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(12) **United States Patent**
Whitten et al.(10) **Patent No.:** **US 7,652,134 B2**(45) **Date of Patent:** **Jan. 26, 2010**(54) **METHODS FOR CONVERTING QUINOLONE ESTERS INTO QUINOLONE AMIDES**

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(60) Provisional application No. 60/611,030, filed on Sep. 17, 2004.

(51) **Int. Cl.****C07D 413/14** (2006.01)**C07D 401/14** (2006.01)(52) **U.S. Cl.** **544/99**; 544/329; 544/59(58) **Field of Classification Search** 544/99,
544/361, 59, 342; 546/66, 75

See application file for complete search history.

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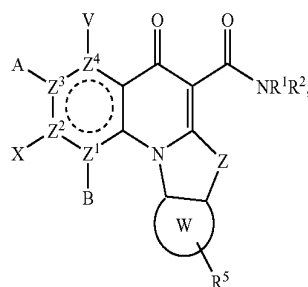
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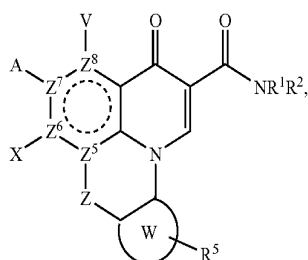
Primary Examiner—Charanjit S Aulakh
(74) *Attorney, Agent, or Firm*—Morrison & Foerster LLP(57) **ABSTRACT**

The present invention relates to methods of preparing compounds having formula (1), (2), (5), and ((6A)-(6D))



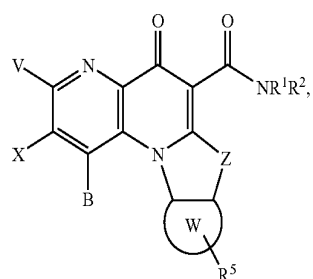
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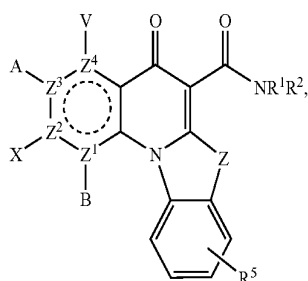


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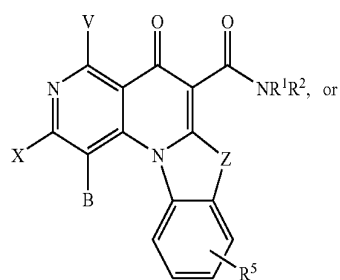
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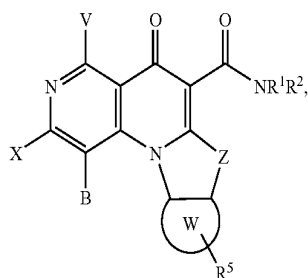
(6B)



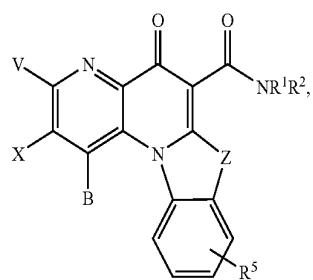
(5)



(6C)



(6A)



(6D)

comprising contacting the corresponding ester, an amine with formula NHR^1R^2 , and a Lewis acid having formula ML_m , wherein L is a halogen atom or an organic radical, n is 3-5, and M is a group III elemental atom, a group IV elemental atom, As, Sb, V or Fe, wherein A, B, V, X, Z, W, R^1 , R^2 , R^5 , Z^1 , Z^2 , Z^3 , Z^4 , Z^5 , Z^6 , Z^7 , and Z^8 are substituents. Z^4 , Z^5 , Z^6 , Z^7 , and Z^8 are substituents.

29 Claims, No Drawings

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**METHODS FOR CONVERTING QUINOLONE
ESTERS INTO QUINOLONE AMIDES**

CROSS REFERENCE

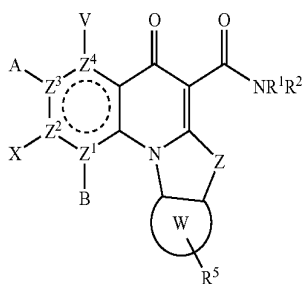
This application claims the benefit of priority of U.S. provisional patent application Ser. No. 60/611,030, filed Sep. 17, 2004, which is incorporated herein by reference.

BACKGROUND

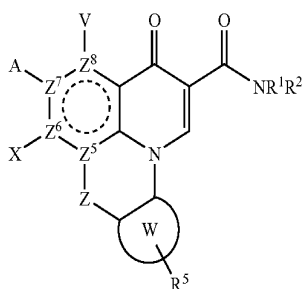
Evidence suggests that quadruplex structures can exist in vivo in specific regions of the genome, including the telomeric ends of chromosomes and oncogene regulatory regions (Han, et al., *Trends Pharm. Sci.* (2000) 21:136-142). Quadruplex structures can form in certain purine-rich strands of nucleic acids. In duplex nucleic acids, certain purine rich strands are capable of engaging in a slow equilibrium between a typical duplex helix structure and in unwound and non-B-form regions. These unwound and non-B forms can be referred to as "paranemic structures." Some forms are associated with sensitivity to S1 nuclease digestion, which can be referred to as "nuclease hypersensitivity elements" or "NHEs." A quadruplex is one type of paranemic structure and certain NHEs can adopt a quadruplex structure.

SUMMARY OF THE INVENTION

The present invention provides methods for preparing compounds having formula 1

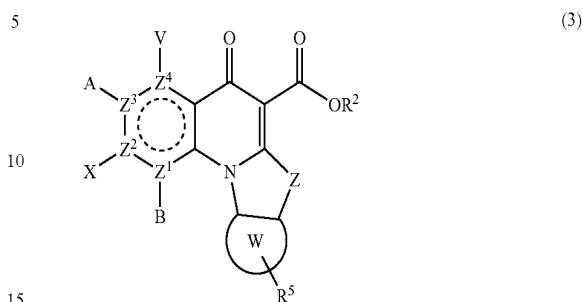


or formula 2

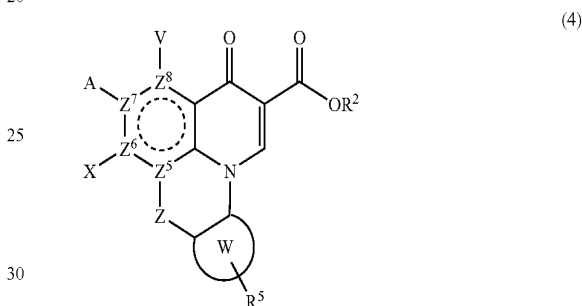


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comprising contacting an ester, NHR^1R^2 , and a Lewis acid, wherein said ester has formula 3



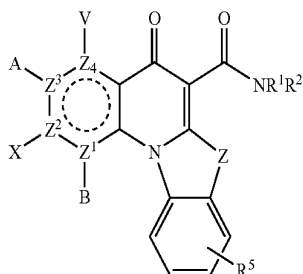
or formula 4



- A, V, and X are independently H, halo, azido, R^2 , CH_2R^2 , SR^2 , OR^2 or NR^1R^2 ; or
- wherein A and X, or A and V may form a carbocyclic ring, heterocyclic ring, aryl or heteroaryl, each of which may be optionally substituted and/or fused with a cyclic ring;
- wherein NR^1R^2 , R^1 and R^2 together with N may form an optionally substituted ring;
- each Z is CH_2 , O, S, or NR^1 ;
- Z^1 , Z^2 , Z^3 , Z^4 , Z^6 , Z^7 , and Z^8 are independently C or N, provided any two N are non-adjacent;
- Z^5 is C or N, provided Z^5 is C if Z is O, S or NR^1 , and further provided that Z and Z^6 are not N if Z^5 is N;
- each R^1 is H or a C_{1-6} alkyl;
- each R^2 is H or a C_{1-10} alkyl or C_{2-10} alkenyl optionally containing one or more non-adjacent heteroatoms selected from N, O, and S, and optionally substituted with a carbocyclic or heterocyclic ring; or R^2 is an optionally substituted carbocyclic ring, heterocyclic ring, aryl or heteroaryl;
- each B is H or halo;
- each W is an optionally substituted aryl or heteroaryl, which may be monocyclic, or fused with a single or multiple ring and optionally containing a heteroatom;
- and each R^5 is a substituent at any position on the fused ring; and is H, OR^2 , NR^1R^2 , C_{1-6} alkyl, C_{2-6} alkenyl, each optionally substituted by halo, $\text{C}=\text{O}$ or one or more heteroatoms; or R^5 is an inorganic substituent; or two adjacent R^5 is linked to obtain a 5-6 membered substituted or unsubstituted carbocyclic or heterocyclic ring, optionally fused to an additional substituted or unsubstituted carbocyclic or heterocyclic ring.

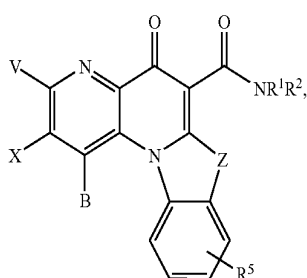
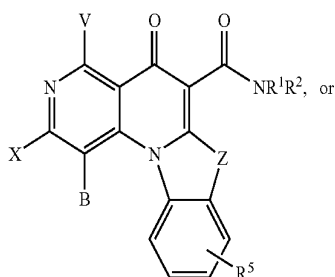
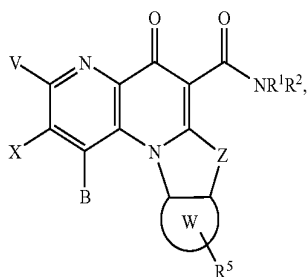
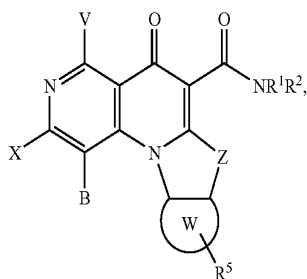
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Furthermore, the present invention also provides methods for preparing compounds having the formula:



comprising contacting the corresponding ester with NHR^1R^2 and a Lewis acid, wherein each substituent is as defined in formula 1.

