyl)-ethyl]-methyl-amide	538
245	2-(4-Fluoro-3-trifluoromethyl-phenyl)-1-[2-((2R,4R)-4-	578

	hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 4-methoxy-benzylamide	
246	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid ((R)-2-hydroxy-1-phenyl-ethyl)-methyl-amide	524
247	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 2-pyridin-2-yl-benzylamide	557
248	3-[(2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carbonyl)-methyl-amino)-methyl]-benzoic acid methyl ester	552
249	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid methyl-(2-trifluoromethyl-benzyl)-amide	562
250	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (3,4-difluorobenzyl)-methyl-amide	530
251	4-[(2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carbonyl)-methyl-amino)-methyl]-benzoic acid methyl ester	552
252	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid methyl-((R)-1-p-tolyl-ethyl)-amide	522
253	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid cyclohexylmethyl-amide	486
254	3-[(2-(4-Fluoro-phenyl)-1-[2-((2R,	552

	4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carbonyl)-methyl-amino)-methyl]-benzoic acid methyl ester	
255	(4R,6R)-6-{2-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(piperidine-1-carbonyl)-imidazol-1-yl]-ethyl}-4-hydroxy-tetrahydro-pyran-2-one	458
256	(4R,6R)-6-{2-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(4-phenyl-piperidine-1-carbonyl)-imidazol-1-yl]-ethyl}-4-hydroxy-tetrahydro-pyran-2-one	534
257	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (6-trifluoromethyl-pyridin-3-ylmethyl)-amide	549
258	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 3-(4-methyl-piperidin-1-ylmethyl)-benzylamide	591
259	(4R,6R)-6-{2-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(3-phenyl-piperidine-1-carbonyl)-imidazol-1-yl]-ethyl}-4-hydroxy-tetrahydro-pyran-2-one	534
260	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid 3-piperidin-1-ylmethyl-benzylamide	577
261	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid dimethylamide	418
262	N-{2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazol-4-yl}-2-phenyl-acetamide	480
263	4-[[{2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carbonyl)-methyl-amino)-methyl]-benzoic acid methyl ester	552
264	1-{2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-	530

	tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carbonyl}-piperidine-4-carboxylic acid ethyl ester	
265	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid cyclopropylmethyl-amide	444
266	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (3-isopropoxy-propyl)-amide	490
267	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid butylamide	446
268	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid ((R)-1-cyclohexyl-ethyl)-amide	500
269	4-Fluoro-N-{2-(4-fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazol-4-yl}-benzamide	484
270	N-{2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazol-4-yl}-4-methoxy-benzamide	496
271	N-{2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazol-4-yl}-benzamide	466
272	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (2-pyridin-4-yl-ethyl)-amide	495
273	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid [2-(4-sulfamoyl-phenyl)-ethyl]-amide	573
274	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid (1-methyl-3-phenyl-propyl)-amide	522
275	N-{2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-	454

	tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazol-4-ylmethyl}-methanesulfonamide.	
276	2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid ethyl amide	418

TABLE II

Example	Sodium Salt (IUPAC)	Mass Spectra (APCI) [M+H] ⁺
277	Sodium; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-phenylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate	499
278	Sodium; (3R,5R)-7-[4-(benzylsulfonyl)-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	518
279	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-(methylsulfonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	442
280	Sodium; (3R,5R)-7-[4-[[benzyl(methyl)amino]carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	512
281	Sodium; (3R,5R)-7-[4-[[[(2,3-dichlorobenzyl)amino]carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	566
282	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-[[[(3-methoxybenzyl)amino]carbonyl]-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	528
283	Sodium; (3R,5R)-7-[4-[[[(2'-fluorobiphenyl-3-yl)methyl]amino]carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	592
284	Sodium; (3R,5R)-7-[4-[[benzyl(isopropyl)amino]carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	540
285	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-[[[(6-phenylpyridin-3-yl)methyl]amino]carbonyl]-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	575
286	Sodium; (3R,5R)-7-[4-[[benzyl(propyl)amino]carbonyl]-2-(4-	540

	fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	
287	Sodium; (3R,5R)-7-[4-({[(1,5-dimethyl-1H-pyrazol-3-yl)methyl]amino}carbonyl)-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	538
288	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-4-({[3'-(hydroxymethyl)biphenyl-3-yl]methyl}amino)carbonyl]-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	604
289	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-({[(3-pyridin-3-ylbenzyl)amino]carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	575
290	Sodium; 7-{2-(4-Fluoro-phenyl)-5-isopropyl-4-[(6-o-tolyl-pyridin-3-ylmethyl)-carbamoyl]-imidazol-1-yl}-3,5-dihydroxyheptanoate	589
291	Sodium; (3R,5R)-7-[4-({[(1S)-1-(4-bromophenyl)ethyl]amino}carbonyl)-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	590
292	Sodium; (3R,5R)-7-[4-({[(1R)-1-(4-bromophenyl)ethyl]amino}carbonyl)-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	590
293	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-({[(1R)-1-(4-methylphenyl)ethyl]amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	526
294	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-({[(1S)-1-(4-methylphenyl)ethyl]amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	526
295	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-({[(1R)-1-(4-methoxyphenyl)ethyl]amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	542
296	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-({[(1S)-1-(4-methoxyphenyl)ethyl]amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	542
297	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-({[(1R)-1-(3-methoxyphenyl)ethyl]amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	542
298	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-({[(1S)-1-(3-methoxyphenyl)ethyl]amino}carbonyl)-1H-imidazol-1-	542

	yl]-3,5-dihydroxyheptanoate	
299	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-({[2'-methylbiphenyl-3-yl)methyl]amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	588
300	Disodium; 3'-[({[1-[(3R,5R)-6-carboxy-3,5-dihydroxyhexyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-4-yl]carbonyl}amino)methyl]biphenyl-3-carboxylate	618
301	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-{[methyl(pyridin-2-ylmethyl)amino]carbonyl}-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	513
302	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-{[methyl(pyridin-3-ylmethyl)amino]carbonyl}-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	513
303	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-{[methyl(pyridin-4-ylmethyl)amino]carbonyl}-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	513
304	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-({[4-(methoxycarbonyl)benzyl]amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	556
305	Sodium; (3R,5R)-7-[4-[(4-[(dimethylamino)sulfonyl]benzyl)amino]carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	605
306	Sodium; (3R,5R)-7-[4-[(3-[(dimethylamino)sulfonyl]benzyl)amino]carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	605
307	Sodium; (3R,5R)-7-[4-[(3-[(dimethylamino)carbonyl]benzyl)amino]carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	569
308	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-({[3-(piperidin-1-ylcarbonyl)benzyl]amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	609
309	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-({[3-(morpholin-4-ylcarbonyl)benzyl]amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	611

310	Sodium; (3R,5R)-7-[4-{{{6-[3-(ethoxycarbonyl)phenyl]pyridin-3-yl}methyl}amino}carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	647
311	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-{{{2'-methoxybiphenyl-3-yl}methyl}amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	604
312	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-{{{(1S)-1-phenylpropyl}amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	526
313	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-{{{(1R)-1-phenylpropyl}amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	526
314	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-{{{(2-phenylpyridin-4-yl)methyl}amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	575
315	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-4-{{{(1S)-2-hydroxy-1-phenylethyl}amino}carbonyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	528
316	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-{{{methyl[(1R)-1-phenylethyl]amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	526
317	Sodium; (3R,5R)-7-[4-{{{(4-chlorobenzyl)(methyl)amino}carbonyl)-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	546
318	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-4-{{{(1R)-2-hydroxy-1-phenylethyl}amino}carbonyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	528
319	Sodium; (3R,5R)-7-[4-{{{(3-chlorobenzyl)(methyl)amino}carbonyl)-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	546
320	Sodium; (3R,5R)-7-[4-{{{(2-chlorobenzyl)(methyl)amino}carbonyl)-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	546
321	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-{{{methyl[(1S)-1-phenylethyl]amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	526

