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Biosynthesis-based artificial evolution of microbial natural products

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[1]
[2]

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N . , , . H , . ; , , . H , , - - , - . / .

biosynthesis, artificial evolution, RiPPs, NRPS, PKS, enzymatic diversity

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1 Introduction

2 . , N , , 3 . 1 . - , , ; , 4 , (, 5 , 6 , 7 ,) ( ) - , , ,) (F 1). , . E , ; , , . N , - - - .

*C (: @ . . ; @ . . .)

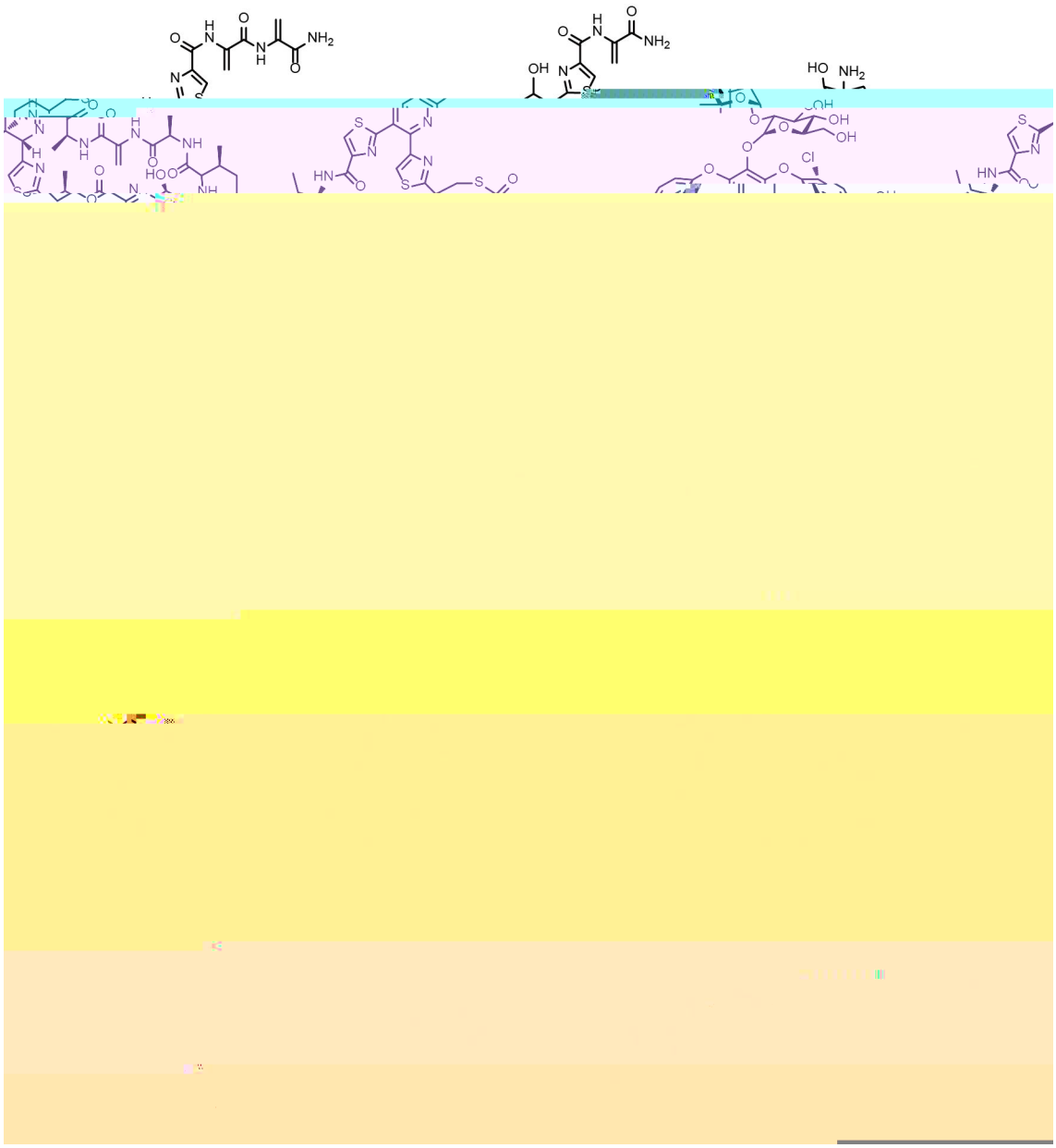

Figure 1

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8 . H ,

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2 Ribosomally synthesized and post-translationally modified peptides