The present invention also provides methods for preparing compounds having formula 6A-6D



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comprising contacting the corresponding esters with NHR^1R^2 and a Lewis acid,

wherein B, V, X, Z, R^1 , R^2 , W, and R^5 are as defined in formula 1.

(5) The present methods involve amide coupling of an ester with an amine in the presence of a Lewis acid such as aluminum chloride. Suitable Lewis acids may be selected by conducting a test reaction, and observing the amount of reaction product produced, as described hereafter. The present methods do not require hydrolysis of the ester to a carboxylic acid prior to amide coupling. Thus, the present methods are simpler. As shown in Example 9, the present methods also provide higher yields and purity than previous methods involving requiring hydrolysis of the ester to the acid (Example 10).

In one embodiment, the Lewis acid has formula ML_n , wherein L is a halogen atom or an organic radical, n is 3-5, and M is a group III elemental atom, a group IV elemental atom, As, Sb, V or Fe.

In the above methods, the contacting step may be performed at room temperature. Alternatively, the ester, amine and Lewis acid may be contacted at cooler or elevated temperatures than room temperature, which may be determined by one skilled in the art.

In one example, the contacting step comprises contacting the ester and amine in an organic solvent to form a solution, and contacting the solution with a Lewis acid. In one example, the organic solvent is methylene chloride. The reaction may also be conducted using other suitable solvents known in the art.

(6B) In one embodiment, an excess of amine in relation to the ester may be used. For example, the ratio of the ester to the amine may be 1:2; 1:1.5; or 1:1.25.

In another embodiment, an equimolar amount of Lewis acid to the amine may be used. Alternatively, the amount of Lewis acid used may be more or less than the amine.

(6C) The above methods may further comprise isolating a compound having any one of the above formula. The isolated compounds may further be purified using any methods known in the art. For example, the isolated compounds may be purified through column chromatography, recrystallization, or both.

In the above methods, the purity of the isolated compounds may be between 90 and 99%. For example, the isolated compounds may have a purity between 90 and 95%.

(6D) In the above methods, the ester may be contacted with NHR^1R^2 ,

wherein R^1 is a $(\text{CR}^3)_2$ group;

R^2 is NR^3R^4 ;

R^3 is H or C_{1-6} alkyl;

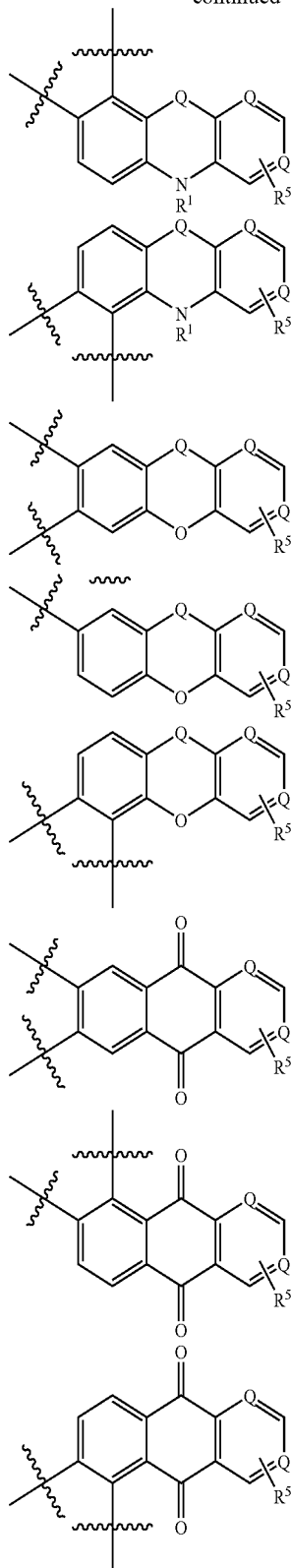
n is 1-6; and

R^4 is H or a C_{1-10} alkyl or C_{2-10} alkenyl optionally containing one or more non-adjacent heteroatoms selected from N, O and S, and optionally substituted with a carbocyclic or heterocyclic ring; and

wherein in NR^3R^4 , R^3 and R^4 may form an optionally substituted ring such as those previously described above.

In the above methods, W if present in any of the above compounds may be selected from the group consisting of

-continued



wherein each Q, Q¹, Q², and Q³ is independently CH or N; Y is independently O, CH, C=O or NR¹; and R⁵ is as defined above.

In the above methods, X in any of the above compounds may be SR², where R² is a C₀₋₁₀ alkyl or C₂₋₁₀ alkenyl optionally substituted with a heteroatom, a carbocyclic ring, a het-

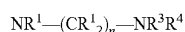
erocyclic ring, an aryl or a heteroaryl. In one example, R² is a C₁₋₁₀ alkyl substituted with an optionally substituted pyrazine.

In the above methods, X and A in any of the above compounds may independently be halo or NR¹R², wherein R¹ may be H and R² may be a C₁₋₁₀ alkyl optionally substituted with a heteroatom, a C₃₋₆ cycloalkyl, aryl or a 5-14 membered heterocyclic ring containing one or more N, O or S. In one example, R² is a C₁₋₁₀ alkyl substituted with an optionally substituted heterocyclic ring, particularly a 5-14 membered heterocyclic ring. Alternatively, R¹ and R² together with N may form an optionally substituted heterocyclic ring containing one or more N, O or S, and particularly a 5-14 membered heterocyclic ring.

Examples of optionally substituted heterocyclic rings include but are not limited to tetrahydrofuran, 1,3-dioxolane, 2,3-dihydrofuran, tetrahydropyran, benzofuran, isobenzofuran, 1,3-dihydro-isobenzofuran, isoxazole, 4,5-dihydroisoxazole, piperidine, pyrrolidine, pyrrolidin-2-one, pyrrole, pyridine, pyrimidine, octahydro-pyrrolo[3,4-b]pyridine, piperazine, pyrazine, morpholine, thiomorpholine, imidazole, aminodithiadazole, imidazolidine-2,4-dione, benzimidazole, 1,3-dihydrobenzimidazol-2-one, indole, thiazole, benzothiazole, thiadiazole, thiophene, tetrahydro-thiophene 1,1-dioxide, diazepine, triazole, guanidine, diazabicyclo[2.2.1]heptane, 2,5-diazabicyclo[2.2.1]heptane, and 2,3,4,4a,9,9a-hexahydro-1H-β-carboline.

In the above methods, A and X in any of the above compounds may independently be halo or NR¹R², where R¹ is H and R² is a C₁₋₁₀ alkyl substituted with morpholine, thiomorpholine, imidazole, aminodithiadazole, pyrrolidine, piperazine, pyridine or piperidine. Alternatively, R¹ and R² together with N may form with N piperidine, pyrrolidine, piperazine, morpholine, thiomorpholine, imidazole, or aminodithiazole.

Alternatively, X in any of the above compounds may be an amine moiety having the formula



wherein R¹ and R³ are independently H or C₁₋₆ alkyl; n is 1-6; and

R⁴ is H or a C₁₋₁₀ alkyl or C₂₋₁₀ alkenyl optionally containing one or more non-adjacent heteroatoms selected from N, O and S, and optionally substituted with a carbocyclic or heterocyclic ring; and

wherein in NR³R⁴, R³ and R⁴ may form an optionally substituted ring.

In the above amine moiety, n may be 2-3. In one example, R³ and R⁴ in NR³R⁴ together form an optionally substituted ring containing one or more N, O or S.

In some embodiments, A, V, B and X, when present, are all H. In other embodiments, three of A, V, B and X are H. In other embodiments, two of A, V, B and X are H. In yet other embodiments, only one of A, V, B and X is H. In certain embodiments, only one of A, V, B and X is a halogen (e.g., fluorine). In other embodiments, two of A, V, B and X are halogen. In still other embodiments, three of A, V, B and X are halogen.

In the above methods, each optionally substituted moiety in any of the above compounds may be substituted with one or more halo, OR², NR¹R², carbamate, C₇₋₁₀ alkyl, C₂₋₁₀ alkenyl, each optionally substituted by halo, C=O, aryl or one or more heteroatoms; inorganic substituents, aryl, carbocyclic or a heterocyclic ring.