322	Sodium; (3R,5R)-7-[4-(3,4-dihydroquinolin-1(2H)-ylcarbonyl)-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	524
323	Sodium; (3R,5R)-7-[4-[[2-(4-fluorobenzyl)amino]carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	534
324	Sodium; (3R,5R)-7-[4-[[2-chloro-6-methylbenzyl)amino]carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	546
325	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-[[1-methyl-1-phenylethyl)amino]carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	526
326	Sodium; (3R,5R)-7-[4-(3,4-dihydroisoquinolin-2(1H)-ylcarbonyl)-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	524
327	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-4-[[2-(2-fluorophenyl)pyridin-4-yl)methyl]amino]carbonyl]-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	593
328	Sodium; (3R,5R)-7-[4-[[3,4-difluorobenzyl)amino]carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	534
329	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-[[2'-methoxybiphenyl-4-yl)methyl]amino]carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	604
330	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-[[2-(trifluoromethyl)benzyl]amino]carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	566
331	Sodium; (3R,5R)-7-[4-[[2-fluorobenzyl)amino]carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	516
332	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-[[2'-methylbiphenyl-4-yl)methyl]amino]carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	588
333	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-[[5-methylpyrazin-2-yl)methyl]amino]carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	514

334	Sodium; (3R,5R)-7-[4-[[{(1H-benzimidazol-2-ylmethyl)amino}carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	538
335	Sodium; (3R,5R)-7-[4-[[{(diphenylmethyl)(methyl)amino}carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	588
336	Sodium; (3R,5R)-7-[4-[[{(4-fluorobenzyl)(methyl)amino}carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	530
337	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-[[{(6-(4-methoxyphenyl)pyridin-3-yl)methyl}amino}carbonyl]-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	605
338	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-[[{(pyridin-2-ylmethyl)amino}carbonyl]-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	499
339	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-[[{(4-(trifluoromethyl)pyridin-2-yl)methyl}amino}carbonyl]-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	567
340	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-[[{(1-pyridin-3-ylethyl)amino}carbonyl]-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	513
341	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-[[{(4-methylbenzyl)amino}carbonyl]-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	512
342	Sodium; (3R,5R)-7-[4-[[{(4-chlorobenzyl)amino}carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	532
343	Sodium; (3R,5R)-7-[4-[[{(biphenyl-2-ylmethyl)amino}carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	574
344	Sodium; (3R,5R)-7-[4-[[{(2R)-2-amino-2-phenylethyl}amino}carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	527
345	Sodium; (3R,5R)-7-[4-[[{(2'-fluorobiphenyl-4-yl)methyl}amino}carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	615

346	Sodium; (3R,5R)-7-[4-{{(1,3-benzodioxol-5-ylmethyl)amino}carbonyl}-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	542
347	Sodium; (3R,5R)-7-[4-{{(4-tert-butylbenzyl)amino}carbonyl}-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	554
348	Sodium; (3R,5R)-7-[4-{{(3-(aminocarbonyl)benzyl)amino}carbonyl}-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	541
349	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-{{(3-(methylsulfonyl)benzyl)amino}carbonyl}-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	576
350	Sodium; (3R,5R)-7-[4-{{(6-(3-acetylphenyl)pyridin-3-yl)methyl}amino}carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	617
351	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-{{(2-methylbenzyl)amino}carbonyl}-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	512
352	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-4-{{(2-hydroxybenzyl)(methyl)amino}carbonyl}-5-isopropyl-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	528
353	Sodium; (3R,5R)-7-[4-{{(2-fluorobenzyl)(methyl)amino}carbonyl}-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	530
354	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-{{(methyl(1-naphthylmethyl)amino}carbonyl)-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	562
355	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-{{(2-methoxybenzyl)amino}carbonyl}-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	528
356	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-{{(3-(methoxycarbonyl)benzyl)amino}carbonyl}-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	556
357	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-{{(4-(morpholin-4-ylmethyl)benzyl)amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	597
358	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-{{(6-	604

	methoxybiphenyl-3-yl)methyl]amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	
359	Sodium; (3R,5R)-7-[4-({(2',3-difluorobiphenyl-4-yl)methyl]amino}carbonyl)-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	610
360	Sodium; (3R,5R)-7-[4-({(4-bromo-2-fluorobenzyl)amino}carbonyl)-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	594
361	Sodium; (3R,5R)-7-[4-({(3-fluoro-2'-methylbiphenyl-4-yl)methyl]amino}carbonyl)-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	606
362	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-({(4-(trifluoromethyl)benzyl)amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	566
363	Sodium; (3R,5R)-7-[4-({(3,4-dichlorobenzyl)(methyl)amino}carbonyl)-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	580
364	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-({(4-((methylsulfonyl)amino)benzyl)amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	591
365	Sodium; (3R,5R)-7-[4-({(3-fluoro-3'-methoxybiphenyl-4-yl)methyl]amino}carbonyl)-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	622
366	Sodium; (3R,5R)-7-[4-({(2-chlorobenzyl)amino}carbonyl)-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	532
367	Sodium; (3R,5R)-7-[4-({(benzylamino)carbonyl)-2-(3,4-difluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	516
368	Sodium; 4-([1-[(3R,5R)-6-carboxy-3,5-dihydroxyhexyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-4-yl]carbonyl)amino)methyl]benzoate	542
369	Sodium; (3R,5R)-7-[2-(3,4-difluorophenyl)-5-isopropyl-4-({(4-(methoxycarbonyl)benzyl)amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	574
370	Sodium; (3R,5R)-7-[2-(3,4-difluorophenyl)-5-isopropyl-4-({(4-methoxybenzyl)amino}carbonyl)-1H-imidazol-1-yl]-3,5-	546

	dihydroxyheptanoate	
371	Sodium; (3R,5R)-7-[4-{{(2,4-difluorobenzyl)(methyl)amino}carbonyl}-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	548
372	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-{{(3-methylbenzyl)amino}carbonyl}-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	512
373	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-{{(4-methoxybenzyl)amino}carbonyl}-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	528
374	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-{{(3-methoxy-4-methylbenzyl)amino}carbonyl}-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	542
375	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-{{[methyl(4-methylbenzyl)amino]carbonyl}-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	526
376	Sodium; (3R,5R)-7-[4-{{(4-[(dimethylamino)carbonyl]benzyl)amino}carbonyl}-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	569
377	Sodium; (3R,5R)-7-[4-{{(3-chloro-4-methylbenzyl)amino}carbonyl}-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	546
378	Sodium; (3R,5R)-7-[4-{{(benzylamino)carbonyl}-2-[4-fluoro-3-(trifluoromethyl)phenyl]-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	566
379	Sodium; (3R,5R)-7-[2-[4-fluoro-3-(trifluoromethyl)phenyl]-5-isopropyl-4-{{[4-(methoxycarbonyl)benzyl]amino}carbonyl}-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	624
380	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-{{(4-pyridin-2-ylbenzyl)amino}carbonyl}-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	575
381	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-{{(2-phenylpyridin-3-yl)methyl}amino}carbonyl]-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	575
382	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-{{(2-phenylpyrrolidin-1-yl)carbonyl}-1H-imidazol-1-yl]-3,5-	538

	dihydroxyheptanoate	
383	Sodium; (3R,5R)-7-[4-[(benzylamino)carbonyl]-5-isopropyl-2-(4-methoxyphenyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	510
384	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-[[4-methoxybenzyl](methyl)amino]carbonyl)-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	542
385	Sodium; (3R,5R)-7-[4-[(3-fluorobenzyl)(methyl)amino]carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	530
386	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-[[3-methoxybenzyl](methyl)amino]carbonyl)-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	542
387	Sodium; (3R,5R)-7-{2-(4-fluorophenyl)-5-isopropyl-4-[(methylamino)carbonyl]-1H-imidazol-1-yl}-3,5-dihydroxyheptanoate	422
388	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-[[[(1S)-1-(3-methoxyphenyl)ethyl](methyl)amino]carbonyl]-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	556
389	Sodium; (3R,5R)-7-(2-[4-fluoro-3-(trifluoromethyl)phenyl]-5-isopropyl-4-[[4-methoxybenzyl]amino]carbonyl)-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	596
390	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-4-[[[(1R)-2-hydroxy-1-phenylethyl](methyl)amino]carbonyl]-5-isopropyl-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	542
391	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-[[2-pyridin-2-ylbenzyl]amino]carbonyl)-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	575
392	Sodium; (3R,5R)-7-[4-[(benzylamino)carbonyl]-2-(2,4-difluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	516
393	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-[[3-(methoxycarbonyl)benzyl](methyl)amino]carbonyl)-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	570
394	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-({methyl[2-(trifluoromethyl)benzyl]amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	580

