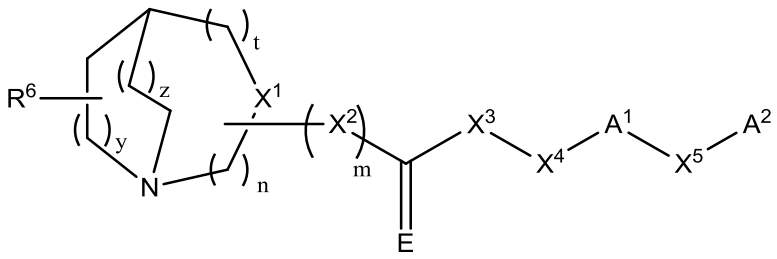
Claims

1. A method of preparing a compound of the formula,



I

wherein:

n is 1, 2 or 3;

m is 1;

t is 0, 1 or 2;

y is 1 or 2;

z is 0, 1 or 2;

E is O;

$X^1$is CR^1;

X^2 is O;

X^3 is -NH;

X^4 is CR^4R^5, CH_2 CR^4R^5 or CH_2 –(C_1-C_6) alkyl-CR^4R^5;

X^5 is a direct bond, O, S, SO_2, CR^4R^5; (C_1-C_6)alkyl, (C_1-C_6)alkyloxy, (C_1-C_6)alkenyl, (C_1-C_6)alkenyloxy;

R^1 is H, CN, (C_1-C_6)alkylcarbonyl, or (C_1-C_6)alkyl;

R^4 and R^5 are independently selected from H, (C_1-C_6)alkyl, or taken together with the carbon to which they are attached to form a spiro (C_3-C_{10})cycloalkyl ring or spiro (C_3-C_{10})cycloalkoxy ring;

R^6 is -H, halogen, -CN, (C_6-C_{12})aryl, (C_6-C_{12})aryloxy, (C_1-C_6)alkyloxy; (C_1-C_6)alkyl optionally substituted by one to four halo or (C_1-C_6)alkyl;

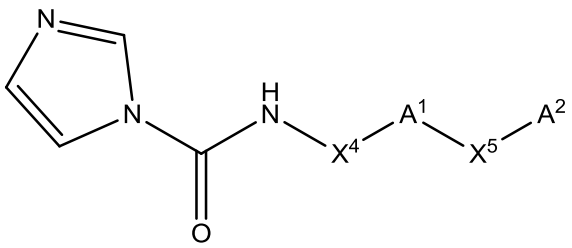
A^1 is (C_2-C_6)alkynyl; (C_3-C_{10})cycloalkyl, (C_6-C_{12})aryl, (C_2-C_9)heteroaryl, (C_2-C_9)heterocycloalkyl or benzo(C_2-C_9)heterocycloalkyl optionally substituted with one or more substituents selected from the group consisting of halo**,** (C_1-C_6)alkyl optionally

substituted by one to three halo; (C_1-C_6)alkenyl, amino, (C_1-C_6)alkylamino, (C_1-C_6)dialkylamino, (C_1-C_6)alkoxy, nitro, CN, -OH, (C_1-C_6)alkyloxy optionally substituted by one to three halo; (C_1-C_6)alkoxycarbonyl, and (C_1-C_6) alkylcarbonyl;

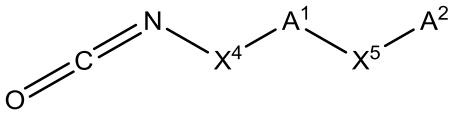
A^2 is H, (C_3-C_{10})cycloalkyl, (C_6-C_{12})aryl, (C_2-C_9)heteroaryl, (C_2-C_9)heterocycloalkyl or benzo(C_2-C_9)heterocycloalkyl optionally substituted with one or more substituents selected from the group consisting of halo**,** (C_1-C_6)alkyl optionally substituted by one to three halo; (C_1-C_6)alkylenyl, amino, (C_1-C_6) alkylamino, (C_1-C_6)dialkylamino, (C_1-C_6)alkoxy, O(C3-C6 cycloalkyl), (C_3-C_6) cycloalkoxy, nitro, CN, OH, (C_1-C_6)alkyloxy optionally substituted by one to three halo; (C_3-C_6) cycloalkyl, (C_1-C_6) alkoxycarbonyl, (C_1-C_6) alkylcarbonyl, (C_1-C_6) haloalkyl;

with the proviso that the sum of n + t + y + z is not greater than 6;

comprising reacting the compounds of Formula II and Formula IV

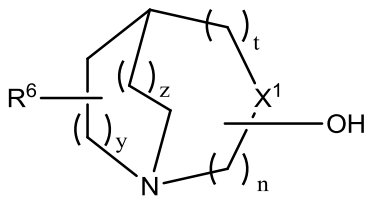


II



IV

with a compound of Formula III



III

wherein n, t, y, z, X^4, A^1, X^5 and A^2 are as defined above.

