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(54) **CEPHALOSPORIN COMPOSITIONS AND METHODS OF MANUFACTURE**

(71) Applicant: **Cubist Pharmaceuticals, Inc.**, Lexington, MA (US)

(72) Inventors: **Jan-Ji Lai**, Westborough, MA (US); **Pradip M. Pathare**, Lexington, MA (US); **Laxma Kolla**, Princeton Jct., NJ (US); **Adrien F. Soret**, Brighton, MA (US)

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A61K 31/546	(2006.01)

(52) **U.S. Cl.**

CPC ***C07D 501/06*** (2013.01); ***A61K 31/546*** (2013.01); ***A61K 31/433*** (2013.01)

USPC **514/202**; 540/222; 548/128

(57) **ABSTRACT**

Provided herein is a method for the synthesis of cephalosporin antibiotic compounds comprising the conversion of a protected 7-amino group into a 7-carboxamide moiety in a single step.

FIG. 1

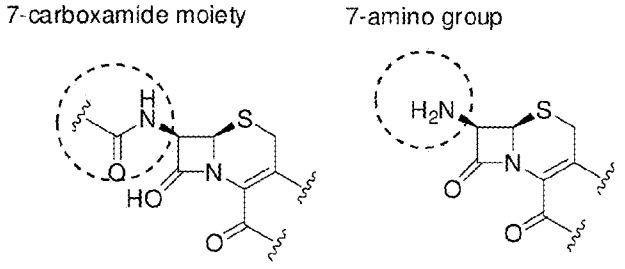
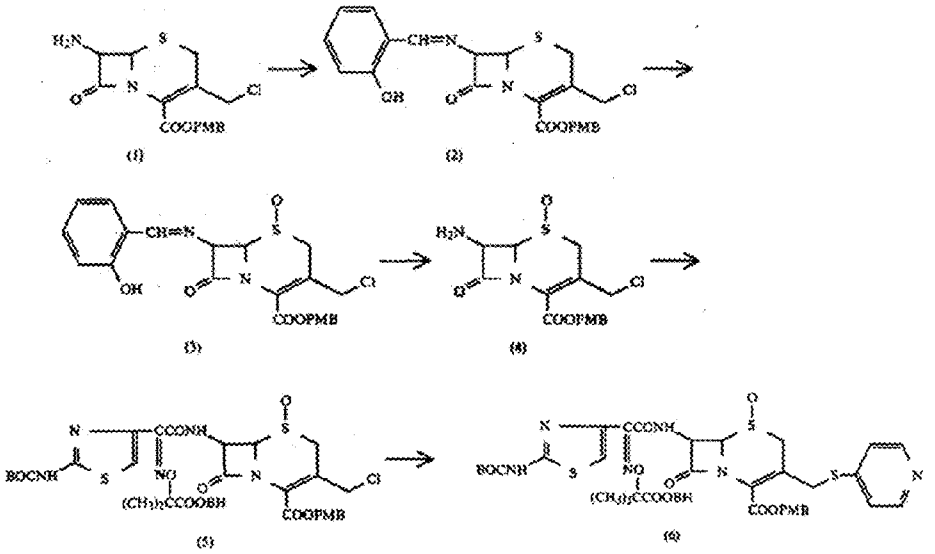


FIG. 2



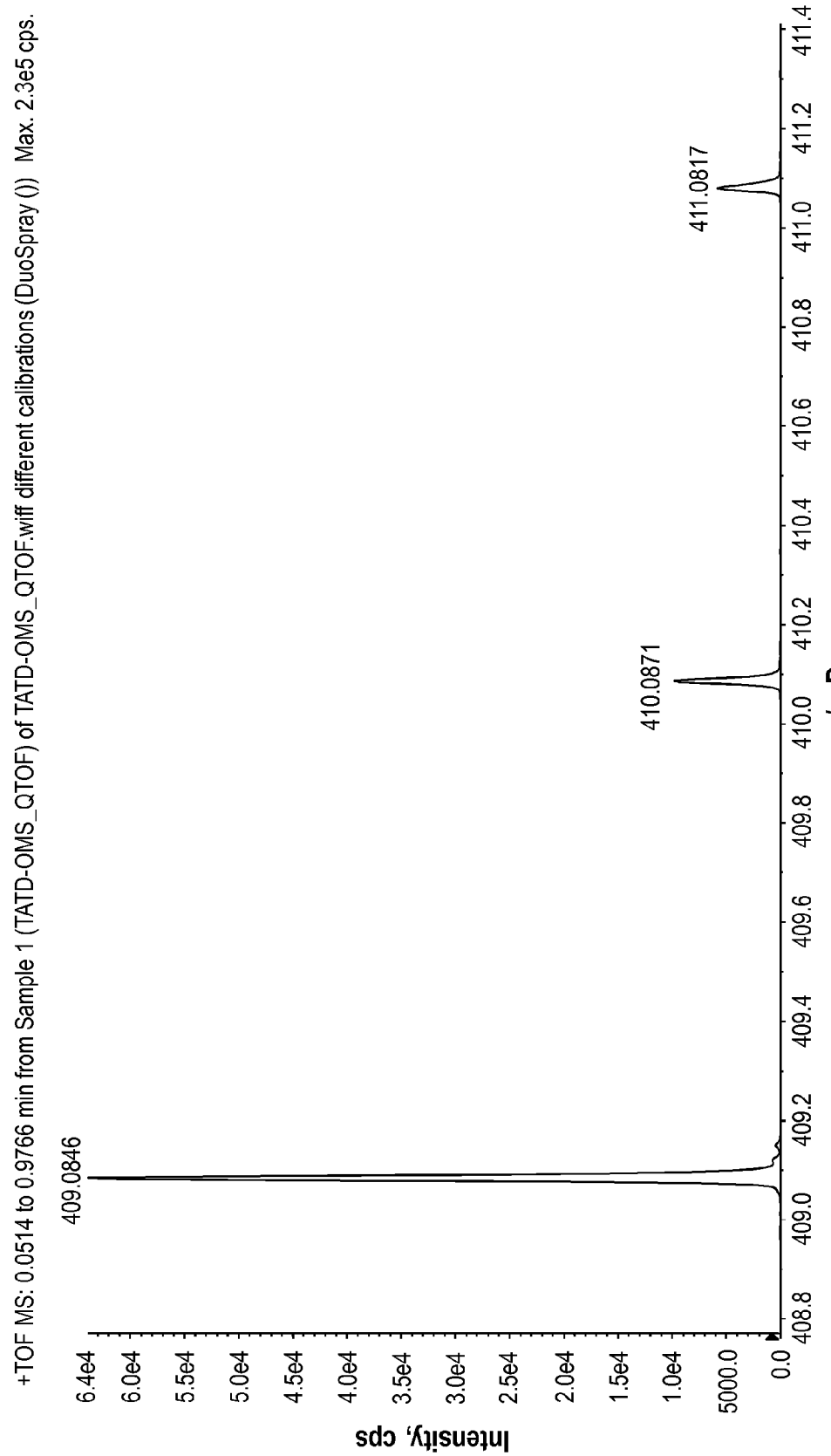

+TOF MS: 0.0514 to 0.9766 min from Sample 1 (TATD-OMS_QTOF) of TATD-OMS_QTOF.wiff different calibrations (DuoSpray ()) Max. 2.3e5 cps.
409.0846
410.0871
411.0817
Intensity, cps
6.4e4
6.0e4
5.5e4
5.0e4
4.5e4
4.0e4
3.5e4
3.0e4
2.5e4
2.0e4
1.5e4
1.0e4
5000.0
0.0
408.8
409.0
409.2
409.4
409.6
409.8
410.0
410.2
410.4
410.6
410.8
411.0
411.2
411.4
m/z, Da

FIG. 3

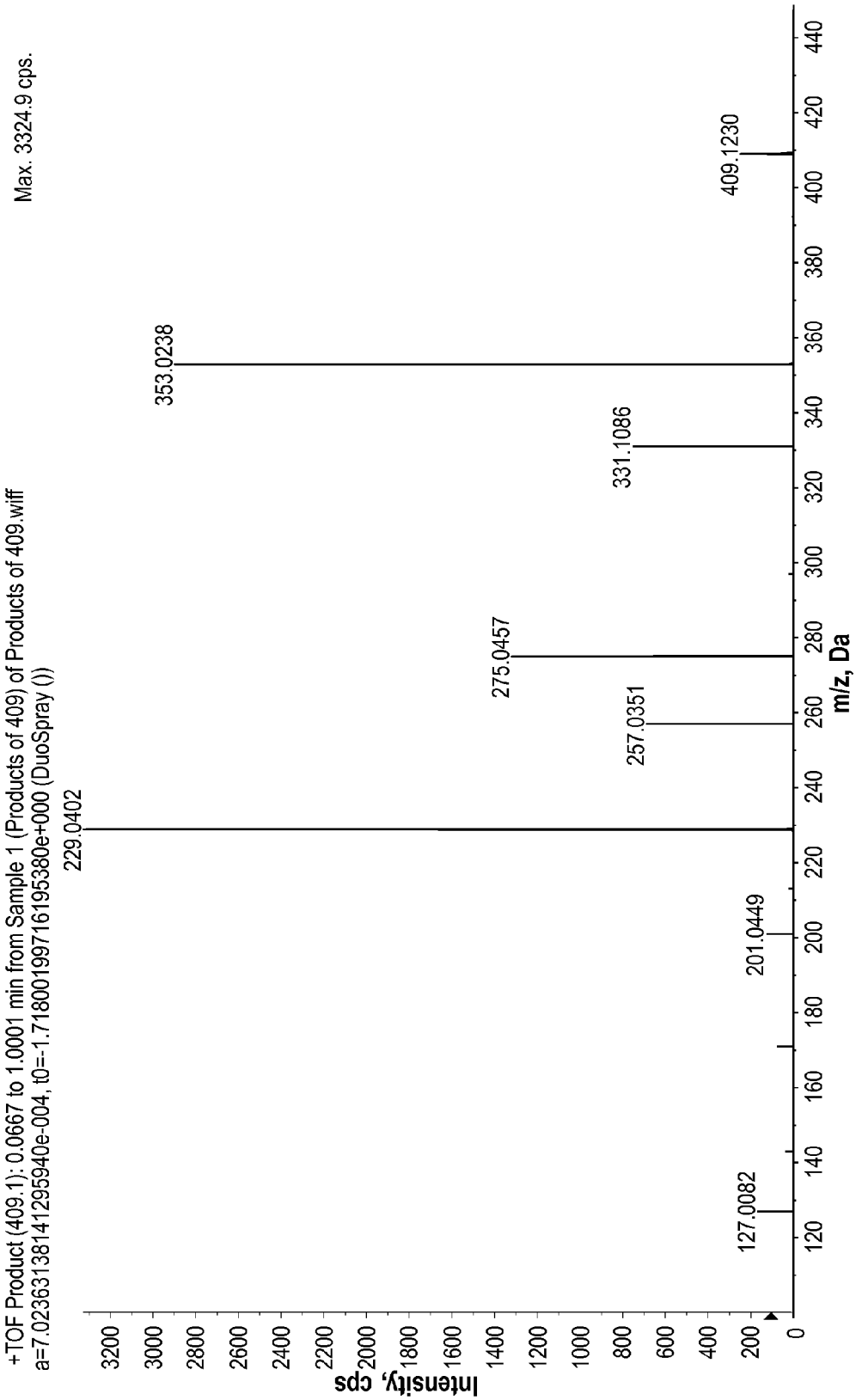

+TOF Product (409.1): 0.0667 to 1.0001 min from Sample 1 (Products of 409) of Products of 409.wiff
a=7.023631381412959 40e-004, t0=-1.718001997161953 80e+000 (DuoSpray ())
Max. 3324.9 cps.
Intensity, cps
m/z, Da
229.0402
353.0238
275.0457
331.1086
257.0351
409.1230
201.0449
127.0082

FIG. 4

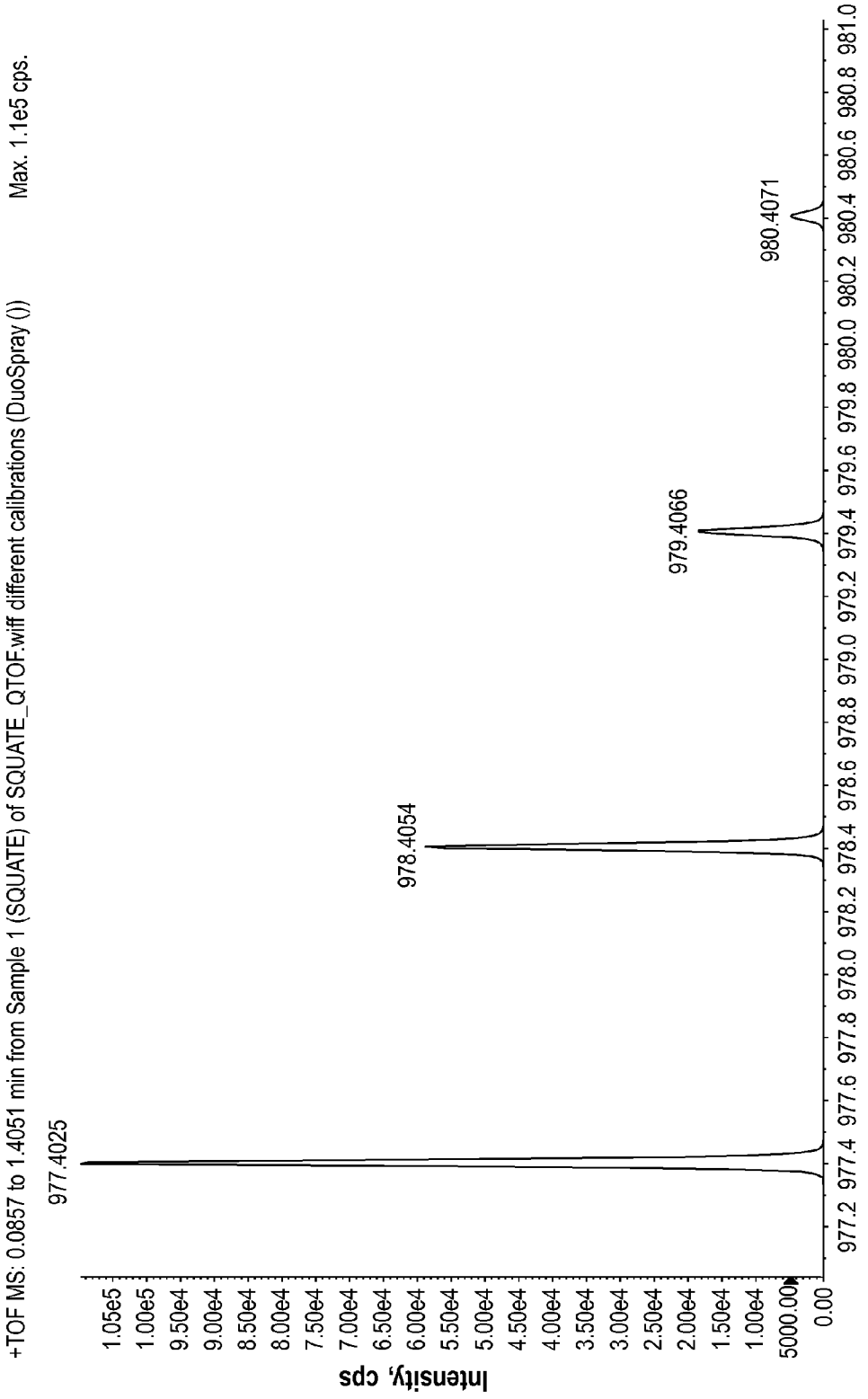

+TOF MS: 0.0857 to 1.4051 min from Sample 1 (SQUATE) of SQUATE_QTOF.wiff different calibrations (DuoSpray ())
Max. 1.1e5 cps.
977.4025
978.4054
979.4066
980.4071
Intensity, cps
m/z, Da