395	Sodium; (3R,5R)-7-[4-[[[(3,4-difluorobenzyl)(methyl)amino]carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	548
396	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-[[[4-(methoxycarbonyl)benzyl](methyl)amino]carbonyl]-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	570
397	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-({methyl[(1R)-1-(4-methylphenyl)ethyl]amino}carbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	540
398	Sodium; (3R,5R)-7-[4-[[[(cyclohexylmethyl)amino]carbonyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	504
399	Sodium; 3-[[[1-[(3R,5R)-6-carboxy-3,5-dihydroxyhexyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-4-yl]carbonyl](methyl)amino]methyl]benzoate	556
400	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-(piperidin-1-ylcarbonyl)-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	476
401	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-[(4-phenylpiperidin-1-yl)carbonyl]-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	552
402	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-[[[6-(trifluoromethyl)pyridin-3-yl]methyl]amino]carbonyl]-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	567
403	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-[[[3-[(4-methylpiperidin-1-yl)methyl]benzyl]amino]carbonyl]-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	609
404	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4-[[[4-methoxy-3-methylbenzyl]amino]carbonyl]-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	542
405	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-[(3-phenylpiperidin-1-yl)carbonyl]-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	552
406	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-4-([3-(piperidin-1-ylmethyl)benzyl]amino)carbonyl]-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	595
407	Sodium; (3R,5R)-7-[4-[(dimethylamino)carbonyl]-2-(4-	436

	fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	
408	Sodium; (3R,5R)-7-{2-(4-fluorophenyl)-5-isopropyl-4-[(phenylacetyl)amino]-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	498
409	Sodium; 4-[[[1-[(3R,5R)-6-carboxy-3,5-dihydroxyhexyl]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-4-yl]carbonyl](methyl)amino]methyl]benzoate	556
410	Sodium; (3R,5R)-7-[4-{[4-(ethoxycarbonyl)piperidin-1-yl]carbonyl}-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	548
411	Sodium; (3R,5R)-7-[4-{[(cyclopropylmethyl)amino]carbonyl}-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	462
412	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-4-{[(3-isopropoxypropyl)amino]carbonyl}-5-isopropyl-1H-imidazol-1-yl)-3,5-dihydroxyheptanoate	508
413	Sodium; (3R,5R)-7-[4-{(butylamino)carbonyl}-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	464
414	Sodium; (3R,5R)-7-[4-{[(1R)-1-cyclohexylethyl]amino]carbonyl}-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	518
415	Sodium; (3R,5R)-7-[4-{[4-(4-fluorobenzoyl)amino]-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	502
416	Sodium; (3R,5R)-7-{2-(4-fluorophenyl)-5-isopropyl-4-{[4-methoxybenzoyl]amino]-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	514
417	Sodium; (3R,5R)-7-[4-(benzoylamino)-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	484
418	Sodium; (3R,5R)-7-[4-{[(4-chlorobenzoyl)amino]methyl}-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	532
419	Sodium; (3R,5R)-7-[4-{(benzoylamino)methyl}-2-(4-fluorophenyl)-5-isopropyl-1H-imidazol-1-yl]-3,5-dihydroxyheptanoate	498

420	Sodium; (3R,5R)-7-(2-(4-fluorophenyl)-5-isopropyl-4- {[(methylsulfonyl)amino]methyl}-1H-imidazol-1-yl)-3,5- dihydroxyheptanoate	472
421	Sodium; (3R,5R)-7-[2-(4-fluorophenyl)-4-({[(4- fluorophenyl)acetyl]amino}methyl)-5-isopropyl-1H-imidazol- 1-yl]-3,5-dihydroxyheptanoate	530
422	Sodium; 7-[4-Ethylcarbamoyl-2-(4-fluoro-phenyl)-5- isopropyl-imidazol-1-yl]-3,5-dihydroxyheptanoate	436
423	Sodium; 7-[4-(4-Chloro-benzoylamino)-2-(4-fluoro-phenyl)-5- isopropyl-imidazol-1-yl]-3,5-dihydroxyheptanoate	518

Example 424

Sodium; (3R,5R)-7-[4-Benzylcarbamoyl-2-(4-fluorophenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoate

Step A

(Benzhydrylideneamino)-acetic acid benzyl ester

A 3-necked, 5 L round-bottomed flask was equipped with a mechanical stirrer, a J-KEM temperature probe, and a N₂ inlet adapter connected to a bubbler. The round-bottomed flask was charged with glycine benzyl ester hydrochloride (505.2 g, 2.51 mol, 1.0 equiv.) and CH₂Cl₂ (3.0 L). The milky, white reaction mixture was treated with benzophenone imine (471.1 g, 97%, 2.6 mol, 1.00 equiv.) and an exotherm (+ 4.5 °C) was observed. The reaction mixture stirred at 20 °C for 3h and TLC (50% ethyl acetate/heptane) showed a trace of starting material . Additional benzophenone imine (25.0 g, 0.14 mol) was added to the reaction mixture and the mixture was stirred for 15h at 20 °C. TLC confirmed reaction completion. This mixture was filtered through a short pad of Celite to remove ammonium chloride, and the filter cake was rinsed with CH₂Cl₂ (1.5 L). The filtrates were concentrated *in vacuo* to produce a white solid that was dried in vacuo to give the desired crude product: 878.7 g (106%); ¹H-NMR(DMSO-d₆): 7.53-7.25 (m, 13H), 7.12 (dd, 2H), 5.10 (s, 2H), and 4.17 (s, 2H). HPLC Purity: > 95%.

Step B

2-Amino-4-methyl-3-oxo-pentanoic acid benzyl ester hydrochloride

A 3-necked, 3 L round-bottomed flask was equipped with a magnetic stir bar, a J-KEM temperature probe, an addition funnel, and a N₂ inlet adapter connected to a bubbler. The flask was charged with potassium *tert*-butoxide (112.0 g, 998 mmol, 1.53 equiv) and THF (750 mL). The white suspension was cooled to -70 °C and was treated with (Benzhydrylideneamino)-acetic acid benzyl ester (215.0 g, 658 mmol, 1.00 equiv.) as a solution in THF (700 mL). The orange solution stirred for 30 min at -70 °C and was then transferred via cannula into a solution of isobutyryl chloride (100.0 mL, 101 g, 947 mmol, 1.45 equiv.) in THF (200 mL) at -70 °C. The addition rate was such that the reaction temperature did not warm past -50

°C. After complete addition, the reaction mixture was held at -50 °C for 1h, and was then warmed to -30 °C. At this temperature, the reaction was quenched with 3 M HCl (670 mL, 2.0 mol, 3.1 equiv.). The cold bath was removed, and the reaction mixture stirred at 20 °C for 15 h. The reaction mixture was concentrated *in vacuo* to produce a yellow residue that was re-dissolved in water (400 mL). The benzophenone side-product was removed by extraction with diethyl ether (2 x 400 mL), and the aqueous layer was concentrated *in vacuo* to produce a light yellow residue that was concentrated twice on the rotary evaporator from methanol (2 x 500 mL) to azeotropically remove water. The resulting residue was then re-dissolved in anhydrous methanol (500 mL) and potassium chloride (KCl, ~82.0 g) was removed by vacuum filtration. The light yellow filtrate was concentrated *in vacuo* to produce a light yellow residue (16, 143.1 g, 81%). ¹H-NMR (DMSO-d₆): 9.08 (s, 3H, NH₃Cl), 7.41-7.31 (m, 5H), 5.48 (s, 1H), 5.26 (s, 2H), 3.05 (sept, 1H), 1.08 (d, 3H, CH₃), and 0.90 (d, 3H, CH₃). HPLC purity: 88.2%. MS: (M-HCl)= 235. This crude residue 16 can be recrystallized from a 1:1 wt/wt ratio of crude 16 to water to provide 16 > 99% HPLC purity.