In certain embodiments, a compound of any one of the formulae above may have the following substituents:

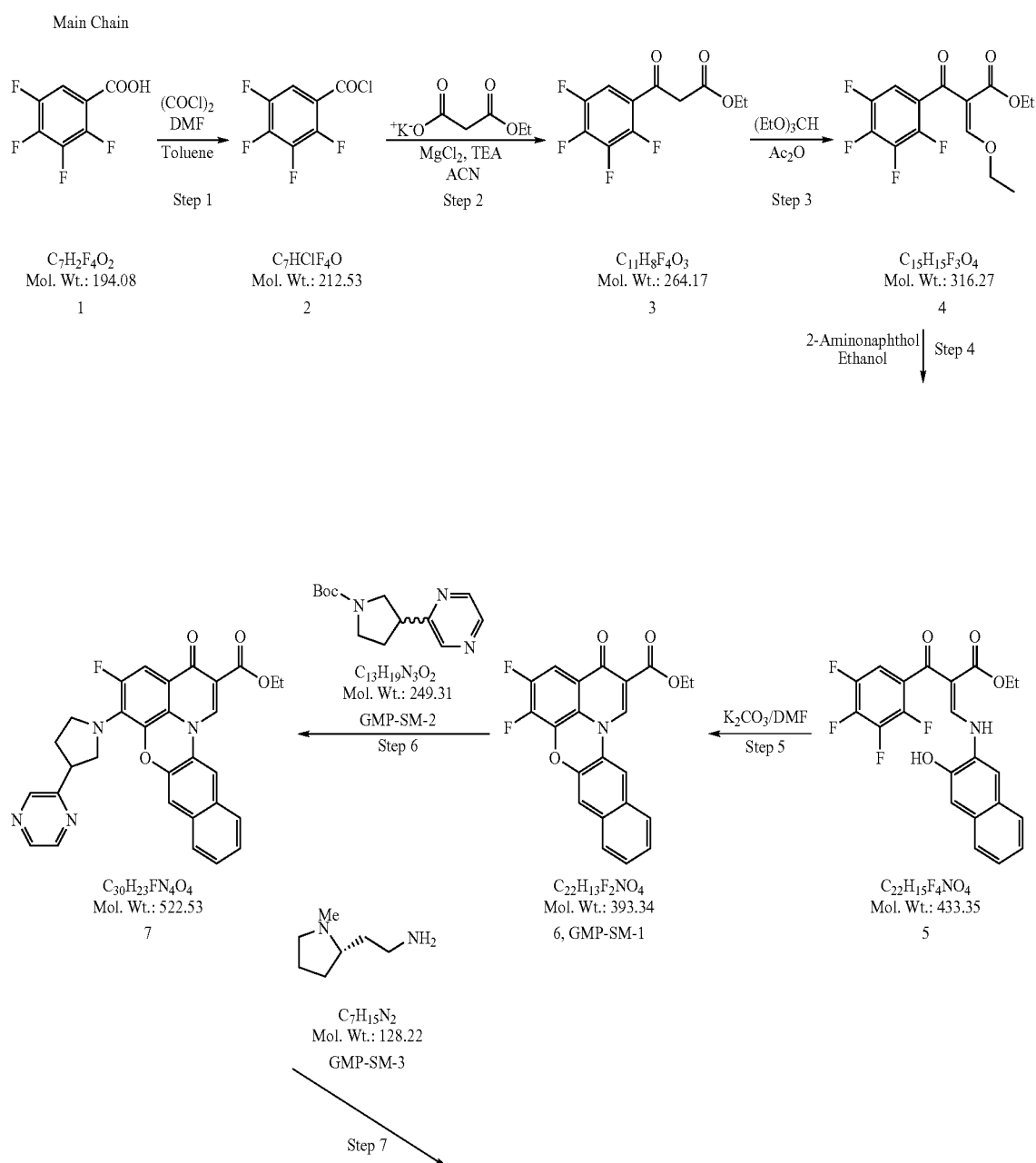
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each of A, V and B is independently H or halogen (e.g., chloro or fluoro);
 X is $-(R^5)R^1R^2$, wherein R^5 is C or N and wherein in each $-(R^5)R^1R^2$, R^1 and R^2 together may form an optionally substituted aryl or heteroaryl ring;
 Z is NH or N-alkyl (e.g., N-CH₃);
 W in formula 1 or 2 is an optionally substituted aryl or heteroaryl ring; and
 R^2 is $-CHR^1-NR^3R^4$, wherein each R^3 or R^4 together with the C may form an optionally substituted heterocyclic or heteroaryl ring, or wherein each R^3 or R^4 together with the N may form an optionally substituted carbocyclic, heterocyclic, aryl or heteroaryl ring.

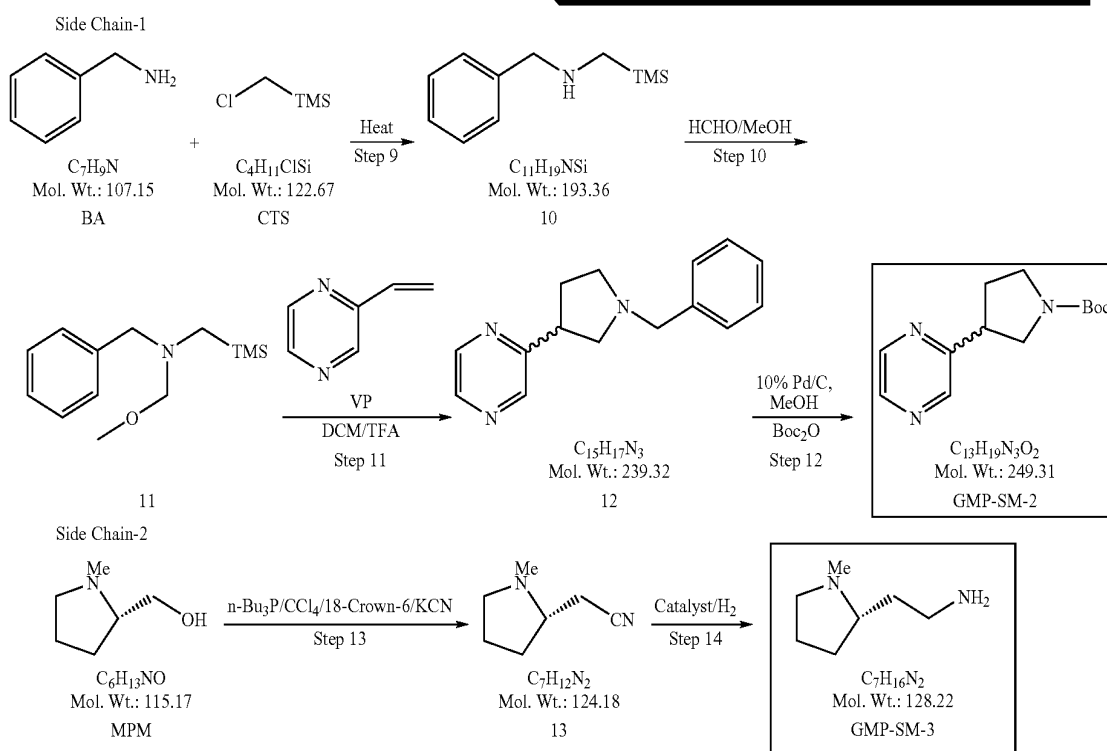
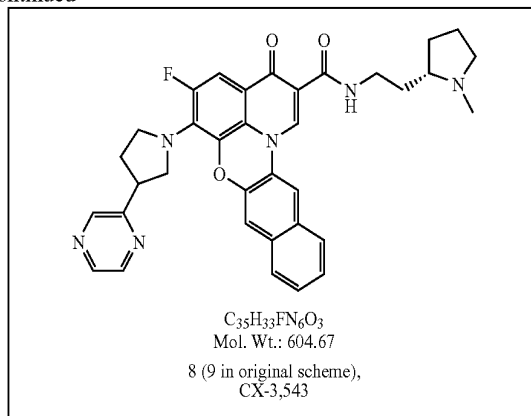
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The methods of the present invention are illustrated as shown in Scheme 1 and in the Examples. The present method encompasses variations in the methods known to those with ordinary skill in the art. For example, various protecting groups may be used in the preparation of the intermediate illustrated in Side-Chain 1. (See, e.g., Example 11.)

Scheme 1



-continued



The compounds prepared according to the methods of the present invention may interact with regions of DNA that can form quadruplexes and act as tumor suppression genes with high affinity. Furthermore, the compounds may induce cell death (e.g., apoptosis), and not interact with regions of DNA that can form quadruplexes. Such compounds may reduce expression of highly proliferate genes and may be utilized to treat a cell proliferative disorder such as a tumor or cancer. Furthermore, the compounds may also exhibit antibacterial or antiviral activity, and may be used for treating bacterial and viral infections.

The compounds of the present invention may be chiral. As used herein, a chiral compound is a compound that is different from its mirror image, and has an enantiomer. Furthermore, the compounds may be racemic, or an isolated enantiomer or stereoisomer. Methods of synthesizing chiral compounds and resolving a racemic mixture of enantiomers are well known to those skilled in the art. See, e.g., March, *Advanced Organic Chemistry*, John Wiley and Sons, Inc., New York, (1985), which is incorporated herein by reference.

Definitions

As used herein, the term "alkyl" refers to a carbon-containing compound, and encompasses compounds containing one or more heteroatoms. The term "alkyl" also encompasses alkyls substituted with one or more substituents including but not limited to OR¹, amino, amido, halo, =O, aryl, heterocyclic groups, or inorganic substituents.

As used herein, the term "carbocycle" refers to a cyclic compound containing only carbon atoms in the ring, whereas a "heterocycle" refers to a cyclic compound comprising a heteroatom. The carbocyclic and heterocyclic structures encompass compounds having monocyclic, bicyclic or multiple ring systems.

As used herein, the term "aryl" refers to a polyunsaturated, typically aromatic hydrocarbon substituent, whereas a "heteroaryl" or "heteroaromatic" refer to an aromatic ring containing a heteroatom. The aryl and heteroaryl structures encompass compounds having monocyclic, bicyclic or multiple ring systems.

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As used herein, the term "heteroatom" refers to any atom that is not carbon or hydrogen, such as nitrogen, oxygen or sulfur.

