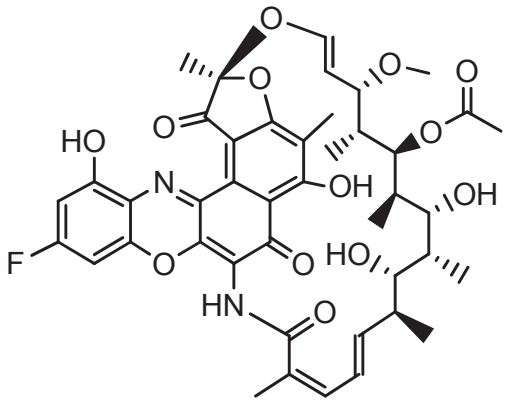
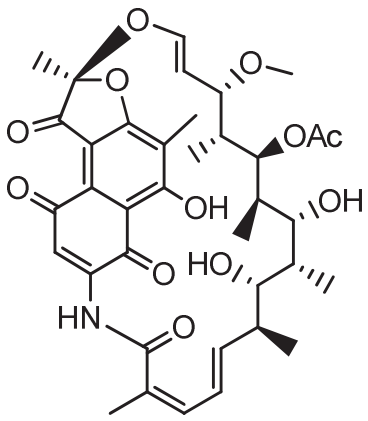
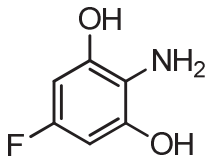


I

comprising reacting rifamycin S **II**, 2-amino-5-fluorobenzene-1,3-diol **III**, and one or more oxidants selected from TEMPO and TEMPO analogs, ambient air, oxygen gas, benzoquinone, manganese oxide (MnO_2), (PhI(OTs)OH, sodium periodate ($NaIO_4$), chloranil, hydrogen peroxide, Fe_2O_3, $Na_2S_2O_8$, $Co(acac)_3$, $Mn(acac)_2$, $Cu(OAc)_2$, CuO, $CuBr_2$, $ZnCl_2$, $InCl_3$, $Ag(OTf)_2$, $Sc(OTf)_3$, and $Yb(OTf)_3$, to form **I**



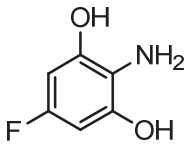
II



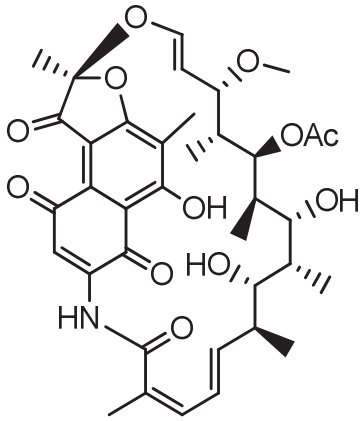
III

wherein the oxidants are kept separate from 2-amino-5-fluorobenzene-1,3-diol **III**.

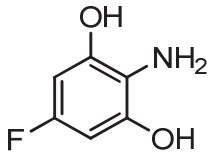
In another example, there is provided a process for the preparation of 2-amino-5-fluorobenzene-1,3-diol **III**, comprising:



III

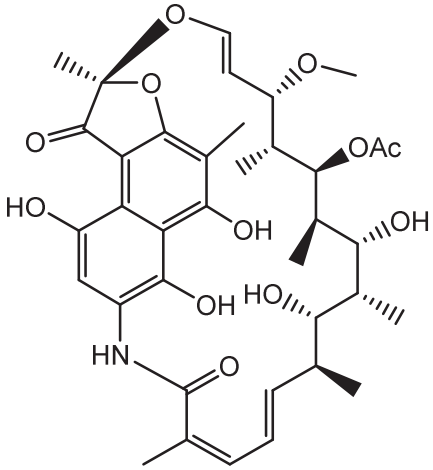


II



III

wherein RIFA SV is formed as a by-product and delivered to a flow-reactor



RIFA SV;