2. A method according to claim 1, wherein n is 1; t is 0; y is 1 and z is 1.

3. A method according to claim 2, wherein X^4 is CR^4R^5.

4. A method according to claim 3, wherein R^4 and R^5 are each methyl.

5. A method according to claim 4, wherein A^1 is $(C_2\text{-}C_9)$heteroaryl.

6. A method according to claim 5, wherein A^1 is thiophene, thiazole, isothiazole, furane, oxazole, isoxazole, pyrrole, imidazole, pyrazole, triazole, pyridine, pymiridine, pyridazine, indole, benzothiazole, benzoisoxazole, benzopyrazole, benzoimidazole, benzofuran or benzooxazole.

7. A method according to claim 6, wherein A^1 is thiazole.

8. A method according to claim 7, wherein R^6 is H.

9. A method according to claim 8, wherein X^5 is a direct bond.

10. A method according to claim 9, wherein A^2 is $(C_6\text{-}C_{12})$aryl.

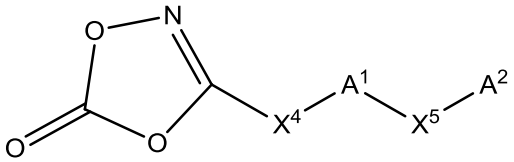
11. A method according to claim 10, wherein A^2 is phenyl.

12. A method according to claim 11, wherein the phenyl group is substituted by halo.

13. A method according to claim 12, wherein the halo group is fluoro.

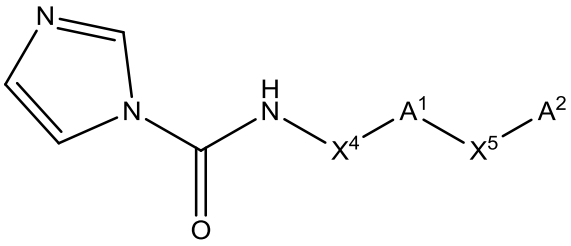
14. A method according to claim 13, wherein R^1 is hydrogen.

15. A method according to claim 1, further including reacting, while heating to reflux, the compound of Formula V

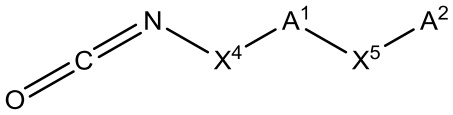


V

with imidazole to form the compounds of Formula II and Formula IV



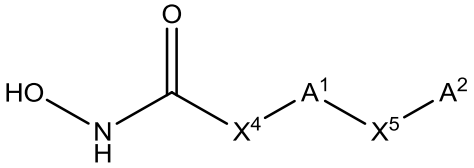
II



IV

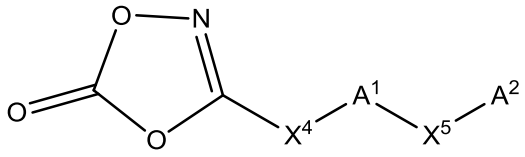
wherein X^4, A^1, X^5 and A^2 are as defined above.

16. A method according to claim0 15, further including reacting the compound of Formula VI



VI

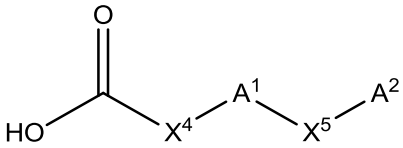
with N, N'- carbonyldiimidazole to form the compound of Formula V



V

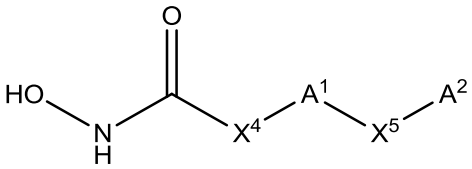
wherein X^4, A^1, X^5 and A^2 are as defined above.