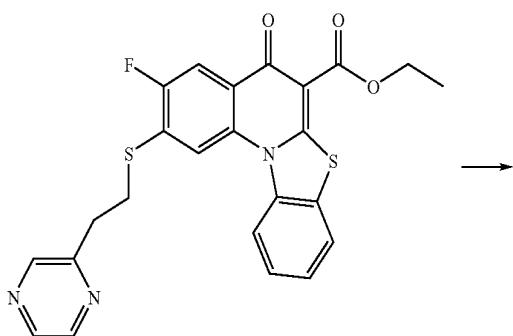
As used herein, the term "Lewis acid" refers to any species that can accept an electron pair, such as metal ions and electron-deficient molecules. In one example, the methods of the present invention use a strong Lewis acid such as aluminum chloride. Other Lewis acids may be used in practicing the methods of the present invention, including species having the formula ML_n , wherein L is a halogen atom or an organic radical such as an alkyl group, n is 3-5, and M is a group III elemental atom (e.g., B, Al, Ga, In), or a group IV elemental atom (e.g., Zr, Ti, Sn). Strong Lewis acidity is also observed for certain group V elemental atoms (e.g., As, Sb, V), and group VIII elemental atoms (e.g. Fe). Group II elemental atoms (e.g., Zn, Cd) generally display moderate Lewis acidity. Particular Lewis acids that may be used to practice the methods of the present invention include but are not limited to: BL_3 ; AlL_3 ; FeL_3 ; GaL_3 ; SbL_5 ; InL_3 ; ZrL_4 ; SnL_4 ; TiL_4 ; TiL_3 ; AsL_3 ; SbL_3 . (See, e.g., D. P. N. Satchell & R. S. Satchell, *Quantitative Aspects of the Lewis Acidity of Covalent Metal Halides and their Organo Derivatives*, 69 CHEM. REV. 251, 253-55 (1969)).

Illustrative examples of heterocycles include but are not limited to tetrahydrofuran, 1,3-dioxolane, 2,3-dihydrofuran, pyran, tetrahydropyran, benzofuran, isobenzofuran, 1,3-dihydro-isobenzofuran, isoxazole, 4,5-dihydroisoxazole, piperidine, pyrrolidine, pyrrolidin-2-one, pyrrole, pyridine, pyrimidine, octahydro-pyrrolo[3,4-b]pyridine, piperazine, pyrazine, morpholine, thiomorpholine, imidazole, imidazolidine-2,4-dione, 1,3-dihydrobenzimidazol-2-one, indole, thiazole, benzothiazole, thiadiazole, thiophene, tetrahydrothiophene 1,1-dioxide, diazepine, triazole, guanidine, diazabicyclo[2.2.1]heptane, 2,5-diazabicyclo[2.2.1]heptane, 2,3,4,4a,9,9a-hexahydro-1H- β -carboline, oxirane, oxetane, tetrahydropyran, dioxane, lactones, aziridine, azetidine, piperidine, lactams, and may also encompass heteroaryls. Other illustrative examples of heteroaryls include but are not limited to furan, pyrrole, pyridine, pyrimidine, imidazole, benzimidazole and triazole.

DESCRIPTION OF THE INVENTION

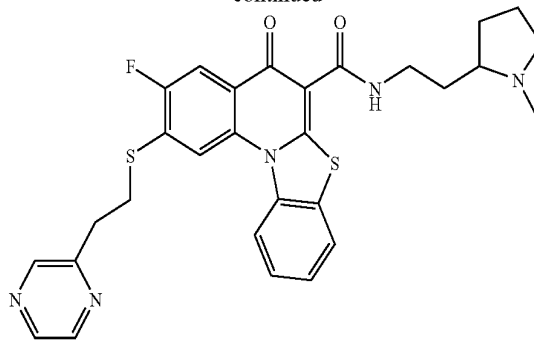
The following examples are offered to illustrate but not to limit the invention.

EXAMPLE 1



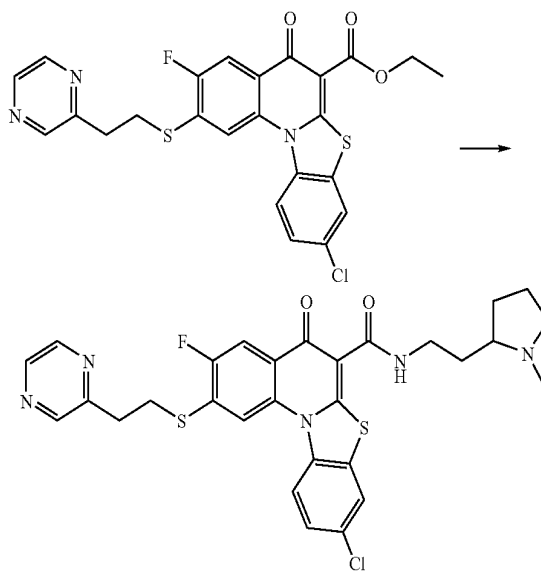
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To a solution of the quinolone ester (60 mg, 0.13 mmol) and 2-(2-aminoethyl)-1-methyl pyrrolidine (30 μ L, 0.19 mmol) in methylene chloride (1.0 mL) was added aluminum chloride (25 mg, 0.19 mmol) and the reaction mixture was allowed to stir for 30 minutes. The solvent was removed in vacuo and saturated L-tartaric acid (1.0 mL) was added, stirring for 45 minutes, until all of the solid dissolved. The aqueous solution was washed with methylene chloride (1.0 mL), basified with 1N NaOH and extracted with methylene chloride. The resulting extract was washed with brine, dried over sodium sulfate, filtered and the solvent was removed in vacuo. The resulting yellow material was purified on preparative TLC (Alumina, 2% Methanol in CH_2Cl_2) to afford the product as a yellowish solid (30 mg, 43%).

EXAMPLE 2

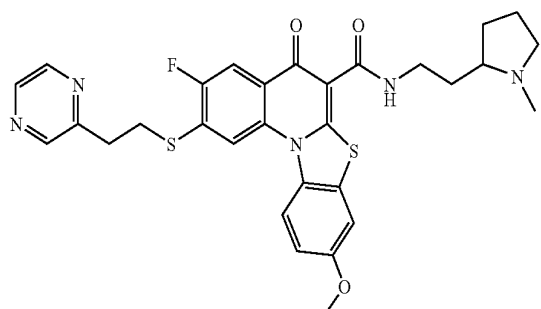
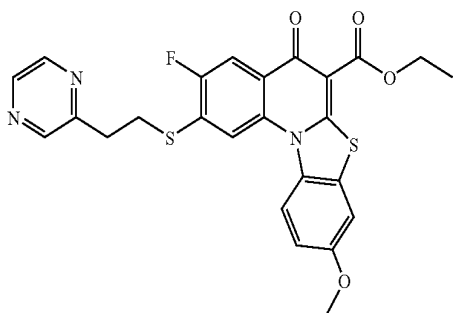


To a solution of the quinolone ester (60 mg, 0.11 mmol) and 2-(2-aminoethyl)-1-methylpyrrolidine (25 μ L, 0.17 mmol) in methylene chloride (1.0 mL) was added aluminum chloride (23 mg, 0.17 mmol) and the reaction mixture was allowed to stir for 30 minutes. The solvent was removed in vacuo and saturated L-tartaric acid (1.0 mL) was added, stirring for 45 minutes, until all of the solid dissolved. The aqueous solution was washed with methylene chloride (1.0 mL), basified with 1N NaOH and extracted with methylene chloride. The resulting extract was washed with brine, dried over sodium sulfate, filtered and the solvent was removed in

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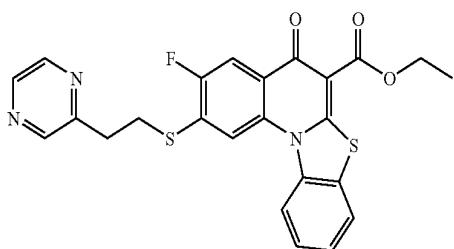
vacuo. The resulting yellow material was purified on preparative TLC (Alumina, 2% Methanol in CH_2Cl_2) to afford the product as a yellowish solid (30 mg, 46%).

EXAMPLE 3



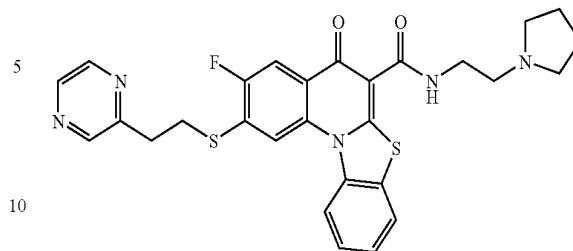
To a solution of the quinolone ester (75 mg, 0.15 mmol) and 2-(2-aminoethyl)-1-methylpyrrolidine (32 μL , 0.22 mmol) in methylene chloride (1.0 mL) was added aluminum chloride (29 mg, 0.22 mmol) and the reaction mixture was allowed to stir for 30 minutes. The solvent was removed in vacuo and saturated L-tartaric acid (1.0 mL) was added, stirring for 45 minutes, until all of the solid dissolved. The aqueous solution was washed with methylene chloride (1.0 mL), basified with 1N NaOH and extracted with methylene chloride. The resulting extract was washed with brine, dried over sodium sulfate, filtered and the solvent was removed in vacuo. The resulting yellow material was purified on preparative TLC (Alumina, 2% Methanol in CH_2Cl_2) to afford the product as a yellowish solid (30 mg, 34%).

EXAMPLE 4



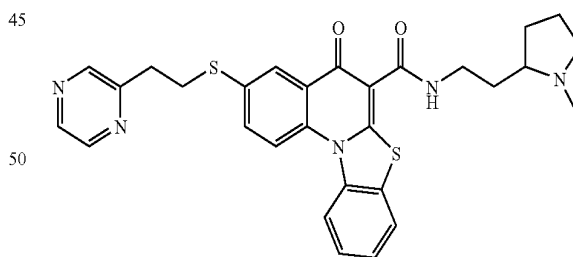
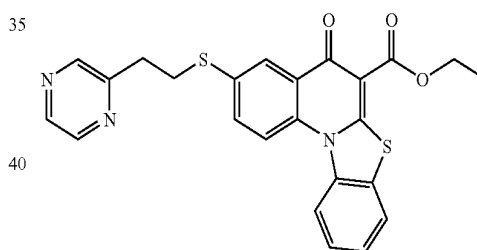
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To a solution of the quinolone ester (34 mg, 0.7 mmol) and 1-(2-aminoethyl) pyrrolidine (15 μL , 0.11 mmol) in methylene chloride (1.0 mL) was added aluminum chloride (15 mg, 0.11 mmol) and the reaction mixture was allowed to stir for 30 minutes. The solvent was removed in vacuo and saturated L-tartaric acid (1.0 mL) was added, stirring for 45 minutes, until all of the solid dissolved. The aqueous solution was washed with methylene chloride (1.0 mL), basified with 1N NaOH and extracted with methylene chloride. The resulting extract was washed with brine, dried over sodium sulfate, filtered and the solvent was removed in vacuo. The resulting yellow material was purified on preparative TLC (Alumina, 2% Methanol in CH_2Cl_2) to afford the product as a yellowish solid (28 mg, 73%).