(PP), ,

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, PP ,
- (P P),
. N
P P -
, 20 110
, -
(P M) (F 2)
9 . ,
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. I
PP , N-
, , ,
C-
10 . B
, .
P P , -
PP - . M
P M ,
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P M
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P P
PP .
H , ,
12 ,
PP .
A PP ,
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( ) -
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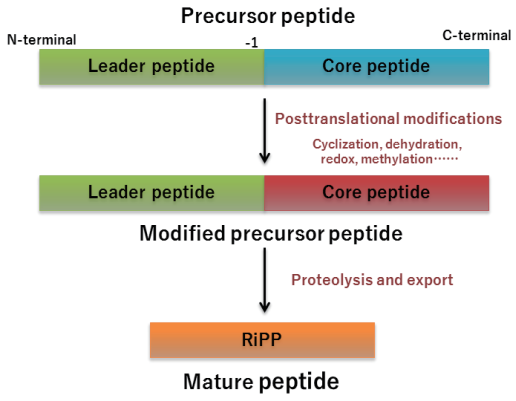

Figure 2 G PP .
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, , GE37468, 13 .
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/ / ,
(D , , D) (
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12,14 .

2.1 General strategies: editing core peptide-encoding genes and engineering PTM enzymes

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- P M
PP ,
-
P M .

2.1.1 E -
- PP
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PP . F -
, K ,
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15,16 , GE37468 17 , 18 20 (F 3( ), ( )
( )). M ,
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21 .
I , -
GE37468 ,
PP . -
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A
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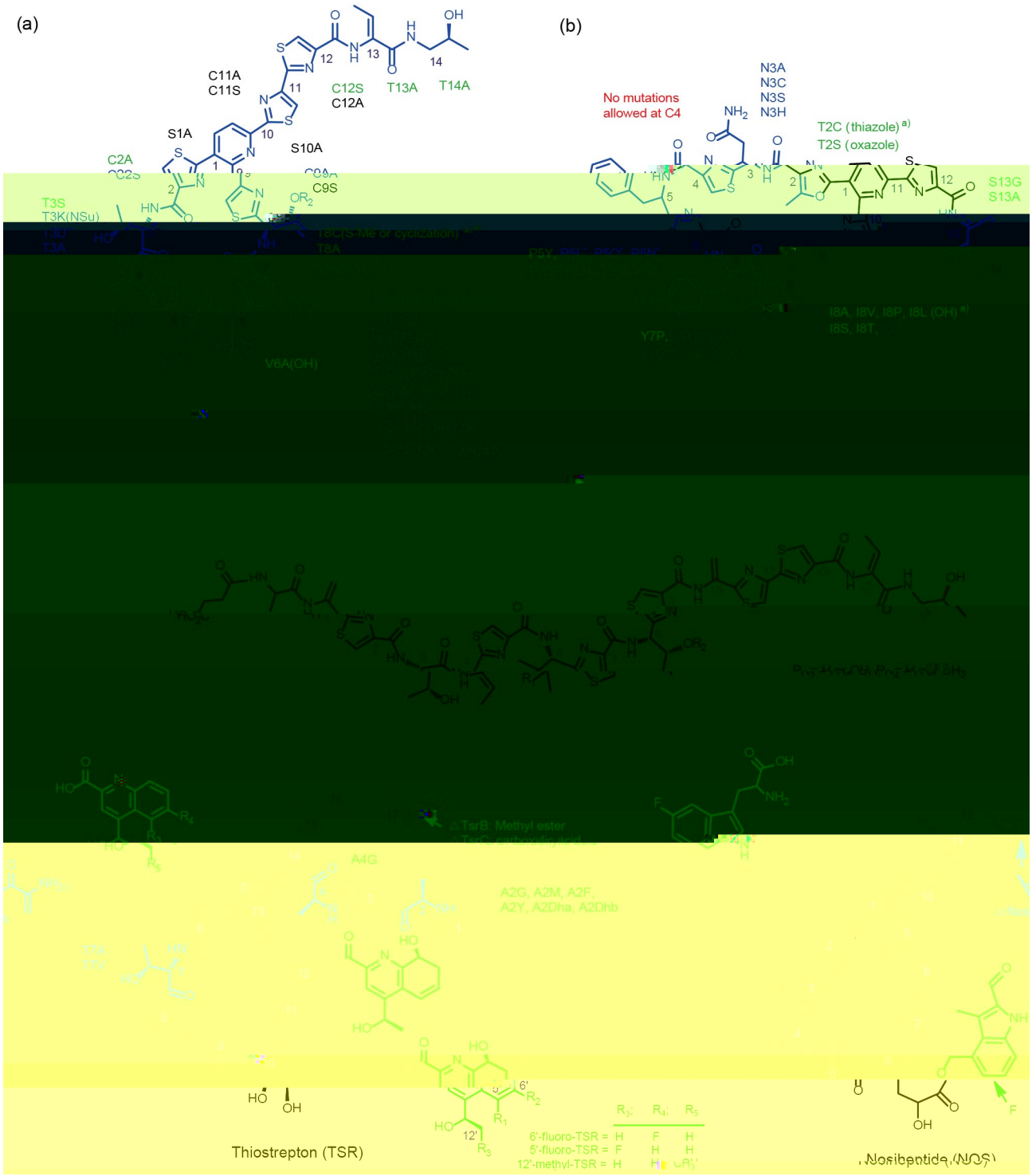