Step C

2-(4-Fluorobenzoylamino)-4-methyl-3-oxo-pentanoic acid benzyl ester

A 4-necked, 5 L round-bottomed flask was equipped with a J-KEM temperature probe and a mechanical stirrer. The flask was charged with 2-Amino-4-methyl-3-oxo-pentanoic acid benzyl ester hydrochloride (427.8 g, 99.6% HPLC purity, 1.57 mol) and CH₂Cl₂ (1.0 L). The resultant solution was cooled to 0 °C and was treated with a solution of potassium carbonate (546 g, 3.95 mol, 2.51 equiv.) in deionized water (1.5 L) to produce a creamy reaction mixture. The pot temperature was kept below 5 °C during the potassium carbonate addition. Then, the mixture was treated with a solution of 4-fluorobenzoyl chloride (209 mL, 276 g, 1.74 mol, 1.11 equiv.) in CH₂Cl₂ (500 mL) at 0 °C at a rate such that the pot temperature was kept below 5 °C. TLC (50% ethyl acetate/50% hexanes) showed reaction completion after 20 min and a phase cut gave the product-containing bottom yellow organic layer. The aqueous layer was extracted with CH₂Cl₂ (1 x 750 mL) and discarded. The combined organic layers were washed with 0.2 M HCl (1 x 90 mL), washed with water (1 x 2 L, deionized), dried over MgSO₄, and filtered. The yellow filtrate was concentrated *in vacuo* to produce a light yellow solid (583.5 g, 104 %) which was recrystallized from into a refluxing mixture of MTBE (1 L) and heptane (2.5 L) to give an solid, which was collected by filtration and washed with heptane (2 x 0.5 L). This material was dried *in vacuo* (35 °C) for 12 h to give the desired product as an off white solid: 504.0 g, (90%); ¹H-NMR (CDCl₃): 7.86 (m, 2H), 7.41-7.10 (m, 7H), 5.59 (d, 1H), 5.27 (dd, 2H), 3.05 (m, 1H), 1.21 (d, 3H), and 1.19 (d, 3H); ¹⁹F-NMR (CDCl₃): -107.54; Low resolution mass spectroscopy (APCI) *m/z* 358 [M+H]⁺.

Step D

N-(1-Benzylcarbamoyl-3-methyl-2-oxo-butyl)-4-fluorobenzamide

A 4-necked, 3 L round-bottomed flask was equipped with a J-KEM temperature probe, a magnetic stirrer, a condenser connected to a bubbler via a N₂ inlet adapter, and an addition funnel. The flask was charged with 2-(4-Fluorobenzoylamino)-4-methyl-3-oxo-pentanoic acid benzyl ester (200.0 g, 0.56 mol, 1.00

equiv.) and NMP (850 mL). The resultant solution was heated to 160 °C and treated in one portion with neat benzylamine (65.0 mL, 31.48 g, 0.29 mol, 1.05 equiv.). The reaction mixture was maintained at 160 °C for 3 h, TLC and HPLC (50:50 ethyl acetate/hexanes) showed desired product and very little starting material. The reaction mixture was cooled to 75 °C and NMP (~600 mL) was removed by vacuum
5 distillation. The concentrated reaction mixture was poured portionwise onto a cold brine solution (1.5 L; approximately 1:2 in ice/water) and was diluted with ethyl acetate (1 L). The organic layer was collected and the aqueous layer was extracted with ethyl acetate (1 x 500 mL). The combined ethyl acetate filtrate was concentrated *in vacuo* to produce a beige solid (~284 g). ¹H-NMR still showed NMP in solid residue. The solid residue was re-dissolved in ethyl acetate (1.5 L) and washed with ½ saturated brine solution (2
0 x 2 L; 1L saturated brine). The organic layer was collected and concentrated *in vacuo* to produce a light yellow solid (~254 g). ¹H-NMR showed very little NMP in crude solid. Using a mechanical stirrer, crude solid (~254 g) was recrystallized with absolute EtOH (700 mL) and deionized water (700 mL) to produce an off-white solid. The off-white solid was collected by filtration and air-dried in the hood over 15 h. The off-white solid (~400 g, wet) was re-slurried in a solution of absolute ethanol (600 mL) and deionized water
5 (600 mL), collected by filtration, and dried *in vacuo* 75 °C (16 h) to give the desired product as an off-white solid: (112.3 g, 56% yield, 90% HPLC purity); ¹H-NMR (CDCl₃): 7.83 (m, 2H), 7.78, (d, 1H), 7.41-7.10 (m, 6H), 5.33 (d, 1H), 4.42 (m, 2H), 3.15 (m, 1H), and 1.10 (m, 6H); ¹⁹F-NMR (CDCl₃): -106.95; Low resolution mass spectroscopy (APCI) *m/z* 357 [M+H]⁺.

Step E

[(4R,6R)-6-(2-Amino-ethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester

A 5-gallon stainless steel reactor was charged with 250 g of Ra-Ni, ((4R,6R)-6-Cyanomethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester (1.0 kg, 3.71 mol), toluene (6 L), methanol (675 mL), and with 6.5M NH₃/MeOH (800 mL). The reactor was sealed, pressure tested to 3.5 bar with N₂, and purged 3 times with 3.5 bar of N₂. The reactor was purged with H₂ to 3.5 bar three times without any agitation.
5 After the reactor was pressurized to 3.5 bar with H₂, the reaction stirred for 2-6 h, and a small exotherm to 30 to 40 °C was observed. Stirring was continued until H₂ uptake ceased, then the reaction mixture was stirred at 30 to 40 °C for a further 30 min. The mixture was cooled to 20 to 25 °C, the H₂ source and the agitator were switched off, and the H₂ was vented from the reactor. The agitator was switched on and the stainless steel reactor was purged with N₂ to 3.5 bar 3 times. Spent Ni catalyst was filtered under a bed of
0 nitrogen, and the stainless steel reactor and spent catalyst bed were washed with toluene (250 mL). The combined filtrates were concentrated to an approximate volume of 500 mL at a maximum temperature of 55 °C under vacuum. [Note: the vacuum was broken with nitrogen]. A saturated sodium chloride solution was added and stirred for 10 minutes under nitrogen. The agitation was stopped and the phases were separated. The lower aqueous layer was discarded, and the organic layer was concentrated to produce
5 the desired product as a yellow oil: (1.054 kg, 104%, ~7% residual toluene); ¹H-NMR (400 MHz, CDCl₃): 4.23-4.19 (m, 1H), 3.99-3.95 (m, 1H), 2.74 (t, J=7.1 Hz, 2H), 2.40-2.36 (m, 1H), 2.27-2.22 (m, 1H), 1.58-

1.41 (m, 2H), 1.40 (s, 9H), 1.31 (s, 6H), 0.89 (s, 9H); Low resolution mass spectroscopy (APCI) m/z 273 $[M+H]^+$.