EXAMPLE 5

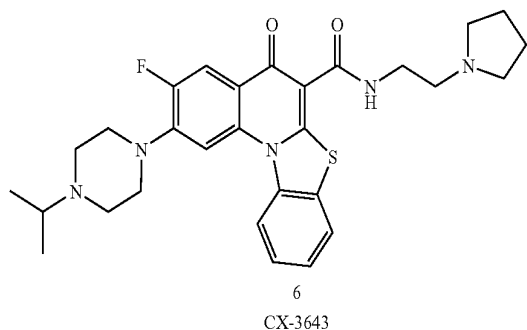
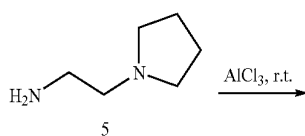
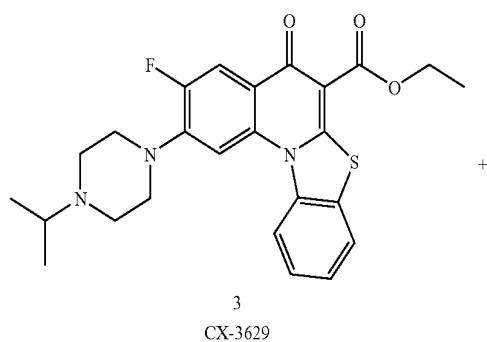


To a solution of the quinolone ester (146 mg, 0.65 mmol) and 2-(2-aminoethyl)-1-methylpyrrolidine (1 mmol) in methylene chloride (1.0 mL) was added aluminum chloride (1 mmol) and the reaction mixture was allowed to stir for 30 minutes. The solvent was removed in vacuo and saturated L-tartaric acid (1.0 mL) was added, stirring for 45 minutes, until the entire solid dissolved. The aqueous solution was washed with methylene chloride (1.0 mL), basified with 1N NaOH and extracted with methylene chloride. The resulting extract was washed with brine, dried over sodium sulfate, filtered and the solvent was removed in vacuo. The resulting

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yellow material was purified on preparative TLC (Alumina, 2% Methanol in CH₂Cl₂) to afford the product as a yellowish solid (1.7 mg, 5%).

EXAMPLE 6

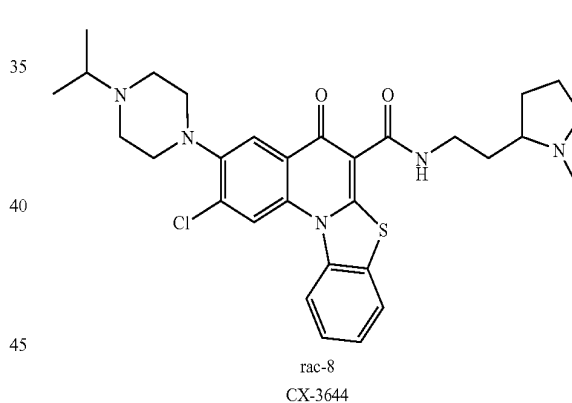
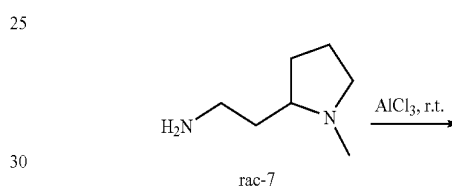
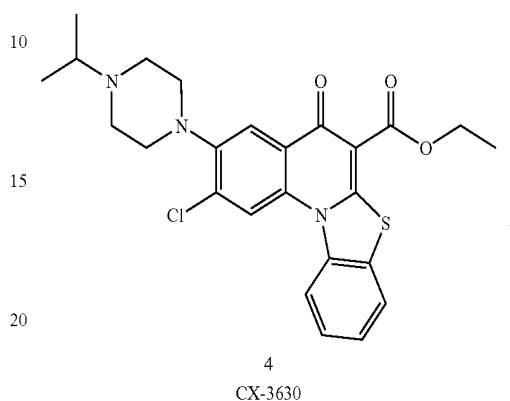


CX-3629 3 (1.0 eq, 126 mg, 0.27 mmol) and amine 5 (2.0 eq, 68 μ L, 0.54 mmol) were dissolved in anhydrous CH₂Cl₂ (1 ml). AlCl₃ (2.0 eq, 72 mg, 0.54 mmol) was added and the mixture was stirred at room temperature for 3 hours. The volatiles were removed in vacuo. The resulting slurry was treated with a saturated aqueous tartaric acid solution (10 ml) and stirred until all solid disappeared (about 1 hr for completion of the hydrolysis). The solution was neutralized by 1N NaOH (to reach pH=14) and the compound extracted with CH₂Cl₂ (4 \times). The organic phase was washed with a concentrated aqueous Sodium Potassium tartrate solution, water (2 \times) and dried over Na₂SO₄. The CH₂Cl₂ solution was concentrated. Addition of AcOEt induced crystallization of the expected compound. After filtration CX-3643 6 was isolated as a pale yellow fluffy solid (76 mg, 53% yield). LCMS (ES): 95% pure, m/z 536 [M+H]⁺; ¹H NMR (CDCl₃, 500 MHz) δ 1.12 (d, J=6.6, 6H), 1.80 (br s, 4H), 2.62 (br s, 4H), 2.79 (m, 7H), 3.36 (m, 4H), 3.67 (q, J=6.0, 2H), 7.45 (t, J=7.2, 1H),

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7.53 (td, J=7.3, J=1.3, 1H), 7.84 (dd, J=7.8, J=1.2, 1H), 7.89 (d, J=6.9, 1H), 8.16 (d, J=13.1, 1H), 8.23 (d, J=8.5, 1H), 10.46 (br t, 1H) ppm.

EXAMPLE 7

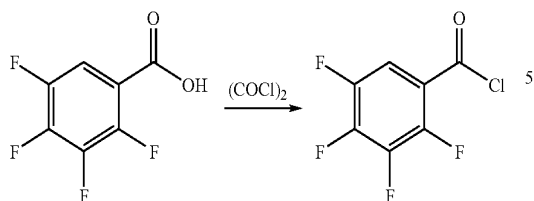


The compound was prepared according to the procedure used for CX-3643, starting from 4 (101 mg, 0.21 mmol) and 7, providing CX-3644 8 as a white fluffy solid (37 mg, 31% yield). LCMS (ES): 95% pure, m/z 566 [M]⁺, 568 [M+2]⁺; ¹H NMR (CDCl₃, 500 MHz) δ 1.13 (d, J=6.5, 6H), 1.57 (m overlapped with water signal, 2H), 1.71 (m, 1H), 1.81 (m, 1H), 2.04-2.18 (m, 4H), 2.34 (s, 3H), 2.78 (m, 5H), 3.06 (br t, J=8.6, 1H), 3.27 (br s, 4H), 3.52-3.59 (m, 2H), 7.47 (t, J=7.3, 1H), 7.57 (td, J=8.4, J=1.1, 1H), 7.84 (d, J=7.8, 1H), 8.19 (s, 1H), 8.27 (d, J=8.4, 1H), 8.57 (s, 1H), 10.38 (br t, J=5.6, 1H) ppm.

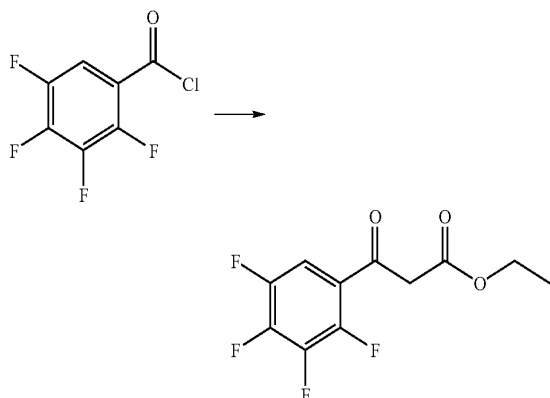
EXAMPLE 8

Example 8 describes a method for preparing a substituted benzoxazine analog from reaction of the corresponding ester with an amine, and aluminum chloride.

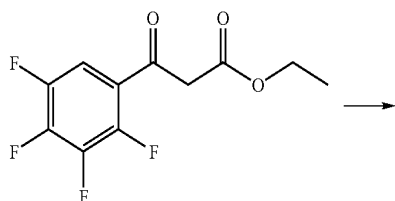
19



To a solution of 2,3,4,5-tetrafluorobenzoic acid (100 g, 510 mmol), in methylene chloride (0.5 L) was added oxalyl chloride (68 g, 540 mmol) and DMF (ca 3 drops) and the reaction mixture was allowed to stir at room temperature overnight allowing for the produced gasses to escape. The solvent was removed in vacuo and the vessel was placed on high vacuum (ca 0.5 mm Hg) for 2 hours to afford the acid chloride as a viscous oil (105 g) and was used in the subsequent reaction without further purification.