Figure 3 P - , P M- , . ( ) ; ( ) GE37469; ( ) - ; ( ) ; ( ) NO . M . - , . A ; ; QA 5- - - ; D D ( ).

3 4 . B , , 23, 29, 32, , D , 35- . N , 23 32-

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PP ,

21 .

2.1.2 E P M

P P ,

P M

PP . I

PP -

. F , A

B,

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C 24 .

NO , C-

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N A. NO

D

25 (F 3( ) ( )). M ,

N N

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N N 4 -

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26 .

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M

27 (F 3( )). ,

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P M

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P M

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2.2 Special strategy: feeding with modified building blocks

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PP . O

PP ,

NO 28 . B

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(QA) (IA) .

QA

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3- -2- .

. F , A QA IA

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5- - -

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NO 29 . F 6- -QA

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6 - - 28 .

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3.1.1 G DEB
- PK
,
K , DH, E . G
PK ,
- .
D K 6 (K 6) E 4
3- -
6,7- 6- EB , (F 5( ))
39,40 . H , -
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DH4 41 . K , DH E
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3-
1 B ,1
1
( ))
3. . H DH H

- 60
( ))
3-
H H

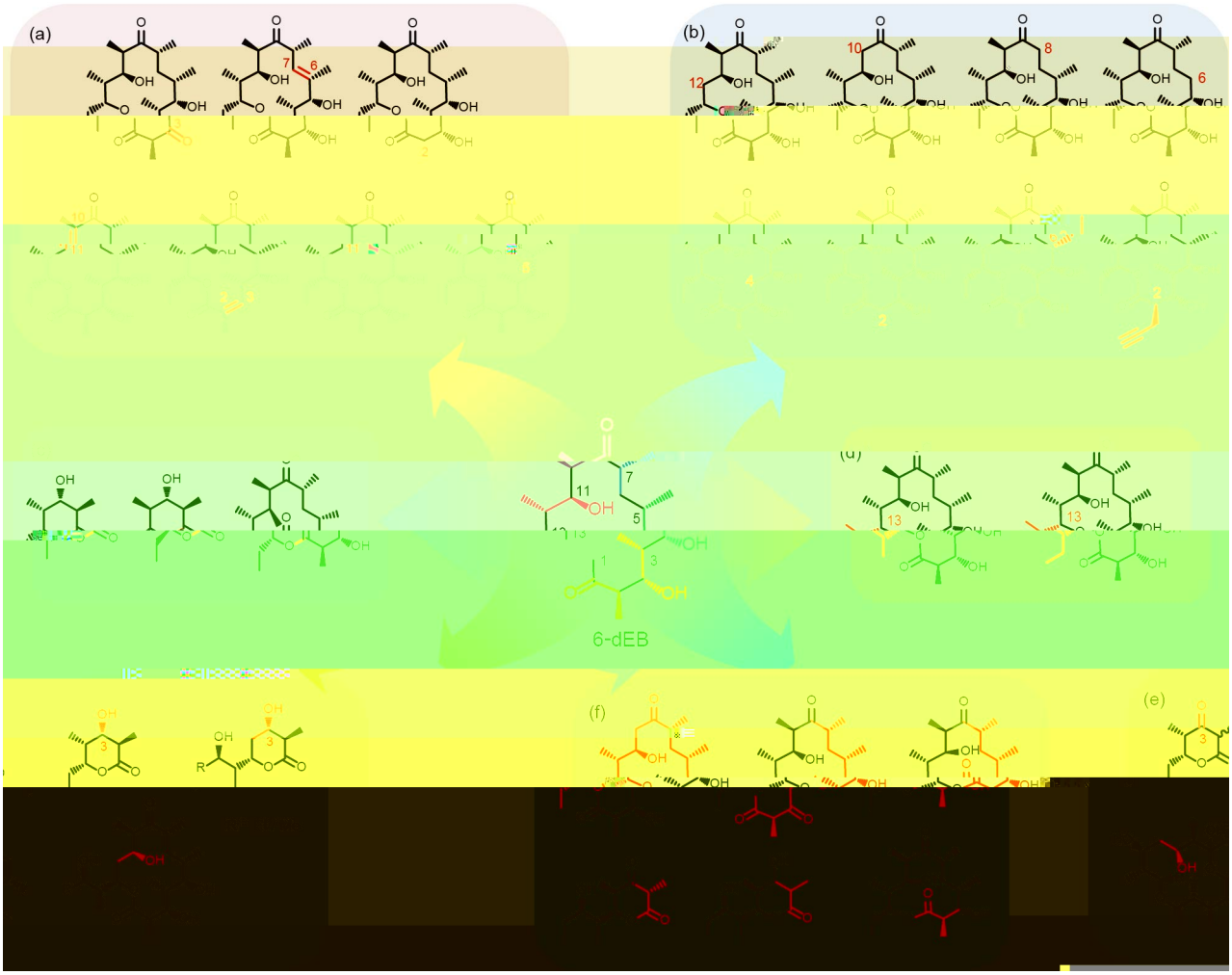

Figure 5 6- EB DEB , , K , DH, E ( ), A ( ), E ( ), ( ), ( ). - ( ).

DEB 57 . A . B DEB 1- E , -PK , ACP1 (DEB) ACP2 (AP) **2** K 2 (AP), - **3** **6**, **5** (IF) K 2 (AP) 58 . PK (F 5( )) 55 . ACP -K +1 . , ACP K +1 56 . A - **2** **5** AP PK **1** **2** DEB 1- E , . H , , . M , **2** **5** AP PK **1** **2** DEB , 14- 16- (F 5( ))

3.1.3 G DEB - C- N- . - , - , 59 . H PK , (PIK) PK - DEB 3 (OLE) . PK 14- , -

- (F 5( )) 60 . - , . - DEB 1 - , N- DEB 2 N- PIK IF 61,62 . , DEB 2 - , **6** DEB 3 **5** IF PK , N- - DEB 3, (F 5( )) 62 . - .

3.2 Special strategies: engineering unusual precursors and tailoring modifications

- . I - - , , . F , ; , 63 .