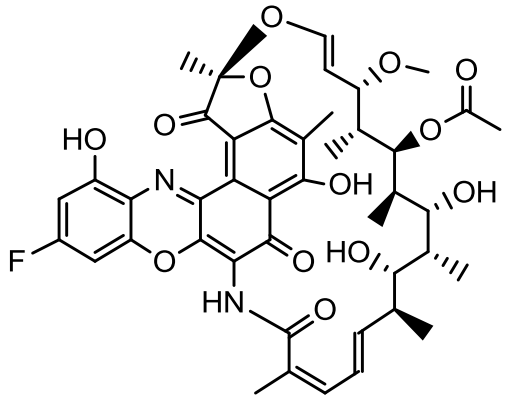
(ii) one or more oxidants oxidizes the RIFA SV to form **II** in the flow-reactor, wherein the one or more oxidants are selected from **2,2,6,6-tetramethyl-1-piperidinyloxy** (TEMPO), oxygen gas comprising 5% to 100% of the reaction gas phase, and benzoquinone; and

(iii) the **II** formed in the flow-reactor is delivered to the batch reactor vessel,

wherein the one or more oxidants and 2-amino-5-fluorobenzene-1,3-diol **III** are kept separate.

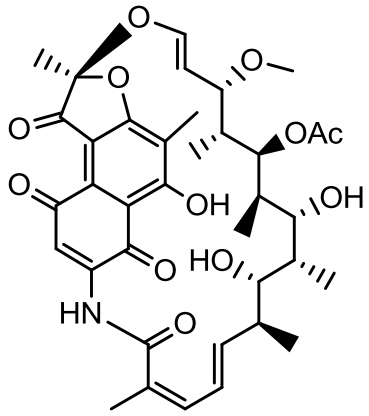
What is claimed is:

1. A process for the preparation of F-benzoxazinorifamycin **I**,

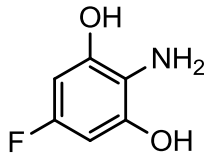


I

comprising reacting rifamycin S **II**, 2-amino-5-fluorobenzene-1,3-diol **III**, and one or more oxidants selected from TEMPO and TEMPO analogs, ambient air, oxygen gas, benzoquinone, manganese oxide (MnO_2), (PhI(OTs)OH, sodium periodate ($NaIO_4$), chloranil, hydrogen peroxide, Fe_2O_3, $Na_2S_2O_8$, $Co(acac)_3$, $Mn(acac)_2$, $Cu(OAc)_2$, CuO, $CuBr_2$, $ZnCl_2$, $InCl_3$, $Ag(OTf)_2$, $Sc(OTf)_3$, and $Yb(OTf)_3$, to form **I**



II



III

wherein the oxidants are kept separate from 2-amino-5-fluorobenzene-1,3-diol **III**.

2. The process of claim 1 wherein the oxidant comprises oxygen gas.

3. The process of claim 2 wherein the oxygen gas comprises from 5% to 100% of the reaction gas phase.

4. The process of claim 2 wherein the oxidant comprises a catalytic amount of TEMPO.

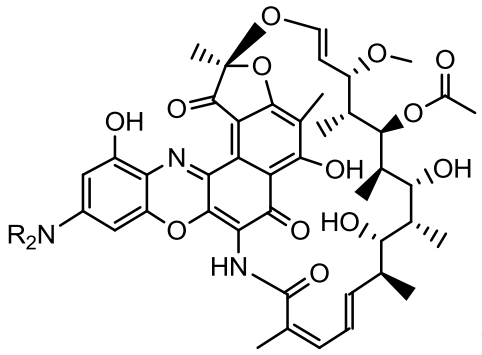
5. The process of claim 2 wherein the oxidant comprises a catalytic amount of a copper salt.

6. The process of claim 5 wherein the copper salt is copper oxide.

7. The process of claim 2 wherein the oxidant is separated from **III** by a semi-continuous process and **II** is reformed and recycled via a loop process.

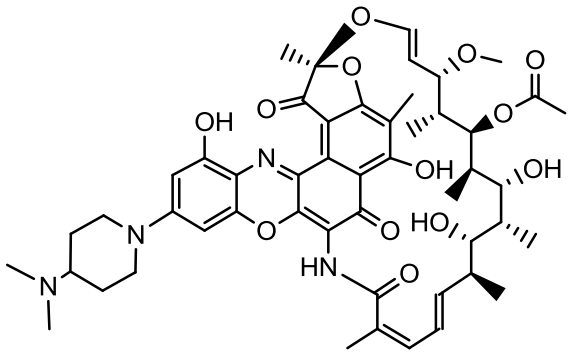
8. The process of claim 1 wherein the reaction of **II** and **III** is conducted in a solvent selected from isopropyl acetate, ethyl acetate, toluene, methanol, and tetrahydrofuran.