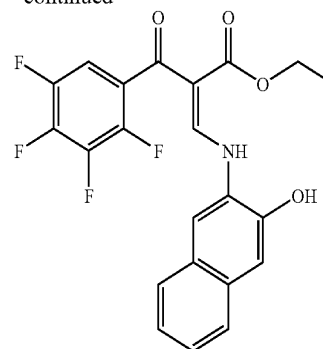


To a suspension of potassium ethyl malonate (97 g, 570 mmol) and magnesium chloride (55 g, 570 mmol) in acetonitrile and the suspension was chilled to 0° C. To this suspension was added the crude 2,3,4,5-benzoyl chloride (105 g, 520 mmol) over 5 minutes. Triethylamine was slowly added at a rate sufficient to keep the reaction temperature below 10° C. and the mixture was allowed to warm to room temperature and was stirred overnight. The solvent was removed in vacuo and replaced with toluene (300 mL) and 1N HCl (500 mL) was added and the mixture was allowed to stir for 1 hour. The organic layer was separated and washed with 1N HCl (100 mL) and brine (100 mL) and dried over sodium sulfate, filtering over a pad of silica gel (50x100 mm), eluting with ethyl acetate. The solvent was removed in vacuo and the resulting oil was dissolved in ethanol/water (9:1) and was allowed to crystallize overnight. The resulting crystals were isolated by filtration, washing with ethanol/water (8:2) to afford the ketoester (43.75 g, 166 mmol) as a white crystalline solid.

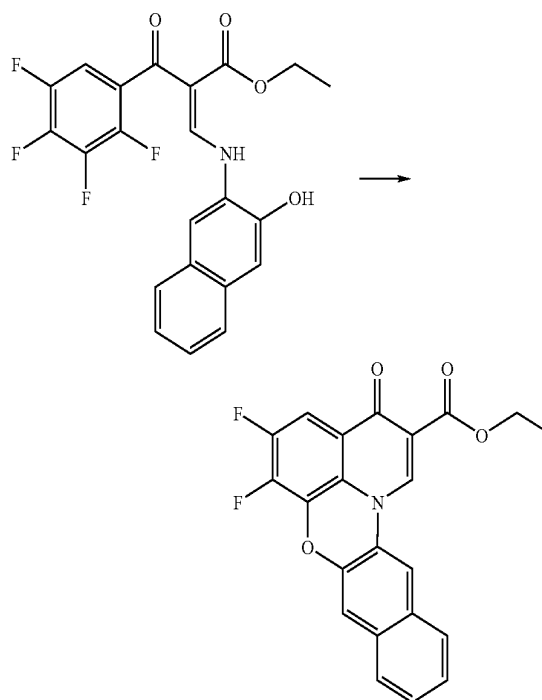


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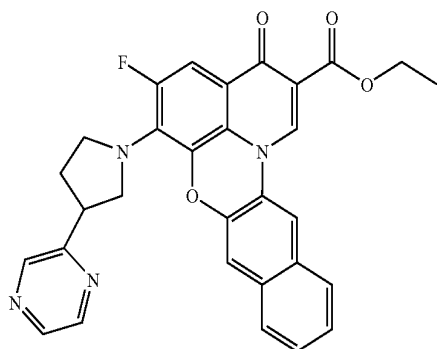
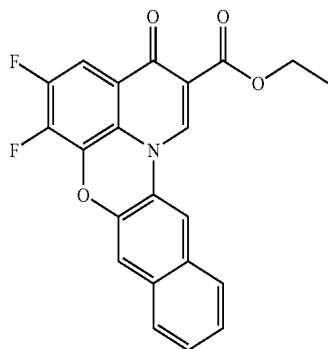


To a 250 mL round bottom flask was added the tetrafluoro-ketoester (10.0 g, 37.9 mmol), triethylorthoformate (8.6 mL, 56.8 mmol) and acetic anhydride (7.15 mL, 75.8 mmol) and the reaction mixture was heated to 145° C. for 2 hours. The reaction was allowed to cool to room temperature and placed on high vacuum (ca 0.5 mm Hg) for 1 hour. The resulting oil was dissolved in ethanol (100 mL) and 2-amino-1-naphthol (6.02 g, 37.9 mmol) was added at room temperature and the solution became briefly clear and then product began to precipitate. The reaction was allowed to stir for 2 hours and was then filtered and washed with ethanol (100 mL) to afford the enamine as a yellow solid (12.5 g, 28.9 mmol).

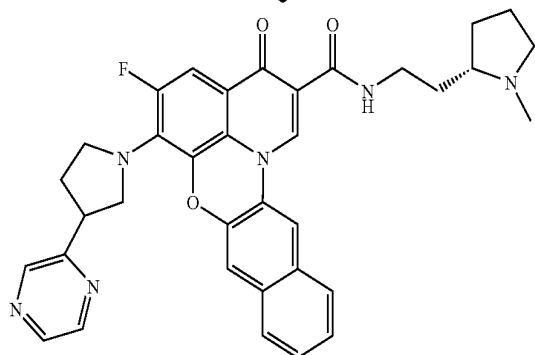
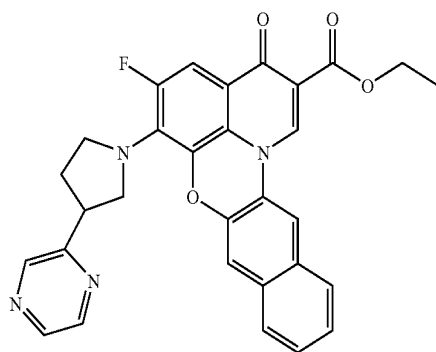


To a solution of the enamine (12.13 g, 27.95 mmol) in dry DMF (50 mL) was added potassium carbonate (4.24 g, 1.1 eq.) and the mixture was heated to 90° C., with constant stirring, for 2 hours. The mixture was allowed to cool to room temperature without stirring and was allowed to remain at room temperature for an additional hour. The crystalline solid was collected by filtration, washing with water. Recrystallization from THF afforded the difluoroester as a white crystalline solid (9.3 g, 23.6 mmol).

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To a solution of the difluoroester (11.0 g, 2.5 mmol) in NMP (10 mL) was added N-Boc-3-(2-pyrazino)pyrrolidine (870 mg, 3.5 mmol) and the mixture was heated to reflux for 3 hours. The reaction mixture was then allowed to cool to room temperature and the product was collected by filtration. Crystallization from THF afforded the pyrazine ester as a yellow solid (910 mg, 1.74 mmol).

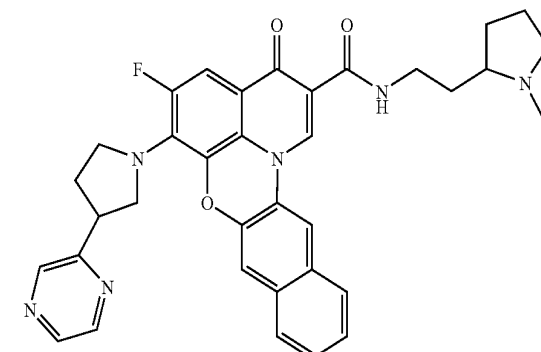
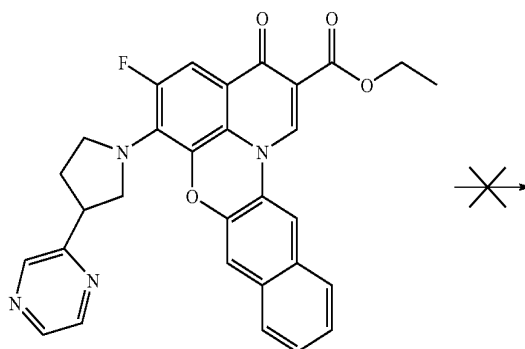


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To a solution of the pyrazine ester (250 mg, 0.48 mmol) and 2-(2-aminoethyl)-1-methylpyrrolidine (80 mg, 0.63 mmol) in methylene chloride at room temperature was added aluminum chloride (83 mg, 0.63 mmol) and the reaction mixture was allowed to stir for 2 hours. The solvent was removed in vacuo and saturated L-tartaric acid was added (5 mL) and the mixture was allowed to stir for 1 hour. Methylene chloride (10 mL) was then added and the mixture was basified with 1N NaOH. The organic layer was separated and washed with a saturated solution of Rochelle's salt, brine and dried over sodium sulfate. The solvent was removed in vacuo and the resulting solid was dissolved in THF and filtered and the solvent was removed again. The crude solid was recrystallized in ethyl acetate to afford the amide as a yellow solid (225 mg, 0.37 mmol, 98.5% pure).

EXAMPLE 9

As shown in Example 9, amide coupling from the corresponding ester resulted in slight or no reaction, where zinc chloride was used as the Lewis acid.

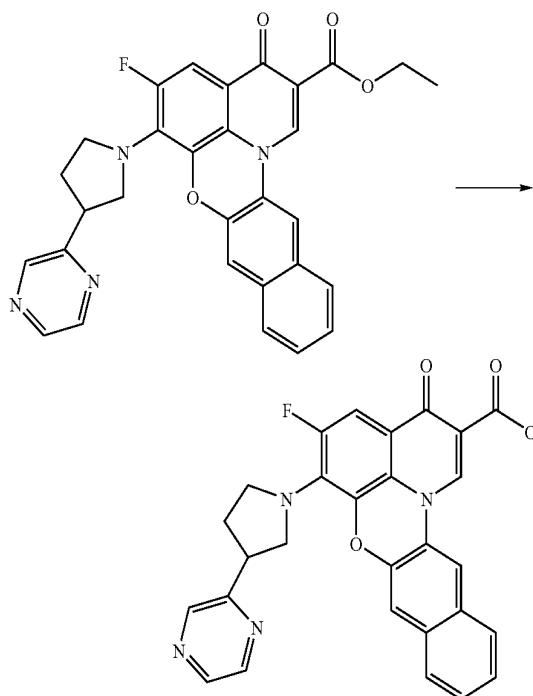


To a solution of the ester (100 mg, 0.19 mmol) and 2-(2-aminoethyl)-1-methylpyrrolidine (80 mg, 0.63 mmol) in methylene chloride at room temperature was added zinc chloride (86 mg, 0.63 mmol) and the reaction mixture was allowed to stir overnight. LCMS indicated that there was no reaction progress, and the reaction was discontinued.