3.2.1 E

, PK N P . I PK , , - , - , , - 64 . A , - PK , PK . I N P , - 65 . A . D PK N P , - . , FK506, . FK506 , FK520 AP, - , PK -N P 66 68 . PK FK506 - 4,5- -1- (DHCHC) 69 , -C A 70 , -ACP 71 , - 72 , - (F 6). FK506, FK520 AP , DHCHC - , 73 . DHCHC, - , F O (K) PK 69 . M - FK506, FK520 AP. DHCHC , 74 77 . I , - N P , F L (L) - 72 . -

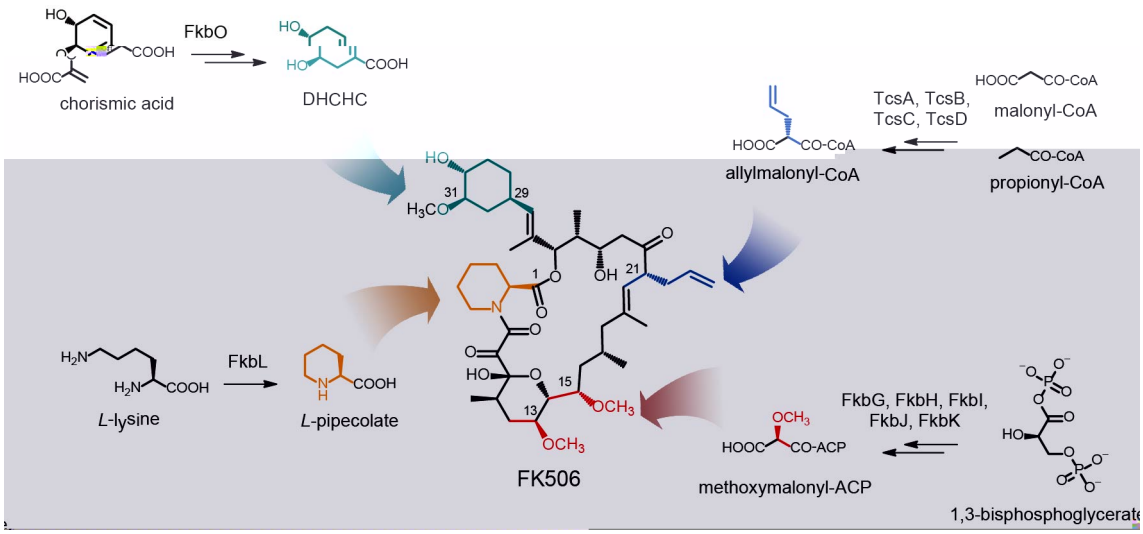

Figure 6 FK506 4 - . DHCHC, PK , F O . A -C A -ACP, PK , - . - , N P , F L - ( ).

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AP 78 .
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FK506
21- , PK
-C A. I
- PK -
, ABCD 70 . A 4
FK506 PK -C A ,
-, -,
-C A ,
FK506D, FK520, FK523, 79 .
-
FK506 FK506D, FK520 FK523,
80 .
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,
-C A FK506
C-21 . A
-
-C A,
, 36- -FK506 81 . C ,
-C A /
(CC)
, - -
PK 82 .
CC A E N P -PK
(AN) . A E
C A ,
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83 . A
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84,85 .

3.2.2 E
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. F , -PK
-N P
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65,86 . G -
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87 . A
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G E G D, -
. -
G D-
(F 7( ))
88 . I - , O D
(OLE)
G E. B 2- -4-
, 11 -
(F 7( )) 89 . G -
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4 Modern strategies focused on protein engineering

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PP , - -
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91 92 ,
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PP , - ,
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. I PK ,
CC
83 . F ,
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, , , -
A 93,94 . I ,
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95 , 86 , 96 , -
86 , -