9. The process of claim 1 further comprising reacting F-rifa **I** and a secondary amine R_2NH selected from dimethylamine, diethylamine, di-n-propylamine, 1-methylpiperazine, N1-isobutylpiperazine, and N,N-dimethylpiperidin-4-amine, to form **IV** ;



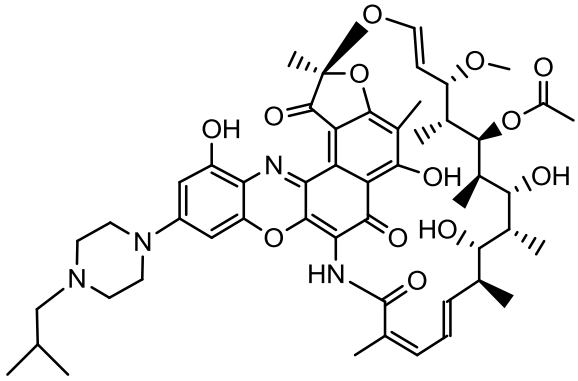
IV .

10. The process of claim 9 wherein the secondary amine is N,N-dimethylpiperidin-4-amine and **IV** has the structure **IVa**:



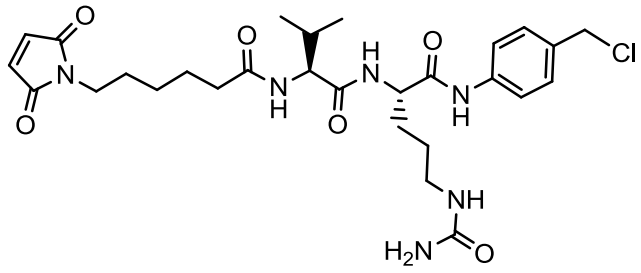
IVa .

11. The process of claim 9 wherein the secondary amine is N1-isobutylpiperazine and **IV** has the structure **IVb**:

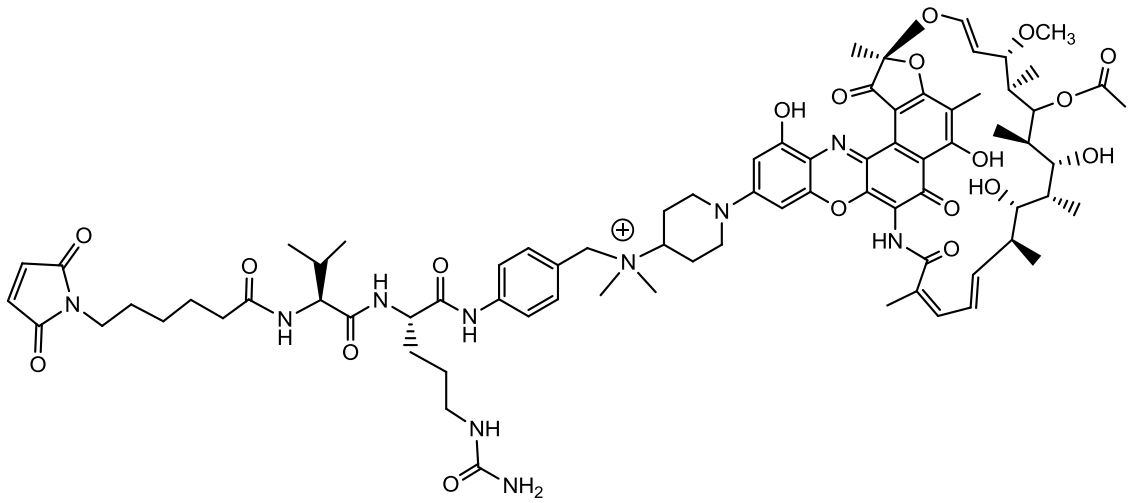


IVb .

12. The process of claim 9 further comprising reacting **IVa** and **V** to form linker-antibiotic **VI** ;



V ;



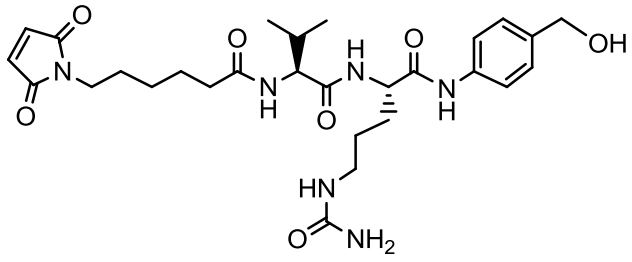
VI .