FIG. 5

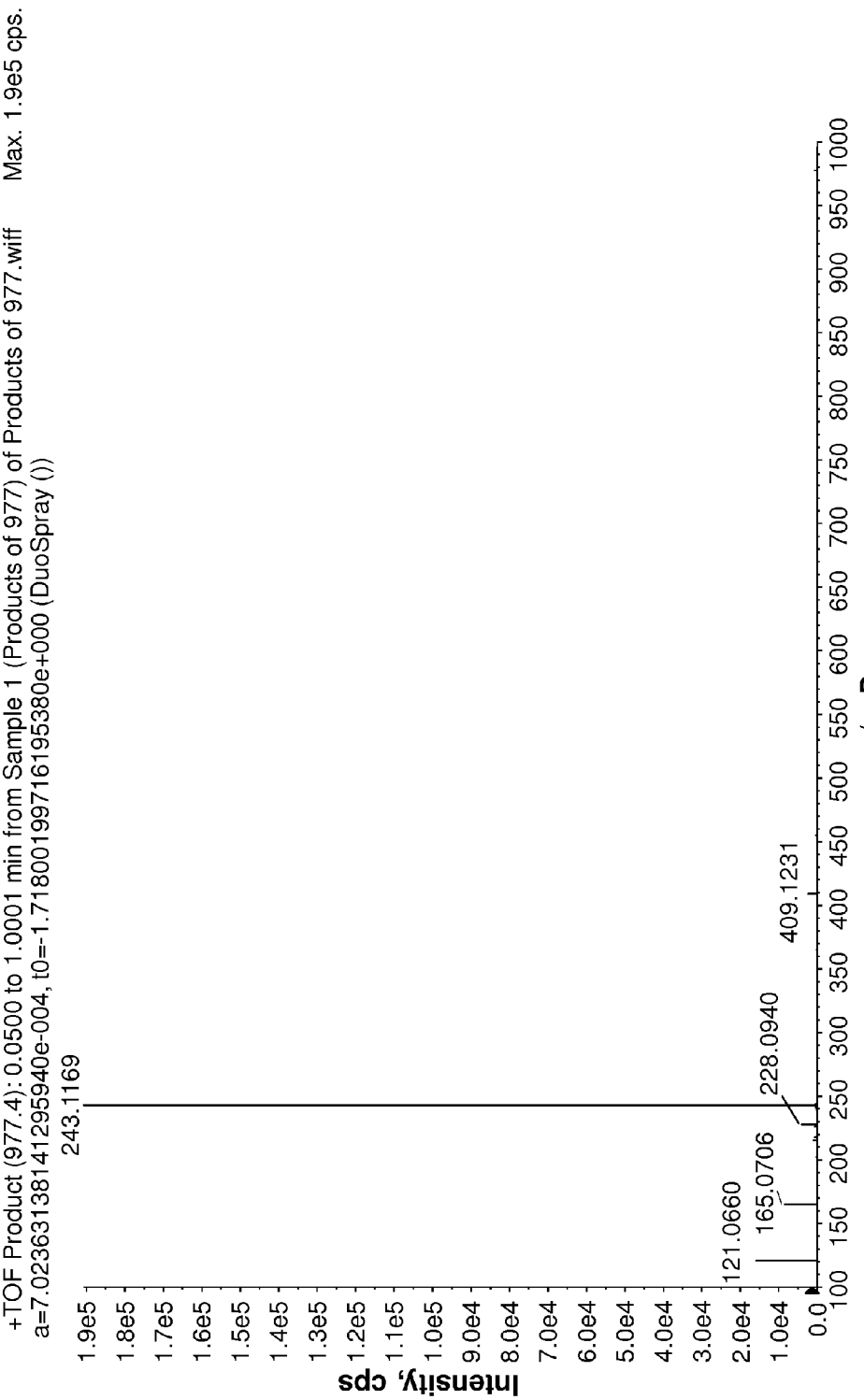

+TOF Product (977.4): 0.0500 to 1.0001 min from Sample 1 (Products of 977) of Products of 977.wiff Max. 1.9e5 cps.
a=7.023631381412959 40e-004, t0=-1.7180019971619538 0e+000 (DuoSpray ())
243.1169
228.0940
409.1231
165.0706
121.0660
Intensity, cps
m/z, Da

FIG. 6

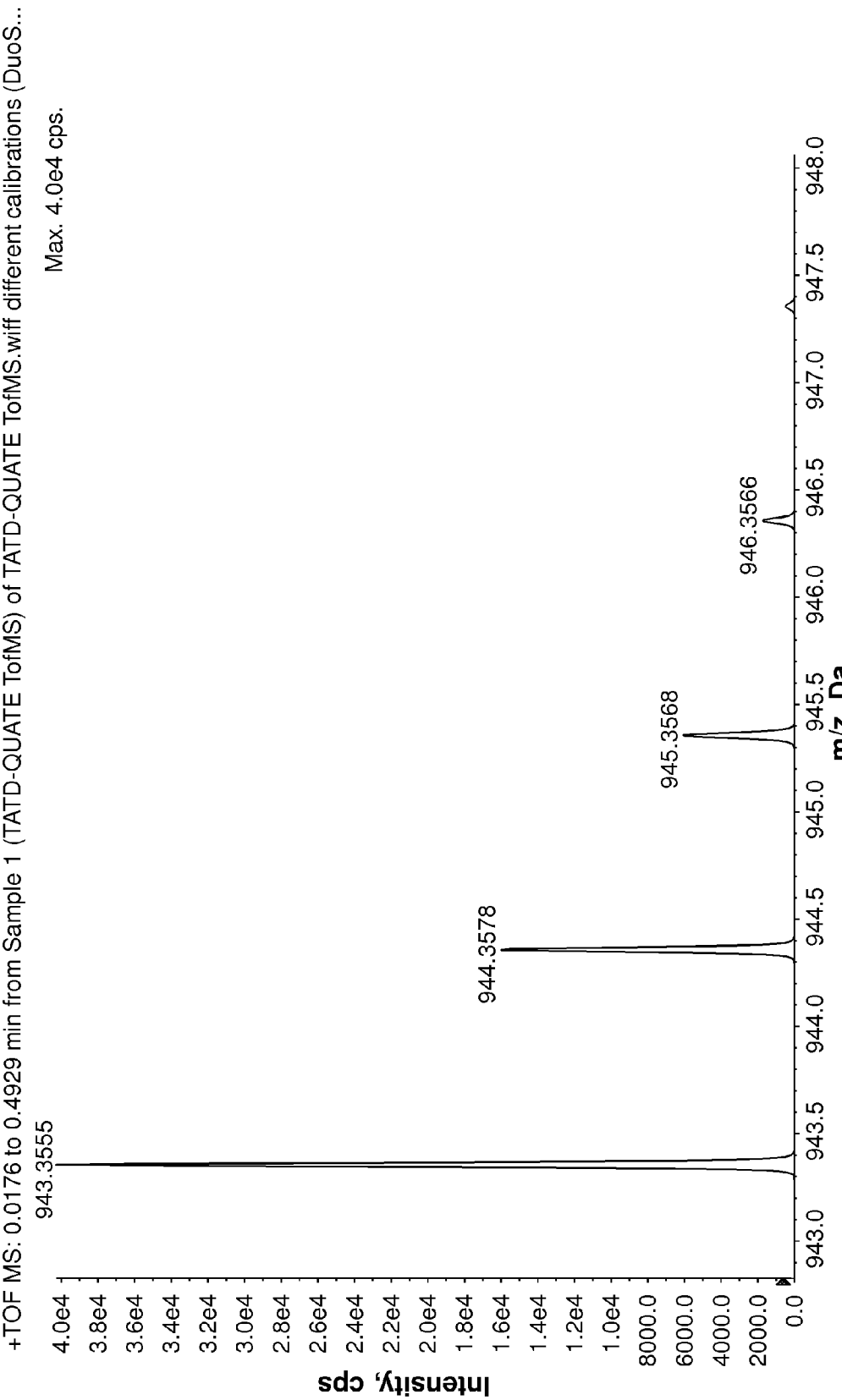

+TOF MS: 0.0176 to 0.4929 min from Sample 1 (TATD-QUATE TofMS) of TATD-QUATE TofMS.wiff different calibrations (DuoS...
Max. 4.0e4 cps.
943.3555
944.3578
945.3568
946.3566
Intensity, cps
m/z, Da
4.0e4
3.8e4
3.6e4
3.4e4
3.2e4
3.0e4
2.8e4
2.6e4
2.4e4
2.2e4
2.0e4
1.8e4
1.6e4
1.4e4
1.2e4
1.0e4
8000.0
6000.0
4000.0
2000.0
0.0
943.0
943.5
944.0
944.5
945.0
945.5
946.0
946.5
947.0
947.5
948.0

FIG. 7

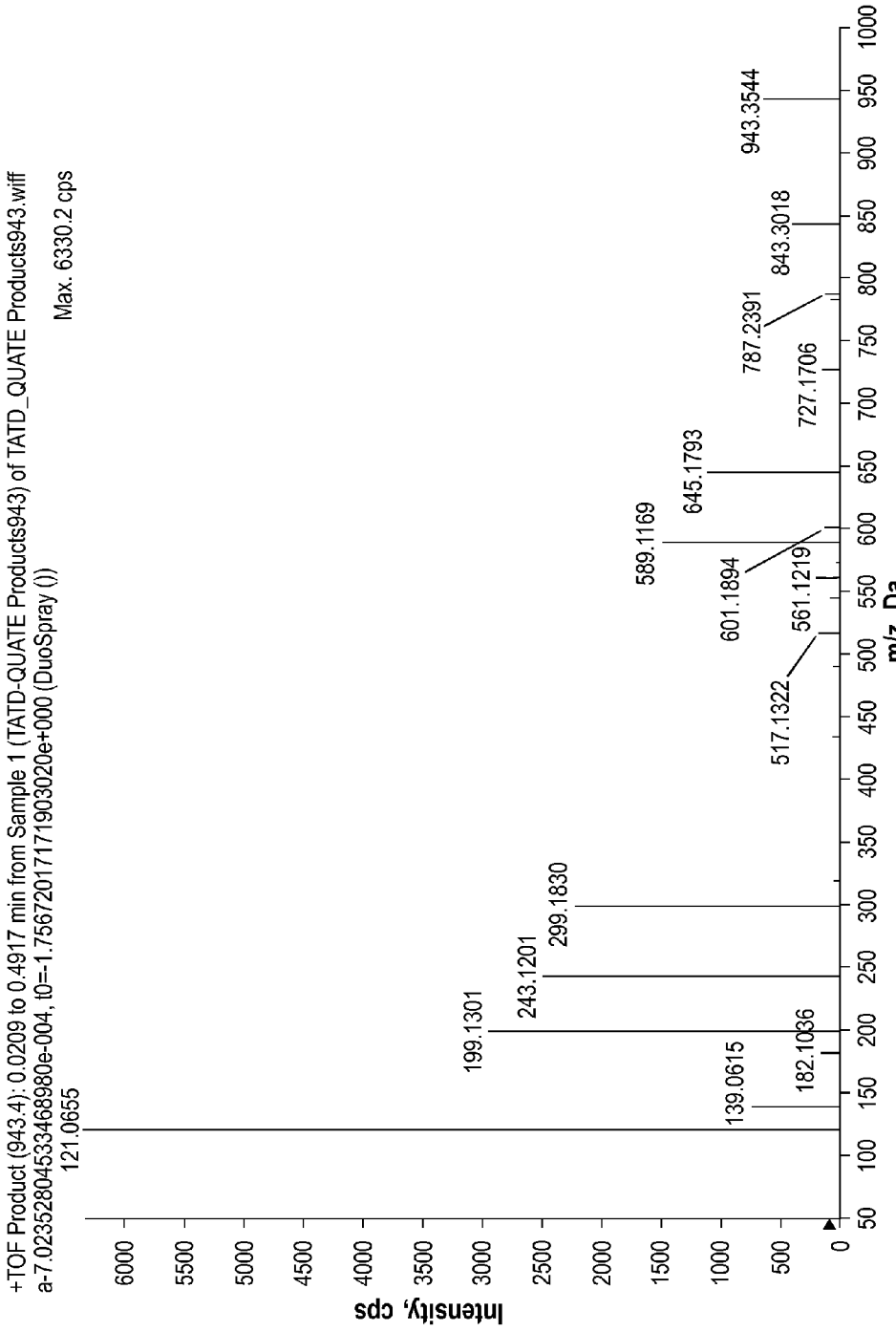

+TOF Product (943.4): 0.0209 to 0.4917 min from Sample 1 (TATD-QUATE Products943) of TATD_QUATE Products943.wiff
a-7.023528045334689 80e-004, t0=-1.756720171719030 20e+000 (DuoSpray ())
Max. 6330.2 cps
Intensity, cps
m/z, Da
121.0655
139.0615
182.1036
199.1301
243.1201
299.1830
517.1322
561.1219
589.1169
601.1894
645.1793
727.1706
787.2391
843.3018
943.3544

FIG. 8

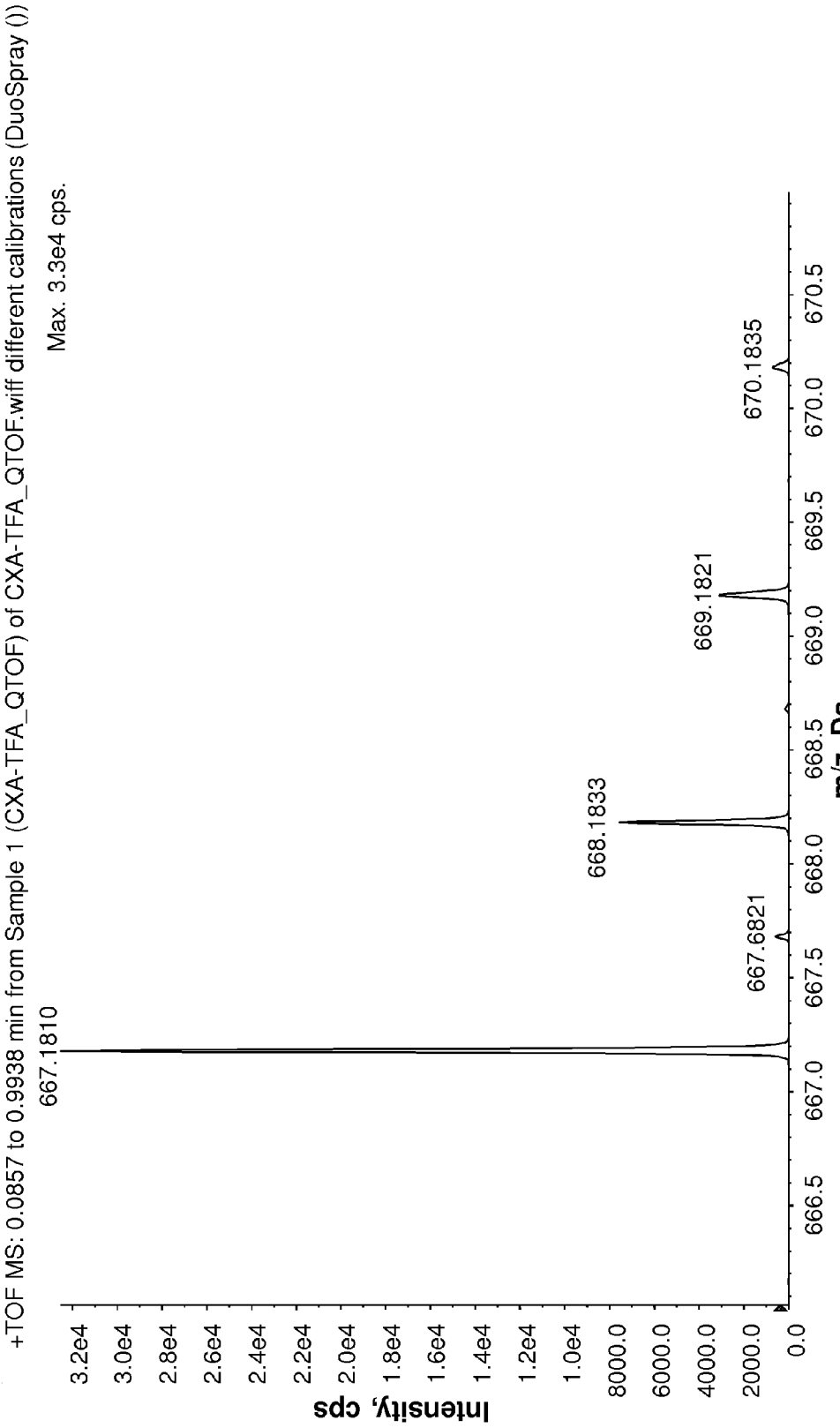

+TOF MS: 0.0857 to 0.9938 min from Sample 1 (CXA-TFA_QTOF) of CXA-TFA_QTOF.wiff different calibrations (DuoSpray ())
Max. 3.3e4 cps.
667.1810
667.6821
668.1833
669.1821
670.1835
Intensity, cps
m/z, Da