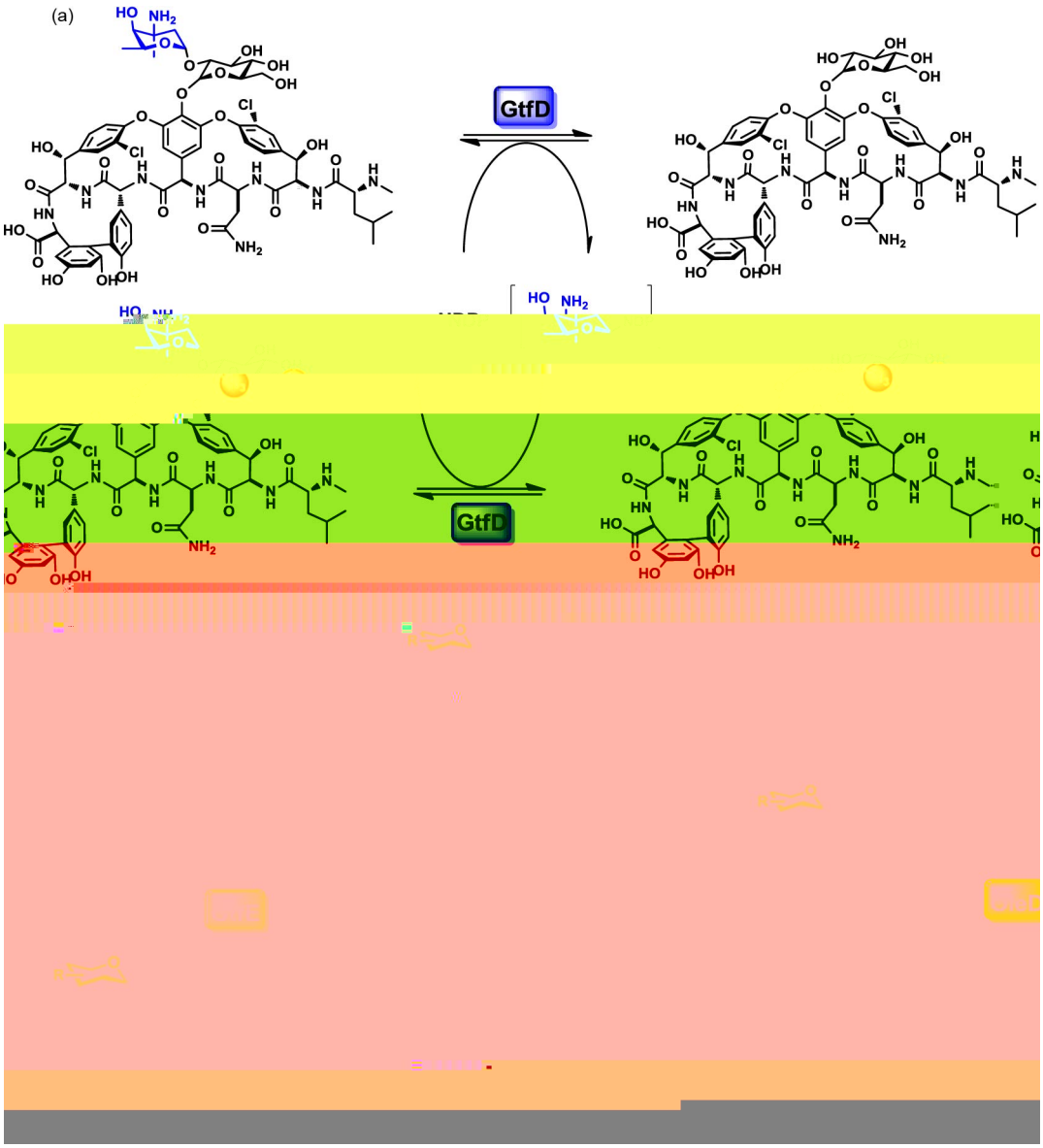

Figure 7 G D G E - . ( ) G D- . -
G D- 6- -
. ( ) A - (G E O D) . NDP-
O D- 88,89 ( ).

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5 Conclusions

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Acknowledgments N N - F C (81402831, 21520102004, 31430005, 21472231) C M (- , C) (14JC1407700, 15JC1400400) C .