Step F

2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid benzylamide

To a 2-L 3-necked, round-bottomed flask outfitted with a mechanical stirrer, a J-KEM/heating mantle setup, and a Dean-Stark trap (with condenser) was charged a mixture of *N*-(1-Benzylcarbamoyl-3-methyl-2-oxo-butyl)-4-fluorobenzamide (123.0 g, 345.1 mmol), benzoic acid (63.0 g, 517.5 mmol, 1.5 equiv.), and heptane (700 mL). This slurry was treated with [(4R,6R)-6-(2-Amino-ethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid *tert*-butyl ester (119.4 g, 414.0 mmol, 1.2 equiv.). The reactor was purged with nitrogen, then heated to reflux (approximately 99 °C) over 14 h in order to azeotropically remove the water formed during the reaction. After 14 h, a small amount of starting material remained by TLC (1:1 heptane:ethyl acetate). A small portion of TBIA (5.0 g, 18.0 mmol, 0.06 equiv) was added to the reactor, and the mixture was stirred at reflux for another 2 h, after which time TLC showed no more starting material remaining. The reactor was cooled to 30 °C, and the contents were fully dissolved with ethyl acetate (600 mL), washed with saturated sodium bicarbonate solution (2 x 400 mL), washed with 10% aqueous sodium chloride, then concentrated *in vacuo* to provide 400.1 g of a very thick orange oily solid. This solid was taken up into MeOH (600 mL) while heating to 40 °C (difficult to dissolve). The solution was charged with a premixed solution of concentrated HCl (136 g) in water (400 mL), and the remaining solution was heated back to 40 °C and held at this temperature for over 2 h. The walls of the reactor were washed down with MeOH (20 mL) and TLC after an additional 1 h showed mainly diol *tert*-butyl ester. To the reaction mixture was added MTBE (500 mL), followed by slow addition (~10 min) of a pre-mixed solution of NaOH (110 g) in water (200 mL). The pH of the mixture at this point was 13.0, and the pot temperature rose to almost 50 °C. The reaction was stirred and slowly cooled to 23 °C over 2 h, after which time TLC (6:1 ethyl acetate:heptane) showed that all *tert*-butyl ester was consumed (only baseline remaining). The mixture was diluted with more MTBE (1 L) and water (500 mL), and was phase separated. The bottom aqueous product-containing layer was extracted again with MTBE (500 mL) and set aside. The combined MTBE layers were vigorously washed with 5% NaOH solution (200 mL), then discarded. The combined aqueous extracts were combined and distilled down to approximately 1/2 volume on the rotary evaporator using full vacuum at 70 °C (CAUTION! Severe bumping was possible; use large round-bottom flask and a bump-trap for this concentration). The mixture was then stirred at 23 °C and treated with 6N HCl (200 mL, added over 1 min), at which point the mixture turned cloudy. The pH of this suspension was 7.0 (pH was measured with pH meter). To this mixture was added ethyl acetate (800 mL), and the mixture was stirred vigorously. The mixture was then treated with 6N HCl until pH of the aqueous layer (phase-cut; lower layer) was 5.5. In total, additional 6N HCl (75 mL) was added to achieve this pH. The layers were separated and the top organic layer was set aside. The aqueous layer was extracted with ethyl acetate (200 mL) and then discarded. The combined organics were washed with water and then concentrated *in*

vacuo to give 175 g of an orange oil that foamed slightly under vacuum. To this mixture was added 1% HCl (1 mL) and toluene (900 mL), and the reaction mixture was heated to reflux under a Dean-Stark trap for 2.5 h [Note: Not completely in solution until near reflux]. TLC showed clean conversion to lactone. The reaction mixture was cooled to 30 °C, and toluene was removed by rotary evaporator to give 171 g of a brown oil that solidified while under vacuum for 2 h. This solid was taken up in dichloromethane (60 mL) and the solution was added to the top of a 900 g silica gel column that was pre-packed in 4:1 ethyl acetate/heptane. A solution of 4:1 ethyl acetate/heptane (4 L) eluted initially a purple impurity of high R_f (0.8), followed by elution of lactone cleanly by ramping eventually to neat ethyl acetate over another 12 L. Additional ethyl acetate (6 L) was charged until the product was completely eluted as indicated by TLC (5:1 ethyl acetate/heptane). Fractions 3-6 (500 mL each) contained the purple impurity, and fractions 10-22 were combined and concentrated to afford 103.5 g of a dark grey oil that formed a tan foamy residue while drying under vacuum. NMR of this residue showed contamination with benzoic acid, so this crude product was re-dissolved in ethyl acetate (500 mL), washed with saturated sodium bicarbonate solution (2 x 200 mL), followed by washing with 100 mL water. The organic solvent was concentrated *in vacuo* to yield the desired product as a pale tan foamy amorphous solid: (88.4 g 53% over 4 combined steps); ^1H -NMR (CDCl_3): 7.61 (m, 2H), 7.34-7.22 (m, 7H), 4.57 (m, 1H), 4.51 (s, 2H), 4.31 (m, 1H), 4.20 (m, 2H), 3.29 (p, 1H), 2.62 (dd, 1H), 2.44 (dd, 1H), 1.90 (m, 2H), 1.71 (m, 2H), and 1.43 (d, 6H); ^{19}F -NMR (CDCl_3): -113.66; Low resolution mass spectroscopy (APCI) m/z 480 $[\text{M}+\text{H}]^+$

Step G

A 3-necked, 3-L round-bottomed flask was outfitted with a large (400mL) Dean-Stark trap (with a condenser) and a J-KEM temperature probe was charged with 2-(4-Fluoro-phenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-5-isopropyl-1H-imidazole-4-carboxylic acid benzylamide (88.4 g, 184 mmol) and 1M NaOH (180.3 mL, 180.3 mmol, 0.98 equiv, based on HPLC purity of lactone 23, 98% purity in this case). The resulting mixture was diluted with water (750 mL) and warmed to 60 °C for 2h to aid in dissolution/conversion of lactone to sodium salt. After 2h, TLC (100% ethyl acetate) showed nearly complete consumption of lactone (R_f = 0.5). The biphasic solution was heated to reflux (~95 °C) to azeotrope off water (~700 mL, some water loss through top of condenser) over 3h. The remaining white slurry was diluted with toluene (500 mL) and concentrated *in vacuo* to produce a beige residue (~110 g). The crude residue was transferred to the vacuum oven at 80 °C for 12 h under a nitrogen sweep to afford a white solid (92.2 g). In a wide-mouth 2-L Erlenmeyer flask with a gentle nitrogen sweep, this solid was dissolved in refluxing MeOH (900 mL) with vigorous stirring. The solution was concentrated down by boiling off methanol until approximately 800 mL of total volume remained. While refluxing, 2-propanol (500 mL) was added dropwise over 60 min (so that the total volume remains ~800 mL; i.e. as methanol continued to boil off, 2-propanol was added at the same rate to keep a constant reaction mixture volume), during which time the refluxing solution began to precipitate sodium salt. After full addition, the mixture was refluxed until the total volume reached 700 mL, after which heating was discontinued (stirring continued), and the slurry was cooled to 23 °C (uncontrolled, no temperature ramp was used). The bright,

white fluffy solid was filtered on a glass fritted filter funnel, and the cake was rinsed with 2-propanol (100 mL). The cake was sucked dry under a nitrogen sweep for 0.5 h to provide 135 g of wet cake that was placed in the vacuum oven at 75 °C for 12 h under a slight nitrogen purge to afford 67.7 g of a white, fluffy solid. ¹H-NMR (CD₃OD): □ ppm 1.48 (m, 7 H), 1.58 (m, 1 H), 1.70 (m, 1 H), 1.81 (m, 1 H), 2.23 (dd, *J*=15.04, 7.42 Hz, 1 H), 2.29 (dd, *J*=15.24, 5.47 Hz, 1 H), 3.46 (m, 1 H), 3.73 (m, 1 H), 4.11-3.92 (m, 2 H), 4.21 (ddd, *J*=14.85, 11.33, 5.08 Hz, 1 H), 4.51 (s, 2 H), 7.33-7.19 (m, 7 H), 7.62 (m, 2 H); ¹⁹F-NMR (CD₃OD): -113.83; Low resolution mass spectroscopy (APCI) *m/z* 498 [M+H]⁺; Anal. calculated for C₂₇H₃₁F₁N₃Na₁O₅: C, 62.42; H, 6.01; N, 8.09; Na, 4.40. Found: C, 62.32; H, 5.93; N, 8.05; Na, 4.39; IR(neat) *v*_{max}= 1657, 1574, 1512, 1411, 1223, 846, and 700 cm⁻¹.

