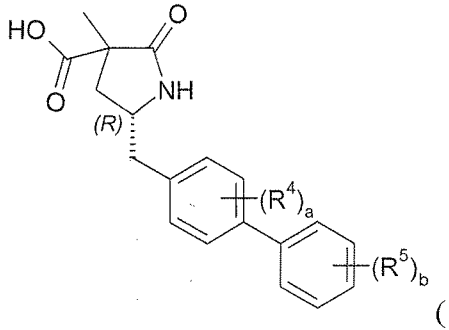
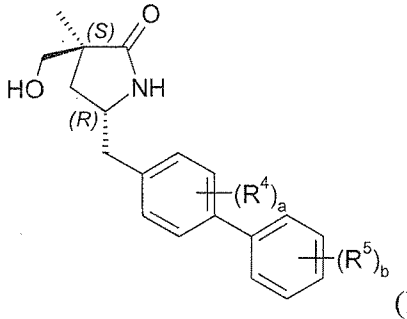


(1)

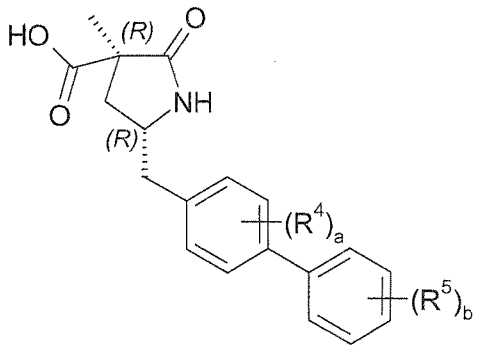
in 2-methyltetrahydrofuran and cyclopentyl methyl ether ~~an ether solvent~~ to form a compound of formula I or a salt thereof.

Another aspect of the present disclosure relates to a process for preparing a compound of formula IIa:



(IIa)

or a salt thereof, where a is 0 or 1; R^4 is selected from halo, $-CH_3$, $-CF_3$, and -CN; b is 0 or an integer from 1 to 3; and each R^5 is independently selected from halo, -OH, $-CH_3$, $-OCH_3$, and $-CF_3$; the process comprising the steps of (a) activation of the carboxyl group of a compound of formula I:



(I);

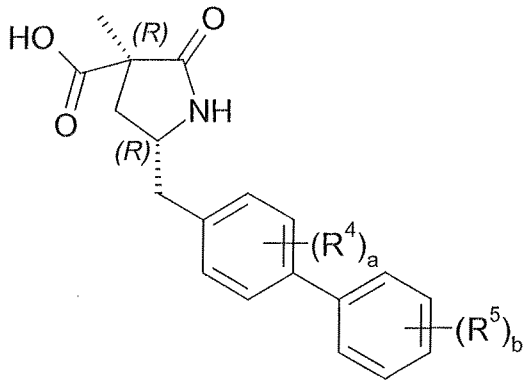
and (b) reacting the resulting product with a reducing agent to form a compound of formula IIa or a salt thereof.

Another embodiment of the present disclosure relates to intermediates used in the processes of the present disclosure. In one such aspect of the present disclosure, the intermediate has formula (II):

CLAIMS

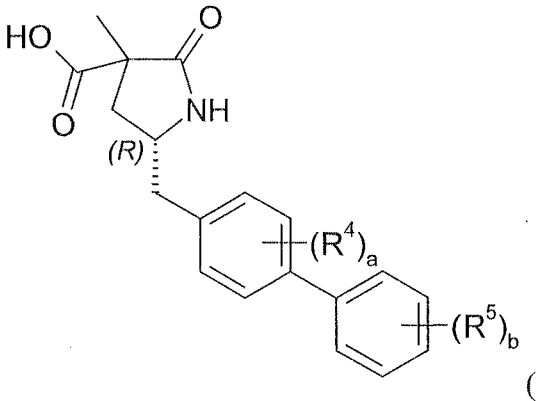
What is claimed is:

1. A process for preparing a compound of formula I:



(I)

or a salt thereof, where a is 0 or 1; R^4 is selected from halo, $-CH_3$, $-CF_3$, and -CN; b is 0 or an integer from 1 to 3; and each R^5 is independently selected from halo, -OH, $-CH_3$, $-OCH_3$, and $-CF_3$; the process comprising the step of reslurrying a compound of formula (1):



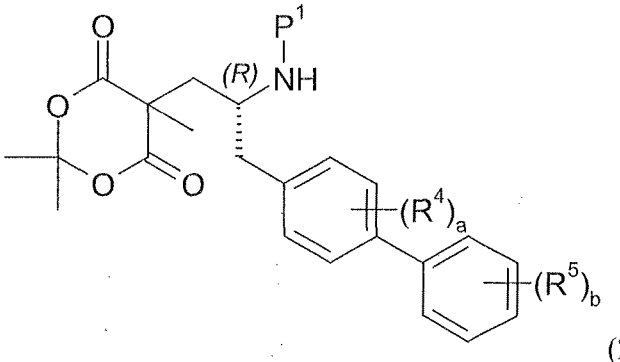
(1)

in 2-methyltetrahydrofuran and cyclopentyl methyl ether ~~an ether solvent~~ to form a compound of formula I or a salt thereof.