FIG. 9

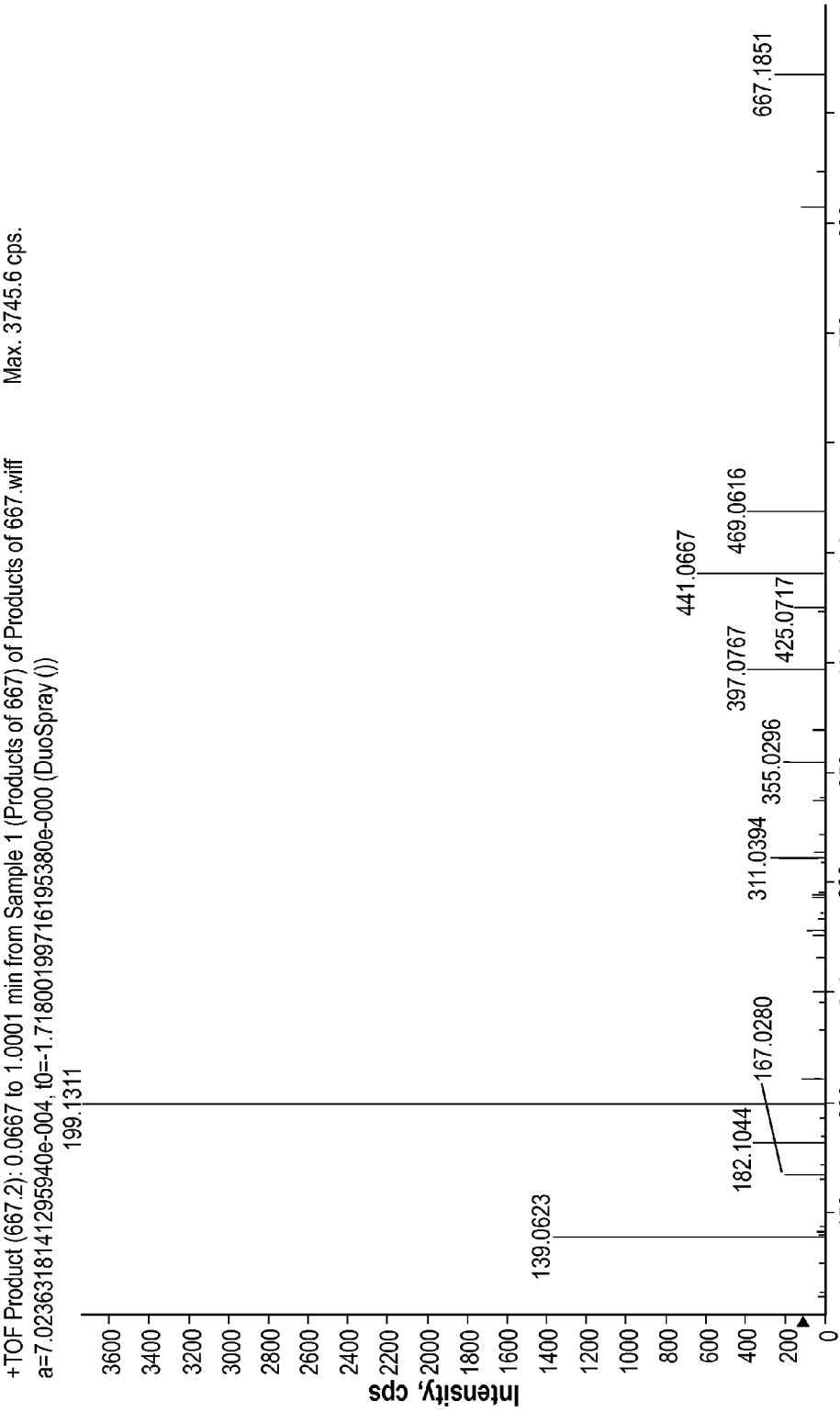
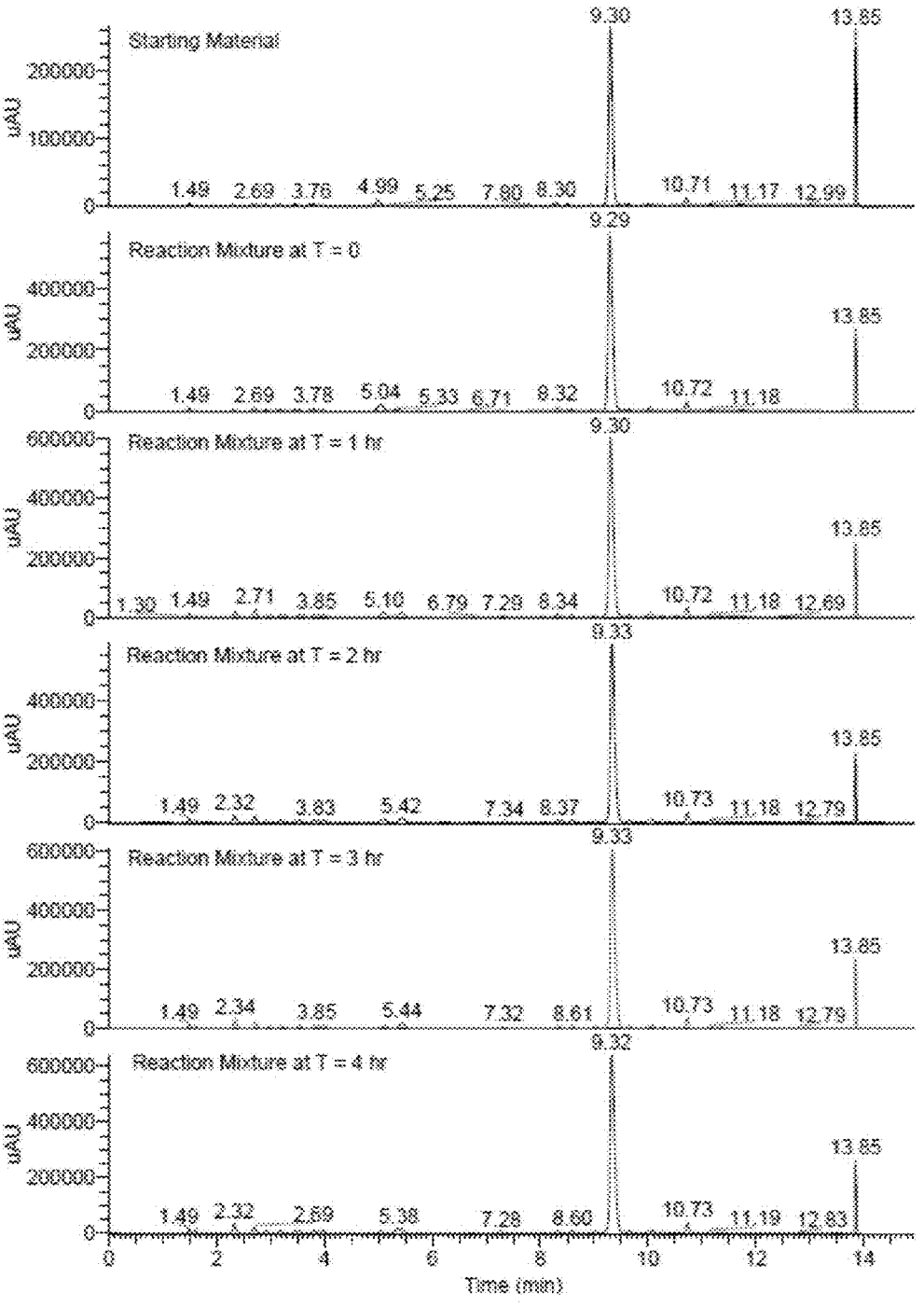

+TOF Product (667.2): 0.0667 to 1.0001 min from Sample 1 (Products of 667) of Products of 667.wiff
a=7.023631814129594 0e-004, t0=-1.7180019971619538 0e-000 (DuoSpray ())
Max. 3745.6 cps.
Intensity, cps
m/z, Da
199.1311
182.1044
167.0280
139.0623
311.0394
355.0296
397.0767
425.0717
441.0667
469.0616
667.1851

FIG. 10

FIG. 11


Starting Material
9.30
13.85
1.49 2.69 3.78 4.99 5.25 7.88 8.30 10.71 11.17 12.99
Reaction Mixture at T = 0
9.29
13.85
1.49 2.69 3.78 5.04 5.33 6.71 8.32 10.72 11.18
Reaction Mixture at T = 1 hr
9.30
13.85
1.30 1.49 2.71 3.85 5.10 6.79 7.29 8.34 10.72 11.18 12.69
Reaction Mixture at T = 2 hr
9.33
13.85
1.49 2.32 3.83 5.42 7.34 8.37 10.73 11.18 12.79
Reaction Mixture at T = 3 hr
9.33
13.85
1.49 2.34 3.85 5.44 7.32 8.61 10.73 11.18 12.79
Reaction Mixture at T = 4 hr
9.32
13.85
1.49 2.32 2.69 5.38 7.28 8.60 10.73 11.19 12.83
uAU
Time (min)

CEPHALOSPORIN COMPOSITIONS AND METHODS OF MANUFACTURE

RELATED APPLICATIONS

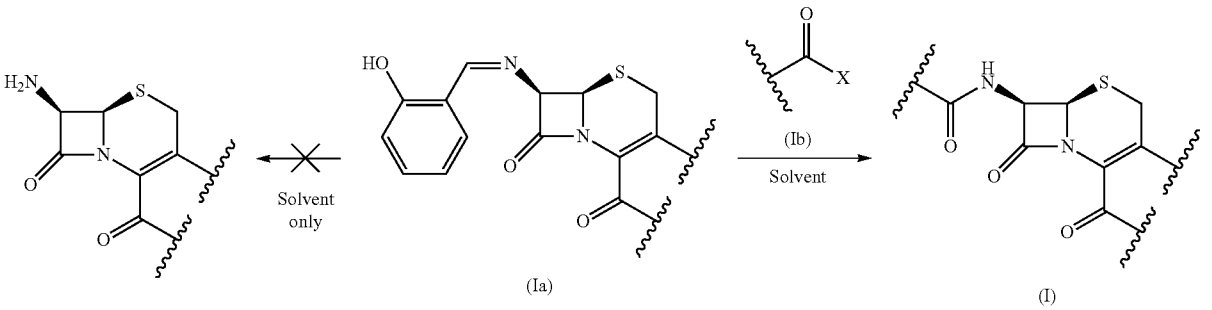
[0001] This application claims priority to U.S. Provisional Application No. 61/782,365, filed Mar. 14, 2013. The entire content of this application is incorporated herein by reference in its entirety.

TECHNICAL FIELD

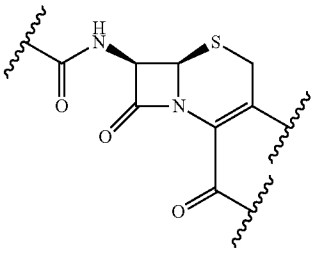
[0002] The present disclosure relates to cephalosporin compositions and the manufacture thereof.

BACKGROUND

[0003] Cephalosporin compounds containing the chemical substructure of formula (I) are important antibacterial therapeutic agents. The manufacture of these cephalosporin compounds is typically performed in a series of synthetic chemical reactions. Reducing the number of synthetic chemical reactions and associated purification steps can increase product yield and decrease the time for production, thereby increasing efficiency and decreasing production costs.



(I)



[0004] Syntheses of antibiotic cephalosporin compounds containing the substructure of formula (I) typically require two reactions for the formation of a 7-carboxamide moiety: (1) deprotection (i.e., removal of a protecting group) of the 7-amino group, and (2) acylation of the 7-amino group to form the 7-carboxamide moiety. One example of this two-step procedure is disclosed in U.S. Pat. No. 5,134,138 (see FIG. **2**). Most cephalosporin antibiotics can be manufactured in an analogous way. Ceftolozane (CXA-101, FR264205) is a cephalosporin antibiotic compound, a synthesis of which is disclosed in U.S. Pat. No. 7,129,232. Additional cephalosporin antibiotic compounds include the compounds of Table 2. There remains an unmet need to identify novel manufacturing processes for synthesizing cephalosporin compounds comprising the chemical substructure of formula (I), including methods for formation of a 7-carboxamide moiety from a protected 7-amino group with fewer chemical synthetic steps.

SUMMARY

[0005] A novel chemical process useful in the manufacture of cephalosporin compounds containing the chemical substructure of Formula (I) can include deprotection (i.e., removal of a nitrogen protecting group) and acylation of the 7-amino group in a single step rather than multiple steps. The invention is based in part on the surprising discovery that salicyladehyde imine derivatives according to formula (Ia) can be reacted with activated carboxylic acid derivatives (Ib) to yield 7-carboxamide compounds according to formula (I) in a single step. This outcome is surprising because the imine derivatives of formula (Ia) are stable to the reaction conditions in the absence of the activated carboxylic acid derivative.

[0006] Accordingly, provided herein is a method for transforming a protected 7-amino group into a 7-carboxamide moiety comprising a single step.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] FIG. **1** depicts a representative 7-carboxamide moiety and 7-amino group.

[0008] FIG. **2** depicts a prior art procedure (U.S. Pat. No. 5,134,138) comprising the deprotection of a protected 7-amino group followed by conversion of the 7-amino group into a 7-carboxamide moiety.

[0009] FIG. **3** depicts the full scan mass spectrum of compound (IV-1).

[0010] FIG. **4** depicts the product ion mass spectrum of compound (IV-1).

[0011] FIG. **5** depicts the full scan mass spectrum of compound (III-1).

[0012] FIG. **6** depicts the product ion mass spectrum of compound (III-1).

[0013] FIG. **7** depicts the full scan mass spectrum of compound (II-1).

[0014] FIG. **8** depicts the product ion mass spectrum of compound (II-1).

[0015] FIG. **9** depicts the full scan mass spectrum of ceftolozane trifluoroacetate.

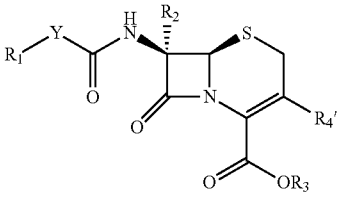
[0016] FIG. **10** depicts the product ion mass spectrum of ceftolozane trifluoroacetate.

[0017] FIG. **11** depicts the HPLC chromatograms of Example 2.

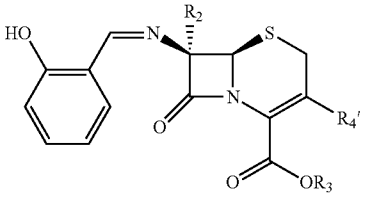
DETAILED DESCRIPTION

[0018] Provided herein is a method for preparing a compound of formula (II), or a salt thereof, comprising the step of reacting a compound of formula (III), or a salt thereof, with a compound of formula (IV), or a salt thereof, under suitable conditions to form a compound of formula (II), or a salt thereof, wherein the compounds of formulas (II), (III) and (IV) are defined according to the variable values below.

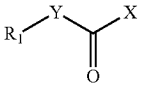
(II)



(III)



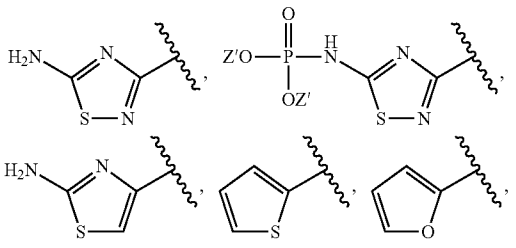
(IV)



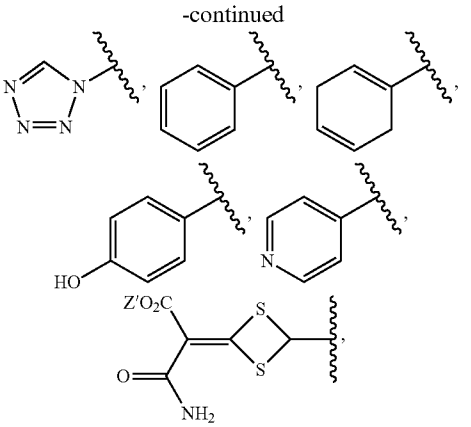
Variable R_1

[0019] In certain embodiments, R_1 is $R_{1'}$—Z; wherein $R_{1'}$ is selected from the group consisting of a bond, aryl, cycloalkyl, cycloalkenyl, heterocyclyl, and heteroaryl; wherein Z is 0-2 instances of a substituent that for each occurrence is independently selected from the group consisting of hydrogen, halogen, hydroxyl, hydroxyalkyl, aminoalkyl, alkyl, alkylidenyl, alkyenyl, heteroalkyl, cyano and amino, wherein Z is optionally, independently substituted one or more times with amino, halogen, carboxyl, oxo, a nitrogen protecting group, an oxygen protecting group or —$P(O)(OZ')_2$; and wherein Z' is independently hydrogen or an oxygen protecting group.

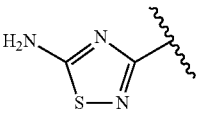
[0020] In one embodiment, R_1 is selected from the group consisting of aryl and heteroaryl moieties. In certain embodiments, R_1 is a substituted or unsubstituted aryl or heteroaryl moiety selected from the group consisting of: thiophene, furan, thiazole, tetrazole, thiadiazole, pyridyl, phenyl, phenol, cyclohexadiene and dithietane. In a particular embodiment, R_1 is selected from the group consisting of the following moieties:



-continued

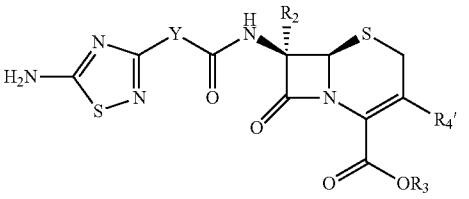


and salts thereof, wherein Z' is defined above. In another particular embodiment, R_1 is



and the compound of formula (II) has the structure of formula (IIa).

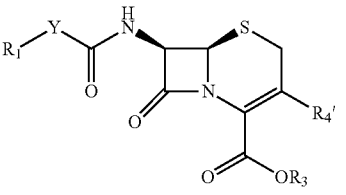
(IIa)



Variable R_2

[0021] In certain embodiments, R_2 is selected from the group consisting of hydrogen and alkoxy. In another embodiment of the method, R_2 is hydrogen, and the compound of formula (II) has the structure of formula (IIb).

(IIb)

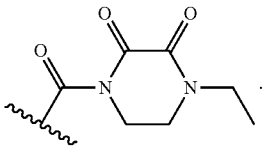


Variable Y

[0022] In certain embodiments, Y is selected from the group consisting of a bond, CH_2, CH_2S, SCH_2, C═C(H) CH_2CO_2R', CH(OR'), C═N(OR'), $CHNR"_2$ and C═NR"; wherein R' is selected from the group consisting of hydrogen, an oxygen protecting group and alkyl, wherein the alkyl is optionally substituted one or more times with halogen,

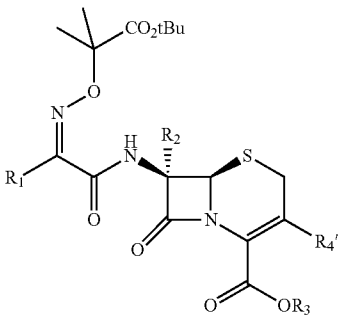
hydroxyl or —CO_2R_5; wherein R" is a substituent that for each occurrence is selected from hydrogen, alkyl, C(O)heterocyclyl, and a nitrogen protecting group, wherein any two R" substituents may combine to form a ring or a single nitrogen protecting group; and wherein R_5 is independently hydrogen or an oxygen protecting group.

