

藥學科技二

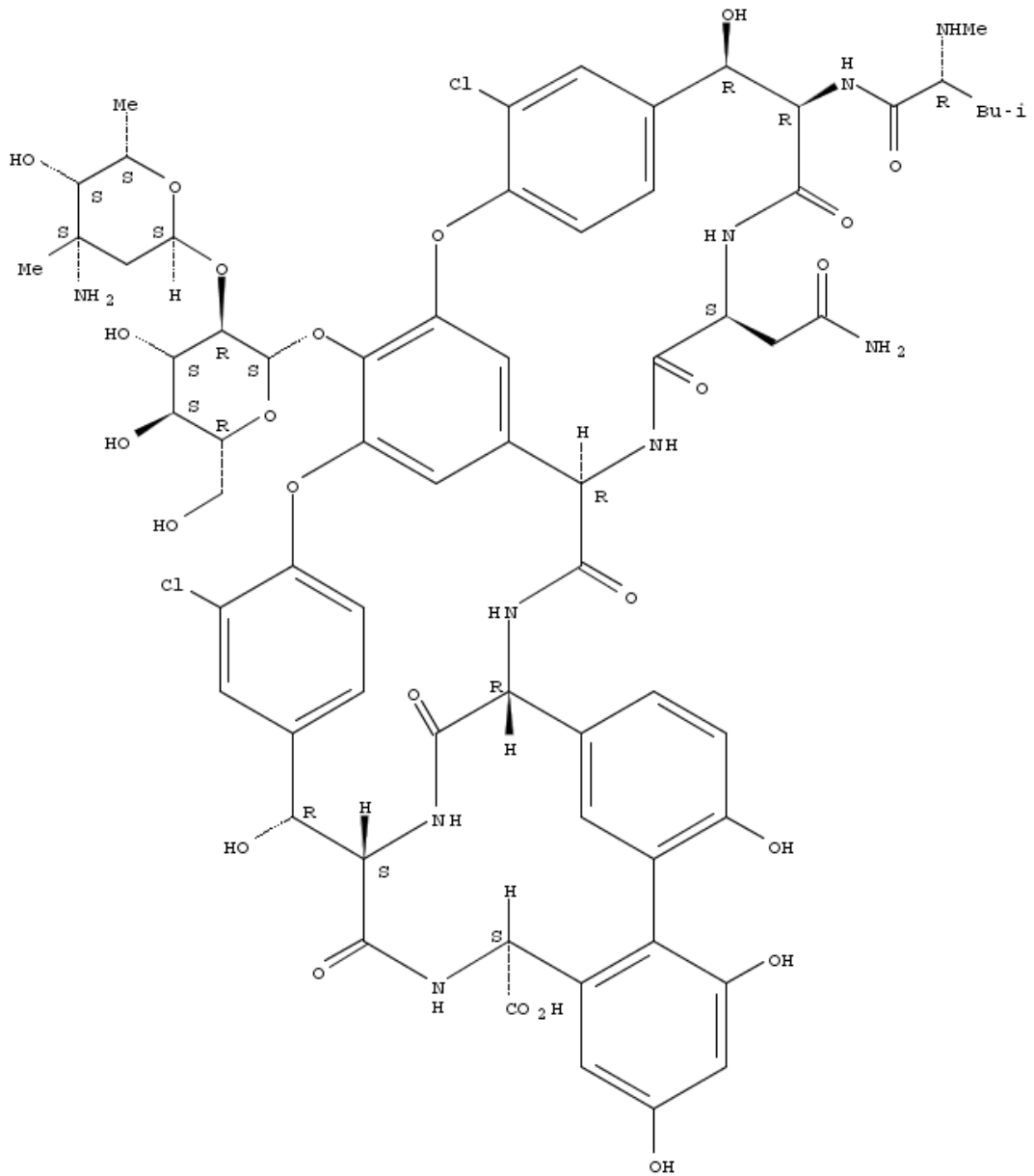
(Scifinder&Thomson Innovation 學習成果)