~~2. The process of Claim 1, where the ether solvent is 2-methyltetrahydrofuran.~~

~~3. The process of Claim 2, where the ether solvent further comprises cyclopentyl methyl ether.~~

42. The process of Claim 1, where the compound of formula (1) is prepared by the acidic deprotection of a compound of formula (2):



(2),

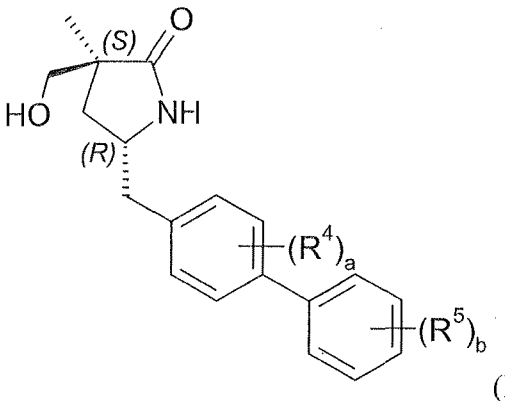
where P^1 is an amino protecting group.

53. The process of Claim 42, where acidic deprotection is conducted with 3M HCl.

64. The process of Claim 42, where P^1 is selected from acetyl, adamantyl-oxycarbonyl, *t*-amyloxycarbonyl, benzothiophene sulfone-2-methoxycarbonyl, benzoyl, benzyl, benzyloxycarbonyl, 2-(*p*-biphenylyl)propyl-2-oxycarbonyl, *t*-butoxycarbonyl, 2-(*t*-butylsulfonyl)-2-propenyloxycarbonyl, 3,4-dimethoxybenzyl, 2,2-dimethyl-3,5-dimethyloxybenzyloxycarbonyl, dithiasuccinoyl, formyl, 9-fluorenylmethoxycarbonyl, 2-furanmethyloxycarbonyl, *p*-methoxybenzyl, *p*-methoxybenzyl carbonyl, 1-methylcyclobutyloxycarbonyl, *o*-nitrophenylsulfenyl, 2-phenylpropyl-2-oxycarbonyl, 2-(*p*-phenylazophenyl)propyl-2-oxycarbonyl, silyl ethers, tosyl, trifluoroacetyl, β-trimethylsilylethyloxycarbonyl, triphenylmethyl, and trityl.

75. The process of Claim 64, where P^1 is *t*-butoxycarbonyl.

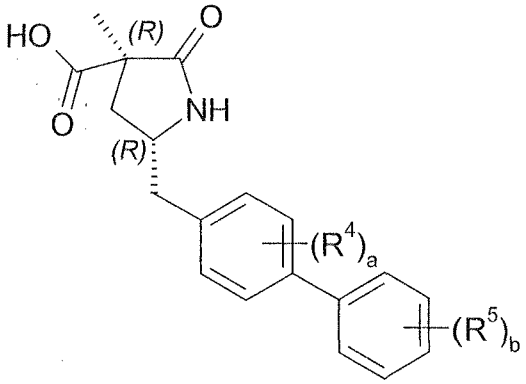
86. A process for preparing a compound of formula IIa:



(IIa)

or a salt thereof, where a is 0 or 1; R^4 is selected from halo, $-CH_3$, $-CF_3$, and -CN; b is 0 or

an integer from 1 to 3; and each R^5 is independently selected from halo, -OH, $-CH_3$, $-OCH_3$, and $-CF_3$; the process comprising the steps of (a) activation of the carboxyl group of a compound of formula I:



(I);

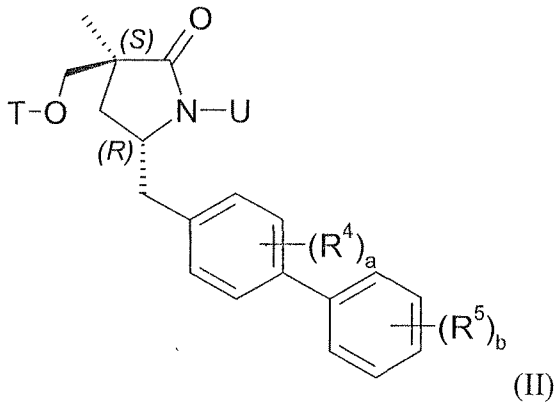
and (b) reacting the resulting product with a reducing agent to form a compound of formula IIa or a salt thereof.