[0023] In one embodiment of the method, Y is selected from a bond, CH_2, CH_2S and C═C(H)CH_2CO_2R', and R' is selected from the group consisting of hydrogen and an oxygen protecting group. In another embodiment, Y is C═N(OR') and R' is selected from the group consisting of an oxygen protecting group, hydrogen, methyl, ethyl, $CH_2CO_2R_5$ and $C(CH_3)_2CO_2R_5$. In yet another embodiment, Y is CH(OR') and R' is hydrogen or an oxygen protecting group. In still another embodiment, Y is $CHNR"_2$ and R" is 1-2 instances of a substituent that for each occurrence is selected from hydrogen, a nitrogen protecting group and



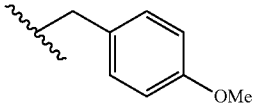
In a particular embodiment, Y is C═N(OR') and R' is $C(CH_3)_2CO_2{}^tBu$, and the compound of formula (II) has the structure of formula (IIc).

(IIc)



Variable R_3

[0024] In certain embodiments, R_3 is selected from the group consisting of hydrogen and an oxygen protecting group. In another embodiment of the method, R_3 is an oxygen protecting group selected from benzyl ethers. Benzyl ethers may be substituted (e.g., with one or more alkoxy substituents) or unsubstituted. In a particular embodiment, R_3 is

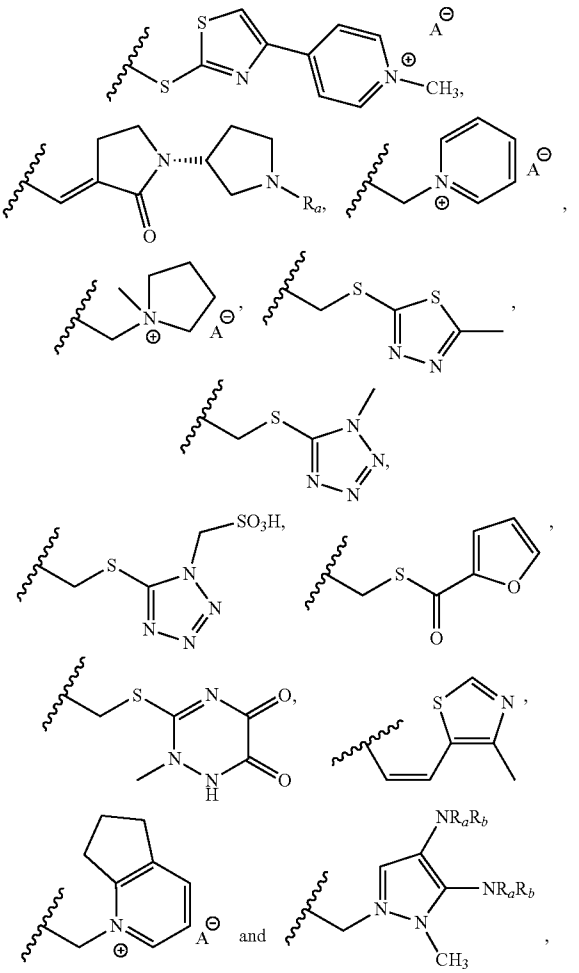


(i.e., 4-methoxybenzyl, PMB, MPM).

Variables R_4 and $R_{4'}$

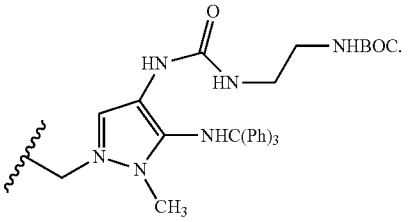
[0025] R_4 and $R_{4'}$, are independently selected from the group consisting of halogen, —R_6-R_7, —CH_2—R_6-R_7 and —CH═R_7; wherein R_6 is selected from the group consisting of a bond, oxygen, sulfur, alkyl, alkenyl, aryl, heteroaryl and heterocyclyl; wherein R_7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkanoyl, aroyl, heteroaroyl, carboxamide, aryl, heteroaryl and heterocyclyl; and wherein R_7 is optionally, independently substituted 1-3 times with a substituent selected from alkyl, alkyl sulfite, heterocyclyl and NR_aR_b; wherein R_a and R_b are independently selected from the group consisting of hydrogen, alkyl, a nitrogen protecting group and $C(O)NHR_c$; wherein R_c is an alkyl group or a heteroalkyl group; and wherein R_4 and $R_{4'}$ are optionally, independently substituted one or more times with an oxygen protecting group or a nitrogen protecting group.

[0026] In another embodiment of the method, R_4 and $R_{4'}$, are independently selected from the group consisting of hydrogen, chlorine, methyl, CH═CH—CH_3, CH═CH_2, $CH_2OC(O)CH_3$, $CH_2OC(O)NH_2$, CH_2OCH_3,

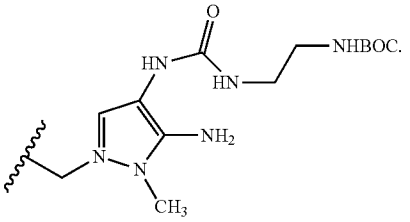


wherein

$A^{\ominus}$, for each occurrence, is independently a pharmaceutically acceptable anion. In certain embodiments, $A^{\ominus}$ is selected from chloride, acetate, trifluoroacetate and bisulfate. In a particular embodiment, $A^{\ominus}$ is trifluoroacetate.



[0027] In a particular embodiment, R_4 is



[0028] In another particular embodiment, $R_{4'}$, is

Variable X

[0029] In certain embodiments, X is selected from the group consisting of halogen, —OC(O)R_8 and —OSO_2R_8; wherein R_8 is selected from the group consisting of alkyl, heteroalkyl, aryl and heteroaryl. In another embodiment of the method, X is —OSO_2R_8. In a particular embodiment, X is —OSO_2CH_3.

(II-1), (III-1) and (IV-1)

[0030] Particular embodiments of the compounds of formulas (II), (III) and (IV) are listed in Table 1. For example, in the synthesis of the antibiotic compound ceftolozane, the compounds of formulas (II), (III) and (IV) can have the structures of formulas (II-1), (III-1) and (IV-1), respectively.

Synthesis

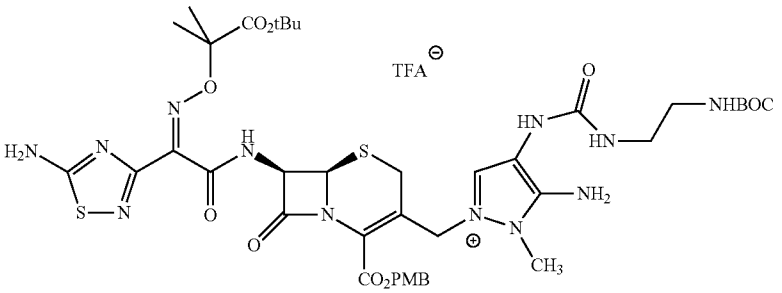
[0031] In one embodiment of the method, the suitable conditions comprise reacting in a mixture comprising an organic solvent and water. Organic solvents can be selected from the group consisting of aromatic solvents, aliphatic solvents, halogenated solvents, halogenated aromatic solvents, halogenated aliphatic solvents, ethers, halogenated ethers, esters and amides. In a particular embodiment, the organic solvent is selected from halogenated solvents. In another particular embodiment, the organic solvent is dichloromethane.

[0032] In another embodiment of the method, the suitable conditions comprise reacting in a mixture comprising an organic solvent and about 6-9 percent (w/w) water relative to the compound of formula (III), or salt thereof. In a particular embodiment, the suitable conditions comprise reaction in a mixture comprising an organic solvent and about 6-8 percent (w/w) water relative to the compound of formula (III), or salt thereof. In still another embodiment, the suitable conditions comprise reacting in a mixture comprising dichloromethane and about 6-9 percent of water relative to the compound of formula (III), or salt thereof.

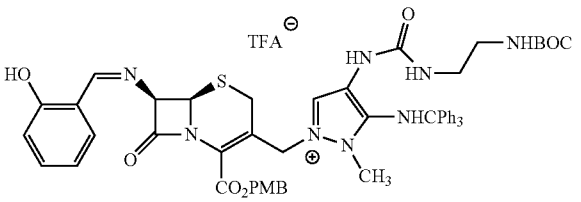
[0033] Notably, the compound of formula (III) is hydrolytically stable under the reaction conditions, in the absence of the compound of formula (IV). As shown in FIG. **11** and described in Example 2, compound (III-1) was combined with dichloromethane and water in the same relative amounts as in Example 1. Upon stirring for four hours, no hydrolysis of (III-1) was observed. In contrast, under the same solvent, temperature and time conditions, but in the presence of compound (IV-1), compound (III-1) reacts to form compound (II-1).

[0034] In some embodiments, the method further comprises the step of reacting the compound of formula (II), or a salt thereof, under suitable conditions to form a compound of formula (V), or a salt thereof, wherein the compound of formula (V) is selected from the compounds of Table 2, or salts thereof. In some embodiments, the suitable conditions comprise reacting the compound of formula (II) with strong acid. In a particular embodiment, the strong acid is trifluoroacetic acid.

(II-1)



(III-1)



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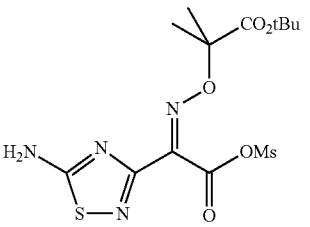

Compositions

[0035] In another aspect, provided herein is a composition comprising the compound of formula (V), or salt a thereof, and one or more compound selected from the group consisting of: the compound of formula (II), or salt a thereof, the compound of formula (III), or salt a thereof, and the compound of formula (IV), or salt a thereof. In one embodiment, the composition comprises the compound of formula (V), or salt a thereof, the compound of formula (I) or salt a thereof, the compound of formula (Ia) or salt a thereof, and the compound of formula (Ib) or salt a thereof. In another embodiment of the composition, the compound of formula (II), or salt a thereof, the compound of formula (III), or salt a thereof, and the compound of formula (IV), or salt a thereof, are present, if at all, in an amount that is less than or equal to 0.05% w/w. In yet another embodiment of the composition, the compound of formula (II), or salt a thereof, the compound of formula (III), or salt a thereof, and the compound of formula (IV), or salt a thereof, are present, if at all, in an amount that is less than or equal to 0.05 mol %. In another aspect, provided herein is a method of treating a bacterial infection in a patient, comprising the step of administering a composition as described above.

DEFINITIONS

[0036] Pharmaceutically acceptable salts are known to those of skill in the art. In some of the embodiments described herein, the compounds of formulas (II) and (III) are trifluoroacetate salts.

[0037] Oxygen and nitrogen protecting groups are known to those of skill in the art. Oxygen protecting groups include, but are not limited to methyl ethers, substituted methyl ethers (e.g., MOM (methoxymethyl ether), MTM (methylthiomethyl ether), BOM (benzyloxymethyl ether), PMBM or MPM (p-methoxybenzyloxymethyl ether), to name a few), substituted ethyl ethers, substituted benzyl ethers, silyl ethers (e.g., TMS (trimethylsilyl ether), TES (triethylsilylether), TIPS (triisopropylsilyl ether), TBDMS (t-butyldimethylsilyl ether), tribenzyl silyl ether, TBDPS (t-butyldiphenyl silyl ether), to name a few), esters (e.g., formate, acetate, benzoate (Bz), trifluoroacetate, dichloroacetate, to name a few), carbonates, cyclic acetals and ketals. Nitrogen protecting groups include, but are not limited to, carbamates (including methyl, ethyl and substituted ethyl carbamates (e.g., Troc), to name a few) amides, cyclic imide derivatives, N-alkyl and N-aryl amines, benzyl amines, substituted benzyl amines, trityl amines, imine derivatives, and enamine derivatives, for example.

[0038] In some embodiments, alkyl groups and groups comprising an alkyl group (e.g., alkoxy, alkanoyl, alkylamino, aminoalkyl, heteroalkyl) comprise 1-6 carbon atoms. In some embodiments, aryl groups and groups comprising aryl groups (e.g., aroyl) comprise 6-12 carbon atoms. In some embodiments, heteroaryl groups and groups comprising heteroaryl groups (e.g., heteroaroyl) comprise 1-10 carbon atoms and 1-4 heteroatoms selected from oxygen, nitrogen and sulfur.

TABLE 1

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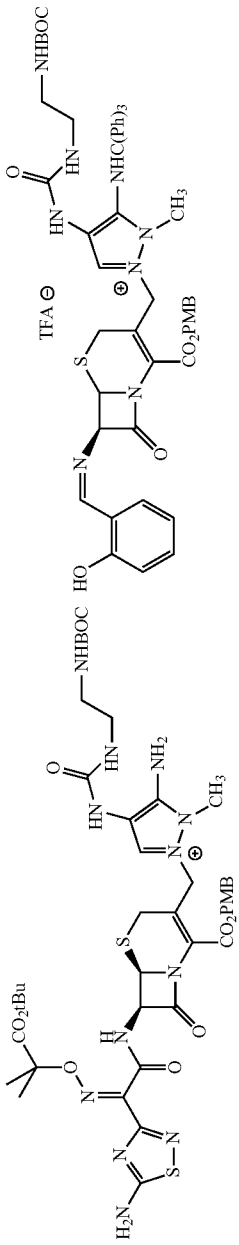
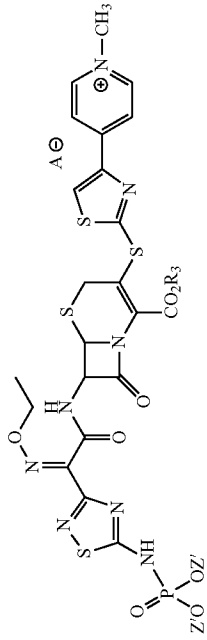
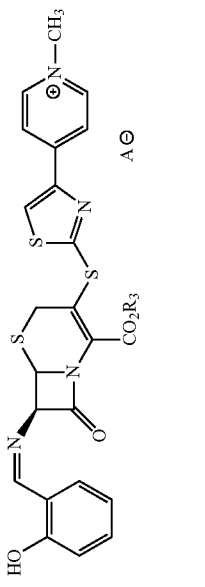
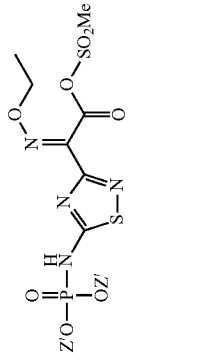
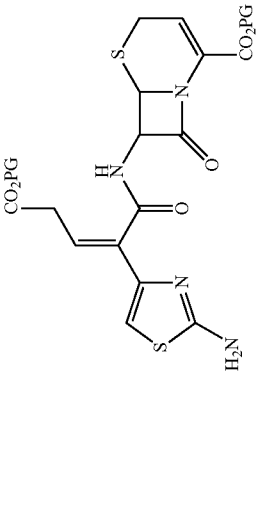
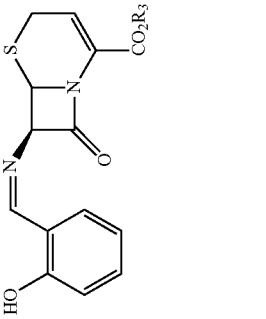
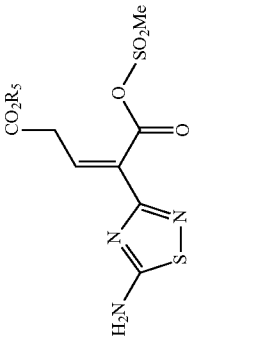
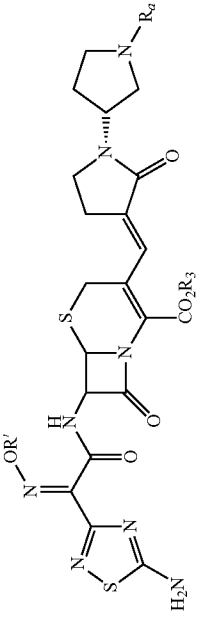
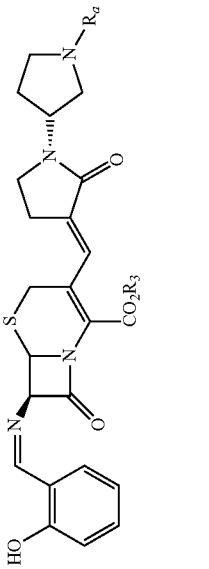
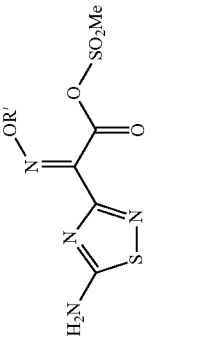
1			
2			
3			
4			