藥三 A 小 b 班 B303098084 辛芷儀

Vancomycin 的 SAR

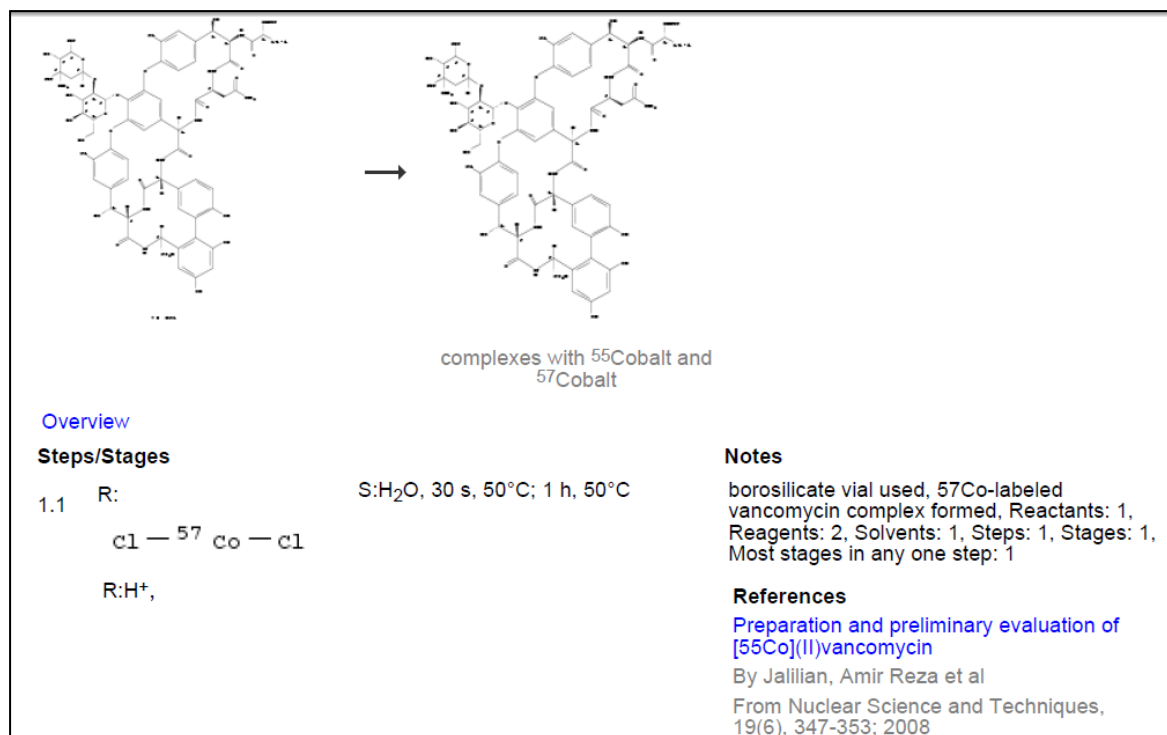
1. 化學式 $C_{66}H_{75}Cl_2N_9O_{24}$
2. 完整學名及別名
 - (1) 22H-8,11:18,21-Dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1H, 16H-[1,6,9]oxadiazacyclohexadecino[4,5-m][10,2,16]benzoxadiazacyclotetracosine, vancomycin deriv.
 - (2) 22H-8,11:18,21-Dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1H, 16H-[1,6,9]oxadiazacyclohexadecino[4,5-m][10,2,16]benzoxadiazacyclotetracosine-26-carboxylic acid,
3-(2-amino-2-oxoethyl)-44-[[2-O-(3-amino-2,3,6-trideoxy-3-C-methyl-Fa-L-lyxo-hexopyranosyl)-β-D-glucopyranosyl]oxy]-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-[[[(2R)-4-methyl-2-(methylamino)-1-oxopentyl]amino]-2,5,24,38,39-pentaoxo-, (3S,6R,7R,22R,23S,26S,36R,38aR)-
 - (3) 22H-8,11:18,21-Dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1H, 16H-[1,6,9]oxadiazacyclohexadecino[4,5-m][10,2,16]benzoxadiazacyclotetracosine-26-carboxylic acid,
3-(2-amino-2-oxoethyl)-44-[[2-O-(3-amino-2,3,6-trideoxy-3-C-methyl-α-L-lyxohexopyranosyl)-β-D-glucopyranosyl]oxy]-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-[[[(2R)-4-methyl-2-(methylamino)-1-oxopentyl]amino]-2,5,24,38,39-pentaoxo-, (3S,6R,7R,22R,23S,26S,36R,38aR)-
 - (4) 22H-8,11:18,21-Dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1H, 16H-[1,6,9]oxadiazacyclohexadecino[4,5-m][10,2,16]benzoxadiazacyclotetracosine-26-carboxylic acid,
3-(2-amino-2-oxoethyl)-44-[[2-O-(3-amino-2,3,6-trideoxy-3-C-methyl-α-L-lyxohexopyranosyl)-β-D-glucopyranosyl]oxy]-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-[[[4-methyl-2-(methylamino)-1-oxopentyl]amino]-2,5,24,38,39-pentaoxo-, [3S-[3R*,6S*(S*),7S*,22S*,23R*,26R*,36S*,38aS*]]]-
 - (5) Diatracin