13. The process of claim 12 further comprising reacting **VI** with an antibody in an aqueous mixture to form an antibody-rifamycin conjugate.

14. The process of claim 13 wherein the aqueous mixture comprises a solvent selected from propylene glycol, N-methylpyrrolidone (NMP), dimethylformamide (DMF), dimethylacetamide (DMA), and dimethylsulfoxide (DMSO).

15. The process of claim 13 wherein the antibody is an anti-wall teichoic acid antibody.

16. The process of claim 12 further comprising reacting **VII** and thionyl chloride to form **V** ;



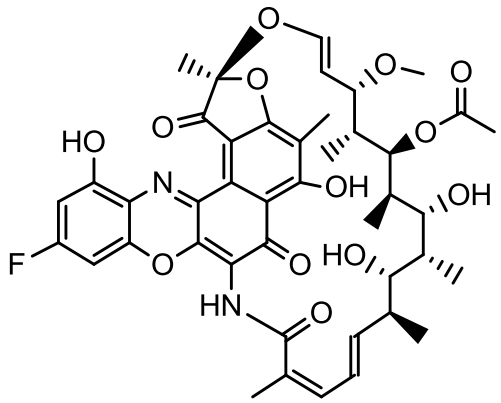
VII .

17. The process of claim 16 wherein **V** is isolated from water.

18. The process of claim 1 wherein the one or more oxidants is benzoquinone.

19. The process of claim 8 wherein the solvent is isopropyl acetate.

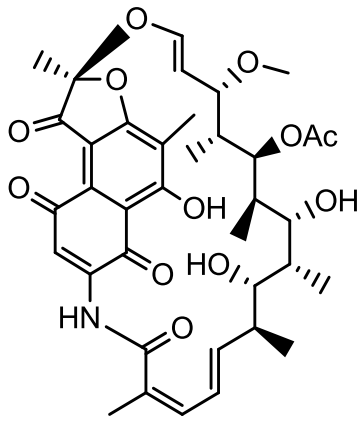
20. A semi-continuous loop process for the preparation of F-benzoxazinorifamycin **I**,



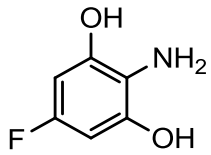
I

comprising:

(i) reacting rifamycin S **II**, and 2-amino-5-fluorobenzene-1,3-diol **III** in a batch reactor vessel to form **I**

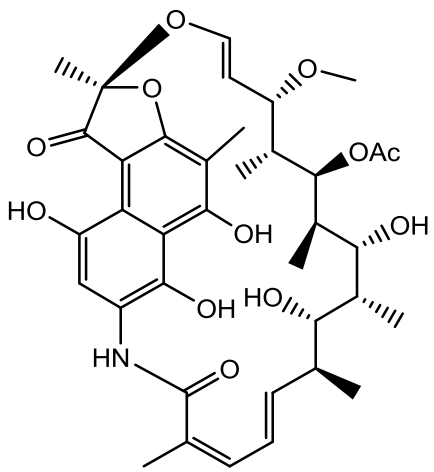


II



III

wherein RIFA SV is formed as a by-product and delivered to a flow-reactor



RIFA SV;

(ii) one or more oxidants oxidizes the RIFA SV to form **II** in the flow-reactor, wherein the one or more oxidants are selected from 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), oxygen gas comprising 5% to 100% of the reaction gas phase, and benzoquinone; and

(iii) the **II** formed in the flow-reactor is delivered to the batch reactor vessel,

wherein the one or more oxidants and 2-amino-5-fluorobenzene-1,3-diol **III** are kept separate.

21. The semi-continuous loop process of claim 20 wherein the one or more oxidants is selected from 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and oxygen gas.

22. The semi-continuous loop process of claim 20 wherein the one or more oxidants is 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).

23. The semi-continuous loop process of claim 20 wherein the one or more oxidants is benzoquinone.

24. The semi-continuous loop process of claim 20 wherein rifamycin S **II**, and 2-amino-5-fluorobenzene-1,3-diol **III** are dissolved in isopropyl acetate (iPrOAc) in the batch reactor vessel.

25. The semi-continuous loop process of claim 20 wherein the one or more oxidants is dissolved in isopropyl acetate (iPrOAc) in the flow-reactor.