~~97~~97. The process of Claim ~~86~~86, where step (a) is conducted with isobutyl chloroformate in the presence of a tertiary amine base.

~~108~~108. The process of Claim ~~97~~97, where the tertiary amine base is *N*-methylmorpholine.

~~119~~119. The process of Claim ~~86~~86, where the reducing agent is sodium tetrahydroborate.

~~1210~~1210. A compound of formula II:



(II)

where:

a is 0 or 1; R^4 is selected from halo, $-CH_3$, $-CF_3$, and -CN;

b is 0 or an integer from 1 to 3; and each R^5 is independently selected from halo,

-OH, -CH_3, -OCH_3, and -CF_3;

T is H or P^2, where P^2 is an alcohol protecting group; and

U is H or P^3, where P^3 is an amino protecting group;

or a salt thereof.

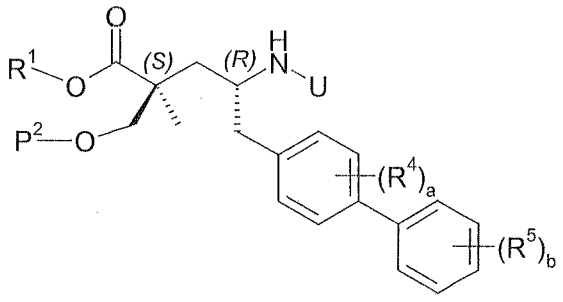
~~13~~11. The compound of Claim ~~12~~10, where P^2 is selected from acetyl, benzoyl, benzyl, *p*-methoxybenzyl ether, β-methoxyethoxymethyl ether, methylthiomethyl ether, pivaloyl, silyl ethers, tetrahydropyranyl, triphenylmethyl, and trityl.

~~14~~12. The compound of Claim ~~13~~11, where T is H or tetrahydropyranyl.

~~15~~13. The compound of Claim ~~12~~10, where P^3 is selected from acetyl, adamantyl-oxycarbonyl, *t*-amyloxycarbonyl, benzothiophene sulfone-2-methoxycarbonyl, benzoyl, benzyl, benzyloxycarbonyl, 2-(*p*-biphenylyl)propyl-2-oxycarbonyl, *t*-butoxycarbonyl, 2-(*t*-butylsulfonyl)-2-propenyloxycarbonyl, 3,4-dimethoxybenzyl, 2,2-dimethyl-3,5-dimethyloxybenzyloxycarbonyl, dithiasuccinoyl, formyl, 9-fluorenylmethoxycarbonyl, 2-furanmethyloxycarbonyl, *p*-methoxybenzyl, *p*-methoxybenzyl carbonyl, 1-methylcyclobutyloxycarbonyl, *o*-nitrophenylsulfenyl, 2-phenylpropyl-2-oxycarbonyl, 2-(*p*-phenylazophenyl)propyl-2-oxycarbonyl, silyl ethers, tosyl, trifluoroacetyl, β-trimethylsilylethyloxycarbonyl, triphenylmethyl, and trityl.

~~16~~14. The compound of Claim ~~15~~13, where U is H or *t*-butoxycarbonyl.

~~17~~15. A compound of formula III':

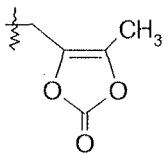


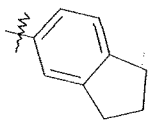
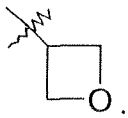
(III')

where:

R^1 is selected from H, -C_{1-8}alkyl, -C_{1-3}alkylene-C_{6-10}aryl, -$[(CH_2)_2O]_{1-3}CH_3$, -C_{1-6}alkylene-$OC(O)R^{10}$, -C_{1-6}alkylene-$NR^{11}R^{12}$, -C_{1-6}alkylene-$C(O)R^{13}$,

-C_{0-6}alkylenemorpholinyl, -C_{1-6}alkylene-SO_2-C_{1-6}alkyl,



,  , and 

;