- (6) Vancocin
 - (7) Vancocin CP
 - (8) Vancocine
 - (9) Vancoled
 - (10) Vancoplus
3. 結構式

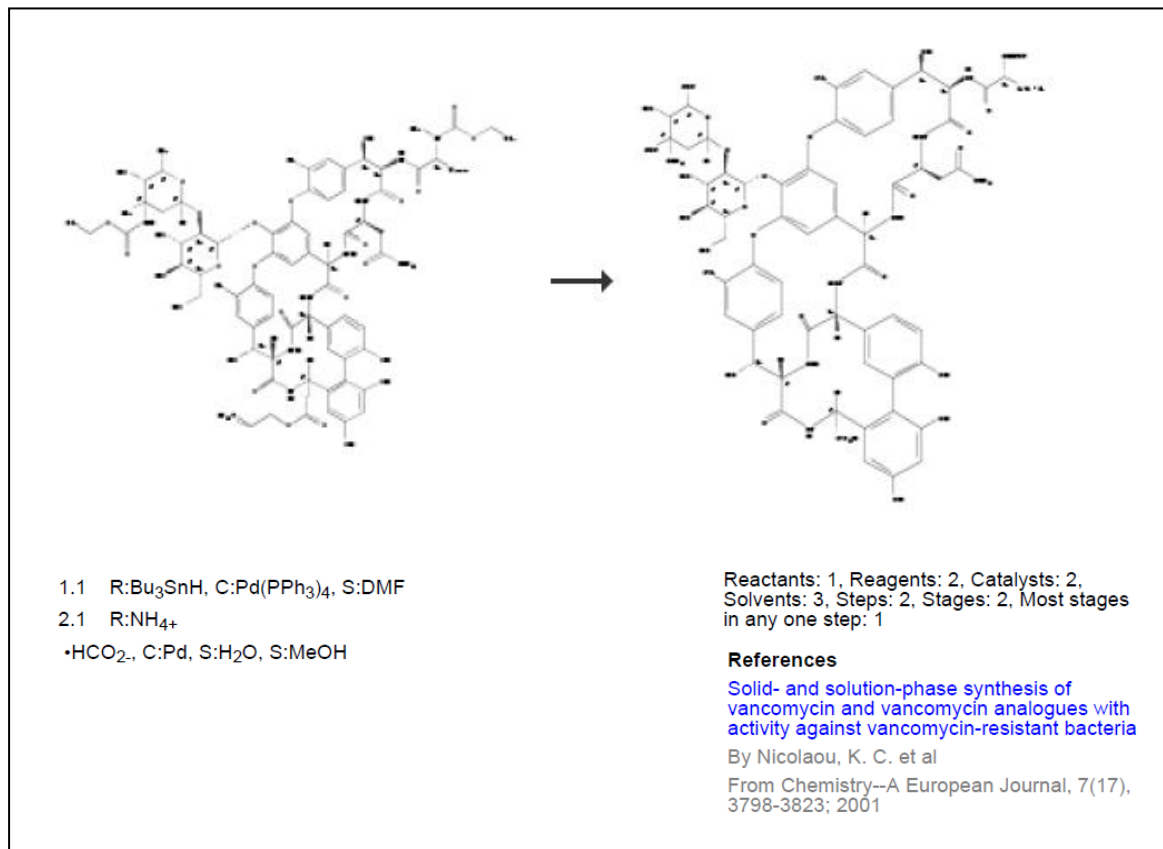


4. 相關合成方法

1. 單步驟

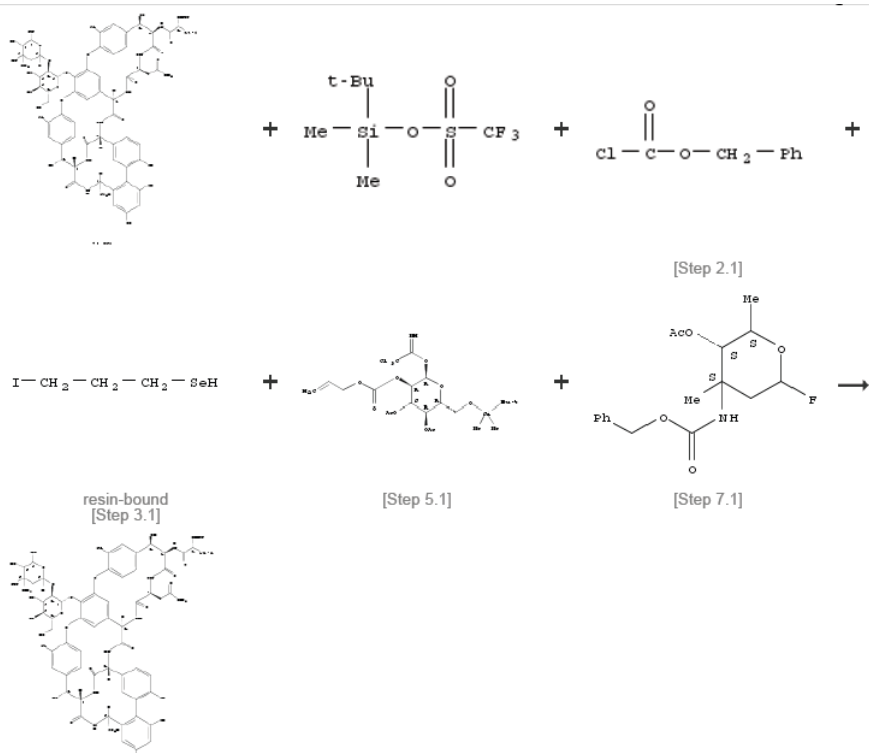


2. 二步驟

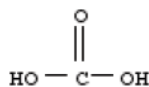


3. 多步驟

11 步驟



- 1.1 R:2,6-Lutidine, S:CH₂Cl₂, S:DMF
- 1.2 R:NaHCO₃, S:H₂O
- 2.1 R:NaHCO₃, S:H₂O, S:Dioxane
- 2.2 R:4-DMAP, R:NaHCO₃, S:H₂O
- 3.1 R: S:DMF



● Cs

- 4.1 R:F₃CCO₂H, S:CH₂Cl₂, S:Me₂S
- 5.1 S:CH₂Cl₂
- 5.2 R:BF₃-Et₂O
- 5.3 R:Et₃N
- 6.1 R:Bu₃SnH, C:Pd(PPh₃)₄, S:CH₂Cl₂
- 7.1 S:CH₂Cl₂
- 7.2 R:BF₃-Et₂O
- 7.3 R:Et₃N
- 8.1 R:H₂O₂, S:H₂O, S:THF
- 8.2 R:Me₂S
- 9.1 R:K₂CO₃, S:MeOH
- 9.2 R:NaHCO₃, R:CsF, S:H₂O, S:DMF
- 10.1 R:Bu₃SnH, C:Pd(PPh₃)₄, S:DMF
- 11.1 R:NH₄⁺
•HCO₂⁻, C:Pd, S:H₂O, S:MeOH