FORMULATIONS

The compounds of the present invention including those exemplified herein and all compounds of Formula I, hereafter referred to as "compound(s)" can be administered alone or in combination with one or more therapeutic agents. These include, for example, other agents for treating, preventing or controlling dyslipidemia, non-insulin dependent diabetes mellitus, obesity, hyperglycemia, hypercholesteremia, hyperlipidemia, atherosclerosis, hypertriglyceridemia, or hyperinsulinemia.

The compounds are thus well suited to formulation for convenient administration to mammals for the prevention and treatment of such disorders.

The following examples further illustrate typical formulations of the compounds provided by the invention.

Formulation 1

Ingredient	Amount
compound	0.5 to 800 mg
sodium benzoate	5 mg
isotonic saline	1000 mL

The above ingredients are mixed and dissolved in the saline for IV administration to a patient.

Formulation 2

Ingredient	Amount
compound	0.5 to 800 mg
cellulose, microcrystalline	400 mg
stearic acid	5 mg
silicon dioxide	10 mg
sugar, confectionery	50 mg

The ingredients are blended to uniformity and pressed into a tablet that is well suited for oral administration to a patient.

Formulation 3

Ingredient	Amount
compound	0.5 to 800 mg
starch, dried	250 mg
magnesium stearate	10 mg

The ingredients are combined and milled to afford material suitable for filling hard gelatin capsules administered to a patient.

Formulation 4

Ingredient	Amount % wt./ (total wt.)
compound	1 to 50
Polyethylene glycol 1000	32 to 75
Polyethylene glycol 4000	16 to 25

The ingredients are combined via melting and then poured into molds containing 2.5 g total weight.

While embodiments of the invention have been illustrated and described, it is not intended that these embodiments illustrate and describe all possible forms of the invention. Rather, the words used in the specification are words of description rather than limitation, and it is understood that various changes may be made without departing from the spirit and scope of the invention.

BIOLOGICAL ASSAYS

The compounds of the invention have demonstrated HMG Co-A reductase inhibition in standard assays commonly employed by those skilled in the art. (See, e.g., J. of Lipid Research 1998; 39:75-84; Analytical Biochemistry, 1991; 196:211-214; RR 740-01077 Pharmacology 8-Nov-82) Accordingly, such compounds and formulations comprising such compounds are useful for treating, controlling or preventing *inter alia* hypercholesterolemia, hyperlipidemia, hypertriglyceridemia or atherosclerosis.

A.) *In Vitro* assay

Rat Liver Microsomal Isolation Procedure:

Male Charles River Sprague-Dawley rats were fed with 2.5% cholestyramine in rat chow diets for 5 days before sacrificing. Livers were minced and homogenized in a sucrose homogenizing solution in an ice bath 10 times. Homogenates were diluted into a final volume of 200 mL, and centrifuged 15 min. with a Sorvall Centrifuge at 5°C, 10,000 rpm (12,000 x G). The upper fat layer was removed and the supernatant decanted into fresh tubes. This step was repeated one more time before transferring the supernatant into

ultracentrifuge tubes and centrifuged at 36,000 rpm (105,000 x G) for an hour at 5°C. The resulting supernatant was discarded and the pellet was added to total of 15 mL 0.2 M KH₂PO₄. Pellets were homogenized gently by hand about 10 times. Samples were pooled and diluted into total of 60 mL buffer. The protein concentration of the homogenate was determined by the Lowry Method using a BCA (Bicinchoninic acid), kit from Pierce Chemical Company. 1 mL aliquots of microsomes were kept frozen in liquid nitrogen.

HMGCoA (3-Hydroxy-3-methylglutaryl CoA) Reductase Assay:

Materials and Methods:

[3-¹⁴C]-HMGCoA (57.0 mCi/mmol) was purchased from Amersham Biosciences, UK. HMGCoA, mevalonolactone, β-NADPH (β-Nicotinamide Adenine Dinucleotide Phosphate, Reduced form) were purchased from Sigma Chemical Co. AG 1-8X resin was purchased from Bio-Rad Laboratory.

1. One μL of dimethyl sulfoxide (DMSO) or 1 μL of DMSO containing a test compound at a concentration sufficient to give a final assay concentration of between 0.1 nM to 1 mM was placed into each well of a Corning 96 well plate. A Volume of 34 μL of buffer (100 mM NaH₂PO₄, 10 mM Imidazole and 10 mM EDTA), (Ethylenediaminetetra acetic acid) containing with 50 μg/mL rat liver microsomes was added into each well. After incubation for 30 min. on ice, 15 μL of ¹⁴C-HMGCoA (0.024 μCi) with 15 mM NADPH, 25 mM DTT, (Dithiothreitol) was added and incubated at 37°C for an additional 45 min. The reaction was terminated by the addition of 10 μL of HCl followed by 5 μL of mevalonolactone. Plates were incubated at room temperature overnight to allow lactonization of mevalonate to mevalonolactone. The incubated samples were applied to columns containing 300 μL of AG1-X8 anion exchange resin in a Corning filter plate. The eluates were collected into Corning 96 well capture plates. Scintillation cocktail (Ultima-Flo-M) was added into each well and plates counted on a Trilux Microbeta Counter. The IC₅₀ values were calculated with GraphPad software (Prism).

Procedure:

2. Add 1 μL DMSO or compounds into the wells according to the protocol
3. Add 35μL incubation buffer with the rat microsomes into each well. Incubate 30 min. at 4°C
4. Add 15 μL ¹⁴C-HMGCoA. Incubate 45 min. at 37°C
5. Add 10 μL HCl stop reagent
6. Add 5μL mevelonolactone. Incubate overnight at room temperature
7. Apply the containing into the AG 1-X8 anion exchange resin in Corning filter plate
8. Collect the eluate into Corning capture plate
9. Add scintillation cocktail Ultima-Flo-M
10. Count on a Trilux Microbeta Counter μ
11. Calculate IC₅₀ values

Compounds of the invention exhibit a range of IC₅₀ values of less than about 500 nM in the aforementioned *in vitro* assay. Preferred compounds of the invention exhibit a range of IC₅₀ values of less

than about 100 nM. More preferred compounds of the invention exhibit a range of IC₅₀ values of less than about 20 nM. See, for example, the compounds of: Example 4, which has an IC₅₀ of 7.9 nM, Example 62, which has an IC₅₀ of 7.2 nM, Example 69, which has an IC₅₀ of 2.2 nM, Example 103, which has an IC₅₀ of 50.4 nM, Example 104, which has an IC₅₀ of 75.8 nM, Example 110, which has an IC₅₀ of 1.38 nM, Example 111, which has an IC₅₀ of 1.17 nM, and Example 112, which has an IC₅₀ of 8.39 nM.

B.) Cell Assay

Protocol for Sterol Biosynthesis in Rat Hepatocytes:

Cell culture, compounds treatment and cell labeling:

Frozen rat hepatocytes purchased from XenoTech (cat# N400572) were seeded on 6-well collagen I coated plates at a density of 10⁵ cells/per well. The cells were grown in DMEM, (Dulbecco's Modified Eagle Medium) (Gibco, #11054-020) containing 10% FBS (Fetal Bovine Serum) and 10 mM HEPES, (N-2-hydroxyethyl-piperazine-N¹-2-ethane sulfonic acid) (Gibco # 15630-080) for 24 hrs. The cells were pre-incubated with compounds for 4 hrs and then labeled by incubating in medium containing 1 uCi/per mL of ¹⁴C acetic acid for an additional 4 hrs. After labeling, the cells were washed twice with 5 mM MOPS, (3-[N-morpholino] propane sulfonic acid) solution containing 150 mM NaCl and 1 mM EDTA and collected in the lysis buffer containing 10% KOH and 80%(vol.) ethanol.