Conflict of interest

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1 N DJ, C GM. , 2012, 75: 311 335
2 K FE, C G . , 2005, 4: 206 220
3 O, D. , 2014, 31: 318 334
4 P G , M , B P . , 1968, 2: 34 38
5 M , , , O . , 1984, 37: 187 189
6 K D. , 1985, 228: 1049 1055
7 H K, L, , D , JA. , 2009, 82: 13 23
8 B H. , 2006, 24: 1533 1540
9 A PG, B MJ, B G, B AA, B , B G, C JA, C DJ, C GL, C J, C PD, C DJ, D M, D E, D , D PC, E KD, F MA, G J , G , G C , H DH, H K, H C, H C, H A , J M, K L, K JP, K OP, L AJ, L , M MA, M DA, M GN, M B , M , N K, N IF, N GE, O BM, O H, P ML, P J, MJ , , P, HG, E , ME, K, B, K, L, , D, J , GL, A , JC, C , JD, C, JM, D A. , 2013, 30: 108 160
10 H L, , M, C, M . , 2012, 19: 1278 1287
11 B BJ, H GA, D KL, M DA. , 2015, 11: 564 570
12 Q, L . , 2013, 30: 218 226
13 L J, Q , H , D L, G, B D, D , L , O H , . , 2012, 7: 45878
14 , , L . , 2013, 17: 626 634
15 A MG, B AA, C . , 2009, 131: 17563 17565
16 B AA, A MG, K A, C . , 2010, 132: 7519 7527
17 , C . , 2011, 108: 13053 13058
18 L C, F, K L. , 2011, 7: 82 90
19 L C, F, K L. , 2012, 48: 558 560
20 F, K L. , 2015, 10: 998 1009
21 M MO, P J, J L A. , 2012, 29: 996 1006
22 , D PC, C . , 2012, 19: 1600 1610
23 B AA, A MG, , C . , 2012, 134: 10313 10316
24 L , L . , 2011, 133: 2852 2855
25 , G H, Q, D L, D , L , L C, B, L . , 2010, 132: 16324 16326
26 , D L, Q, L , D , P H, -P E, G, B, L . , 2009, 4: 855 864
27 B AA, C , A MG. , 2010, 132: 12182 12184
28 D L, , L , L . , 2012, 19: 443 448
29 Q, L , C D, , D L, B, L . , 2011, 7: 154 160
30 Q, , L . , 2014, 70: 7686 7690
31 Q, Q, , J, G Q, L . , 2015, 22: 1002 1007
32 , Q, J, , L Q, , , L . , 2015, 2: 106 109
33 F MA, C . , 2006, 106: 3468 3496
34 H C. , 2009, 48: 4688 4716
35 A, M MA. , 2005, 105: 715 738
36 C . , 2004, 303: 1805 1810
37 C J, H F, GA, B DJ, L PF. , 1990, 348: 176 178
38 J, B. , 1997, 97: 2611 2630
39 D , M A JB, PJ, J M, K L. , 1993, 90: 7119 7123
40 , P M, E, A G, N, C J, D , H C , M D . , 2003, 42: 72 79
41 B DJ, J, L PF. , 1993, 21: 30 30
42 M D , A, G C, F H, B M, B M, A G. , 1999, 96: 1846 1851
43 , P A, DL, D, G, J M, A, K , MJ, D , K L. ,