17. A method according to claim 16, further including reacting the compound of Formula VII



VII

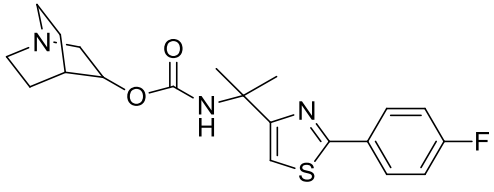
with N, N'- carbonyldiimidazole and hydroxylamine to form the compound of Formula VII



VI

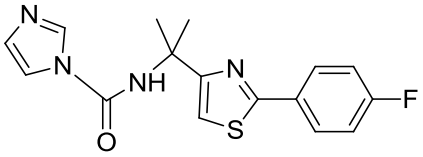
wherein X^4, A^1, X^5 and A^2 are as defined above.

18. A method of preparing the compound of Formula VIII

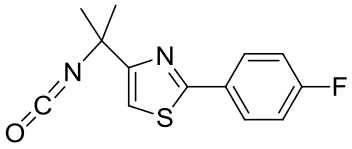


VIII

comprising reacting a compounds of Formula IX and Formula X



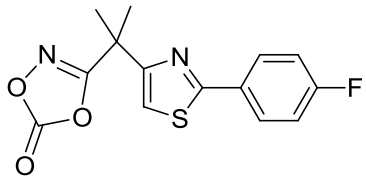
IX;



X

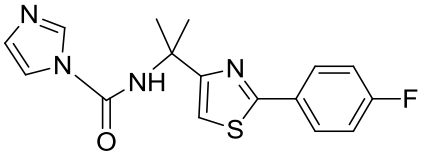
with quinuclidinol.

19. A method according to claim 18, further including reacting, while heating to reflux, the compound of Formula XI

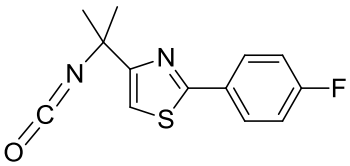


XI

with imidazole to form the compounds of Formula IX and Formula X

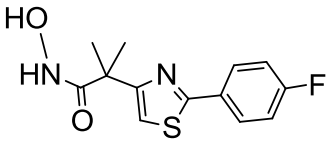


IX;



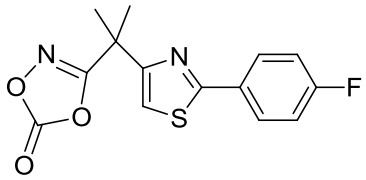
X.

20. A method according to claim 19, further including reacting the compound of Formula XII



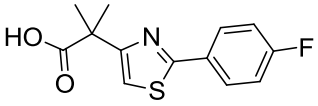
XII

with N, N'- carbonyldiimidazole to form the compound of Formula XI



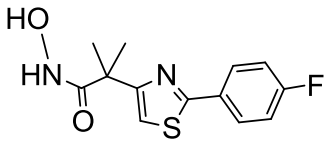
XI.

21. A method according to claim 20, further including reacting the compound of Formula XIII



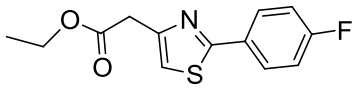
XIII

with N, N'- carbonyldiimidazole and hydroxylamine to form the compound of Formula XII



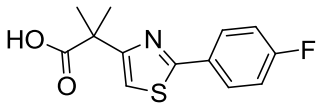
XII.

22. A method according to claim 21, further including reacting the compound of Formula XIV



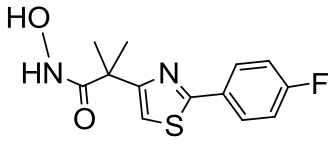
XIV

with potassium tert-butoxide and methyl iodine followed by reacting the ethyl ester so formed with lithium hydroxide to form the compound of Formula XIII



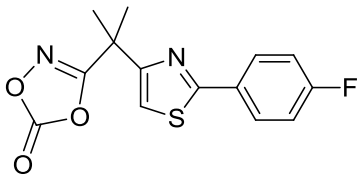
XIII .

23. A compound of Formula XII



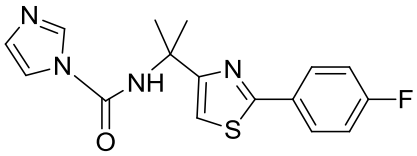
XII .

24. A compound of Formula XI



XI .

25. A compound of Formula IX



IX .