1) ultrasound, 3) solid-supported reaction, solid-supported product, reactant on phenylselenenyl resin, low pressure, mol. sieves used, 4) solid-supported reaction, solid-supported product, reactant on phenylselenenyl resin, 5) stereoselective, solid-supported reaction, solid-supported product, reactant on phenylselenenyl resin, mol. sieves used, 6) solid-supported reaction, solid-supported product, reactant on phenylselenenyl resin, 7) stereoselective, solid-supported reaction, solid-supported product, reactant on phenylselenenyl resin, mol. sieves used, 8) solid-supported reaction, reactant on phenylselenenyl resin, Reactants: 6, Reagents: 13, Catalysts: 2, Solvents: 7, Steps: 11, Stages: 19, Most stages in any one step: 3

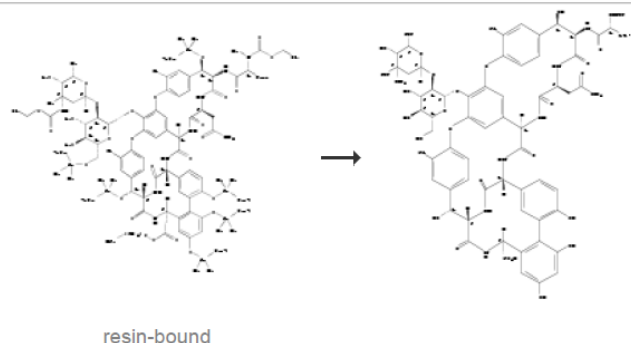
References

Solid- and solution-phase synthesis of vancomycin and vancomycin analogues with activity against vancomycin-resistant bacteria

By Nicolaou, K. C. et al

From Chemistry—A European Journal, 7(17), 3798-3823; 2001

4 步驟



resin-bound

Overview

Steps/Stages

- 1.1 R:H₂O₂, S:H₂O, S:THF
- 1.2 R:Me₂S
- 2.1 R:K₂CO₃, S:MeOH
- 2.2 R:NaHCO₃, R:CsF, S:H₂O, S:DMF
- 3.1 R:Bu₃SnH, C:Pd(PPh₃)₄, S:DMF
- 4.1 R:NH₄⁺
•HCO₂⁻, C:Pd, S:H₂O, S:MeOH

Notes

solid-supported reaction, reactant on phenylselenenyl resin, Reactants: 1, Reagents: 7, Catalysts: 2, Solvents: 4, Steps: 4, Stages: 6, Most stages in any one step: 2

References

[Solid- and solution-phase synthesis of vancomycin and vancomycin analogues with activity against vancomycin-resistant bacteria](#)

By Nicolaou, K. C. et al

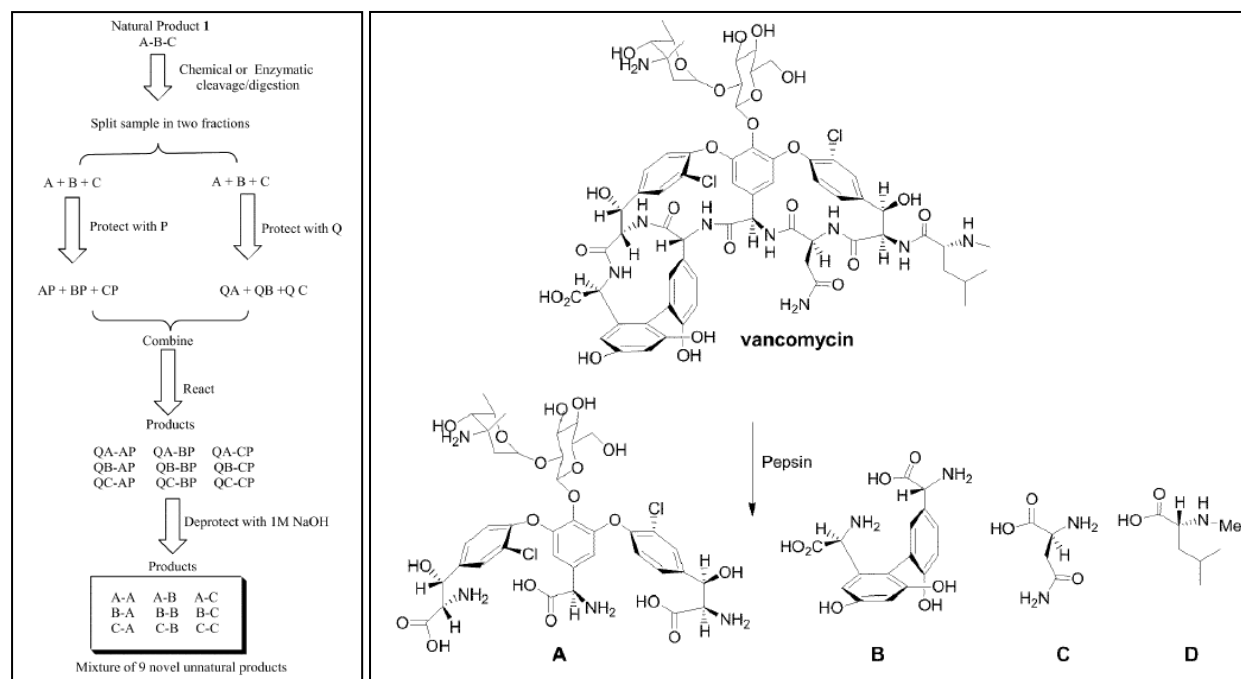
From Chemistry--A European Journal, 7(17), 3798-3823; 2001