R^{10} is selected from -C_{1-6}alkyl, -O-C_{1-6}alkyl, -O-C_{3-7}cycloalkyl, -CH[$CH(CH_3)_2$]-NH_2, and -CH[$CH(CH_3)_2$]-NHC(O)O-C_{1-6}alkyl; R^{11} and R^{12} are -C_{1-6}alkyl or are taken together as -$(CH_2)_{3-6}$-, -C(O)-$(CH_2)_3$-, or -$(CH_2)_2O(CH_2)_2$-; R^{13} is selected from -O-C_{1-6}alkyl, -O-benzyl, and -$NR^{11}R^{12}$;

a is 0 or 1; R^4 is selected from halo, -CH_3, -CF_3, and -CN;

b is 0 or an integer from 1 to 3; each R^5 is independently selected from halo, -OH, -CH_3, -OCH_3, and -CF_3;

P^2 is an alcohol protecting group;

U is H or P^3, where P^3 is an amino protecting group;

and where each alkyl group in R^1 is optionally substituted with 1 to 8 fluoro atoms;

or a salt thereof.

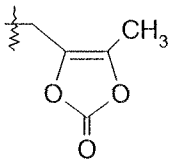
~~18~~16. The compound of Claim ~~17~~15, where P^2 is selected from acetyl, benzoyl, benzyl, *p*-methoxybenzyl ether, β-methoxyethoxymethyl ether, methylthiomethyl ether, pivaloyl, silyl ethers, tetrahydropyranyl, triphenylmethyl, and trityl.

~~19~~17. The compound of Claim ~~18~~16, where P^2 is tetrahydropyranyl.

~~20~~18. The compound of Claim ~~17~~15, where P^3 is selected from acetyl, adamantyl-oxycarbonyl, *t*-amyloxycarbonyl, benzothiophene sulfone-2-methoxycarbonyl, benzoyl, benzyl, benzyloxycarbonyl, 2-(*p*-biphenylyl)propyl-2-oxycarbonyl, *t*-butoxycarbonyl, 2-(*t*-butylsulfonyl)-2-propenyloxycarbonyl, 3,4-dimethoxybenzyl, 2,2-dimethyl-3,5-dimethyloxybenzyloxycarbonyl, dithiasuccinoyl, formyl, 9-fluorenylmethoxycarbonyl, 2-furanmethyloxycarbonyl, *p*-methoxybenzyl, *p*-methoxybenzyl carbonyl, 1-methylcyclobutyloxycarbonyl, *o*-nitrophenylsulfenyl, 2-phenylpropyl-2-oxycarbonyl, 2-(*p*-phenylazophenyl)propyl-2-oxycarbonyl, silyl ethers, tosyl, trifluoroacetyl, β-trimethylsilylethyloxycarbonyl, triphenylmethyl, and trityl.

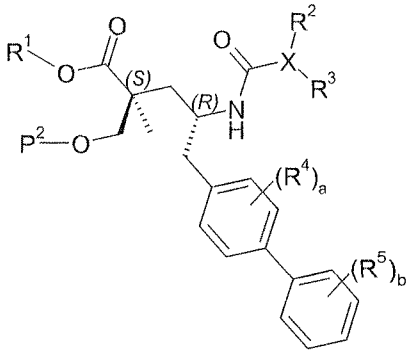
~~21~~19. The compound of Claim ~~20~~18, where U is H or *t*-butoxycarbonyl.

~~22~~20. The compound of Claim ~~17~~15, where R^1 is:



.

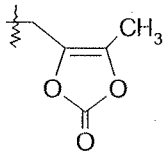
~~23~~21. A compound of formula IV:

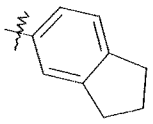


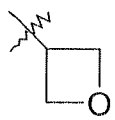
(IV)

where:

R^1 is selected from H, $-C_{1-8}$alkyl, $-C_{1-3}$alkylene-C_{6-10}aryl, $-[(CH_2)_2O]_{1-3}CH_3$, $-C_{1-6}$alkylene-$OC(O)R^{10}$, $-C_{1-6}$alkylene-$NR^{11}R^{12}$, $-C_{1-6}$alkylene-$C(O)R^{13}$, $-C_{0-6}$alkylenemorpholinyl, $-C_{1-6}$alkylene-SO_2-C_{1-6}alkyl,



, 

, and 

;

R^{10} is selected from $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-O-C_{3-7}$cycloalkyl, $-CH[CH(CH_3)_2]-NH_2$, and $-CH[CH(CH_3)_2]-NHC(O)O-C_{1-6}$alkyl; R^{11} and R^{12} are $-C_{1-6}$alkyl or are taken together as $-(CH_2)_{3-6}-$, $-C(O)-(CH_2)_3-$, or $-(CH_2)_2O(CH_2)_2-$; R^{13} is selected from $-O-C_{1-6}$alkyl, -O-benzyl, and $-NR^{11}R^{12}$;