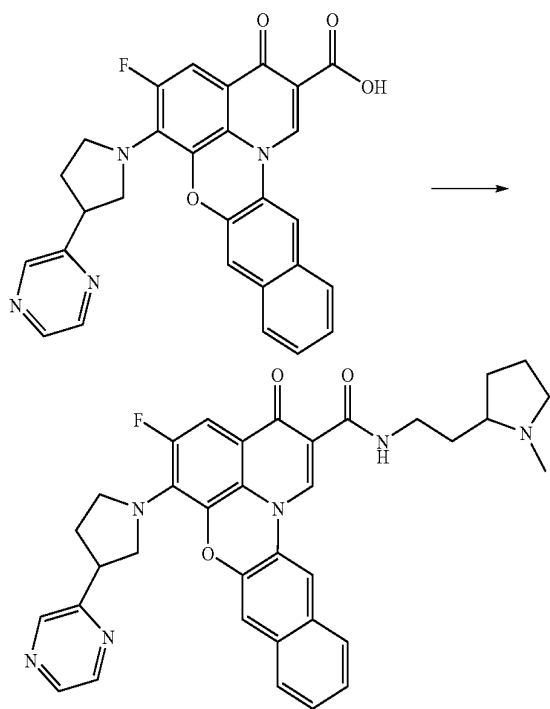
EXAMPLE 10

Example 10 describes a method for preparing a substituted benzoxazine analog from reaction of the corresponding carboxylic acid with an amine.

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The pyrazinoester (2.0 g, 3.8 mmol) was dissolved in ethanol (100 mL) and conc HCl was added (20 mL) and the mixture was refluxed overnight. The mixture was allowed to cool to room temperature and the solid was collected by vacuum filtration, washing with ethanol to afford the pyrazinoic acid as a light tan powder (1.6 g, 3.2 mmol).



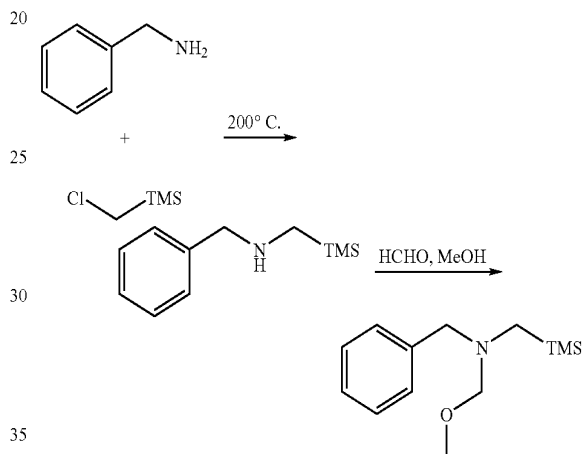
To a mixture of the fluoroaminoacid (1.6 g, 3.2 mmol) and HBTU (2.0 g, 5.3 mmol) in NMP (20 mL) was added N,N-diisopropyl-N-ethylamine (1.0 mL, 6 mmol) and the mixture

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was allowed to stir at room temperature, under argon, for 1 hour (the solution became clear). (S)-2-(2-aminoethyl)-1-methylpyrrolidine (Mizuno, A.; Hamada, Y.; Shioiri, T., Synthesis, 1980, 12 1007)(1.0 mL, 6.9 mmol) was added and the mixture was allowed to stir for 30 minutes. Water (200 mL) was added and the resulting solid was collected by vacuum filtration, washing with water, and dried to afford the pyrazine as a yellow solid. The yellow solid was purified on silica gel (10% MeOH/CH₂Cl₂ first eluting off impurities followed by eluting with 5% NH₄OH/15% MeOH/CH₂Cl₂). The combined fractions were evaporated to afford the compound as a yellow solid. (1.2 g, 2.0 mmol, 85% pure).

EXAMPLE 11

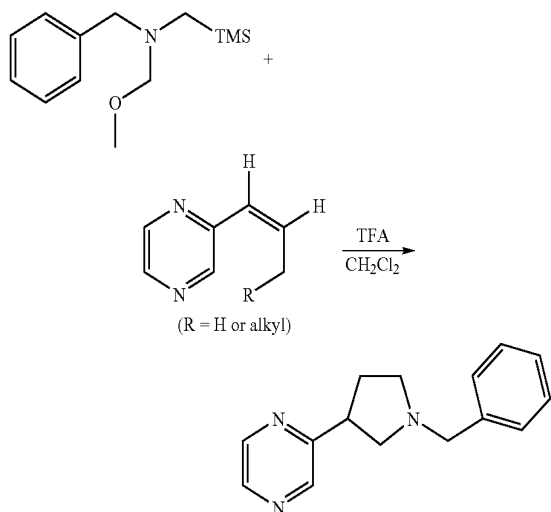
Example 11 describes the preparation of a Boc-protected pyrrolidine reagent, used as an intermediate in the preparation of benzoxazine and benzothiazole compounds.



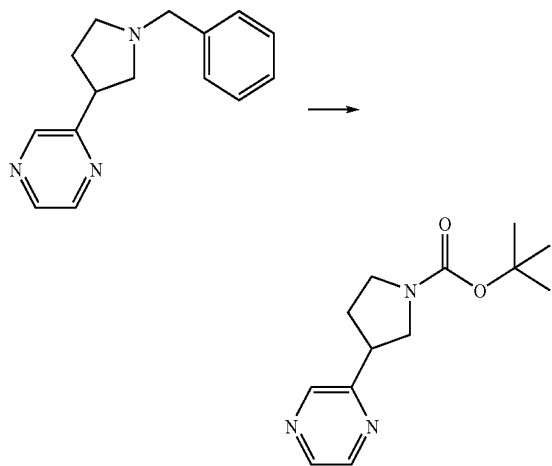
A mixture of benzyl amine (90 g, 841 mmol) and chloromethyltrimethylsilane (30 g, 246 mmol) was heated at 200° C. for 2.5 hours. In general, the trimethylsilyl group may be replaced with a —SiR¹R²R³ moiety, wherein R¹, R² and R³ are independently alkyl or substituted alkyl. The benzyl groups may also be replaced with other suitable protecting groups.

The mixture was allowed to cool to room temperature and treated with 1N sodium hydroxide (250 mL) and ether (200 mL) with stirring. The aqueous layer was extracted with ether (3×100 mL) and the combined organic extracts were washed with brine, dried over magnesium sulfate and filtered over a pad of silica gel (70×50 mm), eluting with ether. The solvent was removed in vacuo and the resulting oil was vacuum distilled (bp=70° C. ca 1 mm Hg) to afford the amine as a colorless oil (60.8 g) that contained a significant amount of benzyl amine. The resulting oil was then chromatographed on a single biotage column (90 g, silica gel, ANALOGIX) eluting with ethyl acetate. The solvent was removed in vacuo to afford the pure amine as a colorless oil (43.55 g, 225 mmol). The resulting amine was then added to 37% formalin (25 mL) and the mixture was stirred at room temperature for 10 minutes, followed by the addition of methanol (25 mL) and potassium carbonate (20 g). The resulting mixture was allowed to stir overnight and then extracted with methylene chloride (3×100 mL) and the combined organic extracts were dried with sodium sulfate. The solvent was removed in vacuo and the resulting oil was vacuum distilled (bp=80° C. ca 1 mm Hg) to afford the amine as a colorless liquid (39.9 g, 168 mmol).

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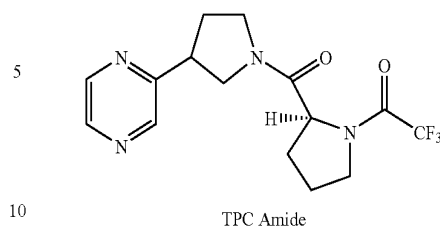


To a solution of vinylpyrazine (10 g, 94.3 mmol) in methylene chloride (200 mL) and trifluoroacetic acid (2 mL) was added dropwise a solution of the silylated amine ether (24.33 g, 102.7 mmol) dissolved in methylene chloride (100 mL) over 4 hours. The volume was then reduced to 100 mL and extracted with 1N HCl (3×75 mL). The aqueous layer was then basified with NaOH and extracted with methylene chloride (3×100 mL), dried over magnesium sulfate and filtered over a pad of silica gel (30×150 mm) eluting with ethyl acetate. The solvent was evaporated to afford the benzylated pyrazinopyrrolidine (26.19 g) as a brownish clear liquid. In general, the pyrazine heterocycle may be replaced with other suitable heterocyclic groups.



To a solution of the benzyl pyrrolidine (7.0 g, 29.3 mmol) and di-tert-butyl dicarbonate (44.7 g, 205 mmol) in methanol (35 mL) was added 10% Pd/C (degussa type, wet) and the vessel was pressurized with Hydrogen (50 PSI) with shaking. The vessel was vented 3 times to control pressure. After 5 hours the reaction was complete and the mixture was filtered and the solvent was removed in vacuo. The resulting material was chromatographed on silica gel (1:1 hexanes/ethyl acetate) to afford the Boc protected pyrrolidine as a light yellow oil (2.3 g, 9.2 mmol).

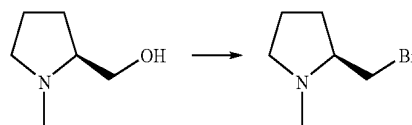
26



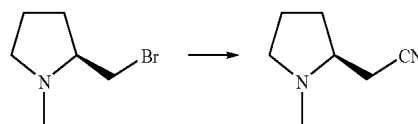
Enantiomeric ratios can be determined by making a TPC (N-trifluoroacetyl-L-prolyl chloride, Regis #440001) and using GCMS (HP 6890N/5973 MSD) on a Phenomenex Zebron capillary column (ZB-50, 50% Phenyl, 50% Dimethylpolysiloxane, 30M×0.25 mm, 0.25 μm film thickness). Chromatography conditions: 1 μL injection split 50:1. Constant Flow He=1.0 mL/min. Oven; 100° C. for 5 min, 5° C./min to 300° C. and hold for 8 minutes. The compound comes at 39.08 and 39.31 min but the resolution is very good.