Cholesterol extraction and data analysis:

In order to separate labeled cholesterol from labeled non-cholesterol lipids, the cells lysates were subject to saponification at 60°C for 2 hrs. The lysates were then combined with 0.5 volume of H₂O and 2 volumes of hexane, followed by 30 minutes of vigorous shaking. After the separation of two phases, the upper-phase solution was collected and combined with 5 volumes of scintillation cocktail. The amount of ¹⁴C cholesterol was quantified by liquid scintillation counting. The IC₅₀ values were calculated with GraphPad software (Prism 3.03).

Compounds of the invention exhibit a range of IC₅₀ values of less than about 1000 nM in the aforementioned cell assay. Preferred compounds of the invention exhibit a range of IC₅₀ values of less than about 100 nM. See, for example, the compounds of: Example 4, which has an IC₅₀ of 0.42 nM, Example 62, which has an IC₅₀ of 0.58 nM, Example 69, which has an IC₅₀ of 0.18 nM, Example 103, which has an IC₅₀ of 0.0880 nM, Example 110, which has an IC₅₀ of 0.218 nM, Example 111, which has an IC₅₀ of 0.146 nM, and Example 112, which has an IC₅₀ of 1.15 nM.

C.) Protocol for Sterol Biosynthesis in L6 Rat Myoblast:

Cell culture, compounds treatment and cell labeling:

L6 rat myoblast purchased from ATCC (CRL-1458) were grown in T-150 vented culture flasks and seeded on 12-well culture plates at a density of 60,000 cells per well. The cells were grown in DMEM, (Dulbecco's Modified Eagle Medium) (Gibco, #10567-014) containing 10% heat inactivated FBS (Fetal Bovine Serum) (Gibco # 10082-139) for 72 hours until reaching confluence. The cells were pre-incubated in media with compound and 0.2% DMSO (dimethyl sulfoxide) for 3 hours and then labeled by incubating in medium containing compound, 0.2% DMSO and 1 uCi/per mL of ¹⁴C acetic acid for an additional 3

hours. After labeling, the cells were washed once with 1x PBS (Gibco #14190-144) then lysed overnight at 4°C in buffer containing 10% KOH and 78%(vol.) ethanol.

Cholesterol extraction and data analysis:

Lipid ester bonds were hydrolyzed by saponification of the lysates at 60°C for 2 hours. Sterols (including cholesterol) were extracted from saponified lysates by combining with 3 volumes of hexane and mixing by pipette 6 times. The upper organic phase solution was collected and combined with an equal volume of 1N KOH in 50% methanol and mixed by pipette 6 times. The upper organic phase was collected in a scintillant-coated plate (Wallac #1450-501) and hexanes removed by evaporation at room temperature for 3 hours. The amount of ¹⁴C cholesterol was quantified by scintillation counting in a Trilux 1450 plate reader (Wallac). The IC₅₀ values were calculated from % inhibitions relative to negative controls vs. compound concentration on Microsoft excel 2000 data analysis wizard using a sigmoid inhibition curve model with formula:

$$y = Bmax (1-(x^n/K^n+x^n)) + y2$$

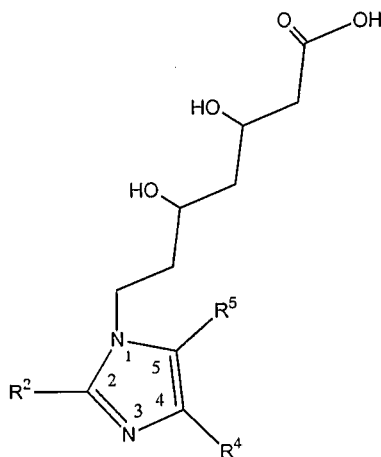
Where K is the IC₅₀ for the inhibition curve, X is inhibitor concentration, Y is the response being inhibited and Bmax+Y2 is the limiting response as X approaches zero. Compounds of the invention have a L6 IC₅₀ value greater than about 100 nM in the aforementioned L6 Rat Myoblast. See, for example, the compounds of: Example 4, which has an L6 IC₅₀ of 3069 nM, Example 62, which has an L6 IC₅₀ of 703 nM, Example 69, which has an L6 IC₅₀ of 159 nM, Example 110, which has an L6 IC₅₀ of 632 nM, Example 111, which has an L6 IC₅₀ of 6400 nM, and Example 112, which has an L6 IC₅₀ of 73,500 nM.

Preferred compounds of the invention exhibit a hepatocyte selectivity greater than about 1000 ((L6 IC₅₀ / Rat hepatocyte IC₅₀) > 1000), and have a L6 IC₅₀ value greater than about 1000 nM.

CLAIMS

What is claimed is:

1. A compound having a Formula I,



Formula I

or a pharmaceutically acceptable salt, ester, amide or stereoisomer thereof wherein:

R^2 and R^5 are each independently H; halogen; C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted;

R^4 is halogen; H; C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted; $-(CH_2)_n C(O)NR^6R^7$; $R^8S(O)_n$;

$-(CH_2)_n NR^6R^7$; $-(CH_2)_n COOR'$; or $-(CH_2)_n COR'$;

R^6 and R^7 are each independently H; C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted with aryl, heteroaryl, lower alkyl, halogen, OR' , $-(CH_2)_n COOR'$, $-(CH_2)_n CONR'R''$, $(CH_2)_n SO_2R'$, $SO_2NR'R''$ or CN;

$-(CH_2)_n COR'$, $-(CH_2)_n COOR'$, $-(CH_2)_n CONR'R''$ or $-(CH_2)_n SO_2R'$; or

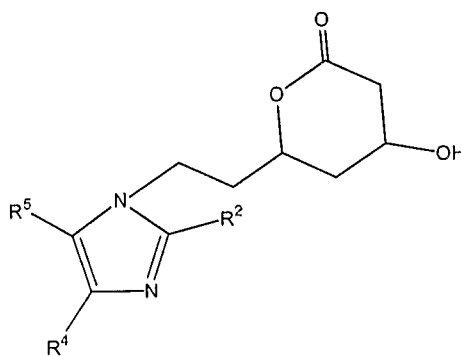
N, R^6 and R^7 taken together form a 4-11 member ring optionally containing up to two heteroatoms selected from O, N and S, said ring being optionally substituted with aryl, aralkyl, heteroaryl, heteroaralkyl, C_1 - C_{10} alkyl, C_3 - C_8 cycloalkyl, halogen, OR' , $-(CH_2)_n COOR'$, $-(CH_2)_n CONR'R''$, $-(CH_2)_n SO_2R'$, $SO_2NR'R''$ or CN;

R^8 is aryl, aralkyl, alkyl, heteroaryl, or heteroaralkyl; optionally substituted;

R' and R'' are each independently H; C_1 - C_{12} alkyl, aryl or aralkyl; optionally substituted; and n is 0-2.

2. The compound of the Formula I of claim 1, a pharmaceutically acceptable salt, ester, amide or stereoisomer thereof wherein R^2 is aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted.