X is selected from pyrazole, imidazole, triazole, benzotriazole, tetrazole, oxazole, isoxazole, thiazole, pyrimidine, pyridazine, benzimidazole, pyran, and pyridyltriazole;

R^2 is absent or selected from H; halo; $-C_{0-5}$alkylene-OH; $-C_{1-6}$alkyl; $-C_{3-7}$cycloalkyl; $-C_{0-2}$alkylene-$O-C_{1-6}$alkyl; $-C(O)C_{1-6}$alkyl; $-C_{0-1}$alkylene-COOH; $-C(O)NR^{20}R^{21}$; -NHC(O)-phenylene-OCH_3; =O; phenyl optionally substituted with one or two groups independently selected from halo, -OH, and $-OCH_3$; pyridinyl; and pyrazinyl; R^{20} is H or $-C_{1-6}$alkyl; R^{21} is

selected from H, -C_{1-6}alkyl, -$(CH_2)_2OH$, -$(CH_2)_2OCH_3$, -$(CH_2)_2SO_2NH_2$, and -C_{0-1}alkylene-C_{3-7}cycloalkyl; or R^{20} and R^{21} are taken together to form a saturated or partially unsaturated -C_{3-5}heterocycle optionally substituted with halo or -OH, and optionally containing an oxygen atom in the ring; and R^2, when present, is attached to a carbon atom;

R^3 is selected from H; -OH; -C_{1-6}alkyl; -C_{1-2}alkylene-COOH; -$CH_2OC(O)CH(R^{30})NH_2$; -$CH[CH(CH_3)_2]$-NHC(O)O-C_{1-6}alkyl; pyridinyl; and phenyl or benzyl optionally substituted with one or more groups selected from halo and -OCH_3; R^{30} is selected from H, -$CH(CH_3)_2$, phenyl, and benzyl; and R^3 is attached to a carbon or nitrogen atom; and when R^3 is attached to nitrogen atom, R^3 can be P^4, where P^4 is an amino protecting group;

a is 0 or 1; R^4 is selected from halo, -CH_3, -CF_3, and -CN;

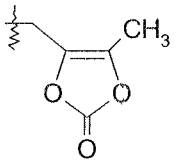
b is 0 or an integer from 1 to 3; each R^5 is independently selected from halo, -OH, -CH_3, -OCH_3, and -CF_3;

P^2 is an alcohol protecting group;

and where each alkyl group in R^1, R^2, and R^3 is optionally substituted with 1 to 8 fluoro atoms;

or a tautomer or salt thereof.

~~24~~22. The compound of Claim ~~23~~21, where R^1 is:



~~25~~23. The compound of Claim ~~23~~21, where X is triazole.

~~26~~24. The compound of Claim ~~23~~21, where R^2 is H.

~~27~~25. The compound of Claim ~~23~~21, where P^4 is selected from acetyl, adamantyl-oxycarbonyl, *t*-amyloxycarbonyl, benzothiophene sulfone-2-methoxycarbonyl, benzoyl, benzyl, benzyloxycarbonyl, 2-(*p*-biphenylyl)propyl-2-oxycarbonyl, *t*-butoxycarbonyl, 2-(*t*-butylsulfonyl)-2-propenyloxycarbonyl, 3,4-dimethoxybenzyl, 2,2-dimethyl-3,5-dimethyloxybenzyloxycarbonyl, dithiasuccinoyl, formyl, 9-fluorenylmethoxycarbonyl, 2-

furanmethyloxycarbonyl, *p*-methoxybenzyl, *p*-methoxybenzyl carbonyl, 1-methylcyclobutyloxycarbonyl, *o*-nitrophenylsulfenyl, 2-phenylpropyl-2-oxycarbonyl, 2-(*p*-phenylazophenyl)propyl-2-oxycarbonyl, silyl ethers, tosyl, trifluoroacetyl, β-trimethylsilylethyloxycarbonyl, triphenylmethyl, and trityl.

~~28~~26. The compound of Claim ~~27~~25, where R^3 is P^4, and P^4 is trityl.

~~29~~27. The compound of Claim ~~23~~21, where P^2 is selected from acetyl, benzoyl, benzyl, *p*-methoxybenzyl ether, β-methoxyethoxymethyl ether, methylthiomethyl ether, pivaloyl, silyl ethers, tetrahydropyranyl, triphenylmethyl, and trityl.

~~30~~28. The compound of Claim ~~29~~27, where P^2 is tetrahydropyranyl.