TABLE 1-continued

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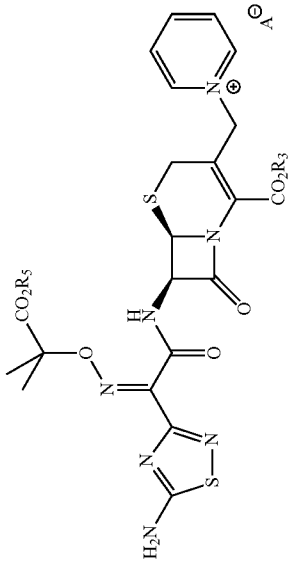
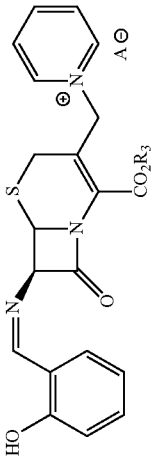
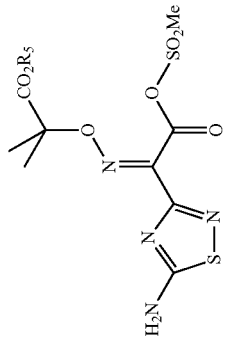
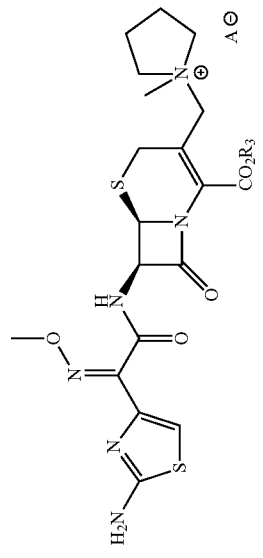
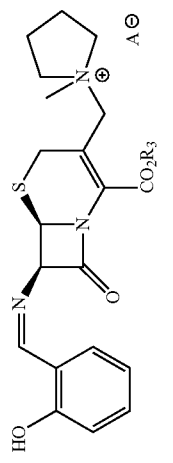
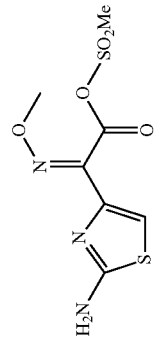
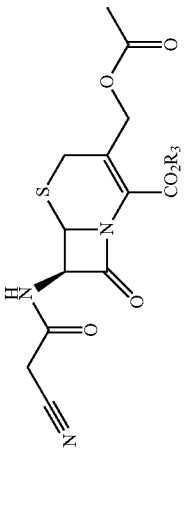
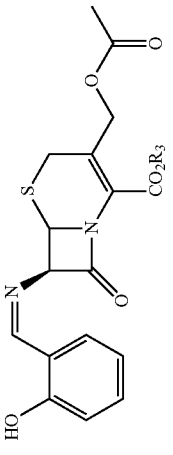
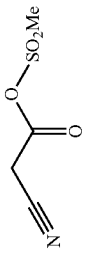
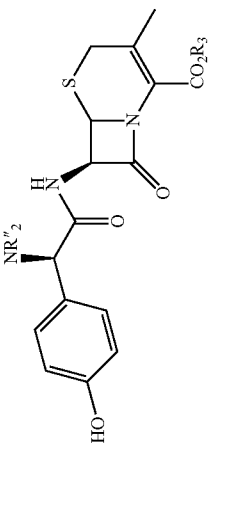
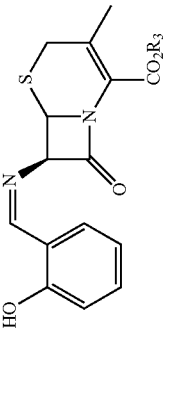
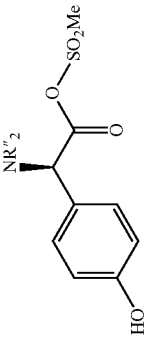
5			
6			
7			
8			

TABLE 1-continued

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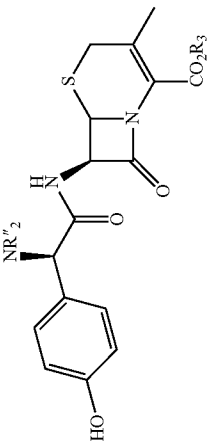
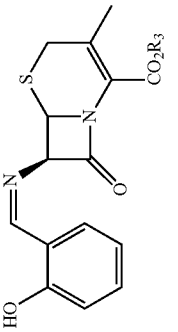
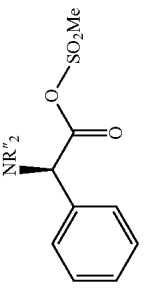
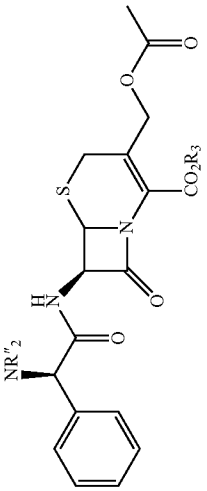
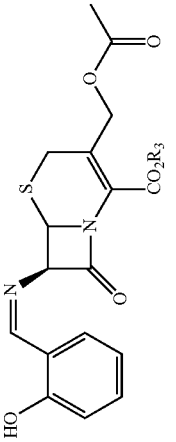
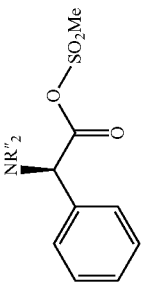
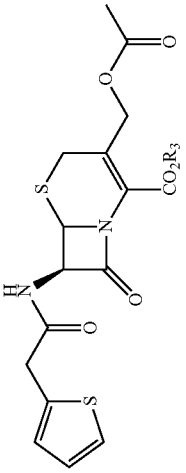
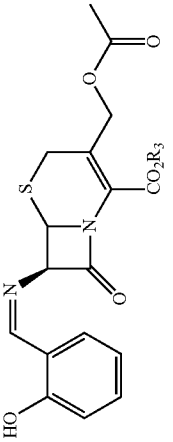
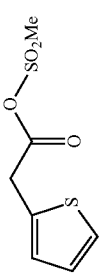
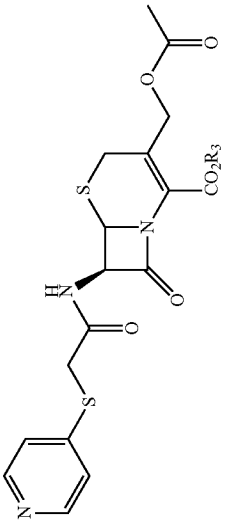
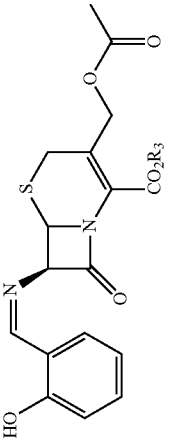
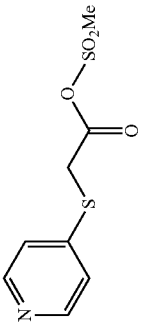
9			
10			
11			
12			

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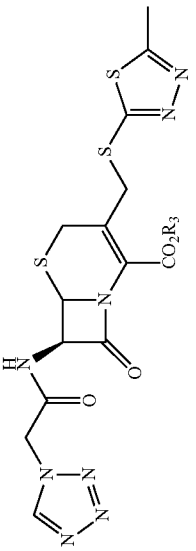
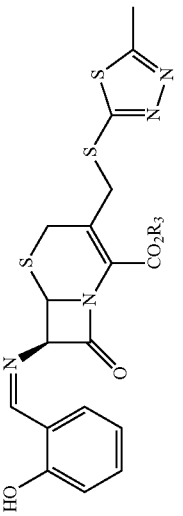
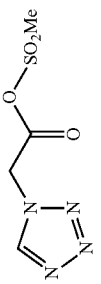
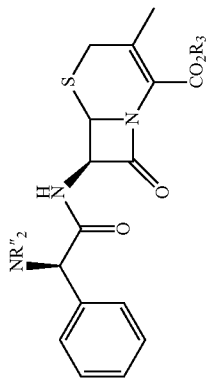
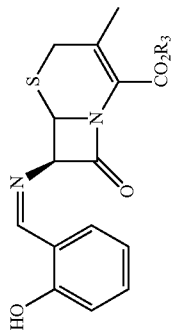
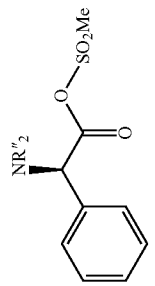
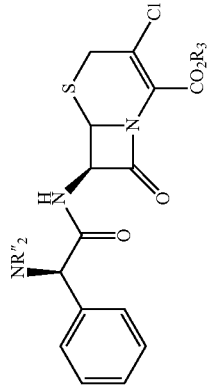
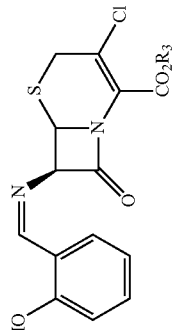
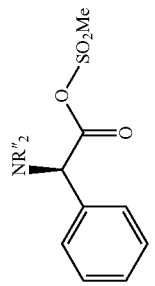
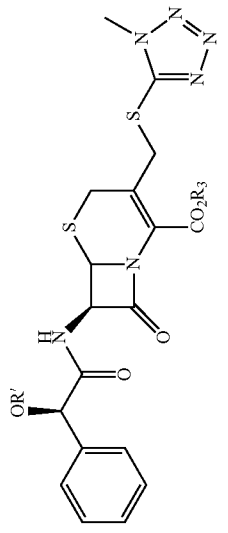
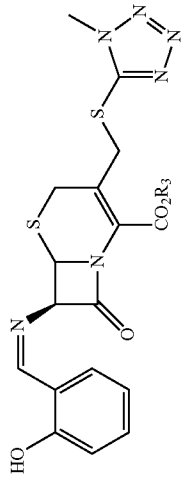
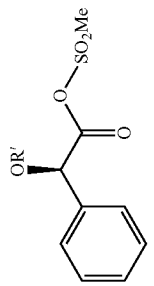
13			
14			
15			
16			

TABLE 1-continued

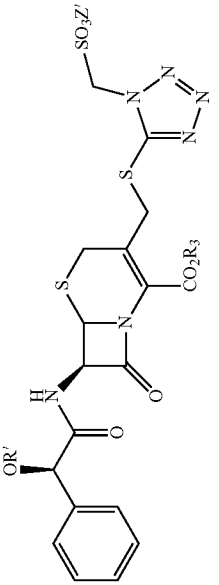
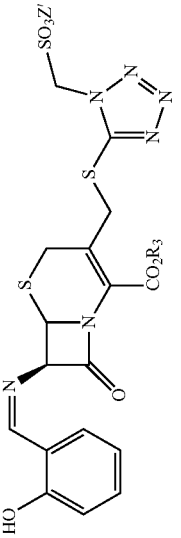
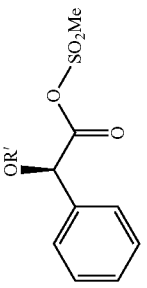
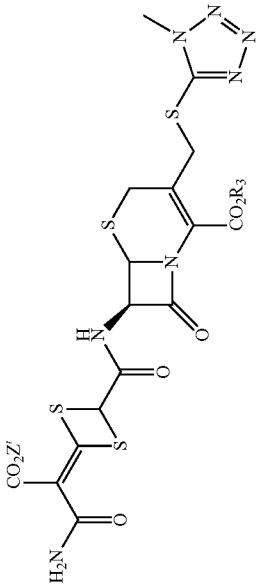
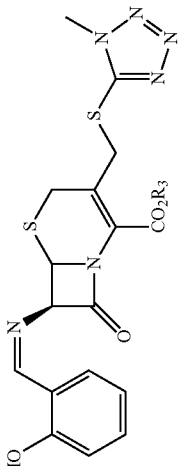
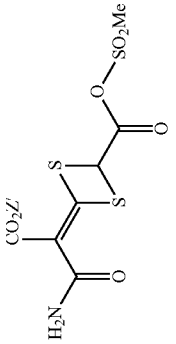
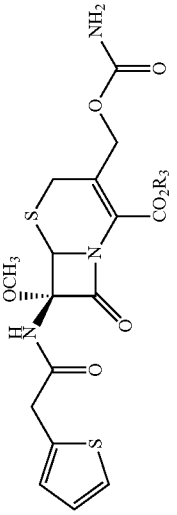
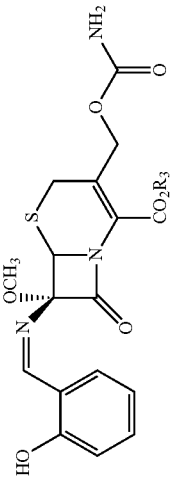
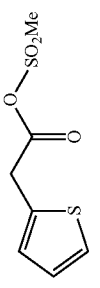
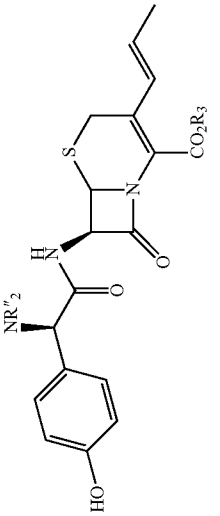
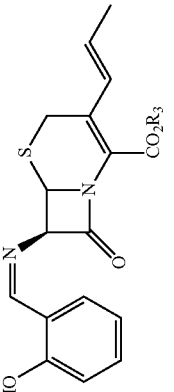
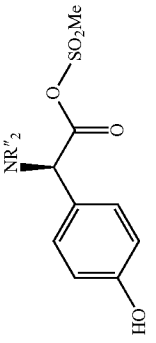
	Formula (II)	Formula (III)	Formula (IV)
17			
18			
19			
20			

TABLE 1-continued

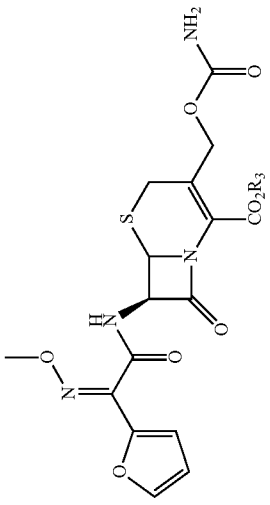
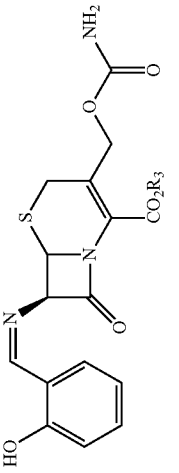
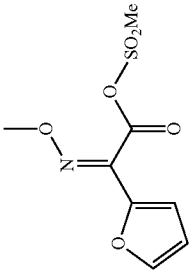
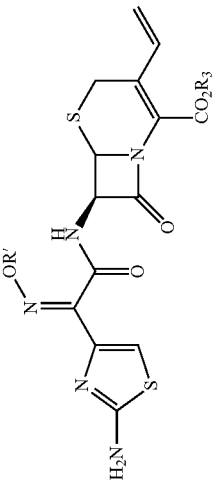
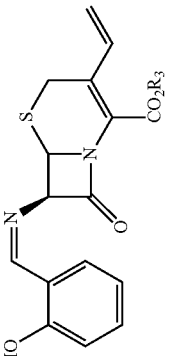
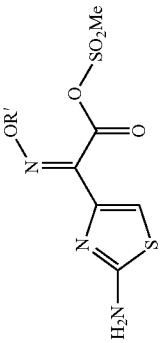
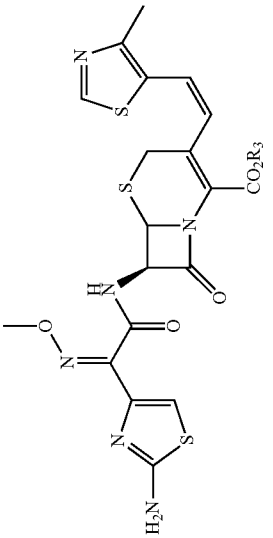
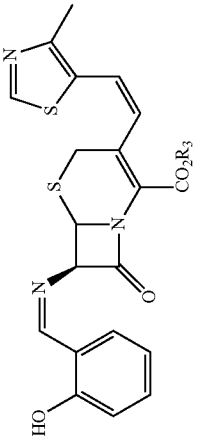
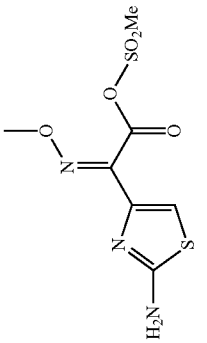
	Formula (II)	Formula (III)	Formula (IV)
21			
22			
23			

TABLE 1-continued

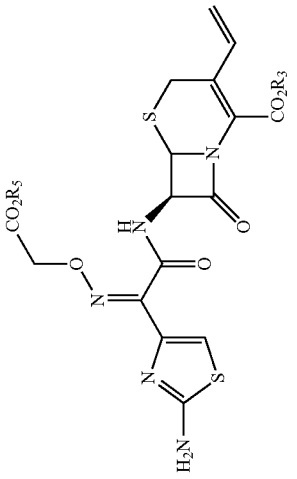
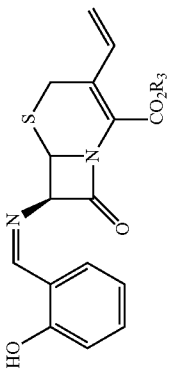
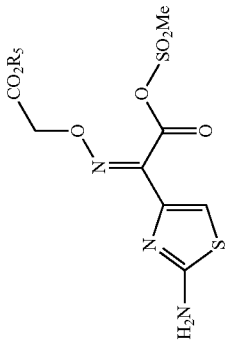
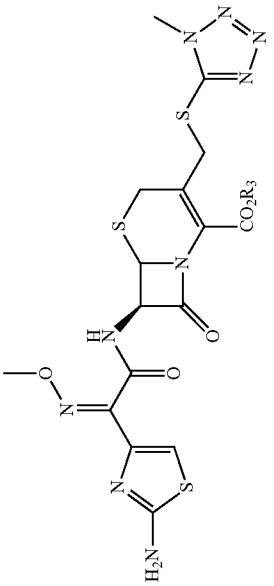
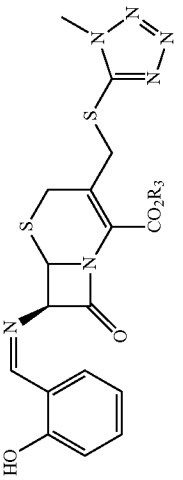
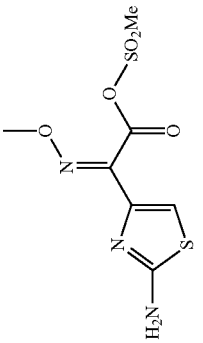
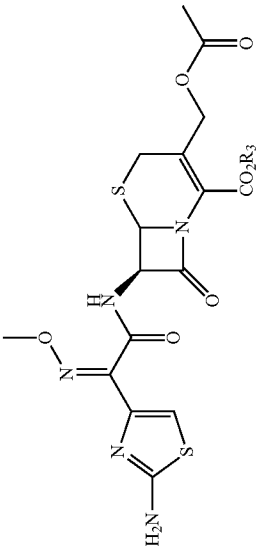
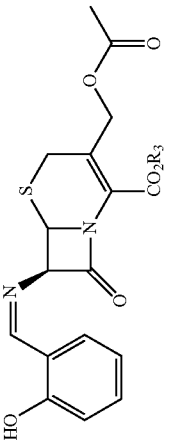
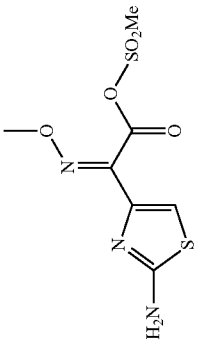
	Formula (II)	Formula (III)	Formula (IV)
24			
25			
26			