EXAMPLE 12

Example 12 describes the preparation of a chiral amine reagent used in amide coupling.



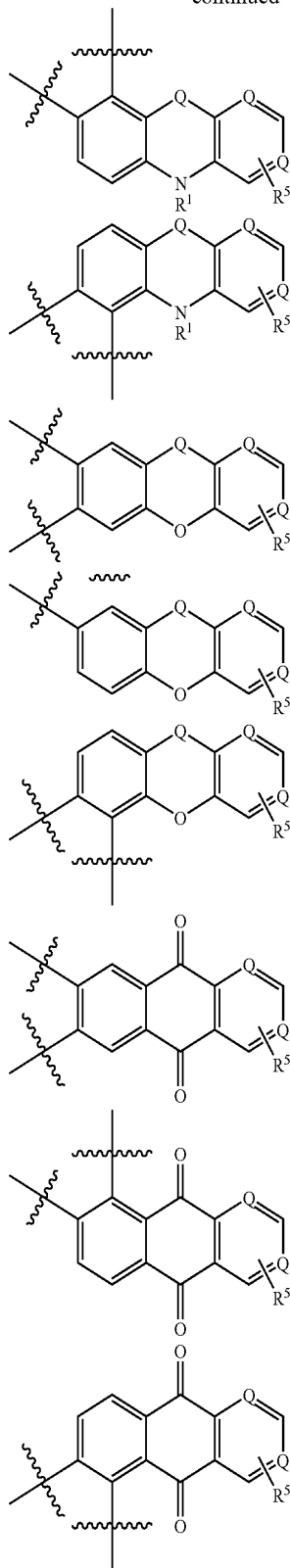
To a solution of the hydroxymethylpyrrolidine (50 g, 434 mmol) in methylene chloride (1 L) was added triphenylphosphine (148 g, 564 mmol) followed by careful addition of carbon tetrabromide (187 g, 564 mmol) at room temperature. The reaction mixture was allowed to stir for 1 hour at room temperature. Water was added and the organic layer was washed with brine, dried over sodium sulfate and the solvent was removed in vacuo. The resulting oil was purified by silica gel chromatography (1:1 hexanes/ethyl acetate) to afford the bromide as a clear oil (35 g, 197 mmol).



To a solution of the bromide (23.0 g, 129 mmol) in a solution of acetonitrile and water (75:15, 200 mL) was added potassium cyanide (12.6 g, 194 mmol) and 18-crown-6 (340 mg, 1.3 mmol) and the reaction was allowed to stir overnight at room temperature. The volume was then reduced to 50 mL, under vacuum, and was extracted twice with methylene chloride (2×200 mL). The resulting extracts were combined and washed with brine, dried over sodium sulfate and the solvent was carefully removed in vacuo to afford the cyanide as a clear oil (17 g).

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-continued



wherein each Q, Q¹, Q², and Q³ is independently CH or N; Y is independently O, CH, C=O or NR¹; and R⁵ as defined in claim 1.

13. The method of claim 1, wherein X in any compound having formula 2 or formula 4 is SR², where R² is a C₁₋₁₀ alkyl

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or C₂₋₁₀ alkenyl optionally substituted with a heteroatom, a carbocyclic ring, a heterocyclic ring, an aryl or a heteroaryl.

14. The method of claim 1, wherein X and A in any compound having formula 2 or formula 4 may independently be halo or NR¹R²,

wherein R¹ is H;

R² is a C₁₋₁₀ alkyl optionally substituted with a heteroatom, a C₃₋₆ cycloalkyl, aryl or a 5-14 membered heterocyclic ring containing one or more N, O or S;

10 or R¹ and R² together with N in NR¹R² may form an optionally substituted heterocyclic ring containing one or more N, O or S.

15. The method of claim 14, wherein R² is a C₁₋₁₀ alkyl substituted with morpholine, thiomorpholine, imidazole, aminodithiazole, pyrrolidine, piperazine, pyridine or piperidine; or wherein R¹ and R² together with N form piperidine, pyrrolidine, piperazine, morpholine, thiomorpholine, imidazole, or aminodithiazole.

16. The method of claim 14, wherein said optionally substituted heterocyclic ring is tetrahydrofuran, 1,3-dioxolane, 2,3-dihydrofuran, tetrahydropyran, benzofuran, isobenzofuran, 1,3-dihydro-isobenzofuran, isoxazole, 4,5-dihydroisoxazole, piperidine, pyrrolidine, pyrrolidin-2-one, pyrrole, pyridine, pyrimidine, octahydro-pynolo [3,4-b]pyridine, piperazine, pyrazine, morpholine, thiomorpholine, imidazole, aminodithiazole, imidazolidine-2,4-dione, benzimidazole, 1,3-dihydrobenzimidazol-2-one, indole, thiazole, benzothiazole, thiadiazole, thiophene, tetrahydro-thiophene 1,1-dioxide, diazepine, triazole, guanidine, diazabicyclo [2.2.1]heptane, 2,5 -diazabicyclo [2.2.1]heptane, or 2,3,4,4a,9,9a-hexahydro-1 H-β-carboline.

17. The method of claim 14, wherein X has the formula

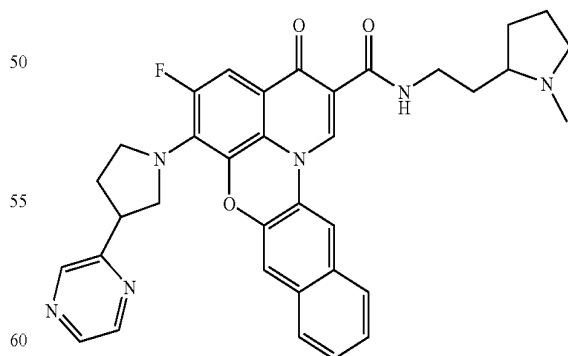


35 wherein R¹ is H; n is 1-6; and R³ and R⁴ together with N in NR³R⁴ form an optionally substituted ring.

18. The method of claim 17, wherein n is 2 or 3.

19. The method of claim 1, wherein each optionally substituted moiety in any compound having formula 2 or formula 4 may be substituted with one or more halo, OR², NR¹R², carbamate, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, each optionally substituted by halo, C=O, aryl or one or more heteroatoms; aryl, carbocyclic or a heterocyclic ring.

20. The method of claim 1, wherein said compound having formula 2 is



21. The method of claim 1, wherein said Lewis acid is BL₃, AlL₃, FeL₃, GaL₃, SbL₅, InL₃, ZrL₄, SnL₄, TiL₄, TiL₃, AsL₃, or SbL₃, wherein L is halo or alkyl.

22. The method of claim 21, wherein said Lewis acid is aluminum chloride.

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23. The method of claim 1, wherein in $\text{—NR}^1\text{R}^2$, R^2 is C_{1-10} alkyl or C_{2-10} alkenyl substituted with a carbocyclic or heterocyclic ring.

24. The method of claim 23, wherein in $\text{—NR}^1\text{R}^2$, R^2 is C_{1-10} alkyl substituted with a heterocyclic ring,

where said heterocyclic ring is selected from tetrahydrofuran, 1,3-dioxolane, 2,3-dihydrofuran, pyran, tetrahydropyran, benzofuran, isobenzofuran, 1,3-dihydroisobenzofuran, isoxazole, 4,5-dihydroisoxazole, piperidine, piperidine, pyffolidine, pyrrolidin-2-one, pyrrole, pyridine, pyrimidine, octahydro-pyrrolo [3,4-b]pyridine, piperazine, pyrazine, morpholine, thiomorpholine, imidazole, imidazolidine-2,4-dione, 1,3-dihydrobenzimidazol-2-one, indole, thiazole, benzothiazole, thiadiazole, thiophene, tetrahydro-thiophene 1,1-dioxide, diazepine, triazole, guanidine, diazabicyclo [2.2.1]heptane, 2,5-diazabicyclo [2.2.1]heptane, 2,3,4,4a,9,9a-hexahydro-1H- β -carboline, oxirane, oxetane, tetrahydropyran, dioxane, lactones, aziridine, azetidine, piperidine, and lactams.

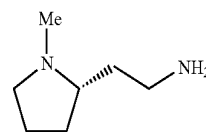
25. The method of claim 1, wherein the amine of formula NHR^1R^2 is 2-(2-aminoethyl)-1-methylpyffolidine or 1-(2-aminoethyl)pyrrolidine.

26. The method of claim 1, wherein the amine of formula NHR^1R^2 is 2-(2-aminoethyl)-1-methylpyffolidine.

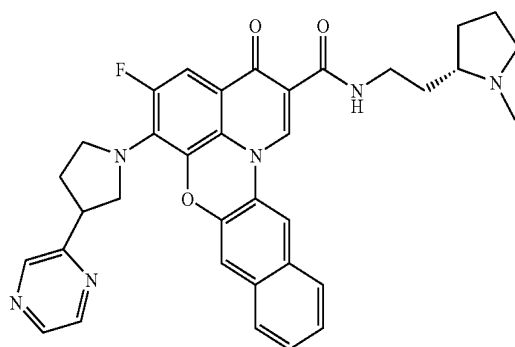
27. The method of claim 1, wherein in $\text{—NR}^1\text{R}^2$, R^2 is an optionally substituted carbocyclic ring, heterocyclic ring, aryl or heteroaryl.

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28. The method of claim 1, wherein NHR^1R^2 is an amine of the formula:



29. The method of claim 28, which produces a compound of formula (2), wherein said compound of formula (2) is:



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