5. 相關文獻

The interaction of vancomycin with DNA

Vancomycin is the store antibiotic, used only in the grave infections treatments (endocarditis, septicemias, pneumonias, meningitis) with the resistance pathogens of other antibiotics. The interaction of vancomycin with calf thymus DNA was studied by the absorbance measurements. The vancomycin self-assocn. has been investigated in terms of Tipping and Schwarz methods. The binding of vancomycin to DNA has been investigated in terms of Benesi-Hildebrand, Scott and Scatchard methods, supposing a 1:1 binding ratio and do not account explicitly for either the dimerization of the drug or cooperativity effects on the binding.

6. 相關專利資料



SUMMARY OF THE INVENTION

[0010] In accordance with the objects outlined above, the present invention provides novel molecules and libraries thereof, as well as methods for their production. One aspect of the invention provides for methods of generating molecular subunits by cleaving a starting molecule. In preferred embodiment, the cleaving is performed enzymatically. In a further preferred embodiment, the enzyme used to perform the cleaving step is selected from the group consisting of hydrolases, oxidases, reductases, proteases, peptidases, esterases, and mono-oxygenases. In a further preferred embodiment, the starting molecule is selected from the group consisting of the group consisting of small molecules, polypeptides, peptidomimetics, nucleic acids, alkaloids, macrolides, terpenes, macrocycles, fermentation products, or molecules from plant, animal, bacterial, or fungal sources.

[0011] A further aspect of the invention provides for a method comprising cleaving one or more starting molecules into molecular subunits and assembling two or more of the subunits to produce at least one recombined molecule which is different from the starting molecule(s). In a preferred embodiment, at least one of the cleaving or assembling steps is mediated by an enzyme. The cleavage step is preferably mediated by an enzyme selected from the group consisting of hydrolases, oxidases, reductases, proteases, peptidases, esterases, mono-oxygenases, lyases and ligases. The assembly step is preferably mediated by an enzyme selected from the group consisting of lyases, ligases, fumarases, glycosyl transferases, glycosidases, haloperoxidases and halohydrin

epoxidases. In a further preferred embodiment, at least one of the recombined molecules is not a recombined nucleic acid or recombined protein. In yet a further preferred embodiment the cleaving step is of two or more different starting molecules and the recombined molecule or molecules comprise intermolecular combinations of subunits from the different molecules. In yet a further preferred embodiment, the recombined molecules or molecules are modified. In addition to the embodiments, the starting molecules are attached to a support.