TABLE 1-continued

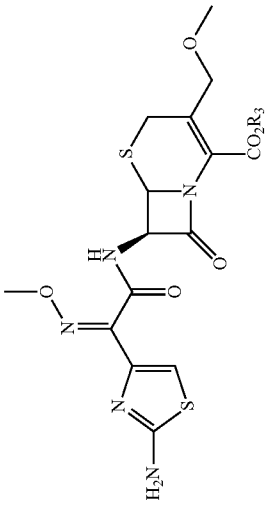
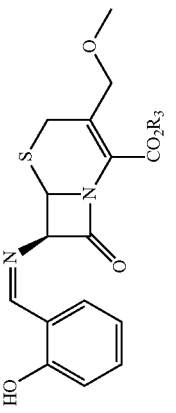
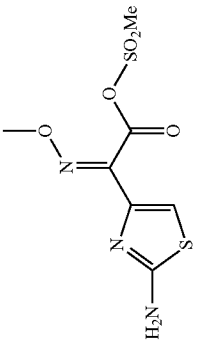
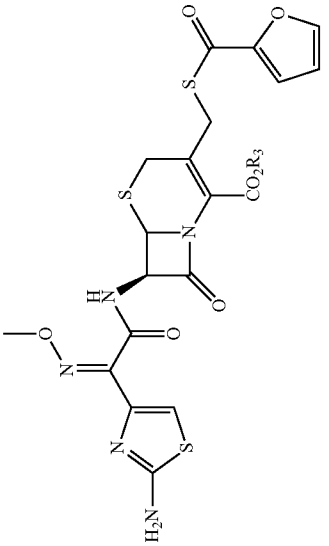
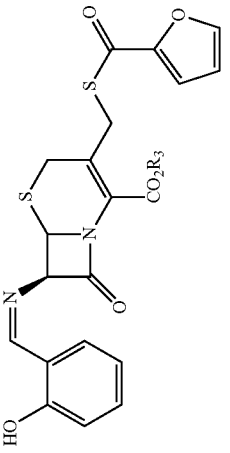
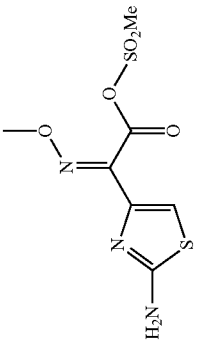
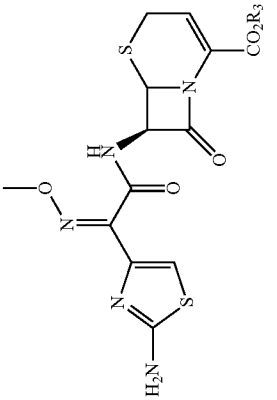
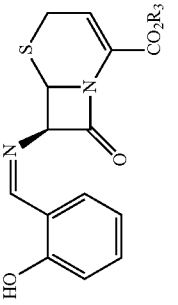
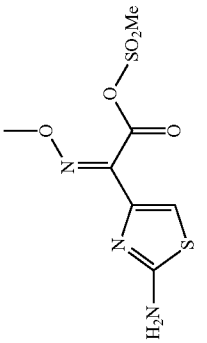
	Formula (II)	Formula (III)	Formula (IV)
27			
28			
29			

TABLE 1-continued

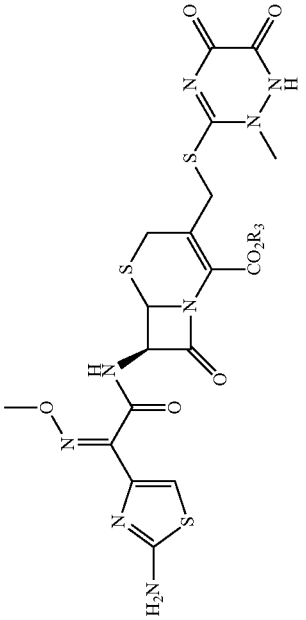
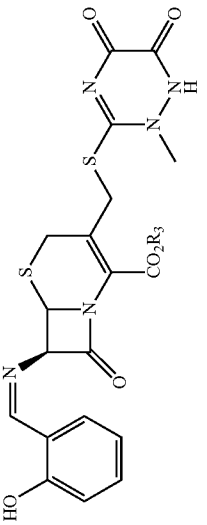
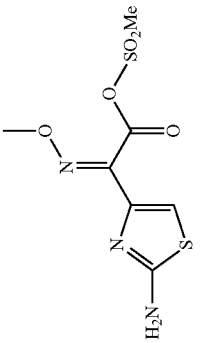
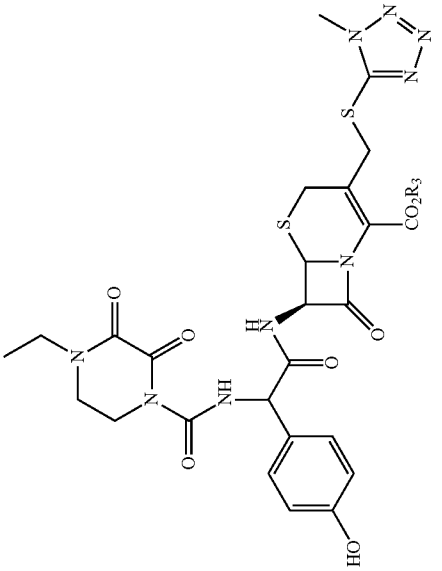
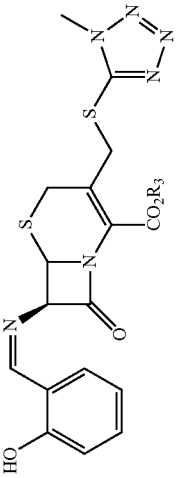
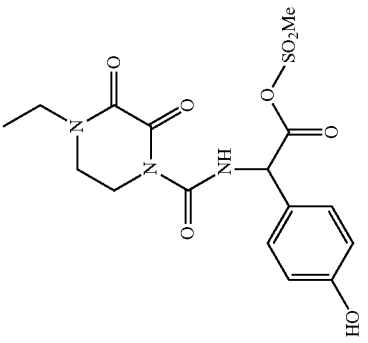
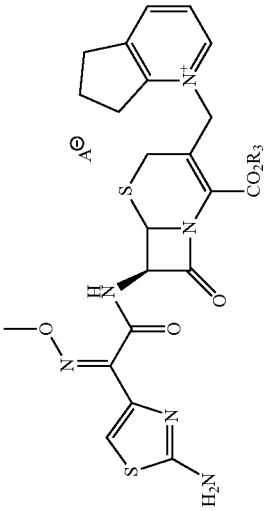
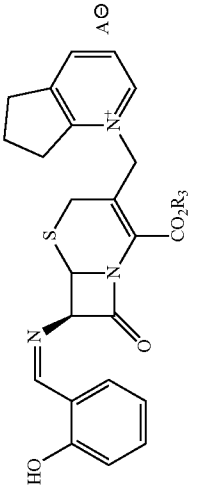
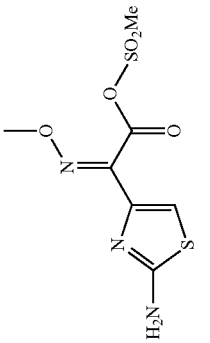
	Formula (II)	Formula (III)	Formula (IV)
30			
31			
32			

TABLE 2

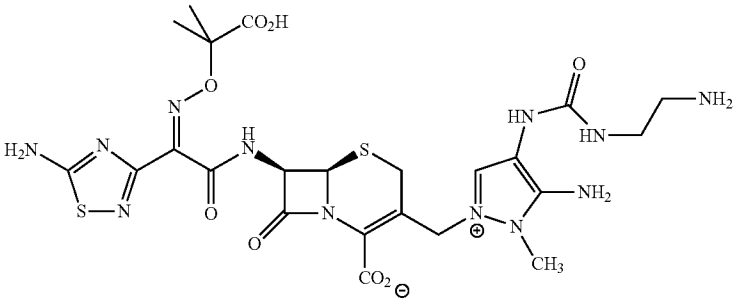
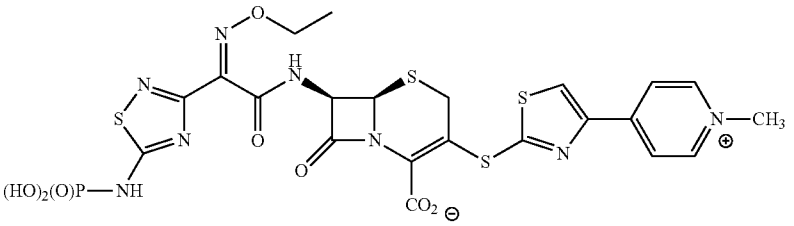
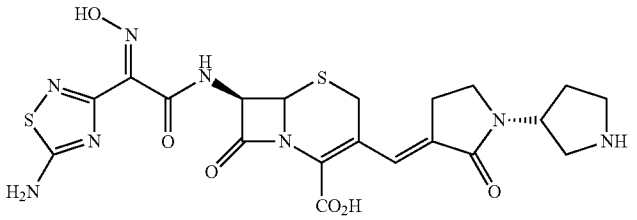
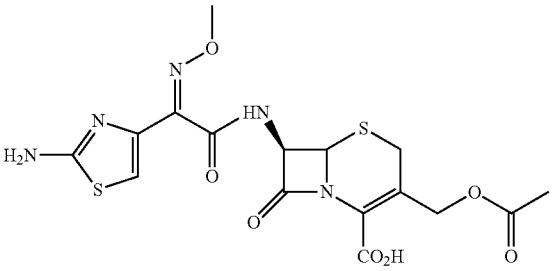
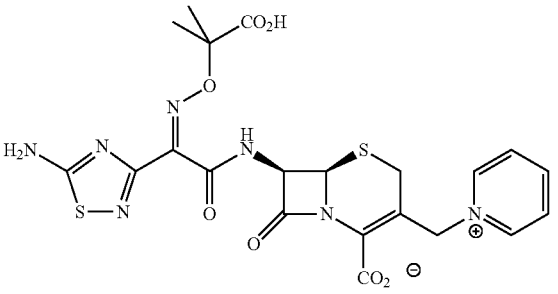
Formula (V)
V-1 
V-2 
V-3 
V-4 
V-5 

TABLE 2-continued

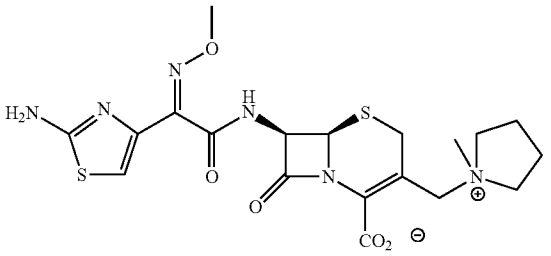
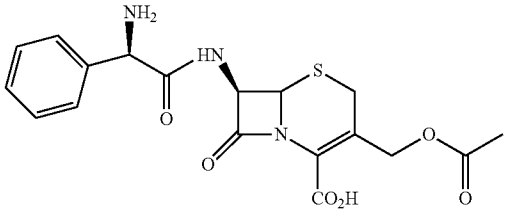
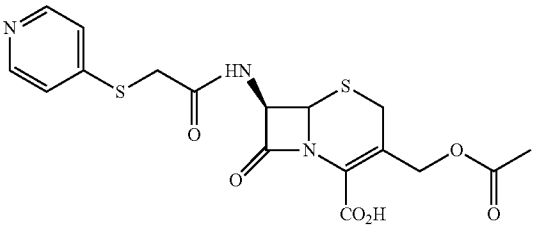
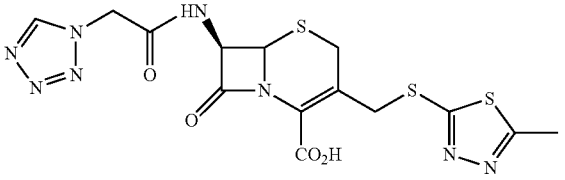
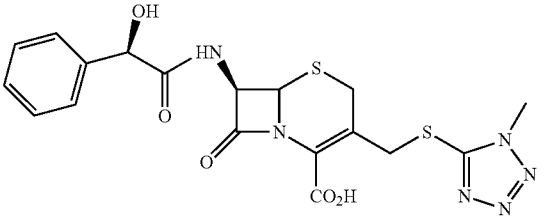
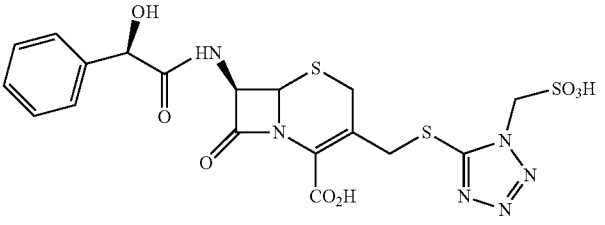
Formula (V)	
V-6	
V-7	
V-8	
V-9	
V-10	
V-11	

TABLE 2-continued

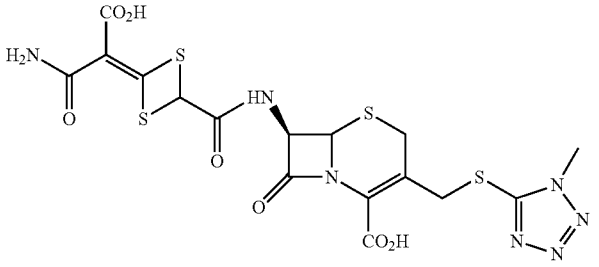
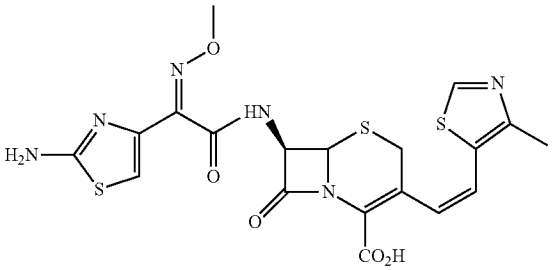
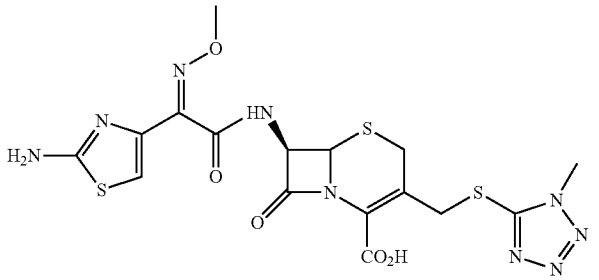
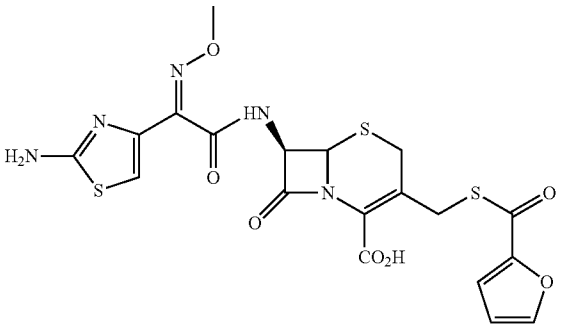
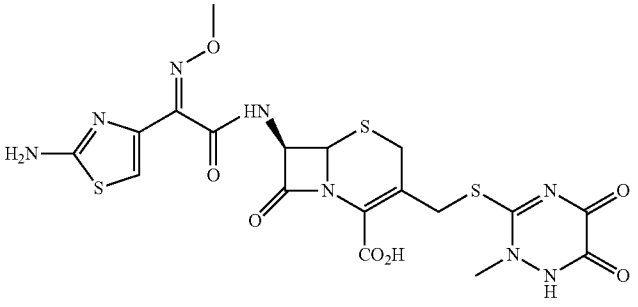
	Formula (V)
V-12	
V-13	
V-14	
V-15	
V-16	