1997, 179: 6416 6425
44 P H, L E, M, B, M CO MICK EL, M A H HAI, J, L PF, K G. , 2003, 56: 543 551
45 L L, A, F H, B M, A G. , 1997, 119: 10553 10554
46 DL, K J, KA, G G, , D, J M, L H, B A, K L. , 1998, 95: 7305 7309
47 CP, L H , K C. , 2008, 105: 4595 4600
48 CD, M , A G , P M, H C , M D . , 2001, 40: 15464 15470
49 B - K, I -A AF, K , K , I , F EK, A, F, -G E. , 2014, 15: 1991 1997
50 K CM, L G, K L, C DE, K C. , 1994, 116: 11612 11613
51 J J , C DE, K C. , 1998, 37: 4928 4934
52 K CM, L G, K L, C DE, K C. , 1995, 117: 9105 9106
53 M AF. , 1998, 279: 199 202
54 P M , D JP, G , L PF, M HAI, M EL, M A, O N, J, J. , 1998, 51: 1029 1034
55 G . , 1999, 284: 482 485
56 M D , K CM, H J, K C. , 1997, 4: 667 674
57 CJ, B I , IP, B, BAM, F G, B AP, PJ, , B AD, J, L PF. , 2001, 8: 475 485
58 I, M CJ, CJ, J, L PF. , 2002, 9: 781 787
59 B , N D, MP, L PF, KJ. , 2003, 10: 723 731
60 L, F H, M D . , 2000, 7: 77 84
61 K B , C A, F G, L , DH, KA. , 2002, 41: 10827 10833
62 K, CCC, B CN, C DE, K C. , 2003, 278: 42020 42026
63 M D , M, H C . , 2005, 105: 543 558
64 L, M B . , 2016, 33: 150 161
65 B, M J. B . I : H DA, E . : . : . D : E A P I ., 2009. 353 378
66 M H, A. , 1998, 256: 528 534
67 , A JF, M I, K A, K LE, H F, O M, C P, C J, L JB. , 1995, 92: 7839 7843
68 K, C L, P, K L, CD. , 2000, 251: 81 90
69 A JN, K G, N - -A M, L O, F A, A , D, D, C NJ, K FE, J , C G , G MA, M CJ, M J, L PF, B. , 2011, 108: 4776 4781
70 M J, K DH, L JH, P J , B DB, B H, J, C , P , C EA, K E, J , L K, P J , L , L MO, L K , K J, K D, P BC, L , K HJ, J , M B , L K, J. , 2011, 133: 976 985
71 C A, B M , P AM, K AK, H J, K NL, MG. , 2006, 103: 14349 14354
72 G , GJ, B M , K NL, C . , 2006, 128: 3838 3847
73 C D, C P, L , . , 2013, 33: 1254 1262
74 K DH, JH, L K , L BM, L MO, L K, M PJ. , 2013, 97: 5881 5892
75 G JM, L , D A, , N - -A M, H DL, B, M J. , 2010, 11: 698 702
76 G JM, L E, NJ, M J. , 2006, 4: 4071 4073
77 B H, L JH, G G , L B, M J, K HJ, J. , 2013, 9: 944 947
78 K LE, B GA, M , J, L PF. , 1998, 180: 809 814
79 C D, Q, Q, C P, , L . , 2012, 78: 5093 5103
80 K G, G D, M P, F , K E, H J, K G, P H. , 2012, 14: 39 46
81 L A, MC, B H, H J, J, M B . , 2013, 2: 379 383
82 MC, M B . , 2012, 29: 72 86
83 , C J, L, Q, H , H, D, A , A I, L . , 2013, 52: 12308 12312
84 L, C J, M , , L , A I. , 2014, 70: 734 737
85 L, M , Q, A , , L , A I. , 2015, 54: 13462 13465
86 O C, M C, JA. , 2010, 27: 571 616
87 L L, L C, L . , 2012, 16: 170 178
88 C. , 2006, 313: 1291 1294
89 G , P -P P, C J, J . , 2011, 7: 685 691
90 P , P J , B H, JK, J. , 2013, 30: 11 20
91 K J, K JD. , 2008, 25: 656 661
92 , G DJ, . , 2014, 31: 1474 1487
93 G KD, C , H JL, F M, G - . , 2010, 11: 119 126
94 L NM, JB. , 2008, 3786
95 C D . , 2008, 12: 141 150
96 C, HL, L J, L J, O PF, L J, JH. , 2014, 15: 2443 2449
97 L , J J, , C DE, C D . , 2008, 469: 184 194
98 L , , C M, K , C DE, C D . , 2007, 466: 260 266
99 H C, M A, D JM, N BM, H B. , 2015, 11: 121 126
100 E B , C , M , H, K NL. , 2011, 18: 601 607
101 K E, M B , J. , 2015, 11: 649 659
102 J, B. , 2001, 5: 159 164