3. The compound of claim 1 or claim 2, a pharmaceutically acceptable salt, ester, amide or stereoisomer thereof wherein R^4 is $-(CH_2)_nC(O)NR^6R^7$.
4. The compound of claim 2, a pharmaceutically acceptable salt, ester, amide or stereoisomer thereof wherein R^2 is phenyl, optionally substituted with one or more halogen.
5. The compound of claim 1 or claim 3, a pharmaceutically acceptable salt, ester, amide or stereoisomer thereof wherein one of R^6 and R^7 is aralkyl, optionally substituted; and the other one of R^6 and R^7 is H.
6. The compound of claim 5, a pharmaceutically acceptable salt, ester, amide or stereoisomer thereof wherein one of R^6 and R^7 is benzyl, optionally substituted.
7. The compound of the Formula I of claim 1, a pharmaceutically acceptable salt, ester, amide or stereoisomer thereof wherein R^5 is isopropyl or cyclopropyl.
8. A pharmaceutically acceptable salt of a compound of the Formula I of claim 1 wherein the salt is a sodium salt.
9. A lactone form of a compound of claim 1 having a Formula C:

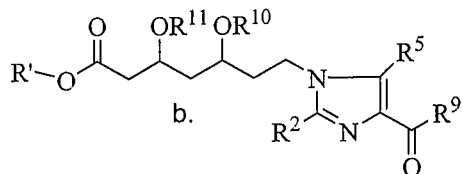


C.

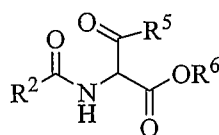
wherein R^2 , R^4 and R^5 are as defined in claim 1.

10. The lactone form of claim 9, wherein R^2 is phenyl optionally substituted with one or more halogen, R^4 is $-(CH_2)_nC(O)NR^6R^7$, one of R^6 and R^7 is aralkyl, optionally substituted, and the other one of R^6 and R^7 is H; and R^5 is C_1 - C_6 alkyl or C_3 - C_8 cycloalkyl.

11. A process for preparing a compound having a Formula b.

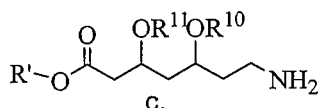


from a compound having a Formula a.



comprising the following steps:

- 1.) Reacting the compound a. with a compound having a formula c.,



in a solvent; and

optionally reacting the compound a. with a compound NHR^6R^7 , in a solvent, prior to the first step;

wherein R^2 and R^5 are each independently H; halogen; $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted;

R^9 is $-\text{OR}^6$ or $-\text{NR}^6\text{R}^7$;

R^6 is H; $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted with aryl, heteroaryl, lower alkyl, halogen, OR' , $-(\text{CH}_2)_n\text{COOR}'$, $-(\text{CH}_2)_n\text{CONR}'\text{R}''$, $(\text{CH}_2)_n\text{SO}_2\text{R}'$, $\text{SO}_2\text{NR}'\text{R}''$ or CN;

R^7 is H; $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl; optionally substituted with aryl, heteroaryl, lower alkyl, halogen, OR' ,

$-(\text{CH}_2)_n\text{COOR}'$, $-(\text{CH}_2)_n\text{CONR}'\text{R}''$, $(\text{CH}_2)_n\text{SO}_2\text{R}'$, $\text{SO}_2\text{NR}'\text{R}''$ or CN; $-(\text{CH}_2)_n\text{COR}'$, $-(\text{CH}_2)_n\text{COOR}'$, $-(\text{CH}_2)_n\text{CONR}'\text{R}''$ or $-(\text{CH}_2)_n\text{SO}_2\text{R}'$; or

N , R^6 and R^7 taken together form a 4-11 member ring optionally containing up to two heteroatoms selected from O, N and S, said ring being optionally substituted with aryl, aralkyl, heteroaryl, heteroaralkyl, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, halogen, OR' , $-(\text{CH}_2)_n\text{COOR}'$, $-(\text{CH}_2)_n\text{CONR}'\text{R}''$, $-(\text{CH}_2)_n\text{SO}_2\text{R}'$, $\text{SO}_2\text{NR}'\text{R}''$ or CN;

R' and R'' are each independently H; $\text{C}_1\text{-C}_{12}$ alkyl, aryl or aralkyl; optionally substituted; n is 0-2;

R^{10} and R^{11} are each independently $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}(\text{O})\text{R}^7$, $-\text{SiR}^{12}\text{R}^{13}\text{R}^{14}$ or R^{10} and R^{11} taken together from isopropyl; and R^{12} , R^{13} and R^{14} are each independently $\text{C}_1\text{-C}_6$ alkyl.

12. A compound of the Formula I of claim 1 selected from the group consisting of:

(3R,5R)-7-[4-Benzylcarbamoyl-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(2-methoxy-ethylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-phenylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[4-(1,3-Dihydro-isoindole-2-carbonyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[4-(Benzyl-ethyl-carbamoyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-[(pyridin-3-ylmethyl)-carbamoyl]-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-(2-pyridin-3-yl-ethylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-((R)-2-phenyl-propylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[4-[2-(4-Chloro-phenyl)-3-hydroxy-propylcarbamoyl]-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-[2-(4-sulfamoyl-phenyl)-ethylcarbamoyl]-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-((S)-1-methyl-3-phenyl-propylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-fluoro-phenyl)-4-[2-(3-fluoro-phenyl)-ethylcarbamoyl]-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-fluoro-phenyl)-4-[(1S,2S)-2-hydroxy-1-methoxymethyl-2-phenyl-ethylcarbamoyl]-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-[2-(4-methoxy-phenyl)-ethylcarbamoyl]-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-fluoro-phenyl)-4-((S)-1-hydroxymethyl-2-phenyl-ethylcarbamoyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-fluoro-phenyl)-4-[(1S,2S)-2-hydroxy-1-hydroxymethyl-2-(4-methylsulfanyl-phenyl)-ethylcarbamoyl]-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[4-[2-(4-chloro-phenyl)-ethylcarbamoyl]-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-((S)-2-phenyl-propylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-[2-(3-methoxy-phenyl)-ethylcarbamoyl]-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-fluoro-phenyl)-4-[2-(4-fluoro-phenyl)-ethylcarbamoyl]-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

5 (3R,5R)-7-[4-[2-(3-chloro-phenyl)-ethylcarbamoyl]-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-(2-pyridin-4-yl-ethylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

0 (3R,5R)-7-[2-(4-fluoro-phenyl)-4-((1R,2R)-2-hydroxy-1-hydroxymethyl-2-phenyl-ethylcarbamoyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-benzylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-phenylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

5 (3S,5R)-7-[2-(4-fluoro-phenyl)-5-isopropyl-4-(toluene-4-sulfonyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid; (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-ethyl-4-(4-fluorophenylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-propyl-4-phenylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-propyl-4-benzylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

0 (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-propyl-4-phenethylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-propyl-4-(4-fluorophenylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-methyl-4-phenylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

5 (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-methyl-4-benzylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-methyl-4-phenethylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[4-[(Biphenyl-3-ylmethyl)-carbamoyl]-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

0 (3R,5R)-7-[2-(4-Fluoro-phenyl)-5-isopropyl-4-phenethylcarbamoyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-5-methyl-4-(4-sulfamoyl-benzylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[4-benzylcarbamoyl-2-phenyl-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

5 (3R,5R)-7-[4-(3-Chloro-benzylcarbamoyl)-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;

(3R,5R)-7-[2-(4-Fluoro-phenyl)-4-(indan-1-ylcarbamoyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;
(3R,5R)-7-[4-Benzylcarbamoyl-5-cyclopropyl-2-(4-fluoro-phenyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;
(3R,5R)-7-[5-Cyclopropyl-2-(4-fluoro-phenyl)-4-(4-methoxy-benzylcarbamoyl)-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid;
and pharmaceutically acceptable salts and lactone forms thereof.

13. The compound as defined in any one of claims 1-12 respectively, selected from the group consisting of (3R,5R)-7-[4-Benzylcarbamoyl-2-(4-fluoro-phenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxy-heptanoic acid; pharmaceutically acceptable salts and lactone forms thereof.

14. A combination of the compound or the pharmaceutically acceptable salt or lactone form thereof, as defined in any one of claims 1-13 respectively, and one or more additional pharmaceutically active agent.

15. A pharmaceutical composition comprising the compound as defined in any one of claims 1-13 respectively, or the combination as defined in claim 14; and a pharmaceutically acceptable carrier, diluent or vehicle.