TABLE 2-continued

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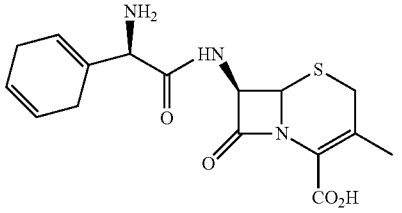
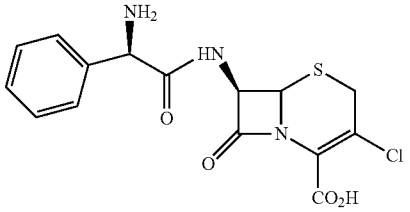
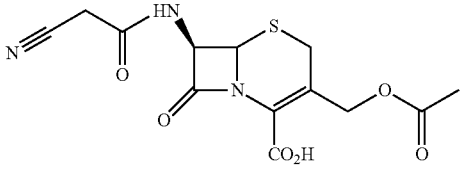
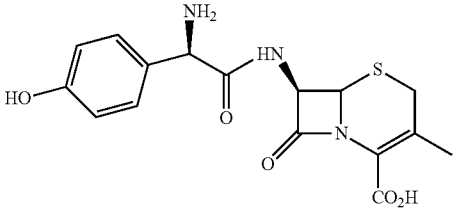
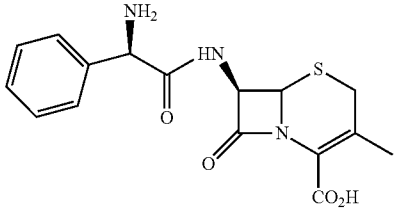
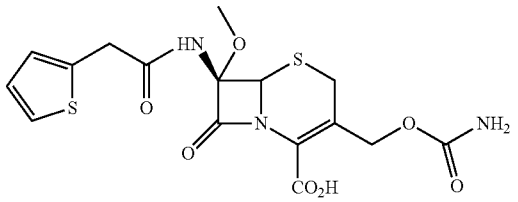
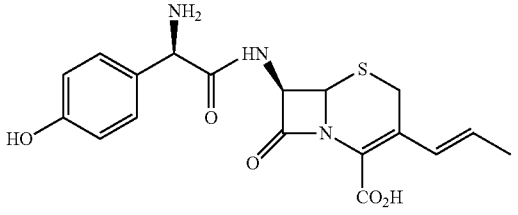
V-17	
V-18	
V-19	
V-20	
V-21	
V-22	
V-23	

TABLE 2-continued

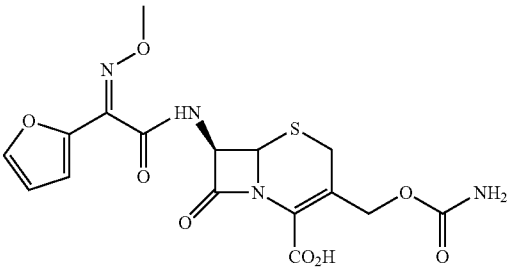
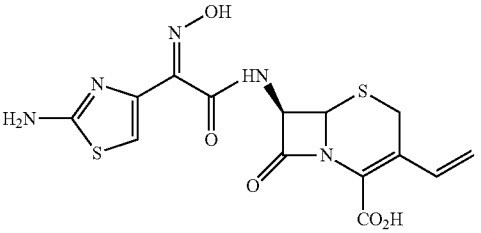
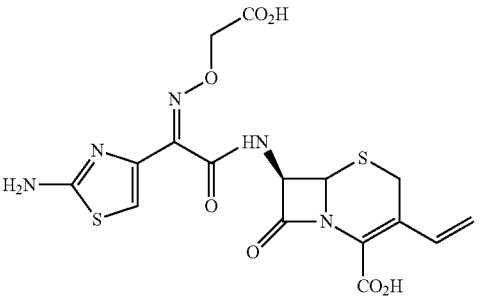
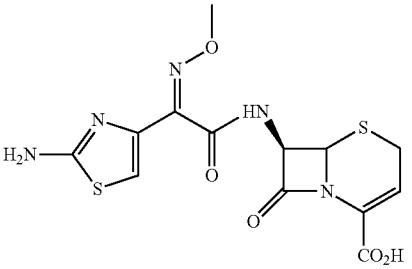
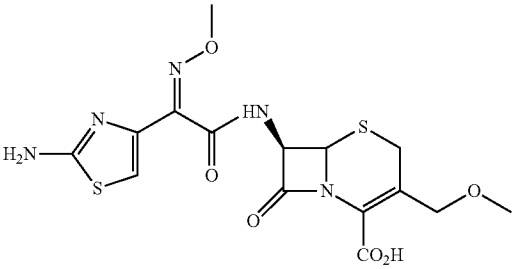
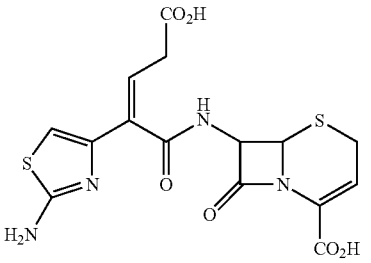
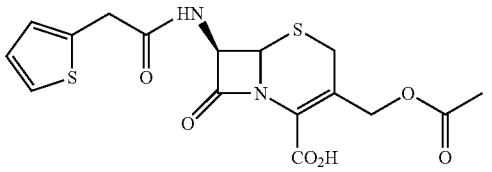
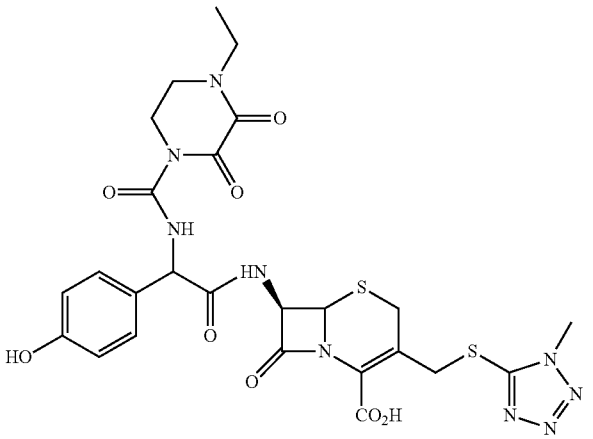
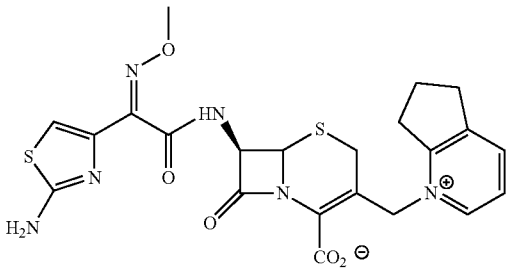
Formula (V)	
V-24	
V-25	
V-26	
V-27	
V-28	

TABLE 2-continued

Formula (V)	
V-29	
V-30	
V-31	
V-32	

EXAMPLES

Materials and Instrumentation

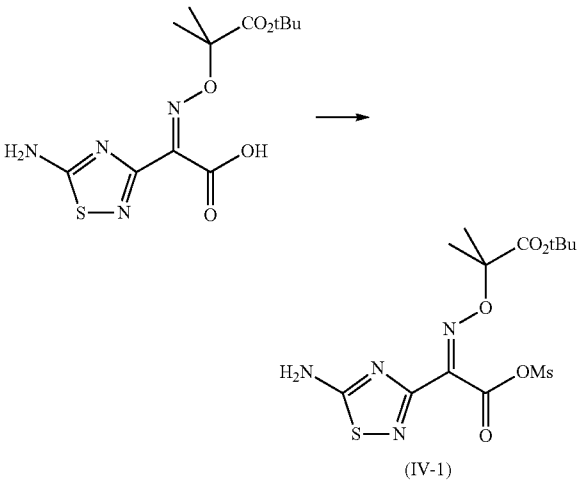
[0039] Compound characterization was obtained by high resolution mass spectrometry (HRMS) and high resolution mass spectrometry/mass spectrometry (HR MS/MS). Samples were dissolved in solution and the sample solutions were directly infused into time-of-flight (TOF) mass spectrometer to obtain parent (MS) and product scans (MS/MS) of analyte. Suitable materials and instrumentation are known to persons of skill in the art.

Example 1

Synthesis of Compound (II-1)

(1) Synthesis of compound (IV-1): (Z)-2-(5-amino-1,2,4-thiadiazol-3-O-2-(((1-(tert-butoxy)-2-methyl-1-oxopropan-2-yl)oxy)imino)acetic methanesulfonic anhydride

[0040]

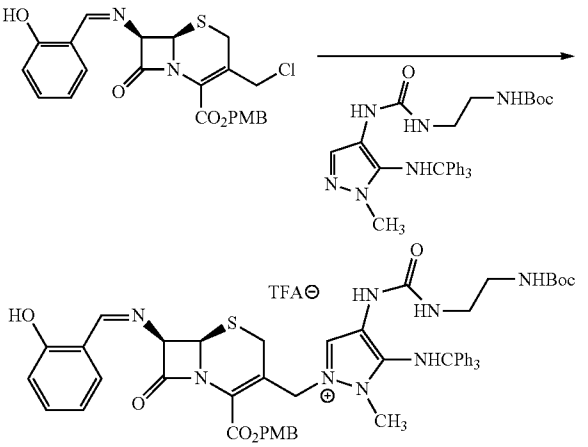


(IV-1)

[0041] A 5.0 liter reactor was charged with N,N-dimethylacetamide (1.4 L). Solid (Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(((1-(tert-butoxy)-2-methyl-1-oxopropan-2-yl)oxy)imino)acetic acid (250 g, 1 eq., prepared according to the method disclosed in U.S. Pat. No. 7,129,232) was added to the reactor at ambient temperature and the mixture was stirred until the solid was dissolved. The solution was cooled to about 4° C. (target: 2-5° C.) and stirred for another 10-15 minutes. Potassium carbonate (106.7 g, 184.9 mmol, 1.1 eq.) was added to the reactor in one portion. Methanesulfonyl chloride (118.0 mL, 2.2 eq.) was added to the reactor at a rate of about 5 mL/min while maintaining the batch temperature <10° C. The reaction was stirred for 1-2 hours at about 6° C., then cooled to about 0-5° C. Ethyl acetate (2.5 L, 10 volumes) was added to the reactor while maintaining a temperature of about 0-5° C. 1.6% HCl (aq) (1.35 L) was added to the reactor, maintaining a temperature of about 10-15° C. The biphasic mixture was agitated and the layers were then separated. The organic layer was washed with sodium chloride solution, dried with sodium sulfate and concentrated under reduced pressure to obtain crude material. The crude material was dissolved in ethyl acetate (150 mL) and filtered over silica gel. The filtrate was concentrated under reduced pressure to yield the title compound (299 g, 96.7%) as a colorless solid. Exact Mass: 408.08. HRMS: 409.0846 (M+1).

(2) Synthesis of compound (III-1): 5-amino-4-(3-(2-((tert-butoxycarbonyl)amino)ethyl)ureido)-2-(((6R,7R)-7-((Z)-(2-hydroxybenzylidene)amino)-2-(((4-methoxybenzyl)oxy)carbonyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl)methyl)-1-methyl-1H-pyrazol-2-ium trifluoroacetate

[0042]

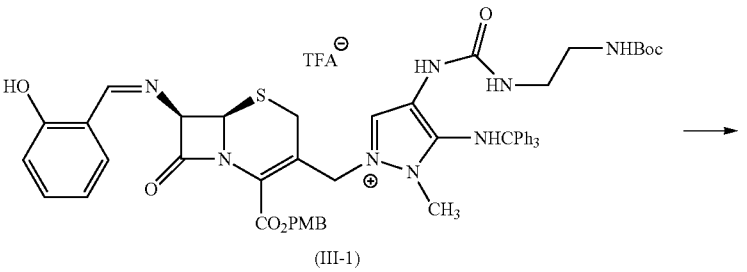


(III-1)

[0043] Compound (III-1) was prepared by coupling the compound (6R,7R)-4-methoxybenzyl 3-(chloromethyl)-7-((Z)-(2-hydroxybenzylidene)amino)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (purchased from Nippon Chemicals, Japan) with the compound tert-butyl (2-(3-(1-methyl-5-(tritylamino)-1H-pyrazol-4-yl)ureido)ethyl) carbamate (prepared according to the method disclosed in U.S. Pat. No. 7,129,232). Exact Mass (-TFA): 977.40. HRMS: 977.4025 (M+).

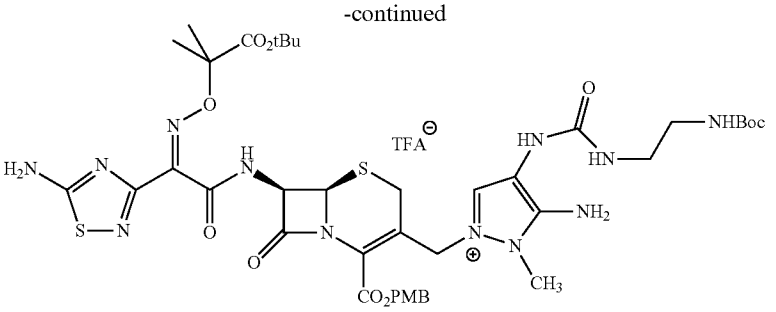
(3) Synthesis of compound (II-1): 5-amino-2-(((6R,7R)-7-((Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(((1-(tert-butoxy)-2-methyl-1-oxopropan-2-yl)oxy)imino)acetamido)-2-(((4-methoxybenzyl)oxy)carbonyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl)methyl)-4-(3-(2-((tert-butoxycarbonyl)amino)ethyl)ureido)-1-methyl-1H-pyrazol-2-ium trifluoroacetate

[0044]



(III-1)

-continued

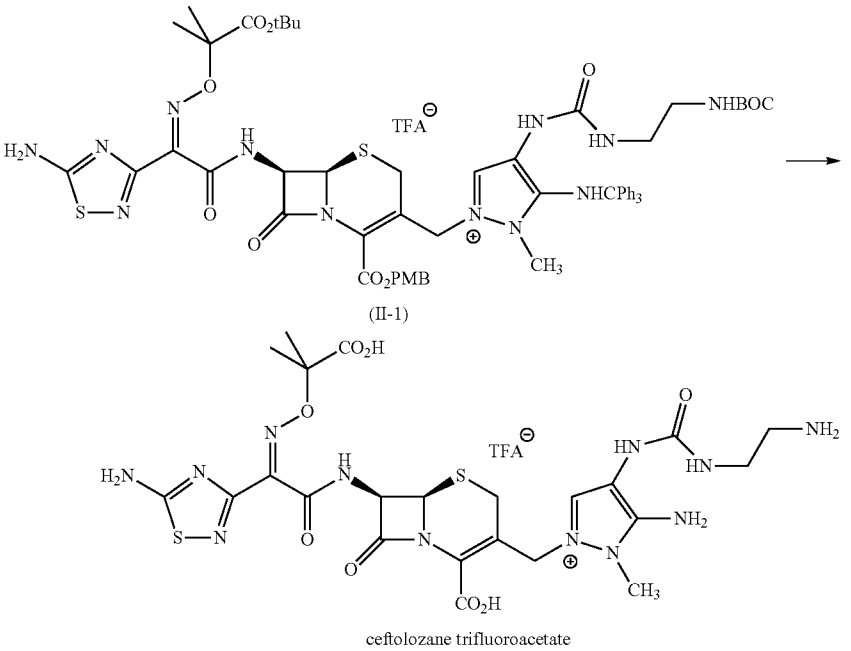


(II-1)

[0045] A reactor was charged with compound (III-1) (150 g), water (11.25 mL), compound (IV-1) (60 g), and dichloromethane (265 mL). The mixture was stirred for three hours at room temperature, then added to methyl tertiary butyl ether (1.5 L) over the course of 2-3 hours, resulting in the formation of a solid. The solid was filtered and the filter cake was washed with additional methyl tertiary butyl ether (1.0 L). The solid was dried under vacuum to yield the title compound (142.1 g, 81.2%). Exact Mass: 943.36 (-TFA). HRMS: 943.3555 (M+).

(4) Synthesis of Ceftolozane Trifluoroacetate

[0046]



ceftolozane trifluoroacetate

-

[0047] Compound (II-1) was dissolved in dichloromethane. Trifluoroacetic acid and anisole were added and the reaction was stirred for about 3 hours. Methyl tertiary butyl ether was added, causing the formation of a precipitate. The precipitate was collected by filtration and dried under vacuum to yield the title compound. Exact Mass (-TFA): 667.18. HRMS: 667.1810 (M+).

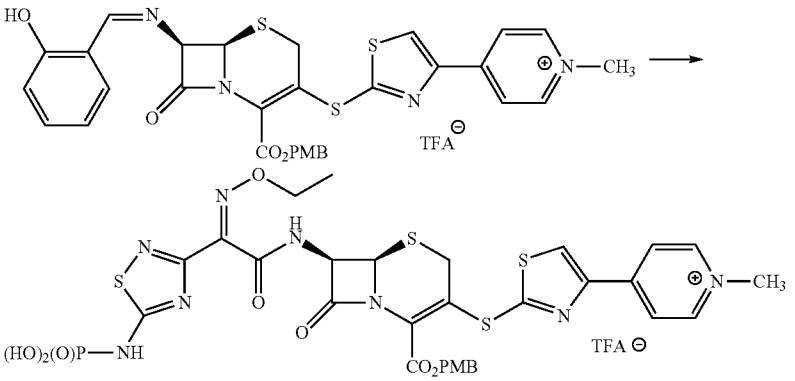
Example 2

[0048] Compound (III-1) (2.12 g) was dissolved in dichloromethane (3.75 ml). Water (160 uL) was added and the mixture was stirred for four hours, with hourly monitoring by HPLC.