[0012] In a further preferred embodiment the starting molecules used to produce the molecular subunits are selected from the group consisting of polypeptides, nucleic acids, alkaloids, macrolides, terpenes, macrocycles, fermentation products, and molecules from plant, animal, bacterial, or fungal sources. Preferably, at least one of the starting molecules is selected from the group consisting of vancomycin, Rifamycin B, erythromycin, camptothecin, 9-hydroxyellipticine, bisamidophthalanide derivatives, rapamycin, actinonin D, avermectin B1, phomopsis A, and cytochalasin D.

[0013] A further aspect of the invention provides a screening for a biological activity of the recombined molecule. In a preferred embodiment, the screen comprises contacting the recombined molecule with a biological target, a determining the effect of the recombined molecule on a property of the biological target.

[0014] A further aspect of the invention provides for a library of recombined molecules made according to the methods described herein.

[0015] A further aspect of the invention provides for a method for screening for a biologically active recombined molecule comprising contacting the library of recombined molecules with a biological target and determining the effect of the library on a property of the biological target. In a preferred embodiment, the library is partially purified prior to contacting with a biological target.

[0016] A further aspect of the invention provides for isolating from the library a recombined molecule with biological activity. In a preferred embodiment, the structure of the recombined molecule with biological activity is identified.

[0017] A further aspect of the invention provides for a biologically active recombined molecule made according to the methods described herein.

[0018] A further aspect of the invention provides for a method comprising cleaving one or more starting molecule(s) into molecular subunits, modifying the molecular subunits, and assembling two or more modified molecular subunits to produce at least one recombined molecule which is different from said starting molecule(s). In a preferred embodiment, at least one of the cleaving or assembling steps is mediated by an enzyme. The cleavage step is preferably mediated by an enzyme selected from the group consisting of hydrolases, oxidases, reductases, proteases, peptidases, esterases, mono-oxygenases, lyases and ligases. The assembly step is preferably mediated by an enzyme selected from the group consisting of lyases, ligases, fumarases, glycosyl transferases, glycosidases, haloperoxidases and halohydrin epoxidases. In a further preferred embodiment, at least one of the recombined molecules is not a recombined nucleic acid or recombined protein.



US 20110312034A1

(19) **United States**

(12) **Patent Application Publication**
Brown

(10) **Pub. No.: US 2011/0312034 A1**
(43) **Pub. Date: Dec. 22, 2011**

(54) **RECOMBINED MOLECULES AND PREPARATION THEREOF**

Publication Classification

(75) **Inventor:** **Dennis M. Brown**, Menlo Park, CA (US)

(51) **Int. Cl.**
C12P 19/44 (2006.01)
C12P 17/04 (2006.01)
C12P 17/18 (2006.01)
C12P 19/02 (2006.01)
C12P 17/16 (2006.01)
C12P 17/10 (2006.01)
C12P 19/26 (2006.01)

(73) **Assignee:** **Valent Technologies**

(21) **Appl. No.:** **13/039,055**

(22) **Filed:** **Mar. 2, 2011**

(52) **U.S. Cl.** **435/74; 435/121; 435/126; 435/84; 435/105; 435/118; 435/119**

Related U.S. Application Data

(63) Continuation of application No. 10/843,148, filed on May 10, 2004, now abandoned.

(60) Provisional application No. 60/490,804, filed on Jul. 29, 2003, provisional application No. 60/484,214, filed on Jul. 1, 2003, provisional application No. 60/468,894, filed on May 8, 2003.

(57) ABSTRACT

The invention relates to novel molecules and libraries thereof as well as methods for their production. Methods of producing the novel molecules include the cleaving of starting molecules into molecular subunits and the assembly of the subunits into novel recombined molecules.

使用心得

在上這兩堂藥學科技之前，我從未接觸過這兩個軟體的相關資訊，甚至沒聽過，使用過後覺得相當值得學習，尤其是 **scifinder**，不但會有新的研究資料，資料比起 **google** 或 **yahoo** 等搜尋引擎所得較具準確性也比較有參考價值，不過 **Thomson innovation** 學校買的版本有許多功能無法使用無法做練習，是滿可惜的地方。然而，**scifinder** 為英文版本，搜尋所得資料也較為專業，要使用它成為平時搜尋工具，我認為自己也需培養好相當程度的專業知識，如此一來才足以利用他並從其中學習到新的知識。