Example 3

Synthesis of 4-(2-W7R)-7-((Z)-2-(ethoxyimino)-2-(5-(phosphonoamino)-1,2,4-thiadiazol-3-yl)acetamido)-2-(((4-methoxybenzyl)oxy)carbonyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl)thio)thiazol-4-yl)-1-methylpyridin-1-ium trifluoroacetate

[0049]

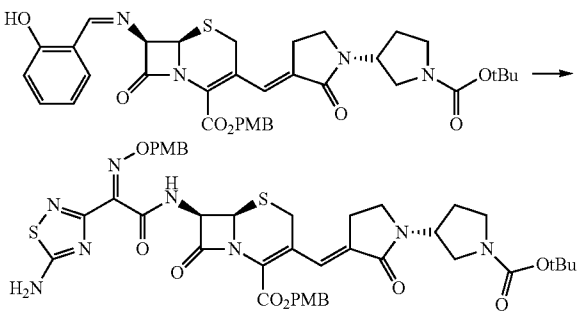


[0050] A reactor is charged with 4-(2-(((7R)-7-((Z)-(2-hydroxybenzylidene)amino)-2-(((4-methoxybenzyl)oxy)carbonyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl)thio)thiazol-4-yl)-1-methylpyridin-1-ium trifluoroacetate (1 eq), water (6-9 weight % relative to the Schiff base), (Z)-2-(5-(phosphonoamino)-1,2,4-thiadiazol-3-yl)-2-(ethoxyimino) acetic methanesulfonic anhydride (2.5 eq) and dichloromethane (1.75 mL per gram of Schiff base). The mixture is stirred for three hours at room temperature, then added to methyl tertiary butyl ether over the course of 2-3 hours, resulting in the formation of a solid. The solid is filtered and the filter cake was washed with additional methyl tertiary butyl ether. The solid is dried under vacuum to yield the title compound.

Example 4

Synthesis of 4-methoxybenzyl 7((Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(((4-methoxybenzyl)oxy)imino) acetamido)-3-(E)-((R)-1'-(tert-butoxycarbonyl)-2-oxo-[1,3'-bipyrrolidin]-3-ylidene)methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

[0051]

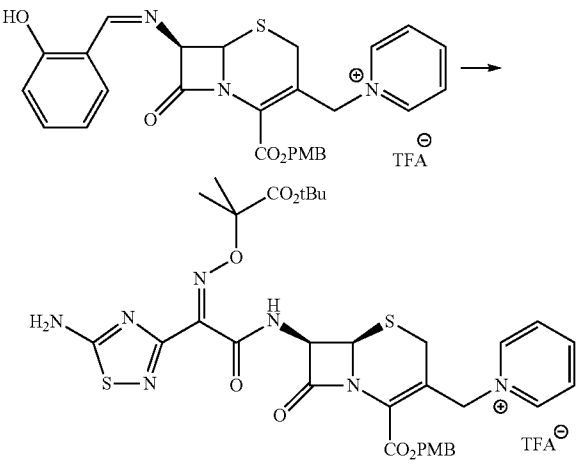


[0052] A reactor is charged with (7R)-4-methoxybenzyl-3-((E)-((R)-1'-(tert-butoxycarbonyl)-2-oxo-[1,3'-bipyrrolidin]-3-ylidene)methyl)-7-((Z)-(2-hydroxybenzylidene) amino)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (1 eq), water (6-9 weight % relative to the Schiff base), (Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(((4-methoxybenzyl)oxy)imino)acetic methanesulfonic anhydride (2.5 eq) and dichloromethane (1.75 mL per gram of Schiff base). The mixture is stirred for three hours at room temperature, then added to methyl tertiary butyl ether over the course of 2-3 hours, resulting in the formation of a solid. The solid is filtered and the filter cake was washed with additional methyl tertiary butyl ether. The solid is dried under vacuum to yield the title compound.

Example 5

Synthesis of 1-W6R,7R)-7-((Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(((1-(tert-butoxy)-2-methyl-1-oxopropan-2-yl)oxy)imino)acetamido)-2-(((4-methoxybenzyl)oxy)carbonyl)-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-en-3-yl)methyl)pyridin-1-ium trifluoroacetate

[0053]



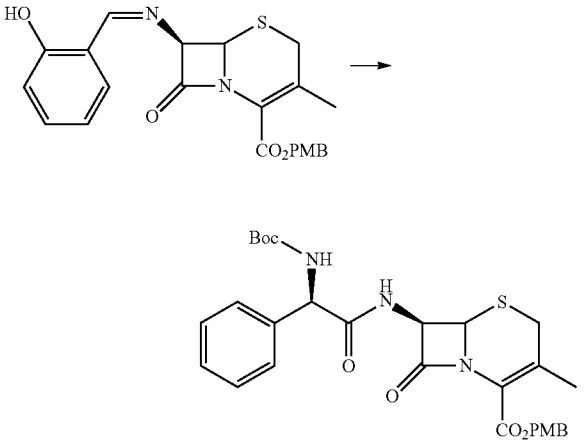
[0054] A reactor is charged with 1-(((7R)-7-((Z)-(2-hydroxybenzylidene)amino)-2-(((4-methoxybenzyl)oxy)car-

bonyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl)methyl)pyridin-1-ium trifluoroacetate (1 eq), water (6-9 weight % relative to the Schiff base), (Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(((1-(tert-butoxy)-2-methyl-1-oxopropan-2-yl)oxy)imino)acetic methanesulfonic anhydride (2.5 eq) and dichloromethane (1.75 mL per gram of Schiff base). The mixture is stirred for three hours at room temperature, then added to methyl tertiary butyl ether over the course of 2-3 hours, resulting in the formation of a solid. The solid is filtered and the filter cake was washed with additional methyl tertiary butyl ether. The solid is dried under vacuum to yield the title compound.

Example 6

Synthesis of (7R)-4-methoxybenzyl 74(R)-2-((tert-butoxycarbonyl)amino)-2-phenylacetamido)-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

[0055]

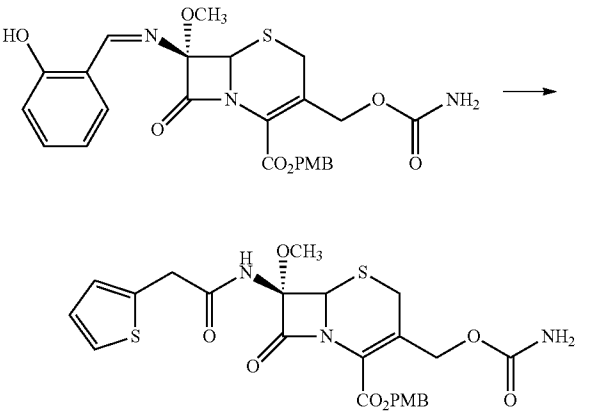


[0056] A reactor is charged with (7R)-4-methoxybenzyl 7-((Z)-(2-hydroxybenzylidene)amino)-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (1 eq), water (6-9 weight % relative to the Schiff base), (R)-2-((tert-butoxycarbonyl)amino)-2-phenylacetic methanesulfonic anhydride (2.5 eq) and dichloromethane (1.75 mL per gram of Schiff base). The mixture is stirred for three hours at room temperature, then added to methyl tertiary butyl ether over the course of 2-3 hours, resulting in the formation of a solid. The solid is filtered and the filter cake was washed with additional methyl tertiary butyl ether. The solid is dried under vacuum to yield the title compound.

Example 7

Synthesis of 4-methoxybenzyl 3-((carbamoyloxy)methyl)-7-methoxy-8-oxo-7-(2-(thiophen-2-yl)acetamido)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

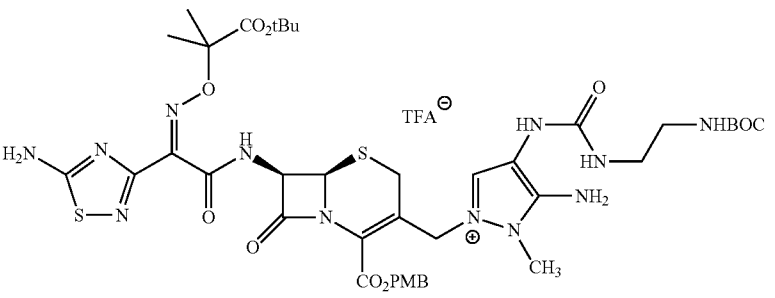
[0057]



[0058] A reactor is charged with (75)-4-methoxybenzyl 3-((carbamoyloxy)methyl)-7-((Z)-(2-hydroxybenzylidene)amino)-7-methoxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (1 eq), water (6-9 weight % relative to the Schiff base), 2-(thiophen-2-yl)acetic methanesulfonic anhydride (2.5 eq) and dichloromethane (1.75 mL per gram of Schiff base). The mixture is stirred for three hours at room temperature, then added to methyl tertiary butyl ether over the course of 2-3 hours, resulting in the formation of a solid. The solid is filtered and the filter cake was washed with additional methyl tertiary butyl ether. The solid is dried under vacuum to yield the title compound.

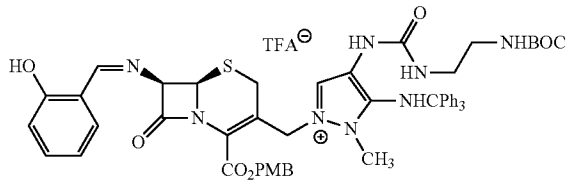
1. A method for preparing a compound of formula (II-1), or a salt thereof,

(II-1)



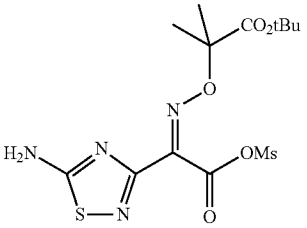
comprising the step of reacting a compound of formula (III-1), or a salt thereof,

(III-1)



with a compound of formula (IV-1), or a salt thereof,

(IV-1)

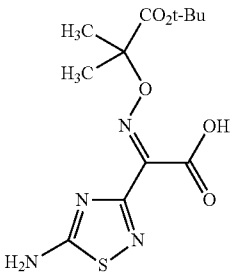


in a mixture comprising an organic solvent and about 6-9 percent (w/w) of water relative to the compound of formula (III-1), or salt thereof.

2. The method of claim **1**, wherein the organic solvent is dichloromethane.

3. The method of claim **1**, wherein the compound of formula (IV-1) is prepared from the compound of formula (IVa):

(IVa)



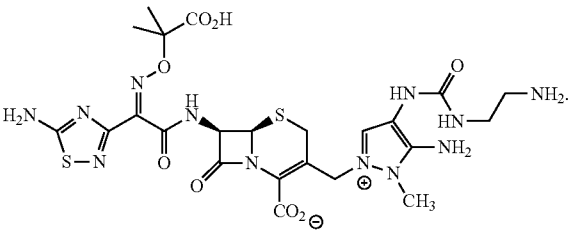
by a process comprising the steps of:

(a) forming a mixture comprising potassium carbonate and the compound of formula (IVa); and

(b) adding methansulfonyl chloride to the mixture of step (a) such that the compound of formula (IV-1) is formed.

4. The method of claim **1**, further comprising the step of reacting the compound of formula (II-1), or a salt thereof, with a strong acid to form a compound of formula (V-1), or a salt thereof:

(V-1)

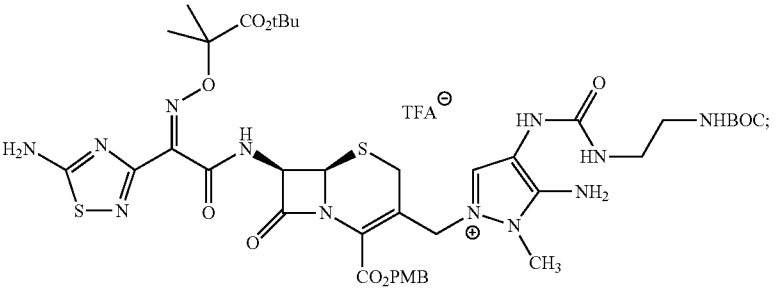


5. The method of claim **4**, wherein the strong acid is trifluoroacetic acid.

6. A composition comprising two or more compounds selected from the group consisting of:

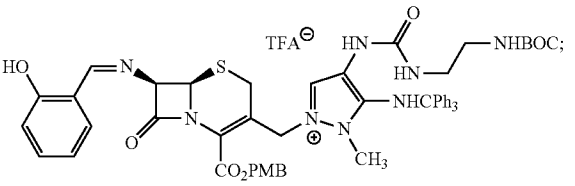
(a) the compound of formula (II-1), or a salt thereof

(II-1)



(b) the compound of formula (III-1), or a salt thereof

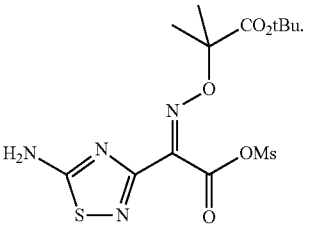
(III-1)



and

(c) the compound of formula (IV-1), or a salt thereof

(IV-1)

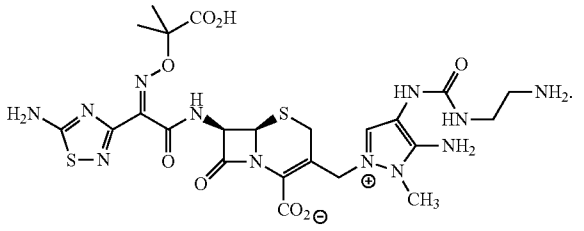


7. The composition of claim **6**, comprising the compound of formula (II-1), or a salt thereof, and the compound of formula (III-1), or a salt thereof.

8. The composition of claim **7**, comprising the compound of formula (II-1), or a salt thereof, the compound of formula (III-1), or a salt thereof, and the compound of formula (IV-1), or a salt thereof.

9. The composition of claim **6**, further comprising the compound of formula (V-1), or salt a thereof

(V-1)



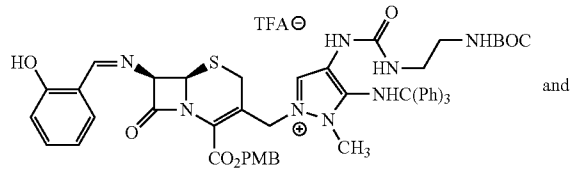
10. The composition of claim **9**, wherein the compound of formula (II-1), or salt a thereof, the compound of formula (III-1), or salt a thereof, and the compound of formula (IV-1), or salt a thereof, are each present in an amount that is less than 0.05%.

11. The composition of claim **9**, prepared by a method comprising the steps of:

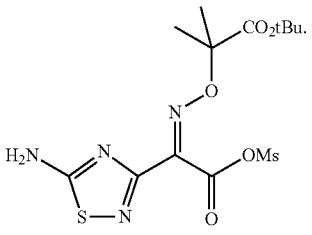
(a) reacting a compound of formula (III-1), or a salt thereof, with a compound of formula (IV-1), or a salt thereof, in a mixture comprising an organic solvent and about 6-9 percent (w/w) of water relative to the compound of formula (III-1), or salt thereof; and

(b) reacting the compound of formula (II-1), or a salt thereof, with a strong acid to form a compound of formula (V-1), or a salt thereof.

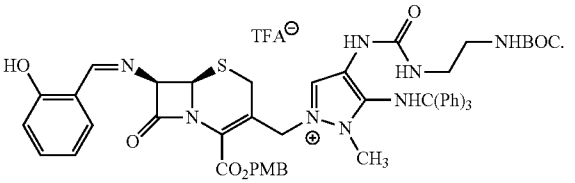
12. A compound selected from the group consisting of:



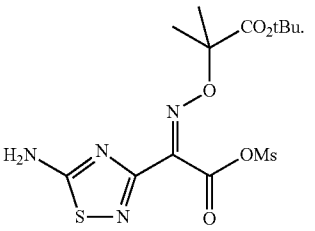
and



13. The compound of claim **12** having the structure



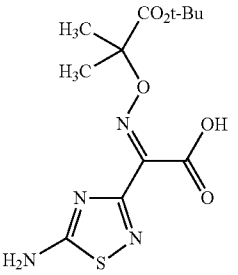
14. The compound of claim **12** having the structure



15. The method of claim **1**, wherein the weight ratio of the compound of formula (III-1) to the compound of formula (IV-1) is 150 g:60 g.

16. The method of claim **1**, wherein the organic solvent is dichloromethane; wherein the compound of formula (IV-1) is prepared from the compound of formula (IVa):

(IVa)



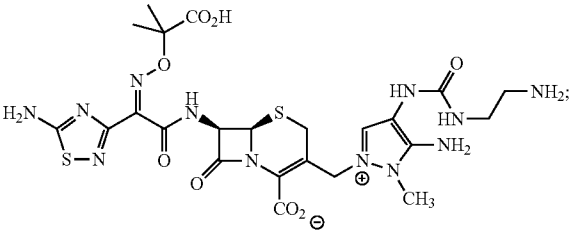
by a process comprising the steps of:

(a) forming a mixture comprising potassium carbonate and the compound of formula (IVa); and

(b) adding methansulfonyl chloride to the mixture of step (a) such that the compound of formula (IV-1) is formed;

wherein the method further comprises the step of reacting the compound of formula (II-1), or a salt thereof, with a strong acid to form a compound of formula (V-1), or a salt thereof:

(V-1)



and

wherein the strong acid is trifluoroacetic acid.

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